Structure-Activity Relationship Studies of Maitotoxin Based on Chemical Synthesis

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Structure-Activity Relationship Studies of Maitotoxin Based on Chemical Synthesis

化学合成に基づいたマイトトキシンの構造活性相関研究

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Abbreviations

Ac	acetyl
acac	acetylacetonate
APCI	atmospheric pressure chemical ionization
ATP	adenosine triphosphate
BHT	dibutylhydroxytoluene
Bn	benzyl
Bu	butyl
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMP	Dess-Martin periodinane
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
EE	ethoxyethyl
ent	enantiomer
eq	equivalent
ESI	electrospray ionization
Et	ethyl
GI_{50}	growth inhibition, 50%
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
IC_{50}	halfmaximal inhibitory concentration
Im	imidazole
IR	infrared absorption spectrometry
LD_{50}	lethal dose, 50%
LHMDS	lithium bis(trimethylsilyl)amide
m	meta
MAD	methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MS	mass spectrum

MS	molecular sieves
Ms	mesyl
MW	molecular weight
n	normal
NAP	2-naphthylmethyl
NBS	*N*-bromo-succinimide
NCI	national cancer institute
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p	para
PFG	pulsed field gradient
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PTLC	preparative thin layer chromatography
Py	pyridine
quant	quantitive
rt	room temperature
RCM	ring closing metathesis
RSM	recovered starting material
s	secondary
t	tertiary
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-buthyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethane sulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

THF	tetrahydrofuran
THP	tetrahydropyrane
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOCSY	totally correlated spectroscopy
TOF	time-of-flight
Tol	tolyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	*p*-toluenesulfonyl

Chapter 1. Introduction

1-1. Maitotoxin

Maitotoxin (MTX, Figure 1-1-1) was found as one of the causative toxins of ciguatera, seafood poisoning suffered from consumption of fishes inhabit sea in subtropical and tropical regions.[1] Ciguatera causes neurological, gastrointestinal, and cardiovascular disorders, and affects more than 50,000 people annually. MTX was first found in the sea fish “maito” living in the ocean around Tahiti island by Yasumoto and co-workers in 1976,[2] and it was revealed that this toxin was produced by dinoflagellate *Gambierdiscus toxicus* (Figure 1-1-2) in 1997.[3a]

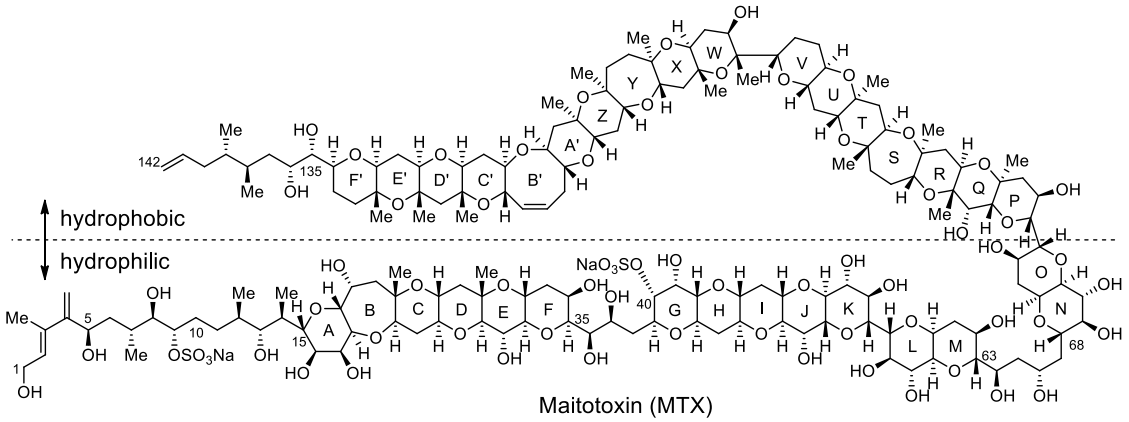


Figure 1-1-1. Structure of maitotoxin (MTX).

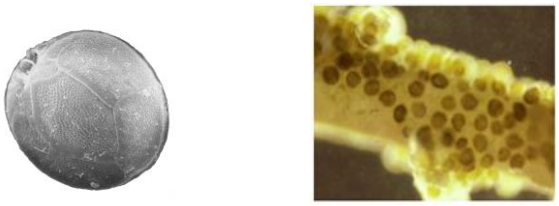


Figure 1-1-2. Pictures of electron microscopy (left) and clinging to the seaweed (right) of dinoflagellate *Gambierdiscus toxicus.*

It took more than fifteen years to determine the structure of MTX because of the large and complex structure.[3] It was assigned by extensive instrumental analysis, particularly ^{1}H- and ^{13}C-NMR including 2D (^{1}H-^{1}H COSY, TOCSY, HMBC, NOESY) and 3D (PFG NOESY -HMQC) technique by Yasumoto and Murata groups.[3b,c] In 1996, the complete stereochemistry of MTX was determined based on chemical synthesis of the partial structures and degradation of the natural product by Kishi and Tachibana groups, independently.[3d-g]

MTX is a ladder shaped polyether compound possessing ninety-eight chiral centers and thirty-two cyclic ethers, which is one of the largest secondary metabolites reported to date (MW 3422).[3a,c] Interestingly, MTX has both hydrophobic and hydrophilic parts (Figure 1-1-1). The hydrophilic property is elicited by the presence of twenty-eight hydroxy groups and two sulfate esters.

MTX is known as one of the most toxic compounds toward mammals (LD_{50} = 50 ng/kg (mice i.p.)).[3c] In addition, MTX elicits potent biological activities at extremely low concentrations; for instance, it causes hemolysis of red blood cells at 15 nM.[4a] The most remarkable biological activities caused by MTX is a profound influx of Ca^{2+} into cells at extremely low concentration (0.3 nM), a phenomenon that has been demonstrated in all cell types examined to date, including rat glioma C6 cells.[4b]

1-2. Identification of target proteins

Although target proteins of MTX have been explored using biological method by a number of scientists, not only the target proteins but also its precise mode of action at the molecular level has not been elucidated. In 1982, the possibility that MTX affected the voltage depended Ca^{2+} channel was reported by Takahashi et al.[5] They investigated the influence of Mn^{2+}, verapamil (specific calcium channel blocker) and tetracaine (local anesthetics) for the [^{3}H]norepinephirine release and Ca^{2+} influx induced by MTX, K^+ and A23187 (calcium ionophore). The both effects of MTX or K^+ were significantly blocked or diminished by all additives. However, the effect of A23187 was inhibited by only Mn^{2+}. Since the Ca^{2+} channel in the presynaptic nerve terminals was known to be sensitive to polyvalent cations and prevented by local anesthetics, direct interaction of MTX to Ca^{2+} channel was indicated.

In 1998, Range et al. reported that MTX might activate a cation conductance from the result of the electrophysiological response study of *Xenopus laevis* oocytes to MTX.[6c] It was also found that conductance induced by MTX might have nonselectivity for monovalent cations by ion substitution experiments. On the other hands, Schilling et al. revealed that MTX caused conversion of the plasmalemmal Ca^{2+} pump into a Ca^{2+}-permeable nonselective cation channel.[7] They were inspired by studies of palytoxin having similar structure and showed that the effect of MTX was strongly blocked by knockdown of the plasmalemmal Ca^{2+}-ATPase (PMCA). In addition, enzymatic activity of PMCA was reduced by MTX. These results supported that PMCA was the most promising candidate of the target protein of MTX at present.

An attempt to identify the target protein of MTX using the photoactive and biotinylating probe was reported by Konoki et al (Figure 1-2-1).[8] Inhibition test which was carried out prior to labeling experiments disclosed that brevetoxin B (PbTx2) blocked MTX-induced Ca^{2+} influx. According to the results, they evaluate specific photolabeling by the probe in the presence or absence of PbTx. As a result, it was found that one band at around 23 kDa was diminished in the presence of PbTx. However, covalently conjugation with the probe (4 kDa) prevented them from identifying the labeled protein. Unfortunately, the lack of natural source and poor reproducibility made further investigations difficult.

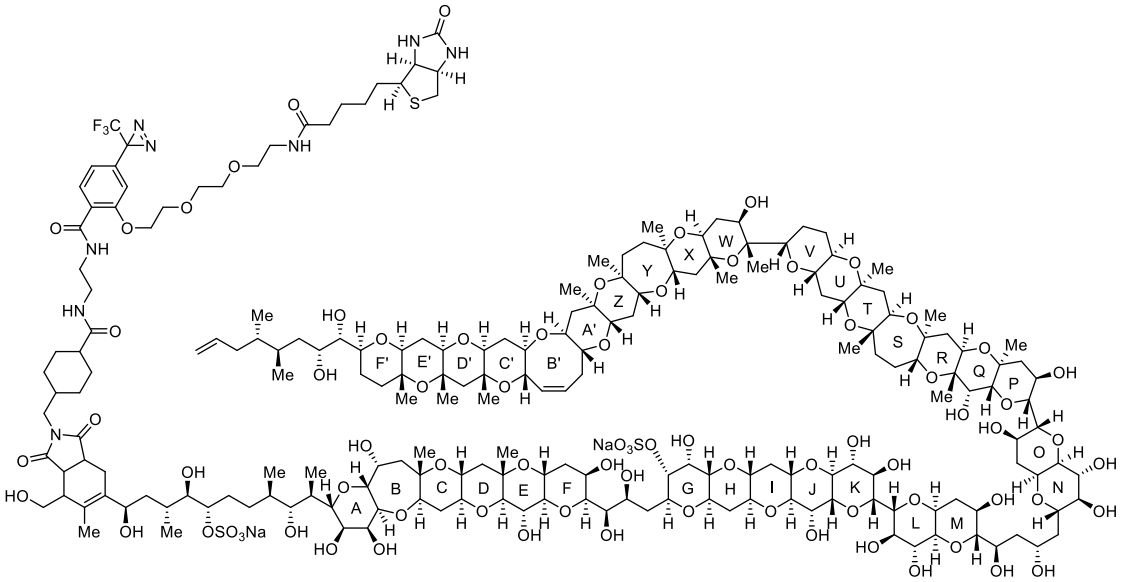
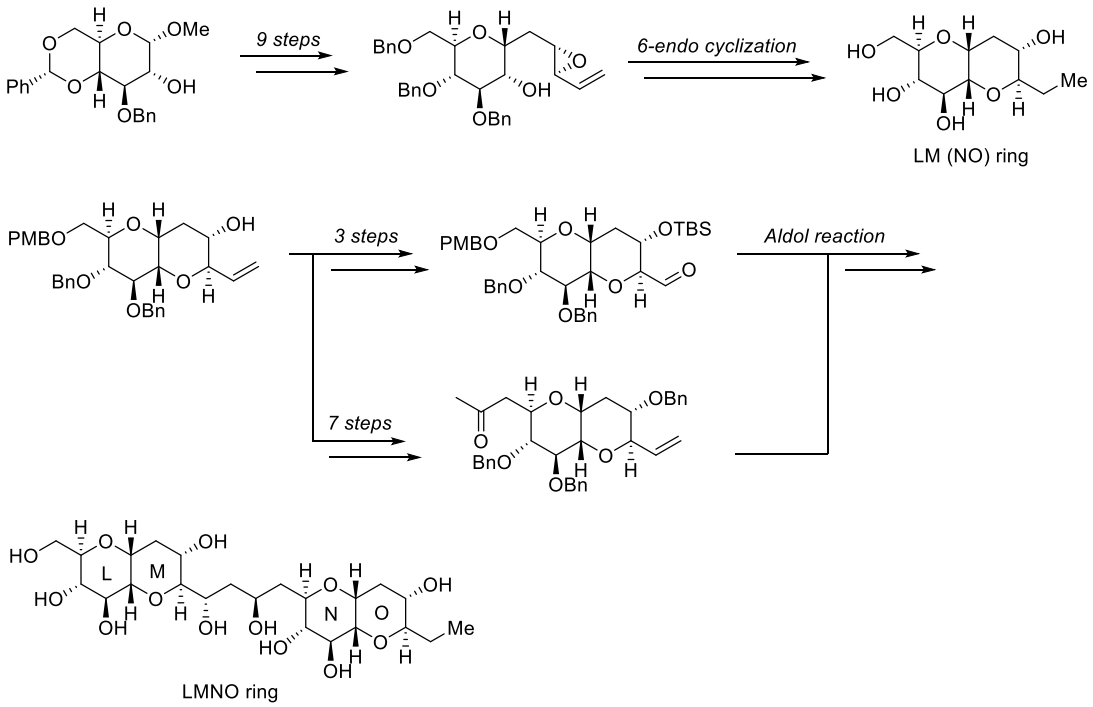


Figure 1-2-1. Photoaffinity probe derived from MTX.

1-3. Synthetic studies of maitotoxin

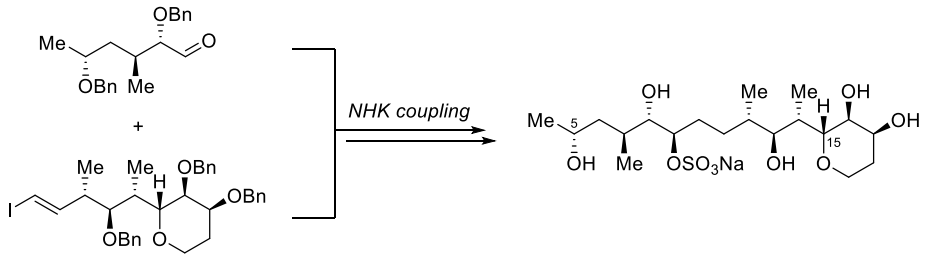
Sasaki and Tachibana group

Synthetic studies of MTX were carried out by a number of synthetic chemists because of its attractive structure and lack of natural samples. In 1994 and 1995, Sasaki et al. reported synthesis of several partial structures of MTX for determination of relative configuration. The LMNO ring of MTX was synthesized through aldol reaction between aldehyde and methyl ketone (Scheme 1-3-1).[9b] These building blocks were prepared from a common intermediate which was derived from tetrahydropyrane derivative by 6-*endo* cyclization of vinyl epoxide.[9a]



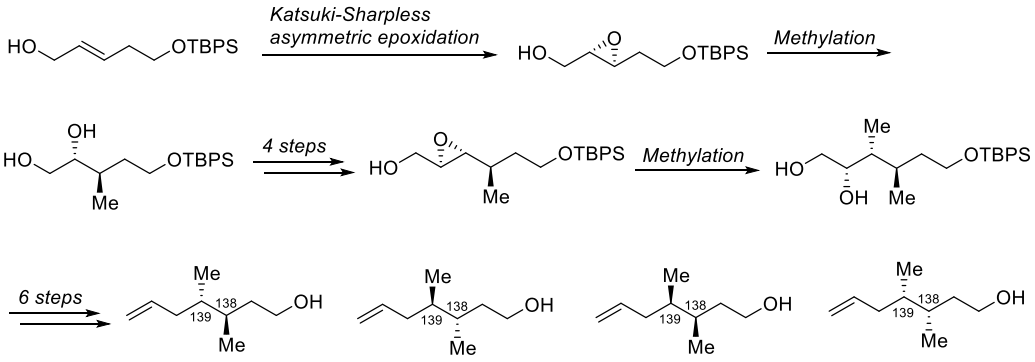
Scheme 1-3-1. Synthesis of the LMNO ring.

In 1996, they synthesized the C1–C14 side chain via NHK coupling of iodo olefin with aldehyde and determined relative configuration of this region (Scheme 1-3-2).[9c]



Scheme 1-3-2. Synthesis and determination of relative configuration of the C1–C14 side chain.

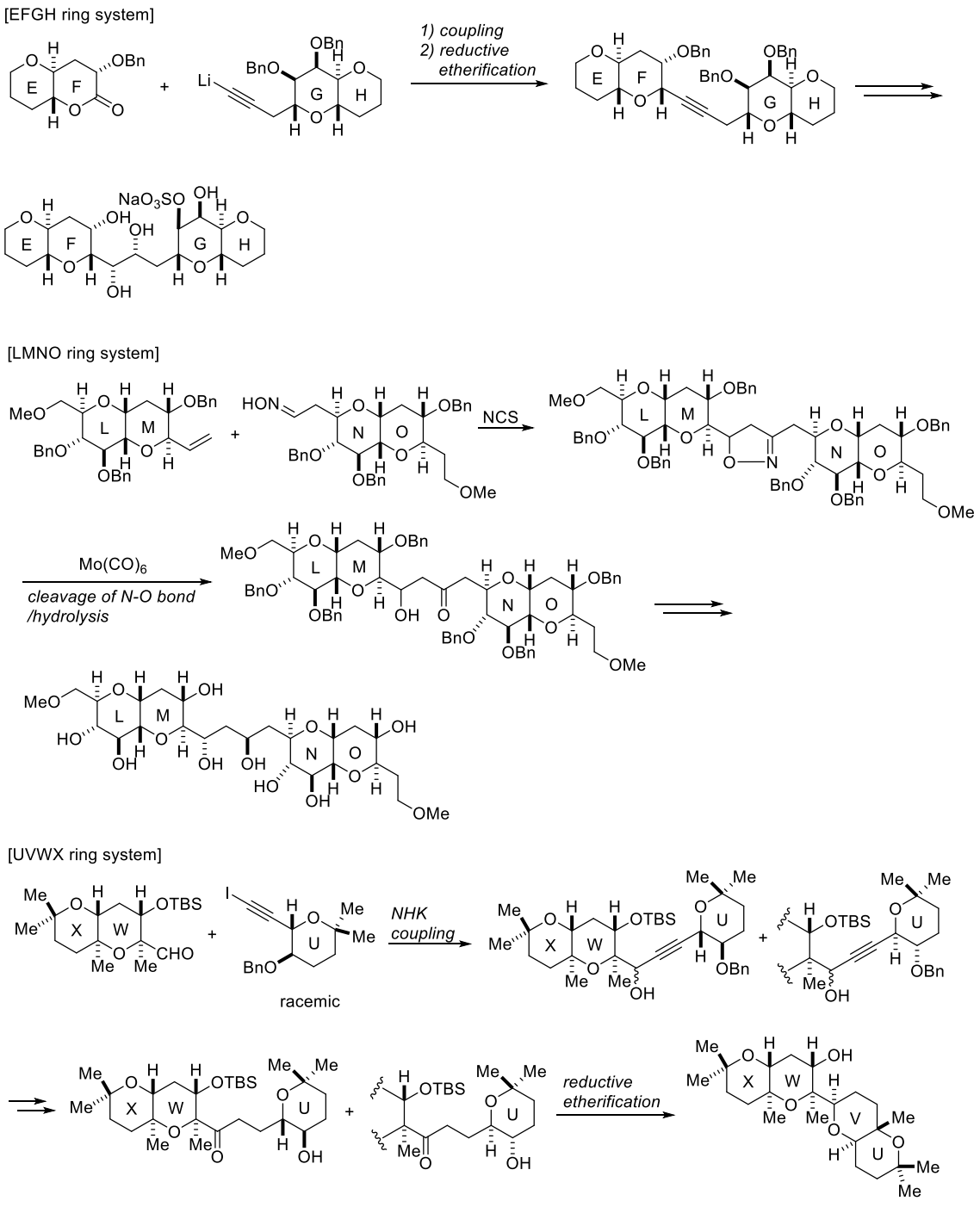
In addition, to elucidate the absolute configuration of MTX, four possible diastereomers corresponding to the C135–C142 section were synthesized via successive methylation of optically active epoxide derived from 3-butene-1-ol (Scheme 1-3-3).[9d] Herewith, longstanding structural determination of MTX was completed.



Scheme 1-3-3. Synthesis and determination of absolute configuration of the C135–C142 side chain.

Kishi group

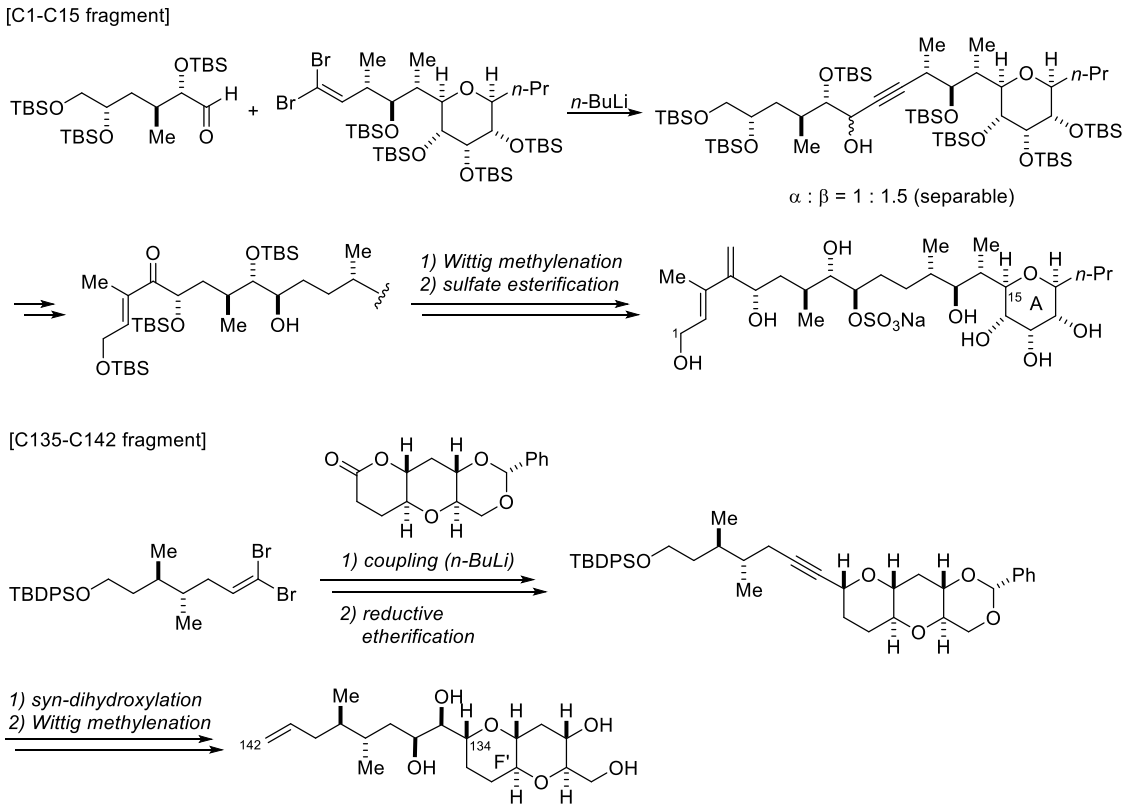
Synthesis of the EFGH, LMNO, and UVWX ring systems of MTX was reported by Kishi et al. for determination of relative conformation of MTX (Scheme 1-3-4).[10a] The EFGH ring system was derived through coupling of lithium acetylide (GH ring) with lactone (EF ring) followed by reductive etherificaiton. Coupling of the NO ring and the LM ring via 1,3-dipolar addition followed by cleavage of the N–O bond of the resulting five-membered ring and hydrolysis by using molybdenum complex generated the LMNO ring system. In addition, synthesis of the UVWX ring system was achieved by NHK coupling between aldehyde and alkynyl iodide followed by reductive etherification.



Scheme 1-3-4. Synthesis of the EFGH, LMNO, and UVWX ring systems.

They also achieved synthesis of C1–C15 and C134–C142 fragment locating in both end of the molecule (Scheme 1-3-5).[10b] C1–C15 fragment was obtained through

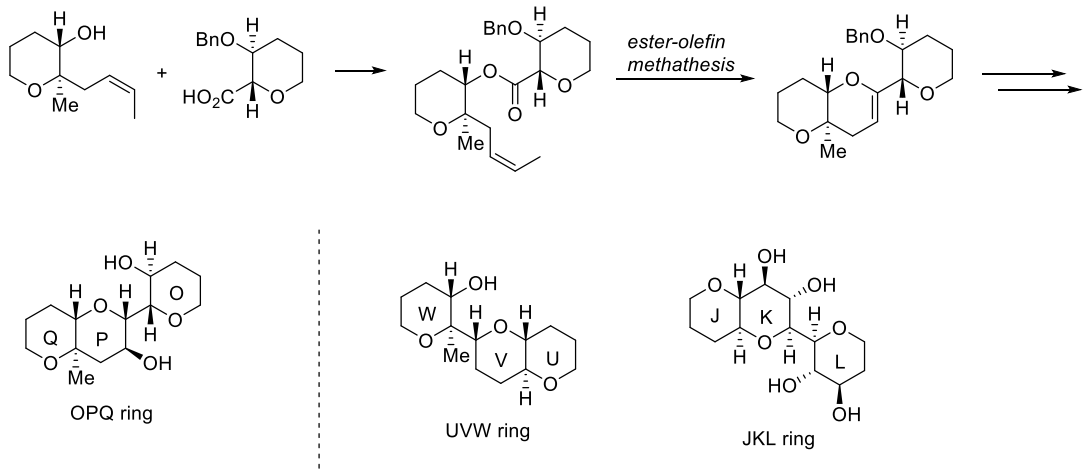
coupling of aldehyde (C1–C11) with dibromo olefin (C11–C15) in the presence of *n*-BuLi followed by Wittig reaction and introduction of the sulfate ester. On the other hands, after acetylide (C135–C141) was connected to lactone (C134), reductive etherification and *syn*-dihydroxylation furnished C134–C142 fragment.



Scheme 1-3-5. Synthesis of C1–C15 and C134–C142 fragments.

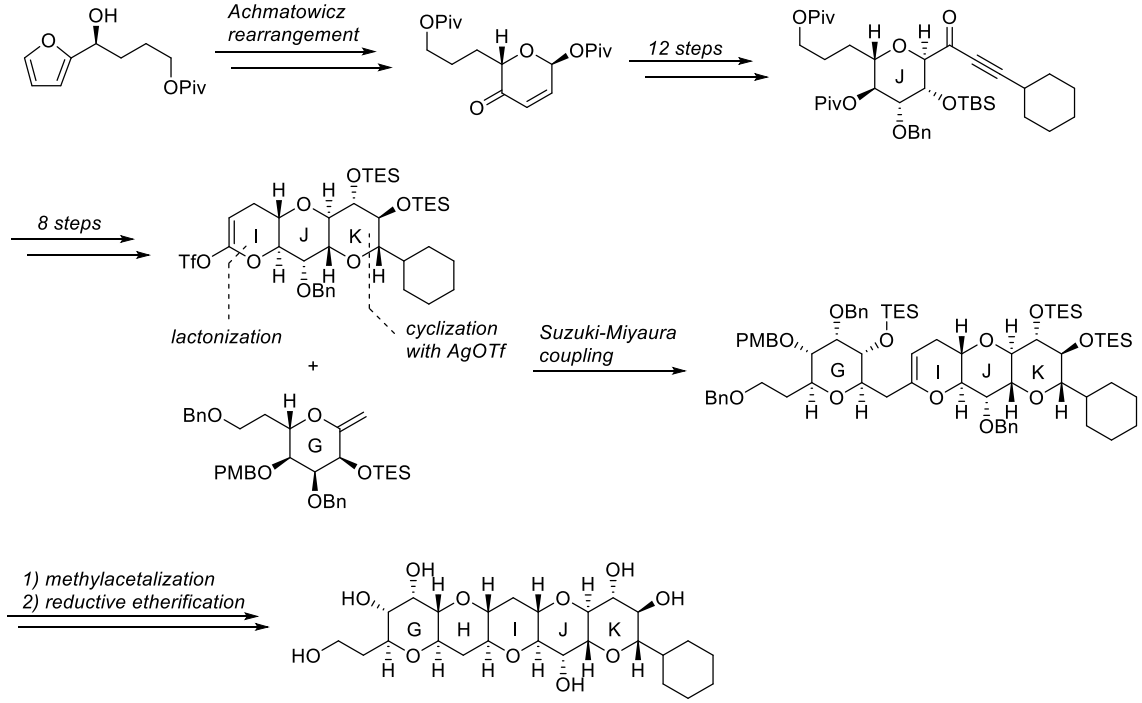
Nicolaou group

Nicolaou et al. were one of the most energetic groups for synthetic studies of MTX. In 1996, three substructures, the JKL, OPQ, and UVW ring system of MTX, were synthesized based on a strategy via the ester–olefin methathesis reaction with Tebbe reagent (Scheme 1-3-6).[11a]



Scheme 1-3-6. Synthesis of the JKL, OPQ, and UVW ring.

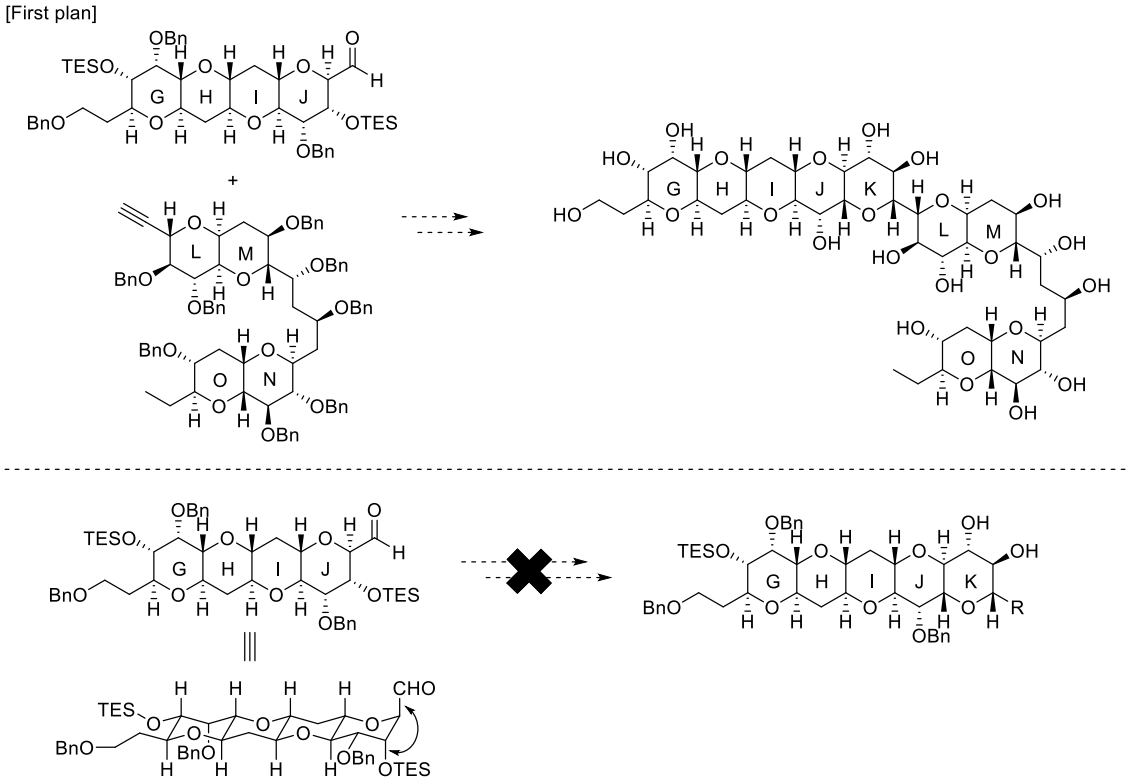
The synthesis of the hydrophilic heptacyclic compound was achieved in 2007 (Scheme 1-3-7).[11b] The G and J rings were constructed via Achmatowicz rearrangement of furan derivatives. Then, intramolecular cyclization of THP derivative, treatment of ynone with AgOTf and intramolecular lactonization, afforded the IJK ring system. The synthesis of the GHIJK ring system was completed through Suzuki–Miyaura coupling between the G and IJK ring fragments.



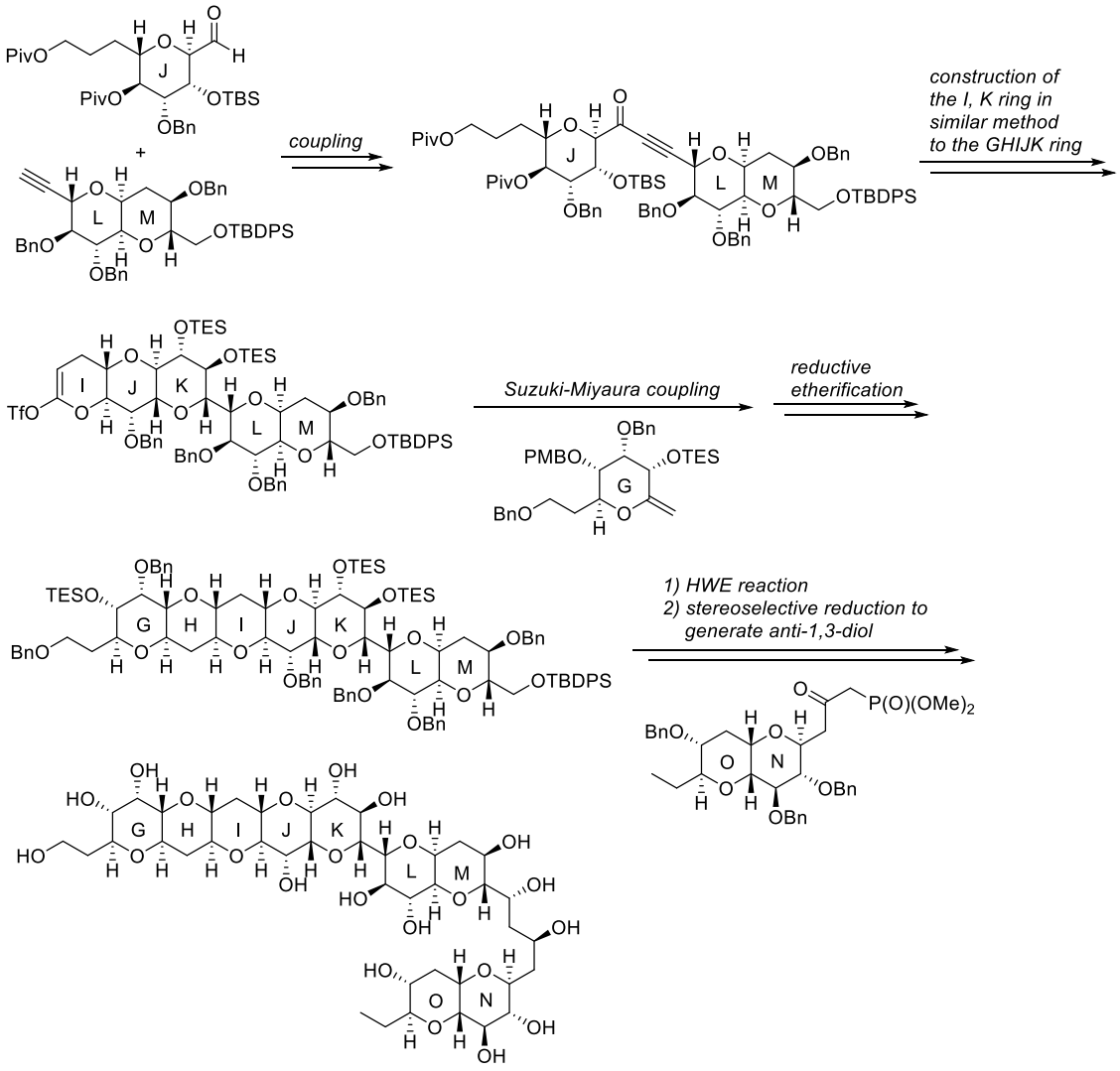
Scheme 1-3-7. Synthesis of the GHIJK ring system.

In 2008, synthesis of the nonacyclic compound including the GHIJK ring was examined.[11c] The target compound was attempted to be obtained by connection of the GHIJ ring fragment and the LMNO ring fragment (Scheme 1-3-8). However, all attempts to assemble the fifth ring (K) on the tetracyclic intermediate (GHIJ) failed because of the diaxial arrangement of the tail-end substituent on the J ring and rigid polyether framework. Therefore, this initial approach was forced to be revised.

The four key building blocks (G, J, NO, LM ring systems) for new strategy were prepared by using above strategy (Scheme 1-3-7) through assembling THP ring through Achmatowicz rearrangement of furan derivative. Finally, the elaboration of the GHIJKLMNO ring system was completed via three different couplings between each fragment (Scheme 1-3-9).

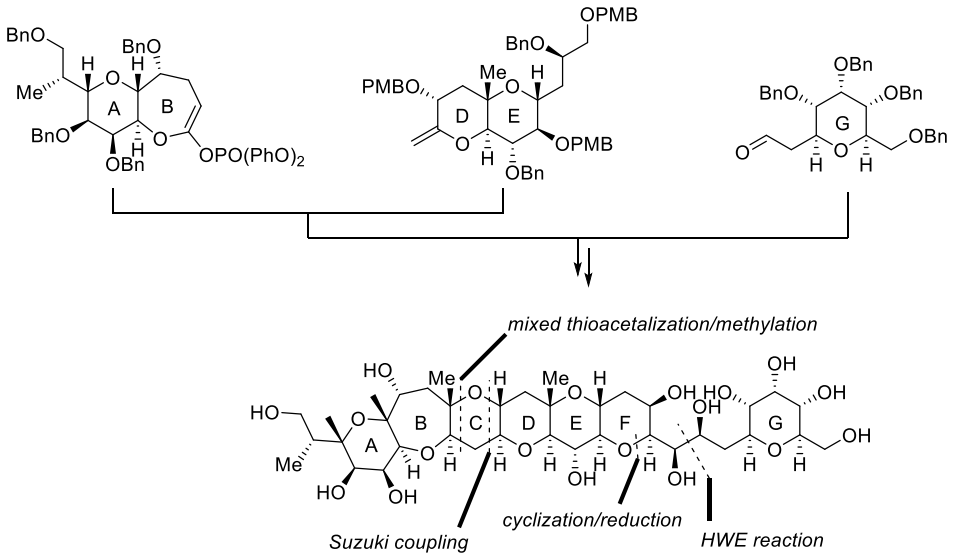


Scheme 1-3-8. First attempt to synthesize the GHIJKLMNO ring system.

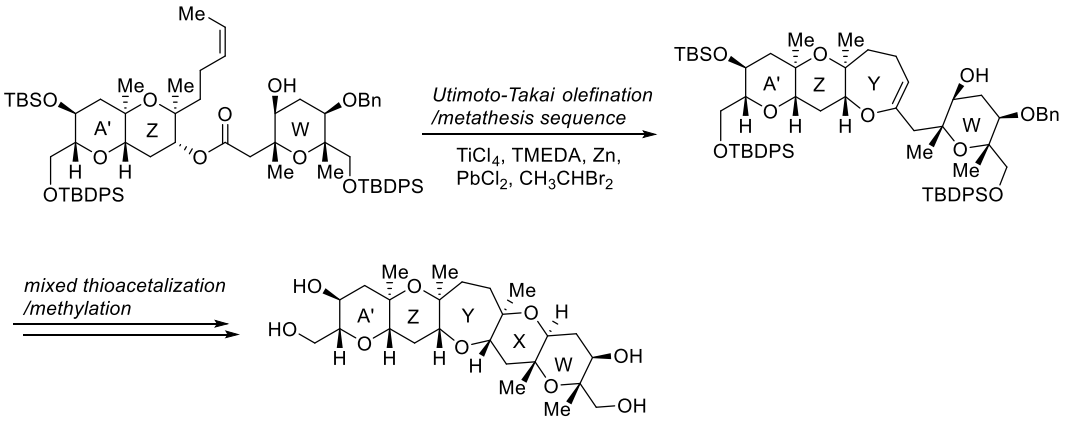


Scheme 1-3-9. Revised synthetic route of the GHIJKLMNO ring system.

In 2010, Nicolaou group released four papers about synthetic studies of MTX. The ABCDEFG ring system was constructed through Suzuki–Miyaura coupling, mixed-thioacetalization/methylation, reductive etherification and Hornar–Wadsworth–Emmons (HWE) reaction (Scheme 1-3-10),[11d] and the synthesis of the WXYZA' ring system was achieved by the Utimoto–Takai olefination/metathesis sequence (Scheme 1-3-11). [11e]

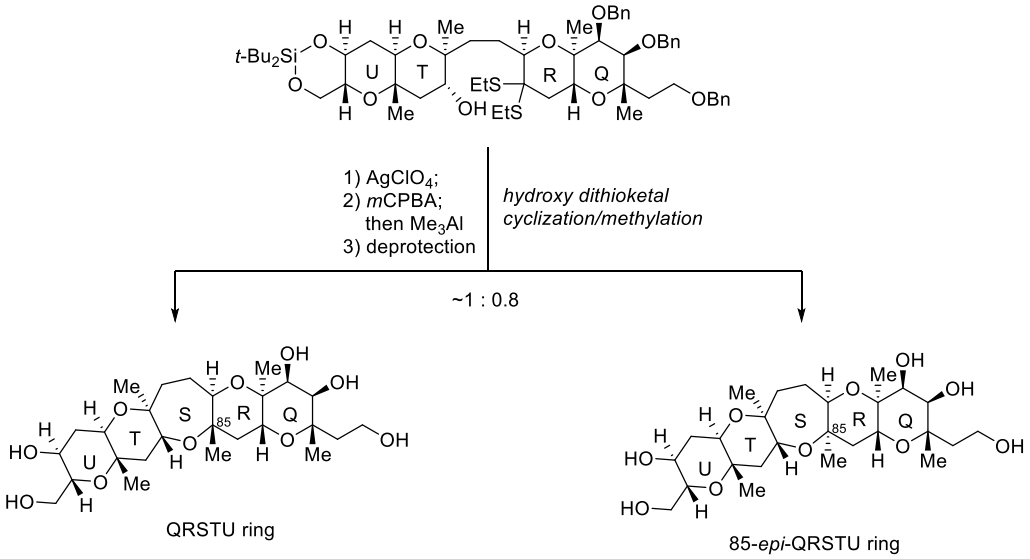


Scheme 1-3-10. Synthesis of the ABCDEFG ring system.



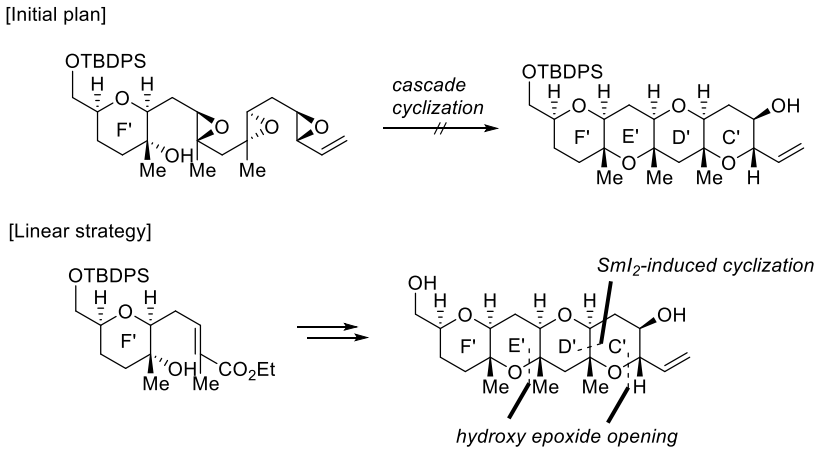
Scheme 1-3-11. Synthesis of the WXYZA' ring system.

Synthesis of the QRSTU ring system was also reported.[11f] However, this route had some problems for hydroxy dithioketal cyclization/methylation (Scheme 1-3-12). It was surprising that this key reaction furnished a diastereomeric mixture contrary to their expectations. This interesting result indicated that the mechanism of methylation might be not as simple as assumed.



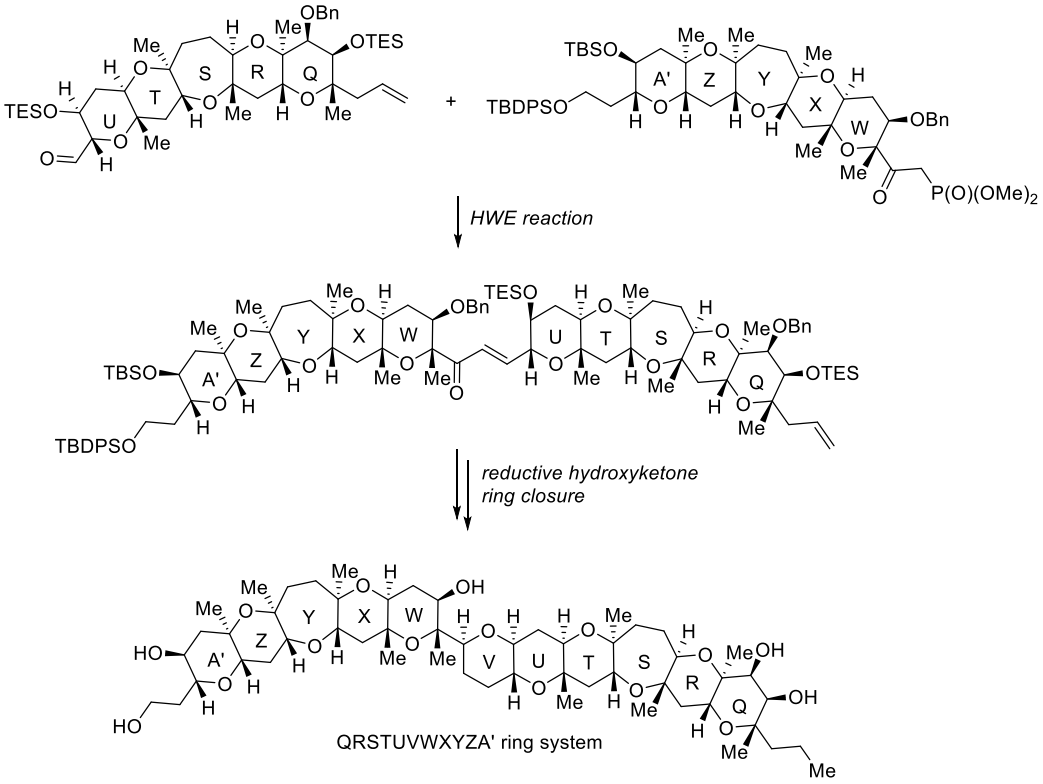
Scheme 1-3-12. Synthesis of the QRSTU ring system.

The development of a biomimetic strategy for the synthesis of the C'D'E'F' ring system was examined (Scheme 1-3-13).[11g] Although this attempt was attractive challenge, the key cascade cyclization of polyepoxide was not successful because of the presence of sterically hindered methyl groups. Finally, a linear strategy was devised via hydroxy epoxide openings for the construction of the C' and E' ring and SmI_2-induced cyclization for the D' ring to afford the C'D'E'F' ring.



Scheme 1-3-13. Synthesis of the C'D'E'F' ring system.

Recently, the synthesis of the QRSTUVWXYZA' ring system was reported by Nicolaou et al. (Scheme 1-3-14).[11h] It was the largest synthetic partial structure with eleven ether rings. Connection of the WXYZA' ring fragment and the QRSTU ring fragment by HWE reaction afforded desired compound.

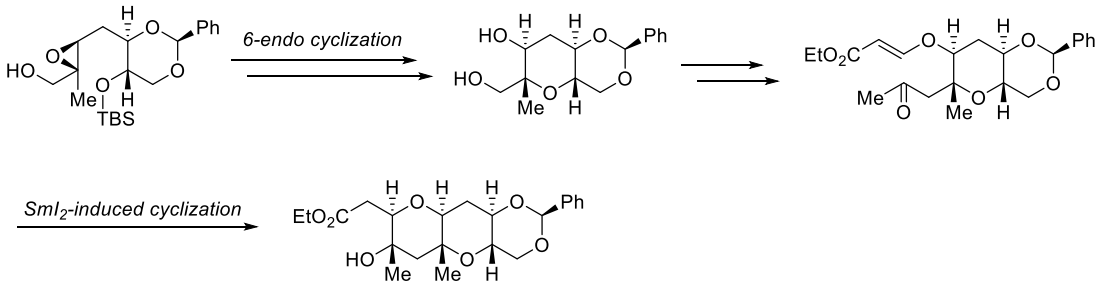


Scheme 1-3-14. Synthesis of the QRSTUVWXYZA' ring system.

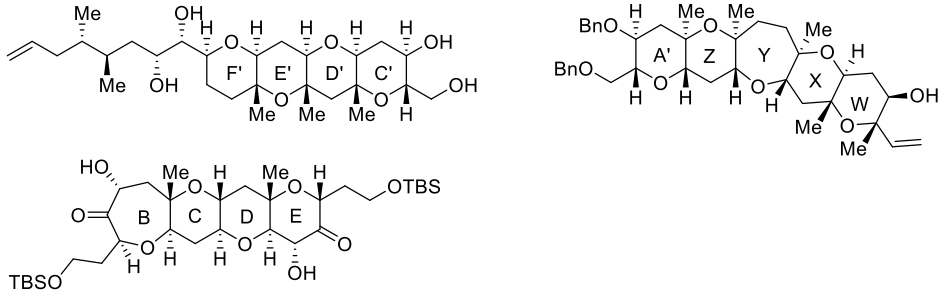
Nakata group

Nakata et al. developed the unique and powerful strategy for construction of ladder-shaped polyether framework with combination of SmI_2-induced cyclization of β-alkocyacrylate and 6-*endo* cyclization of hydroxy vinylepoxide (Scheme 1-3-15).[12a,b,c,d] Syntheses of several partial structures of MTX were achieved by using this strategy. On the other hand, synthesis of the *ent*-ZA'B'C'D' ring system via Suzuki–Miyaura coupling and radical reduction of the *O*,*S*-acetal was reported (Scheme 1-3-16).[12e]

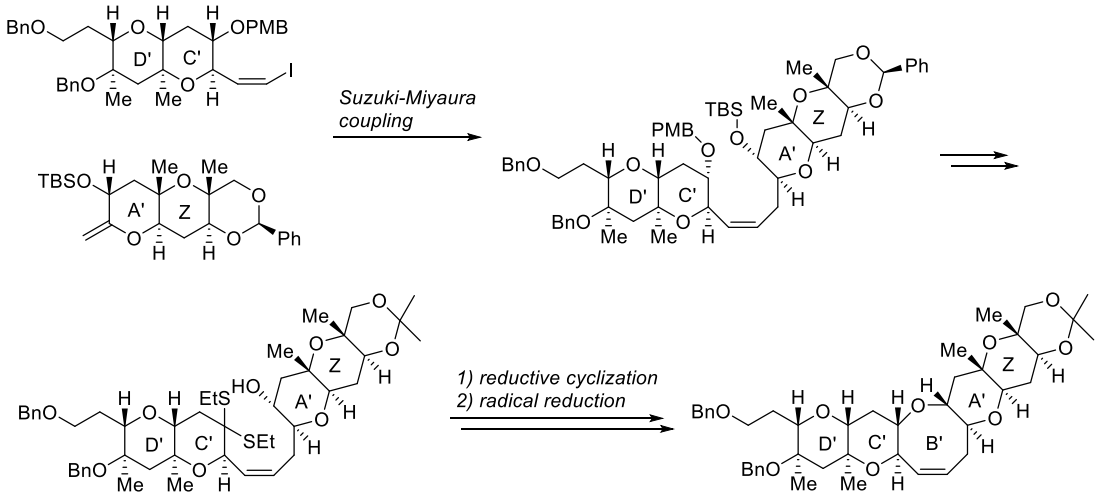
[Strategy for construction of polyether framework]



[Synthetic partial structures]



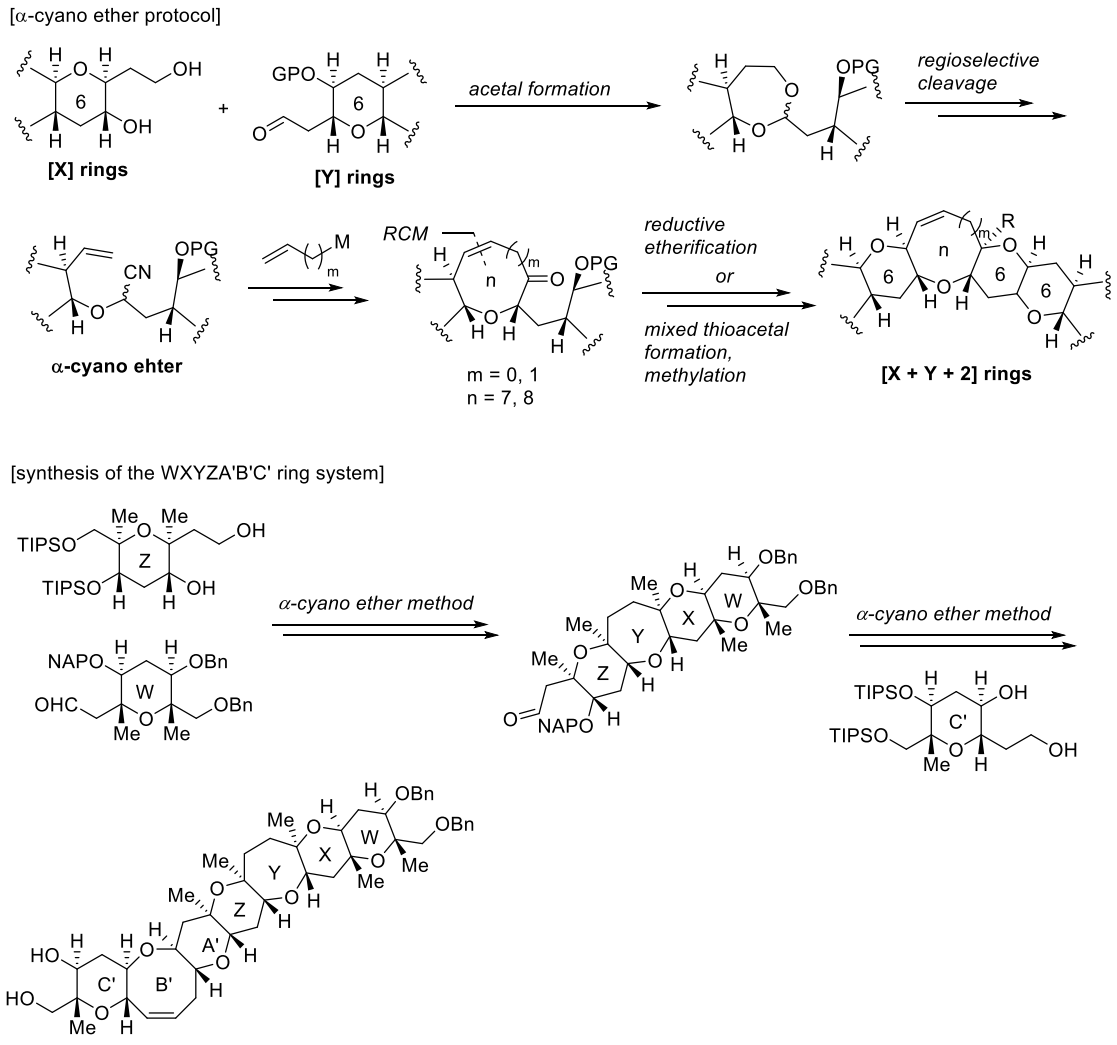
Scheme 1-3-15. Synthesis of the C'D'E'F', WXYZA' and BCDE ring systems by useful strategy for polyether-framework construction.



Scheme 1-3-16. Synthesis of the *ent*-ZA'B'C'D'E' ring system.

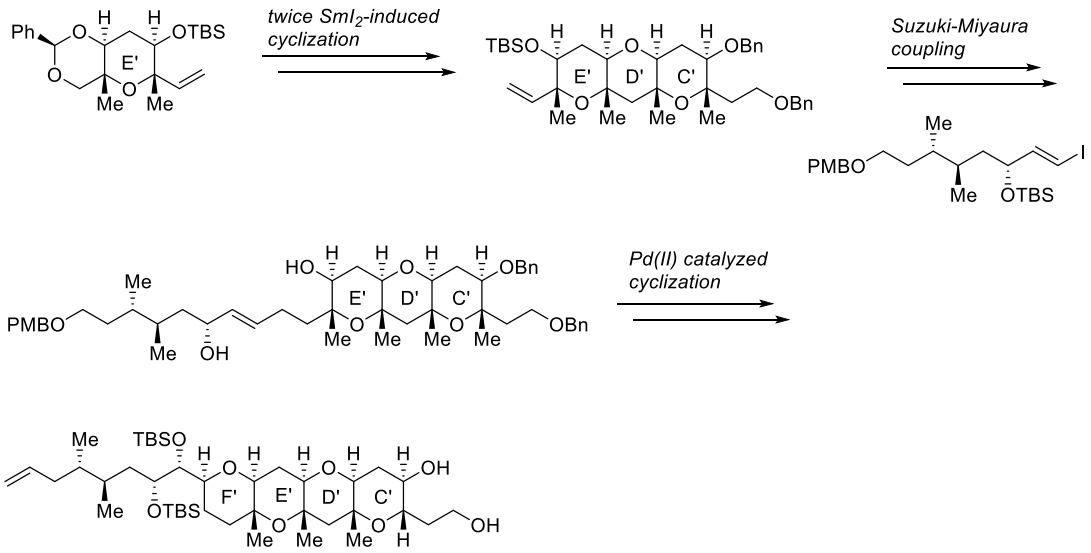
Our group

Our group has also made a great effort of synthetic studies of MTX and developed the convergent method via α-cyano ethers.[13a] Its utility was proven by the application to synthesize the WXYZA'B'C' ring system.[13b] The key intermediate, α-cyano ether, was generated through (i) connecting of two THP derivatives having diol and aldehyde, (ii) regioselective cleavage of the resulting seven-membered ring acetal, and (iii) elimination of the primary alcohol to afford a terminal olefin by Nishizawa–Grieco method. After reduction of nitrile to aldehyde, introduction of a suitable alkenyl group and ring-closing metathesis gave seven- or eight-membered ring. Finally, construction of polyether framework was completed through mixed thioacetal formation followed by oxidation/methylation or reductive etherification (Scheme 1-3-17).



Scheme 1-3-17. Synthesis of the WXYZA'B'C' ring system by α-cyano ether method.

Synthesis of the C'D'E'F' ring system via coupling of tricyclic compound and side chain was also reported (Scheme 1-3-18).[13c] The tricyclic fragment corresponding to the C'D'E'F' ring was prepared by construction of the D' and C' ring through SmI_2-induced cyclization starting from the E' ring fragment. After Suzuki–Miyaura coupling of the C'D'E' ring with the side chain, the construction of the F' ring by Pd (II)-catalyzed cyclization of an allylic alcohol furnished the C'D'E'F' ring system.



Scheme 1-3-18. Synthesis of the C'D'E'F' ring system.

1-4. Structure-activity relationship studies of maitotoxin

Tachibana and Konoki were interested in the interactions between MTX and natural- or synthetic polyether compounds with a similar structure.[14] Brevetoxins (PbTx1 and PbTx2) were hydrophobic ladder-shaped polyether, and known to interact with voltage-sensitive calcium channel (VSCC). Interestingly, this structually similar natural products blocked MTX-induced Ca^{2+} influx (IC_{50} = 13 or 16 μM, respectively, Figure 1-4-1). On the other hand, it was observed that synthetic hydrophilic partial structures of MTX, the *ent*-EFGH and *ent*-LMNO ring systems, also inhibited MTX-induced Ca^{2+} influx (IC_{50} = 200 μM, 500 μM, respectively, Figure 1-4-1). According to the results, it was hypothesized that hydrophobic tail of MTX penetrated into a plasma membrane, whereas its hydrophilic portion remained outside (Figure 1-4-2). A part of Ca^{2+}-ATPase, the most promising candidate of the target protein of MTX, located outside of membrane, supporting this proposal.

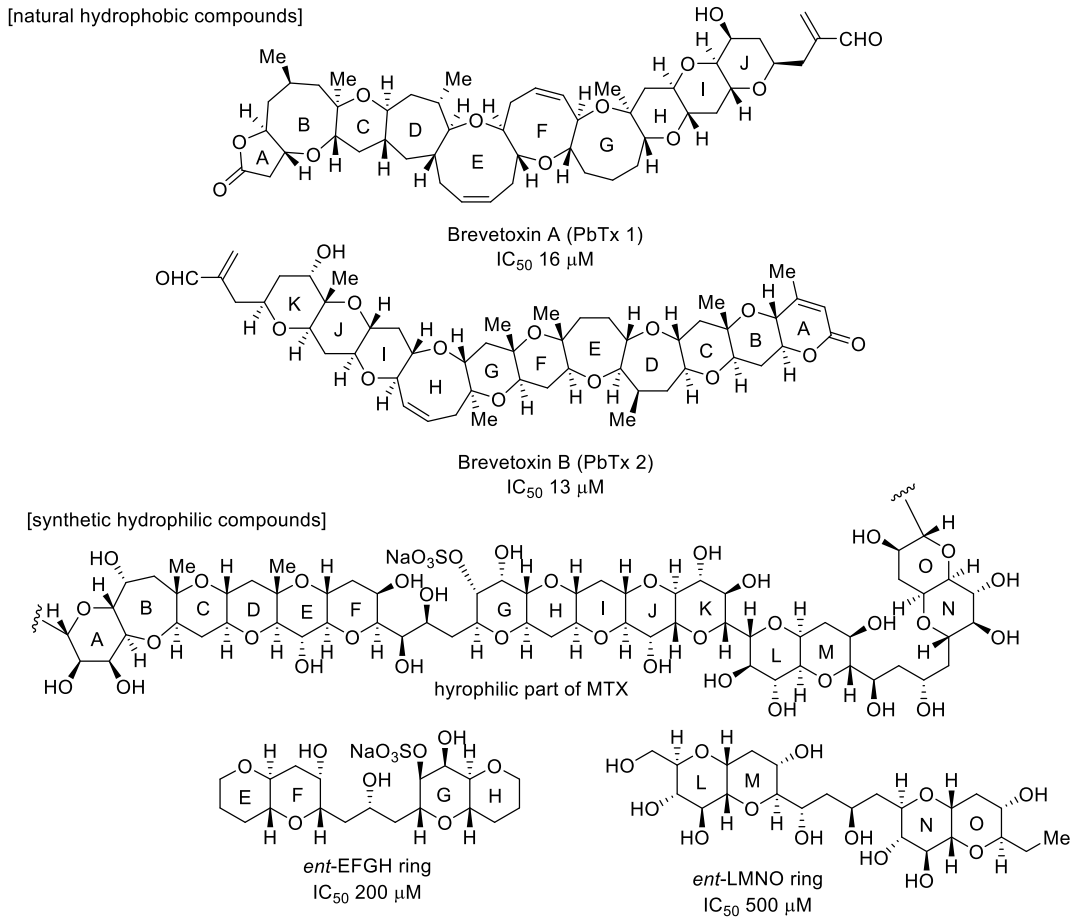


Figure 1-4-1. Bioactivity of natural- or unnatural- polyether compounds.

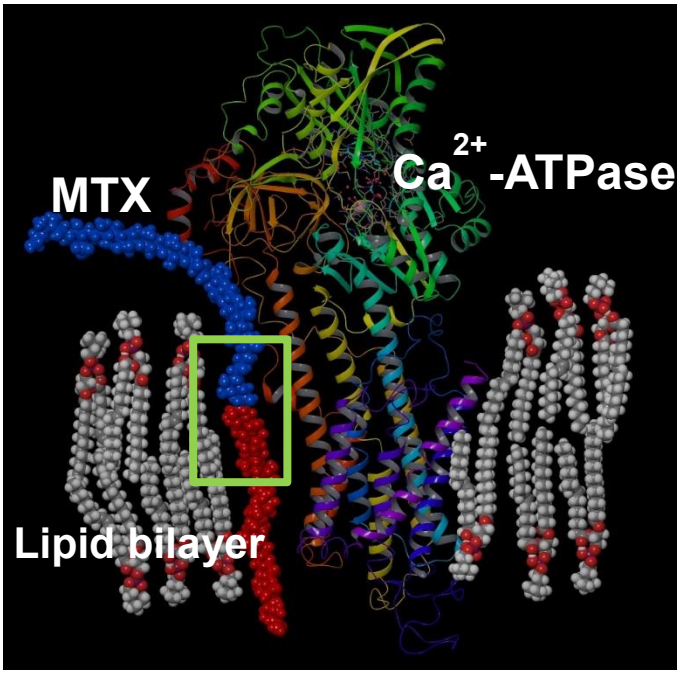


Figure 1-4-2. Hypothesis of behavior of MTX in interaction with membrane proteins.

Since brevetoxins showed more potent activity than hydrophilic parts of MTX as described above, it was considered that hydrophobic region of MTX was more important for its activity. Our group obtained interesting outcomes that the synthetic fragments corresponding to the WXYZA'B'C' and C'D'E'F' ring system corresponding to the hydrophobic region, blocked MTX-induced Ca^{2+} influx (IC_{50} = 30 μM, 59 μM, respectively, Figure 1-4-3).[13b,c] In addition, it was also found that lack of Bn groups of the WXYZA'B'C' ring caused significant reduction of this activity. On the other hand, it was reported that artificial ladder-shaped polyethers (ALPs) also showed inhibition activity and 6/7/6/7/6/6-heptacyclic compound was stronger inhibitor than tetracyclic or decacyclic compounds (Figure 1-4-4).[15] This comparison implied the importance of molecular length for insertion into transmembrane region. Interestingly, potent inhibitors, ALP7B and PbTx-2, had similar structures to the Q–X ring and the W–E' ring part of MTX, respectively. Therefore, suitable size of partial structures of MTX is expected to become more potent inhibitor.

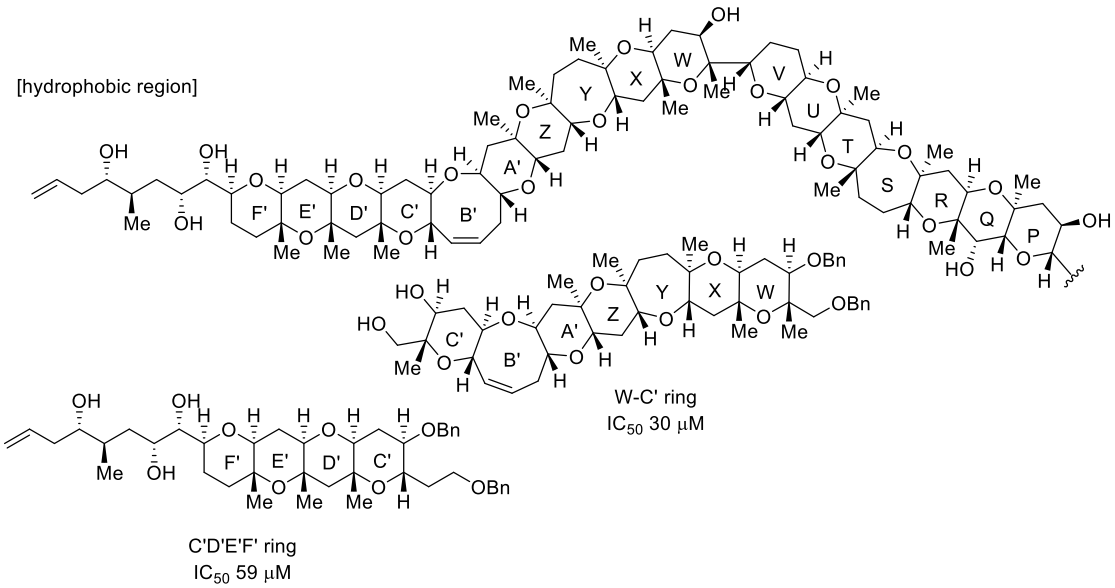


Figure 1-4-3. Bioactivity of the WXYZA'B'C' and C'D'E'F' ring system.

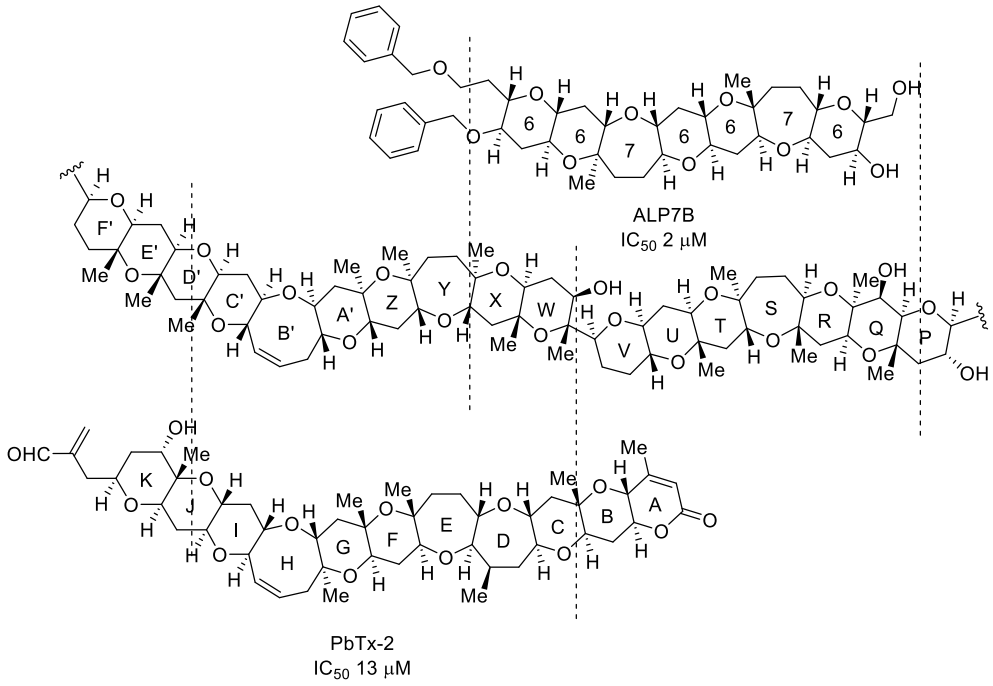


Figure 1-4-4. Comparison of the structures with MTX and bioactivity of ALP and PbTx.

Recently, Nicolaou et al. investigated the bioactivity of synthetic compounds (Figure 1-4-5). The QRSTUVWXYZA' ring system, which was largest partial structure, elicited the most potent inhibitory activity against MTX-induced Ca^{2+} influx (IC_{50} = 3.2 μM).[11h] In addition, they also examined growth inhibition (GI_{50}) and cytotoxicity against the NCI-60 DTP Human Tumor Cell Line. As a result, the Q–A' ring system showed significant growth inhibition against various cancer cells (e.g. leukemia, renal cancer, breast cancer and melanoma, GI_{50} = 1.26 ~ 4.50 μM).

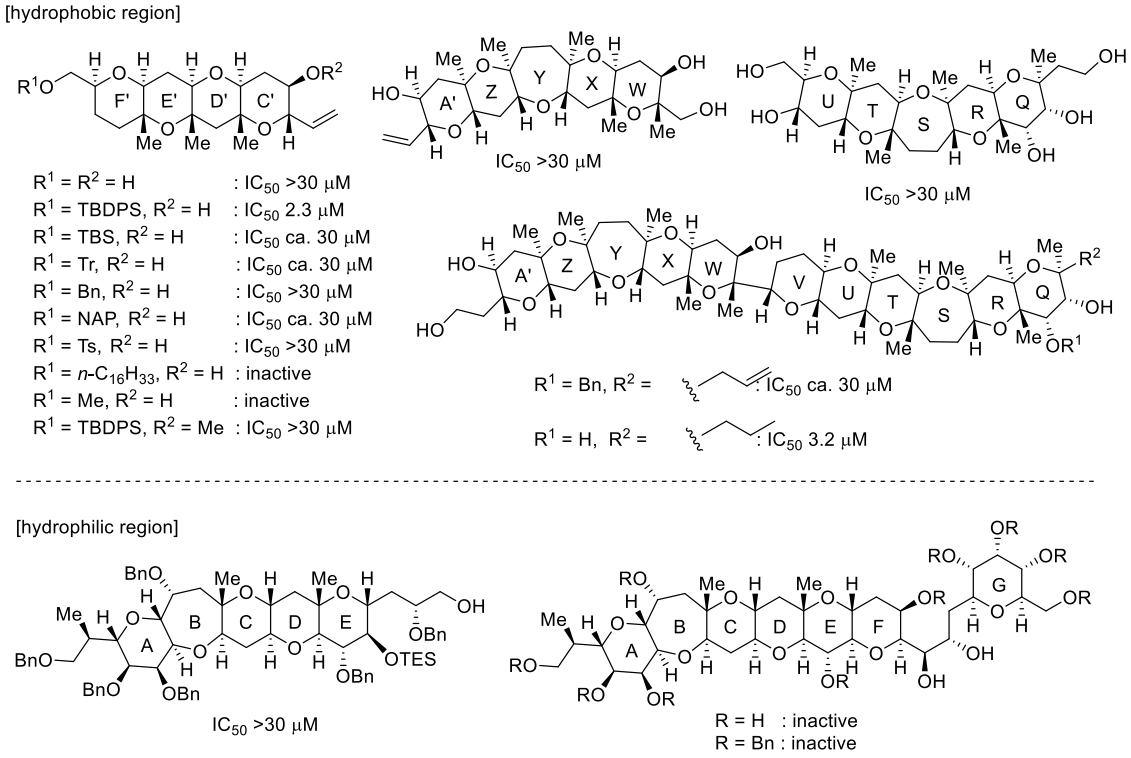


Figure 1-4-5. Structure-activity relationship studies of MTX by Nicolaou group.

MTX had special bioactivity to induce intracellular Ca^{2+} influx, and so it was expected as a potent biological tool and a candidate of innovative drug. As described above, it was indicated that MTX contributed for development of novel antitumor agents. Recently, Martínez et al. found the new possibility of MTX.[16] It was supposed that MTX activated non-selective cation channels (NSCC) in *Xenopus laecis* oocytes at pM concentrations and had potential to be a selective activator of the endogenous transient receptor potential canonical type 1 (TRPC1), suggesting that MTX could become a useful pharmacological tool for investigation of TRPC.

1-5. Objective

In an effort to develop inhibitors against MTX-induced Ca^{2+} ion influx, we hypothesized that the partial structures corresponding to the hydrophobic parts of MTX might competitively bind to the target proteins to inhibit the Ca^{2+} ion influx induced by MTX (Figure 1-5-1). It was supported by various reports by our group and others that hydrophobic polyether compounds including PbTx and ALPs blocked its activity.[13b,c,14,15]

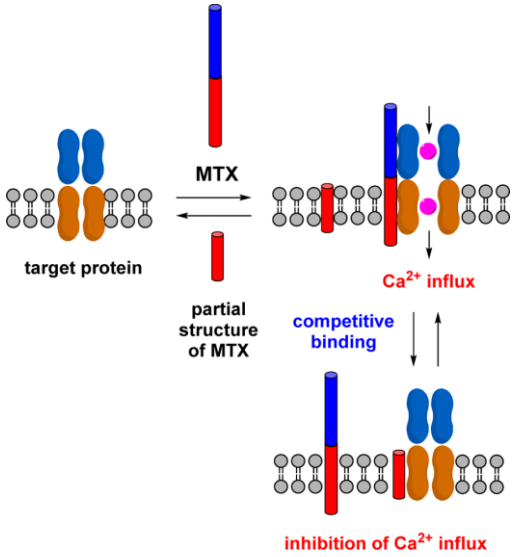


Figure 1-5-1. Hypothetical scheme for the inhibition of MTX-induced Ca^{2+} influx activity by partial structures corresponding to the hydrophobic part of MTX.

In fact, the W–C' ring and the C' –F' ring of MTX corresponding to hydrophobic partial structures showed inhibition activity. On the other hand, the LMNO ring and EFGH ring of MTX corresponding to hydrophilic partial structures also elicited weak inhibition, while they were antipodal natural enantiomer.[14] Thus, synthetic compounds having correct stereochemistry with MTX should be evaluated.

Although the amphiphilicity is the most characteristic feature of MTX among the ladder-shaped polyethers, there is no precedent to evaluate partial structures possessing both hydrophobic and hydrophilic regions. It is interesting to elucidate the combination of both the hydrophobic and hydrophilic regions could elicit biological activity in a synergistic or counteracting manner.

The objective in this study is as follows.[17]

1. Synthesis of the QRS ring and the WXYZA’B’C’D’E’F’ ring of MTX corresponding to the hydrophobic region in order to develop more potent inhibitors (Section 2-1 and 3-3).
2. Synthesis and evaluation of inhibitory activity of the LMNO ring of MTX corresponding to hydrophilic part possessing correct (natural) stereochemistry (Section 2-2).
3. Synthesis and evaluation of inhibitory activity of the NOPQR(S) ring of MTX possessing border region of the hydrophobic and hydrophilic region (Section 2-3).

This study has carried out in part in collaboration with Tomomi Baba (Section 2-1), Erina Ishikawa (Section 2-2), Yoshiki Toma and Naoya Osato (Section 2-3), and Prof. Keiichi Konoki (evaluation of biological activity).

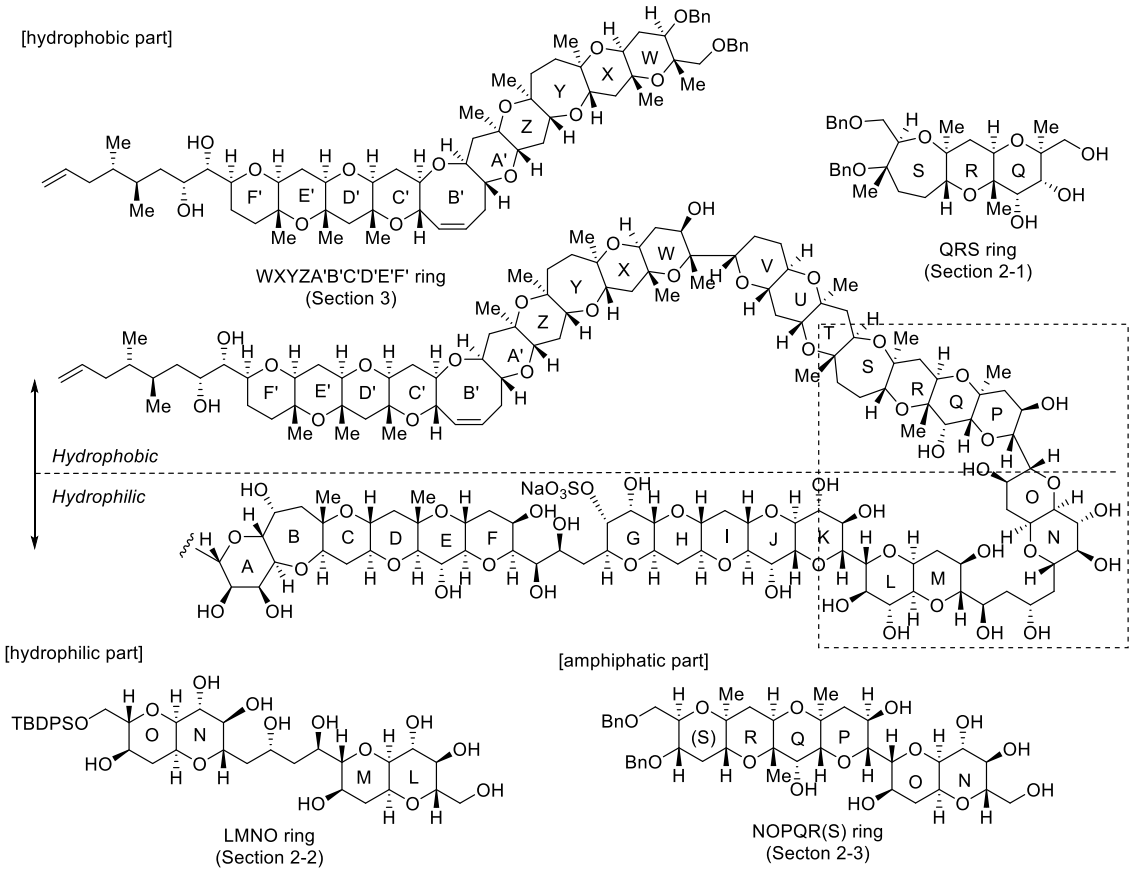


Figure 1-5-2. Designed compounds for evaluation of biological activity.

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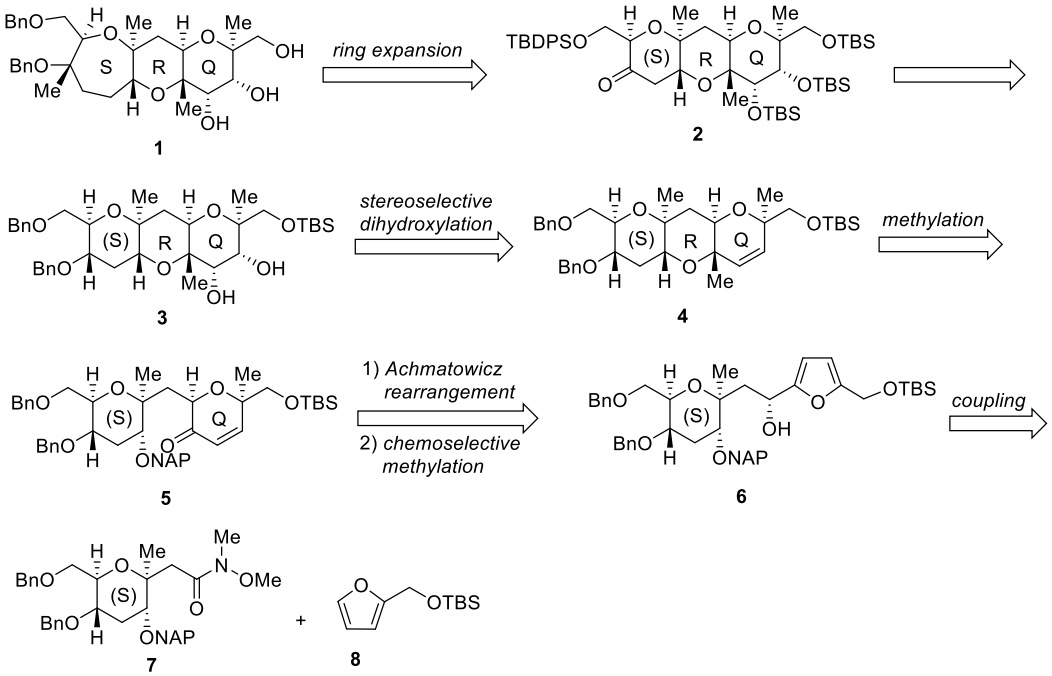
Chapter 2. Synthesis of the QRS, LMNO and NOPQR(S) ring system of maitotoxin

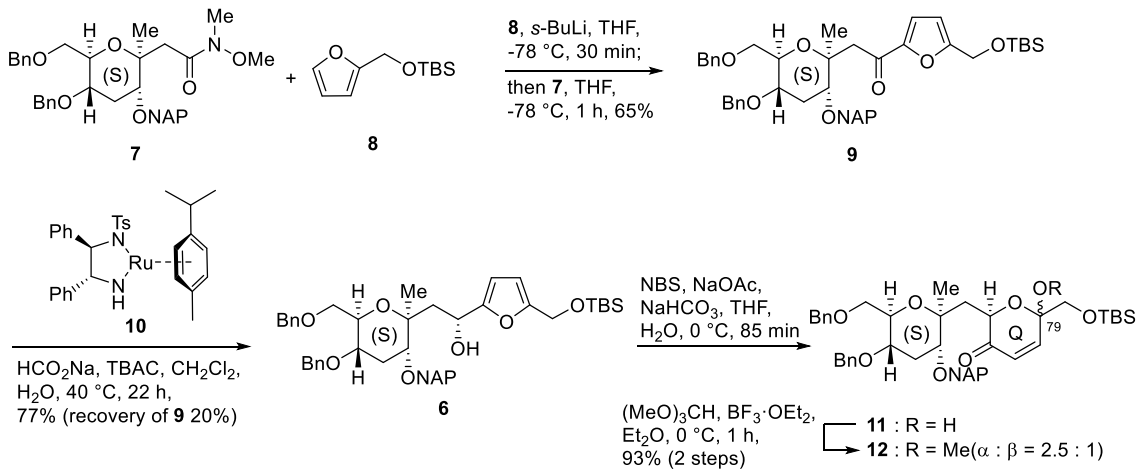
2-1. Synthesis of the QRS ring system

Synthesis plan of the QRS ring system (**1**) of MTX is shown in Scheme 2-1-1. The target molecule **1** would be obtained via the ring expansion of six-membered ring ketone **2**, which is to be derived from tricyclic compound **3**. α-Diol moiety on the Q ring of **3** is to be introduced through diastereoselective dihydroxylation of olefin **4**. The R ring of **4** would be constructed via methylacetal formation, followed by methylation of the resulting methyl acetal derived from pyranone **5**. For the synthesis of **5**, Achmatowicz rearrangement and chemoselective methylation was envisaged from furfurylalchol **6**, which could trace back to Weinreb amide **7** and furan derivative **8**. In this strategy, it remained uncertain whether the ring expansion of six-membered ring ketone **2** would proceed successfully, and the introduction of angular methyl groups and dihydroxylation of sterically hindered olefin of **4** would proceed stereoselectively to afford desired isomer.



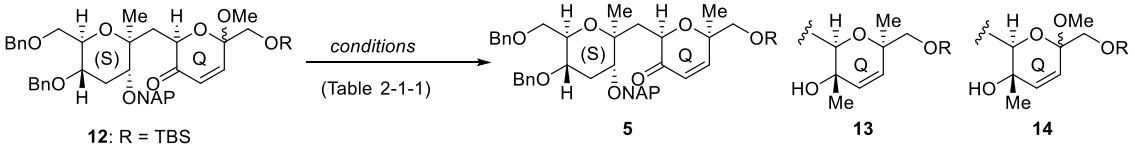
Scheme 2-1-1. Synthesis plan of the QRS ring fragment of MTX.

Synthesis of the QRS ring (**1**) commenced with coupling of the known Weinreb amide **7**[1] and lithiofurane derivative prepared from **8** by treatment with *s*-BuLi to afford ketone **9** in 65% yield (Scheme 2-1-2). Stereoselective reduction of ketone **9** was achieved by asymmetric transfer hydrogenation with Noyori catalyst **10**[2] to produce furfuryl alchol **6** in 77% yield as a single diastereomer with recovery of the starting material in 20% yield. Achmatowicz reaction[3] of **6** with NBS furnished dihydropyranone **11**, and the resulting hemiacetal was treated with methyl orthoformate and $BF_3 \cdot OEt_2$ in Et_2O at 0 °C[4] to give methylacetal **12** as an inseparable mixture of C79-diastereomers (α : β = 2.5 : 1) in 93 % yield for two steps.



Scheme 2-1-2. Synthesis of pyranone **12**.

Chemoselective methylation of the pyranone **12** was examined as shown in Table 2-1-1. When Me_3Al was used as a reagent (entry 1), methylation occurred selectively at the carbonyl group to give tertiary alcohol **14** with an inseparable mixture of C79-diastereomers in 81% yield. In contrast, when Me_3Al was used in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid (entry 2), both the carbonyl and methoxy groups were methylated to furnish **13** as a single isomer (96%). Interestingly, when Me_2Zn was used instead of Me_3Al in the presence of $BF_3 \cdot OEt_2$ (entry 3), chemoselective methylation of the methoxy group was achieved in a stereoselective manner to afford desired enone **5** as a single isomer (81%). Thus, chemoselective and stereoselective methylation was successfully achieved by choosing appropriate reagents.



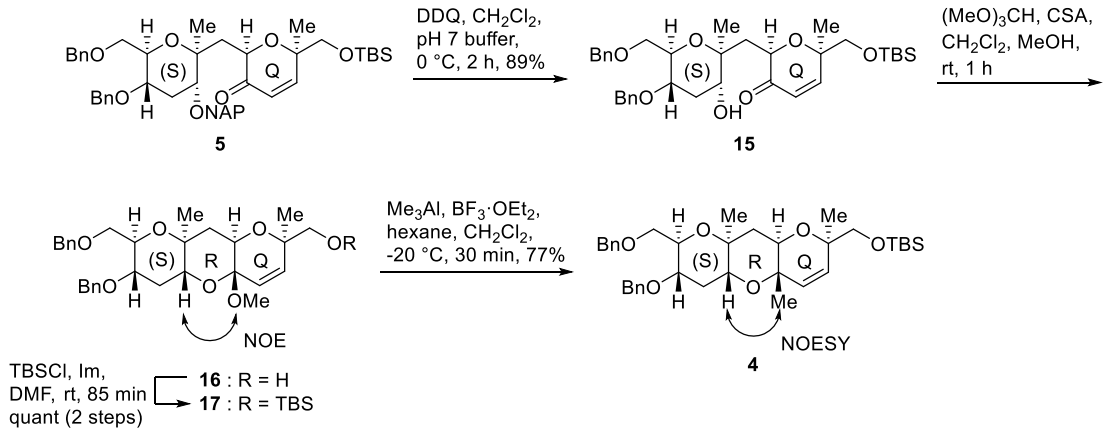
12: R = TBS　　**5**　　**13**　　**14**

Table 2-1-1. Chemoselective methylation of **12**. [a]

Entry	Reagent	Lewis acid	Temp. / °C	Time / min	Products / %		
					5	**13**	**14**
1	Me_3Al	none	-20	50	-	-	81
2	Me_3Al	$BF_3{\cdot}OEt_2$	-20	35	-	96	-
3	Me_2Zn	$BF_3{\cdot}OEt_2$	rt	240	81	-	-

[a] These reactions were carried out in CH_2Cl_2.

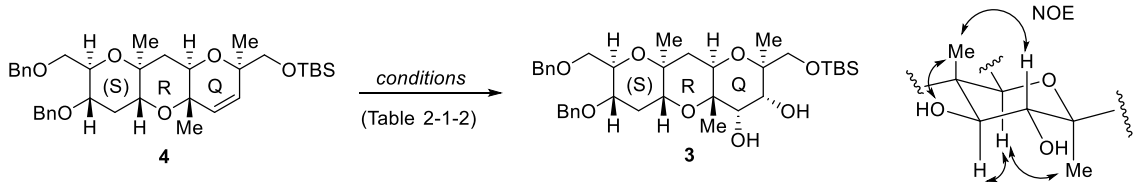
Next, conversion of ketone **5** to tricyclic compound **4** was carried out (Scheme 2-1-3). Removal of the NAP group with DDQ (89%), followed by treatment of the resulting hydroxyl ketone **15** with methyl orthoformate in the presence of CSA gave methyl acetal **16**. Under the acidic conditions, the TBS group was removed, but the resulting primary alcohol **16** was reprotected as TBS ether by treating with TBSCl and imidazole to afford **17** quantitatively for two steps. Methylation of methyl acetal **17** with Me_3Al and $BF_3{\cdot}OEt_2$ at –20 °C proceeded successfully to furnish **4** as a single isomer in 77% yield. Stereochemistries of the methoxy group of **17** and the methyl group of **4** were determined by NOE and NOESY experiments, respectively.



5　　**15**　　**4**

Scheme 2-1-3. Synthesis of tricyclic compound **4**.

Dihydroxylation of the sterically hindered olefin **4**, which was one of the key steps, was examined as shown in Table 2-1-2. Although dihydroxylation of **4** by using OsO_4 in the presence of TMEDA[6] afforded desired diol **3** in 91% yield as a single isomer (entry 1). However, more than stoichiometric amount of OsO_4 (4.8 eq) was needed. Therefore, dihydroxylation under the standard catalytic conditions using OsO_4 and NMO,[7] called "Upjohn process", was examined. Although diol **3** was obtained as a single isomer in 72% yield, the starting material was recovered in 21% yield (entry 2). Fortunately, the reaction was accelerated in the presence of citric acid[8] to furnish diol **3** in 91% yield as a single isomer (entry 3). Stereochemistry of **3** was confirmed by NOE experiments.

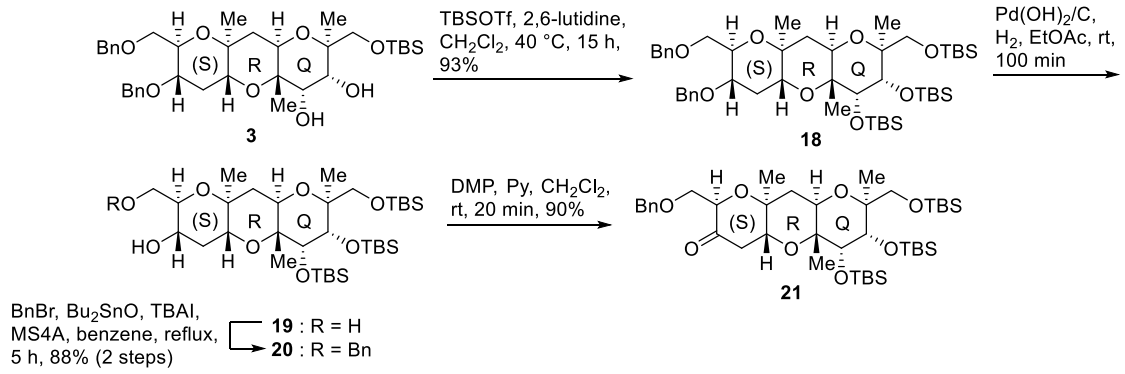


4 **3**

Table 2-1-2. Dihydroxylation of **4**.

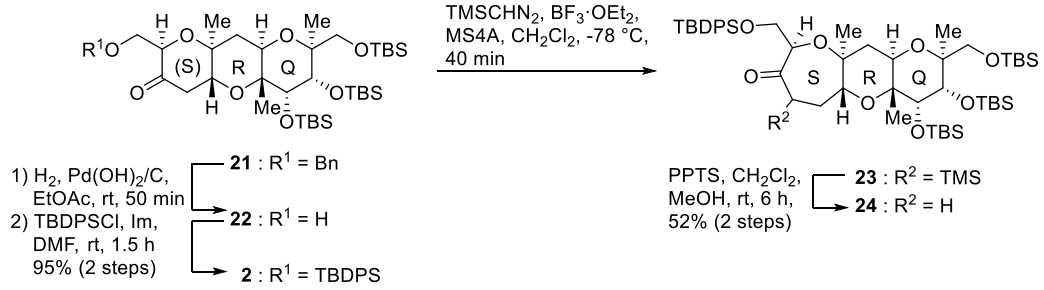
Entry	OsO_4 / eq	Conditions	Product / %	
			4	**3**
1	4.8	TMEDA (4.8 eq), CH_2Cl_2, 0 to 30 °C, 5.5 h; then $Na_2S_2O_5$ aq, THF, reflux, 3 h	–	91
2	0.41	NMO (20 eq), *t*-BuOH / acetone / H_2O, rt, 24 h	21	72
3	0.19	NMO (10 eq), citric acid (10 eq), *t*-BuOH / acetone / H_2O, rt, 22h	–	91

Synthesis of ketone **21** is described in Scheme 2-1-4. Protection of diol **3** as TBS ethers by treatment with TBSOTf and 2,6-lutidine gave **18** in 93% yield, which was followed by hydrogenolysis of benzyl ethers of **18** to afford diol **19**. Then, selective protection of the primary alcohol as benzyl ether was achieved by treating with BnBr in the presence of *n*-Bu_2SnO via stannylidene acetal to give **20** in 89% yield for two steps.[9] Six-membered ring ketone **21** was obtained via oxidation of the remaining secondary alcohol by using Dess–Martin periodinane in 91% yield.



Scheme 2-1-4. Synthesis of ketone **21**.

The protecting group of neighboring primary alcohol was important for ring expansion of the six-membered ring ketone, and it is reported that Bn group was not suitable for this reaction.[10] On the other hand, it was reported that the yield was improved using TBDPS ether as protecting group.[11] Therefore, the benzyl ether **21** was replaced with TBDPS ether **2** in quantitative yield via hydrogenolysis, followed by treatment of the resulting primary alcohol with TBDPSCl in the presence of imidazole in quantitatively for two steps (Scheme 2-1-5). Then, the ring expansion reaction of **2** was carried out under the same reaction conditions to give desired seven-membered ring ketone **23**. After the removal of the TMS group with PPTS, seven-membered ring ketone **24** was obtained in 56% yield for two steps.



Scheme 2-1-5. Synthesis of seven-membered ketone **24**.

Stereoselective introduction of the angular methyl group to the carbonyl group on the S ring was examined as shown in Table 2-1-3. Murai et al. reported that methylation of seven-membered ring ketone by treatment with methylmagnesium bromide in toluene

proceeded stereoselectively to afford desired *trans*-isomer in a 15 : 1 ratio in 97% yield.[12] Therefore, the ketone **24** was subjected to the same reaction conditions. However, desired compound **25** was obtained as a separable mixture of its diastereomer **26** in a 1 : 1.3 ratio in 87% yield (entry 1). Although MeLi and Me_3Al were also used, the selectivity was not improved (entries 2 and 3). On the other hand, Yamamoto et al. reported diastereoselective methylation giving equatorial alcohol (Figure 2-1-1).[13] Treatment of 4-*tert*-butylcyclohexanone **27** with the bulky aluminum reagent (MAD, **28**) prepared in situ from Me_3Al and BHT in toluene, followed by addition of MeLi gave equatorial alcohol **30** in high selectivity and yield. It is considered that axial attack of MeLi to ketone precedes predominantly because the bulky Lewis acid coordinated to the carbonyl group to take equatorial position. Accordingly, methylation of ketone **24** was carried out in the same reaction conditions, and the selectivity was improved to furnish **25** as a separable mixture of its diastereomer **26** in 93% yield in a 2.1 : 1 ratio (entry 3).

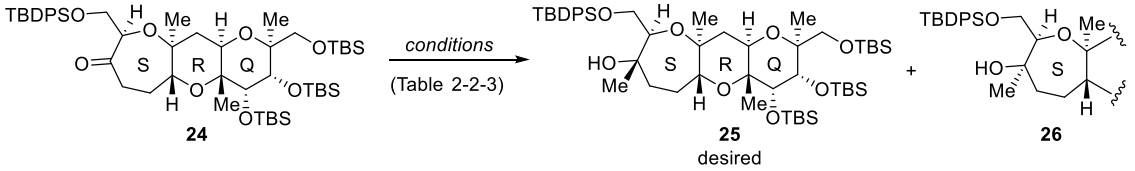


Table 2-1-3. Methylation of seven-membered ketone **24**.

Entry	Reagent / eq	Solvent	Temp. / °C	Yield / %	Ratio (**25** : **26**)
1	MeMgBr / 10	toluene	-78 to 0	87	1.0 : 1.3
2	MeLi / 2.9	THF	-78	82	1.0 : 1.3
3	Me_3Al / 20	CH_2Cl_2	-78 to rt	8[a)]	1.0 : 1.0
4	MAD[b)] / 15, MeLi / 15	toluene	-78	93	2.1 : 1.0

[a] TBS group was removed and starting material was recovered (40%).
[b] Prepared in situ from Me_3Al (15 eq) and BHT (30 eq) in toluene at room temperature for 1 h.

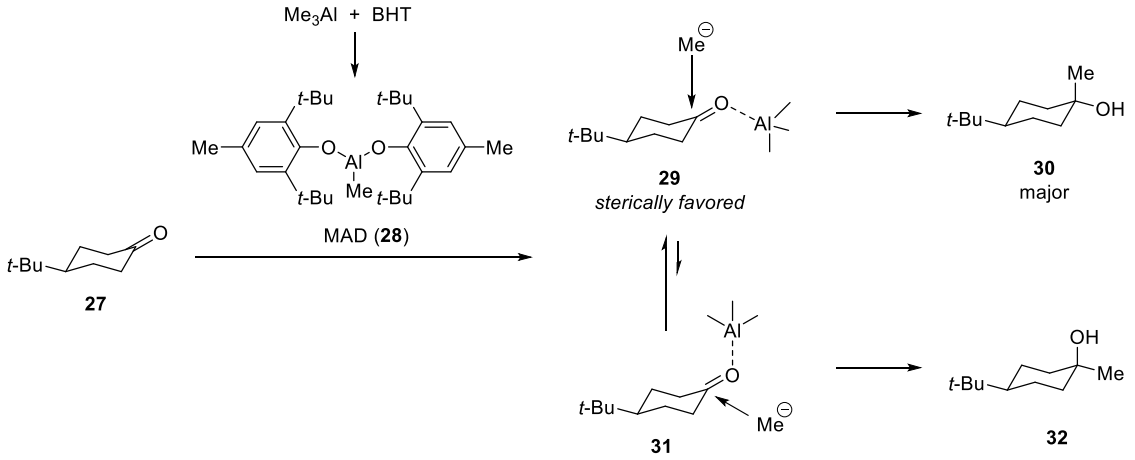
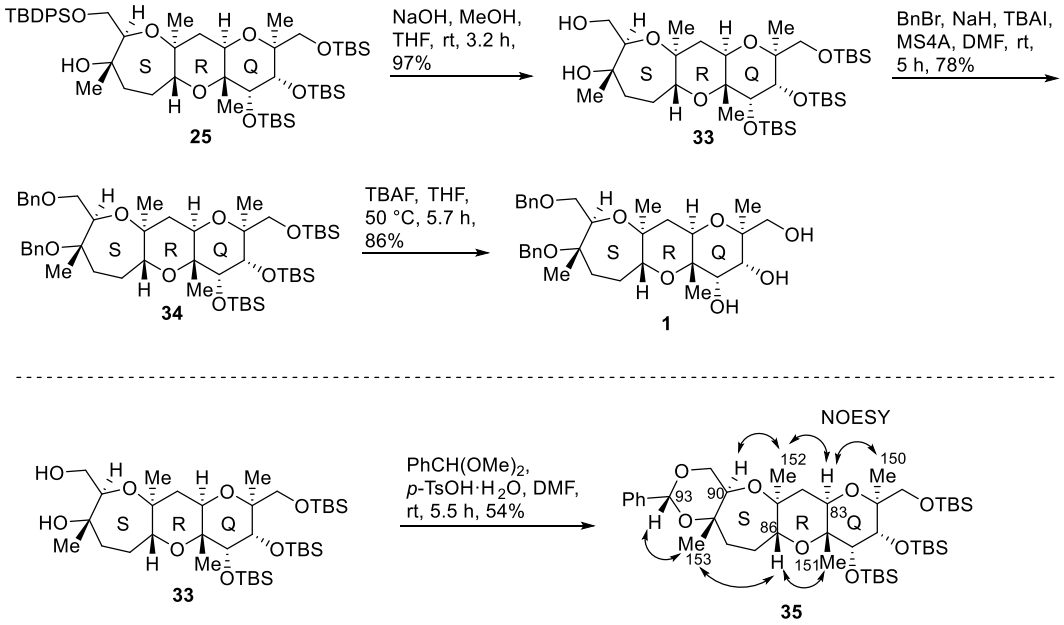


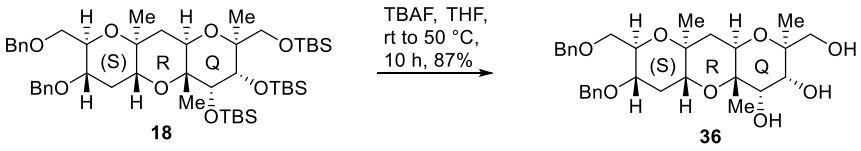
Figure 2-1-1. Selective methylation by using MAD developed by Yamamoto et al.

Synthesis of the QRS ring system of MTX (**1**) is shown in Scheme 2-1-6. Selective removal of the TBDPS group of **25** under the basic conditions using sodium hydroxide furnished **33** in 97% yield, and protection of the resulting diol as benzyl ethers gave **34** in 78% yield. Finally, removal of the TBS groups with TBAF afforded the QRS ring system **1** in 86% yield.[14] The structure of **1** was unambiguously determined by NOESY experiments on benzylidene acetal **35**, which was derived from diol **33** by treatment with $PhCH(OMe)_2$ in the presence of *p*-$TsOH \cdot H_2O$ in 54% yield.



Scheme 2-1-6. Synthesis of the QRS ring system **1**.

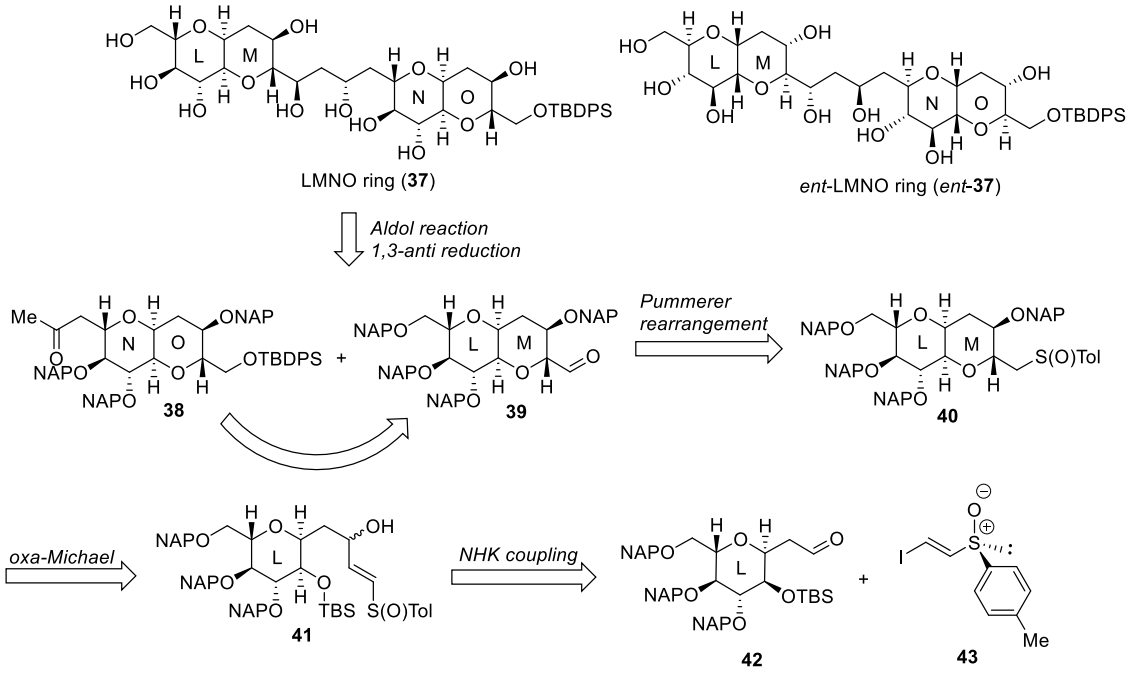
To examine the effect on the biological activity of their ring size of the S ring, the QR(S) ring system (**36**) having six-membered S ring was designed and prepared (Scheme 2-1-7). Removal of TBS groups with TBAF proceeded smoothly to afford the QR(S) ring system (**36**) in 87% yield.



Scheme 2-1-7. Synthesis of the QR(S) ring system **36**.

2-2. Synthesis of the LMNO ring system

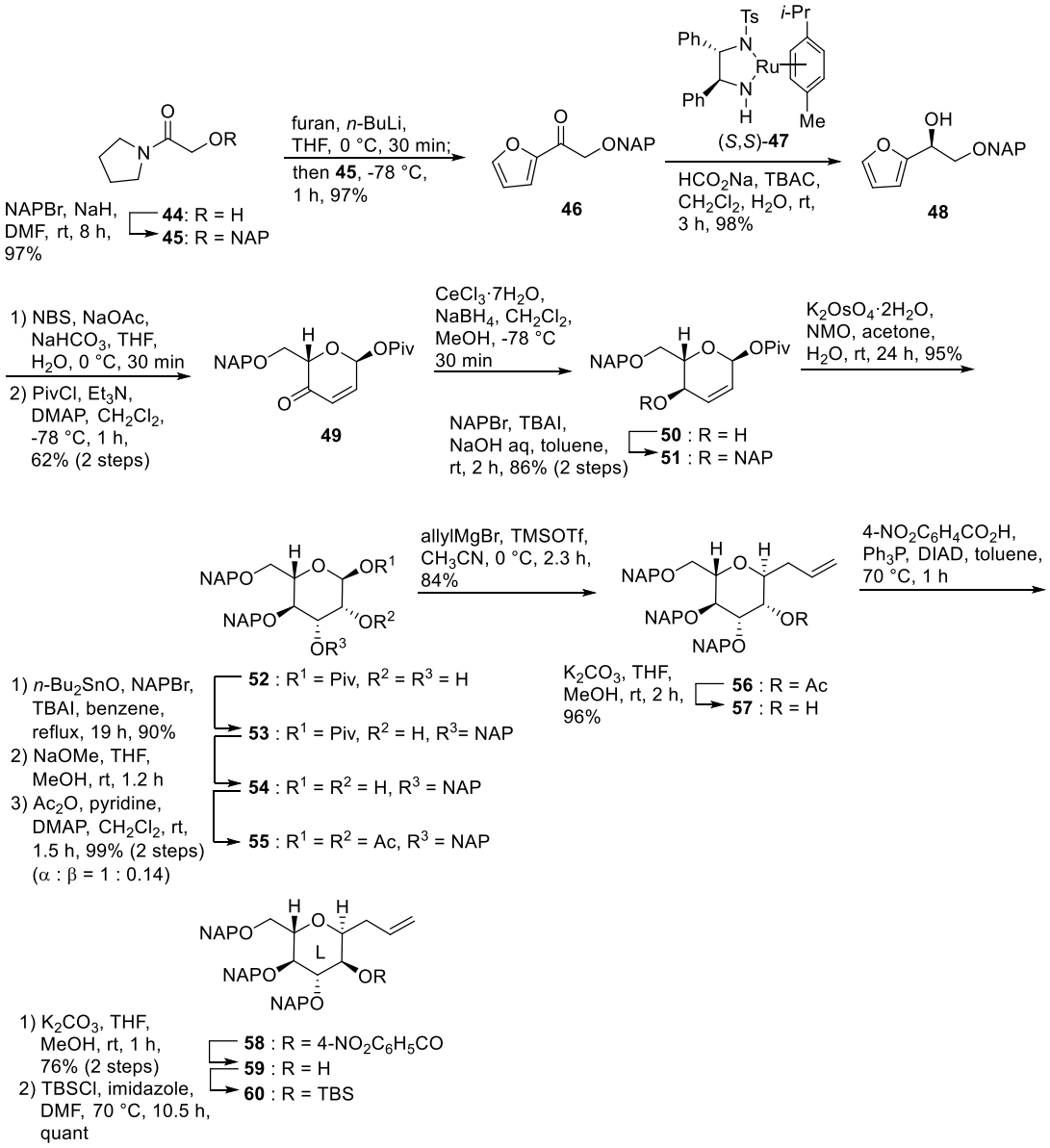
Synthesis plan of the LMNO ring system (**37**) of MTX is shown in Scheme 2-2-1. The target compound **37** would be derived from the LM ring aldehyde **39** and the NO ring methyl ketone **38** via an aldol reaction, followed by the 1,3-*anti* selective reduction[15] of a β-hydroxy ketone, as reported by Tachibana et al.[16] The LM ring **39**, which was envisaged to be a precursor of the NO ring **38**, could be derived from the L ring aldehyde **42** and the known sulfoxide **43**[17] through successive Nozaki–Hiyama–Kishi (NHK) reaction[18] to give the α,β-unsaturated sulfoxide **41** followed by an intramolecular oxa-Michael addition[19] and Pummerer rearrangement.[20,21] Although similar approach was reported by Kishi et al.,[22] advantage of this strategy is to use the sulfoxide, which is expected to work as both an electron-withdrawing group for the oxa-Michael addition as well as a precursor to the Pummerer rearrangement. This approach could reduce the number of steps needed to construct the M ring, while there are no precedent studies describing the use of sulfoxide **43** for the NHK reaction to our knowledge.



Scheme 2-2-1. Synthesis plan of the LMNO ring fragment of MTX.

The L-ring **60**, a precursor to the aldehyde **42**, was synthesized according to the procedure reported by Nicolaou et al.,[23] with the exception that the secondary hydroxy

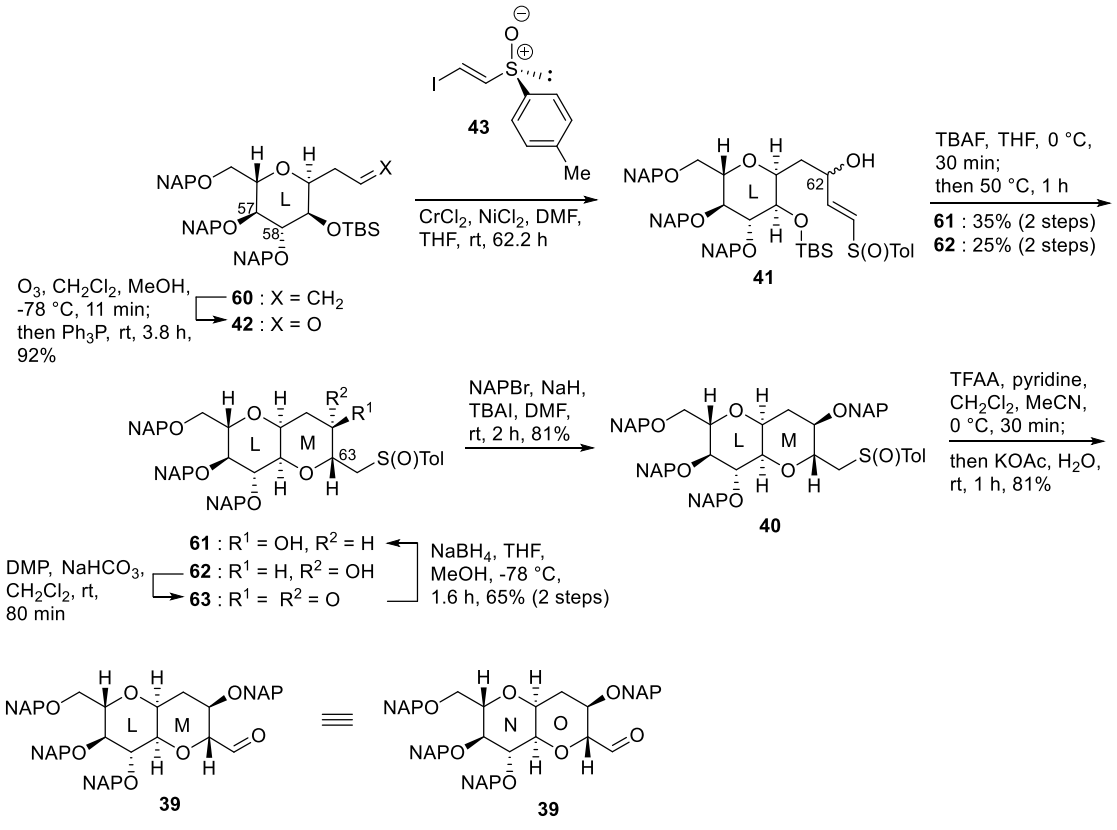
groups at C57 and C58 were protected with NAP rather than Bn (Scheme 2-2-2). The hydroxy group of the amide **44**[24] was protected as a NAP ether by treatment with NaH and NAPBr in DMF to afford **45** in 97% yield. The amide **45** was then treated with 2-lithiofuran generated from furan and *n*-BuLi at –78°C to furnish the furylketone **46** in 97% yield. The ketone was converted to a chiral secondary alcohol **48** in 98% yield by a Noyori asymmetric hydrogen transfer reaction using the ruthenium catalyst (*S*,*S*)-**47** and HCO_2Na as a reductant.[25] An Achmatowicz rearrangement[3,26] of the furfuryl alcohol **48** with NBS, followed by acylation of the resulting hemiacetal with PivCl, afforded pivaloate **49** in 62% yield for two steps, with the concomitant formation of its β-anomer in 28% yield. Luche reduction[27] of the enone **49** resulted in the formation of the alcohol **50** as a single isomer, which was protected as the NAP ether **51** in 86% yield for two steps. Dihydroxylation of the olefin **51** furnished the α-diol **52** as a single isomer in 95% yield, and the equatorial hydoxy group was selectively protected as a NAP ether via stannylidene to afford **53** in 90% yield.[28] After removing the Piv group, the resulting diol **54** was protected as an acetate by treatment with Ac_2O in pyridine to furnish **55** as a diastereomixture (α : β = 1 : 0.14) in 99% yield for two steps. *C*-glycosylation of the acetate **55** using allylsilane in the presence of TMSOTf proceeded stereoselectively to afford **56** in 84% yield.[29] In this reaction, conversion of the Piv group to an Ac group was necessary because *C*-glycosylation of the corresponding pivaloate resulted in low yields. Removal of the acetyl group of **56** using K_2CO_3 as a base in methanol afforded **57** in 96% yield. Inversion of the secondary alcohol **57** via a Mitsunobu reaction,[30] followed by methanolysis of the resulting 4-nitrobenzoate **58**, gave the alcohol **59** in 76% yield for two steps. Protection of the secondary alcohol **59** as a TBS ether furnished the key intermediate **60** in quantitative yield.



Scheme 2-2-2. Synthesis of the L-ring **60**.

The synthesis of the LM ring **39** is illustrated in Scheme 2-2-3. Ozonolysis of the terminal alkene **60** gave the aldehyde **42**, which was subjected to unprecedented Nozaki–Hiyama–Kishi (NHK) reaction[18] with the iodoolefin **43**[17] possessing *p*-toluenesulfoxide moiety. Fortunately, the coupling product **41** was obtained yield as a mixture of the diastereomers at C62, whereas preliminary attempts to achieve the asymmetric version of the NHK reaction[31] were unsuccessful. Treatment of **41** with TBAF at 0 °C removed the TBS group and raising the reaction temperature to 50 °C

concomitantly promoted the intramolecular oxa-Michael addition of the resulting alkoxide to give the desired isomer **61** in 35% yield and its C63-epimer **62** in 25% yield for two steps, respectively. The structures of these compounds were determined by NOE experiments (Figure 2-2-1). The stereochemistry at C63 was presumably controlled by the favored transition state A compared over B, as shown in Figure 2-2-2. The epimer **62** was converted to **61** through a Dess–Martin oxidation of the alcohol, followed by reduction of the resulting ketone **63** with $NaBH_4$ at –78 °C in 65% yield for two steps. Thus, the M ring was constructed from the L ring **42** in only two steps (four steps, including the conversion of the C63-epimer), and the resulting sulfoxide is directly used as a precursor for the subsequent Pummerer rearrangement.[20,21] After protecting the secondary alcohol **61** with NAP group in 81% yield, treatment of the resulting **40** with trifluoroacetic anhydride in the presence of pyridine,[23] followed by hydrolytic workup, afforded the aldehyde **39** in 81% yield, which corresponded to not only the LM ring but also the NO ring system.



Scheme 2-2-3. Synthesis of the LM ring system **39**.

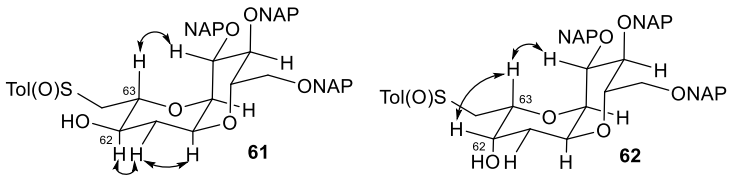


Figure 2-2-1. NOE experiments of compound **61** and **62**.

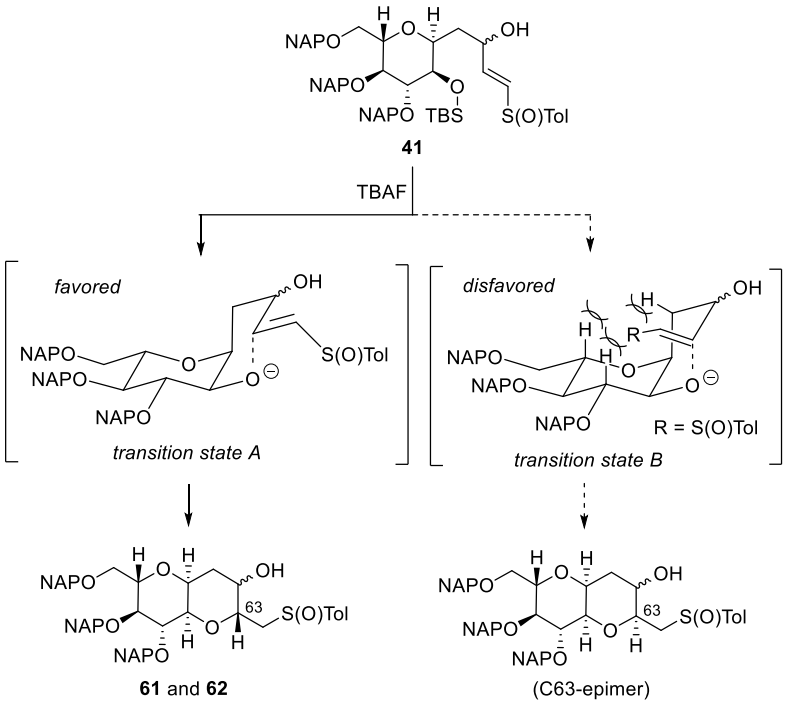
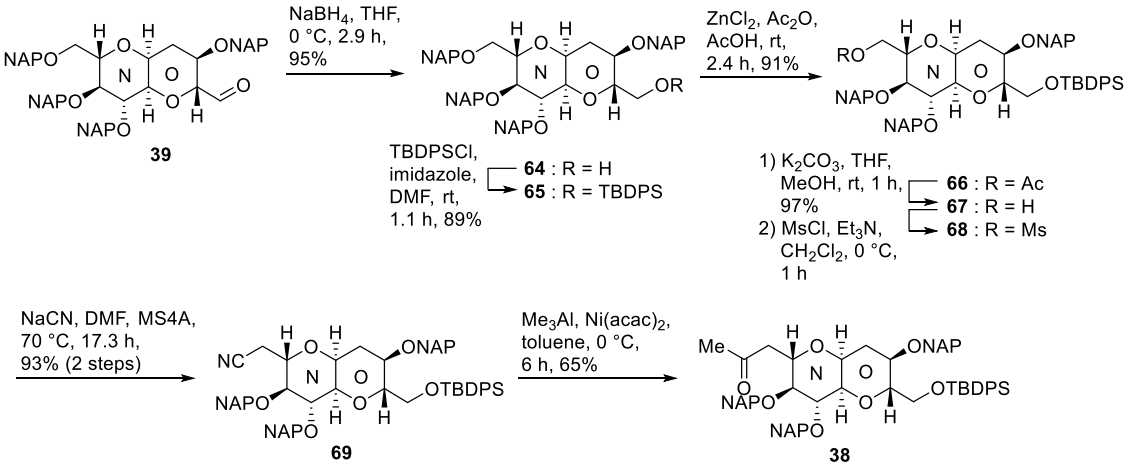


Figure 2-2-2. Stereochemical outcome of intramolecular oxa-Michael reaction of **41**.

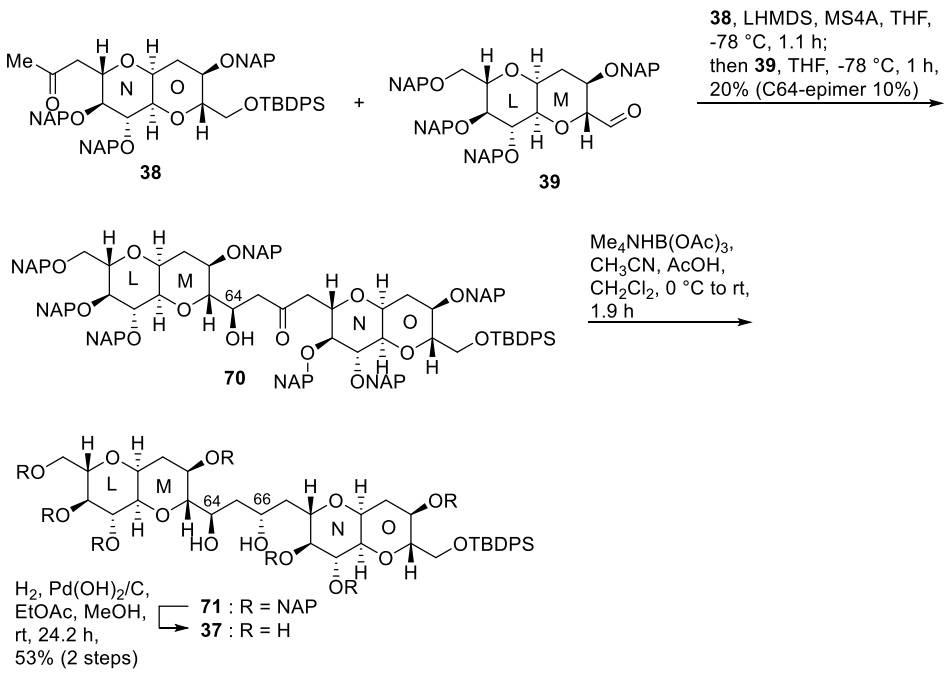
Synthesis of the methyl ketone **38** is shown in Scheme 2-2-4. Reduction of the aldehyde **39** with $NaBH_4$ furnished the alcohol **64** in 95% yield, and the resulting primary hydroxy group was protected as a TBDPS ether **65** in 89% yield. Treatment of **65** with $ZnCl_2$ in Ac_2O/AcOH[32] resulted in the selective removal of the primary NAP group with concomitant acetylation to form the acetate **66** in 91% yield. Removal of the acetyl group of **66** by methanolysis with K_2CO_3 furnished the primary alcohol **67** in 97% yield, which was transformed to the nitrile **69** via the mesylate **68** in 93% yield for two steps. Attempts to convert the nitrile **69** into the methyl ketone **38** by treatment with MeMgBr or MeLi, followed by hydrolytic workup, were unsuccessful. The yields were low, with significant

decomposition and recovery of the starting material. On the other hand, treatment of **69** with Me_3Al in the presence of $Ni(acac)_2$ as a catalyst provided **38** in 65% yield.[33]



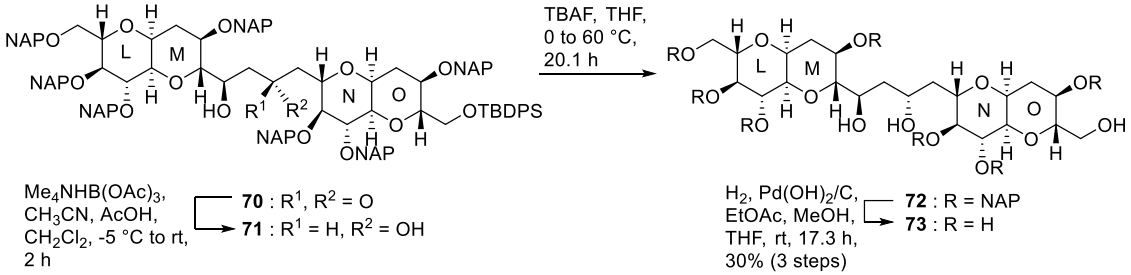
Scheme 2-2-4. Synthesis of the NO ring fragment **38**.

The next transformation was a crucial step in the synthesis: coupling of the LM ring (**39**) and the NO ring (**38**) by using aldol reaction (Scheme 2-2-5). The yield of a similar transformation was reported to be 37% by Tachibana et al.[16] Although the aldol reaction was unsuccessful under the reaction conditions reported in the literature, after considerable experimentation, treatment of the methylketone **38** with LHMDS, followed by the addition of the aldehyde **39**, furnished the desired hydroxy ketone **70** in a low yield (20%) with the concomitant formation of byproducts containing its C64-epimer (10%). Although the yield of the aldol reaction should be improved, the stereoselective reduction of the β-hydroxyketone **70** with the Saksena–Evans reagent[15] gave the 1,3-*anti*-diol **71** as an inseparable mixture with the C66-epimer. Finally, the global removal of NAP groups from **71** with $Pd(OH)_2/C$ under a hydrogen atmosphere afforded the LMNO ring system **37** in 53% yield for two steps as a single isomer.



Scheme 2-2-5. Synthesis of the LMNO ring system **37**.

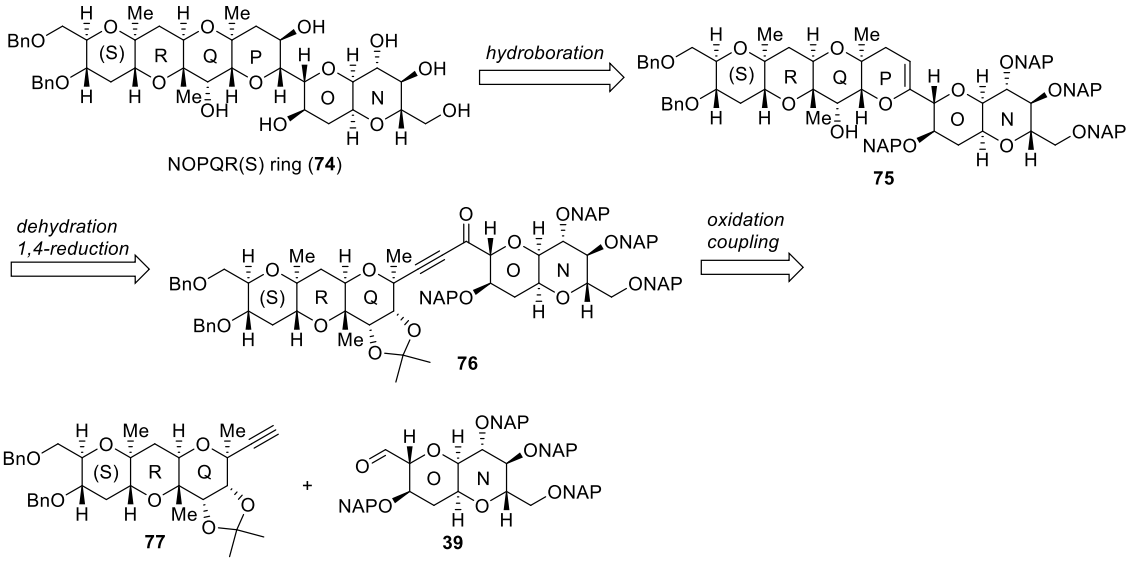
To verify the effect of TBDPS group for biological activity, compound **73** was prepared from **70** (Scheme 2-2-6). Removal of the TBDPS group with TBAF, followed by the global removal of NAP groups from **72** with $Pd(OH)_2/C$ under a hydrogen atmosphere afforded **73** in 30% yield for three steps as a single isomer.



Scheme 2-2-6. Synthesis of the deprotected LMNO ring system **73**.

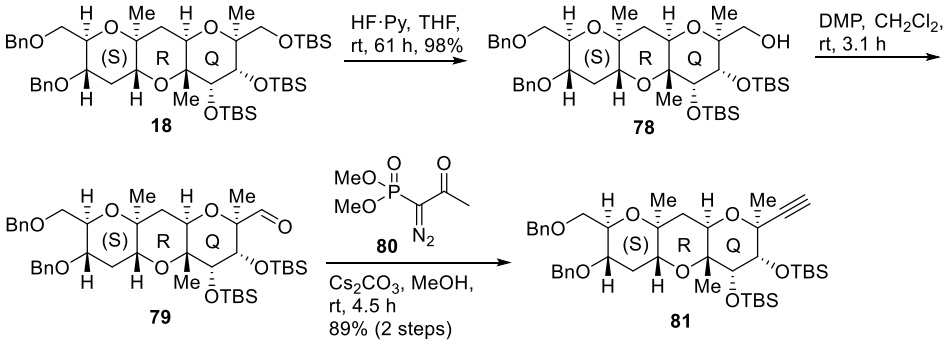
2-3. Synthesis of the NOPQR(S) ring system

Synthesis plan of the NOPQR(S) ring system **74** is shown in Scheme 2-3-1. The target compound **74** would be derived from dihydropyran **75** via hydroboration, which is to be synthesized from ynone **76** through 1,4-reduction and dehydration. For the construction of ynone **76**, coupling of the QR(S) ring alkyne **77** derived from an intermediate in the synthesis of the QRS ring system and the NO ring aldehyde **39** (common intermediate with the LM ring) was envisaged.



Scheme 2-3-1. Synthesis plan of the NOPQR(S) ring fragment of MTX.

Synthesis of the NOPQR(S) ring system commenced with the conversion of the QR(S) ring **18** to alkyne **81** (Scheme 2-3-2). Selective removal of the TBS group of **18** with HF·Py afforded **78** in 98% yield. Oxidation of primary alcohol **78** with Dess–Martin periodinane, followed by treatment of the resulting aldehyde **79** with Ohira–Bestmann reagent (**80**)[34] in the presence of Cs_2CO_3 as a base gave desired alkyne **81** in 89% yield for two steps.



Scheme 2-3-2. Synthesis of the QR(S) ring fragment **81**.

Having obtained the QR(S) ring fragment **81**, coupling reaction with the NO ring fragment (**39**) was examined (Table 2-3-1). Alkynyllithium prepared from **81** by treatment with *n*-BuLi in situ was subjected to coupling reaction with aldehyde **39** in THF at −78 °C to afford desired product **82** in 13% yield as a single isomer, but the stereochemistry of C76-hydroxy group was not determined (entry 1). Attempts to improve the yield, higher reaction temperature (entries 2 and 3) or addition of $CeCl_3$ (entry 4),[35] were unsuccessful.

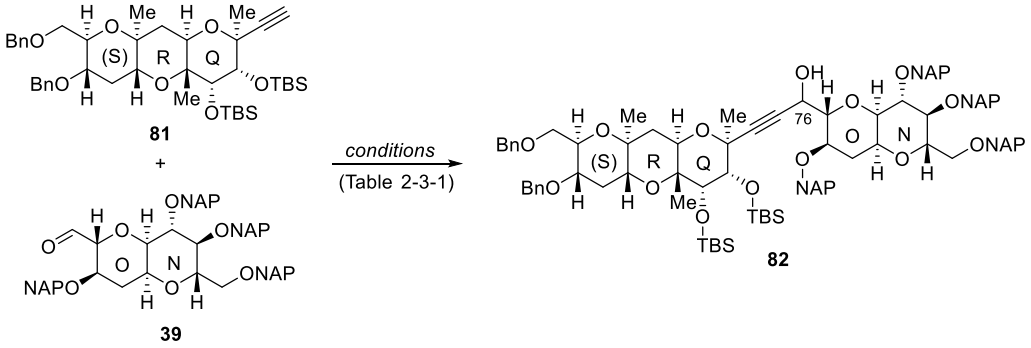
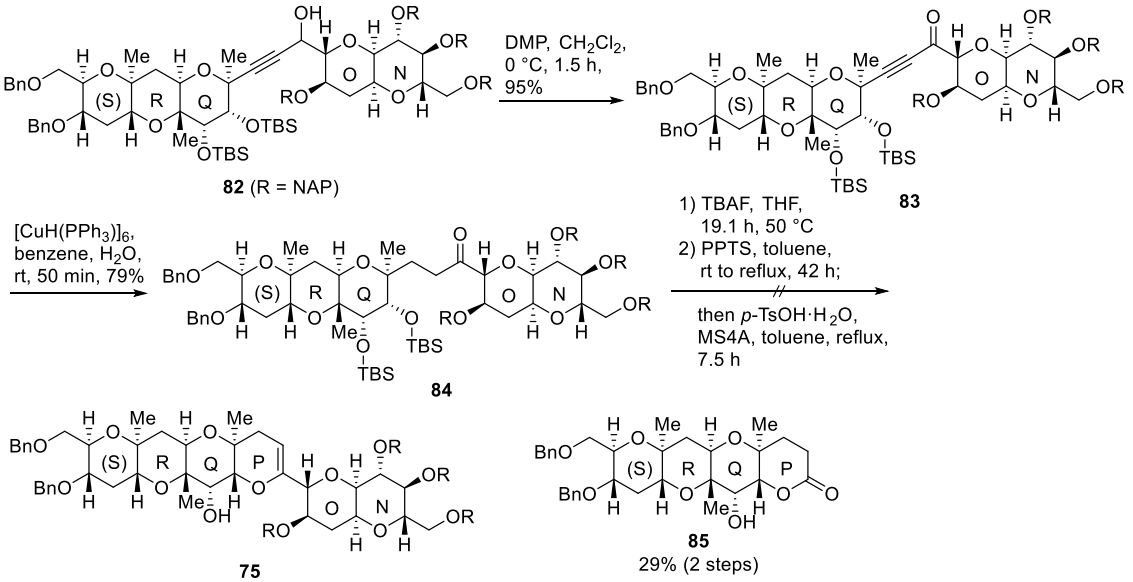


Table 2-3-1. Coupling of the QRS ring fragment **81** and the NO ring fragment **39** [a]

entry	QRS / eq	*n*-BuLi / eq	$CeCl_3$ / eq	Temp. / °C (lithiation)	Temp. / °C (coupling)	Yield / %
1	2.5 [b]	2.5	–	-78	-78	13
2	4.0 [b]	4.0	–	-78	-78 to rt	20
3	4.1	3.7	–	0	-60 to 0	19
4	3.0	3.0	3.4	-78	-78 to rt	20

[a] These reactions were carried out in THF. Substrates were dried by toluene azeotropy and using MS4A.
[b] Dried by only toluene azeotropy.

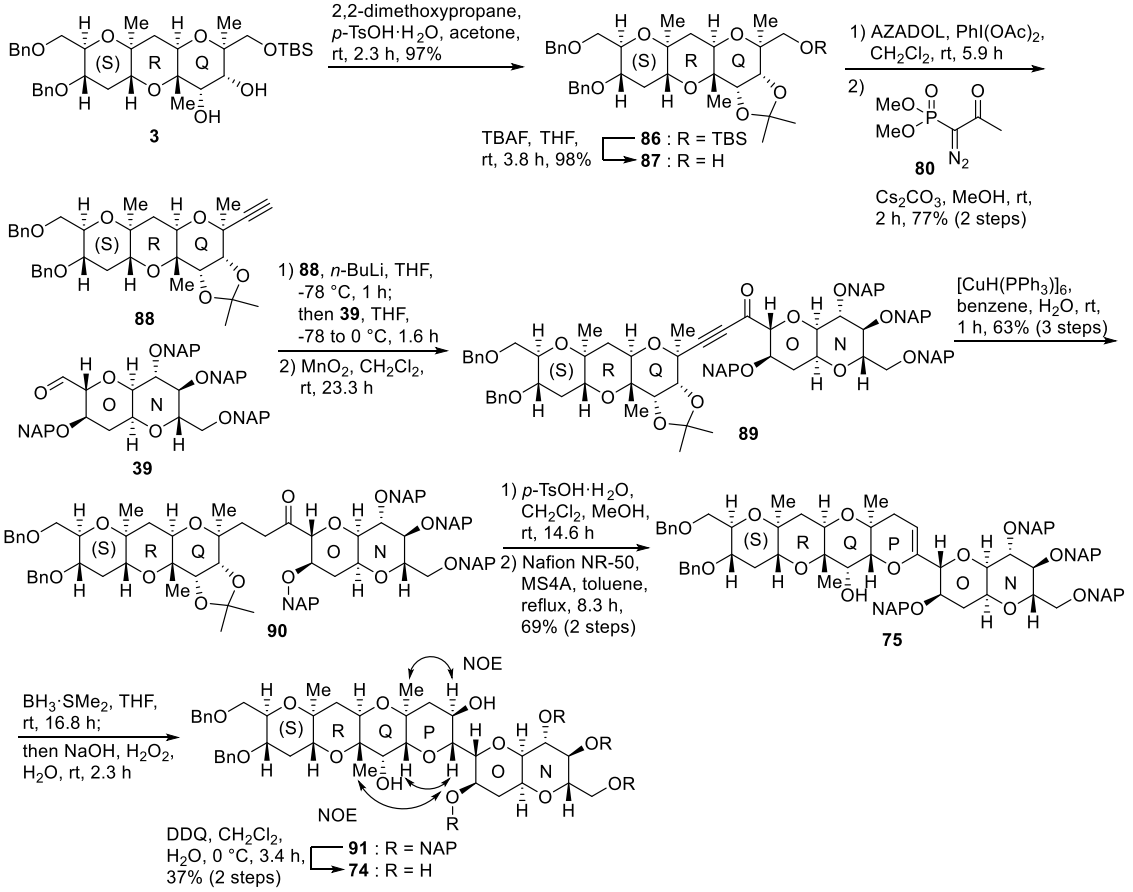
Synthesis of hexacyclic compound **75** was attempted (Scheme 2-3-3). Oxidation of alcohol **82** with Dess-Martin periodinane gave ketone **83** in 95% yield. Although selective hydrogenation of alkyne **83** by using Pd/C(en)[36] under H_2 atmosphere was unsuccessful, 1,4-reduction of alkynylketone with Stryker's reagent ($[CuH(PPh_3)]_6$)[37] furnished ketone **84** in 79% yield. Since treatment of **84** with TBAF at room temperature caused no reaction, reaction temperature was elevated to 50 °C. Although removal of the TBS groups probably proceeded, complex inseparable mixture was obtained. Surprisingly, treatment of the mixture with *p*-TsOH·H_2O afforded lactone **85**. It was considered that exposure of **84** to basic conditions at high temperature caused decomposition of the substrate. Therefore, treatment of **84** with TBAF in the presence of acetic acid as buffer solution was examined, but the TBS groups were not removed. Deprotection of the TBS groups with HF·Py was also unsuccessful.



Scheme 2-3-3. An attempt to synthesize **75** from alkynylalcohol **82**.

Sterically hindered silyl groups near the reactive site seemed to prevent from coupling reaction and it was difficult to remove TBS groups. Therefore, protecting group of the QR(S) ring fragment was changed to acetonide (Scheme 2-3-4). Protection of the diol **3** as an acetonide with 2,2-dimethoxypropane (97%), followed by removal of the TBS group of **86** with TBAF gave the alcohol **87** in 98% yield. Oxidation of the primary alcohol in the presence of catalytic amounts of AZADOL[38] using $PhI(OAc)_2$ as a co-oxidant afforded an aldehyde, which was then treated with the Ohira–Bestmann reagent

(**80**)[34] in the presence of Cs_2CO_3 as a base to furnish the alkyne **88** in 77% yield for two steps. Coupling reaction of the QR(S) ring fragment **88** and the NO ring fragment **39** was then carried out. Treatment of the terminal alkyne **88** with *n*-BuLi to generate the corresponding lithium acetylide, followed by the addition of the aldehyde **39**, afforded a secondary alcohol as a mixture of diastereomers in a 2:1 ratio, which was then oxidized with MnO_2 to give the ynone **89**. 1,4-reduction of **89** with Stryker reagent $[CuH(PPh_3)]_6$[37] gave the saturated ketone **90** in 63% yield for three steps. Methanolysis of the acetonide **90** with *p*-TsOH·H_2O resulted in the formation of a mixture of a keto alcohol and a hemiacetal. Although dehydration to obtain the dihydropyran derivative **75** by treatment with PPTS or *p*-TsOH·H_2O was unsuccessful, that with Nafion NR-50[39] afforded **75** in 69% yield for two steps. Hydroboration of the olefin **75** with BH_3·SMe_2, followed by an oxidative workup, furnished the desired alcohol **91** as a single diastereomer. The stereochemistry of **91** was confirmed by NOE experiments. Finally, the synthesis of the NOPQR(S) ring system **74** was achieved through global removal of the NAP groups with DDQ in 37% yield for two steps.[40]



Scheme 2-3-4. Synthesis of the NOPQR(S) ring system **74**.

2-4. Biological activities

Having synthesized the QRS, LMNO, and NOPQR(S) ring, biological activity was evaluated. A solution of 1 nM MTX induced a 10-fold increase in the Ca^{2+} influx, compared to the control, in rat C6 glioma cells, and this value was defined as 100% Ca^{2+} influx (Figure 2-5-1).

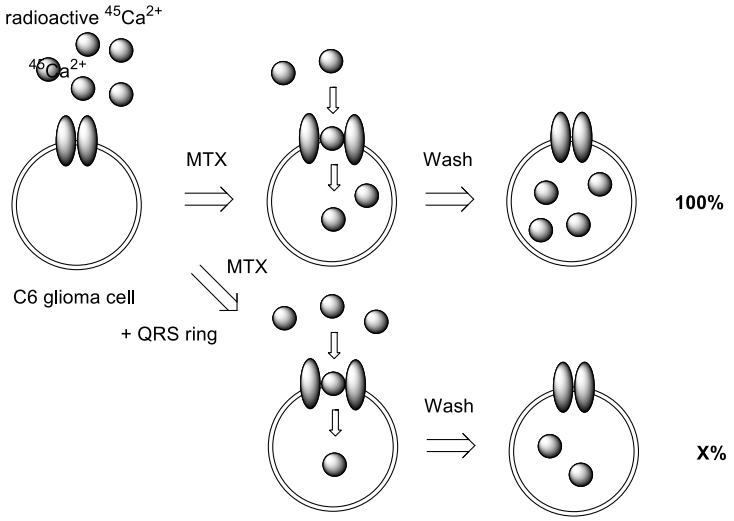


Figure 2-5-1. Evaluation of the inhibitory activities of the partial structures of MTX. The level of Ca^{2+} influx induced by 1 nM MTX was defined as 100%.

The QRS ring (tricyclic) system **1** blocked Ca^{2+} influx activity in a dose-dependent manner, and the IC_{50} value was estimated to be 44 μM (Figure 2-5-2).[14] It is noteworthy that inhibitory activity of the tricyclic compound **1** is comparable to that of the longer partial structures, the W–C' (heptacyclic) and the C'–F' (tetracyclic) ring system.[41] In addition, it is interesting to note that 6/6/6-tricyclic ether **36** also inhibited MTX-induced Ca^{2+} influx with IC_{50} value at 240 μM (Figure 2-5-2).

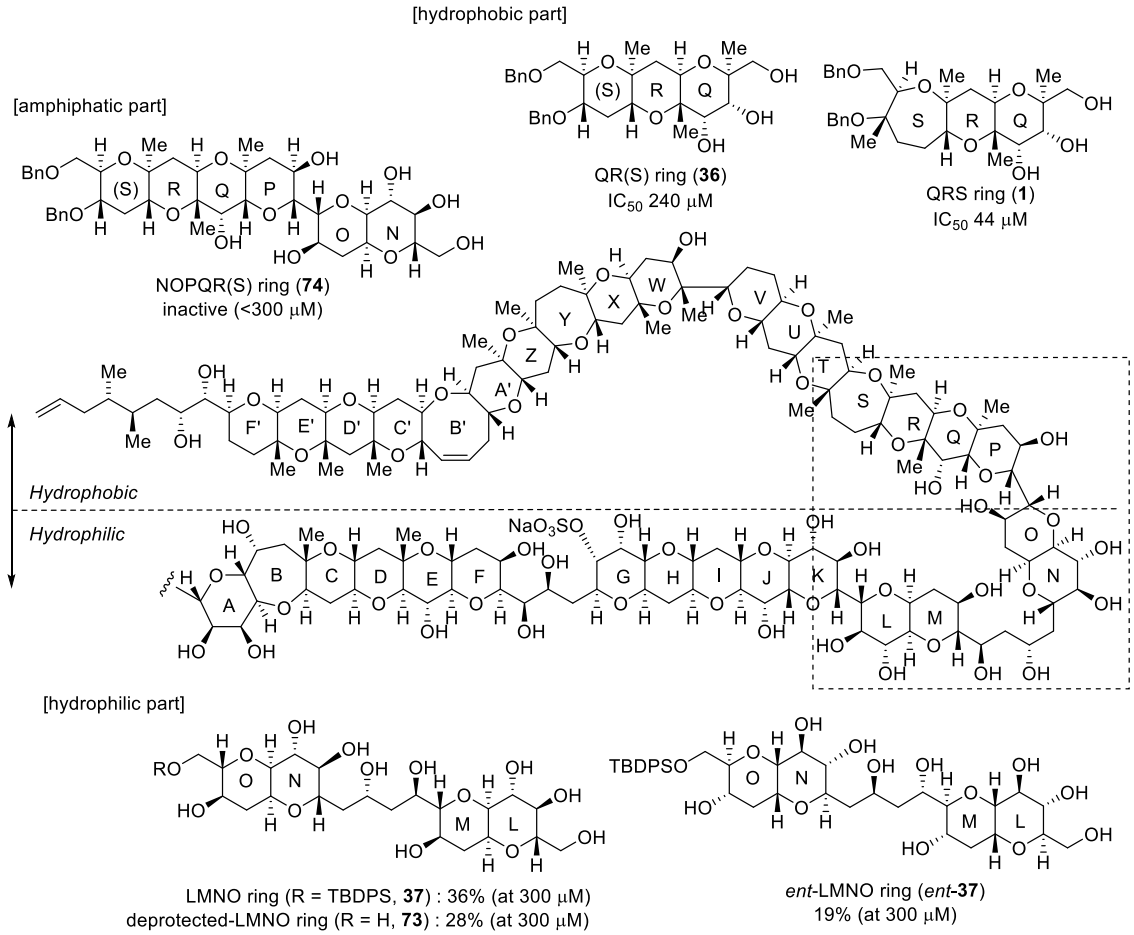


Figure 2-5-2. Structure-activity relationship studies of MTX.

Since the inhibitory activities of the LMNO (**37**) and NOPQR(S) ring systems (**74**) were not so potent, the values are listed as inhibition percentages at 300 μM, not IC_{50} values, and the values were compared with those of the QR(S) (**36**) and the QRS ring system (**1**),[14] namely, 54% and 91% inhibition, respectively (Figure 2-5-3). The inhibitory activity of the LMNO ring system (**37**) was 36%, whereas that of its enantiomer (*ent*-**37**) which was prepared for comparison in our group[40] was slightly less potent (19% inhibition). In addition, the activity was not significantly changed by deprotection of a TBDPS group (28% inhibition). These results are comparable to those reported by Konoki et al.[42] Thus, the biological activity did not depend significantly on the chirality. Therefore, the inhibitory activity of the hydrophilic region may not be due to specific binding to the target proteins, suggesting that the hydrophilic region may not be a promising inhibitor. These results are supporting our hypothesis: the partial structures

corresponding to the hydrophobic region of MTX might bind competitively to the target proteins to inhibit the biological activity due to MTX.

On the other hand, it was surprising that no inhibition was observed with the NOPQR(S) ring system (**74**) (< 300 μM), possessing hydrophobic and hydrophilic moieties and a large number of rings (hexacyclic) than the LMNO (tetracyclic, **37**) and the QRS (tricyclic, **1**) ring systems. Although the mechanism underlying the activity of the NOPQR(S) ring system (**74**) remains a point of debate, the combination of the hydrophobic and hydrophilic regions influenced the biological activity in contradictory manners.

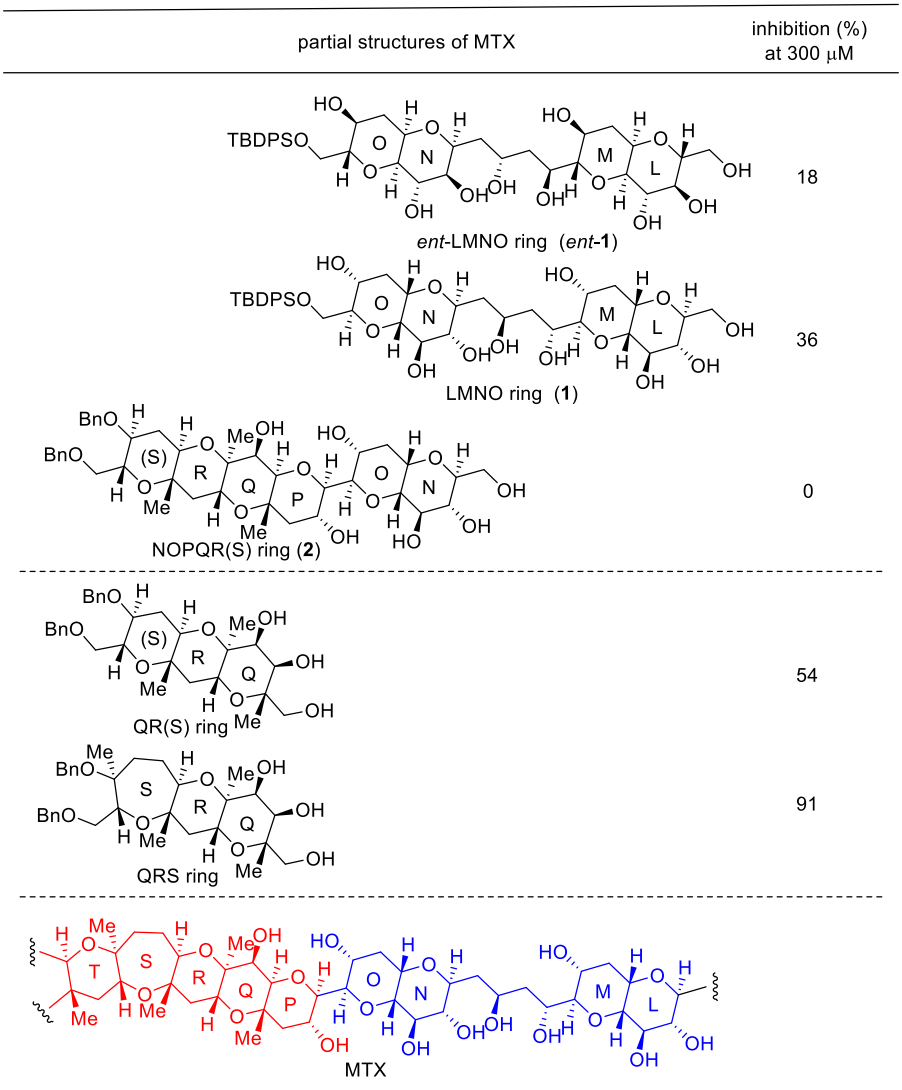


Figure 2-5-3. Summary of the inhibitory activity of the synthetic specimens against Ca^{2+} influx induced by MTX and comparison of the molecular structures with that of MTX.

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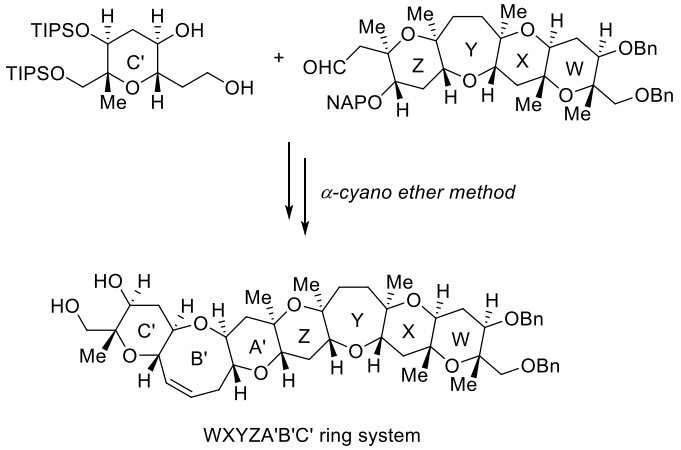
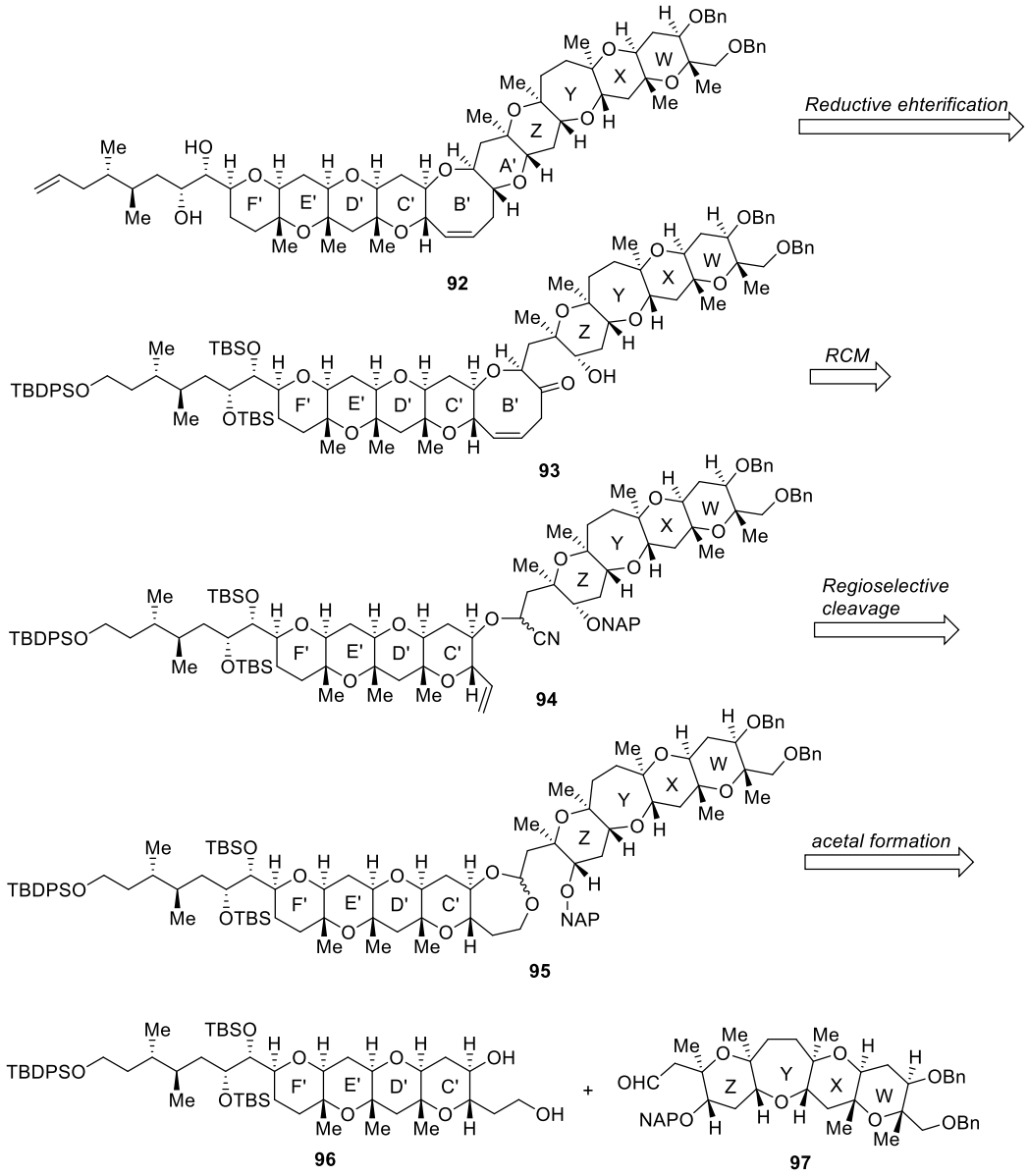
Chapter 3. Synthesis of the WXYZA'B'C'D'E'F' ring system of maitotoxin

3-1. Synthesis plan

Since the synthesis of the WXYZA'B'C' ring system was completed in our laboratory based on convergent strategy via α-cyano ethers (Scheme 3-1-1),[1] the similar strategy was envisaged for the synthesis of the WXYZA'B'C'D'E'F' ring system as shown in Scheme 3-1-2. The WXYZA'B'C'D'E'F' ring system **92** would be derived from hydroxy ketone **93** via reductive etherification with construction of the A' ring. Construction of the B' ring is to be achieved through ring-closing metathesis.[2] Regioselective cleavage of acetal **95** could generate to α-cyano ether **94**, and this precursor would be obtained by intermolecular acetal formation between diol and aldehyde corresponding to C'D'E'F' ring **96**[3] and WXYZ ring **97**,[1b] respectively.



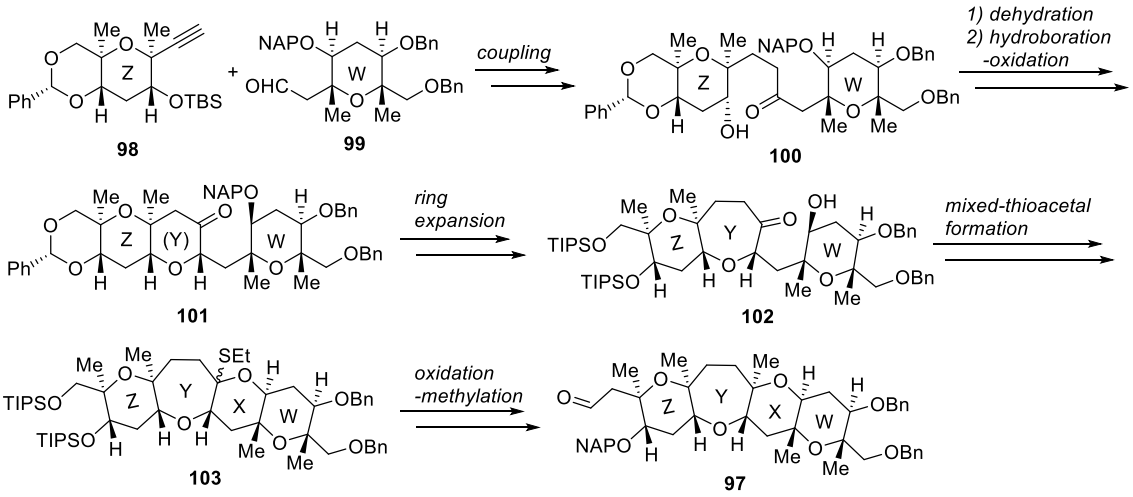
Scheme 3-1-1. Convergent synthesis of the WXYZA'B'C' ring system via α-cyano ether method.



Scheme 3-1-2. Synthetic plan of the WXYZA'B'C'D'E'F' ring system.

3-2. Synthesis of the WXYZ and C'D'E'F' ring system

Although the synthesis of the WXYZ ring fragment was achieved by α-cyano ether protocol in our laboratory,[1] novel convergent strategy to construct 6/7/6/6-tetracyclic ether system having contiguous angular methyl groups was developed (Scheme 3-2-1).[4] Hydroxy ketone **100** was derived from alkyne **98** and aldehyde **99** via coupling reaction, and dehydration followed by hydroboration-oxidation afforded **101**. Ring expansion of six-membered ring ketone **101** gave seven-membered ring ketone **102**, and compound **103** was obtained by mixed thioacetal formation of hydroxy ketone **102**. Synthesis of aldehyde **97** was achieved through oxidation and methylation of common intermediate **103**.



Scheme 3-2-1. Synthesis of the WXYZ ring system in combination of novel and previous strategies.

However, there was a problem in preparation of mixed-thioacetal. Therefore, optimization of the reaction conditions was examined (Table 3-2-1).[1b] As reported, treatment of the hydroxy ketone with EtSH in the presence of $Zn(OTf)_2$ afforded the desired mixed-thioacetal **103** (42%) with concomitant formation of dithioacetal **104** (8%) and recovery of the starting material **102** (42%) (entry 1). This reaction didn't proceed in the presence of MS4A (entry 2), and other Lewis acids such as $Sc(OTf)_3$ and $In(OTf)_3$ showed no significant improvement (entries 3, 4). On the other hand, the use of TfOH furnished desired compound **103** in 66% yield (entry 5). Although the yield was decreased, reducing the amount of EtSH reduced to generate byproducts such as dithioacetal **104** or

rearrangement product **105**. TfOH was added portionwise (0.1 eq, four times) in the presence of MS4A gave better results, and **103** was obtained in 74% yield as a mixture of diastereomers (α : β = 4.8 : 1) after protection of the partially desilylated products.

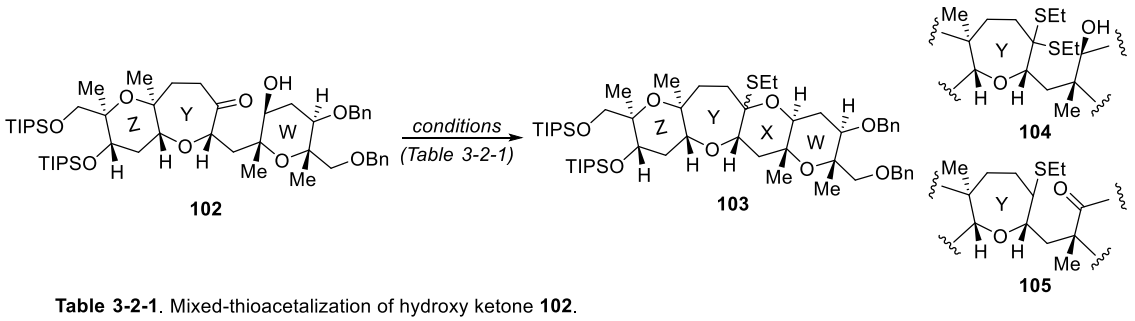
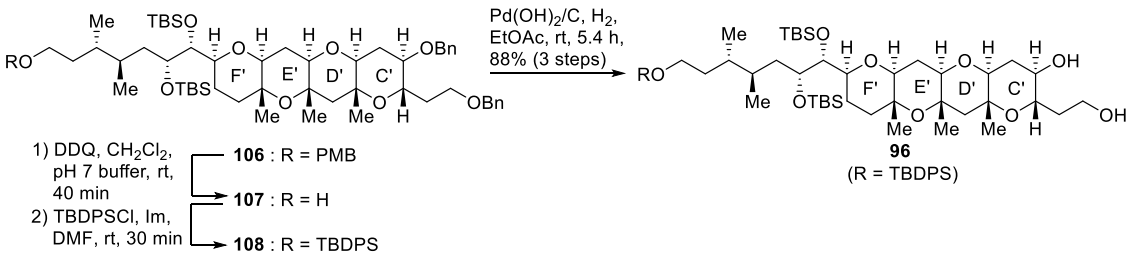


Table 3-2-1. Mixed-thioacetalization of hydroxy ketone **102**.

Entry	Acid / eq	EtSH / eq	MS4A / wt%	Temp. / °C	Time / min	Products / %			
						102	**103**	**104**	**105**
1	$Zn(OTf)_2$ / 1.2	100	-	0	270	42	42	8	-
2	$Zn(OTf)_2$ / 1.2	100	200	0 to rt	390	no reaction			
3	$Sc(OTf)_3$ / 1.2	100	-	0 to rt	300	no reaction			
4[b]	$In(OTf)_3$ / 1.2	100	200	0	20	4	56	18	-
5[c]	TfOH / 0.1	100	200	0	30	7	66	18	4
6[c]	TfOH / 0.1	20	200	0	360	58	29	-	-
7[c]	TfOH / 0.1 x 4	20	200	0	100	5	74	14[d]	

[a] All reactions were carried out in CH_2Cl_2. [b] Followed by treatment with TIPSCl and 2,6-lutidine in DMF at rt.
[c] Followed by treatment with TIPSOTf and 2,6-lutidine in CH_2Cl_2 at -78 to -30 °C. [d] Mixture of byproducts.
[e] Entry 1~6 were carried out by Mr. Hasegawa.

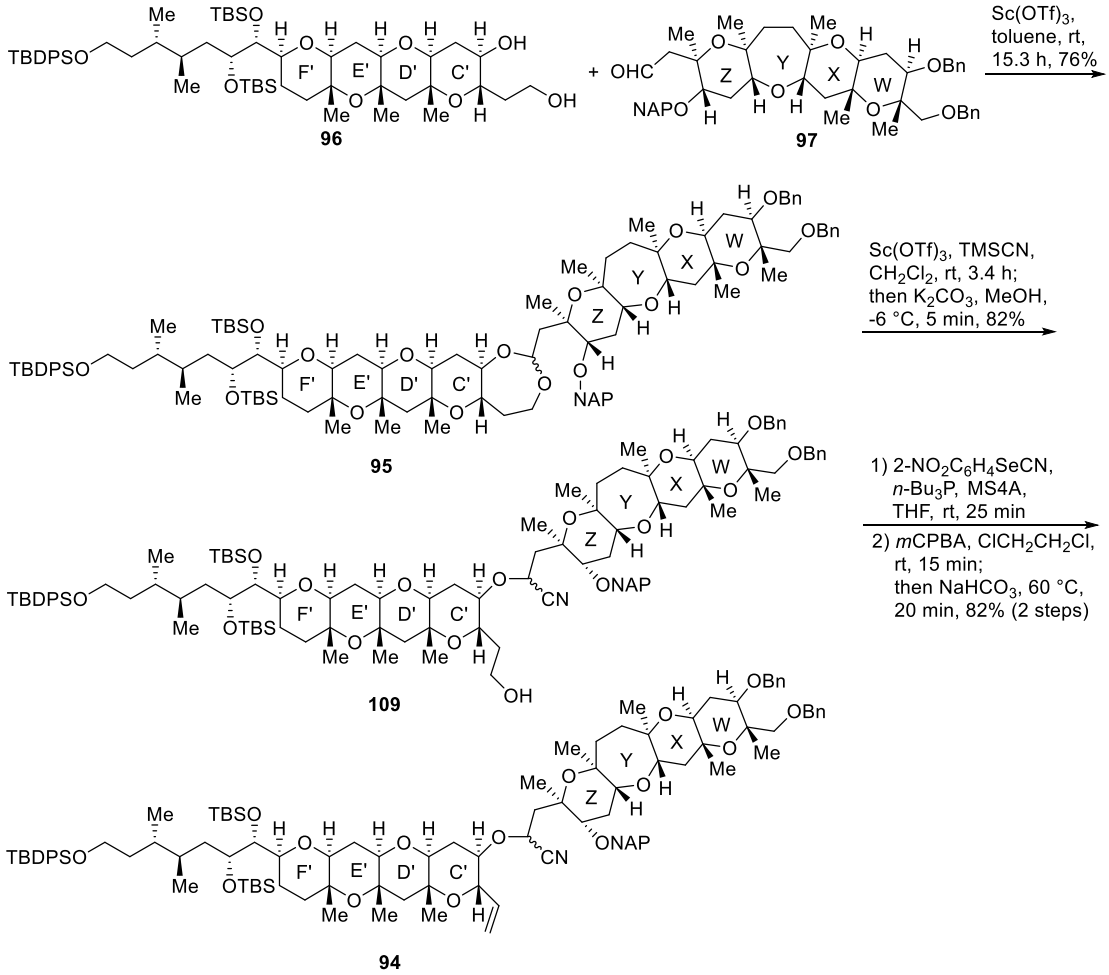
The C'D'E'F' ring fragment **96** was prepared from known compound **106** as shown in Scheme 3-2-2.[3] Thus, deprotection of a PMB group with DDQ followed by protection of the resulting primary alcohol as a TBDPS ether afforded **108**. Subsequently, Bn groups were removed with Pearlman's catalyst under hydrogen atmosphere to generate the C'D'E'F' ring fragment **96** in 88% yield for three steps.



Scheme 3-2-2. Synthesis of the C'D'E'F' ring fragment **96**.

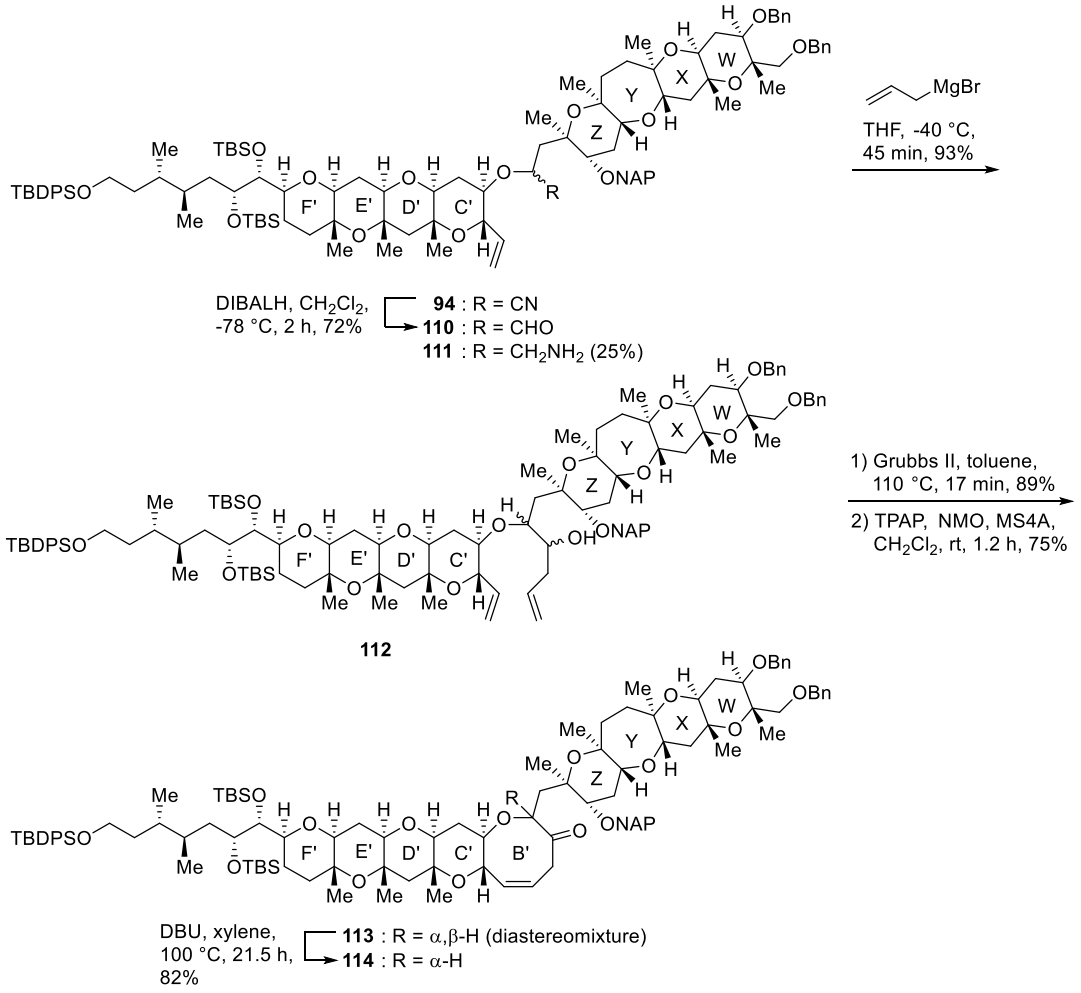
3-3. Synthesis of the WXYZA'B'C'D'E'F' ring system

Synthesis of the WXYZA'B'C'D'E'F' ring system was carried out through α-cyano ether method[1] (Scheme 3-3-1). After treatment of diol **96** and aldehyde **97** with $Sc(OTf)_2$ to generate **95** in 76% yield, regioselective cleavage of the resulting acetal with TMSCN in the presence of $Sc(OTf)_2$[5] afforded a key intermediate, α-cyano ether **109**, in 82% yield. In this reaction, basic work-up with K_2CO_3 in MeOH for removal of the TMS group was carefully and quickly carried out to avoid removal of TBDPS and TBS groups. Elimination of the primary alcohol **109** was achieved by Nishizawa–Grieco protocol.[6] Thus, after treatment of primary alcohol with 2-nitrophenyl selenocyanate in the presence of *n*-Bu_3P, oxidation of the resulting aryl selenide to selenoxide followed by heating under basic conditions generated terminal olefin **94** in 82% yield for two steps.



Scheme 3-3-1. Synthesis of α-cyano ether **94**.

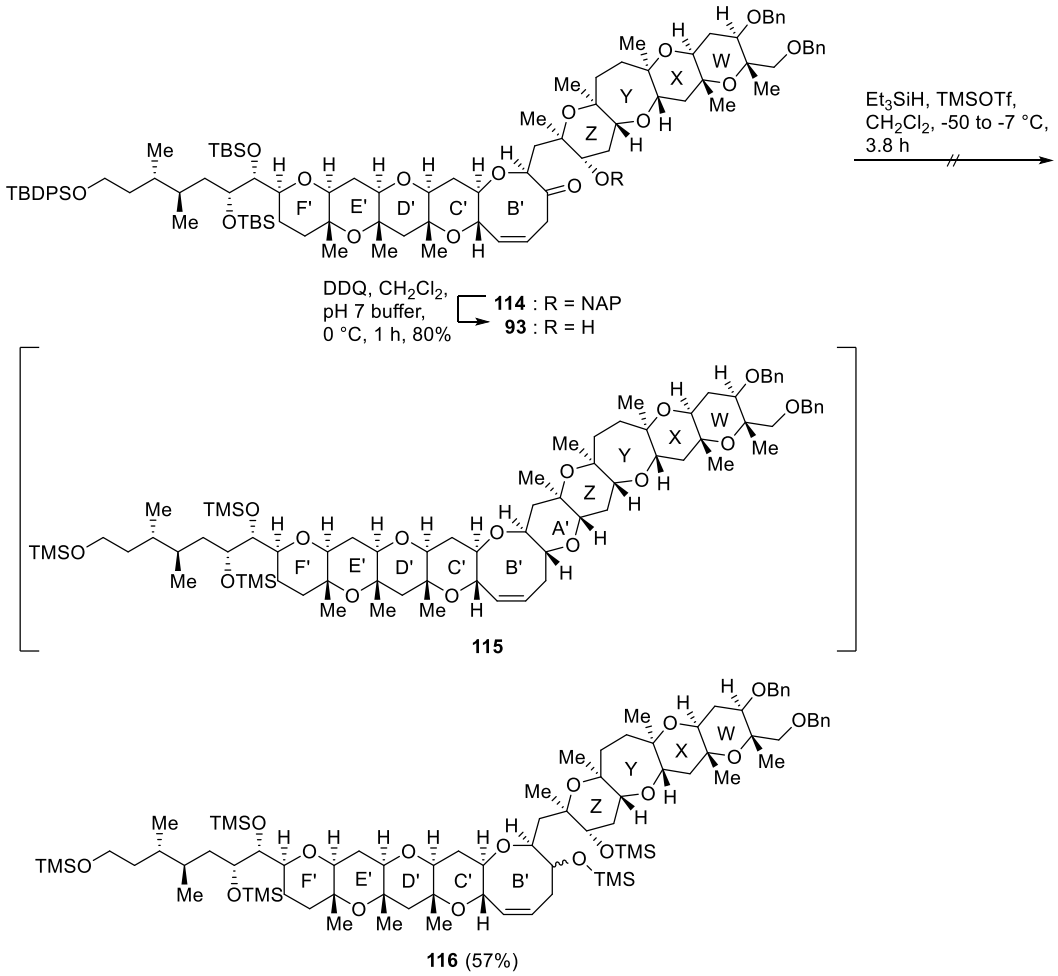
The B' ring was constructed as shown in Scheme 3-3-2. Reduction of nitrile **94** with DIBALH afforded aldehyde **110** in 72% yield with concomitant formation of primary amine **111** (25%) due to overreduction, and then alkenyl group was introduced with allymagnesium bromide to furnish **112** as a mixture of four diastereomeres in 93% yield. Ring closing metathesis of **112** to construct eight-membered ring proceeded smoothly by using Grubbs catalyst 2nd generation.[2] After Ley–Griffith oxidation[7] of the resulting alcohol giving ketone **113** in 75% yield, desired compound **114** was successfully obtained as a single isomer through isomerization under basic conditions in 82% yield.



Scheme 3-3-2. Synthesis of eight-membered ring ketone **114**.

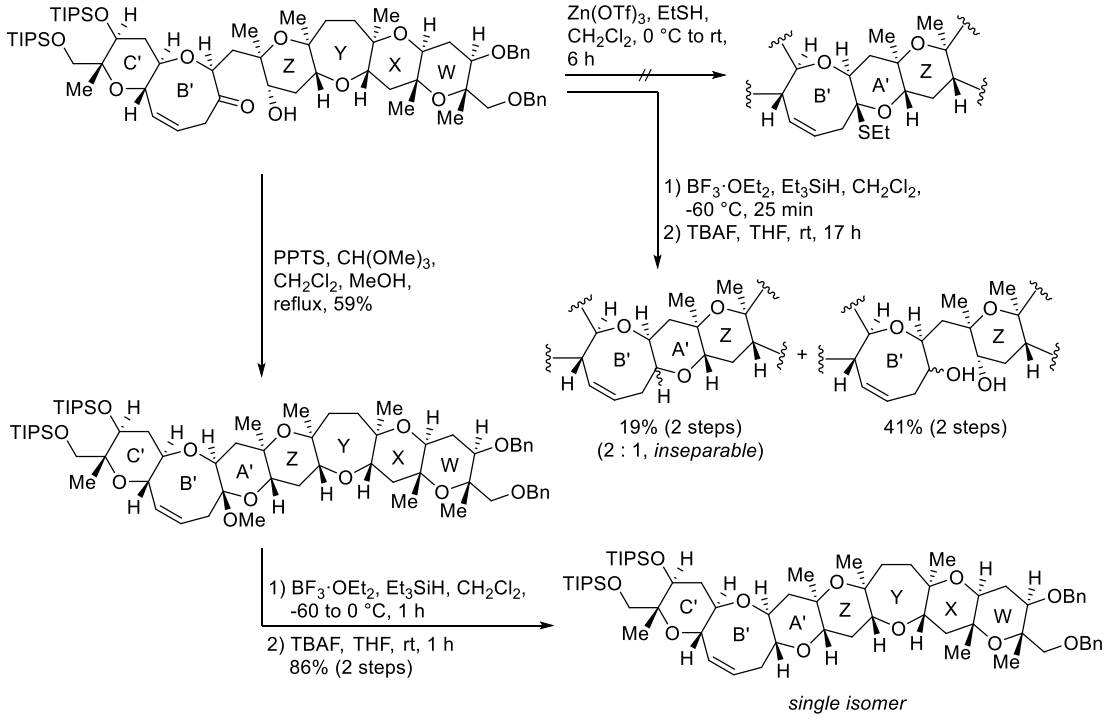
After removal of a NAP group with DDQ giving **93** in 80% yield, direct reductive etherification of hydroxy ketone **93** including hemiacetal was attempted

(Scheme 3-3-3). Unfortunately, no desired compound **115** was obtained by treatment with Et_3SiH in the presence of TMSOTf, but TMS ether **116** was formed in 57% yield through reduction of the ketone with concomitant substitution of the TBDPS and TBS groups with TMS groups.



Scheme 3-3-3. Attempt of direct reductive etherification of hydroxy ketone **93**.

It was known that construction of the A' ring was problematic in our previous report as shown in Scheme 3-3-4.[1b,8] Direct reductive etherification of hydroxy ketone afforded desired compound as an inseparable diastereomixture in 19% yield for two steps and reduction of ketone mainly occurred. Mixed-thioacetal formation of hydroxy ketone gave no desired compound. Fortunately, cyclization prior to reductive etherification as methyl acetal overcame these problems to furnish target compound as a single isomer in 86% yield for two steps.[1b]



Scheme 3-3-4. Problems and solution for construction of the A' ring in our previous report.

Therefore, methyl acetal formation of **93** was examined (Table 3-3-1). Hydroxy ketone **93** was exposed under acidic conditions with PPTS in the presence of $CH(OMe)_3$ (entry 1). While methylacetal was obtained, removal of silyl groups was also observed. Furthermore, it was disappointing that 1,3-dioxolane **119** was formed from 1,2-diol in the side chain. Therefore, the use of trimethyl orthoformate was abandoned. Although MS3A was added as an alternative dehydrating agent, the reaction was not proceeded (entry 2). Fortunately, it was found that calcium chloride was a suitable additive, and desired methyl acetal **117** was obtained in 88% yield as a single isomer with removal of the TBDPS and TBS groups (entry 3). However, the product included a small amount of contaminant and the reaction time was too long (72 h). In order to obtain pure compound and shorten the reaction time, other acids were tested. Although the purity of the product was not improved, reaction time was significantly cut down by using CSA (entry 4). On the other hand, the reaction was not completed in the presence of $Sc(OTf)_2$ as a Lewis acid and dehydrating agent (entry 5).

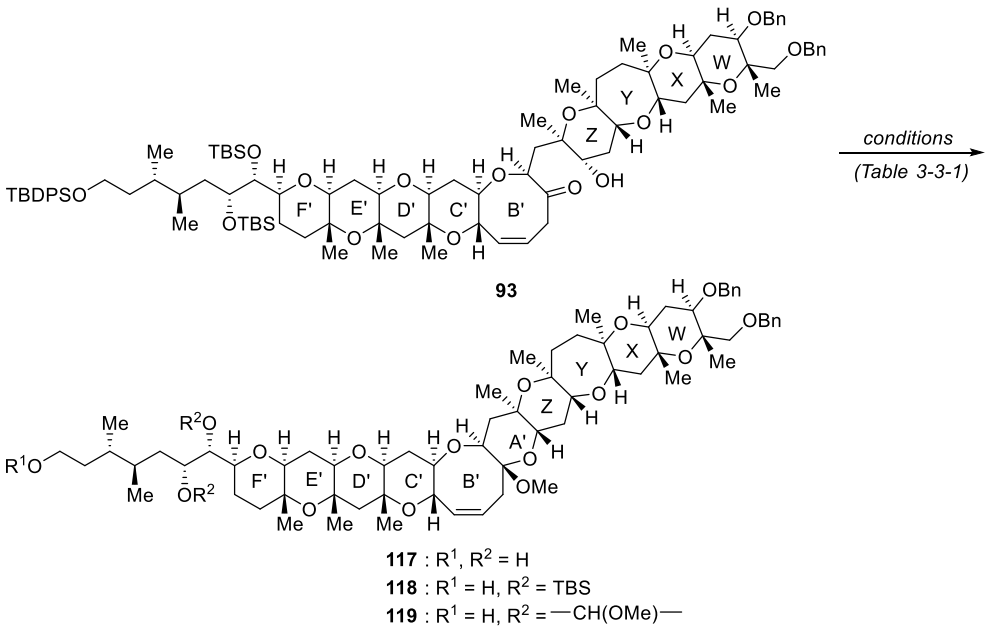


Table 3-3-1. Methylacetalization of hydroxy ketone **93**.

Entry	Acid / eq	Additive / eq	Temp. / °C	Time / h	Products / %		
					117	**118**	**119**
1[a]	PPTS / 17	$CH(OMe)_3$ / 234	65	30	-	24	[d]
2[a]	PPTS / 17	MS3A	65	21	no reaction		
3[b]	PPTS / 32	$CaCl_2$ / 75	85	72	<88	-	-
4[b]	CSA / 11	$CaCl_2$ / 46	85	7	<79	-	-
5[c]	$Sc(OTf)_3$ / 3.6	-	rt to 65	57	[e]	-	-

[a] CH_2Cl_2/MeOH (1/1), [b] in 1,2-dichloroethane/MeOH (1/1), [c] in toluene/MeOH (1/1)
[d] detected by MS (included with slightly amount of other byproducts)
[e] observed as an inseparable mixture with deprotected **93**

Reductive etherification of the obtained methylacetal **118** was examined (Table 3-3-2). When methylacetal **118** was treated with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$,[9] hydrolysis of acetal was observed (entry 1). Although this side reaction was suppressed by addition of molecular sieves (entry 2), it was surprising to obtain undesired diastereomer **121** as a major product. When the reaction was carried out at lower temperature, complex mixture was given (entry 3). Although Me_2PhSiH was used as a reducing reagent,[10] a mixture of diastereomers was afforded in 42% yield (entry 4). When TMSOTf was used as a Lewis acid, undesired compound **121** was obtained as a single isomer in 57% yield (entry 5). In addition, reduction with DIBALH was also unsuccessful (entry 6). Stereoselectivity was not improved in any conditions of reductive etherification.

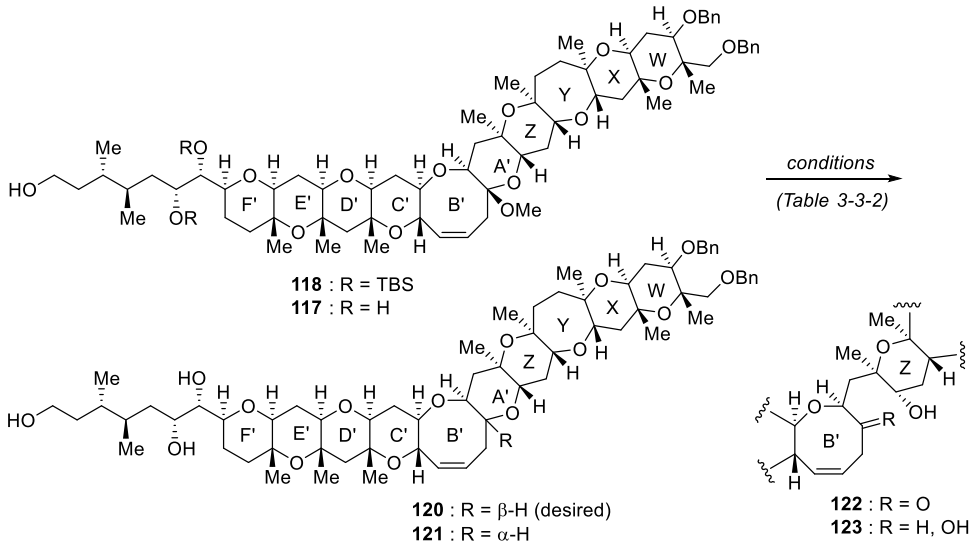


Table 3-3-2. Reductive etherification of methylacetal **118** or **117**.

Entry	SM	Acid / eq	Hydride / eq	Additive / eq	Temp. / °C	Time / h	Products / %			
							120	**121**	**122**	**123**
1[a]	**118**	$BF_3{\cdot}OEt_2$ / 114	Et_3SiH / 586	-	-50 to 0	6.8		33[b]	[c]	
2[a]	**118**	$BF_3{\cdot}OEt_2$ / 92	Et_3SiH / 352	MS4A	-50 to 0	4.2		49[b]	-	-
3[a]	**117**	$BF_3{\cdot}OEt_2$ / 82	Et_3SiH / 288	MS4A	-78 to -20	8.8		complex mixture		
4[a]	**117**	$BF_3{\cdot}OEt_2$ / 82	Me_2PhSiH / 2227	MS4A	-50 to -5	4.6		42[b]		
5[a]	**117**	TMSOTf / 36	Et_3SiH / 204	MSAW300	0	0.7	-	57[d]	-	-
6[a]	**117**	-	DIBALH / 103	-	-4 to 40	4.1		no reaction		

[a] CH_2Cl_2 [b] Inseparable diastereomixture. Undesired product was major component. [c] Only detected by MS
[d] After removal of TMS group with *p*-TsOH·H_2O.

Since reduction of methylacetal resulted in the formation of undesired diastereomer as a major product, radical reduction of *O,S*-acetal was examined (Table 3-3-3). Methylacetal **117** was converted to mixed-thioacetal **124** by treating with EtSH and $Zn(OTf)_2$ in 47% yield, and then the resulting mixed-thioacetal **124** was treated with Ph_3SnH in the presence of catalytic amount of AIBN as a radical initiator.[11] However, targeting material was not obtained, and mixture of starting material and byproduct which seemed to be diene **125** was formed (entry 1). When excess amounts of reagents were used, and decomposition of substrate occurred (entry 2). Therefore, it was necessary to explore milder and more efficient conditions. VA-044 was one of the water-soluble radical initiator and used for radical polymerization. Recently, it was noticed in the field of organic synthesis because of its low toxicity and ease in handling.[12] Thus, treatment of mixed-thioacetal **124** with VA-044 was attempted, and $(TMS)_3SiH$ which was known as

a nontoxic source of hydrogen radical was used. In addition, it was reported that catalytic amount of EtSH promoted radical reduction of xanthate,[13] therefor, it was also used for this reaction. Fortunately, desired reductive product **120** was obtained in 41% yield for two steps, and its stereochemistry was confirmed by NMR analysis (^{1}H NMR, ^{1}H-^{1}H COSY, NOE, and NOESY). Although terminal olefin of side chain is lacking, construction of framework corresponding the WXYZA'B'C'D'E'F' ring system was achieved.

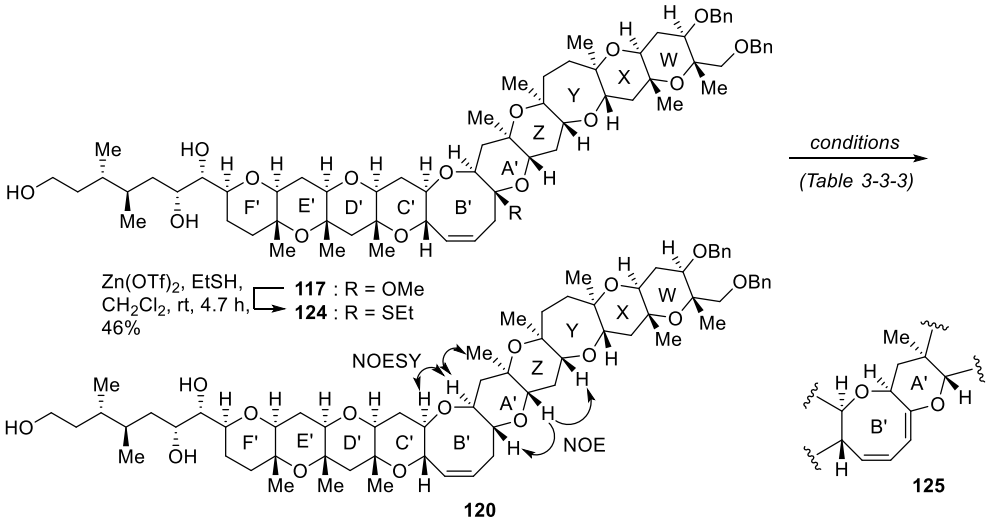


Table 3-3-3. Radical reduction of mixed-thioacetal **124**.

Entry	Radical initiator / eq	Chain carrier / eq	Additive / eq	Temp. / °C	Time / h	Products / %		
						120	**125**	**124**
1[a]	AIBN / 0.2	Ph_3SnH / 56	-	110	3.3	-	mixture[c]	
2[a]	AIBN / 34	Ph_3SnH / 300	-	110	2.3	decomposed		
3[b]	VA-044 / 3	$(TMS)_3SiH$ / 86	PhSH / 2.6	70	0.6	41[d]	-	-

[a] in toluene [b] in EtOH, H_2O [c] inseparable and detected by ^{1}H NMR and/or MS
[d] A mixture of mixed-thioacetal **124** and dithioacetal was used as substrate, and yield for two steps was shown.

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Chapter 4. Conclusion

In this study, four compounds corresponding to the partial structures of MTX were synthesized, and their bioactivities were evaluated to elucidate the important region for eliciting biological activities of MTX.

1. Synthesis of the QRS ring system was completed via construction of contiguous four stereogenic centers by chemoselective methylation and dihydroxylation. It was found that the tricyclic compound (the QRS ring, IC_{50} 44 μM) showed comparable inhibition activity to tetracyclic (the C'D'E'F' ring, IC_{50} 59 μM) and heptacyclic (the WXYZA'B'C' ring, IC_{50} 30 μM) compounds. The QR(S) ring analog having six-membered S ring and lacked an angular methyl group elicited lower biological activity (IC_{50} 240 μM) than that of the QRS ring system.

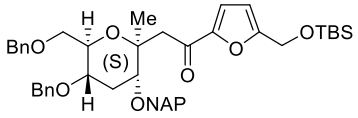
2. The LMNO ring system having the correct stereochemistry with MTX was synthesized via aldol reaction of the NO ring and LM ring fragments. Contrary to expectations, there were little differences between activity of natural- and non-natural enantiomers of the LMNO ring system, suggesting that stereochemistry may not be important for molecular recognition of hydrophilic region.

3. First synthesis of border part between hydrophobic and hydrophilic regions corresponding to the NOPQR(S) ring was completed. Although it was surprising that this synthetic compound elicited no inhibition.

4. Decacyclic framework of the WXYZA'B'C'D'E'F' ring system was constructed by α-cyano ether protocol developed in our laboratory. Although construction of the A' ring was not an easy task as expected, radical reduction of mixed-thioacetal successfully afforded desired compound.

Experimental Section

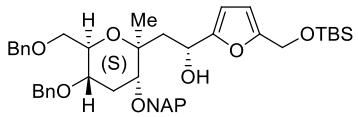
General methods for organic synthesis. All reactions sensitive to air or moisture were performed under argon atmosphere with dry glassware unless otherwise noted in particular. The dehydrated solvents, CH_2Cl_2, tetrahydrofuran (THF), toluene, *N*,*N*-dimethylformamide (DMF), Et_2O, benzene and MeOH were used without further dehydration. BnBr, $BF_3{\cdot}OEt_2$, TBSOTf, 2,6-lutidine, TBDPSCl, TMSOTf, TMSCN, Ac_2O, DBU and $BH_3{\cdot}SMe_2$ were distilled before using. Molecular sieves (MS4A and MS3A) were preactivated by heating *in vacuo*. All other chemicals were obtained from local venders and used as supplied unless otherwise stated. Thin-layer chromatography (TLC) was performed using precoated TLC glass plates (silica gel 60 F_{254}, 0.25 mm thickness) for the reaction analyses. Silica gel was used for column chromatography (spherical, neutral, 100–210 μm) or for flash chromatography (40–50 μm). Optical rotations were recorded on a polarimeter. IR spectra were recorded on a FT/IR equipment. ^{1}H NMR spectra were recorded at 600 or 400 MHz, and ^{13}C NMR spectra were recorded at 150 or 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane (TMS) with reference to internal residual solvent [^{1}H NMR: $CHCl_3$ (7.26), CD_2HOD (3.31), C_6HD_6 (7.16), CD_3COCD_2H (2.05), CD_2HCN (1.94); ^{13}C NMR: $CDCl_3$ (77.16), CD_3OD (48.94), C_6D_6 (128.06), $(CD_3)_2CO$ (29.84), CD_3CN (1.32). The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet. High resolution mass spectra (HRMS) were recorded on ESI-TOF or APCI-TOF equipment.



9

Ketone (9). *s*-BuLi (1.05 M in cyclohexane, *n*-hexane, 23.2 mL, 24.4 mmol) was added to a solution of furan **8** (7.78 g, 36.6 mmol) in THF (124 mL) at −78 °C. After the resultant mixture was stirred at −78 °C for 30 min, a cold (−78 °C) solution of Weinreb amide **7** (4.75 g, 8.14 mmol) in THF (27.6 mL) was added via cannula. After stirring at −78 °C for 1 h, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20/1 → 7/1) to give ketone **9** (3.87 g, 5.27 mmol, 65%) as a pale yellow oil.

R_f = 0.35 (hexane/EtOAc = 4/1); $[\alpha]_D^{22}$ +4.86 (*c* 0.28, $CHCl_3$); IR (neat) 2952, 2929, 2857, 1661, 1519, 1455, 1362, 1345, 1254, 1213, 1205, 1085, 1073, 1027, 1017, 837, 815, 785, 748, 697, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84–7.80 (m, 3H), 7.75 (s, 1H), 7.50–7.45 (m, 3H), 7.32–7.19 (m, 10H), 7.11 (d, *J* = 3.4 Hz, 1H), 6.26 (d, *J* = 3.4 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.57 (d, *J* = 14.8 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.37 (*J* = 13.7 Hz, 1H), 4.34 (*J* = 13.7 Hz, 1H), 3.72 (dd, *J* = 12.1, 4.8 Hz, 1H), 3.62−3.59 (m, 1H), 3.57–3.54 (m, 2H), 3.37 (ddd, *J* = 11.3, 10.0, 4.8 Hz, 1H), 3.16 (d, *J* = 12.7 Hz, 1H), 2.89 (d, *J* = 12.7 Hz, 1H), 2.47 (ddd, *J* = 11.8, 4.8, 4.8 Hz, 1H), 1.59 (ddd, *J* = 12.1, 11.8, 11.3 Hz, 1H), 1.40 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.1, 159.6, 153.4, 138.8, 138.2, 136.2, 133.4, 133.1, 128.5 (2C), 128.4 (2C), 128.14, 128.06, 127.9 (2C), 127.8 (2C), 127.7 (2C), 127.5, 126.3, 126.2, 125.9 (2C), 120.0, 108.9, 77.0, 76.8, 73.6 (2C), 72.7, 71.34, 71.25, 70.1, 58.7, 47.8, 30.6, 25.9 (3C), 18.5, 16.7, −5.2 (2C); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{45}H_{54}O_7SiNa$ 757.3531, found 757.3536.

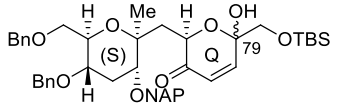


6

Alcohol (6). TBAC (601 mg, 2.16 mmol), sodium formate (34.1 g, 501 mmol), Noyori's (*R*,*R*)-cat **10** (434 mg, 723 μmol) were added to a solution of ketone **9** (5.29 g, 7.20 mmol) in CH_2Cl_2/H_2O (1:1, v/v, 72.0 mL) at room temperature. After stirring at 40 °C for 4 h,

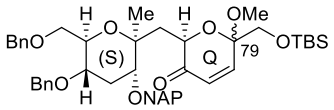
the reaction mixture was cooled to room temperature and Noyori's (*R*,*R*)-cat **10** (217 mg, 362 μmol) was added. After stirring at 40 °C for 14.3 h, the reaction mixture was cooled to room temperature and Noyori's (*R*,*R*)-cat **10** (215 mg, 358 μmol) was added. After stirring at 40 °C for 3.7 h, the reaction mixture was diluted with H_2O, extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1 → 5/1) to give alcohol **6** (4.09 g, 5.55 mmol, 77%) as a colorless oil with a recovery of ketone **9** (1.04 g, 1.41 mmol, 20%).

R_f = 0.35 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ +33.8 (*c* 0.33, $CHCl_3$); IR (neat) 3475, 2949, 2927, 2880, 2856, 1454, 1362, 1254, 1216, 1070, 1016, 948, 835, 815, 778, 748, 697, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85–7.81 (m, 3H), 7.75 (s, 1H), 7.50–7.45 (m, 3H), 7.32−7.20 (m, 10H), 7.11 (d, *J* = 3.5 Hz, 1H), 6.26 (d, *J* = 3.5 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 7.6 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 2H), 4.35 (d, *J* = 11.7 Hz, 1H), 3.73 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.62–3.59 (m, 1H), 3.57–3.54 (m, 2H), 3.38 (m, 1H), 3.17 (d, *J* = 12.7 Hz, 1H), 2.89 (d, *J* = 12.7 Hz, 1H), 2.48 (ddd, *J* = 11.6, 4.8, 4.8 Hz, 1H), 3.07 (d, *J* = 4.1 Hz, 1H), 2.77 (brs, 1H), 2.55 (ddd, *J* = 11.6, 4.8, 4.8 Hz, 1H), 1.99 (m, 2H), 1.64 (ddd, *J* = 11.7, 11.7, 11.6 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H), 1.20 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 153.4, 138.3, 138.0, 135.7, 133.3, 133.1, 128.6 (2C), 128.5 (2C), 128.3, 128.01, 127.96 (3C), 127.91 (2C), 127.84, 127.7, 126.5, 126.3, 126.1, 125.8, 108.0, 106.1, 79.8, 78.1, 73.6, 72.8, 72.6, 71.8, 71.3, 69.9, 65.5, 58.5, 45.3, 30.5, 26.0 (3C), 18.5, 14.6, −5.0 (2C); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{45}H_{56}O_7SiNa$ 759.3688, found 759.3696.



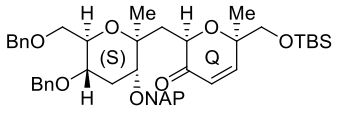
11

Heimiacetal (11). NaOAc (214 mg, 2.61 mmol), $NaHCO_3$ (437 mg, 5.20 mmol) and NBS (460 mg, 2.58 mmol) were added to a solution of alcohol **6** (1.90 g, 2.58 mmol) in THF/H_2O (4:1, v/v, 32.3 mL) at 0 °C. After stirring at 0 °C for 85 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual crude pyranone **11** was immediately used in the next reaction without further purification.



12

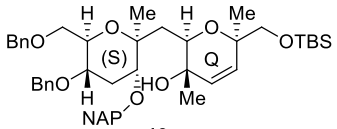
Methylacetal (12). $(MeO)_3CH$ (3.39 mL, 31.0 mmol) and $BF_3 \cdot OEt_2$ (478 μL, 3.87 mmol) were added to a solution of the above crude hemiacetal **11** in Et_2O (25.8 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with Et_3N and saturated aqueous solution of $NaHCO_3$. The resultant mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1 → 13/1) to give methylacetal **12** (1.83 g, 2.39 mmol, 93% for two steps, diastereomixture) as a pale yellow syrup.
R_f = 0.6 (hexane/EtOAc = 3/1); IR (neat) 2951, 2928, 2880, 2856, 1693, 1496, 1470, 1454, 1386, 1361, 1254, 1208, 1170, 1122, 1101, 1089, 1072, 1053, 889, 836, 780, 743, 697, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84–7.79 (m, 3H), 7.77 (s, 0.29H), 7.74 (s, 0.71H), 7.50–7.45 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.32–7.23 (m, 8H), 7.21 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.96 (d, *J* = 10.8 Hz, 0.71H), 6.73 (d, *J* = 10.8 Hz, 0.29H), 6.31 (d, *J* = 10.8 Hz, 0.29H), 6.08 (d, *J* = 10.8 Hz, 0.71H), 4.95 (dd, *J* = 8.4, 1.8 Hz, 0.29H), 4.86 (dd, *J* = 8.4, 1.8 Hz, 0.71H), 4.78 (d, *J* = 11.4 Hz, 0.29H), 4.76 (d, *J* = 12.0 Hz, 0.71H), 4.73 (d, *J* = 11.4 Hz, 0.29H), 4.65 (d, *J* = 12.0 Hz, 0.71H), 4.58 (d, *J* = 11.4 Hz, 0.71H), 4.58 (d, *J* = 11.4 Hz, 0.29H), 4.55 (d, *J* = 11.4 Hz, 1.29H), 4.50 (d, *J* = 11.4 Hz, 0.71H), 4.41 (d, *J* = 11.4 Hz, 0.71H), 4.39 (d, *J* = 11.4 Hz, 0.29H), 3.88 (d, *J* = 10.8 Hz, 0.29H), 3.85 (d, *J* = 10.8 Hz, 0.71H), 3.77 (d, *J* = 12.0, 4.2 Hz, 0.29H), 3.75 (d, *J* = 10.8 Hz, 0.29H), 3.72–3.67 (m, 1.42H), 3.67−3.63 (m, 2H), 3.57 (dd, *J* = 10.8, 5.4 Hz, 0.29H), 3.46 (d, *J* = 11.4 Hz, 0.71H), 3.44–3.39 (m, 0.71H), 3.37–3.29 (m, 0.29H), 3.27 (s, 2.13H), 3.21 (s, 0.87H), 2.57 (dd, *J* = 15.0, 3.0 Hz, 0.71H), 2.53–2.47 (m, 1.29H), 2.11 (dd, *J* = 15.0, 8.4 Hz, 0.29H), 1.94 (dd, *J* = 15.0, 8.4 Hz, 0.71H), 1.65–1.57 (m, 1H), 1.31 (s, 0.87H), 1.29 (s, 2.13H), 0.88 (s, 6.39H), 0.84 (s, 2.61H), 0.04 (s, 2.13H), 0.03 (s, 2.13H), 0.01(s, 0.87H), 0.01 (s, 0.87H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 147.6, 145.4, 138.6, 138.3, 136.3, 133.4, 133.1, 131.3, 128.5 (2C), 128.4 (2C), 128.2, 128.0, 127.9 (2C), 127.83 (2C), 127.80 (2C), 127.7, 127.6, 127.5, 126.9, 126.2, 126.1, 126.0, 125.8, 125.7, 96.2, 78.1, 75.3, 75.1, 75.0, 73.5, 73.4, 73.2, 72.8, 71.8, 71.6, 71.3, 71.2, 71.1, 70.2, 69.9, 67.2, 63.3, 50.6, 50.3, 40.2, 39.3, 30.9, 30.8, 26.0, 25.9 (3C), 18.4, 17.5, 17.1, −5.26, −5.31, −5.4; HRMS (APCI-TOF) *m/z* $[M + H]^+$ calcd for $C_{46}H_{59}O_8Si$ 767.3974, found 767.3994.



5

Enone (5). Me_2Zn (1.05 M in *n*-hexane, 37.0 mL, 38.9 mmol) followed by $BF_3{\cdot}OEt_2$ (9.60 mL, 77.8 mmol) was added to a solution of methylacetal **12** (5.95 g, 7.76 mmol) in CH_2Cl_2 (49.2 mL) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with a mixed solution of pH 7 buffer/Et_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NH_4Cl, $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1 → 13/1) to give enone **5** (4.71 g, 6.27 mmol, 81%) as a colorless syrup.

R_f = 0.4 (hexane/EtOAc = 4/1); $[\alpha]_D^{24}$ +66.4 (*c* 0.39, $CHCl_3$); IR (neat) 2952, 2929, 2857, 1691, 1470, 1455, 1387, 1362, 1334, 1253, 1216, 1106, 1087, 849, 837, 816, 776, 749, 697, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.83–7.80 (m, 3H), 7.75 (s, 1H), 7.49–7.44 (m, 3H), 7.33–7.24 (m, 10H), 6.95 (d, *J* = 10.3 Hz, 1H), 6.02 (d, *J* = 10.3 Hz, 1H), 4.77 (d, *J* = 4.8 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.74–3.67 (m, 3H), 3.51–3.44 (m, 3H), 2.55–2.51 (m, 2H), 2.00 (dd, *J* = 15.1, 8.2 Hz, 1H), 1.66–1.61 (m, 1H), 1.30 (s, 3H), 1.30 (s, 3H), 0.87 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 152.4, 138.9, 138.4, 136.5, 133.4, 133.0, 128.5 (2C), 128.4 (2C), 128.1, 128.0, 127.83 (2C), 127.81, 127.79, 127.6, 127.4, 126.2, 126.0, 125.9, 125.8, 125.3, 77.6, 75.9, 75.0, 73.4, 73.31, 73.25, 71.7, 71.6, 71.3, 69.9, 38.6, 30.9, 25.9 (3C), 18.3, 18.2, 17.6, −5.37, −5.41 (a signal of ethereal region is overlapped with solvent); HRMS (APCI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{46}H_{59}O_7Si$ 751.4025, found 751.4053.

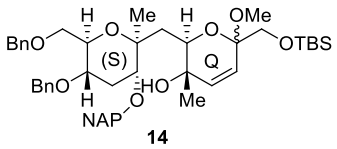


13

Allylalcohol (13). Me_3Al (1.09 M in *n*-hexane, 2.8 mL, 3.05 mmol) and $BF_3{\cdot}OEt_2$ (190 μL, 1.54 mmol) was slowly added to a solution of dihydropyranone **12** (117 mg, 152 μmol) in CH_2Cl_2 (1.5 mL) at −20 °C. After stirring at −20 °C for 35 min, the reaction mixture was quenched with Et_3N and MeOH and diluted with EtOAc. After addition of saturated aqueous Rochelle's salt, the resultant suspension was stirred vigorously at room

temperature. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 → 5/1) to give allylalcohol **13** (112 mg, 145 μmol, 96%) as a pale yellow syrup.

R_f = 0.20 (hexane/EtOAc = 4/1); $[\alpha]_D^{23}$ +52.6 (*c* 1.12, $CHCl_3$); IR (neat) 3458, 3061, 3029, 2952, 2928, 2856, 1455, 1361, 1253, 1091, 838, 816, 741, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86–7.80 (m, 3H), 7.77 (s, 1H), 7.50–7.44 (m, 3H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.31–7.24 (m, 4H), 7.21 (d, *J* = 7.2 Hz, 2H), 5.73 (d, *J* = 10.2 Hz, 1H), 5.62 (d, *J* = 10.2 Hz, 1H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.00–3.95 (m, 2H), 3.79 (brs, 1H), 3.72 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.67–3.56 (m, 3H), 3.44 (d, *J* = 9.0 Hz, 1H), 3.40 (d, *J* = 9.0 Hz, 1H), 2.55 (dt, *J* = 11.4, 4.8 Hz, 1H), 2.15 (dd, *J* = 15.0, 3.6 Hz, 1H), 2.00 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.64 (q, *J* = 11.4 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.2, 136.3, 134.5, 133.4, 133.1, 130.1, 128.5 (2C), 128.4 (2C), 128.2, 128.1 (2C), 128.0, 127.90 (2C), 127.87, 127.8, 127.7, 126.2, 126.1, 125.9, 125.8, 76.33, 76.30, 75.7, 73.5, 73.0, 72.5, 71.92, 71.88, 71.4, 71.1, 69.1, 68.6, 40.3, 30.8, 26.0 (3C), 22.2, 20.9, 18.4, 18.4, −5.3 (2C); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{47}H_{62}O_7SiNa$ 789.4157, found 789.4144.

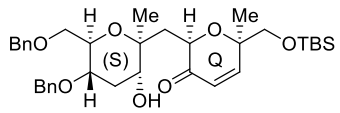


14

Allylalcohol (14). Me_3Al (1.07 M in *n*-hexane, 350 μL, 375 μmol) was added to a solution of dihydropyranone **12** (56.5 mg, 73.7 μmol) in CH_2Cl_2 (740 μL) at −20 °C. After stirring at −20 °C for 50 min, the reaction mixture was quenched with MeOH and diluted with EtOAc. After addition of saturated aqueous Rochelle salt, the resultant suspension was stirred vigorously at 0 °C. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1) to give allylalcohol **14** (46.9 mg, 59.9 μmol, 81%, diastereomixture) as a colorless oil.

R_f = 0.43 (hexane/EtOAc = 4/1); IR (neat) 3446, 3062, 3029, 2928, 2856, 1456, 1362, 1253, 1100, 838, 817, 741, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85–7.80 (m, 3H),

7.77 (s, 1H), 7.50–7.43 (m, 3H), 7.38–7.32 (m, 4H), 7.31–7.24 (m, 4H), 7.19 (d, *J* = 5.4 Hz, 0.32H),7.18 (d, *J* = 6.0 Hz, 1.68H), 6.10 (d, *J* = 10.2 Hz, 0.16H), 5.89 (d, *J* = 10.2 Hz, 0.84H), 5.74 (d, *J* = 10.2 Hz, 0.84H), 5.58 (d, *J* = 10.2 Hz, 0.16H), 4.81 (d, *J* = 11.4 Hz, 0.84H), 4.80 (d, *J* = 11.4 Hz, 0.16H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 0.16H), 4.49 (d, *J* = 12.0 Hz, 0.84H), 4.37 (d, *J* = 12.0 Hz, 0.16H), 4.35 (d, *J* = 12.0 Hz, 0.84H), 4.25 (brs, 1H), 4.17 (dd, *J* = 9.6, 3.6 Hz, 0.84H), 4.09 (dd, *J* = 7.8, 4.2 Hz, 0.16H), 3.98 (dd, *J* = 11.4, 4.2 Hz, 0.84H), 3.93 (dd, *J* = 12.0, 4.2 Hz, 0.16H), 3.71 (t, *J* = 10.8 Hz, 2H), 3.66–3.59 (m, 2.16H), 3.66–3.59 (m, 2.16H), 3.56 (d, *J* = 9.6 Hz, 1H), 3.36 (d, *J* = 10.2 Hz, 0.84H), 3.23 (s, 0.48H), 3.14 (s, 2.52H), 2.56−2.51 (m, 1H), 2.23 (dd, *J* = 15.0, 3.6 Hz, 0.16H), 2.19 (dd, *J* = 15.0, 3.6 Hz, 0.84H), 2.03 (dd, *J* = 15.0, 9.6 Hz, 1H), 1.65–1.58 (m, 1H), 1.35 (s, 2.52H), 1.32 (s, 0.48H), 1.31 (s, 0.48H), 1.21 (s, 2.52H), 0.88 (s, 7.56H), 0.80 (s, 1.44H), 0.04 (s, 5.04H), −0.07 (s, 0.48H), −0.09 (s, 0.48H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.2, 138.0, 136.3, 133.4, 133.0, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1, 128.0, 127.93 (2C), 127.89, 127.8 (2C), 126.2, 125.9, 125.8, 125.6, 125.5, 125.1, 97.4, 76.5, 75.0, 73.6, 73.1, 72.2, 71.7, 71.5, 71.3, 68.7, 65.2, 49.8, 40.5, 30.6, 26.1 (3C), 26.0, 21.4, 18.5, 18.4, 18.3, −5.26, −5.33; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{47}H_{62}O_8SiNa$ 805.4112, found 805.4109.

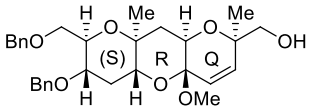


15

Alcohol (15). DDQ (2.17 g, 9.56 mmol) was added to a solution of naphthylmethyl ether **5** (4.66 g, 6.20 mmol) in CH_2Cl_2/pH 7 phosphate buffer (4:1, v/v, 62.5 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 9/1 → 4/1) to give alcohol **15** (3.37 g, 5.52 mmol, 89%) as a colorless syrup.

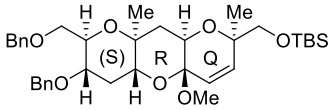
R_f = 0.2 (hexane/EtOAc = 4/1); $[\alpha]_D^{22}$ +62.0 (*c* 0.30, $CHCl_3$); IR (neat) 3516, 2952, 2929, 2900, 2882, 1692, 1471, 1462, 1454, 1388, 1362, 1252, 1218, 1101, 1089, 1062, 1028, 837, 778, 751, 736, 697, 667 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.23 (m,10H), 6.90 (d, *J* = 10.3 Hz, 1H), 6.04 (d, *J* = 10.3 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.53 (m, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 3.72–

3.63 (m, 4H), 3.56 (d, J = 9.7 Hz, 1H), 3.54 (d, J = 9.7 Hz, 1H), 3.49 (ddd, J = 11.0, 10.0, 5.5 Hz, 1H), 2.75 (d, J = 4.8 Hz, 1H), 2.52 (d, J = 15.8 Hz, 1H), 2.33 (ddd, J = 11.7, 4.8, 4.5 Hz, 1H), 1.80 (dd, J = 15.1, 8.9 Hz, 1H), 1.70 (q, J = 11.7 Hz, 1H), 1.34 (s, 3H), 1.23 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6, 151.9, 139.0, 138.4, 128.5 (2C), 128.4 (2C), 127.9 (2C), 127.8, 127.5 (2C), 127.4, 125.7, 76.1, 75.8, 73.63, 73.55, 73.3, 71.6, 71.2, 69.9, 69.7, 68.9, 39.2, 32.5, 25.9 (3C), 18.4, 17.9, 16.7, −5.30, −5.34; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{35}H_{50}O_7SiNa$ 633.3218, found 633.3225.



16

Alcohol (16). $(MeO)_3CH$ (1.5 mL, 13.7 mmol) and CSA (952 mg, 4.10 mmol) were added to a solution of hydroxyketone **15** (3.37 g, 5.52 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 110 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was used in the next reaction without further purification.

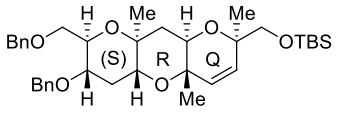


17

Methylacetal (17). Imidazole (1.21 g, 17.8 mmol) and TBSCl (1.23 g, 8.16 mmol) were added to a solution of the above crude alcohol **16** in DMF (27.0 mL) at 0 °C. After stirring at room temperature for 85 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1 → 10/1) to give olefin **17** (3.47 g, 5.55 mmol, quant for two steps) as a cloudy viscous syrup.

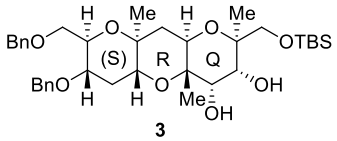
R_f = 0.53 (hexane/EtOAc = 3/1); $[\alpha]_D^{24}$ +83.4 (c 0.27, $CHCl_3$); IR (neat) 2952, 2929, 2905, 2883, 2857, 1470, 1463, 1455, 1372, 1362, 1278, 1196, 1158, 1092, 1059, 1027, 849, 836, 815, 774, 750, 735, 696, 667 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.19 (m, 10H), 5.97 (d, J = 10.3 Hz, 1H), 5.94 (d, J = 10.3 Hz, 1H), 4.64 (d, J = 12.4 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 4.41 (d, J = 12.4 Hz, 1H), 3.74–3.68 (m, 4H), 3.65 (dd, J = 12.6, 4.1 Hz, 1H), 3.57 (ddd, J = 11.0, 10.0, 4.6 Hz, 1H), 3.51 (d,

J = 9.6 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 2.26 (ddd, J = 11.7, 4.6, 4.1 Hz, 1H), 1.98 (dd, J = 12.4, 11.3 Hz, 1H), 1.84 (dd, J = 11.3, 4.1 Hz, 1H), 1.65 (q, J = 12.0 Hz, 1H), 1.31 (s, 3H), 1.28 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 138.2, 137.4, 128.5 (2C), 128.4 (2C), 127.90 (2C), 127.86, 127.8 (2C), 127.6, 126.0, 93.4, 77.8, 73.9, 73.4, 72.8, 71.3, 71.2, 70.8, 69.8, 69.6, 49.0, 38.5, 30.0, 26.0 (3C), 20.6, 18.4, 15.5, −5.26, −5.33 (a signal of ethereal region is overlapped with solvent); HRMS (APCI-TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{53}O_7Si$ 625.3555, found 625.3550.



4

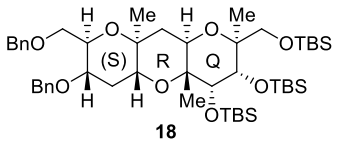
Olefin (4). Me_3Al (1.07 M in *n*-hexane, 1.43 mL, 1.53 mmol) and $BF_3{\cdot}OEt_2$ (94.2 μL, 763 μmol) were added to a solution of olefin **17** (191 mg, 305 μmol) in CH_2Cl_2 (1.53 mL) at −20 °C. After being stirred at −20 °C for 30 min, the reaction mixture was quenched with a mixed solution of saturated aqueous $NaHCO_3$ and Et_2O, diluted with EtOAc. After addition of saturated aqueous Rochelle salt, the suspension was stirred vigorously at 0 °C and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1 → 13/1) to give olefin **4** (143 mg, 235 μmol, 77%) as a colorless syrup.
R_f = 0.33 (hexane/EtOAc = 5/1); $[\alpha]_D^{22}$ +83.9 (*c* 0.25, $CHCl_3$); IR (neat) 2952, 2928, 2902, 2883, 2857, 1463, 1455, 1382, 1362, 1274, 1253, 1219, 1205, 1155, 1097, 1060, 1028, 986, 836, 813, 776, 749, 734, 696, 667 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.19 (m, 10H), 5.97 (d, J = 10.3 Hz, 1H), 5.52 (d, J = 10.3 Hz, 1H), 4.63 (d, J = 12.5 Hz, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.56 (d, J = 12.5 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 3.75–3.64 (m, 4H), 3.55 (ddd, J = 10.8, 10.3, 5.0 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.47 (d, J = 9.6 Hz, 1H), 3.44 (dd, J = 12.5, 3.8 Hz, 1H), 2.23 (ddd, J = 11.4, 5.0, 3.8 Hz, 1H), 1.89 (dd, J = 12.0, 4.1 Hz, 1H), 1.74 (dd, J = 12.9, 12.0 Hz, 1H), 1.61 (q, J = 12.0 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 134.4, 130.8, 128.54 (2C), 128.46 (2C), 128.0 (2C), 127.90 (2C), 127.87, 127.7, 78.8, 74.2, 73.7, 73.6, 73.5, 72.7, 71.7, 71.1, 71.0, 70.4, 69.9, 39.4, 30.5, 26.1 (3C), 21.2, 18.5, 17.4, 16.0, −5.22, −5.24; HRMS (APCI-TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{53}O_6Si$ 609.3606, found 609.3617.



3

1,2-*syn* Diol (3). NMO (4.48 g, 38.2 mmol), citric acid monohydrate (8.04 g, 38.3 mmol) and OsO_4 (179 mg, 704 μmol) were added to a solution of olefin **4** (2.31 g, 3.79 mmol) in acetone (11.0 mL), *t*-BuOH (24.0 mL) and H_2O (2.40 mL) at 0 °C. After stirring at room temperature for 22 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 13/1 → 4/1) to give diol **3** (2.21 g, 3.44 mmol, 91%) as a colorless oil.

R_f = 0.20 (hexane/EtOAc = 2/1); $[\alpha]_D^{22}$ +73.9 (*c* 1.01, $CHCl_3$); IR (neat) 3450, 2952, 2928, 2883, 2857, 1496, 1470, 1462, 1455. 1409, 1386, 1362, 1353, 1333, 1253, 1219, 1095, 1064, 1046, 1029, 1004, 991, 983, 938, 924, 903, 871, 837, 817, 774, 752, 737, 697, 668 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.30–7.02 (m, 10H), 4.50 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 12.4 Hz, 1H), 4.27 (d, *J* = 11.7 Hz, 1H), 4.15 (dd, *J* = 10.3, 4.1 Hz, 1H), 4.12 (dd, *J* = 13.0, 4.8 Hz, 1H), 3.86 (d, *J* = 3.8 Hz, 1H), 3.81–3.79 (m, 1H), 3.77 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.70 (d, *J* = 10.3 Hz, 1H), 3.66–3.61 (m, 1H), 3.65 (d, *J* = 10.3 Hz, 1H), 3.49 (d, *J* = 10.3 Hz, 1H), 3.46 (dd, *J* = 12.4, 3.4 Hz, 1H), 2.52 (brs, 1H), 2.31 (brs, 1H), 2.13 (ddd, *J* = 11.0, 4.5, 3.5 Hz, 1H), 2.02 (dd, *J* = 11.6, 4.1 Hz, 1H), 1.86 (dd, *J* = 12.4, 11.7 Hz, 1H), 1.57 (ddd, *J* = 11.7, 11.7, 11.0 Hz, 1H), 1.26 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.97 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, 139.1, 128.6 (2C), 128.5 (2C), 128.3, 127.6, 79.4, 76.6, 75.7, 73.81, 73.75, 73.7, 73.4, 71.1, 70.9, 70.4, 69.2, 67.0, 63.7, 39.5, 30.8, 26.2 (3C), 18.7, 16.1, 15.5, 13.8, −4.9, −5.2 (signals of aromatic region are overlapped with solvent); HRMS (APCI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{55}O_8Si$ 643.3661, found 643.3643.

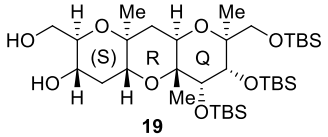


18

BisTBS ether (18). 2,6-Lutidine (1.07 mL, 9.22 mmol) and TBSOTf (1.06 mL, 4.61 mmol) were added to a solution of diol **3** (296 mg, 461 μmol) in CH_2Cl_2 (3.00 mL) at 0 °C. After stirring at 40 °C for 15 h, the reaction mixture was diluted with Et_2O, quenched

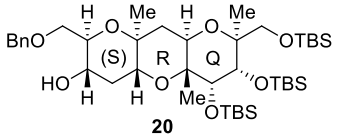
with saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with water and saturated aqueous solution of $KHSO_4$, $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 50/1 → 30/1) to give bisTBS ether **18** (373 mg, 427 μmol, 93%) as a colorless oil.

R_f = 0.60 (hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ +36.1 (*c* 0.24, $CHCl_3$); IR (neat) 2952, 2928, 2894, 2883, 2856, 1471, 1463, 1385, 1361, 1251, 1217, 1094, 1060, 987, 889, 867, 835, 809, 774, 753, 734, 696, 678, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.18 (m, 10H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 12.4 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 4.08 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.80 (d, *J* = 2.4 Hz, 1H), 3.73–3.71 (m, 1H), 3.68–3.64 (m, 2H), 3.53 (ddd *J* = 10.9, 10.3, 5.5 Hz, 1H), 3.46 (d, *J* = 10.7 Hz, 1H), 3.46–3.43 (m, 1H), 3.22 (d, *J* = 10.7 Hz, 1H), 2.18 (ddd, *J* = 11.7, 4.5, 4.1 Hz, 1H), 1.81 (dd, *J* = 11.0, 3.5 Hz, 1H), 1.67–1.58 (m, 2H), 1.32 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 128.52 (2C), 128.45 (2C), 128.1 (2C), 127.9 (2C), 127.8, 127.7, 79.3, 78.8, 74.1, 73.8, 73.6, 72.6, 71.1, 70.4, 70.0, 67.6 (2C), 63.7, 39.1, 30.3, 26.54 (3C), 26.46 (3C), 26.2 (3C), 18.8, 18.7, 18.4, 16.1, 16.0, 14.6, −2.3, −2.4, −4.5 (2C), −4.7, −5.2 (a signal of ethereal region is overlapped with solvent); HRMS (APCI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{48}H_{83}O_8Si_3$ 871.5390, found 871.5421.



19

Diol (19). $Pd(OH)_2/C$ (20% Pd, 13.4 mg, 25.2 μmol) was added to a solution of dibenzylether **18** (89.6 mg, 103 μmol) in EtOAc (1.3 mL) at room temperature. After stirring at room temperature for 100 min under H_2 atmosphere, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude was used for next reaction without further purification.

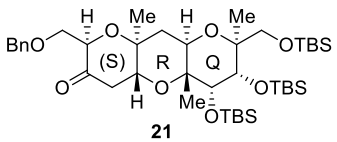


20

Monobenzyl ether (20). *n*-Bu_2SnO (266 mg, 1.07 mmol), TBAI (375 mg, 1.02 mmol) and BnBr (170 μL, 1.43 mmol) were added to a mixture of the above crude diol **19** and

powdered MS4A (142 mg) in benzene (1.5 mL) at room temperature. After stirring under reflux for 5 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1) to give monobenzyl ether **20** (70.7 mg, 90.5 μmol, 88% for two steps) as a pale yellow oil.

R_f = 0.3 (hexane/EtOAc = 5/1); $[\alpha]_D^{21}$ +8.25 (*c* 0.33, $CHCl_3$); IR (neat) 3448, 2952, 2932, 2883, 2857, 1472, 1463, 1385, 1362, 1253, 1219, 1133, 1112, 1097, 1063, 1045, 892, 868, 837, 809, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.11 (d, *J* = 3.1 Hz, 1H), 4.07 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.79 (d, *J* = 3.1 Hz, 1H), 3.73–3.69 (m, 3H), 3.53 (d, *J* = 7.6, 5.5 Hz, 1H), 3.45 (d, *J* = 9.6 Hz, 1H), 3.45 (m, 1H), 3.21 (d, *J* = 11.0 Hz, 1H), 3.12 (brs, 1H), 2.00 (ddd, *J* = 12.4, 3.4, 3.4 Hz, 1H), 1.74 (dd, *J* = 11.0, 4.1 Hz, 1H), 1.67 (ddd, *J* = 11.7, 11.3, 11.3 Hz, 1H), 1.50 (dd, *J* = 12.4, 11.7 Hz, 1H), 1.32 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5, 128.7 (2C), 128.2, 128.1 (2C), 79.3, 78.7, 76.9, 74.2, 74.0, 73.3, 71.34, 71.29, 70.2, 67.6, 67.5, 63.6, 39.0, 32.6, 26.5 (3C), 26.4 (3C), 26.2 (3C), 18.7, 18.6, 18.4, 16.1, 16.0, 14.4, −2.3, −2.4, −4.5 (2C), −4.7, −5.2; HRMS (APCI-TOF) *m/z* $[M + H]^+$ calcd for $C_{41}H_{77}O_8Si_3$ 781.4921, found 781.4955.

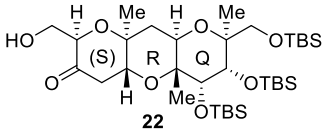


21

Ketone (21). Pyridine (72.0 μL, 894 μmol) and Dess−Martin periodinane (382 mg, 901 μmol) were added to a solution of secondary alcohol **20** (280 mg, 359 μmol) in CH_2Cl_2 (3.59 mL) at 0 °C. After stirring at room temperature for 20 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 50/1 → 30/1) to give ketone **21** (252 mg, 323 μmol, 90%) as a colorless amorphous solid.

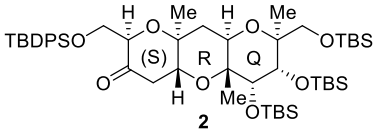
R_f = 0.43 (hexane/EtOAc = 3/1); $[\alpha]_D^{24}$ +16.4 (*c* 0.45, $CHCl_3$); IR (neat) 2954, 2930, 2896, 2885, 2857, 1726, 1472, 1463, 1383, 1361, 1253, 1134, 1103, 1082, 1063, 867, 837, 809 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.17 (brs, 1H), 4.13 (d, *J* = 2.7 Hz, 1H), 4.08 (dd, *J* = 12.8, 4.1 Hz, 1H), 4.05 (dd, *J* = 12.4, 5.9 Hz, 1H), 3.84 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.81 (d, *J* = 2.7 Hz,

1H), 3.75 (dd, J = 10.3, 2.8 Hz, 1H), 3.47 (d, J = 11.0 Hz, 1H), 3.24 (d, J = 11.0 Hz, 1H), 2.64 (dd, J = 18.5, 5.9 Hz, 1H), 2.43 (dd, J = 18.5, 12.4 Hz, 1H), 1.91 (dd, J = 12.0, 4.1 Hz, 1H), 1.74 (dd, J = 12.8, 12.0 Hz, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 138.2, 128.5 (2C), 127.7, 127.6 (2C), 79.4, 78.6 (2C), 76.7, 73.7 (2C), 71.1, 68.6, 67.6 (2C), 63.4, 41.1, 38.6, 26.6 (3C), 26.4 (3C), 26.2 (3C), 18.8, 18.6, 18.4, 16.2, 16.0, 14.3, −2.2, −2.4, −4.3, −4.5, −4.6, −5.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{41}H_{74}O_8Si_3Na$ 801.4584, found 801.4581.



22

Alcohol (22). $Pd(OH)_2/C$ (20% Pd, 14.8 mg, 27.8 μmol) was added to a solution of benzylether **21** (254 mg, 326 μmol) in EtOAc (3.26 mL) at room temperature. After stirring at room temperature for 50 min under H_2 atmosphere, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude was used for the next reaction without further purification.

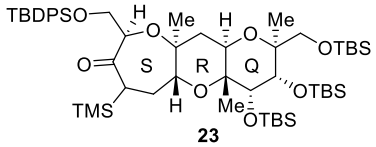


2

TBDPS ether (2). Imidazole (121 mg, 1.78 mmol) and TBDPSCl (210 μL, 810 μmol) were added to a solution of the above crude alcohol **22** in DMF (3.0 mL) at 0 °C. After stirring at room temperature for 1.5 h, the reaction mixture was quenched with saturated aqueous of NH_4Cl and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 100/1 → 75/1) to give TBDPS ether **2** (288 mg, 310 μmol, 95% for two steps) as a colorless amorphous solid.

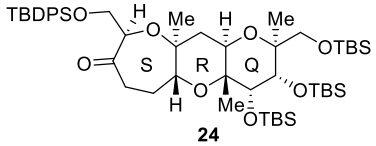
R_f = 0.6 (hexane/EtOAc = 6/1); $[\alpha]_D^{22}$ +39.5 (c 0.71, $CHCl_3$); IR (neat) 2953, 2929, 2893, 2885, 2857, 1726, 1472, 1463, 1428, 1387, 1383, 1362, 1273, 1253, 1133, 1112, 1105, 1084, 1063, 891, 867, 837, 809, 775, 741, 708, 702, 670 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.43–7.37 (m, 6H), 4.25 (dd, J = 12.4, 6.9 Hz, 1H), 4.14 (d, J = 2.4 Hz, 1H), 4.11 (dd, J = 12.8, 4.8 Hz, 1H), 4.08−4.06 (m, 2H), 3.83 (d, J = 2.4 Hz, 1H), 3.82 (dd, J = 11.0, 2.1 Hz, 1H), 3.50 (d, J = 11.0 Hz, 1H), 3.27 (d, J = 11.0 Hz, 1H), 2.72 (dd, J = 19.2, 6.9 Hz, 1H), 2.51 (dd, J = 19.2, 12.4 Hz, 1H), 1.96 (dd, J = 11.9, 4.8 Hz, 1H), 1.84 (dd, J = 12.8, 11.9 Hz, 1H), 1.31 (s, 3H),

1.21 (s, 3H), 1.20 (s, 3H), 1.02 (s, 9H), 0.94 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.5, 135.8 (2C), 135.7 (2C), 133.3, 133.1, 129.9, 129.8, 127.9 (2C), 127.8 (2C), 79.9, 79.4, 78.6, 76.6, 73.4, 68.5, 67.7, 65.9, 63.3, 60.5, 41.1, 38.6, 26.8 (3C), 26.6 (3C), 26.4 (3C), 26.2 (3C), 19.4, 18.8, 18.6, 18.4, 16.6, 16.0, 14.4, 14.2, −2.2, −2.4, −4.3, −4.5, −4.6, −5.1; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{50}H_{86}O_8Si_4Na$ 949.5292, found 949.5274.



23

Seven-membered ketone (23). $TMSCHN_2$ (1.05 mL, 630 μmol) and a solution of $BF_3{\cdot}OEt_2$ (0.74 M in CH_2Cl_2, 310 μL, 229 μmol) were added to a mixture of ketone **2** (192 mg, 207 μmol) and powdered MS4A (969 mg) in CH_2Cl_2 (3.0 mL) at −78 °C. After stirring at −78 °C for 40 min, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

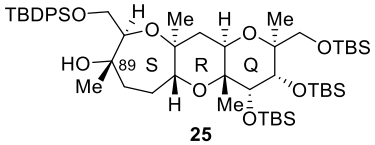


24

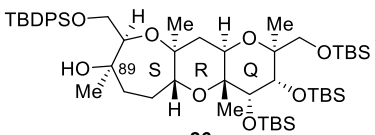
Seven-membered ketone (24). PPTS (69.4 mg, 276 μmol) was added to a solution of the above crude in CH_2Cl_2 (2.0 mL) and MeOH (2.0 mL) at 0 °C. After stirring at room temperature for 6 h, the reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 150/1) to give ketone **24** (101 mg, 107 μmol, 52% for two steps) as a colorless oil.

R_f = 0.63 (hexane/EtOAc = 30/1 x 2); $[\alpha]_D^{22}$ +56.3 (*c* 0.26, $CHCl_3$); IR (neat) 2952, 2929, 2886, 2856, 1714, 1472, 1462, 1252, 1219, 1109, 1100, 1081, 1066, 1049, 1008, 987, 887, 869, 835, 775, 761, 741, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.43–7.36 (m, 6H), 4.25 (dd, *J* = 12.4, 6.9 Hz, 1H), 4.14 (d, *J* = 2.4 Hz, 1H), 4.11 (dd, *J* = 12.4, 6.8 Hz, 1H), 4.08–4.06 (m, 2H), 3.82 (d, *J* = 2.4 Hz, 1H), 3.82 (dd, *J* = 11.7, 2.8 Hz, 1H), 3.49 (d, *J* = 10.8 Hz, 1H), 3.26 (d, *J* = 10.8 Hz, 1H),

2.71 (dd, J = 18.5, 6.2 Hz, 1H), 2.51 (dd, J = 18.5, 11.6 Hz, 1H), 1.96 (dd, J = 12.0, 4.1 Hz, 1H), 1.84 (dd, J = 12.4, 12.0 Hz, 1H), 1.30 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.01 (s, 9H), 0.93 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 216.3, 136.0 (2C), 135.8 (2C), 133.34, 133.30, 129.9, 129.8, 127.8 (2C), 127.7 (2C), 81.4, 79.3, 78.7, 77.9, 76.1, 67.7 (2C), 66.9, 63.4, 55.7, 40.9, 40.1, 26.9 (3C), 26.6 (3C), 26.4 (3C), 26.2 (3C), 25.8, 19.4, 18.8, 18.6, 18.4, 16.3, 16.0, 14.1, −2.2, −2.6, −4.4, −4.5, −4.6, −5.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{51}H_{88}O_8Si_4Na$ 963.5448, found 963.5439.



25



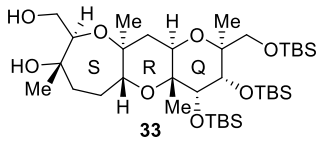
26

Alcohol (25) and C89-epimer (26). Me_3Al (1.07 M in *n*-hexane, 1.50 mL, 1.61 mmol) was added to a solution of BHT (702 mg, 3.19 mmol) in toluene (1.25 mL) at 0 °C. After stirring at room temperature for 1 h, a solution of ketone **24** (99.8 mg, 106 μmol) predried over MS4A in toluene (1.25 mL) and MeLi (1.06 M in ether, Br free, 1.50 mL, 1.59 mmol) were added to the resulting solution via cannula at −78 °C. After stirring at −78 °C for 1.5 h, the reaction mixture was quenched with a mixture solution of saturated aqueous of NH_4Cl and Et_2O and diluted with Et_2O. After addition of saturated aqueous Rochelle salt, the resultant suspension was stirred vigorously at 0 °C. The mixture was extracted with Et_2O, and the organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 50/1 → 30/1) to give alcohol **25** (63.9 mg, 66.7 μmol, 63%) and C89-epimer **26** (30.2 mg, 31.5 μmol, 30%) as a colorless oil, respectively.

25: R_f = 0.23 (hexane/EtOAc = 30/1 × 2); $[\alpha]_D^{24}$ +3.04 (c 0.09, $CHCl_3$); IR (neat) 3503, 2953, 2929, 2894, 2884, 2857, 1472, 1463, 1387, 1362, 1252, 1133, 1112, 1091, 1073, 892, 869, 837, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 8.2 Hz, 4H), 7.46–7.40 (m, 6H), 4.08 (d, J = 2.8 Hz, 1H), 3.98 (dd, J = 12.4, 4.1 Hz, 1H), 3.87 (dd, J = 8.9, 5.5 Hz, 1H), 3.78–3.75 (m, 2H), 3.68 (brs, 1H), 3.60 (dd, J = 10.3, 5.5 Hz, 1H), 3.43 (d, J = 11.0 Hz, 1H), 3.40 (dd, J = 10.3, 2.8 Hz, 1H), 3.17 (d, J = 11.0 Hz, 1H), 1.98–1.93 (m, 1H), 1.90–1.84 (m, 1H), 1.71–1.66 (m, 1H), 1.44 (dd, J = 12.4, 11.7 Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.05 (s, 9H), 0.93 (s, 9H), 0.89 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.73 (2C), 135.69 (2C), 132.6, 132.5, 130.2, 130.1,

128.04 (2C), 128.02 (2C), 79.2, 78.8, 77.6, 75.9, 75.4, 74.3, 67.7, 67.6, 65.4, 63.8, 41.5, 40.0, 27.0 (3C), 26.6 (3C), 26.5 (3C), 26.2 (3C), 25.2, 24.6, 19.2, 18.72, 18.69, 18.4, 16.6, 15.9, 14.4, −2.2, −2.6, −4.46, −4.48, −4.7, −5.3; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{52}H_{92}O_8Si_4Na$ 979.5761, found 979.5789.

26: R_f = 0.33 (hexane/EtOAc = 30/1 × 2); $[\alpha]_D^{23}$ +36.6 (*c* 0.09, $CHCl_3$); IR (neat) 3530, 2953, 2929, 2885, 2856, 1471, 1463, 1428, 1383, 1361, 1253, 1220, 1135, 1111, 1076, 1007, 890, 869, 836, 775, 741, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.8 Hz, 2H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.44–7.37 (m, 6H), 4.14 (d, *J* = 2.8 Hz, 1H), 4.03 (dd, *J* = 12.0, 4.1 Hz, 1H), 3.99 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.89 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.81 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.79 (d, *J* = 2.8 Hz, 1H), 3.55−3.54 (m, 1H), 3.51–3.48 (m, 2H), 3.25 (d, *J* = 11.0 Hz, 1H), 1.88–1.79 (m, 3H), 1.77–1.65 (m, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.06 (s, 9H), 0.93 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.9 (2C), 135.7 (2C), 133.4, 133.0, 129.9, 129.8, 127.9 (2C), 127.8 (2C), 79.2, 78.9, 76.3, 75.5 (2C), 75.0 73.9, 67.8 (2C), 66.8, 63.6, 40.5, 38.6, 28.9, 26.9 (3C), 26.6 (3C), 26.5 (3C), 26.4, 26.2 (3C), 19.4, 18.8, 18.7, 18.5, 16.7, 16.0, 14.4, −2.1, −2.6, −4.36, −4.41, −4.6, −5.1; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{52}H_{92}O_8Si_4Na$ 979.5761, found 979.5772.

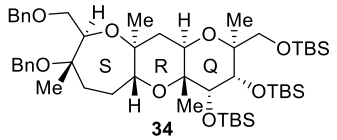


33

Diol (33). 10% NaOH solution in MeOH (40 μL, 100 μmol) was added to a solution of alcohol **25** (9.70 mg, 10.1 μmol) in THF (500 μL) at room temperature. After stirring at room temperature for 3.2 h, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → 5/1) to give diol **33** (7.10 mg, 9.87 μmol, 97%) as colorless solid.

R_f = 0.15 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ +25.4 (*c* 0.19, $CHCl_3$); IR (neat) 3675, 2954, 2929, 2887, 2857, 1558, 1541, 1521, 1473, 1457, 1253, 1135, 1072, 867, 837 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$) δ 4.11 (d, *J* = 3.6 Hz, 1H), 4.02 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.81–3.74 (m, 3H), 3.60–3.55 (m, 2H), 3.46 (d, *J* = 10.8 Hz, 1H), 3.21 (d, *J* = 10.8 Hz, 1H), 2.26 (brs, 1H), 1.91–1.75 (m, 3H), 1.71 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.68–1.61 (m, 1H), 1.58 (t,

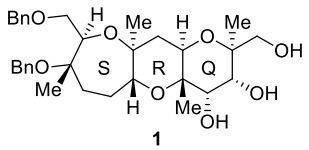
J = 12.6 Hz, 1H), 1.37 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 79.2, 78.7, 77.5, 77.2, 75.9, 75.8, 74.9, 67.7, 67.6, 63.6, 62.8, 41.2, 40.3, 26.6, 26.5, 26.2, 25.0, 24.2, 18.74, 18.66, 18.4, 17.1, 16.0, 14.3, −2.17, −2.57, −4.39, −4.46, −4.65, −5.22; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{36}H_{74}O_8Si_3Na$ 741.4584, found 741.4591.



34

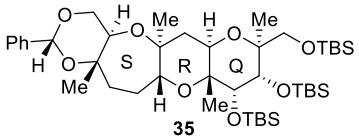
Bisbenzyl ether (34). MS4A (117 mg) was added to a solution of diol **33** (37.5 mg, 52.1 μmol) in dry DMF (1.70 mL) at room temperature. After stirring at room temperature for 30 min, BnBr (310 μL, 2.66 mmol), TBAI (196 mg, 531 μmol) and NaH (60% in mineral oil, 108 mg, 2.71 mmol) were added to the reaction mixture at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was diluted with Et_2O, quenched with H_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 80/1 → 50/1) to give dibenzylated compound **34** (36.6 mg, 40.7 μmol, 78%) as colorless oil.

R_f = 0.57 (hexane/EtOAc = 7/1); $[\alpha]_D^{22}$ +27.3 (*c* 0.16, $CHCl_3$); IR (neat) 2951, 2930, 2857, 1716, 1699, 1670, 1653, 1558, 1541, 1507, 1128, 837 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.30 (m, 6H), 7.29–7.25 (m, 4H), 4.61 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.17 (d, J = 7.2 Hz, 1H), 4.15 (d, J = 2.4 Hz, 1H), 4.12 (dd, J = 13.2, 4.2 Hz, 1H), 3.86 (d, J = 9.6 Hz, 1H), 3.80 (d, J = 2.4 Hz, 1H), 3.50–3.45 (m, 3H), 3.24 (d, J = 11.4 Hz, 1H), 2.22 (ddd, J = 13.2, 6.6, 2.4 Hz, 1H), 1.97−1.89 (m, 1H), 1.87 (dd, J = 11.4, 4.2 Hz, 1H), 1.68–1.61 (m, 2H), 1.58–1.51 (m, 1H), 1.44 (s, 3H), 1.230 (s, 3H), 1.228 (s, 3H), 1.18 (s, 3H), 0.94 (s, 9H), 0.92 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 139.1, 128.4 (2C), 127.5 (2C), 127.4, 127.34, 127.26 (2C), 79.5, 79.3, 78.8, 78.1, 76.1, 75.6, 73.2, 71.3, 67.6, 63.9 (2C), 63.5, 40.1, 36.3, 26.6 (3C), 26.5 (3C), 26.2 (3C), 25.6, 22.0, 18.8, 18.7, 18.4, 17.2, 16.0, 14.5, −2.2, −2.5, −4.4, −4.5, −4.7, −5.2 (a signal of ethereal region is overlapped with solvent); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{50}H_{86}O_8Si_3Na$ 921.5523, found 921.5521.



1

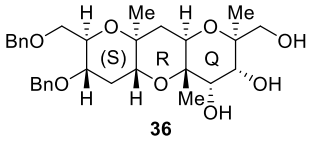
The QRS ring system (1). A solution of TBAF (1.0 M in THF, 820 μL, 820 μmol) was added to a solution of **34** (36.6 mg, 40.7 μmol) in dry THF (820 μL) at 0 °C. After stirring at 50 °C for 5.7 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1 → 1/2) to give the QRS ring system **1** (19.5 mg, 35.0 μmol, 86%) as colorless solid. R_f = 0.17 (hexane/EtOAc = 1/2); $[\alpha]_D^{22}$ +62.7 (*c* 0.13, $CHCl_3$); IR (neat) 3445, 2941, 1455, 1386, 1262, 1093, 1047, 735, 697 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.24 (m, 10H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.43 (t, *J* = 12.0 Hz, 2H), 4.13 (d, *J* = 7.2 Hz, 1H), 4.10 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.02 (brs, 1H), 3.95 (d, *J* = 3.0 Hz, 1H), 3.85 (d, *J* = 9.6 Hz, 1H), 3.54–3.40 (m, 4H), 2.73 (s, 1H), 2.67 (brs, 1H), 2.18 (ddd, *J* = 15.0, 7.2, 2.4 Hz, 1H), 2.11 (brs, 1H), 1.90 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.88–1.80 (m, 1H), 1.73 (t, *J* = 12.6 Hz, 1H), 1.65 (ddd, *J* = 15.0, 10.2, 3.6 Hz, 1H), 1.58–1.52 (m, 1H), 1.41 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 139.0, 128.44 (2C), 128.42, 127.44 (2C), 127.38, 127.2 (2C), 79.3, 79.1, 78.1, 76.8, 76.3, 75.2, 75.0, 73.3, 71.2, 68.2, 66.9, 63.9, 63.5, 39.9, 35.6, 25.3, 21.5, 16.5, 16.3, 14.1; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{44}O_8Na$ 579.2928, found 579.2917.



35

Benzylideneacetal (35). A solution of $PhCH(OMe)_2$ (0.3 M in DMF, 110 μL, 33 μmol) and a solution of *p*-TsOH·H_2O (0.1 M in DMF, 20.0 μL, 2.00 μmol) were added to a solution of diol **33** (4.80 mg, 6.67 μmol) predried over MS4A in dry DMF (150 μL) and dry CH_2Cl_2 (200 μL) at 0 °C. After stirring at room temperature for 3.5 h, a solution of $PhCH(OMe)_2$ (0.3 M in DMF, 110 μL, 330 μmol) was added at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with Et_3N and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of $KHSO_4$, $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by PTLC (HPTLC 10 cm × 5 cm,

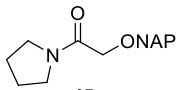
hexane/EtOAc = 30/1 × 3) to give acetal **35** (2.90 mg, 3.59 μmol, 54%) as colorless oil. R_f = 0.70 (hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ +49.1 (*c* 0.045, $CHCl_3$); IR (neat) 2953, 2927, 2856, 2098, 1472, 1386, 1259, 1061, 1028, 868, 837, 698 cm^{-1}, ^1H NMR (600 MHz, C_6D_6) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 3H), 5.59 (s, 1H), 4.31 (d, *J* = 2.4 Hz, 1H), 4.19 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.96 (d, *J* = 2.4 Hz, 1H), 3.92 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.85 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.80 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.67 (t, *J* = 10.8 Hz, 1H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.34 (d, *J* = 10.8 Hz, 1H), 1.99–1.81 (m, 5H), 1.71–1.65 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H), 1.13 (s, 9H), 1.02 (s, 9H), 0.99 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 126.9, 94.5, 79.5, 79.3, 78.6, 77.6, 76.0, 74.0, 68.4, 68.2, 68.0, 66.2, 63.8, 40.5, 38.9, 26.8 (3C), 26.7 (3C), 26.3 (3C), 25.6, 18.94 (2C), 18.89, 18.6, 16.8, 16.3, 14.4, −2.0, −2.3, −4.2, −4.3, −4.4, −5.1 (signals of aromatic region are overlapped with solvent); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{43}H_{78}O_8Si_3Na$ 829.4897, found 829.4902.



36

Triol (36). TBAF (1.0 M in THF, 450 μL, 450 μmol) was added to a solution of TBS ether **18** (39.4 mg, 45.2 μmol) in THF (900 μL) at 0 °C. After stirring at room temperature for 4.2 h, the solution was warmed up to 50 °C. After stirring at 50 °C for 3.2 h, TBAF (1.0 M in THF, 450 μL, 450 μmol) was added to the solution at 0 °C and stirred at 50 °C for 2.6 h. Then the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 → 1/2) to give triol **36** (20.7 mg, 39.2 μmol, 87%) as a colorless oil.
R_f = 0.18 (hexane/EtOAc = 1/2); $[\alpha]_D^{22}$ +67.2 (*c* 0.15, $CHCl_3$); IR (neat) 3447, 2948, 2873, 1699, 1646, 1558, 1541, 1507, 1496, 1456, 1386, 1267, 1099, 1047, 988 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 8H), 7.20 (d, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.08 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.02 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.96 (d, *J* = 4.2 Hz, 1H), 3.75–3.71 (m, 1H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.58–3.50 (m, 2H), 3.47 (dd, *J* = 11.4, 4.2 Hz, 1H),s 3.42 (d, *J* = 10.8 Hz, 1H), 2.72 (s, 1H), 2.68 (d, *J* = 10.2 Hz, 1H), 2.19 (dt, *J* = 11.4, 4.2 Hz, 1H), 2.13–2.08 (m, 1H), 1.88 (dd, *J* = 11.4, 4.8 Hz, 1H), 1.74–1.66 (m, 1H),

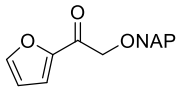
1.59 (q, J = 11.4 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 138.0, 128.6 (2C), 128.5 (2C), 128.0 (2C), 127.9 (2C), 127.7 (2C), 79.3, 76.2, 75.0, 73.8, 73.5 (2C), 72.7, 71.2, 70.7, 69.8, 68.2, 66.8, 63.6, 38.8, 30.4, 16.2, 15.6, 14.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{40}O_8$ 551.2615, found 551.2610.



45

NAP ether (45). To a stirred solution of primary alcohol **44** (12.9 g, 100 mmol) in DMF (160 mL) was added NAPBr (22.1 g, 100 mmol) at 0 °C, followed by NaH (60% in mineral oil, 4.83 g, 120 mmol), and the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reprecipitation and flash column chromatography (silica gel, hexane/EtOAc = 1/0→3/1) to give NAP ether **45** (26.3 g, 97.7 mmol, 97%) as a colorless amorphous solid.

R_f = 0.47 (hexane/ EtOAc = 0/1); IR (neat) 3053, 2971, 2950, 2872, 1644, 1603, 1508, 1446, 1422, 1337, 1296, 1272, 1253, 1217, 1192, 1171, 1126, 1111, 1160, 1033, 1021, 987, 951, 913, 896, 856, 819 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85–7.81 (m, 4H), 7.53–7.46 (m, 3H), 4.81 (s, 2H), 4.13 (s, 2H), 3.51 (t, J = 6.9 Hz, 2H), 3.37 (t, J = 6.9 Hz, 2H), 1.93 (tt, J = 6.9, 6.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.9, 135.1, 133.4, 133.2, 128.4, 128.0, 127.8, 127.0, 126.3, 126.12, 126.10, 73.4, 69.5, 46.0, 45.8, 26.3, 24.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{19}NO_2Na$ 292.1308, found 292.1312.

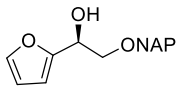


46

Furyl ketone (46). To a stirred solution of furan (2.50 mL, 33.4 mmol) in THF (150 mL) was added a solution of *n*-BuLi (1.73 M in hexane, 16.1 mL, 27.9 mmol) at 0 °C. The resulting solution was allowed to stir for 30 min and then cooled to −78 °C. A solution of amide **45** (5.00 g, 18.6 mmol) in THF (80 mL) was then added and the resulting mixture was allowed to stir at −78 °C for 1 h, at which time a solution of saturated aqueous NH_4Cl was added. The biphasic mixture was allowed to warm to room temperature and then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reprecipitation and flash column

chromatography (silica gel, hexane/EtOAc = 7/1→5/1) to give furyl ketone **46** (4.81 g, 18.1 mmol, 97%) as a pale brown amorphous solid.

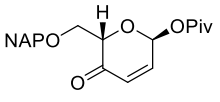
R_f = 0.63 (hexane/EtOAc = 1/1); IR (neat) 3031, 3054, 3020, 2925, 2866, 2360, 1687, 1602, 1570, 1509, 1467, 1393, 1360, 1301, 1267, 1254, 1223, 1170, 1156, 1128, 1083, 1031, 1018, 980, 961, 907, 893, 882, 856, 819 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) : δ 7.87–7.82 (m, 4H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.55–7.46 (m, 3H), 7.32 (d, *J* = 3.5 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.4 Hz, 1H), 4.85 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.7, 151.1, 146.7, 134.8, 133.4, 133.3, 128.5, 128.1, 127.9, 127.1, 126.3, 126.2, 126.0, 118.3, 112.4, 73.8, 72.2; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{14}O_3Na$ 289.0835, found 289.0829.



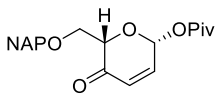
48

Furyl alcohol (48). To a stirred solution of furyl ketone **46** (1.60 g, 6.00 mmol) in CH_2Cl_2 (20 mL) were added TBAC (501 mg, 1.80 mmol), a solution of sodium formate (4.08 g, 60.0 mmol) in H_2O (20 mL) and (*S*,*S*)-**47** (18.0 mg, 0.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h, at which time the mixture was diluted with H_2O. The biphasic mixture was then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/ EtOAc = 5/1) to provide chiral alcohol **48** (1.58 g, 5.89 mmol, 98%) as a colorless solid.

R_f = 0.27 (hexane/EtOAc = 3/1); $[\alpha]_D^{26}$ −8.6 (*c* 1.00, $CHCl_3$); IR (neat) 3559, 3431, 3055, 3017, 2908, 2863, 2372, 2351, 2332, 2321, 1602, 1507, 1470, 1440, 1366, 1348, 1316, 1271, 1215, 1172, 1146, 1124, 1107, 1085, 1068, 1009, 961, 950, 929, 917, 894, 884, 856, 817 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.89–7.81 (m, 3H), 7.77 (br s, 1H), 7.51-7.45 (m, 3H), 7.37 (br s, 1H), 6.34 (dd, *J* = 2.8, 1.4 Hz, 1H), 6.32 (d, *J*= 2.8 Hz, 1H), 4.96 (dt, *J* = 11.0, 4.9 Hz, 1H), 4.77 (dd, *J* = 17.1, 11.6 Hz, 2H), 3.80 (d, *J* = 8.3 Hz, 2H), 2.71 (d, *J* = 4.9, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 153.5, 142.4, 135.3, 133.4, 133.2, 128.5, 128.0, 127.9, 126.8, 126.4, 126.2, 125.8, 110.4, 107.2, 73.7, 72.6, 67.0; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{16}O_3Na$ 291.0992, found 291.0997.



49



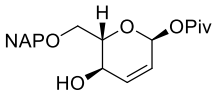
epimer-**49**

Dihydropyrane (49). To a stirred solution of chiral furan **48** (3.97 g, 14.8 mmol) in THF (90 mL) and H_2O (36 mL) were added $NaHCO_3$ (2.49 g, 29.6 mmol), NaOAc (1.21 g,

14.8 mmol), and NBS (2.63 g, 14.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, at which time a solution of saturated aqueous $NaHCO_3$ was added. The resulting biphasic mixture was then extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filterd and concentrated under reduced pressure to give crude enone, which was used in the next step directly without purification.

The crude mixture of hemiacetals was then dissolved in CH_2Cl_2 (65 mL) and cooled to −78 °C. To the stirred solution were added DMAP (90.4 mg, 0.74 mmol), Et_3N (3.0 mL, 29.6 mmol) and PivCl (2.2 mL, 17.8 mmol) and the reaction mixture was stirred at −78 °C for 1 h. The cold mixture was then rapidly poured into a mixed solution of saturated aqueous NH_4Cl and EtOAc. H_2O was added, and the organic layer was removed and then washed with H_2O and saturated aqueous NaCl. The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/0→7/1) to afford pyranone **49** (3.36 g, 9.12 mmol, 62% for two steps) as a colorless solid as well as the more polar, undesired β-isomer was also obtained (1.52 g, 4.12 mmol, 28%) as a colorless syrup.

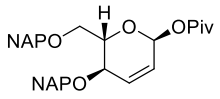
R_f = 0.47 (hexane/EtOAc = 2/1); $[\alpha]_D^{26}$ +102.8 (*c* 1.00, $CHCl_3$); IR (neat) 3056, 3022, 2975, 2935, 2872, 2363, 1740, 1701, 1636, 1605, 1511, 1480, 1458, 1397, 1370, 1278, 1215, 1125, 1101, 1030, 1003, 930, 857, 817, 748, 668 cm cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.84–7.81 (m, 3H), 7.76 (br s, 1H), 7.51–7.42 (m, 3H), 6.95 (dd, *J* = 10.3, 4.1 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.27 (d, *J* = 10.3 Hz, 1H), 4.74 (s, 2H), 4.66 (dd, *J* = 4.8, 2.8 Hz, 1H), 3.97 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.93 (dd, *J* = 11.0, 2.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.4, 177.0, 142.5, 135.4, 133.4, 133.2, 129.0, 128.3, 128.0, 127.8, 126.6, 126.2, 126.0, 125.8, 87.2, 76.6, 74.0, 68.8, 39.4, 27.2 (3C); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{24}O_5Na$ 391.1516, found 391.1505.



50

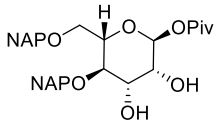
Secondary alcohol (50). To a stirred solution of enone **49** (7.29 g, 19.8 mmol) in CH_2Cl_2/MeOH (180 mL, 1:1) was added $CeCl_3 \cdot 7H_2O$ (3.71 g, 9.96 mmol) at room temperature. The solution was stirred for 15 min, and then cooled to −78 °C. To the stirred solution at −78 °C was added $NaBH_4$ (752 mg, 19.9 mmol) and the resulting mixture was stirred at −78 °C for 30 min before it was quenched with saturated aqueous NH_4Cl. After warming to room temperature, the resulting biphasic mixture was diluted with EtOAc and

the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude allylic alcohol **50** was used in the next step without further purification.



51

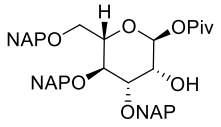
NAP ether (51). To a stirred solution of crude allylic alcohol **50** in toluene (90 mL) were added NAPBr (21.8 g, 98.6 mmol) and TBAI (3.65 g, 9.86 mmol) at 0 °C. An aqueous solution of NaOH (25%, 90 mL) was added and the mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with saturated aqueous NaCl and EtOAc and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/0→8/1) to give NAP ether **51** (8.71 g, 17.1 mmol, 86% yield for two steps) as a colorless syrup.
R_f = 0.55 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −30.7 (*c* 1.00, $CHCl_3$); IR (neat) 3051, 3018, 2973, 2934, 2907, 2870, 1734, 1633, 1600, 1508, 1480, 1459, 1395, 1369, 1275, 1194, 1119, 1094, 1025, 1006, 919, 857, 815, 790, 750, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.82–7.76 (m, 4H), 7.75 (br s, 1H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.71–7.66 (m, 2H), 7.48–7.42 (m, 5H), 7.29 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.33 (d, *J* = 2.0 Hz, 1H), 6.21 (d, *J* = 10.3 Hz, 1H), 5.79 (ddd, *J* = 10.3, 3.4, 2.0 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.29 (dd, *J* = 9.6, 1.4 Hz, 1H), 3.99 (ddd, *J* = 9.7, 4.0, 2.0 Hz, 1H), 3.81 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.77 (dd, *J* = 11.0, 2.1 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.6, 135.7, 135.2, 133.4, 133.3, 133.19, 133.17, 132.1, 128.4, 128.3, 128.1, 128.0, 127.84, 127.81, 127.0, 126.8, 126.3, 126.24, 126.18, 126.1, 126.01, 125.99, 125.0, 88.7, 73.6, 72.01, 71.96, 70.0, 68.6, 39.1, 27.2 (3C); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{34}O_5Na$ 533.2298, found 533.2297.



52

Diol (52). To a stirred solution of olefin **51** (2.85 g, 5.59 mmol) in acetone/H_2O (78 mL, 5:1) were added NMO (1.96 g, 16.8 mmol) and $K_2OsO_4 \cdot 2H_2O$ (93.2 mg, 0.25 mmol) at room temperature and the reaction mixture was allowed to stir for 24 h. The reaction

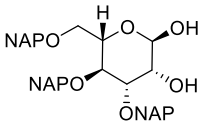
mixture was then quenched with saturated aqueous $Na_2S_2O_3$ and the resulting biphasic mixture was stirred vigorously for 30 minutes, and then extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reprecipitation and flash column chromatography (silica gel, hexane/EtOAc = 4/1→1/1) to give diol **52** (2.89 g, 5.30 mmol, 95 %) as a colorless amorphous solid.
R_f = 0.35 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ −8.5 (*c* 1.00, $CHCl_3$); IR (neat) 3057, 3016, 2976, 2935, 2906, 2872, 2360, 1739, 1603, 1509, 1479, 1461, 1397, 1367, 1275, 1215, 1168, 1114, 1088, 1030, 957, 940, 893, 857, 817, 745, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.83–7.77 (m, 5H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1 H), 7.51–7.41 (m, 5H), 7.29 (dd, *J* = 8.9, 1.4 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 3.98–3.94 (m, 2H), 3.92 (br s, 1H), 3.88 (dd, *J* = 11.7, 4.0 Hz, 1H), 3.85–3.81 (m, 1H), 3.78 (dd, *J* = 11.0, 2.1 Hz, 1H), 2.58 (br s, 1H), 2.43 (br s, 1H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 176.3, 135.50, 135.45, 133.4, 133.3, 133.21, 133.18, 128.6, 128.4, 128.1 (3C), 127.9, 127.8, 127.1 (2C), 126.3 (3C), 126.2, 126.1, 126.0, 93.2, 75.1, 73.9, 73.6, 71.9, 70.2, 68.5, 39.2, 27.2 (3C); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{33}H_{36}O_7Na$ 567.2353, found 567.2340.



53

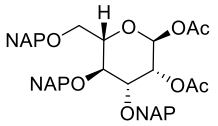
NAP ether (53). A stirred solution of diol **52** (2.89 g, 5.30 mmol), *n*-Bu_2SnO (1.32 g, 5.30 mmol), TBAI (1.96 g, 5.30 mmol) and NAPBr (1.64 g, 7.43 mmol) in benzene (100 mL) was heated at reflux in a flask equipped with a Dean–Stark apparatus for 19 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by reprecipitation and flash column chromatography (silica gel, hexane/EtOAc = 6/1→3/1) to give NAP ether **53** (3.22 g, 4.71 mmol, 90%) as a colorless amorphous solid.
R_f = 0.28 (hexane/EtOAc = 2/1); $[\alpha]_D^{24}$ −44.1 (*c* 1.00, $CHCl_3$); IR (neat) 3055, 3013, 2974, 2932, 2906, 2871, 2372, 2350, 2324, 1739, 1634, 1602, 1509, 1478, 1461, 1396, 1366, 1344, 1310, 1273, 1216, 1170, 1156, 1122, 1091, 1031, 955, 940, 893, 856, 814, 747, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.83–7.75 (m, 8H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.9 Hz, 1H), 7.53 (s, 1 H), 7.50–7.40 (m, 8H), 7.22 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.19 (d, *J* = 1.3 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.90 (s, 2H), 4.82 (d, *J* = 11.7 Hz, 1H),

4.71 (d, J = 11.0 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 4.12-3.88 (m, 1H), 3.96–3.93 (m, 1H), 3.90 (dd, J = 9.6, 3.4 Hz, 1H), 3.85 (dd, J =13.0, 4.1 Hz, 1H), 3.75 (dd, J = 13.0, 2.8 Hz, 1H), 2.60–2.57 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 176.2, 135.7, 135.6, 135.0, 133.4, 133.34 (2C), 133.29, 133.2, 133.1, 128.7, 128.33, 128.25, 128.1 (2C), 128.0, 127.9, 127.84, 127.75, 127.2, 126.94, 126.86, 126.5, 126.4, 126.23, 126.21, 126.14, 126.13, 126.02 (2C), 125.99, 93.0, 79.3, 75.6, 74.0, 73.9, 73.8, 72.6, 68.5, 68.1, 39.1, 27.0 (3C); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{44}H_{44}O_7Na$ 707.2979, found 707.2965.

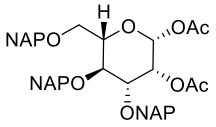


54

Diol (54). To a stirred solution of pivalate **53** (5.14 g, 7.51 mmol) in THF (37.0 mL) and MeOH (37.0 mL) was added NaOMe (1.21 g, 22.5 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1.2 h and then quenched with saturated aqueous NH_4Cl. The biphasic mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude diol **54** was used in the next step without further purification.



55



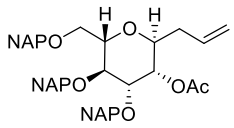
β-isomer

Diacetate (55). To a stirred solution of crude diol **54** in CH_2Cl_2 (36.1 mL) were added pyridine (4.80 mL, 59.7 mmol), DMAP (58.2 mg, 0.476 mmol) and Ac_2O (2.80 mL, 29.6 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 80 min and then H_2O was added. The organic phase was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 7/1→3/1) to give diacetate **55 (**4.46 g, 6.51 mmol, 87% for two steps) and β-isomer (0.624 g, 0.911 mmol, 12% for two steps) as colorless amorphous solid.

55 : R_f = 0.28 (hexane/EtOAc = 3/1); $[\alpha]_D^{27}$ −10.8 (c 0.58, $CHCl_3$); IR (neat) 3055, 3019, 2924, 2856, 1749, 1541, 1508, 1369, 1217, 1155, 1124, 1104, 1028, 963, 899, 856, 819, 753 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82–7.75 (m, 8H), 7.68 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 8.4 Hz, 2H), 7.51–7.40 (m, 9H), 7.17 (d, J = 7.2 Hz, 1H), 6.17 (d, J = 1.2 Hz, 1H), 5.45 (s, 1H), 5.04 (d, J = 11.4 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 12.6

Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.67 (d, J = 10.8 Hz, 1H), 4.65 (d, J = 12.6 Hz, 1H), 4.10-4.03 (m, 2H), 3.93–3.87 (m, 2H), 3.77 (d, J = 9.6 Hz, 1H), 2.21 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 168.6, 135.7, 135.6, 135.2, 133.35, 133.31, 133.1, 133.0, 128.4, 128.3, 128.2, 128.0 (4C), 127.84, 127.82, 127.7, 127.1, 126.9, 126.6, 126.3 (2C), 126.2, 126.1 (2C), 126.03, 125.97, 125.9, 91.5, 77.8, 75.5, 74.0, 73.9, 73.8, 72.1, 68.5, 67.7, 21.2, 21.0; HRMS (ESI-TOF) cald for $C_{43}H_{40}O_8Na$ [$(M+Na)^+$] 707.2615, found 707.2611.

β-isomer : R_f = 0.23 (hexane/EtOAc = 3/1); $[\alpha]_D^{27}$ +21.1 (*c* 0.21, $CHCl_3$); IR (neat) 3053, 2951, 2925, 2856, 1744, 1368, 1240, 1168, 1094, 1059, 962, 894, 857, 820, 752 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81–7.74 (m, 8H), 7.69 (d, J = 7.2 Hz, 1H), 7.56 (dd, J = 7.2, 3.6 Hz, 1H), 7.49–7.40 (m, 9H), 7.12 (d, J = 7.8 Hz, 1H), 5.78 (s, 1H), 5.69 (d, J = 3.0 Hz, 1H), 5.02 (d, J = 11.4 Hz, 1H), 4.91 (d, J = 11.4 Hz, 1H), 4.84 (d, J = 12.6 Hz, 1H), 4.68 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 12.0 Hz, 2H), 3.99 (d, J = 9.6 Hz, 1H), 3.87–3.80 (m, 3H), 3.66–3.62 (m, 1H), 2.26 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.0, 135.6, 135.5, 134.9, 133.34, 133.27, 133.19, 133.16, 133.0, 128.5, 128.3, 128.12, 128.08, 128.0 (2C), 127.84, 127.81, 127.7, 127.1, 127.0, 126.5, 126.3 (2C), 126.22, 126.17, 126.14, 126.10 (2C), 126.03, 125.96, 125.8, 91.5, 80.0, 76.3, 75.3, 73.81, 73.77, 71.8, 68.5, 67.5, 21.2, 21.0; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{43}H_{40}O_8Na$ 707.2615, found 707.2596.

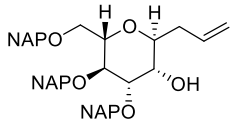


56

Olefin (56). To a stirred solution of mixture of acetate **55** and its isomer (5.04 g, 7.36 mmol) and allylTMS (35.0 mL, 221 mmol) in distilled MeCN (38.6 mL) which was predried over MS3A was added TMSOTf (2.70 mL, 14.9 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2.3 h and then quenched with saturated aqueous $NaHCO_3$. The resulting biphasic mixture was then extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8/1→7/1) to give allylated product **56** (4.11 g, 6.16 mmol, 84%) as a colorless amorphous solid.

R_f = 0.43 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −4.5 (*c* 1.03, $CHCl_3$); IR (neat) 3055, 3017, 2908, 2864, 2360, 1737, 1641, 1602, 1508, 1469, 1440, 1370, 1346, 1270, 1239, 1217, 1170, 1144, 1123, 1098, 1044, 1017, 982, 962, 952, 917, 894, 856, 817 cm^{-1}; ^{1}H NMR (600

MHz, $CDCl_3$): δ 7.80–7.72 (m, 8H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.58–7.55 (m, 1H), 7.49 (s, 1 H), 7.47–7.39 (m, 8H), 7.16 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.82–5.74 (m, 1H), 5.38 (dd, *J* = 2.8, 2.1 Hz, 1H), 5.09–5.03 (m, 2H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.82 (t, *J* = 12.4 Hz, 1H), 4.67–4.61 (m, 2H), 4.11–4.07 (m, 1H), 3.96–3.91(m, 2H), 3.83 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.78–3.72 (m, 2H), 2.52–2.45 (m, 1H), 2.34–2.28 (m, 1H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 135.80, 135.76, 135.3, 133.38, 133.35 (2C), 133.3, 133.2, 133.1, 133.0, 128.4, 128.3, 128.2, 128.02 (2C), 127.99, 127.83, 127.81, 127.7, 127.1, 126.8, 126.5, 126.24, 126.20, 126.17, 126.11 (2C), 126.08, 126.0, 125.9 (2C), 117.9, 77.5, 75.0 (2C), 74.8, 73.7, 73.1, 71.9, 69.9, 69.3, 33.8, 21.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{44}H_{42}O_6Na$ 689.2874, found 689.2843.

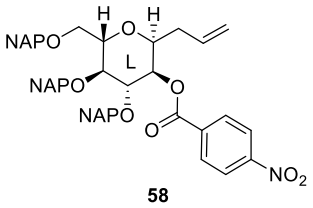


57

Alcohol (57). To a stirred solution of acetate **56** (5.32 g, 7.98 mmol) in THF/MeOH (80 mL, 1:1) was added K_2CO_3 (445 mg, 3.22 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h before it was quenched with saturated aqueous NH_4Cl and EtOAc. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5/1→1/1) to give secondary alcohol **57** (4.78 g, 7.65 mmol, 96%) as a colorless oil.

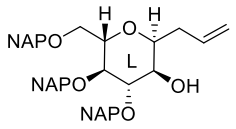
R_f = 0.32 (hexane/EtOAc = 2/1); $[\alpha]_D^{21}$ −21.7 (*c* 0.95, $CHCl_3$); IR (neat) 3422, 3054, 3013, 2974, 2912, 2864, 2372, 2349, 2333, 2326, 1951, 1914, 1691, 1639, 1602, 1572, 1508, 1468, 1441, 1393, 1365, 1344, 1315, 1271, 1217, 1171, 1146, 1124, 1086, 1008, 960, 951, 915, 894, 884, 856, 816 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82–7.69 (m, 9H), 7.64–7.61 (m, 2H), 7.55 (s, 1 H), 7.49–7.39 (m, 8H), 7.23 (dd, *J* = 8.9, 1.4 Hz, 1H), 5.83–5.77 (m, 1H), 5.04 (d, *J* = 4.8 Hz, 1H), 5.02 (s, 1H), 4.78 (s, 2H), 4.74 (d, *J* = 12.4 Hz, 1H), 4.69–4.64 (m, 2H), 4.02–3.98 (m, 1H), 3.95–3.91(m, 2H), 3.86 (dd, *J* = 8.0, 3.4 Hz, 1H), 3.85–3.81 (m, 1H), 3.79 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.74 (dd, *J* = 10.3, 3.4 Hz, 1H), 2.50 (d, *J* = 4.8 Hz, 1H), 2.45–2.41 (m, 1H), 2.37–2.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.8, 135.7 135.1, 134.2 (2C), 133.4, 133.3 (2C), 133.2, 133.12, 133.09, 128.6, 128.28, 128.25, 128.0 (2C), 127.9, 127.8, 127.8, 127.0, 126.72, 126.69, 126.4, 126.3, 126.19, 126.16, 126.1, 126.00, 125.95 (2C), 125.9, 117.5, 79.2, 75.2, 74.5, 74.3, 73.6, 73.1, 72.3, 69.1, 68.5, 34.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{42}H_{40}O_5Na$ 647.2768, found

647.2784.



58

4-Nitrophenyl ester (58). To a stirred solution of alcohol **57** (4.94 g, 7.91 mmol) in toluene (76.0 mL) were added Ph_3P (4.73 g, 18.0 mmol), 4-nitrobenzoic acid (2.68 g, 16.0 mmol), and diisopropyl azodicarboxylate (DIAD) (9.40 mL, 17.9 mmol) at room temperature and the resulting mixture was heated at 70 °C for 1 h. After the cooled reaction mixture was concentrated under reduced pressure, the residue was roughly purified by flash silica gel column chromatography and the resulting impure nitrobenzoate **58** was used in the next step without further purification.

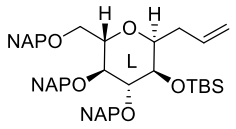


59

Alcohol (59). To a stirred solution of impure nitrobenzoate **58** in THF/MeOH (80.0 mL, 1:1) was added K_2CO_3 (463 mg, 3.35 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h before it was quenched with saturated aqueous NH_4Cl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1→5/1) to give alcohol **59** (3.77 g, 6.03 mmol, 76% for two steps) as a pale yellow solid.

R_f = 0.28 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −19.5 (*c* 0.70, $CHCl_3$); IR (neat) 3501, 3054, 3013, 2976, 2925, 2861, 2371, 2351, 2336, 2323, 1953, 1918, 1747, 1641, 1602, 1508, 1469, 1463, 1440, 1414, 1366, 1344, 1271, 1248, 1216, 1171, 1142, 1123, 1079, 961, 952, 915, 893, 855, 816 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.81–7.77 (m, 3H), 7.74–7.67 (m, 6H), 7.76–7.72 (m, 2H), 7.56 (s, 1 H), 7.50-7.39 (m, 7H), 7.30–7.27 (m, 3H), 5.87–5.79 (m, 1H), 5.14 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.06 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.79–4.69 (m, 5H), 4.64 (d, *J*= 12.4 Hz, 1H), 4.14–4.11 (m, 1H), 4.00–3.96 (m, 1H), 3.89 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.89 (dd, *J* = 5.5, 4.8 Hz, 1H), 3.76 (dd, *J* =10.3, 4.8 Hz, 1H), 3.74–3.70 (m, 2H), 2.98–2.90 (m, 1H), 2.50–2.44 (m, 1H), 2.44–2.37 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.7, 135.5, 135.0, 134.8, 133.4, 133.32, 133.29, 133.2, 133.1 (2C), 128.5,

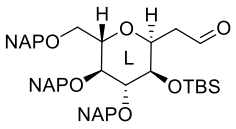
128.4, 128.3, 128.1, 128.0 (2C), 127.9, 127.85, 127.82, 126.8, 126.6, 126.5, 126.4, 126.3, 126.25, 126.20, 126.16, 126.0, 125.9, 125.8, 125.6, 117.2, 77.7, 74.9, 73.7, 73.6, 73.5, 73.0, 71.3, 69.3, 68.2, 33.4; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{42}H_{40}O_5Na$ 647.2768, found 647.2743.



60

TBS ether (60). To a stirred solution of alcohol **59** (3.77 g, 6.03 mmol) in DMF (7.2 mL) at was added imidazole (1.73 g, 25.4 mmol), followed by TBSCl (1.98 g, 13.1 mmol) at 0 °C. The reaction mixture was warmed to 70 °C and stirred for 10.5 h. The reaction was then quenched with saturated aqueous NH_4Cl and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1→8/1) to give TBS ether **60** (4.51 g, quant) as a colorless oil.

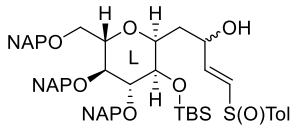
R_f = 0.70 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +21.8 (*c* 0.72, $CHCl_3$); IR (neat) 3055, 3020, 2951, 2927, 2896, 2883, 2856, 2377, 2353, 2321, 1730, 1640, 1603, 1527, 1509, 1470, 1462, 1441, 1406, 1386, 1362, 1343, 1270, 1254, 1126, 1169, 1156, 1142, 1122, 1113, 1088, 1036, 1005, 961, 952, 912, 892, 854, 837, 815 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82–7.71 (m, 8H), 7.69 (d, 1H, *J* = 7.6 Hz), 7.49–7.34 (m, 10H), 7.24 (s, 1 H), 6.95 (dd, *J* = 8.2, 1.4 Hz, 1H), 5.91–5.83 (m, 1H), 5.13 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.11–5.07 (m, 2H), 4.97 (d, *J* = 11.7 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 10.3 Hz, 1H), 4.00 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.80 (dd, *J* = 10.3, 3.5 Hz, 1H), 3.76–3.71 (m, 2H), 3.70–3.66 (m, 2H), 2.54–2.51 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.6, 135.7, 135.6, 135.2, 133.5, 133.3, 133.24, 133.16, 133.0 (3C), 128.3, 128.1 (2C), 128.03, 128.00, 127.84, 127.80, 127.6, 127.1, 126.5, 126.3, 126.2, 126.1, 126.0, 125.9 (2C), 125.83 (2C), 125.80, 125.6, 116.9, 83.5, 78.4, 76.7, 75.6, 75.2, 73.8, 73.4, 71.2, 69.0, 29.2, 26.0 (3C), 18.1, −4.3, −4.5; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{48}H_{54}O_5SiNa$ 761.3633, found 761.3671.



42

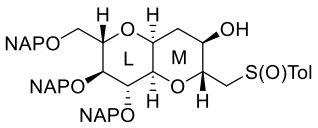
Aldehyde (42). A stirred solution of terminal olefin **60** (1.18 g, 1.60 mmol) in CH_2Cl_2 (16.7 mL) and MeOH (3.3 mL) was cooled to −78 °C. A steam of O_3 was then bubbled through the solution for 11 min and the O_3 was removed by bubbling O_2 gas. PPh_3 (504 mg, 1.92 mmol) was then added and the solution was warmed to room temperature over 3.8 h and concentrated under the reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 15/1→5/1) to afford aldehyde **42** (1.09 g, 1.47 mmol, 92%) as a colorless oil.

R_f = 0.25 (hexane/EtOAc = 5/1); $[\alpha]_D^{24}$ +23.6 (*c* 1.09, $CHCl_3$); IR (neat) 3055, 2952, 2927, 2883, 2856, 1727, 1634, 1603, 1509, 1470, 1462, 1386, 1362, 1343, 1254, 1219, 1170, 1155, 1125,1091, 1006, 961, 952, 891, 854, 838, 816, 775, 754, 699, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.82–9.71 (m, 1H), 7.83–7.70 (m, 9H), 7.51–7.36 (m, 10H), 7.27 (s, 1H), 6.98 (dd, *J*= 8.2, 1.4 Hz, 1H), 5.05 (d, *J* = 11.7 Hz, 1H), 4.98 (d, *J* = 11.7 Hz, 1H), 4.87 (d, *J* = 10.3 Hz, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.72–4.68 (m, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.04 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.83-3.75 (m, 2H), 3.70–3.63 (m, 3H), 2.91–2.80 (m, 2H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.4, 136.3, 135.5, 135.3, 133.4, 133.9, 133.3, 133.22, 133.18, 133.0, 128.4, 128.11, 128.06, 128.04 (2C), 127.99, 127.82, 127.80, 127.7, 127.1, 126.4, 126.3, 126.2, 126.13, 126.06, 126.0, 125.91, 125.88, 125.86, 125.7, 125.5, 83.2, 78.0, 75.6, 75.1, 73.9, 72.4, 72.2 (2C), 68.7, 40.5, 26.0 (3C), 18.0, −4.3, −4.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{47}H_{52}O_6SiNa$ 763.3425, found 763.3407.

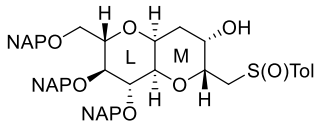


41

Diastereomixture of secondary alcohol (41). To a suspension of $CrCl_2$ (932 mg, 7.58 mmol) and $NiCl_2$ (23.0 mg, 177 μmol) in distilled DMF (8.30 mL) was added a solution of aldehyde **41** (1.09 g, 1.47 mmol) and vinyl iodide **43** (2.17 g, 7.43 mmol) in freshly distilled THF (8.30 mL) at 0 °C, then rinsed with THF (4.10 mL) and DMF (3.80 mL). The reaction mixture was stirred at room temperature for 62.2 h, then filtered through Celite and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 9/1→1/1) and the resulting impure allyl alcohol **41** was used in the next step without further purification.



61



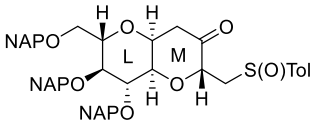
62

Alcohol (61 and 62). To a stirred solution of allyl alcohol **41** in THF (40.5 g) was added TBAF (1 M in THF, 4.10 mL, 4.10 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was warmed to 50 °C and stirred for 1 h. The reaction mixture was then quenched with saturated aquous NH_4Cl and the resulting biphasic mixture was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1→1/3) to give bicyclic system **61** (409 mg, 515 μmol, 35% for two steps) as a pale yellow amorphous solid and **62** (298 mg, 375 μmol, 25% for two steps) as a pale yellow amorphous solid.

61: R_f = 0.36 (hexane/EtOAc = 1/2); $[\alpha]_D^{22}$ +10.4 (*c* 0.37, $CHCl_3$); IR (neat) 3377, 3298, 3054, 3011, 2923, 2869, 2373, 2363, 2327, 1634, 1602, 1510, 1494, 1459, 1441, 1398, 1365, 1344, 1303, 1271, 1247, 1217, 1171, 1124, 1085, 1074, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.78–7.72 (m, 8H), 7.71–7.68 (m, 1H), 7.64 (s, 1H), 7.54–7.51 (m, 2H), 7.46–7.36 (m, 11H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.05 (dd, *J* = 8.2, 1.4 Hz, 1H), 4.90 (d, *J* = 2.7 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 2H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.50 (s, 2H), 4.26–4.21 (m, 1H), 4.03 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.96 (dd, *J* = 9.7, 8.2 Hz, 1H), 3.79 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.78–3.73 (m, 1H), 3.73–3.65 (m, 3H), 3.44 (ddd, *J* = 9.0, 5.4, 3.0 Hz, 1H), 2.97 (dd, *J* = 15.0, 3.0 Hz, 1H), 2.84 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.24 (s, 3H), 2.18–2.14 (m, 1H), 1.89 (dd, *J* = 23.4, 12.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 142.0, 138.0, 136.1, 135.5, 135.4, 133.33(2C), 133.28, 133.2, 133.1, 133.0, 130.3 (2C), 128.4, 128.23, 128.18, 128.0 (2C), 127.9, 127.84, 127.77, 127.7, 127.1, 126.7, 126.5, 126.34, 126.30, 126.27, 126.2, 126.13 (3C), 126.06, 126.0, 125.8, 124.3 (2C), 78.4, 75.7, 75.3, 74.9, 73.9, 72.4, 71.1, 70.3, 68.8, 68.2, 59.9, 31.6, 21.4; HRMS (APCI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{50}H_{48}O_7SNa$ 815.3013, found 815.2983.

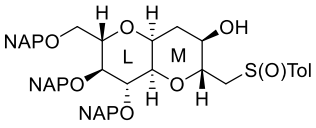
62: R_f = 0.32 (hexane/EtOAc = 1/2); $[\alpha]_D^{23}$ +13.6 (*c* 0.31, $CHCl_3$); IR (neat) 3378, 3054, 3011, 2924, 2868, 2359, 1634, 1601, 1509, 1494, 1469, 1459, 1449, 1397, 1364, 1344, 1271, 1217, 1171, 1125, 1090, 1043, 1012, 952, 896, 855, 816 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.79–7.72 (m, 9H), 7.56–7.52 (m, 2H), 7.48–7.39 (m, 9H), 7.35 (d, *J*= 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 12.4 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.60–4.55 (m, 1H), 4.20 (dd, *J* = 9.7, 6.2 Hz, 1H), 4.16–4.12 (m, 1H), 4.04 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.83–3.80 (br d, 1H), 3.76 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.72–3.67 (m, 3H), 3.65 (br d, 1H), 3.01 (dd, *J* = 13.4, 11.6 Hz, 1H), 2.77

(dd, J = 13.7, 3.4 Hz 1H), 2.35 (s, 3H), 2.03–2.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.9, 139.1, 136.3, 135.55, 135.48, 133.38, 133.36, 133.3 (2C), 133.2, 133.1, 133.0, 130.3, 128.4, 128.3, 128.2, 128.1, 128.0 (3C), 1128.9, 128.8, 127.7, 127.0, 126.7, 126.6, 126.34, 126.27, 126.21, 126.17, 126.13, 126.10, 126.05, 126.01, 125.9, 124.1 (2C), 78.3, 76.4, 75.2, 74.6, 73.9, 72.5, 69.1, 68.8, 67.0, 57.6, 30.1, 21.5; HRMS (APCI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{50}H_{48}O_7SNa$ 815.3013, found 815.2947



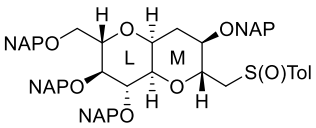
63

Ketone (63). To a stirred solution of a diastereomixture of secondary alcohol (66.6 mg, 84.0 μmol, **62** : **61** = 1 : 0.47) in CH_2Cl_2 (1.00 mL) at 0 °C were added $NaHCO_3$ (14.1 mg, 168 μmol) and Dess–Martin periodinane (55.0 mg, 130 μmol). After stirring at room temperature for 45 min, $NaHCO_3$ (8.1 mg, 96.4 μmol) and Dess–Martin periodinane (27.7 mg, 65.3 μmol) were added. The reaction mixture was stirred at room temperature for 35 min before it was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and diluted with Et_2O. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude ketone **63** was used in the next step without further purification.



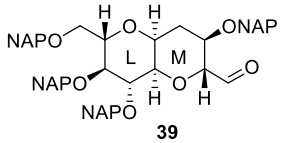
61

Alcohol (61). To a stirred solution of crude ketone **63** in THF/MeOH (1.05 mL, 1:1) was added $NaBH_4$ (20.8 mg, 550 μmol) at −78 °C and the resulting mixture was stirred at −78 °C for 1.6 h before it was quenched with saturated aqueous NH_4Cl. After warming to room temperature, the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1→1/3) to give alcohol **61** (43.5 mg, 54.9 μmol, 65% for two steps) as a colorless oil.



40

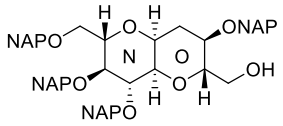
NAP ether (40). To a stirred solution of secondary alcohol **61** (333 mg, 420 μmol) in DMF (4.2 mL) was added TBAI (65.3 mg, 177 μmol), NAPBr (193 mg, 873 μmol) and NaH (7.5 mg, 188 μmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. After NaH (7.1 mg, 178 μmol) was added to the reaction solution, the resulting solution was stirred at room temperature for 30 min. After NaH (8.5 mg, 213 μmol) was added to the reaction solution, the resulting solution was stirred at room temperature for 30 min again. The reaction mixture was then quenched with saturated aqueous NH_4Cl and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1→0/1) to give naphthylmethyl ether **40** (316 mg, 339 μmol, 81%) as a colorless oil.
R_f = 0.53 (hexane/EtOAc = 1/1); $[\alpha]_D^{22}$ −9.2 (*c* 0.60, $CHCl_3$); IR (neat) 3053, 3013, 2936, 2920, 2866, 2374, 2365, 2359, 2349, 2328, 2319, 2309, 1602, 1509, 1493, 1459, 1441, 1398, 1364, 1343, 1302, 1271, 1246, 1219, 1172, 1141, 1124, 1083, 1044, 1016, 958, 893, 856, 816 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.85–7.81 (m, 4H), 7.80–7.73 (m, 8H), 7.70 (brd, J = 7.6 Hz, 1H), 7.55 (br d, J = 7.6 Hz, 2H), 7.51 (d, J = 8.2 Hz, 1H), 7.50–7.39 (m, 13H), 7.23 (br d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.9 Hz, 1H), 5.10 (d, J = 11.6 Hz, 1H), 4.97 (dd, J = 11.7, 11.7 Hz, 1H), 4.96 (d, J = 11.6 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 4.63 (d, J = 11.0, Hz, 1H), 4.27-4.22 (m, 2H), 4.19 (dd, J = 10.3, 6.2 Hz, 1H), 3.87 (ddd, J = 10.3, 10.3, 4.1 Hz, 1H), 3.85–3.81 (m, 1H), 3.78–3.68 (m, 4H), 3.16 (dd, J = 13.7, 4.1 Hz, 1H), 2.80 (dd, J = 13.7, 4.1 Hz, 1H), 2.38 (s, 3H), 2.35–2.31 (m, 1H), 2.92 (dd, J = 23.3, 11.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 142.0, 141.6, 136.2, 135.6, 135.4 (2C), 133.40, 133.37, 133.36, 133.3, 133.2 (2C), 133.1 (2C), 133.0, 130.1, 128.42, 128.40, 128.3, 128.2, 128.1, 128.09, 128.07, 128.0, 127.9, 127.8, 127.7, 127.0, 126.9, 126.7, 126.5, 126.32, 126.29, 126.23, 126.16, 126.14, 126.12, 126.08, 126.0, 125.8, 124.4 (2C), 78.5, 77.3, 76.0, 75.3, 75.1, 74.8, 73.9, 72.4, 71.3, 70.1, 69.9, 69.1, 60.4, 29.9, 21.5; HRMS (APCI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{61}H_{56}O_7SNa$ 955.3639, found 955.3682.



39

Aldehyde (39). To a solution of sulfoxide **40** (198 mg, 212 μmol) in MeCN/CH_2Cl_2/pyridine (4.25 mL, 4/4/1) was added TFAA (290 μL, 2.10 mmol) at 0 °C.

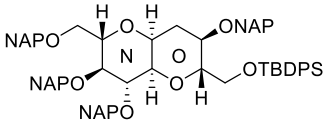
After being stirred 30 min at 0 °C, the reaction mixture was added KOAc (679 mg, 6.92 mmol) in H_2O (3.4 mL) and stirred at room temperature for 1 h. Then, the mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1→1/1) gave aldehyde **39** (140 mg, 173 μmol, 81%) as a colorless amorphous solid.
R_f = 0.10 (hexane/EtOAc = 2/1); $[\alpha]_D^{22}$ −102.1 (*c* 0.75, $CHCl_3$); IR (neat) 3465, 3054, 3020, 2930, 2904, 2866, 2360, 2341, 1739, 1634, 1602, 1509, 1460, 1441, 1363, 1344, 1271, 1219, 1170, 1123, 1083, 1018, 961, 952, 893, 855, 817, 771, 754, 705, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.86–7.70 (m, 12H), 7.68 (s, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.52-7.41 (m, 11H), 7.35 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.13 (dd, *J* = 8.6, 1.3, 1H), 5.03 (d, *J* = 11.9 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 12.8 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.21–4.09 (m, 3H), 3.79–3.68 (m, 5H), 3.64 (ddd, *J* = 10.0, 10.0, 4.1 Hz, 1H), 2.37-2.29 (m, 1H), 2.25–1.95 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.9, 135.8, 135.5, 135.3, 134.7, 133.34, 133.31, 133.30, 133.28, 133.23, 133.18, 133.1, 133.0, 128.6, 128.4 (2C), 128.2, 128.1, 128.0 (3C), 127.9 (2C), 127.79, 127.75, 127.02, 126.97, 126.9, 126.5, 126.4, 126.3 (2C), 126.24, 126.15, 126.1 (3C), 126.0, 125.79, 125.75, 78.5, 76.4, 76.2, 75.7, 75.2, 74.5, 73.9, 72.6, 72.5, 71.1, 69.3, 69.0, 29.8: HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{54}H_{48}O_7Na$ 831.3292, found 831.3296.



64

Alcohol (64). To a stirred solution of aldehyde **39** (128 mg, 158 μmol) in THF/MeOH (2.0 mL, 1:1) was added $NaBH_4$ (35.7 mg, 944 μmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1.5 h. After addition of $NaBH_4$ (6.8 mg, 180 μmol), the resulting mixture was stirred at 0 °C for 1.4 h before it was quenched with saturated aqueous NH_4Cl. After warming to room temperature, the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4/1→2/1) to give primary alcohol **64** (121 mg, 149 μmol, 95%) as a colorless amorphous solid.
R_f = 0.52 (hexane/EtOAc = 1/1); $[\alpha]_D^{24}$ −72.0 (*c* 1.00, $CHCl_3$); IR (neat) 3482, 3053, 3017, 2918, 2872, 2360, 1922, 1634, 1602, 1509, 1460, 1401, 1362, 1344, 1271, 1219, 1170,

1124, 1088, 1070, 961, 952, 893, 855, 816, 772, 753, 686, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.85–7.81 (m, 3H), 7.80-7.73 (m, 9H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.50–7.39 (m, 12H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.97 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 2H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.64 (dd, *J* = 11.0, 4.9 Hz, 2H), 4.25 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.16–4.08 (m, 2H), 3.84 (dd, *J* = 11.7, 2.0 Hz, 1H), 3.77–3.71 (m, 4H), 3.68 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.60–3.54 (m, 2H), 2.36–2.31 (m, 1H), 2.00-1.93 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.1, 135.6, 135.4, 135.3, 133.44, 133.37 (2C), 133.3, 133.21 (2C), 133.15, 133.0, 128.5, 128.43, 138.36, 128.2, 128.1, 128.0 (3C), 127.9(2C) , 127.8, 127.7, 127.0, 126.8, 126.7, 126.5, 126.4, 126.3, 126.20 (2C), 126.17, 126.12 (2C), 126.09, 126.02, 125.97, 125.8 (2C), 78.6, 77.0 75.9, 75.3, 75.0, 73.9, 73.1, 72.8, 72.5, 71.1, 70.4, 69.2, 62.7, 29.5; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{54}H_{50}O_7Na$ 833.3449, found 833.3446.

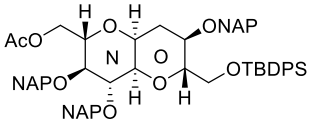


65

TBDPS ether (65). To a stirred solution of primary alcohol **64** (120 mg, 148 μmol) in DMF (740 μL) at was added imidazole (42.3 mg, 621 μmol), followed by TBDPSCl (77.0 μL, 297 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.1 h. The reaction was then quenched with saturated aqueous NH_4Cl and the resulting biphasic mixture was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1→5/1) to give TBDPS ether **65** (138 mg, 131 μmol, 89%) as a colorless oil.

R_f = 0.23 (hexane/EtOAc = 5/1); $[\alpha]_D^{24}$ −58.3 (*c* 1.00, $CHCl_3$); IR (neat) 3053, 3015, 2928, 2878, 2855, 2372, 2351, 2346, 2323, 1717, 1602, 1509, 1470, 1461, 1428, 1388, 1362, 1343, 1271, 1257, 1169, 1080, 1005, 962, 951, 891, 854, 817, 749, 704, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.84–7.81 (m, 1H), 7.80–7.72 (m, 10H), 7.71 (s, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.49-7.28 (m, 18H), 7.09 (d, *J* = 8.3 Hz, 1H), 5.16 (d, *J* = 11.0 Hz, 1H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.78 (dd, *J* = 12.4, 6.9 Hz, 2H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.61 (dd, *J* = 11.7, 2.8 Hz, 2H), 4.28 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.19-4.13 (m, 2H), 3.96 (d, *J* = 11.0 Hz, 1H), 3.87 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.78–3.72

(m, 3H), 3.69–3.62 (m, 3H), 2.37–2.32 (m, 1H), 2.04–1.97 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.3, 136.0 (3C), 135.82, 135.76 (3C), 135.6 (2C), 133.9, 133.5, 133.4 (3C), 133.3, 133.2, 133.14, 133.07, 133.0, 129.74, 129.69, 128.4 (2C), 128.1, 128.0 (4C), 127.9, 127.83, 127.78 (2C), 127.75 (2C), 127.7 (2C), 126.9 (2C), 126.59, 126.57, 126.4, 126.2 (2C), 126.1, 126.05 (2C), 126.03, 125.98, 125.9 (2C), 125.85, 125.83, 78.3, 76.2, 75.3, 74.7, 74.3, 73.8, 72.5, 72.3, 71.3, 70.5, 69.4, 63.8, 29.7, 27.0 (3C), 19.5; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{70}H_{68}O_7SiNa$ 1071.4627, found 1071.4641.

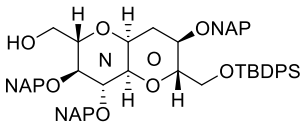


66

Acetate (66). To a stirred solution of tetra NAP ether **65** (139 mg, 132 μmol) in Ac_2O/AcOH (2.4 mL. 2/1) was added $ZnCl_2$ (361 mg, 2.65 mmol) in Ac_2O/AcOH (2.4 mL. 2/1) at 0 °C. The reaction mixture was stirred at room temperature for 2.4 h. The reaction mixture was then quenched with H_2O and the resulting biphasic mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous Na_2CO_3 and H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1→4/1) to give acetate **66** (115 mg, 121 μmol, 91%) as a colorless amorphous solid.

R_f = 0.12 (hexane/EtOAc = 5/1); $[\alpha]_D^{22}$ −59.6 (*c* 1.00, $CHCl_3$); IR (neat) 3053, 3015, 2929, 2881, 2856, 2371, 2345, 2321, 1739, 1632, 1601, 1589, 1509, 1471, 1461, 1428, 1387, 1363, 1345, 1234, 1218, 1169, 1083, 1053, 893, 855, 818, 752, 703, 666 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84–7.80 (m, 2H), 7.79–7.63 (m, 13H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.49–7.28 (m, 15H), 5.19 (d, *J* = 11.0 Hz, 1H), 5.05 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.76 (d, *J* = 11.6, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.36–4.29 (m, 2H), 4.25 (dd, *J* = 11.7, 4.1 Hz, 1H), 4.15–4.06 (m, 2H), 3.96 (d, *J* = 11.0, 1H), 3.88 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.80–3.76 (m, 1H), 3.66 (s, 2H), 3.54 (dd, *J* = 8.9, 8.9 Hz, 1H), 2.34–2.30 (m, 1H), 2.01–1.95 (m, 1H), 1.95 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 136.1, 136.0 (2C), 135.7 (3C), 135.51, 135.47, 133.9, 133.5, 133.4 (2C), 133.2 (2C), 133.1, 129.8, 129.7, 128.4 (2C), 128.2, 128.12 (2C), 128.08 (2C), 128.0, 127.79 (4C), 127.76 (3C), 127.01, 126.97, 126.62, 126.56, 126.3, 126.2, 126.1 (3C), 125.92, 125.87, 77.7, 76.1, 75.3, 74.8, 74.4, 72.5, 71.5, 70.7, 70.4, 63.75, 63.71, 29.8, 27.0 (3C), 20.9, 19.5; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{61}H_{62}O_8SiNa$ 973.4106,

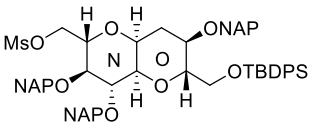
found 973.4144.



67

Alcohol (67). To a stirred solution of acetate **66** (112 mg, 117 μmol) in THF/ MeOH (1.8 mL, 1/1) at 0 °C was added K_2CO_3 (7.3 mg, 67.3 μmol) and the mixture was stirred at room temperature for 1 h before it was quenched with saturated aqueous NH_4Cl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1→2/1) to give primary alcohol **67** (104 mg, 114 μmol, 97%) as a colorless oil.

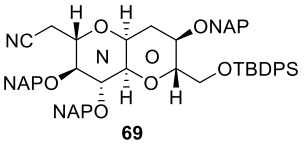
R_f = 0.17 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −48.3 (*c* 1.00, $CHCl_3$); IR (neat) 3471, 3052, 3013, 2929, 2880, 2857, 2373, 2343, 2334, 2325, 2309, 1633, 1602, 1589, 1509, 1471, 1461, 1427, 1389, 1361, 1344, 1270, 1217, 1187, 1168, 1084, 1058, 1007, 962, 891, 854, 817, 753, 703, 688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.84 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.77–7.71 (m, 6H), 7.71–7.65 (m, 5H), 7.62(d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.49–7.44 (m, 4H), 7.43–7.28 (m, 11H), 5.15 (d, *J* = 11.7 Hz, 1H), 5.07 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.0 Hz), 4.28 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.13–4.06 (m, 2H), 3.94 (d, *J* = 11.0 Hz, 1H), 3.89–3.83 (m, 2H), 3.73 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.70–3.60 (m, 3H), 3.57 (dd, *J* = 8.9, 8.9 Hz,1H), 2.32–2.27 (m, 1H), 2.03–1.95 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.2, 136.0 (3C), 135.7 (3C), 135.6, 133.9, 133.5, 133.42, 133.36 (2C), 133.2, 133.13, 133.09, 129.8, 129.7, 128.4, 128.3, 128.2, 128.11, 128.06 (2C), 127.80 (3C), 127.77 (2C), 127.7 (2C), 126.9, 126.8, 126.6, 126.5, 126.3, 126.2, 126.11, 126.07, 126.02, 125.99, 125.9 (2C), 78.3, 76.8, 76.3, 75.4, 74.8, 74.3, 72.6, 72.5, 71.4, 70.4, 63.7, 62.7, 30.1, 27.0 (3C), 19.5; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{59}H_{60}O_7SiNa$ 931.4001, found 931.4030.



68

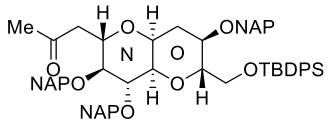
Msylate (68). To a mixture of alcohol **67** (103 mg, 113 μmol) in CH_2Cl_2 (2.0 mL) were added Et_3N (95.0 μL, 682 μmol) and MsCl (26.0 μL, 336 μmol) at 0 °C. After stirring at

0 °C for 1 h, the reaction mixture was quenched with H_2O at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with saturated aqueous $KHSO_4$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a crude mesylate **68** which was used in the next reaction without purification.



69

Nitrile (69). To a solution of the crude mesylate **68** and powdered MS4A (47.6 mg) in DMF (2.0 mL) was added NaCN (52.3 mg, 1.07 μmol) at 0 °C. After stirring at 70 °C for 17.3 h, the reaction mixture was cooled to 0 °C, diluted with Et_2O and quenched saturated aqueous $NaHCO_3$. After filtration through Celite, the aqueous layer was extracted with Et_2O, and the combined organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1→5/1) to give nitrile **69** (96.7 mg, 105 μmol, 93% for two steps) as a colorless amorphous solid.
R_f = 0.58 (hexane/EtOAc = 3/1); $[\alpha]_D^{24}$ −44.5 (*c* 0.94, $CHCl_3$); IR (neat) 3053, 3016, 2954, 2928, 2882, 2856, 2359, 2340, 2253, 1724, 1633, 1602, 1589, 1509, 1488, 1470, 1461, 1428, 1387, 1361, 1346, 1333, 1272, 1217, 1188, 1169, 1142, 1124, 1083, 1008, 961, 952, 893, 855, 819, 770, 756, 704, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.84–7.81 (m, 2H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.77–7.71 (m, 6H), 7.70–7.61 (m, 7H), 7.50–7.47 (m, 4H), 7.45–7.28 (m, 11H), 5.18 (d, *J* = 11.0 Hz, 1H), 5.13 (d, *J* = 11.7 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.27 (dd, *J* = 8.9, 8.9 Hz, 1H), 4,16 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.14–4.10 (m, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 3.87 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.79-3.75 (m, 1H), 3.69–3.64 (m, 2H), 3.42 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.70 (dd, *J* = 17.2, 3.5 Hz, 1H), 2.51 (dd, *J* = 16.5, 1.2 Hz, 1H), 2.38–2.33 (m, 1H), 1.97–1.91 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.0 (2C), 135.9, 135.7 (2C), 135.4, 135.2, 133.8, 133.4, 133.3, 133.2, 133.1, 129.8, 129.7, 128.5, 128.4, 128.3, 128.1, 128.0 (2C), 127.84 (3C), 127.80 (3C), 127.76 (3C), 127.0, 126.9, 126.7, 126.5, 126.4, 126.3, 126.2, 126.13, 126.10, 126.0, 125.89, 125.87, 117.2, 80.6, 76.6, 76.0, 75.6, 74.7, 74.4, 72.3, 71.5, 70.6, 68.5, 63.6, 29.84, 29.80, 27.0 (3C), 21.7, 19.4; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{60}H_{59}NO_6SiNa$ 940.4004, found 940.4036.

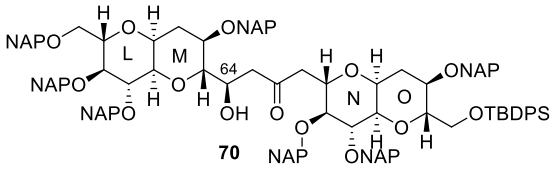


38

Methyl ketone (38). Nitrile **69** (90.9 mg, 99.0 μmol) was dissolved in dry toluene (1.9 mL) and cooled to 0 °C. Me_3Al (1.09 M solution in hexane, 1.4 mL, 1.53 mmol) was added and then followed by the addition of $Ni(acac)_2$ (10 mg/mL solution in benzene, 380 μL, 14.8 μmol). After stirring at 0 °C for 1.5 h, Me_3Al (1.09 M solution in hexane, 1.4 mL, 1.53 mmol) and $Ni(acac)_2$ (10 mg/mL solution in benzene, 380 μL, 14.8 μmol) were added. After stirring at 0 °C for 2.3 h, Me_3Al (1.09 M solution in hexane, 1.4 mL, 1.53 mmol) and $Ni(acac)_2$ (10 mg/mL solution in benzene, 380 μL, 14.8 μmol) were added again. The resulting mixture was stirred at 0 °C for 2 h, and then quenched with MeOH. After addition of EtOAc and saturated aqueous Rochelle's salt, the resulting mixture was stirred vigorously at room temperature. The biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1→5/1) to give methyl ketone **38** (60.3 mg, 64.5 μmol, 65%) as a colorless amorphous solid.

R_f = 0.35 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −32.2 (*c* 0.60, $CHCl_3$); IR (neat) 3052, 3014, 2955, 2929, 2856, 2360, 2340, 2331, 1716, 1634, 1603, 1589, 1509, 1469, 1462, 1427, 1389, 1360, 1330, 1271, 1239, 1214, 1169, 1143, 1124, 1112, 1104, 1083, 1054, 1020, 1008, 998, 961, 952, 894, 855, 818, 772, 752, 704, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.87–7.80 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.76–7.71 (m, 5H), 7.70–7.66 (m, 4H), 7.65 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.49–7.45 (m, 4H), 7.43–7.28 (m, 11H), 5.17 (d, *J* = 11.0 Hz, 1H), 5.09 (d, *J* = 11.6 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H, 4.75 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.28 (dd, *J* = 8.9, 8.9 Hz), 4.13–4.08 (m, 2H), 4.03–3.99 (m, 1H), 3.96 (d, *J* = 11.0 Hz, 1H), 3.86 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.68–3.61 (m, 2H), 3.29 (dd, *J* = 8.9, 8.9 Hz, 1H), 2.78 (dd, *J* = 15.8, 2.8 Hz, 1H), 2.48 (dd, *J* =15.8, 9.6 Hz, 1H), 2.36–2.31 (m, 1H), 2.10 (s, 3H), 2.08–2.03 (m, 1H), 0.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.6, 136.04, 135.98 (2C), 135.72 (2C), 135.69, 135.5, 133.8, 133.44, 133.37, 133.3, 133.13, 133.07, 129.74, 129.69, 128.5, 128.4, 128.3, 129.2, 128.05 (2C), 128.01, 127.8, 127.8 (2C), 127.7 (2C), 127.0, 126.7, 126.62, 126.57, 126.32, 126.26, 126.2, 126.1, 126.02, 126.00, 125.91, 125.88, 125.6, 125.3, 81.5, 77.1, 76.4, 75.3, 74.8, 74.4, 72.4, 71.3, 70.4, 68.8, 65.6, 63.8, 46.5, 30.8, 29.6, 27.0 (3C), 19.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{61}H_{62}O_7SiNa$

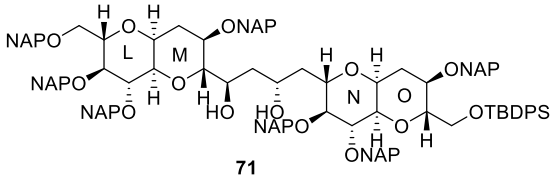
957.4157, found 957.4148.



Hydroxy ketone (70). A flask containing activated MS4A (35.0 mg) and LHMDS (21.0 mg, 126 μmol) was charged with THF (100 μL) and cooled at −78 °C while a solution of methyl ketone **38** (72.9 mg, 77.9 μmol) in THF (560 μL) was added dropwise precooling along the side of the reaction flask. The reaction mixture was stirred at −78 °C for 1.1 h, and a solution of aldehyde **39** (40.2 mg, 49.7 μmol) in THF (400 μL) was added dropwise precooling along the side of reaction flask. The mixture was stirred at −78 °C for 1 h, and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1→1/1) and PTLC (20 cm × 20 cm, hexane/EtOAc = 3/2 × 4) to give aldol **70** (17.6 mg, 10.1 μmol, 20%) as a colorless oil and C64-epimer (8.5 mg, 4.90 μmol, 10%).

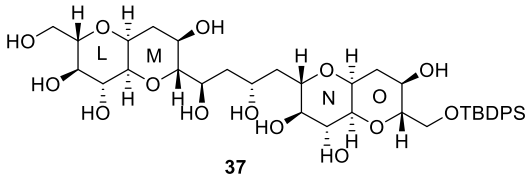
R_f = 0.23 (hexane/EtOAc = 3/2); $[\alpha]_D^{23}$ −29.0 (*c* 0.44, $CHCl_3$); IR (neat) 3054, 3013, 2929, 2881, 2858, 2360, 1172, 1633, 1602, 1509, 1470, 1460, 1427, 1362, 1343, 1271, 1217, 1169, 1124, 1083, 1009, 962, 951, 893, 855, 827, 753, 705, 687, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.86–7.66 (m, 23 H), 7.64–7.62 (m, 3H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.55–7.27 (m, 30 H), 7.24 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.3, 1.4 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.92 (d, *J* = 11.6 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.55–4.51 (m, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.22–4.16 (m, 2H), 4.16-4.11 (m, 1H), 3.95 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.91–3.79 (m, 5H), 3.79-3.71 (m, 4H), 3.67 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.46–3.41 (m, 2H), 3.33 (br d, *J* = 8.9 Hz, 1H), 3.34–2.97 (m, 2H), 2.92 (d, *J* = 4.9 Hz, 1H), 2.54 (dd, *J* =15.1, 2.8 Hz, 1H), 2.37–2.34 (m, 1H), 2.31 (dd, *J* = 17.8, 2.0 Hz, 1H), 2.19 (dd, *J* = 15.1, 8.9 Hz, 1H), 2.22–2.27 (m, 1H), 1.98 (dd, *J* = 23.4, 11.6 Hz, 1H), 1.71 (dd, *J* = 23.4, 11.7 Hz), 0.98 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.2, 136.2, 136.03, 135.98 (3C), 135.8, 135.72 (3C), 135.65, 135.5 (2C), 135.4, 133.9, 133.5, 133.40 (2C), 133.35, 133.33 (3C), 133.29, 133.22, 133.19, 133.12, 133.11, 133.05 (2C), 133.01, 129.74, 129.68, 128.5 (2C), 128.41, 128.36, 128.3, 128.2 (2C), 128.10 (2C), 128.06 (3C), 128.0, 127.9 (3C), 127.82 (2C),

127.77 (2C), 127.7 (3C), 127.0, 126.92, 126.85, 126.7, 126.5, 126.42, 126.38 (2C), 126.36, 126.3 (2C), 126.21 (2C), 126.16 (2C), 126.13 (2C), 126.08, 126.02 (3C), 125.99, 125.97, 125.9, 125.85, 125.77 (2C), 125.5, 81.5, 78.7, 77.8, 76.3, 75.6, 75.2 (2C), 75.0, 74.9, 74.7, 74.3, 73.9 (2C), 72.5, 72.3, 72.2, 71.7, 71.1, 70.23, 70.21, 69.2, 68.9, 65.2, 63.4, 47.2, 46.2, 29.7, 29.3, 27.0 (3C), 19.4: HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{115}H_{110}O_{14}SiNa$ 1766.7589, found 1766.7579.



71

***Anti*-diol (71).** To a solution of β-hydroxy ketone **70** (9.9 mg, 5.7 μmol) in MeCN (680 μL), AcOH (340 μL) and CH_2Cl_2 (100 μL) was added $Me_4NHB(OAc)_3$ (9.4 mg, 30.4 μmol) at 0 °C. After stirring at 0 °C for 1.3 h, the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 0.6 h, and then quenched with saturated aqueous solution of Rochelle's salt. The resulting biphasic mixture was stirred vigorously for 1.3 h. The biphasic mixture was then extracted with EtOAc and combined organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1→1/1) and the resulting impure diol **71** was used in the next step without further purification.

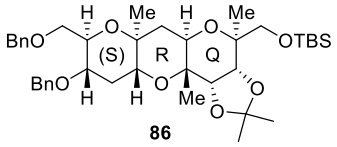


37

The LMNO ring system (37). To a stirred solution of *anti*-diol **71** in EtOAc (500 μL) and MeOH (500 μL) was added $Pd(OH)_2/C$ (20% Pd, 4.1 mg, 48 wt%) at room temperature and the solution was purged with H_2 and then stirred for 19.4 h under an atmosphere of H_2 (baloon). After addition of EtOAc (500 μL) and MeOH (500 μL), the reaction mixture was stirred under H_2 atmosphere at room temperature for 4.8 h. The reaction mixture was filtered through a short pad of Celite, and then concentrated. The residue was purified by reverse phase PTLC (10 cm × 10 cm, MeOH/H_2O = 2/1) to give the LMNO ring system **37** (2.3 mg, 3.0 μmol, 53% for two steps) as a colorless oil.

R_f = 0.20 (MeOH/H_2O = 2/1); $[\alpha]_D^{22}$ −26.7 (*c* 0.10, MeOH); IR (neat) 3360, 2947, 2872, 2832, 1725, 1637, 1601, 1459, 1450, 1397, 1384, 1365, 1319, 1285, 1162, 1108, 1064, 1028 cm^{-1}; ^1H NMR (600 MHz, CD_3CN/H_2O, 1/1): δ 7.66 (t, *J* = 7.2 Hz, 4H), 7.47–7.36

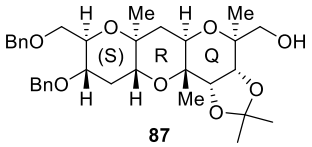
(m, 6H), 4.05–3.93 (m, 5H), 3.90–3.84 (m, 1H), 3.80 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.71–3.54 (m, 8H), 3.49–3.45 (m, 1H), 3.45–3.41 (m, 1H), 3.22 (t, *J* = 9.6 Hz, 1H), 3.16 (d, *J* = 9.6 Hz, 1H), 3.05 (t, *J* = 9.6 Hz, 1H), 2.01-1.82 (m, 4H), 1.76–1.70 (m, 1H), 1.54–1.46 (m, 1H), 1.46–1.39 (m, 1H), 1.24–1.16 (m, 4H), 0.98 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN/H_2O, 1/1) δ 136.5 (6C), 130.9 (2C), 128.8 (4C), 76.4, 75.6, 75.2, 75.1, 74.9, 74.4, 71.5, 70.71 (2C), 70.66 (2C), 68.5, 68.4, 66.3, 66.0, 65.6, 65.5, 62.1, 41.9, 40.4, 32.7, 27.2 (3C), 19.7, 15.2; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{56}O_{14}SiNa$ 787.3332, found 787.3336.



86

Acetonide (86). *p*-TsOH·H_2O (55.9 mg, 294 μmol) was added to a solution of diol **3** (1.87 g, 2.91 mmol) in acetone/2,2-dimethylpropane (1:1, v/v, 14.6 mL) at 0 °C. After stirring at room temperature for 2.3 h, the reaction mixture was quenched with Et_3N (2.00 mL, 14.3 mmol), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 12/1→8/1) to give acetonide **86** (1.93 g, 2.82 mmol, 97%) as a colorless amorphous solid.

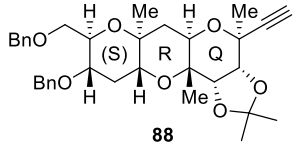
R_f = 0.65 (hexane/EtOAc = 2/1); $[\alpha]_D^{20}$ +58.1 (*c* 1.25, $CHCl_3$); IR (neat) 2987, 2951, 2883, 2857, 1463, 1454, 1381, 1277, 1249, 1098, 1066, 1044, 991, 882, 837, 734, 697, 679, 668, 660 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 8H), 7.19 (d, *J* = 6.6 Hz, 2H), 4.63 (d, *J* = 13.2 Hz, 1H), 4.56 (d, *J* = 13.2 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 1H), 3.95 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.74–3.70 (m, 2H), 3.53 (dt, *J* = 12.0, 4.8 Hz, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.44 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 2.24 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.89 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.70 (q, *J* = 12.0 Hz, 2H), 1.56 (s, 3H), 1.40 (s, 3H), 1.32 (s, 6H), 1.13 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.2, 128.5(2C), 128.4(2C), 127.95(2C), 127.87(2C), 127.8, 127.6, 110.8, 79.5, 78.9, 74.6, 74.5, 73.64, 73.62, 73.5, 72.6, 71.0, 70.8, 70.4, 70.0, 63.8, 39.3, 30.8, 26.3, 26.1(3C), 25.6, 19.6, 18.6, 16.9, 15.5, −5.0, −5.3; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{39}H_{58}O_8Na$ 705.3793, found 705.3798.



87

Alcohol (87). TBAF (1.0 M in THF, 5.50 mL, 5.50 mmol) was added to a solution of TBS ether **86** (1.88 g, 2.75 mmol) in THF (28.8 mL) at 0 °C. After stirring at room temperature for 3.2 h, TBAF (1.0 M in THF, 1.40 mL, 1.40 mmol) was added to the solution at 0 °C. After stirring at room temperature for 35 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1→1/1) to give alcohol **87** (1.54 g, 2.70 mmol, 98%) as a colorless amorphous solid.

R_f = 0.23 (hexane/EtOAc = 1/1); $[\alpha]_D^{22}$ +67.8 (*c* 1.13, $CHCl_3$); IR (neat) 3501, 2988, 2944, 2881, 1496, 1455, 1382, 1248, 1209, 1137, 1095, 1063, 1029, 988, 908, 876, 736, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.26 (m, 8H), 7.19 (d, *J* = 7.8 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 6.6 Hz, 1H), 4.02 (dd, *J* = 12.0 Hz, 1H), 3.73 (ddd, *J* = 10.2, 4.8, 2.4 Hz, 1H), 3.70–3.64 (m, 2H), 3.53 (dt, *J* = 12.0, 4.8 Hz, 1H), 3.47 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.43 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.39 (dd, *J* = 11.4, 9.0 Hz, 1H), 2.24 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.94 (dd, *J* = 9.0, 4.2 Hz, 1H), 1.90 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.70 (q, *J* = 12.0 Hz, 1H), 1.58 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 128.6 (2C), 128.4 (2C), 127.91 (2C), 127.86 (3C), 127.6, 111.3, 79.3, 79.0, 74.7, 74.3, 73.6, 73.53, 73.46, 72.6, 71.0, 70.9, 70.2, 69.8, 64.0, 39.2, 30.7, 26.2, 25.7, 19.4, 17.2, 15.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{44}O_8Na$ 591.2928, found 591.2927.



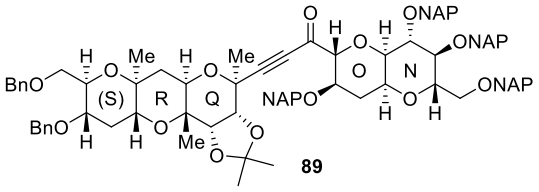
88

Alkyne (88). AZADOL (2.8 mg, 18.3 μmol) and (diacetoxyiodo)benzene (83.6 mg, 260 μmol) were added to a solution of alcohol **87** (99.4 mg, 175 μmol) in CH_2Cl_2 (1.70 mL) at 0 °C. After stirring at room temperature for 5.9 h, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual crude aldehyde was immediately used in the next reaction without further purification.

Cs_2CO_3 (177 mg, 543 μmol) was added to a solution of the above crude aldehyde and

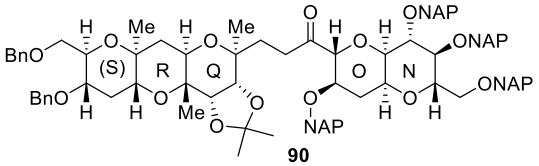
Ohira–Bestmann reagent (**80**) (177 mg, 921 μmol) in MeOH (3.50 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1→5/1) to give alkyne **88** (75.3 mg, 134 μmol, 77% for two steps) as a colorless solid.

R_f = 0.46 (hexane/EtOAc = 2/1); $[\alpha]_D^{20}$ +111.8 (*c* 1.01, $CHCl_3$); IR (neat) 2988, 2934, 2880, 1462, 1448, 1383, 1266, 1249, 1213, 1092, 1065, 1046, 910, 883, 822, 746, 698, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 8H), 7.20 (d, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 12.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.56 (d, *J* = 12.6 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 6.6 Hz, 1H), 3.92 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.71 (dt, *J* = 12.0, 1.8 Hz, 1H), 3.67 (d, *J* = 3.0 Hz, 2H), 3.52 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.39 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.56 (s, 1H), 2.25 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.96 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.66 (q, *J* = 12.0 Hz, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.2, 128.5(2C), 128.4(2C), 127.90(2C), 127.87(2C), 127.8, 127.6, 109.5, 87.2, 80.2, 77.9, 74.2, 73.6, 73.44, 73.37, 73.0, 72.7, 71.0, 70.7(2C), 69.8, 65.2, 39.6, 30.8, 26.4(2C), 24.0, 17.9, 15.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{34}H_{42}O_7Na$ 585.2823, found 585.2840.



Ynone (89). *n*-BuLi (1.6 M in *n*-hexane, 390 μL, 624 μmol) was added to a solution of alkyne **88** (375.2 mg, 667 μmol, predried with MS4A) in THF (6.7 mL) at −78 °C. After the resultant mixture was stirred at −78 °C for 1 h, a solution of aldehyde **39** (71.4 mg, 88.3 μmol, predried with MS4A) in THF (0.88 mL) was added via cannula. After stirring at −78 °C for 35 min and at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1→3/1) to give alcohol as a diastereomixture including a small amount of unreacted aldehyde **39**, and they were immediately used in the next reaction without further purification, respectively.

MnO_2 (732.5 mg, 8.43 mmol) was added to a soluion of secondary alcohol in CH_2Cl_2 (900 μL) at 0 °C. After stirring at room temperature for 2 h, MnO_2 (806.1 mg, 9.27 mmol) was added to the reaction mixture. After stirring at room temperature for 19 h, MnO_2 (224.8 mg, 2.59 mmol) was added to the reaction mixture. After stirring at room temperature for 2.3 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The residual crude ynone **89** was immediately used in the next reaction without further purification.

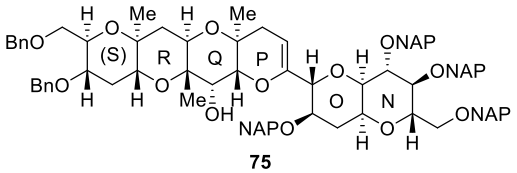


90

Ketone (90). A solution of the above crude ynone **89** in degassed benzene (3.3 mL) and degassed H_2O (33 μL) were added to Stryker's reagent (214 mg, 98.2 μmol) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ and Et_2O. After stirring under air at room temperature for 1 h, the reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1→3/2) to give ketone **90** (76.2 mg, 55.5 μmol, 63% for three steps) as a colorless oil.

R_f = 0.55 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ −5.6 (*c* 0.49, $CHCl_3$); IR (neat) 3056, 2989, 2937, 1731, 1508, 1456, 1381, 1273, 1247, 1210, 1124, 1067, 954, 889, 856, 818, 753, 697, 681, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82–7.72 (m, 11H), 7.68 (d, *J* = 4.2 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.49–7.39 (m, 12H), 7.37–7.26 (m, 8H), 7.19 (d, *J* = 6.6 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 2H), 4.77 (d, *J* = 12.6 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.23-4.15 (m, 3H), 4.12 (q, *J* = 12.6 Hz, 1H), 4.04 (d, *J* = 9.0 Hz, 1H), 3.82 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.79 (d, *J* = 6.0 Hz, 1H), 3.75–3.62 (m, 8H), 3.48 (dt, *J* = 11.4, 4.8 Hz, 1H), 3.30 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.69–2.63 (m, 1H), 2.47–2.40 (m, 1H), 2.35–2.30 (m, 1H), 2.19 (dt, *J* = 11.4, 4.8 Hz, 1H), 1.99 (q, *J* = 12.0 Hz, 1H), 1.76 (dd, *J* = 12.0, 4.2 Hz, 1H), 1.71 (quintet, *J* = 4.8 Hz, 2H), 1.65 (q, *J* = 11.4 Hz, 1H), 1.57 (t, *J* = 12.0 Hz, 1H), 1.46 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 138.6, 138.2, 136.0,

135.6, 135.4, 135.0, 133.4, 133.35, 133.29, 133.2, 133.1, 133.0, 128.54(3C), 128.51, 128.45(3C), 128.4, 128.3, 128.2, 128.1, 128.0(3C), 127.92(3C), 127.87(4C), 127.8, 127.7, 127.6, 127.0, 126.9, 126.5, 126.4(2C), 126.3, 126.2, 126.13(2C), 126.09(2C), 126.02, 125.97, 125.9, 125.83, 125.78, 111.1, 79.4, 79.2, 78.3, 77.7, 76.0, 75.2, 74.8, 74.3, 73.9, 73.7, 73.6, 73.50, 73.47(2C), 72.6, 72.5, 71.2, 71.0, 70.8, 69.9, 69.6, 69.1, 39.2, 37.2, 35.3, 30.7, 29.7, 26.2, 25.5, 21.3, 17.4, 15.4; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{88}H_{92}O_{14}Na$ 1395.6379, found 1395.6485.



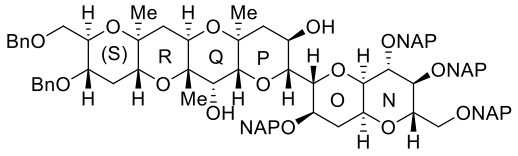
75

Glycal (75). *p*-TsOH·H_2O (7.0 mg, 36.8 μmol) was added to a solution of ketone **90** (74.6 mg, 54.3 μmol) in CH_2Cl_2/MeOH (1:2, v/v, 2.7 mL) at 0 °C. After stirring at room temperature for 14.6 h, the reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1→1/1) to give an inseparable mixture of hemiacetal and hydroxy ketone, and it was immediately used in the next reaction without further purification.

Nafion NR-50 (1.11 g) was added to a solution of the above mixture and powdered MS4A (664 mg) in toluene (1.0 mL) at room temperature. After stirring at 120 °C for 4.7 h, Nafion NR-50 (614 mg) was added to the solution at room temperature. After stirring at 120 °C for 3.6 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1→1/1) to give dihydropyran **75** (49.5 mg, 37.6 μmol, 69% for two steps) as a colorless amorphous solid.

R_f = 0.38 (hexane/EtOAc = 1/1); $[\alpha]_D^{26}$ +26.1 (*c* 0.24, $CHCl_3$); IR (neat) 3055, 3026, 2922, 2857, 1508, 1455, 1364, 1346, 1273, 1166, 1124, 1083, 1056, 953, 855, 817, 752, 698, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.68 (m, 13H), 7.57–7.37 (m, 14H), 7.35–7.25 (m, 8H), 7.20 (d, *J* = 6.6 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 4.81 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 2H), 4.66–4.60 (m, 4H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.55 (f, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.28 (t, *J* = 9.6 Hz, 1H), 4.22 (dd, *J* = 13.2, 4.2 Hz, 2H), 4.15 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.98 (d, *J* = 10.8 Hz, 1H), 3.88 (d, *J* = 3.0 Hz, 1H), 3.79 (dt, *J* = 10.8, 4.2 Hz, 1H), 3.76–3.70 (m, 4H), 3.68–3.61 (m, 4H), 3.54 (dt, *J* =

10.2, 5.4 Hz, 1H), 3.41 (dd, *J* = 12.6, 3.6 Hz, 1H), 2.54 (s, 1H), 2.36-2.31 (m, 1H), 2.22–2.13 (m, 2H), 1.99 (q, *J* = 10.8 Hz, 1H), 1.90 (d, *J* = 9.6 Hz, 2H), 1.70–1.58 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 136.4, 135.8, 135.6, 135.5, 133.43, 133.35(2C), 133.3, 133.2, 133.1(2C), 128.6(2C), 128.5(2C), 128.4, 128.3, 128.2, 128.13, 128.11, 128.05(2C), 127.98, 127.95(2C), 127.92, 127.90(2C), 127.86(2C), 127.8, 127.73, 127.69, 127.0, 126.7, 126.44, 126.41, 126.38, 126.35, 126.26, 126.2(2C), 126.12, 126.09, 126.0, 125.94, 125.92, 125.8, 125.6, 78.2, 77.8, 76.8, 76.3, 75.3, 74.8, 74.4, 73.9, 73.8, 73.6, 73.5(2C), 73.4, 73.1, 72.8, 72.4, 71.4, 71.2, 70.7, 70.1, 69.8, 69.3, 64.9, 39.3, 38.9, 30.4, 30.3, 18.3, 15.7, 14.6 (a signal of ethereal region is overlapped with solvent); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{85}H_{86}O_{13}Na$ 1337.5961, found 1337.6094.

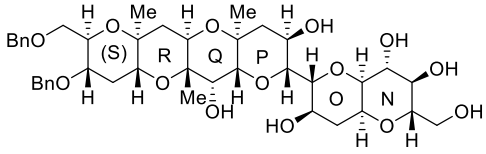


91

Alcohol (91). $BH_3{\cdot}SMe_2$ (210 μL, 2.21 mmol) was added to a solution of dihydropyran **75** (11.6 mg, 8.8 μmol) in THF (670 μL) at 0 °C. After the resultant mixture was stirred at room temperature for 16.8 h, NaOH (3 M in H_2O, 3.67 mL, 11.0 mmol) and H_2O_2 (30% in H_2O, 1.12 mL, 11.0 mmol) were added to the reaction solution at 0 °C. After stirring at room temperature for 2.3 h, the reaction mixture was diluted with H_2O and THF, quenched with $Na_2S_2O_3$ (7.03 g, 44.5 mmol) and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1→1/1) to give alcohol **91** as an impure mixture including inseparable byproducts, and it was immediately used in the next reaction without further purification.

R_f = 0.35 (hexane/ EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85–7.72 (m, 13H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.50–7.38 (m, 12H), 7.35–7.26 (m, 8H), 7.21 (d, *J* = 6.0 Hz, 2H), 7.07 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.05 (s, 2H), 4.92 (d, *J* = 11.4 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.6 Hz, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.31–4.24 (m, 2H), 4.19–4.11 (m, 2H), 4.09–4.02 (m, 2H), 3.95 (dt, *J* = 9.6, 4.2 Hz, 1H), 3.89 (d, *J* = 9.6 Hz, 1H), 3.79 (d, *J* = 2.4 Hz, 1H), 3.79–3.65 (m, 7H), 3.59–3.52 (m, 2H), 3.44 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.16 (d, *J* = 2.4 Hz, 1H), 2.99 (s, 1H, + contamination), 2.32 (dt, *J* = 11.4, 4.2 Hz, 1H), 2.16 (dt, *J* = 11.4, 4.2 Hz, 1H), 2.02 (q,

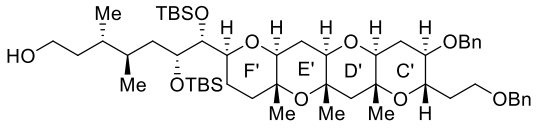
J = 11.4 Hz, 1H), 1.85 (dt, J = 11.4, 6.0 Hz, 2H), 1.68–1.59 (m, 2H), 1.38 (s, 3H), 1.35 (t, J = 11.4 Hz, 1H), 1.31 (s, 3H), 1.17 (s, 3H), 1.08 (d, J = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.6, 138.1, 136.8, 135.8, 135.6, 135.5, 133.5, 133.4 (2C), 133.3, 133.2, 133.1, 133.0 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3, 128.14, 128.05 (4C), 127.94 (3C), 127.90 (2C), 127.85 (3C), 127.71, 127.68, 127.0, 126.6, 126.5, 126.4, 126.31, 126.26, 126.2 (2C), 126.07, 126.05, 126.0, 125.93, 125.87, 125.8, 125.5, 125.2, 82.0, 80.4, 78.8, 77.8, 76.7, 75.3, 75.0, 74.7, 74.4, 74.2, 73.9 (2C), 73.6, 73.5, 72.8, 72.4, 72.0, 71.7, 71.2, 70.8, 70.21, 70.17, 69.8, 69.3, 63.9, 63.8, 48.9, 38.8, 30.4, 30.3, 18.9, 15.7, 15.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{85}H_{88}O_{14}Na$ 1355.6066, found 1355.6121.



74

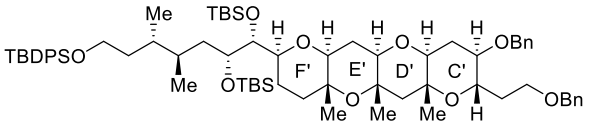
The NOPQR(S) ring system (74). DDQ (23.0 mg, 101 μmol) was added to a solution of the diol **91** in CH_2Cl_2 (880 μL) and H_2O (440 μL) at 0 °C. After stirring at 0 °C for 2.1 h, DDQ (23.6 mg, 104 μmol) was added to the solution at 0 °C. After stirring at 0 °C for 1.3 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (RP-18, MeOH/H_2O = 1/1→3/2) to give NOPQRS ring analog **74** (2.5 mg, 3.2 μmol, 37% for two steps) as a pale yellow oil.

R_f = 0.47 (MeOH/EtOAc = 1/6); $[\alpha]_D^{26}$ +25.7 (c 0.22, $CHCl_3$); IR (neat) 3358, 2943, 2870, 1456, 1385, 1273, 1092, 1060, 1040, 789, 754, 699 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.37–7.25 (m, 10H), 4.65 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 12.6 Hz, 1 H), 4.52 (d, J = 12.6 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.24 (dd, J = 13.2, 4.2 Hz, 1H), 4.20–4.07 (m, 4H), 4.03 (dt, J = 12.6, 6.0 Hz, 1H), 3.91 (brs, 1H), 3.90–3.85 (m, 1H), 3.77–3.56 (m, 12H), 3.52–3.44 (m, 3H), 3.34–3.29 (m, 2H), 2.22–2.17 (m, 1H), 2.10–1.94 (m, 3H), 1.75 (dd, J = 11.4, 4.2 Hz, 1H), 1.58 (t, J = 12.0 Hz, 1H), 1.55–1.47 (m, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 140.0, 139.8, 129.1(2C), 129.0(2C), 128.6(2C), 128.5(2C), 128.3, 128.1, 82.7, 80.8, 77.6, 76.1, 75.4, 75.0, 74.9, 74.8, 74.5, 74.4, 73.7(2C), 72.6, 72.0, 71.3(2C), 71.1, 70.8, 68.6, 65.1, 64.4, 63.3, 49.4, 40.0, 33.9, 31.1, 19.6, 15.8, 15.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{41}H_{56}O_{14}Na$ 795.3562, found 795.3565.



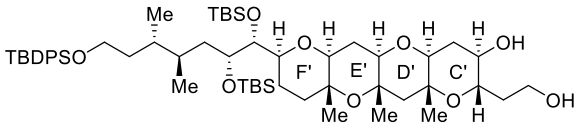
107

Primary alcohol (107). DDQ (301 mg, 1.32 mmol) was added to a solution of PMB ether **106** (693 mg, 654 μmol) in CH_2Cl_2 (13.0 mL) and pH 7 buffer (6.5 mL) at 0 °C. After stirring at room temperature for 40 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was used for the next reaction without further purification.



108

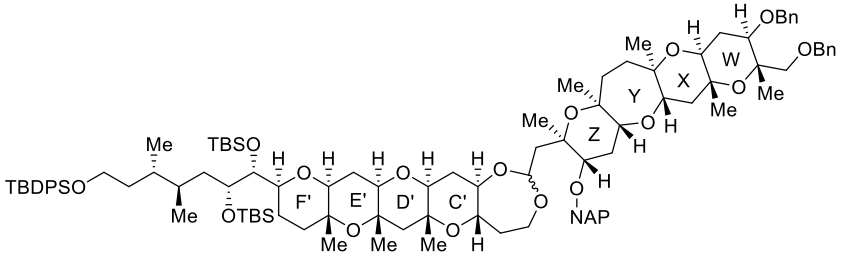
TBDPS ether (108). Imidazole (295 mg, 4.33 mmol) and TBDPSCl (510 μL, 1.97 mmol) were added to a solution of the above crude in DMF (3.2 mL) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, silica gel, hexane/EtOAc = 30/1 → 10/1) to give slightly impure TBDPS ether **108**, and it was used for the next reaction without further purification.



96

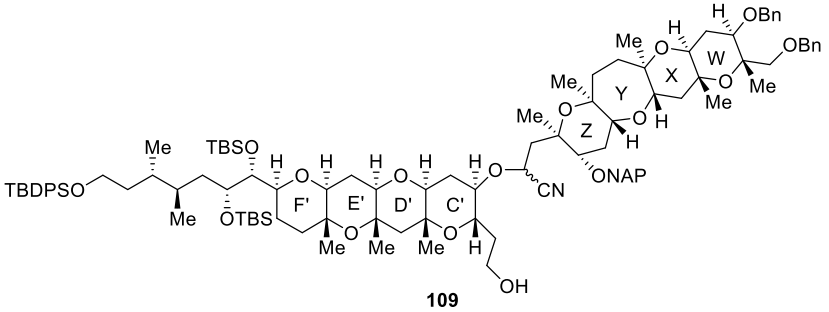
C'D'E'F' ring fragment (96). $Pd(OH)_2/C$ (77.9 mg, 10.7 wt%) was added to a solution of the above TBDPS ether in THF (12.0 mL) at room temperature. After stirring at room temperature for 5.4 h under H_2 atmosphere, the reaction mixture was filtered through a pad of Hyflo and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1 → 1/1) to give C'D'E'F' ring fragment **96** (572 mg, 573 μmol, 88% for three steps) as a colorless amorphous solid.
R_f = 0.20 (hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.2, 1.2 Hz,

4H), 7.44–7.36 (m, 6H), 3.82–3.75 (m, 2H), 3.74–3.69 (m, 1H), 3.69–3.62 (m, 3H), 3.51–3.46 (m, 2H), 3.42 (dd, J = 6.0, 3.6 Hz, 1H), 3.29 (dd, J = 12.0, 2.4 Hz, 1H), 3.21 (dd, J = 12.6, 3.6 Hz, 1H), 3.11 (dd, J = 12.0, 3.6 Hz, 1H), 2.78 (brs, 2H), 2.19 (ddd, J = 11.4, 5.4, 3.6 Hz, 1H), 2.01 (d, J = 12.6 Hz, 1H), 2.03–1.94 (m, 2H), 1.83 (q, J = 12.0 Hz, 1H), 1.80–1.73 (m, 2H), 1.72–1.54 (m, 6H), 1.52–1.46 (m, 1H), 1.43 (s, 3H), 1.43–1.37 (m, 2H), 1.36 (s, 3H), 1.36–1.32 (m, 1H), 1.30 (s, 3H), 1.30–1.25 (m, 1H), 1.02 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.78 (d, J = 12.6 Hz, 3H), 0.76 (d, J = 12.6 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7 (4C), 134.33, 134.30, 129.6 (2C), 127.7 (4C), 86.2, 83.12, 83.09, 80.0, 77.3, 74.9, 74.5, 74.0, 73.3, 71.4, 62.8, 61.4, 53.1, 38.8, 36.2 (2C), 35.8, 34.8 (2C), 33.7, 33.3, 27.9, 27.1 (3C), 26.08 (3C), 26.05 (3C), 21.7, 21.5, 19.4, 18.5, 18.3, 18.2, 16.4, 16.0, −3.5, −3.8, −4.5 (2C) (a signal is overlapped with solvent); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{56}H_{96}O_9Si_3Na$, found .



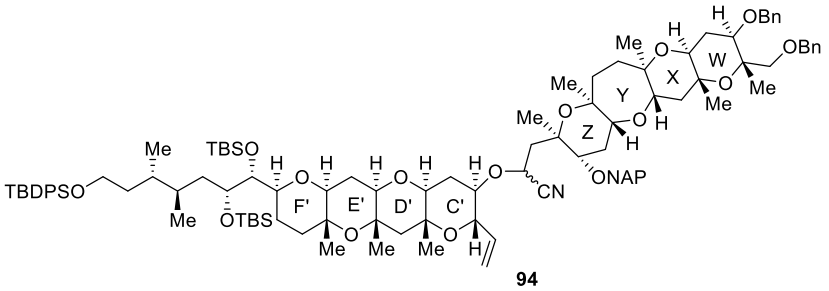
95

Acetal (95). A solution of C'D'E'F' ring fragment **86** (271 mg, 272 μmol) and WXYZ ring fragment **97** (69.7 mg, 90.5 μmol) in toluene (2.7 mL) was added to a suspension of $Sc(OTf)_3$ (26.8 mg, 54.5 μmol) in toluene (940 μL) at room temperature. After stirring at room temperature for 15.3 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 → 1/1) to give acetal **95** (120 mg, 68.6 μmol, 76%, diastereomixture) as a colorless amorphous solid.



109

α-Cyano ether (109). A solution of acetal **95** (65.4 mg, 37.5 μmol) and TMSCN (94 μL, 751 μmol) in CH_2Cl_2 (1.9 mL) was added to a suspension of $Sc(OTf)_3$ (10.9 mg, 22.1 μmol) in CH_2Cl_2 (560 μL) at 0 °C. After stirring at room temperature for 3.4 h, K_2CO_3 (25.3 mg, 183 μmol) and MeOH (1.2 mL) were added to the reaction mixture at −6 °C. After stirring at −6 °C for 5 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and H_2O, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1 → 0/1) to give α-cyano ether **109** (54.6 mg, 30.9 μmol, 82%, diastereomixture) as a colorless amorphous solid.

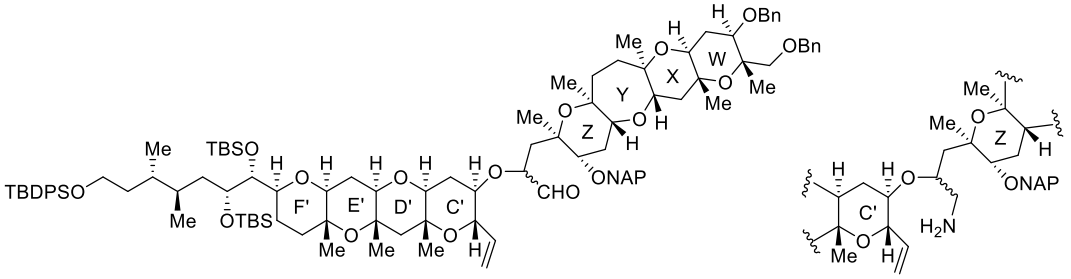


94

Terminal olefin (94). α-Cyano ether **109** (94.8 mg, 53.6 μmol), *o*-$NO_2C_6H_4SeCN$ (243 mg, 1.07 mmol), and powdered MS4A (100 mg) were suspended in THF (3.5 mL). After stirring at room temperature for 25 min, *n*-Bu_3P (330 μL, 1.32 mmol) was rapidly added to the suspension at room temperature. After stirring at room temperature for 25 min, the reaction mixture was diluted with CH_2Cl_2 and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 = 1/1 → hexane/EtOAc = 4/1), and slightly impure mixture was used for the next reaction.

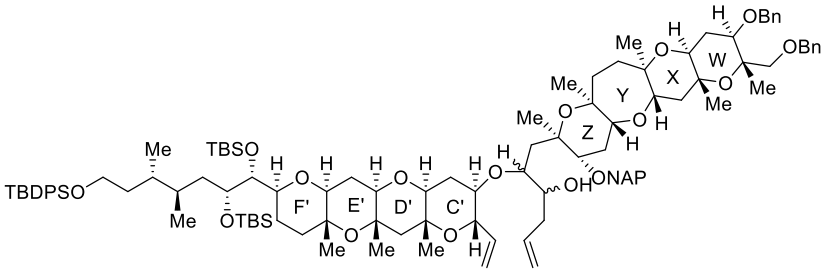
*m*CPBA (30.9 mg, 129 μmol) was added to a solution of the above mixture in dichloroethane (3.4 mL) at 0 °C. After stirring at room temperature for 15 min, $NaHCO_3$ (15.6 mg, 186 μmol) was added to the reaction mixture. After stirring at 60 °C for 20 min,

the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of Na_2CO_3 and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 = 1/1 → hexane/EtOAc = 5/1) to give terminal olefin **94** (77.0 mg, 44.0 μmol, 82% for two steps, diastereomixture) as a pale yellow amorphous solid.



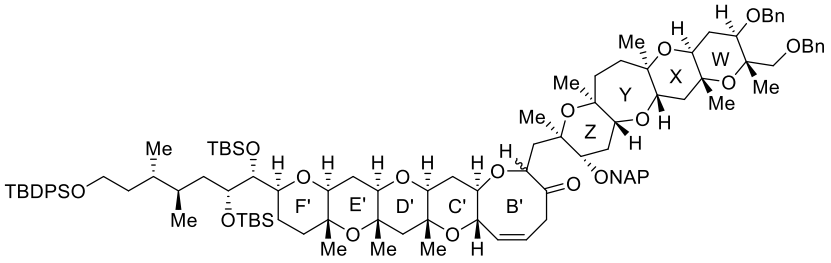
110 111

Aldehyde (110). DIBALH (1 M in hexane, 66.0 μL, 66.0 μmol) was added to a solution of nitrile **94** (77.0 mg, 44.0 μmol) in CH_2Cl_2 (2.2 mL) predried over MS4A at −78 °C. After stirring at −78 °C for 1 h, DIBALH (1 M in hexane, 66.0 μL, 66.0 μmol) was added to the reaction solution. After stirring at −78 °C for 40 min, DIBALH (1 M in hexane, 66.0 μL, 66.0 μmol) was added to the reaction solution, again. After stirring at −78 °C for 20 min, the reaction mixture was quenched with MeOH and saturated aqueous solution of $KHSO_4$. After stirring at 0 °C for 45 min and at room temperature for 20 min, the resulting solution was diluted with EtOAc and saturated aqueous solution of Rochelle's salt. After stirring at room temperature for 1.3 h, the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → MeOH/EtOAc = 1/9) to give aldehyde **110** (55.5 mg, 31.6 μmol, 72%, diastereomixture) as a pale yellow amorphous solid and amine **111** (19.2 mg, 10.9 μmol, 25%, diastereomixture) as a colorless amorphous solid.



112

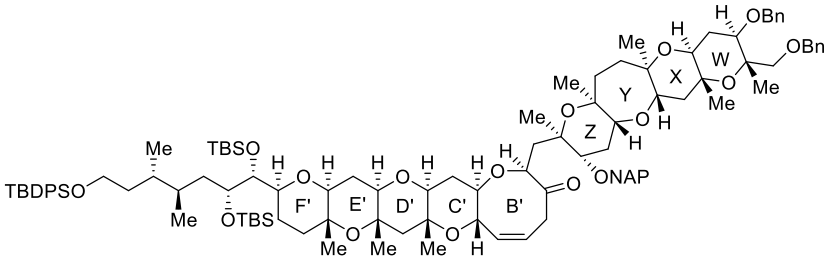
Olefin (112). Ally magnesium bromide (1 M in Et_2O, 110 μL, 110 μmol) was added to a solution of aldehyde **110** (26.1 mg, 14.9 μmol) in THF (1.0 mL) at −40 °C. After stirring at −40 °C for 45 min, the reaction mixture was quenched with H_2O and saturated aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → 4/1) to give olefin **112** (24.9 mg, 13.8 μmol, 93%, diastereomixture) as a pale yellow amorphous solid.



113

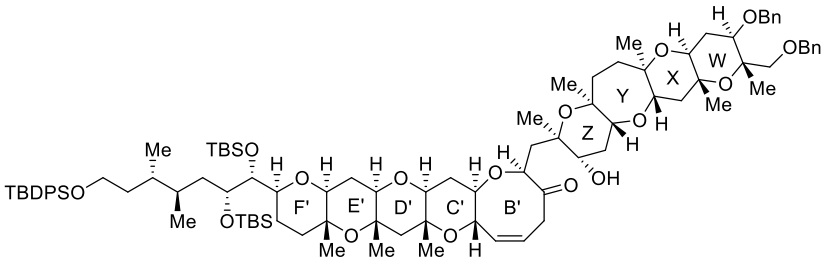
Eight-membered ring ketonw (113). A solution of Grubbs' catalyst 2nd generation (7.0 mg, 8.25 μmol) in degassed toluene (1.1 mL) was added to a solution of olefin **112** (120 mg, 66.7 μmol) in degassed toluene (5.6 mL) at 110 °C. After stirring at 110 °C for 17 min, Et_3N (140 μL) was added to the reaction mixture at room temperature. After stirring at room temperature under air for 1.1 h, the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane = 10/1 → 2/1) to give eight-membered ring (105 mg, 59.3 μmol, 89%, diastereomixture) as a pale brown amorphous solid.

NMO (9.6 mg, 81.9 μmol) and TPAP (5.2 mg, 14.8 μmol) were added to a solution of alcohol (48.8 mg, 27.6 μmol) and MS4A (62.2 mg) in CH_2Cl_2 (1.0 mL) at 0 °C. After stirring at room temperature for 1.2 h, the resulting solution was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → 4/1) to give ketone **113** (36.5 mg, 20.7 μmol, 75%, diastereomixture) as a colorless amorphous solid.



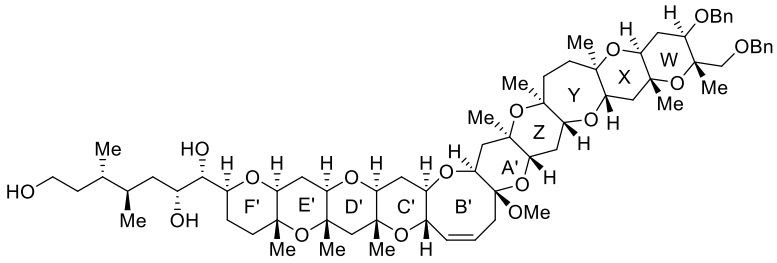
114

Ketone (114). After diastereomixture **113** (83.5 mg, 47.3 μmol) was dissolved in xylene, the resulting solution was dispensed to fifteen NMR tubes, and each solution was diluted to 800 μL with xylene. DBU (16 μL, 107 μmol) was added to each NMR tube at room temperature. After incubated at 100 °C for 21.5 h, the reaction mixture was cooled to room temperature. The resulting solution was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → 4/1) to give ketone **114** (68.7 mg, 38.9 μmol, 82%) as a single isomer as a colorless amorphous solid.



93

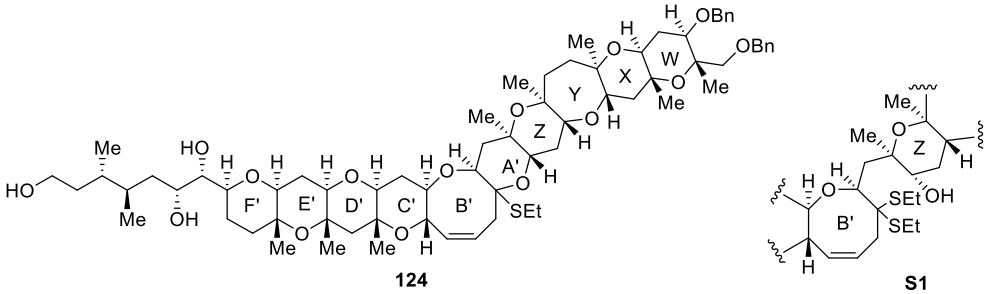
Hydroxy ketone (93). DDQ (55.3 mg, 244 μmol) was added to a solution of NAP ether **114** (55.3 mg, 31.3 μmol) in CH_2Cl_2 (3.0 mL) and pH 7 buffer (600 μL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 → 2/1) to give hydroxy ketone **93** (40.9 mg, 25.1 μmol, 80%) as an equilibirium mixture with hemiacetal as a colorless amorphous solid.



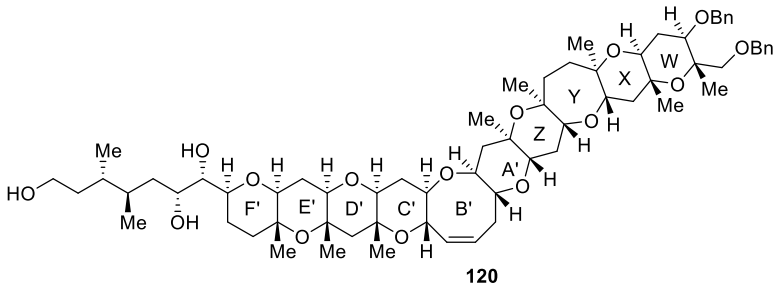
117

Methylacetal (117). $CaCl_2$ (grinded and activated by heat-gun, 90.7 mg, 817 μmol) and PPTS (88.0 mg, 350 μmol) were added to a solution of hydroxy ketone **114** (17.8 mg, 10.9 μmol) in 1,2-dichloroethane (1.1 mL) and MeOH (1.1 mL) at 0 °C. After stirring at 85 °C for 72 h, the reaction mixture was quenched with Et_3N (500 μL) and saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. The organic layer was washed

with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 → 0/1) to give methylacetal **117** (11.3 mg, 9.63 μmol, 88%) as a single isomer as a colorless amorphous solid.



Mixed-thioacetal (124). A solution of methylacetal **117** (9.2 mg, 7.84 μmol) and EtSH (600 μL, 8.11 mmol) in CH_2Cl_2 (300 μL) predried over MS3A (75.9 mg) was added to a suspension of $Zn(OTf)_2$ (35.0 mg, 96.3 μmol, preactivated by heat-gun) in CH_2Cl_2 (100 μL) at 0 °C. After stirring at room temperature for 2.8 h, the reaction mixture was quenched with saturated aqueous solution of Et_3N and saturated aqueous of $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 → 0/1) to give a mixture of mixed-thioacetal **124** and dithioacetal **S1**, and it was used for the next reaction without further purification.

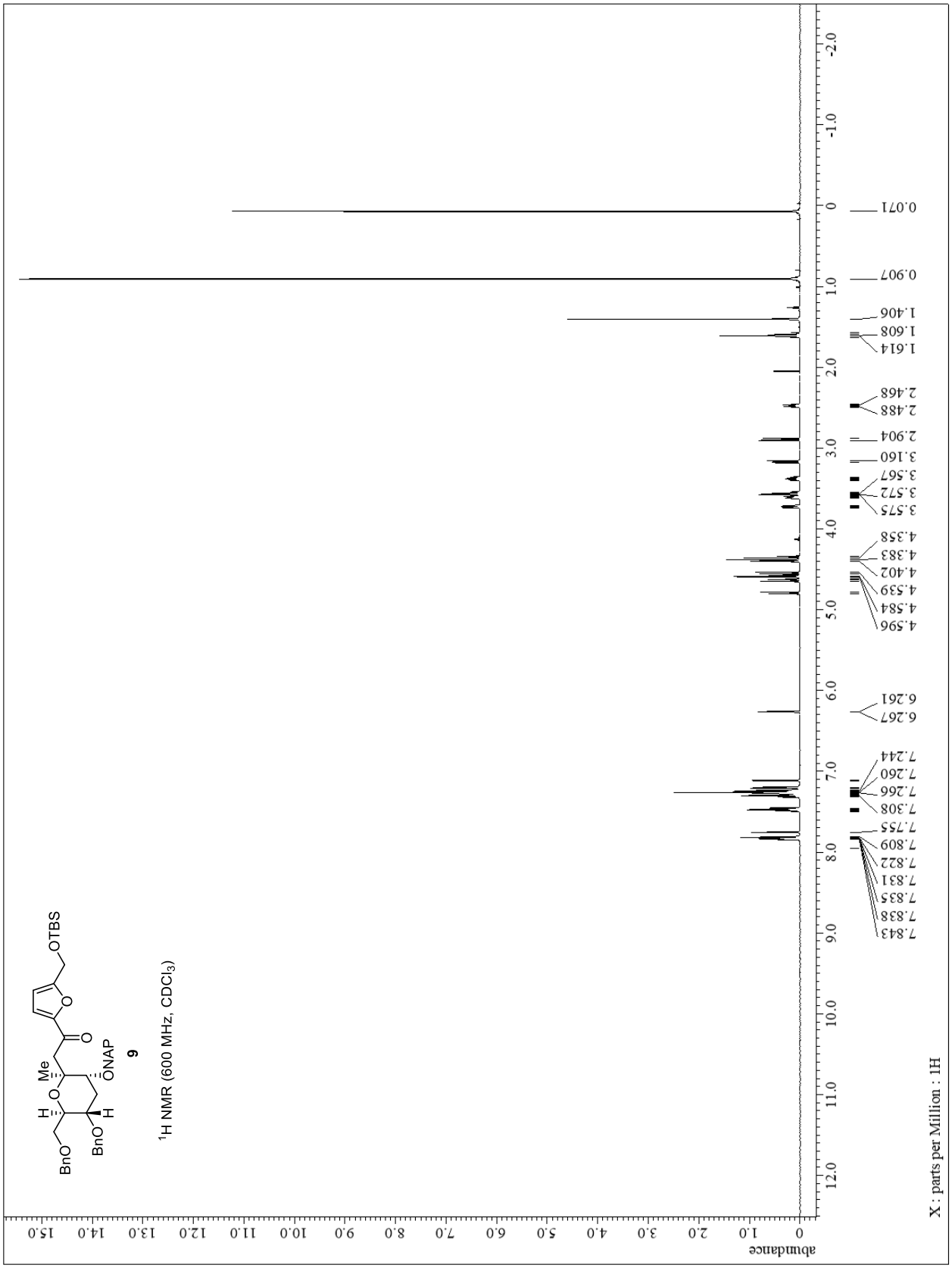


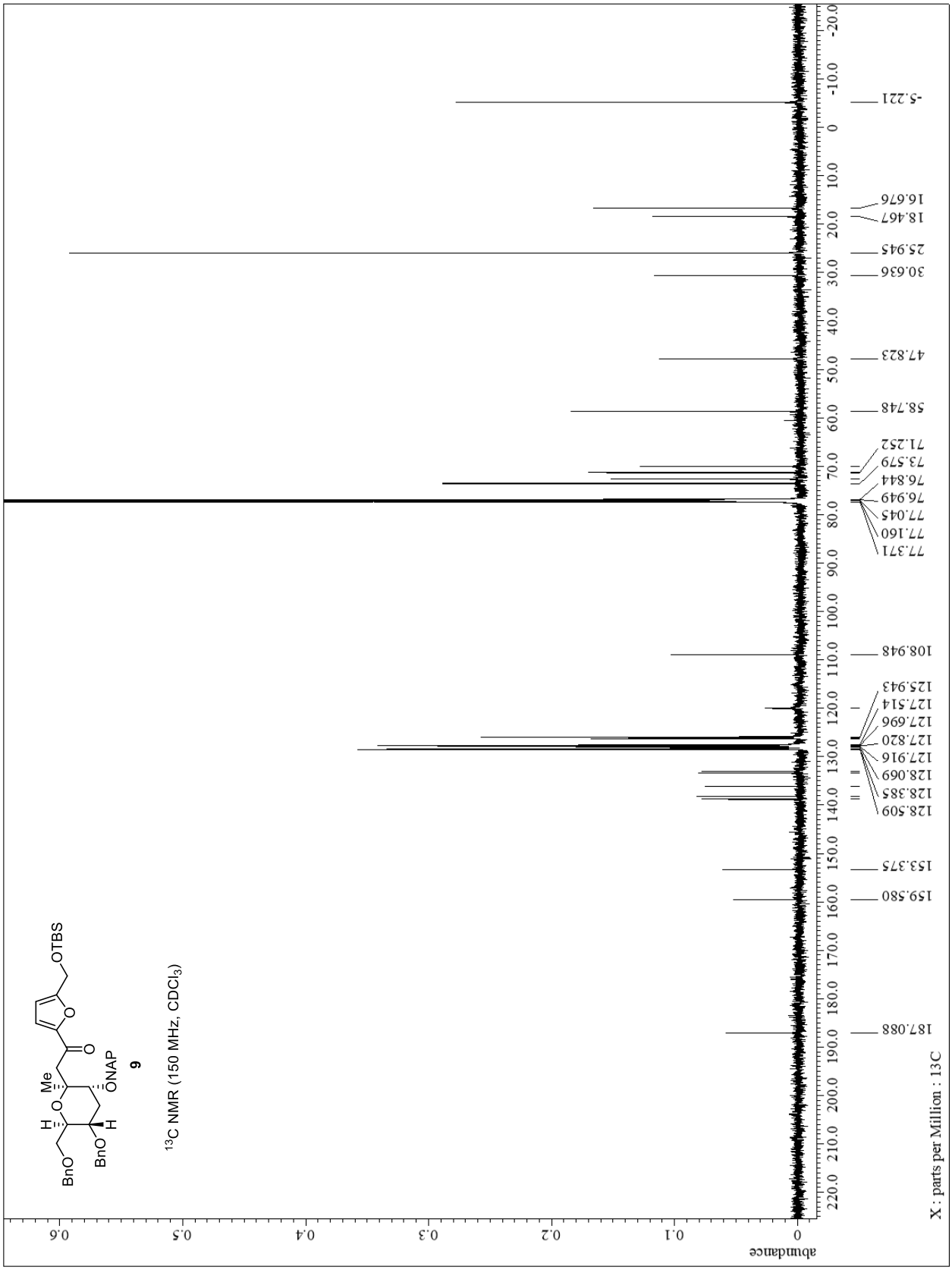
The WXYZA'B'C'D'E'F' ring system (120). $(TMS)_3SiH$ (200 μL, 648 μmol), PhSH (2 μL, 19.6 μmol), and VA-044 (0.67 M in H2O, 34.0 μL, 22.6 μmol) were added to a solution of an above mixture in EtOH (200 μL) at room temperature. After stirring at 70 °C for 40 min, the resulting solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 → 1/20) to give the WXYZA'B'C'D'E'F' ring **120** (3.7 mg, 3.24 μmol, 41% for two steps) as a colorless amorphous solid.

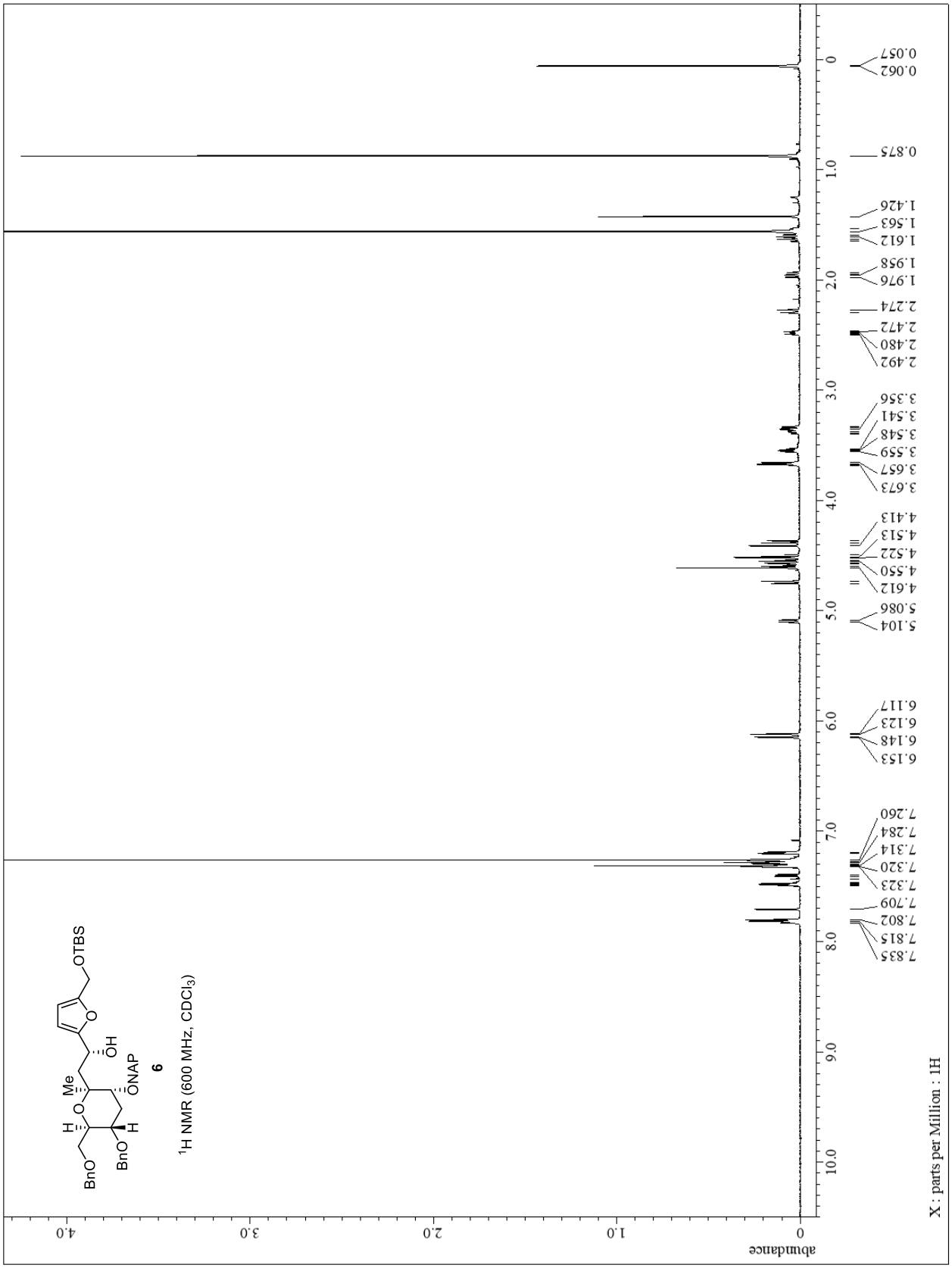
R_f = 0.23 (hexane/EtOAc = 1/10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.26–7.22 (m, 6H), 7.19–7.16 (m, 2H), 5.76 (dd, *J* = 12.6, 6.6 Hz, 1H), 5.64 (q, *J* = 12.6 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 2H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.35 (t, *J* = 6.6 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.91 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.86 (dt, *J* = 10.8, 3.6 Hz, 1H), 3.76 (dt, *J* = 12.0, 4.2 Hz, 1H), 3.71–3.64 (m, 2H), 3.64–3.58 (m, 2H), 3.46–3.29 (m, 8H), 3.25–3.20 (m, 2H), 3.10 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.80–2.74 (m, 1H), 2.31 (dd, *J* = 12.6, 6.6 Hz, 1H), 2.13–2.07 (m, 3H), 2.10–1.59 (m, 21H), 1.50 (dt, *J* = 12.6, 4.8 Hz, 1H), 1.43 (t, *J* = 12.0 Hz, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.33–1.29 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.27–1.24 (m, 1H), 1.233 (s, 3H), 1.226 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 0.86 (d, *J* = 6.0 Hz, 3H), 0.79 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 139.9, 136.5, 129.19 (2C), 129.15 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 126.8, 87.7, 86.9, 84.7, 84.5, 84.2, 84.1, 83.8, 81.5, 80.3, 79.6, 79.1, 78.8, 77.7, 77.6, 77.0, 76.9, 76.8, 75.4, 74.8, 74.7, 74.2, 74.1, 73.4, 72.4, 72.3, 71.8, 70.2, 61.2, 54.0, 46.8, 42.8, 40.4, 39.4, 39.1, 37.6, 37.1, 35.7, 34.2, 33.4, 31.5, 30.3, 28.8, 27.9, 26.5, 23.5, 22.2, 21.9, 21.7, 21.6, 20.3, 18.3, 18.2, 16.7, 16.6; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{67}H_{98}O_{15}Na$ 1165.6798, found 1165.6814.

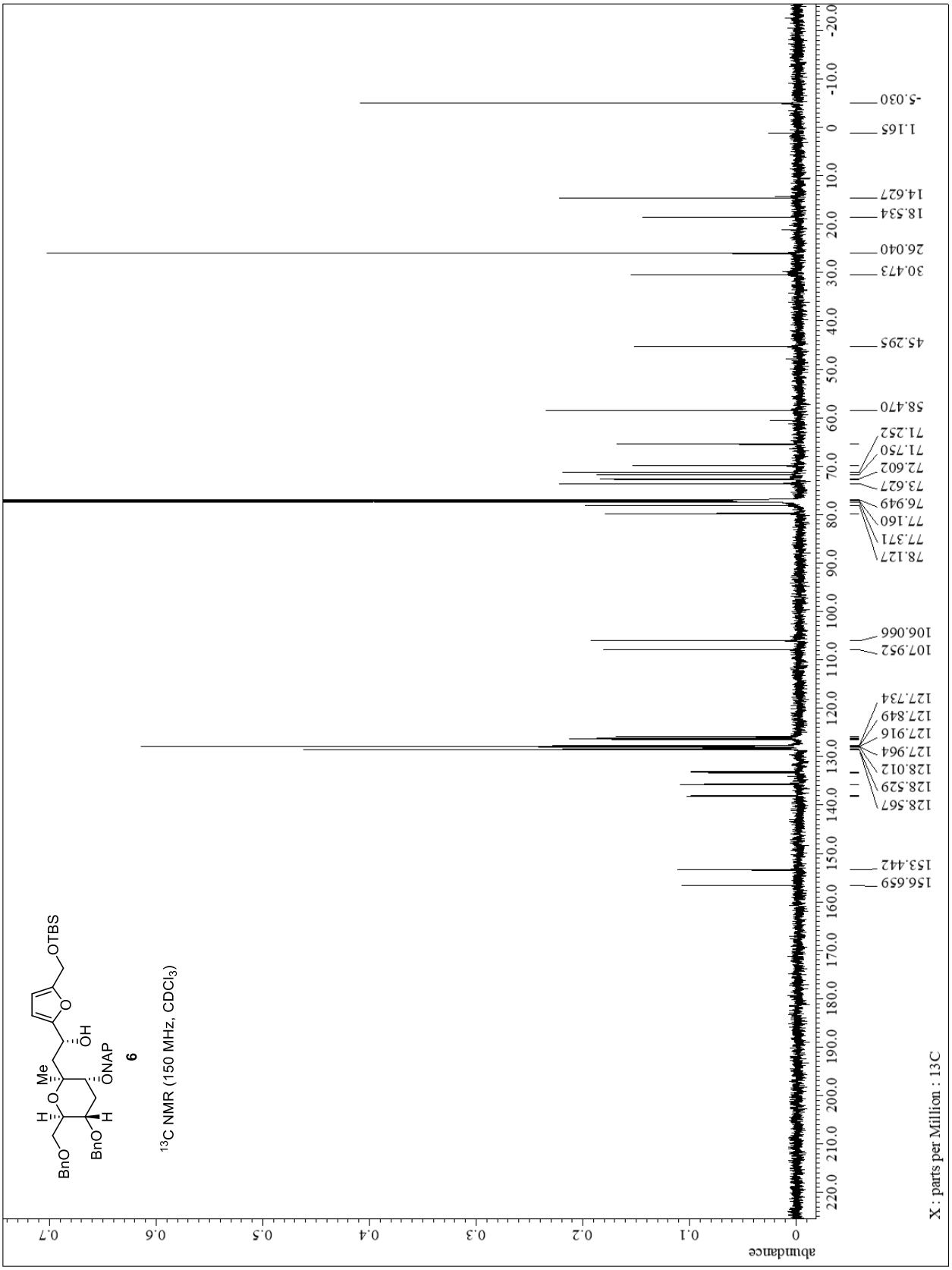
Spectral data

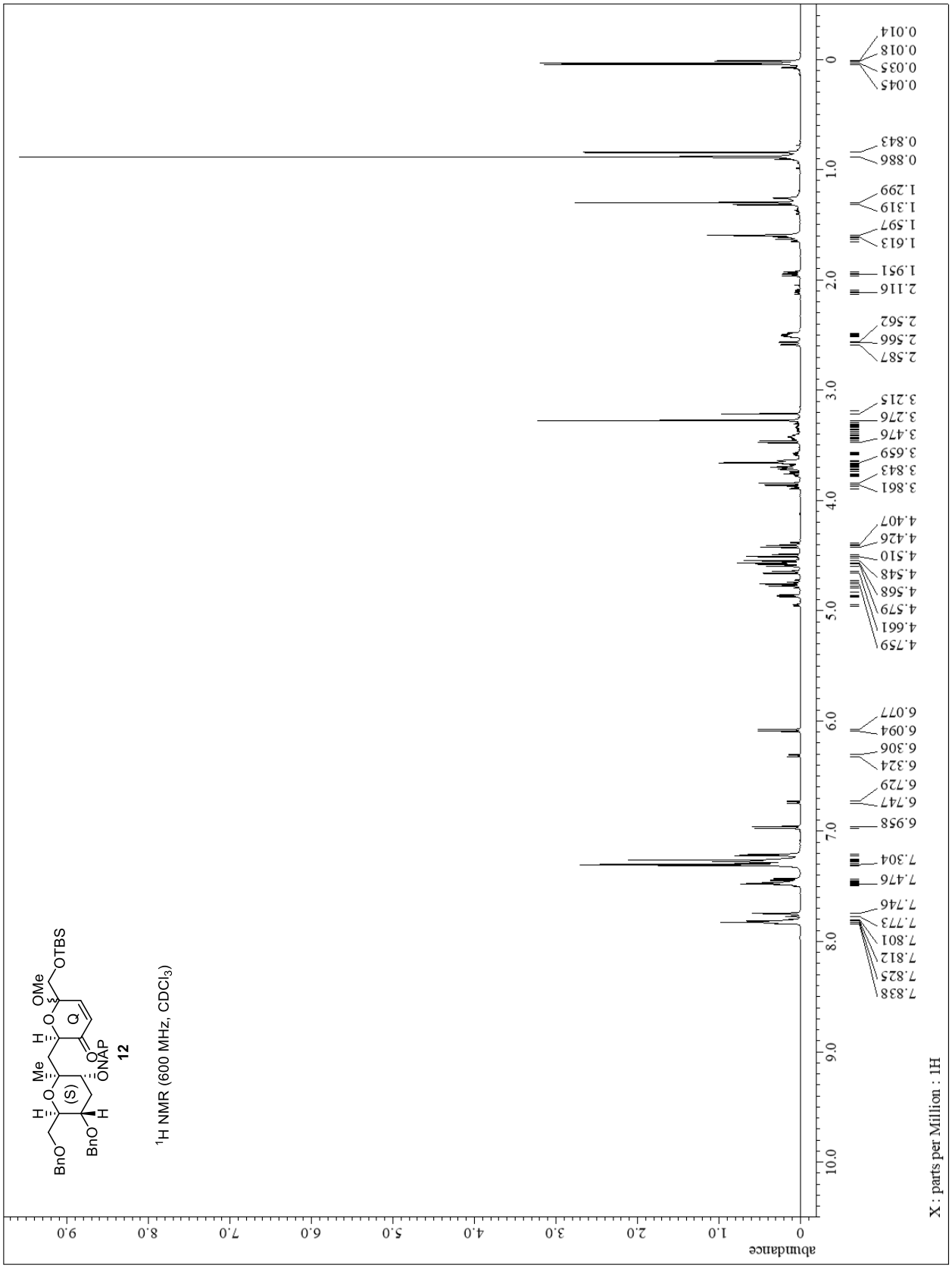
Section 2-1

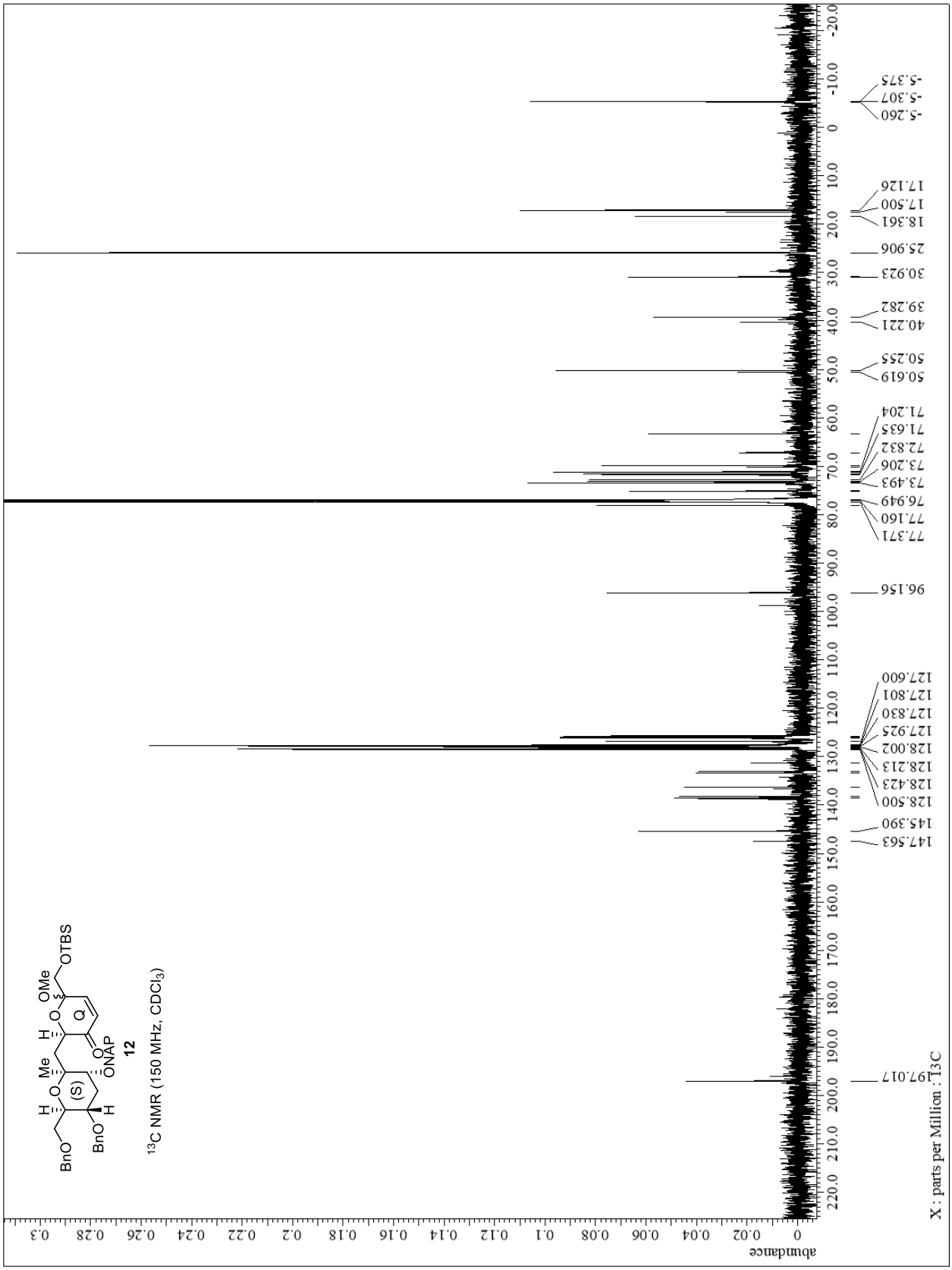

OTBS
O
O
Me
O
ONAP
H
H
BnO
BnO
9
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
0.071
0.907
1.406
1.608
1.614
2.468
2.488
2.904
3.160
3.567
3.572
3.575
4.358
4.383
4.402
4.539
4.584
4.596
6.261
6.267
7.244
7.260
7.266
7.308
7.755
7.809
7.822
7.831
7.835
7.838
7.843

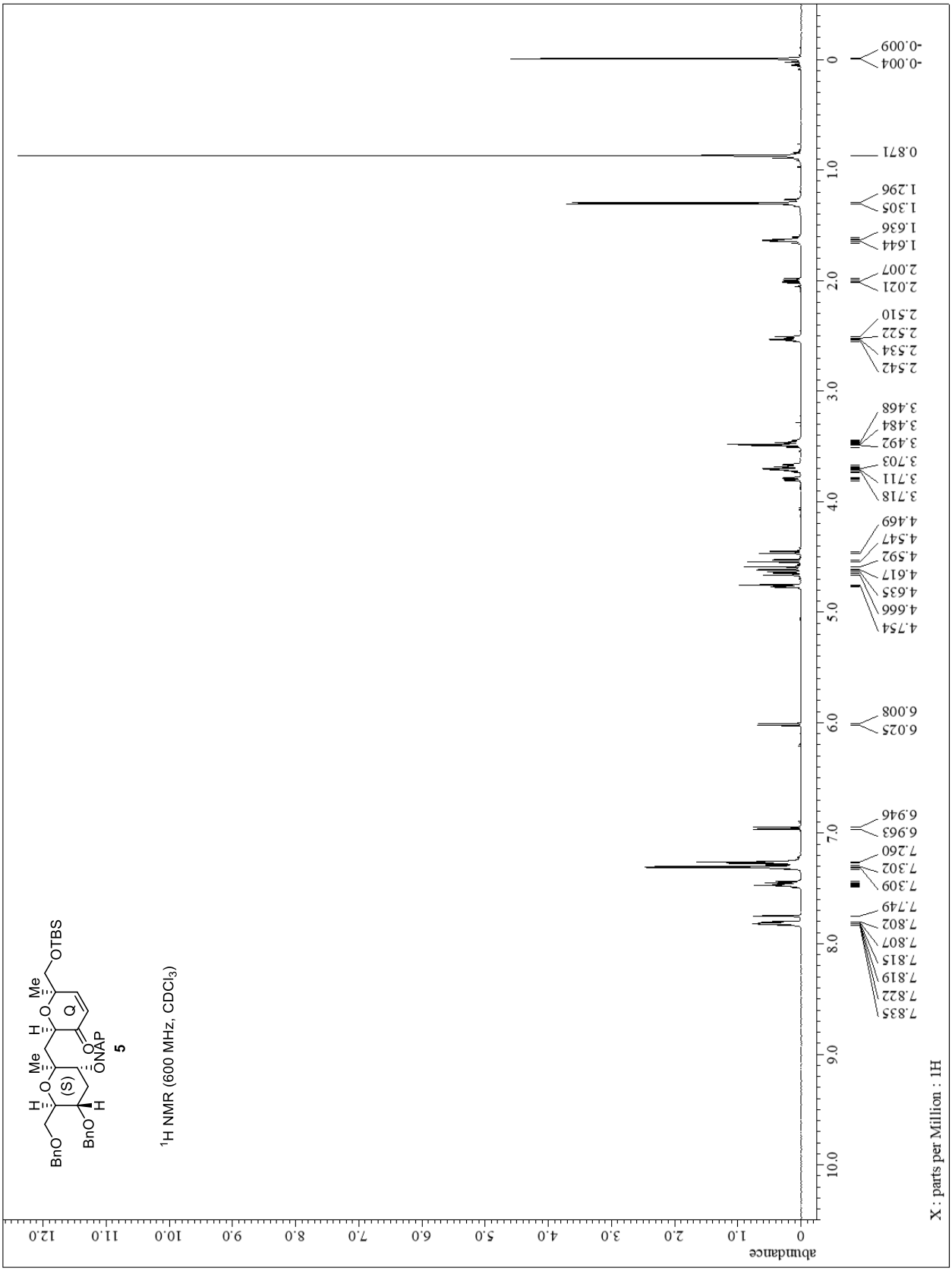

OTBS
O
O
Me
O
H
ONAP
BnO
H
BnO
9
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
-5.221
16.676
18.467
25.945
30.636
47.823
58.748
71.252
73.579
76.844
76.949
77.045
77.160
77.371
108.948
125.943
127.514
127.696
127.820
127.916
128.069
128.385
128.509
153.375
159.580
187.088

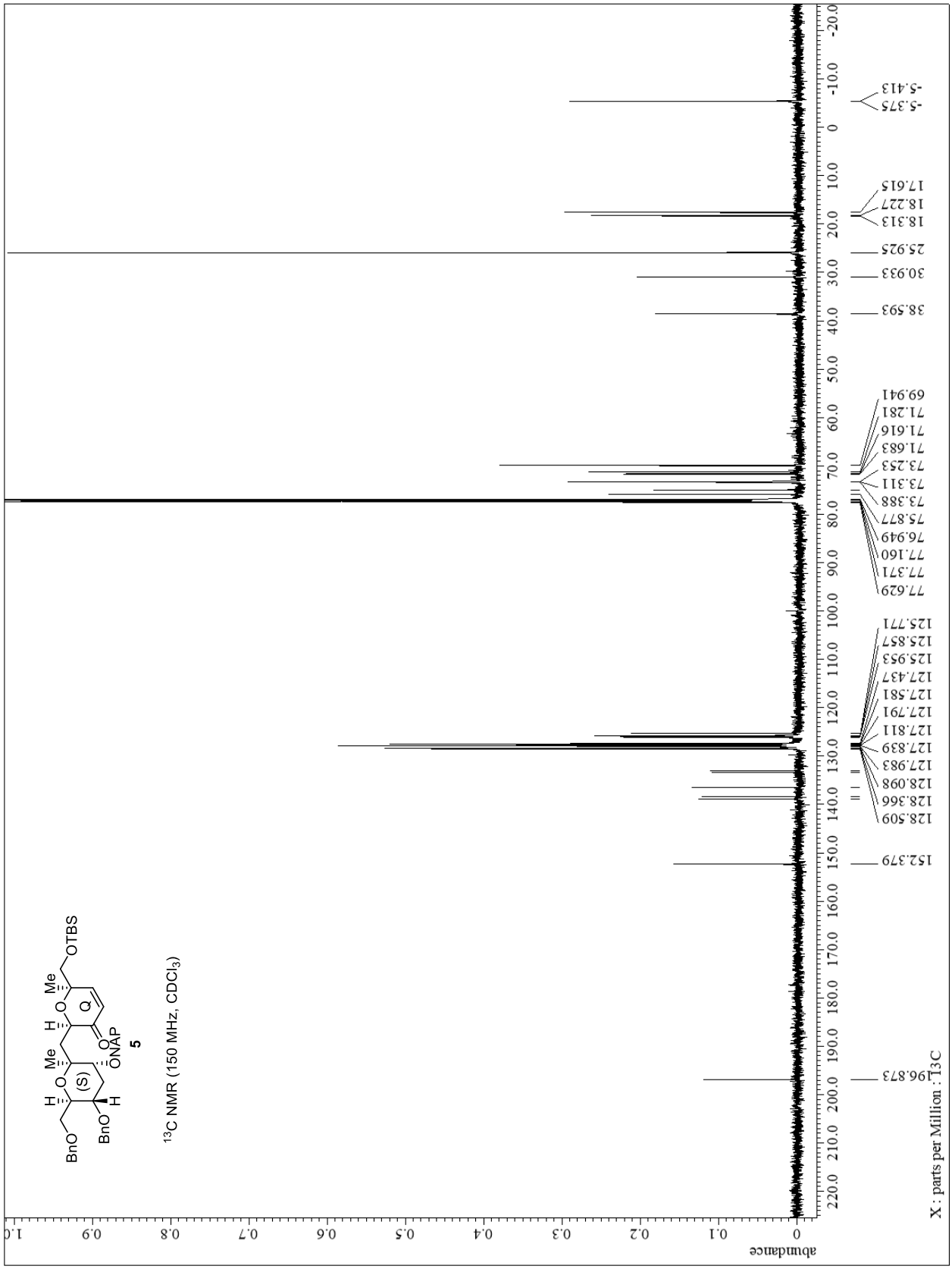

OTBS
OH
ONAP
Me
BnO
BnO
H
H
O
O
6
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
0.057
0.062
0.875
1.426
1.563
1.612
1.958
1.976
2.274
2.472
2.480
2.492
3.356
3.541
3.548
3.559
3.657
3.673
4.413
4.513
4.522
4.550
4.612
5.086
5.104
6.117
6.123
6.148
6.153
7.260
7.284
7.314
7.320
7.323
7.709
7.802
7.815
7.835

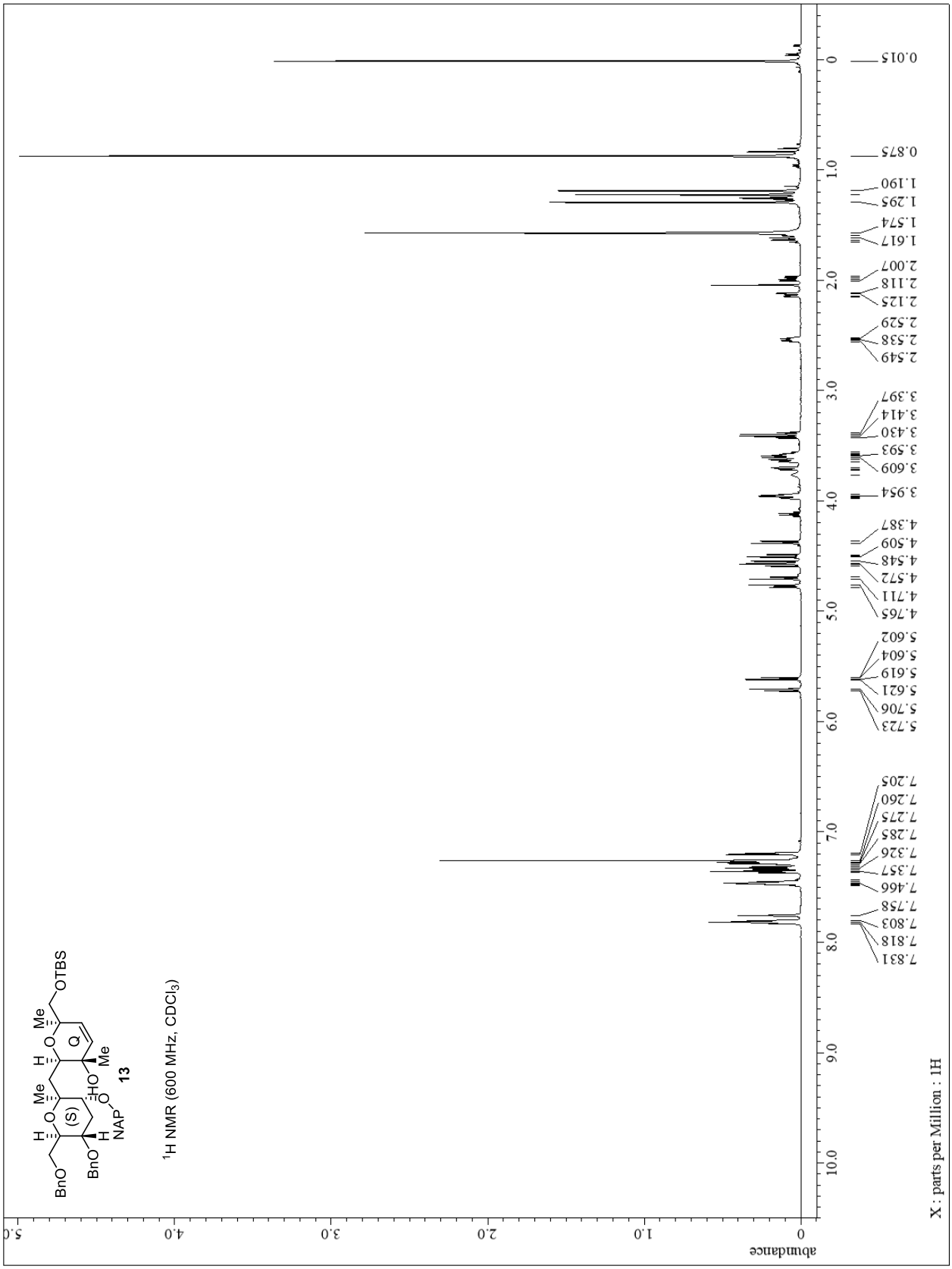

OTBS
OH
Me
ONAP
BnO
BnO
H
H
6
^{13}C NMR (150 MHz, $CDCl_3$)
-5.030
1.165
14.627
18.534
26.040
30.473
45.295
58.470
71.252
71.750
72.602
73.627
76.949
77.160
77.371
78.127
106.066
107.952
127.734
127.849
127.916
127.964
128.012
128.529
128.567
153.442
156.659
abundance
X : parts per Million : 13C

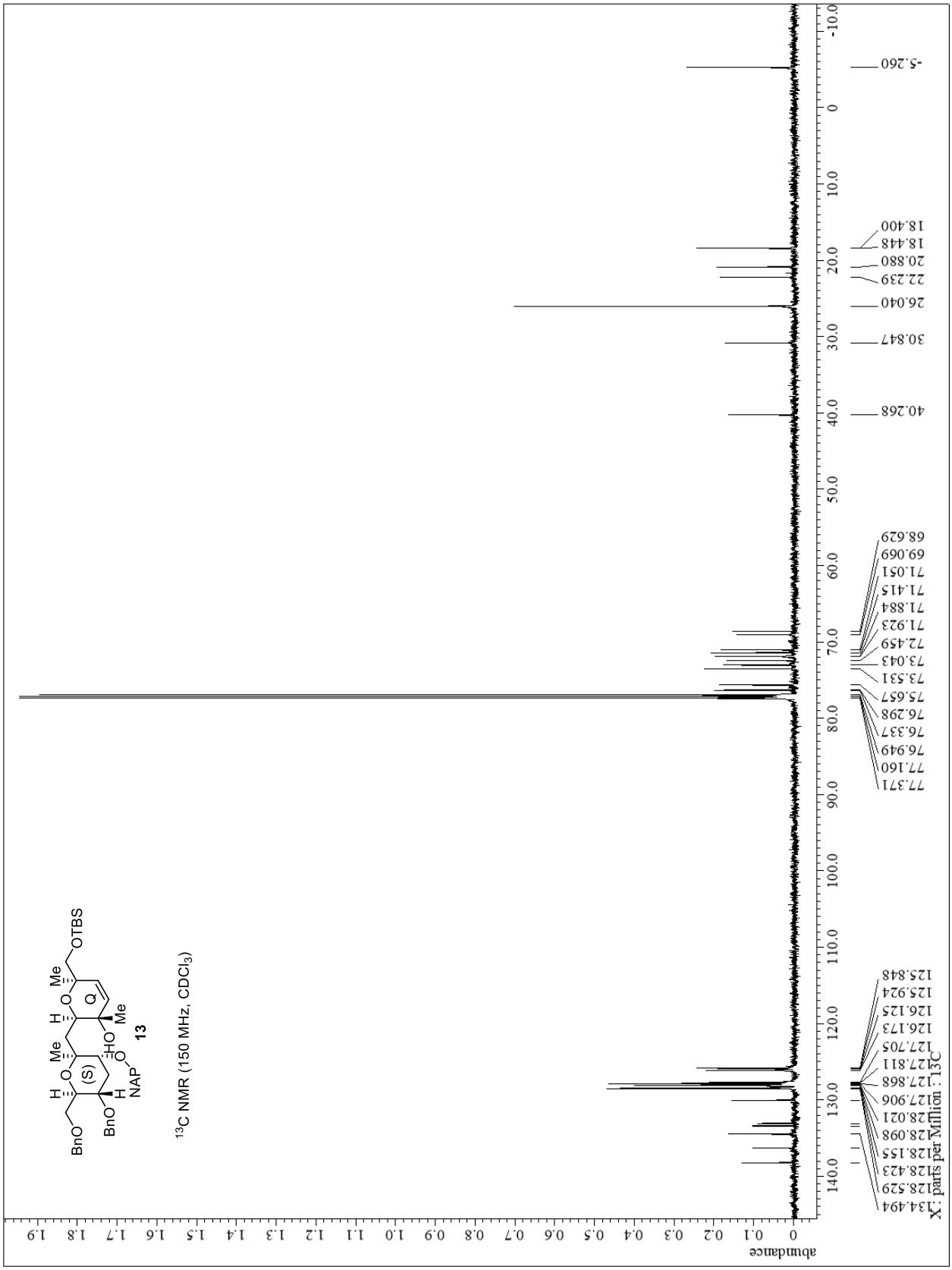

12
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

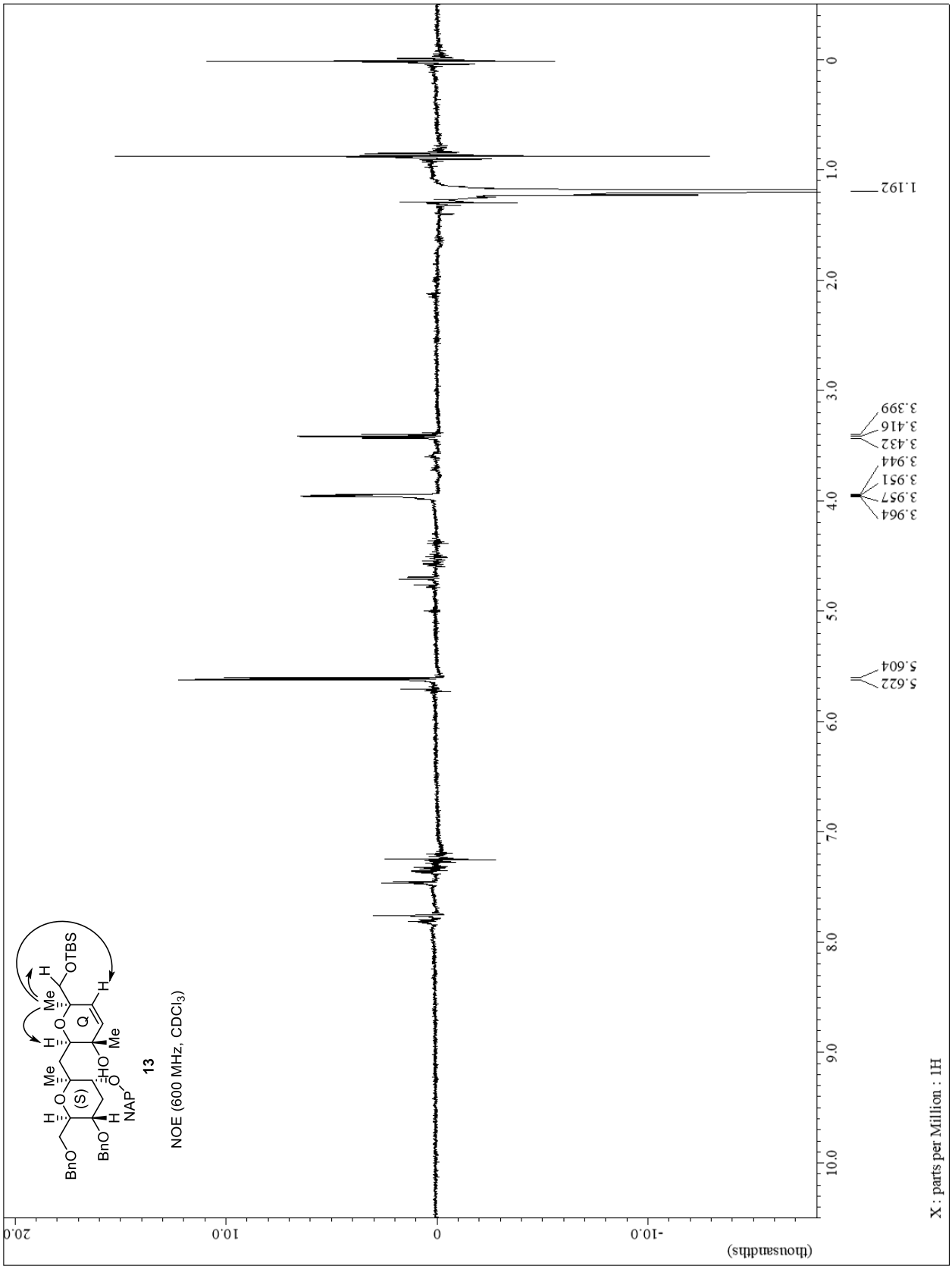

12
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : ^{13}C
abundance
197.017
147.563
145.390
128.500
128.423
128.213
128.002
127.925
127.830
127.801
127.600
96.156
77.371
77.160
76.949
73.493
73.206
72.832
71.635
71.204
50.619
50.255
40.221
39.282
30.923
25.906
18.361
17.500
17.126
-5.260
-5.307
-5.375

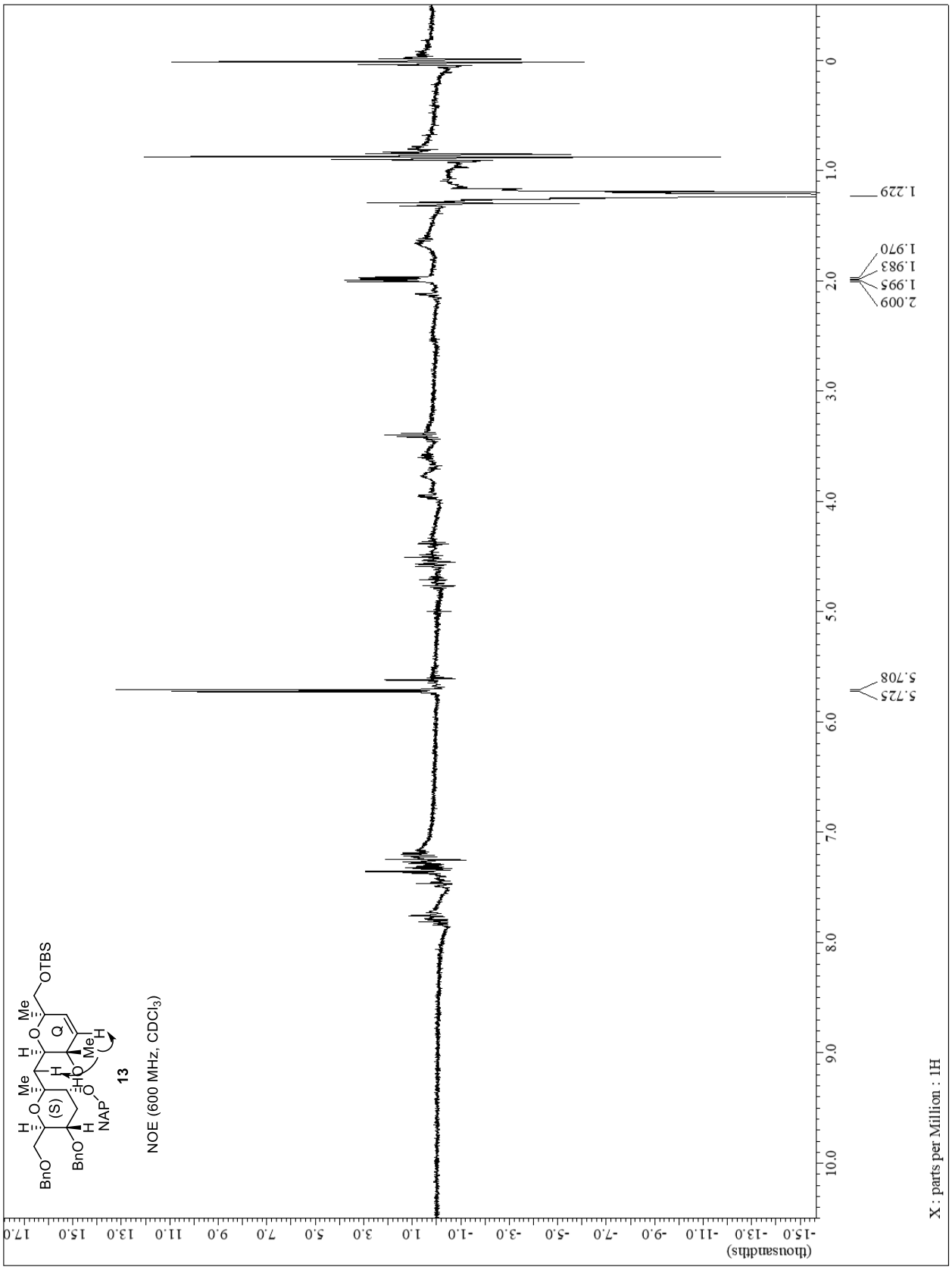

BnO
H
O
Me
(S)
H
O
Me
BnO
H
O
Q
OTBS
ONAP
5
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
-0.009
-0.004
0.871
1.296
1.305
1.636
1.644
2.007
2.021
2.510
2.522
2.534
2.542
3.468
3.484
3.492
3.703
3.711
3.718
4.469
4.547
4.592
4.617
4.635
4.666
4.754
6.008
6.025
6.946
6.963
7.260
7.302
7.309
7.749
7.802
7.807
7.815
7.819
7.822
7.835

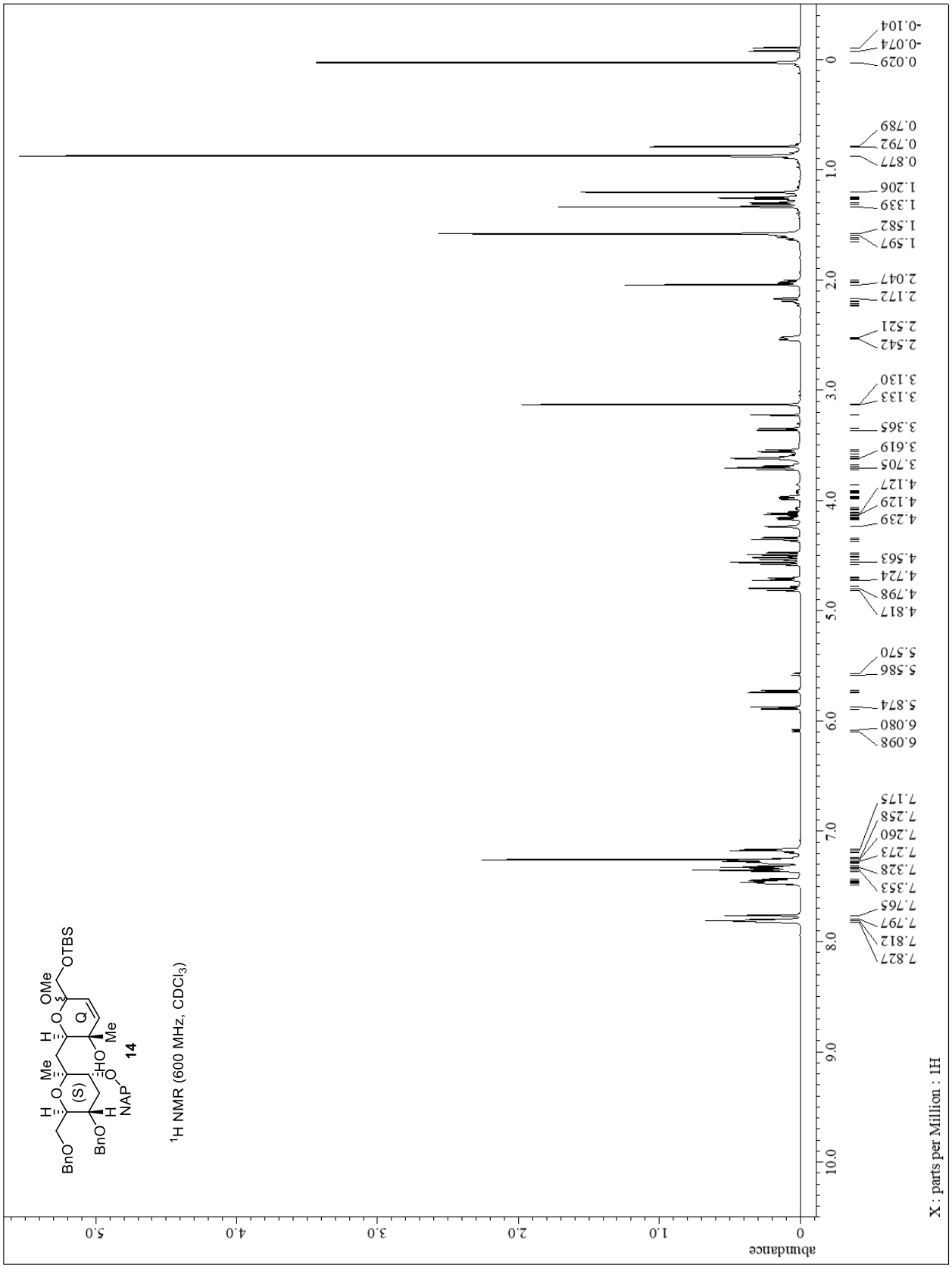

OTBS
Me
H
O
Me
Q
BnO
(S)
BnO
H
ONAP
5
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
196.873
152.379
128.509
128.366
128.098
127.983
127.839
127.811
127.791
127.581
127.437
125.953
125.857
125.771
77.629
77.371
77.160
76.949
75.877
73.388
73.311
73.253
71.683
71.616
71.281
69.941
38.593
30.933
25.925
18.313
18.227
17.615
-5.375
-5.413

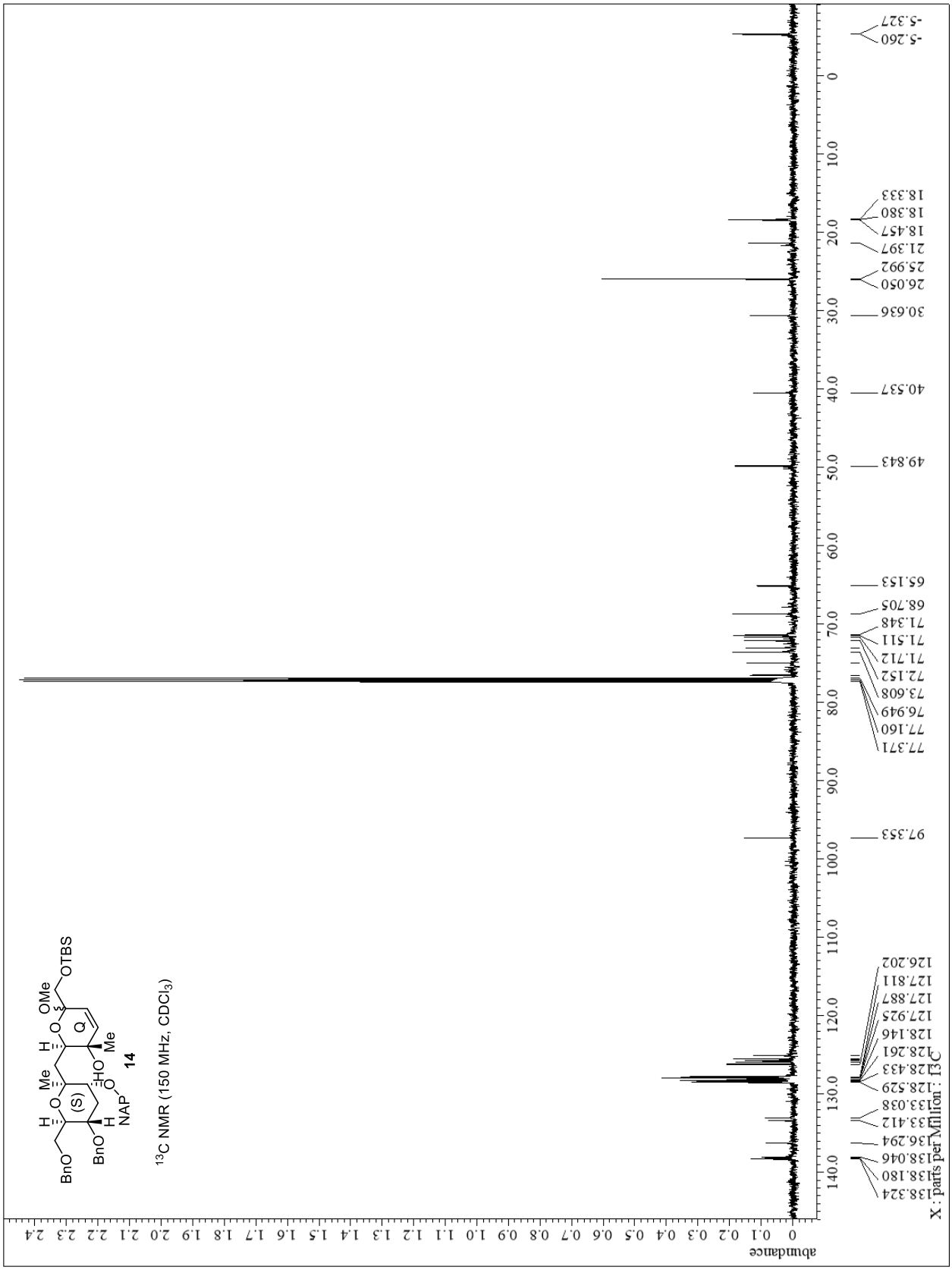

BnO
H
O
Me
(S)
H
NAP
BnO
H
O
Me
HO
Me
O
Q
H
O
Me
OTBS
13
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
0.015
0.875
1.190
1.295
1.574
1.617
2.007
2.118
2.125
2.529
2.538
2.549
3.397
3.414
3.430
3.593
3.609
3.954
4.387
4.509
4.548
4.572
4.711
4.765
5.602
5.604
5.619
5.621
5.706
5.723
7.205
7.260
7.275
7.285
7.326
7.357
7.466
7.758
7.803
7.818
7.831


13
^{13}C NMR (150 MHz, $CDCl_3$)
X: parts per Million : 13C
abundance
-5.260
18.400
18.448
20.880
22.239
26.040
30.847
40.268
68.629
69.069
71.051
71.415
71.884
71.923
72.459
73.043
73.531
75.657
76.298
76.337
76.949
77.160
77.371
125.848
125.924
126.125
126.173
127.705
127.811
127.868
127.906
128.021
128.098
128.155
128.423
128.529
134.494


13
NOE (600 MHz, CDCl3)
X : parts per Million : 1H
(thousandths)
1.192
3.399
3.416
3.432
3.944
3.951
3.957
3.964
5.604
5.622


NOE (600 MHz, CDCl3)
13
X : parts per Million : 1H
(thousandths)
1.229
1.970
1.983
1.995
2.009
5.708
5.725


14
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.827
7.812
7.797
7.765
7.353
7.328
7.273
7.260
7.258
7.175
6.098
6.080
5.874
5.586
5.570
4.817
4.798
4.724
4.563
4.239
4.129
4.127
3.705
3.619
3.365
3.133
3.130
2.542
2.521
2.172
2.047
1.597
1.582
1.339
1.206
0.877
0.792
0.789
0.029
-0.074
-0.104


OTBS
OMe
Me
BnO
(S)
BnO
HO
Me
NAP
14
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
138.324
138.180
136.294
133.412
133.038
128.529
128.433
128.261
128.146
127.925
127.887
127.811
126.202
97.353
77.371
77.160
76.949
73.608
72.152
71.712
71.511
71.348
68.705
65.153
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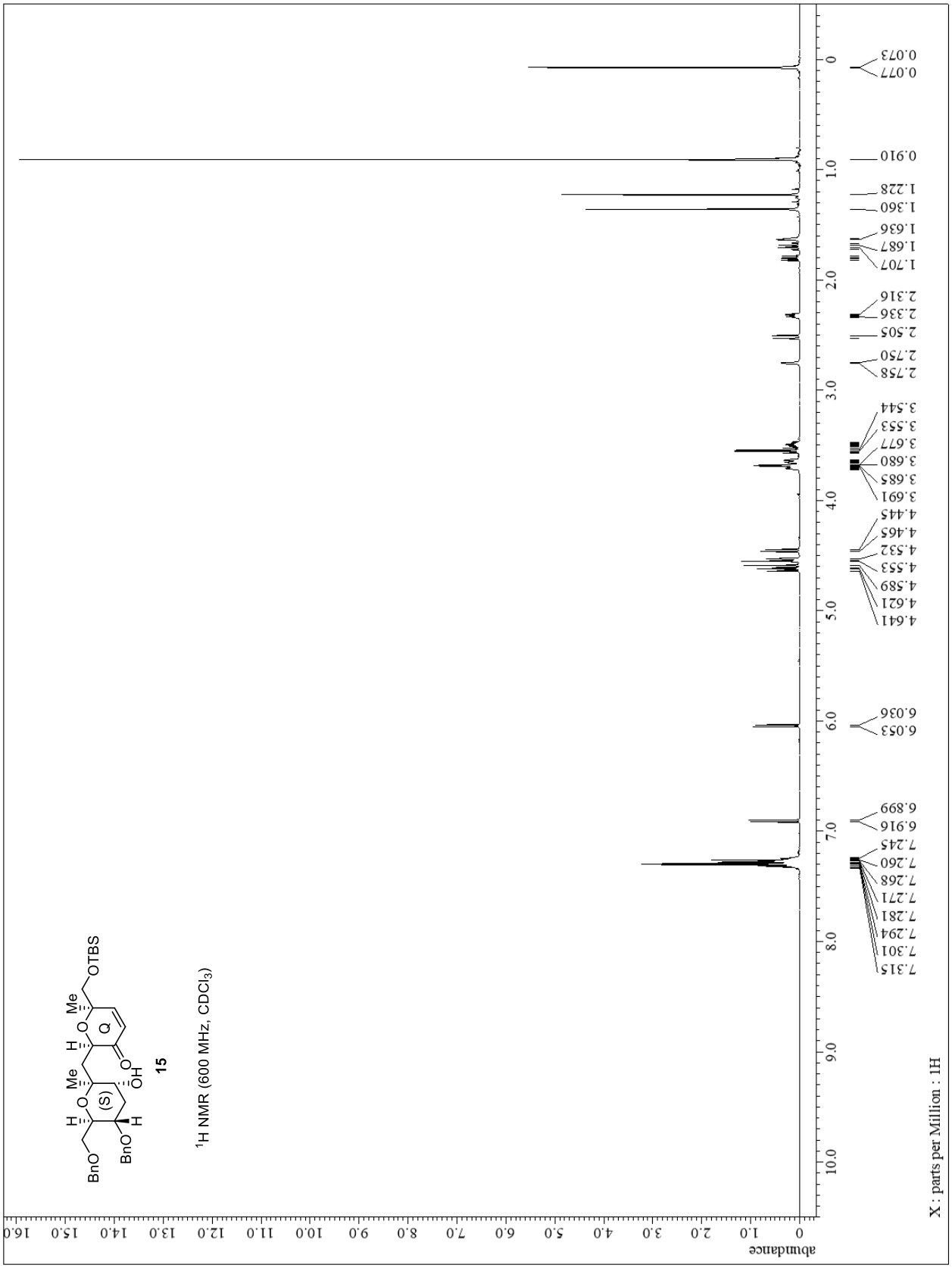
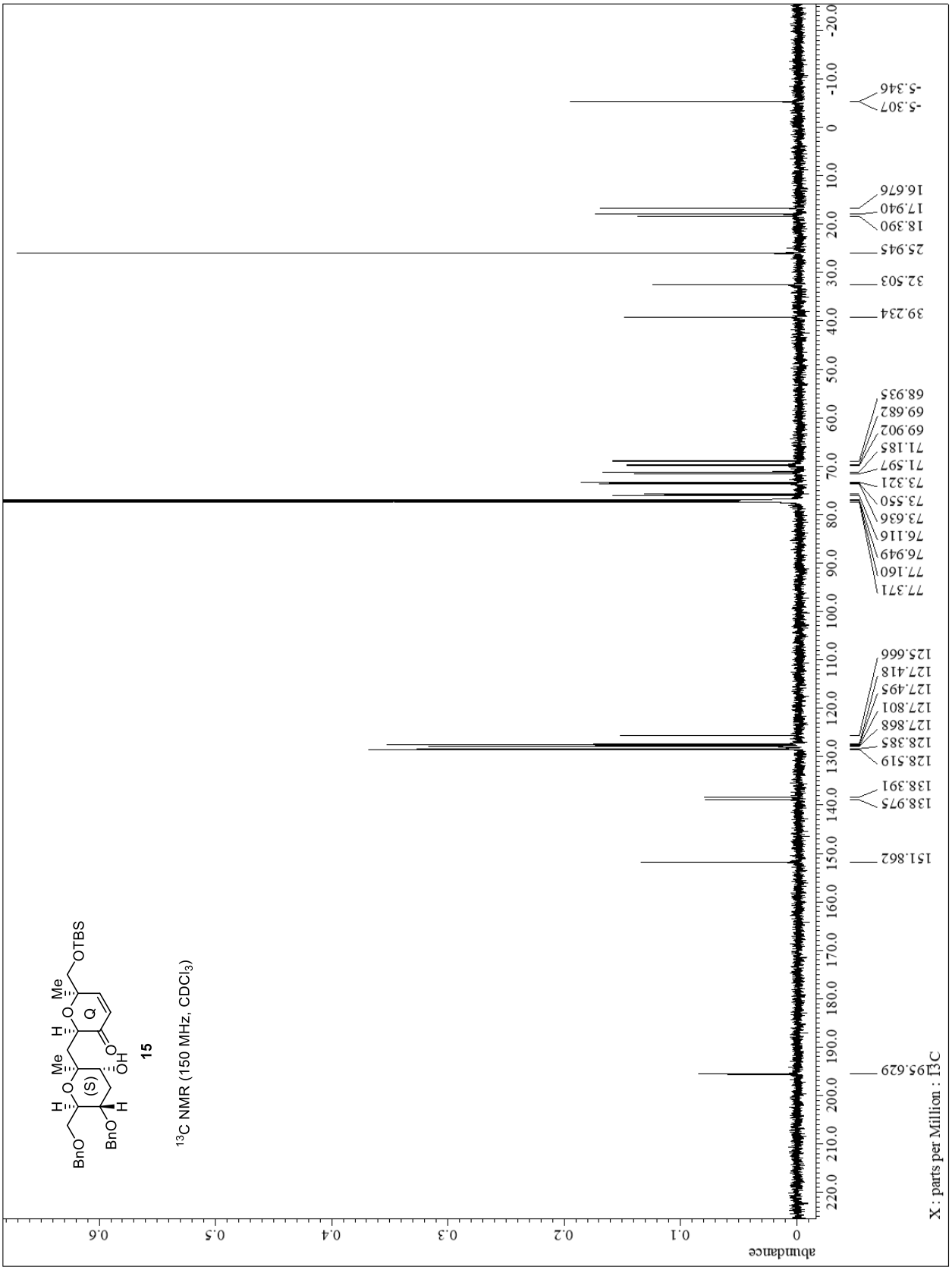
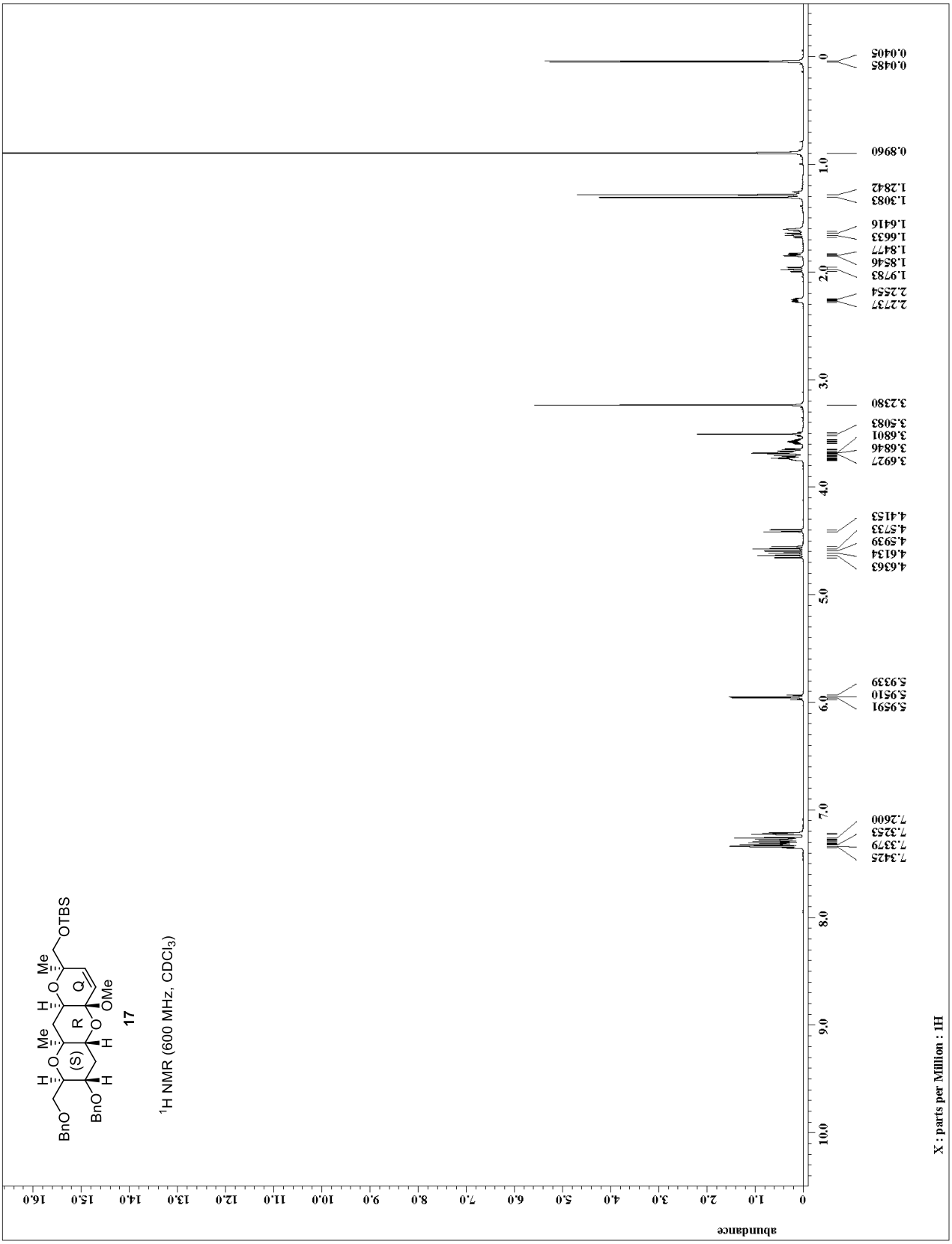
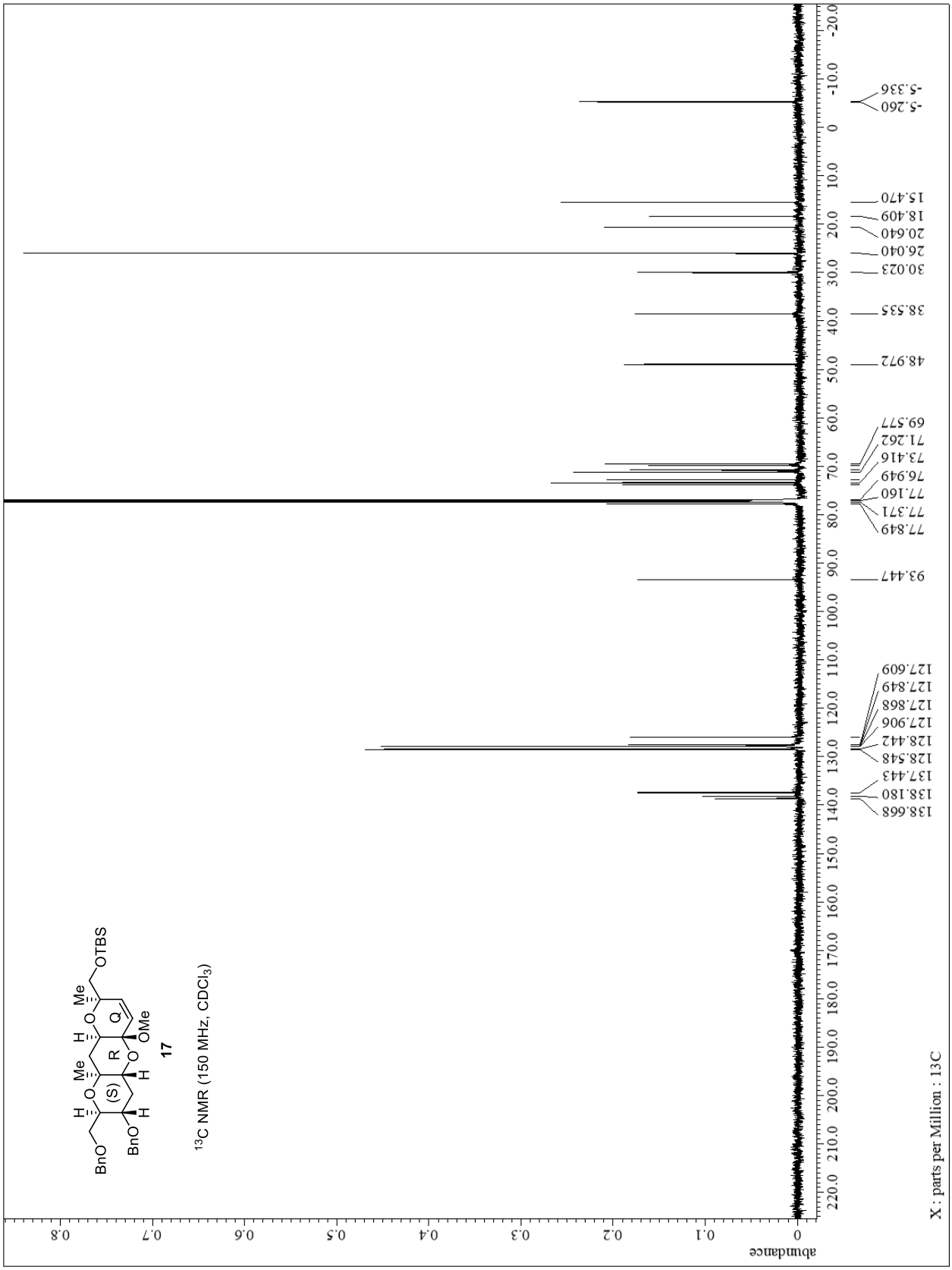
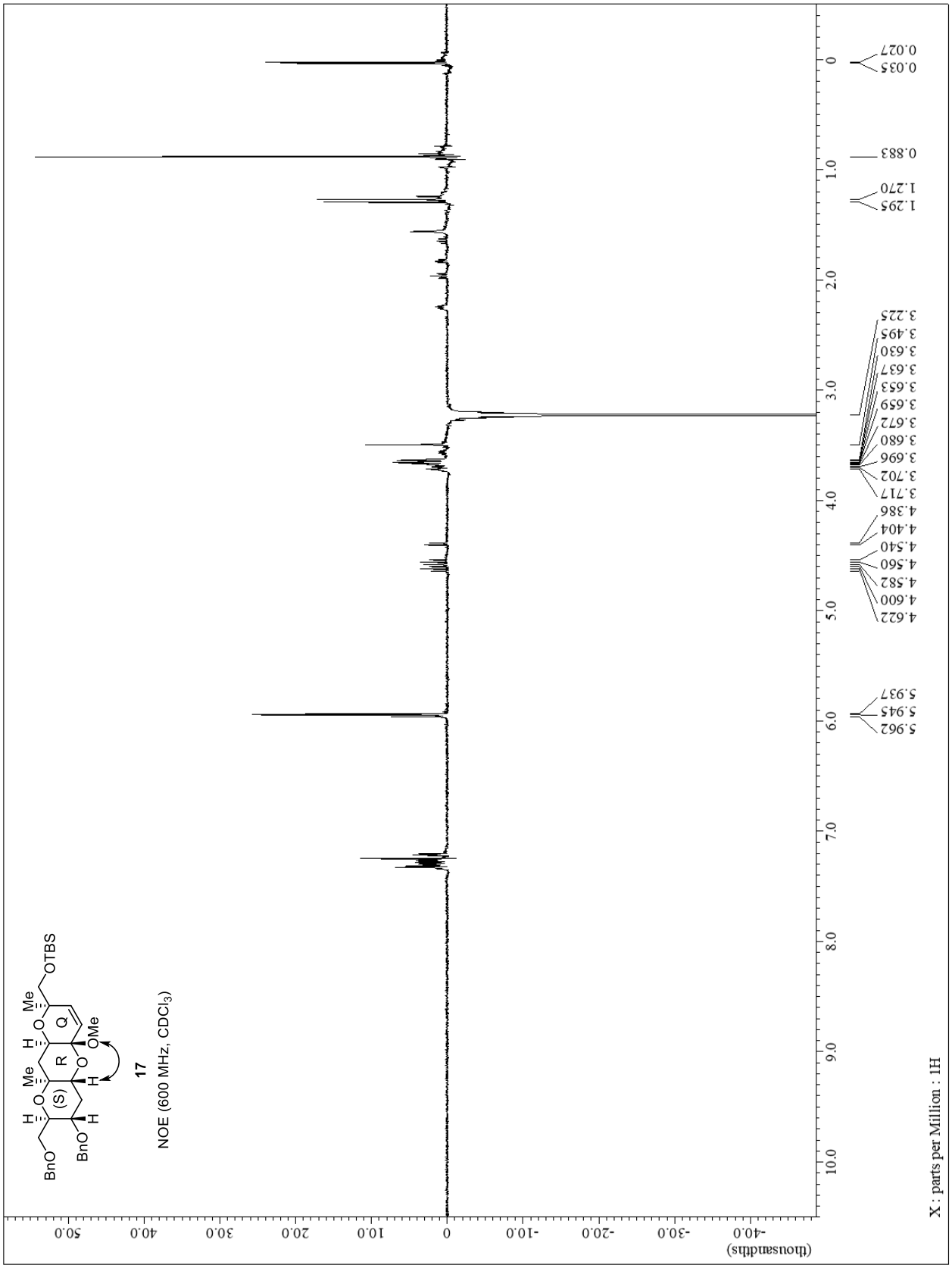
21.397
18.457
18.380
18.333
-5.260
-5.327

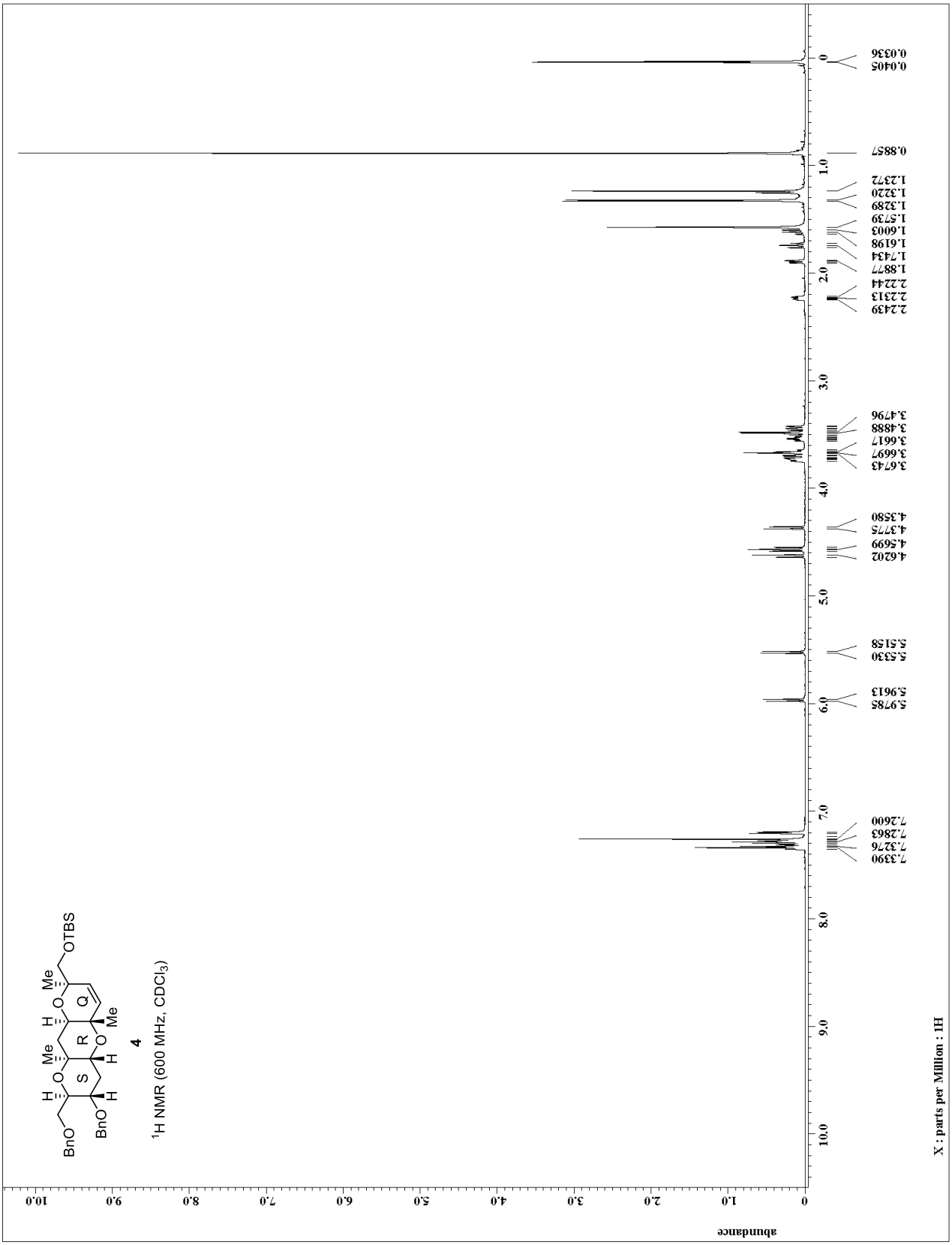

OTBS
Me
Me
H
O
Q
O
OH
(S)
H
O
H
BnO
BnO
15
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
0.073
0.077
0.910
1.228
1.360
1.636
1.687
1.707
2.316
2.336
2.505
2.750
2.758
3.544
3.553
3.677
3.680
3.685
3.691
4.445
4.465
4.532
4.553
4.589
4.621
4.641
6.036
6.053
6.899
6.916
7.245
7.260
7.268
7.271
7.281
7.294
7.301
7.315

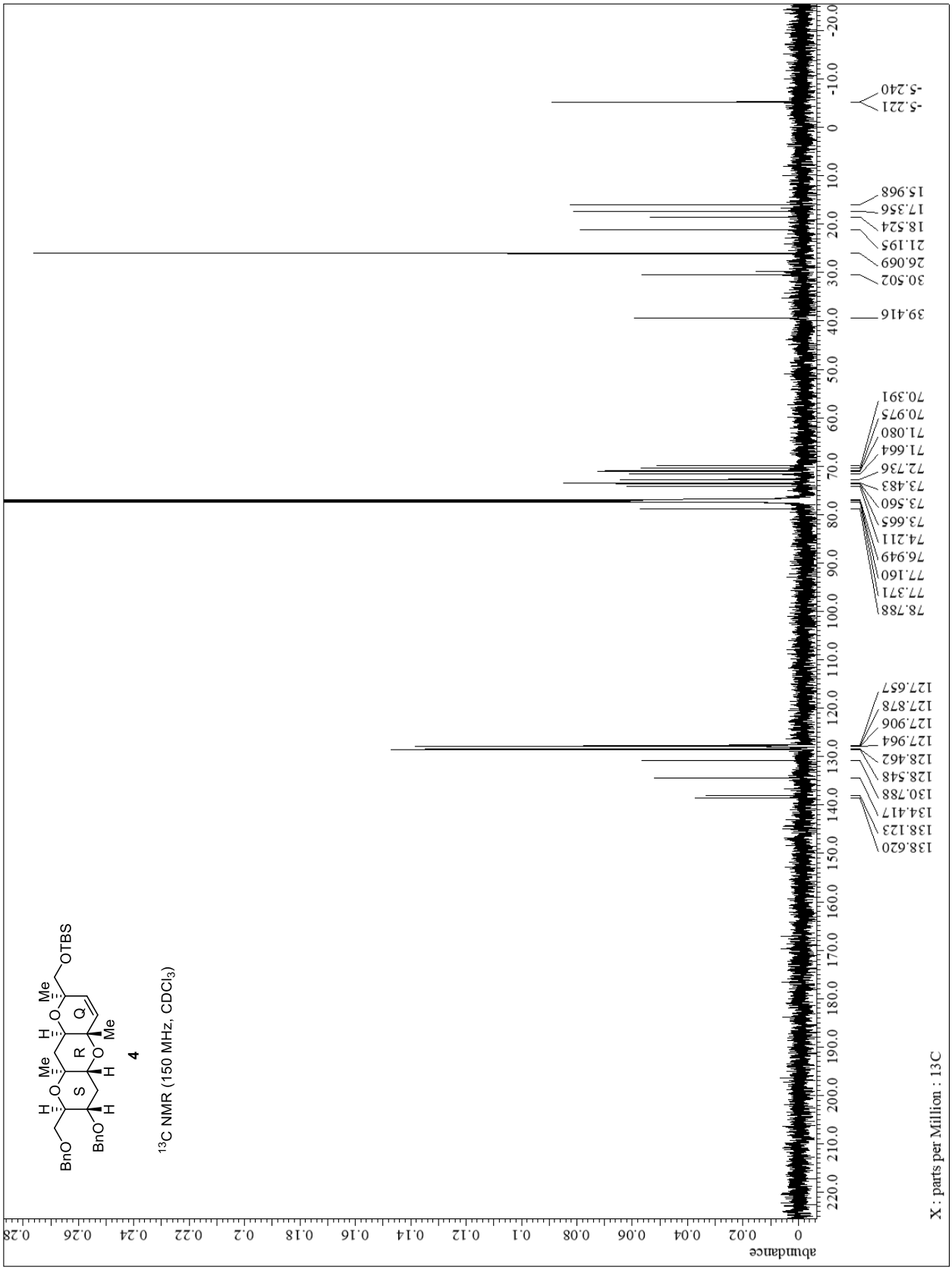

15
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : ^{13}C
abundance
-5.346
-5.307
16.676
17.940
18.390
25.945
32.503
39.234
68.935
69.682
69.902
71.185
71.597
73.321
73.550
73.636
76.116
76.949
77.160
77.371
125.666
127.418
127.495
127.801
127.868
128.385
128.519
138.391
138.975
151.862
195.629

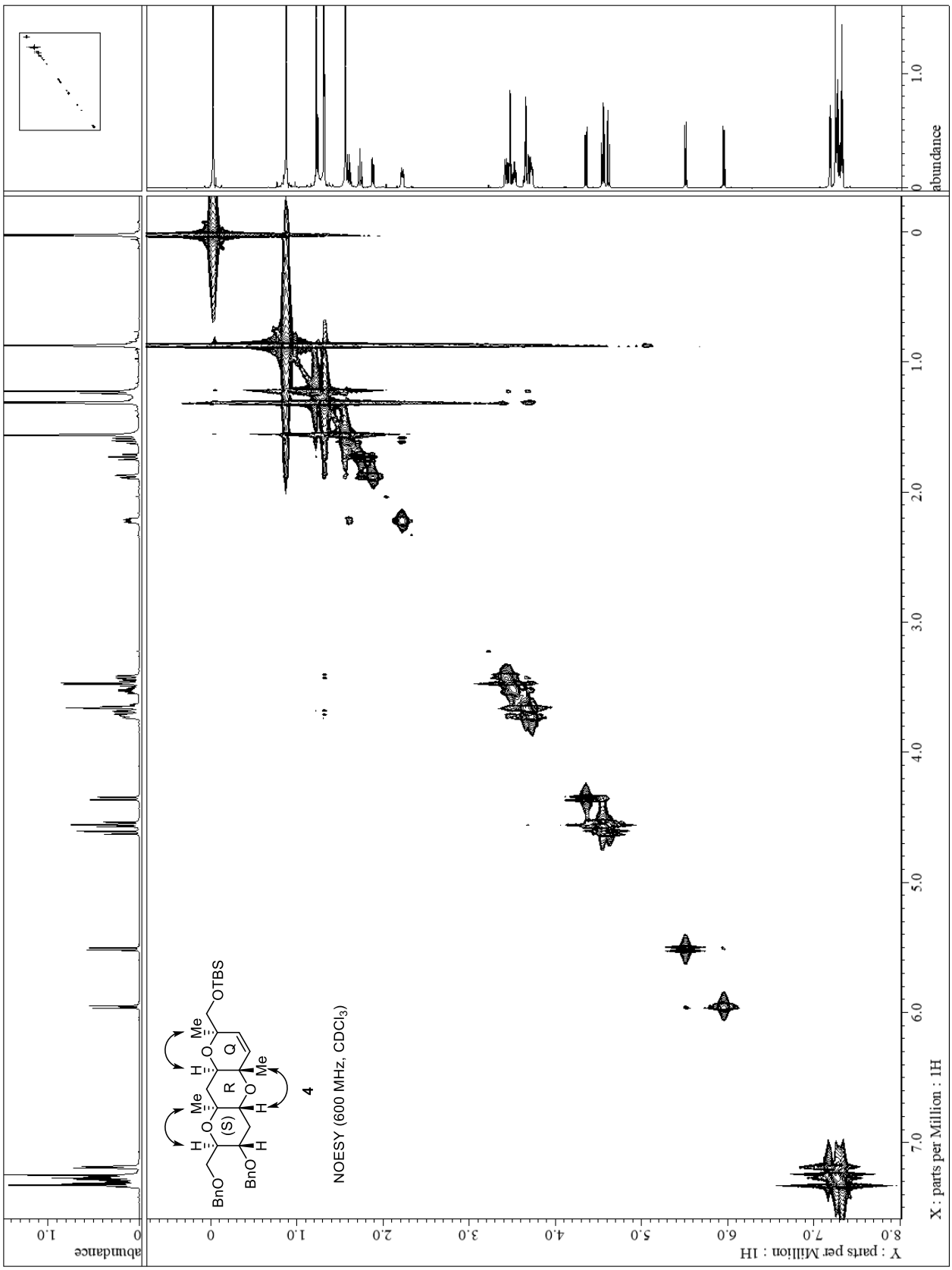

17
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.3425
7.3379
7.3253
7.2600
5.9591
5.9510
5.9339
4.6363
4.6134
4.5939
4.5733
4.4153
3.6927
3.6846
3.6801
3.5083
3.2380
2.2737
2.2554
1.9783
1.8546
1.8477
1.6633
1.6416
1.3083
1.2842
0.8960
0.0485
0.0405

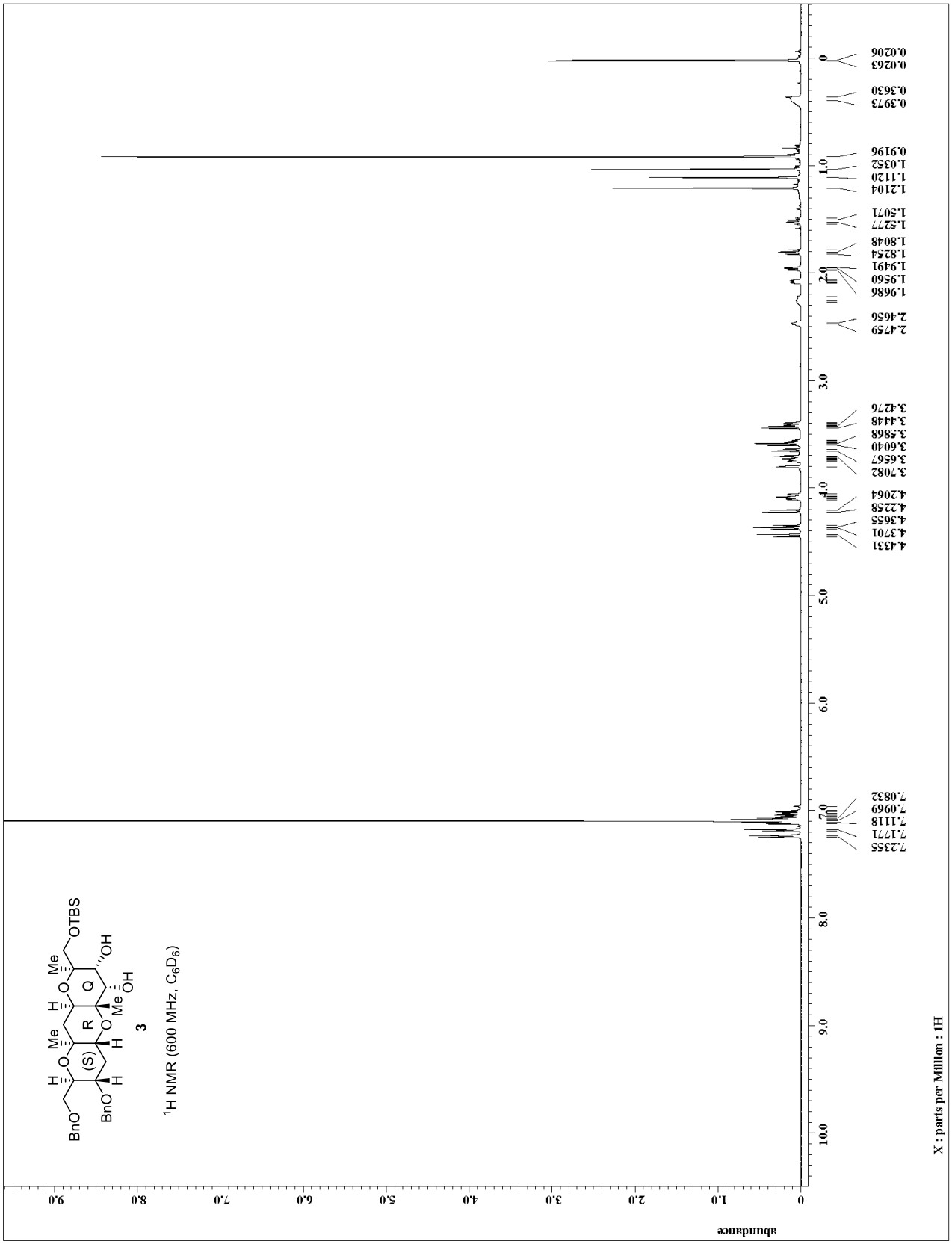

17
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
-5.336
-5.260
15.470
18.409
20.640
26.040
30.023
38.535
48.972
69.577
71.262
73.416
76.949
77.160
77.371
77.849
93.447
127.609
127.849
127.868
127.906
128.442
128.548
137.443
138.180
138.668

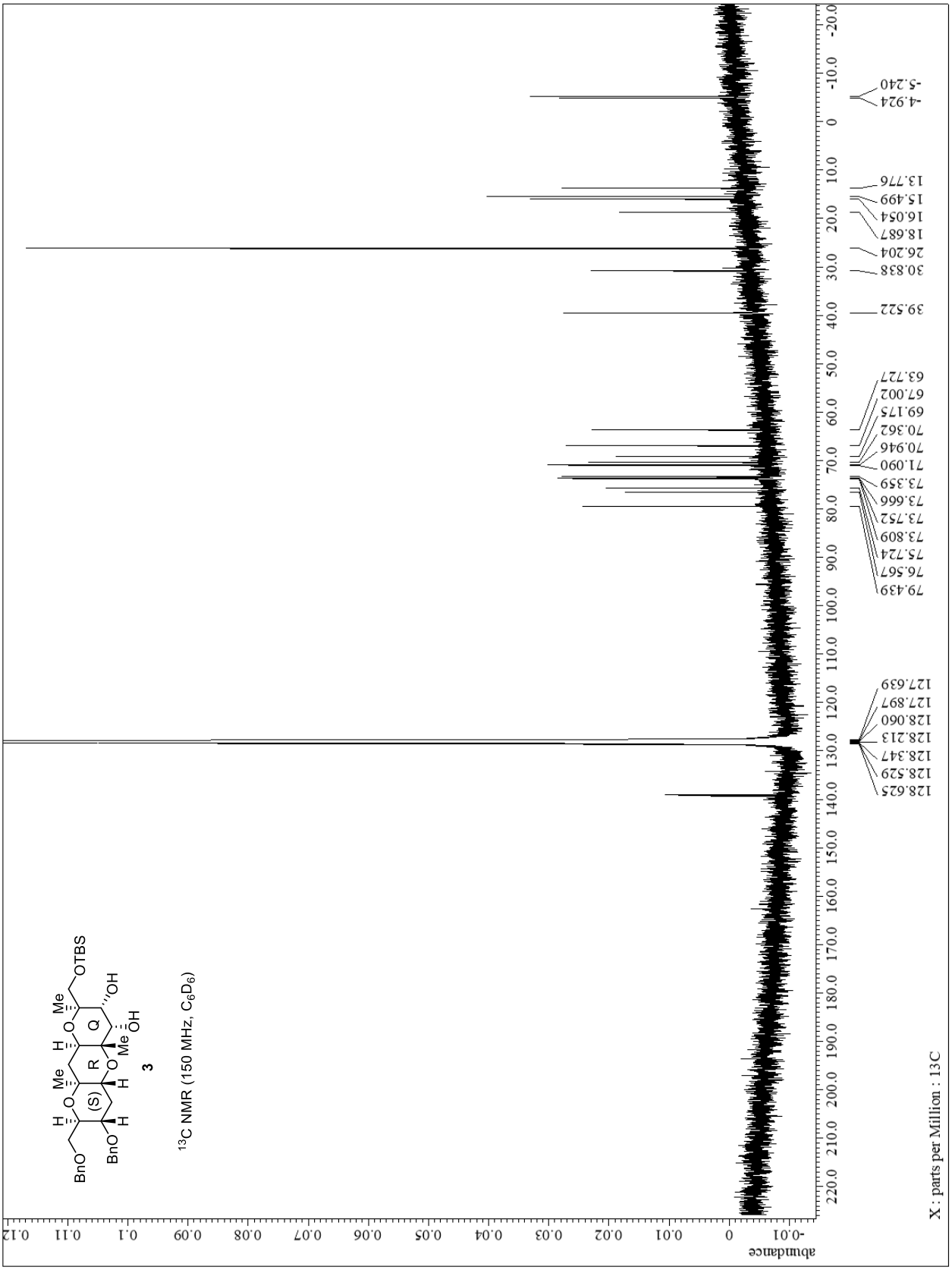

17
NOE (600 MHz, CDCl3)
X : parts per Million : 1H
(thousandths)
0.027
0.035
0.883
1.270
1.295
3.225
3.495
3.630
3.637
3.653
3.659
3.672
3.680
3.696
3.702
3.717
4.386
4.404
4.540
4.560
4.582
4.600
4.622
5.937
5.945
5.962

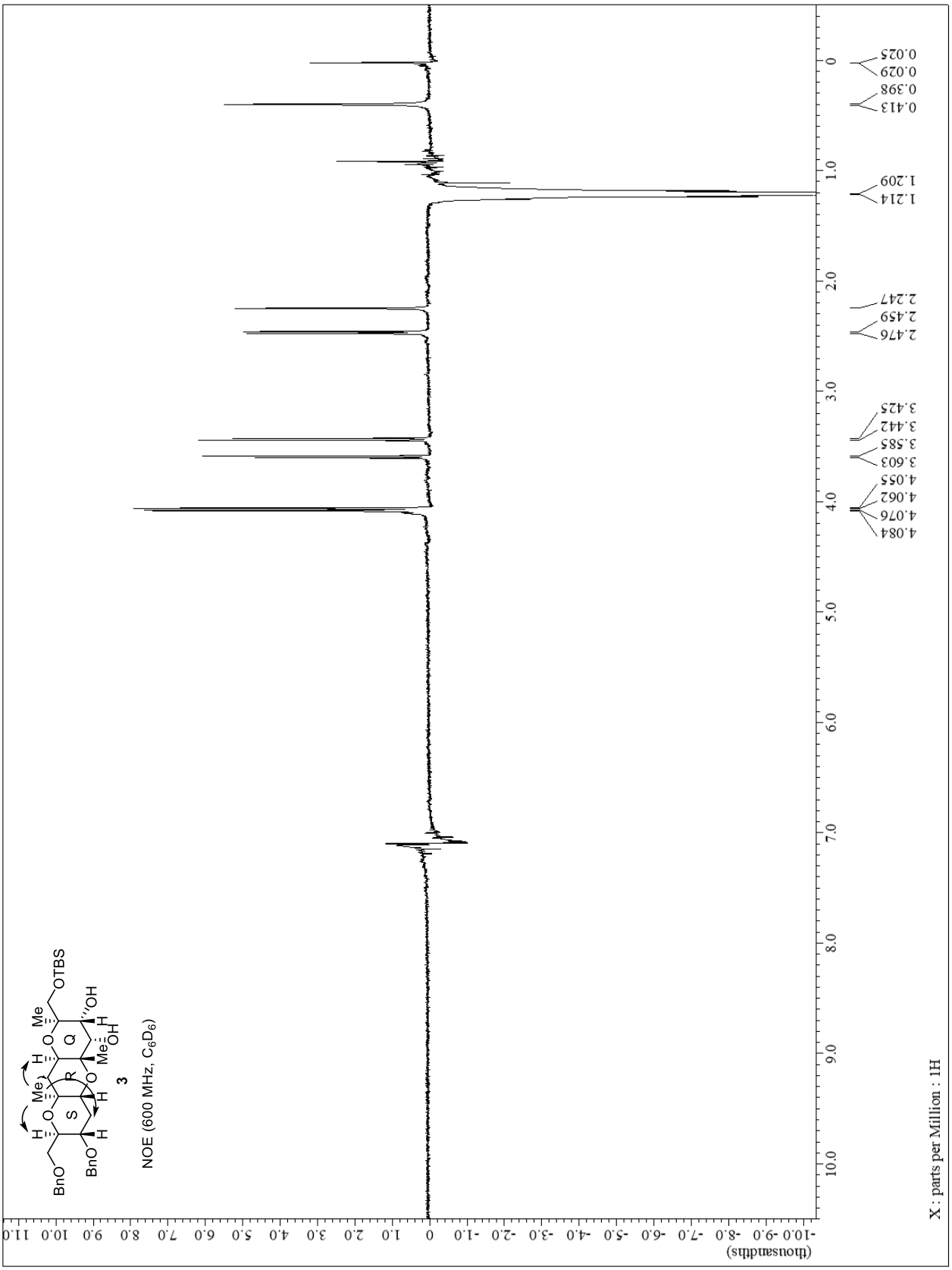

4
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance
0.0405
0.0336
0.8857
1.2372
1.3220
1.3289
1.5739
1.6003
1.6198
1.7434
1.8877
2.2244
2.2313
2.2439
3.4796
3.4888
3.6617
3.6697
3.6743
4.3580
4.3775
4.5699
4.6202
5.5158
5.5330
5.9613
5.9785
7.2600
7.2863
7.3276
7.3390

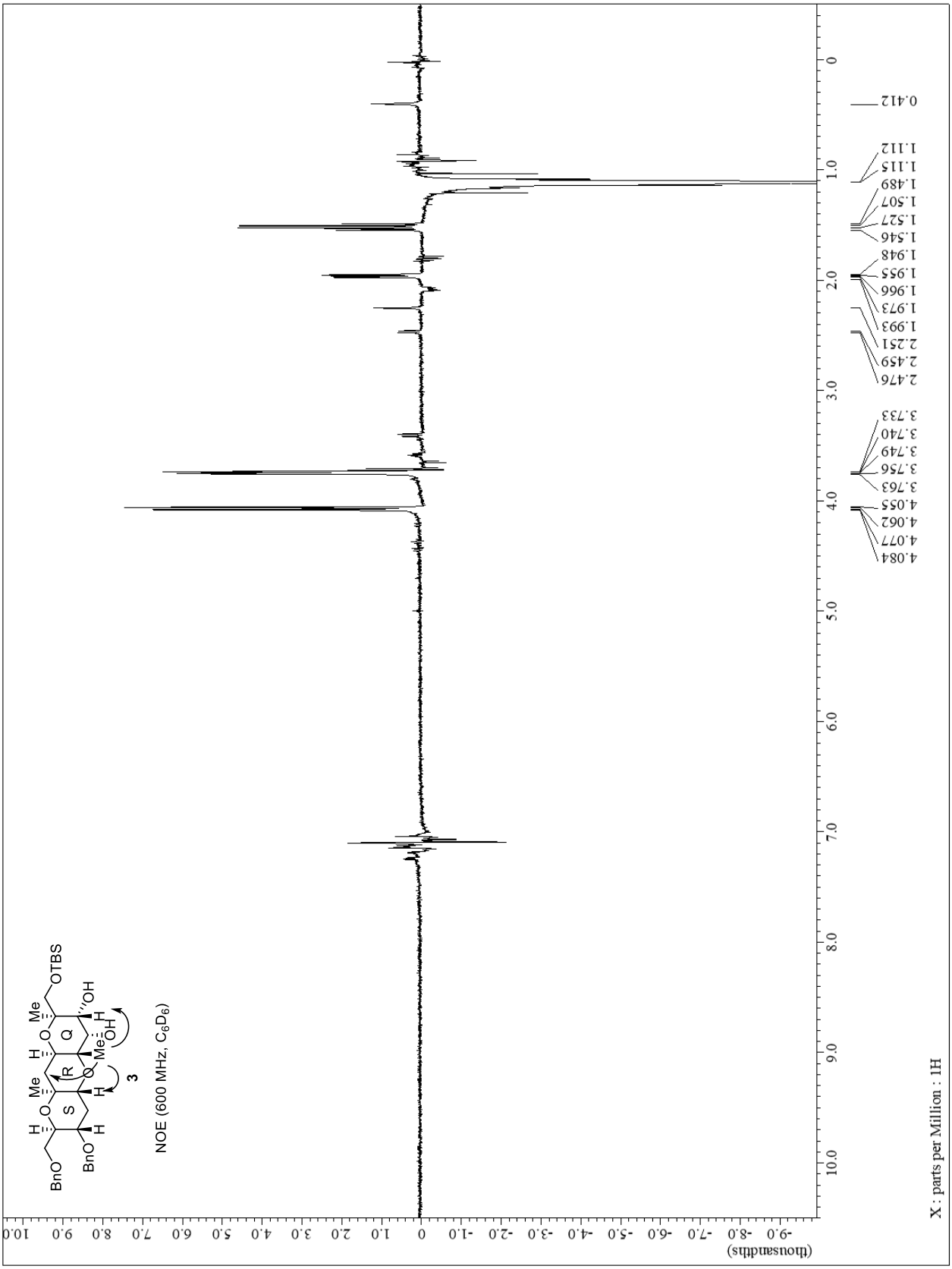

OTBS
Me
H
O
Q
Me
H
O
R
Me
H
O
S
H
BnO
BnO
4
^{13}C NMR (150 MHz, CDCl$_3$)
X : parts per Million : 13C
abundance
-5.221
-5.240
15.968
17.356
18.524
21.195
26.069
30.502
39.416
70.391
70.975
71.080
71.664
72.736
73.483
73.560
73.665
74.211
76.949
77.160
77.371
78.788
127.657
127.878
127.906
127.964
128.462
128.548
130.788
134.417
138.123
138.620

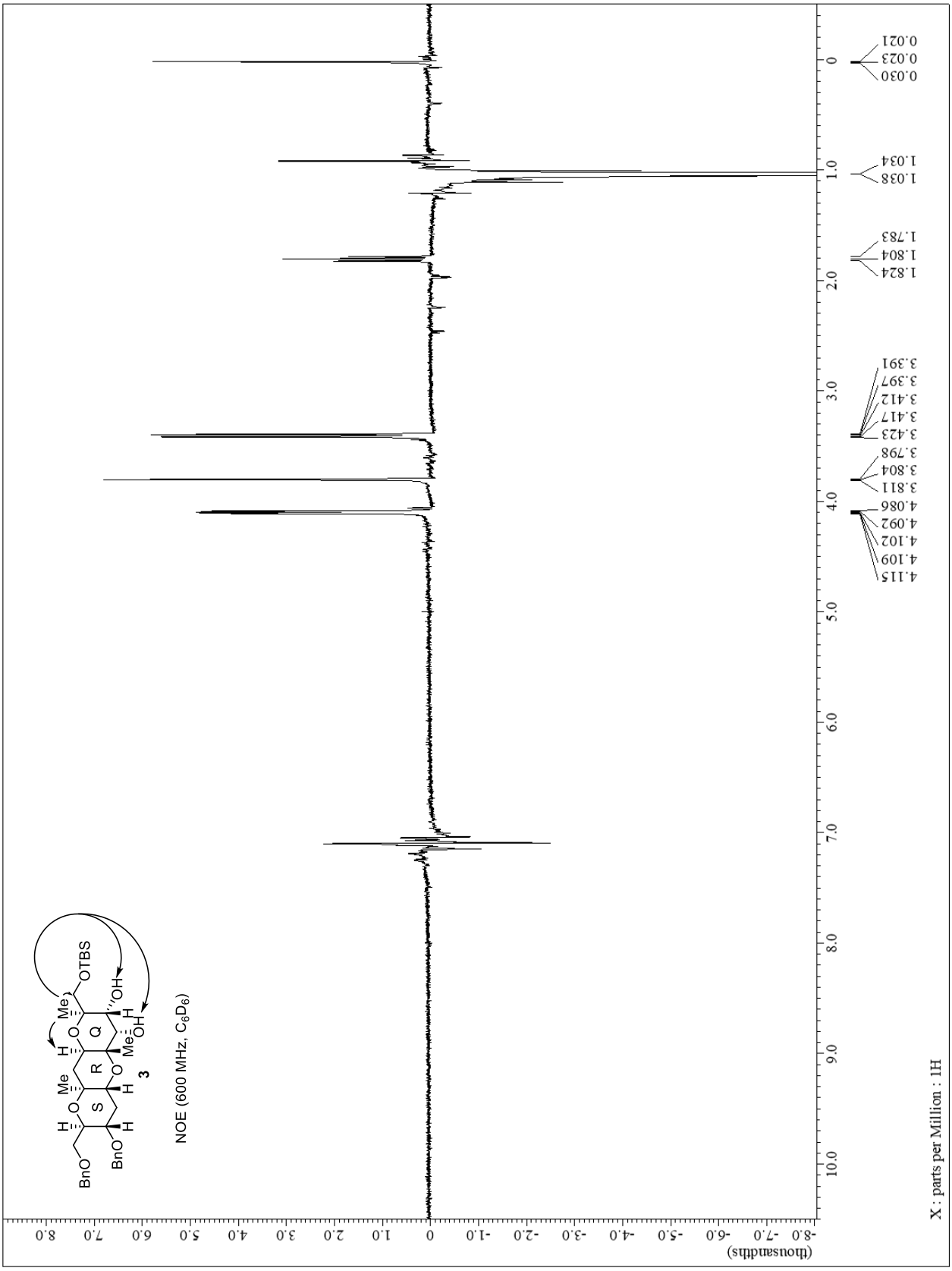

NOESY (600 MHz, CDCl3)
4
X : parts per Million : 1H
Y : parts per Million : 1H
abundance

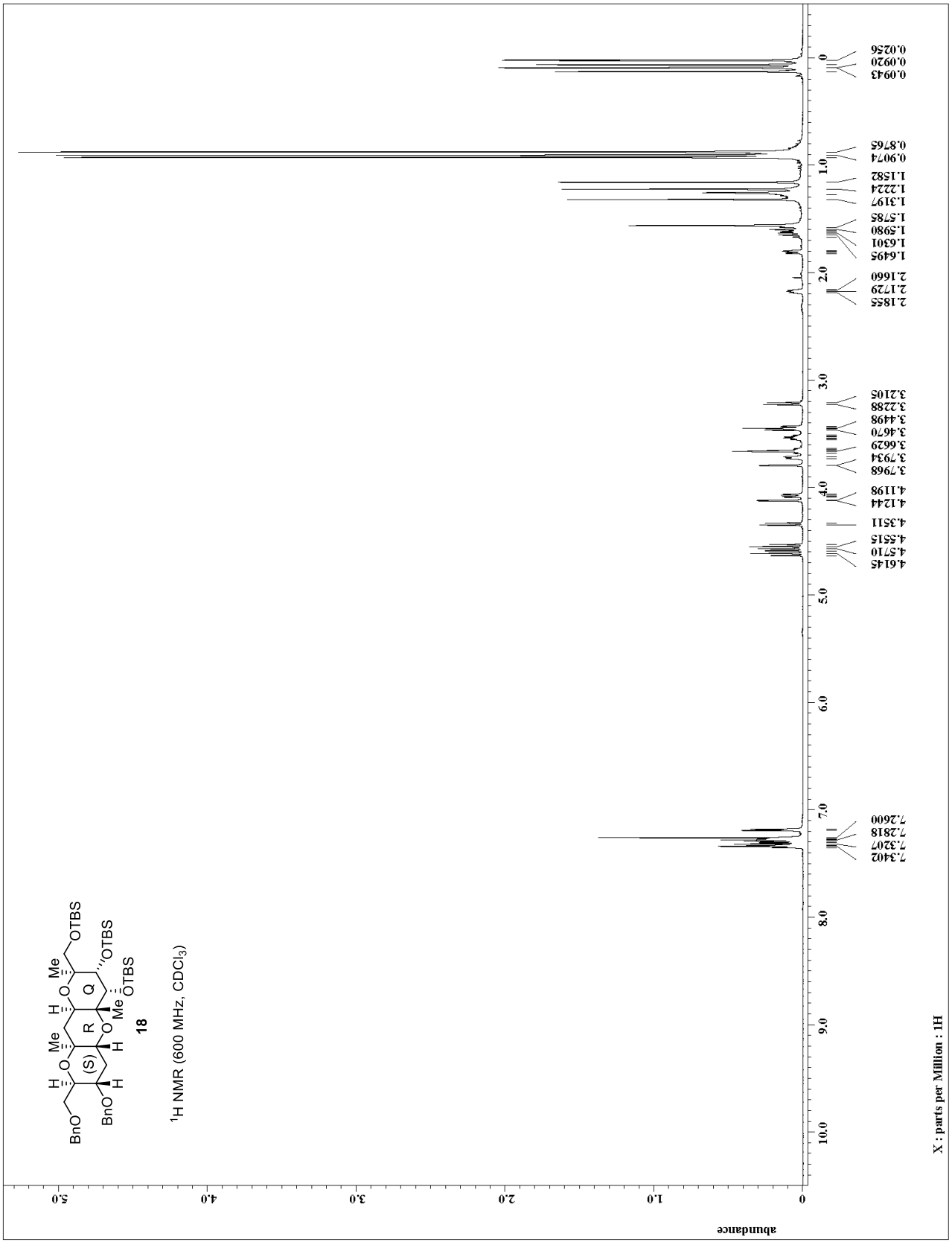

OTBS
Me
OH
Me
H
O
Q
(S)
R
O
Me
OH
H
H
BnO
BnO
3
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H
7.2355
7.1771
7.1118
7.0969
7.0832
4.4331
4.3701
4.3655
4.2258
4.2064
3.7082
3.6567
3.6040
3.5868
3.4448
3.4276
2.4759
2.4656
1.9686
1.9560
1.9491
1.8254
1.8048
1.5277
1.5071
1.2104
1.1120
1.0352
0.9196
0.3973
0.3630
0.0263
0.0206

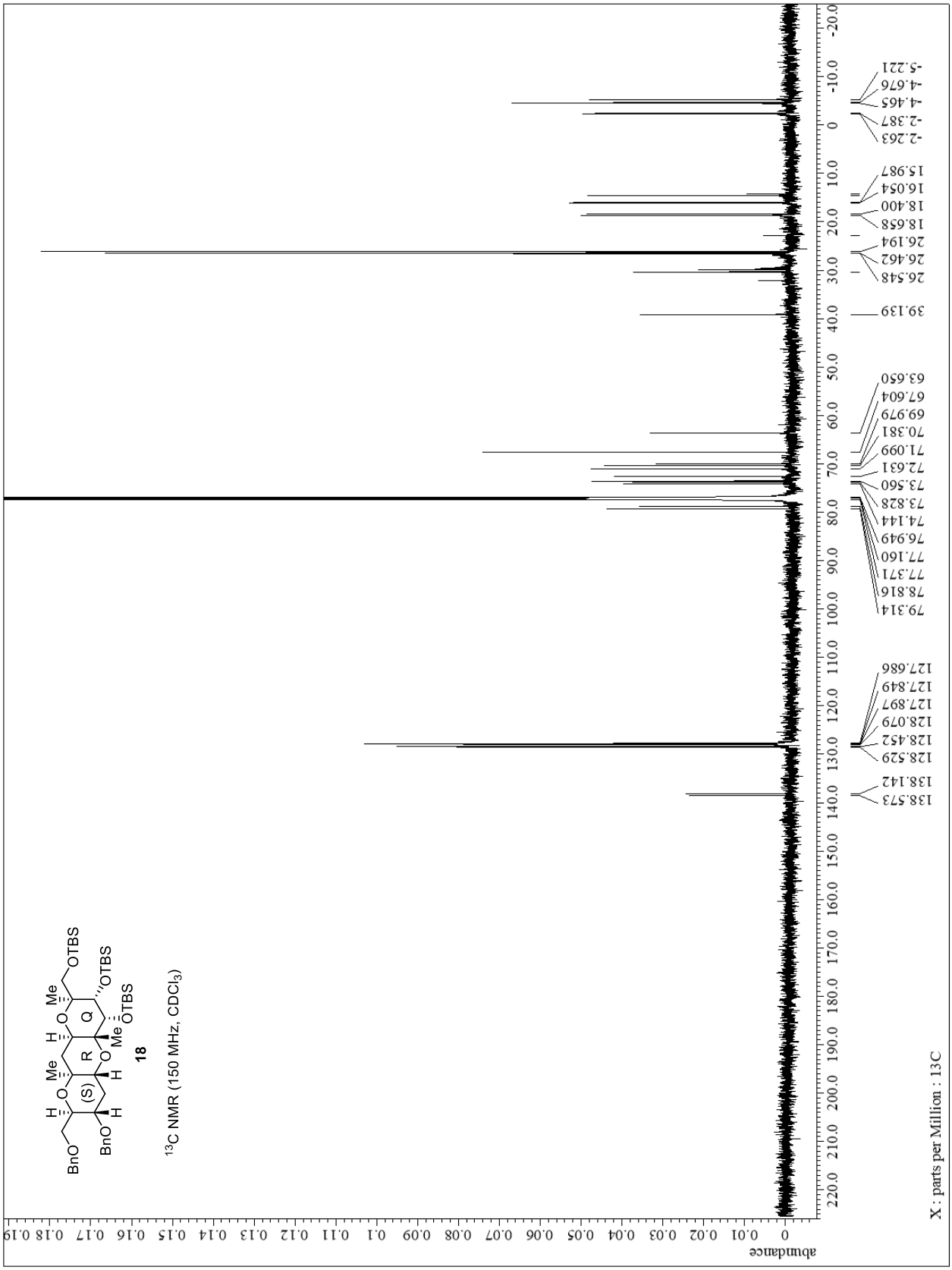

3
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
128.625
128.529
128.347
128.213
128.060
127.897
127.639
79.439
76.567
75.724
73.809
73.752
73.666
73.359
71.090
70.946
70.362
69.175
67.002
63.727
39.522
30.838
26.204
18.687
16.054
15.499
13.776
-4.924
-5.240

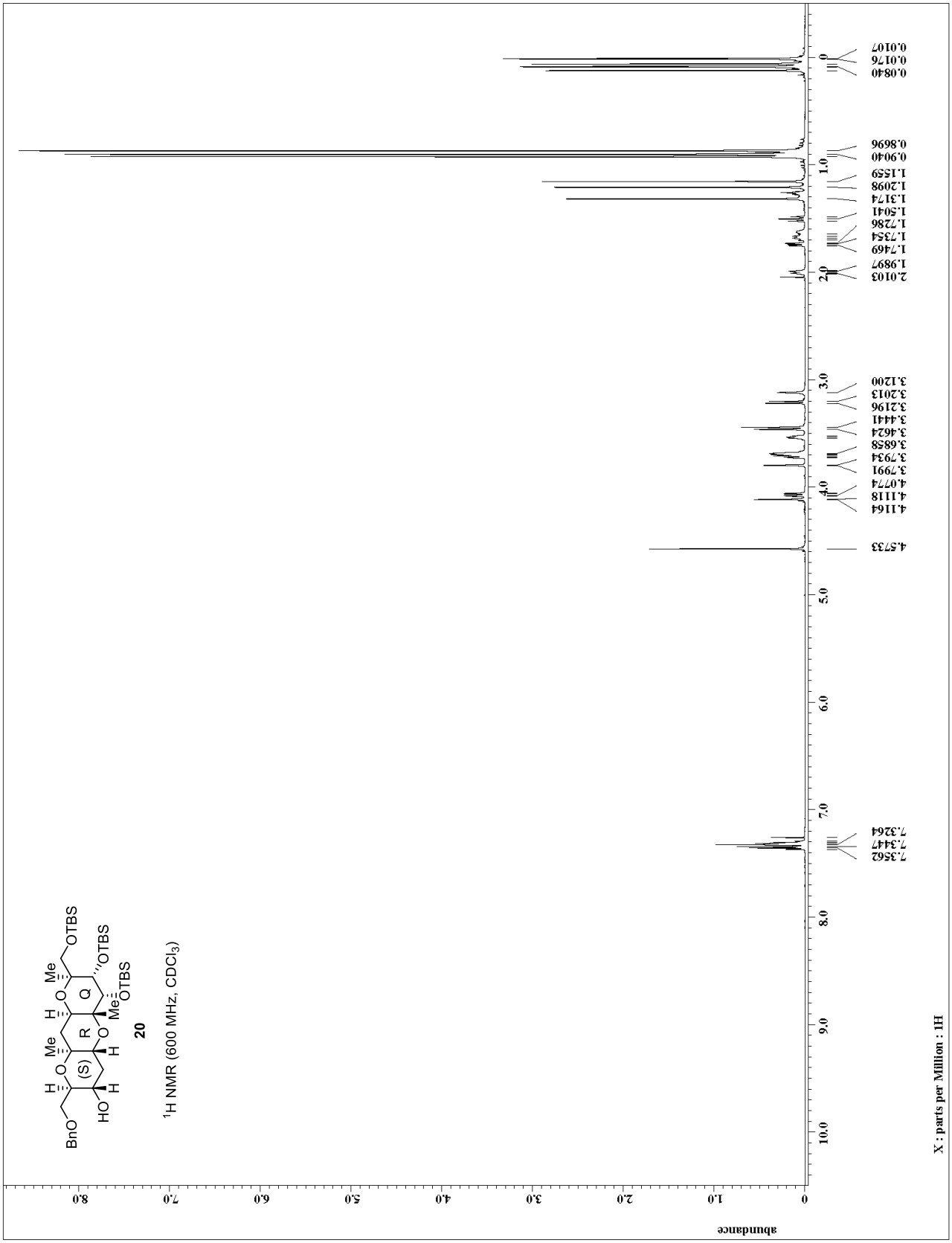

NOE (600 MHz, C6D6)
3
BnO
OTBS
Me
OH
Me
H
O
Q
R
S
(thousandths)
X : parts per Million : 1H
0.025
0.029
0.398
0.413
1.209
1.214
2.247
2.459
2.476
3.425
3.442
3.585
3.603
4.055
4.062
4.076
4.084

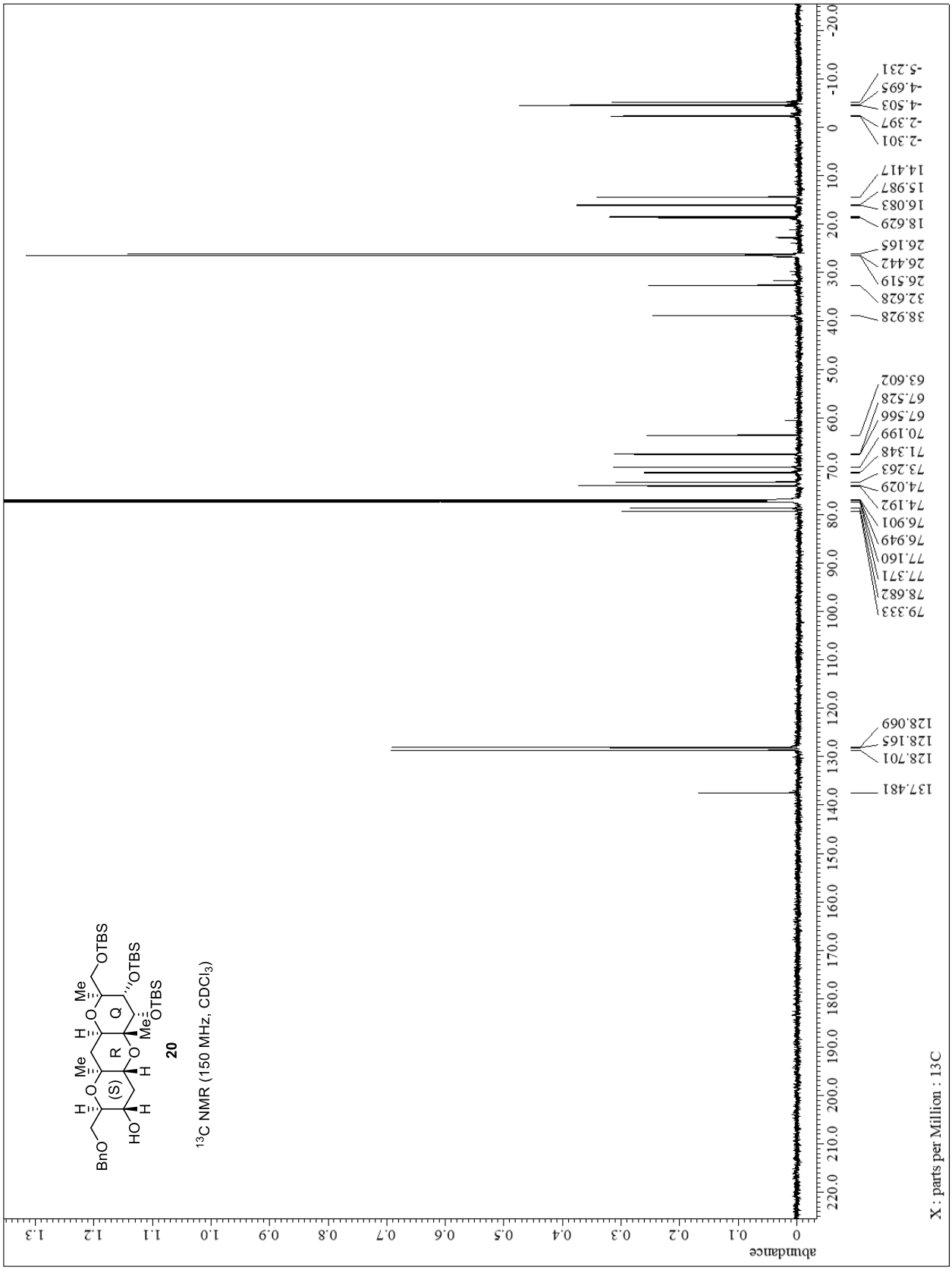

NOE (600 MHz, C6D6)
3
X : parts per Million : 1H
(thousandths)
0.412
1.112
1.115
1.489
1.507
1.527
1.546
1.948
1.955
1.966
1.973
1.993
2.251
2.459
2.476
3.733
3.740
3.749
3.756
3.763
4.055
4.062
4.077
4.084

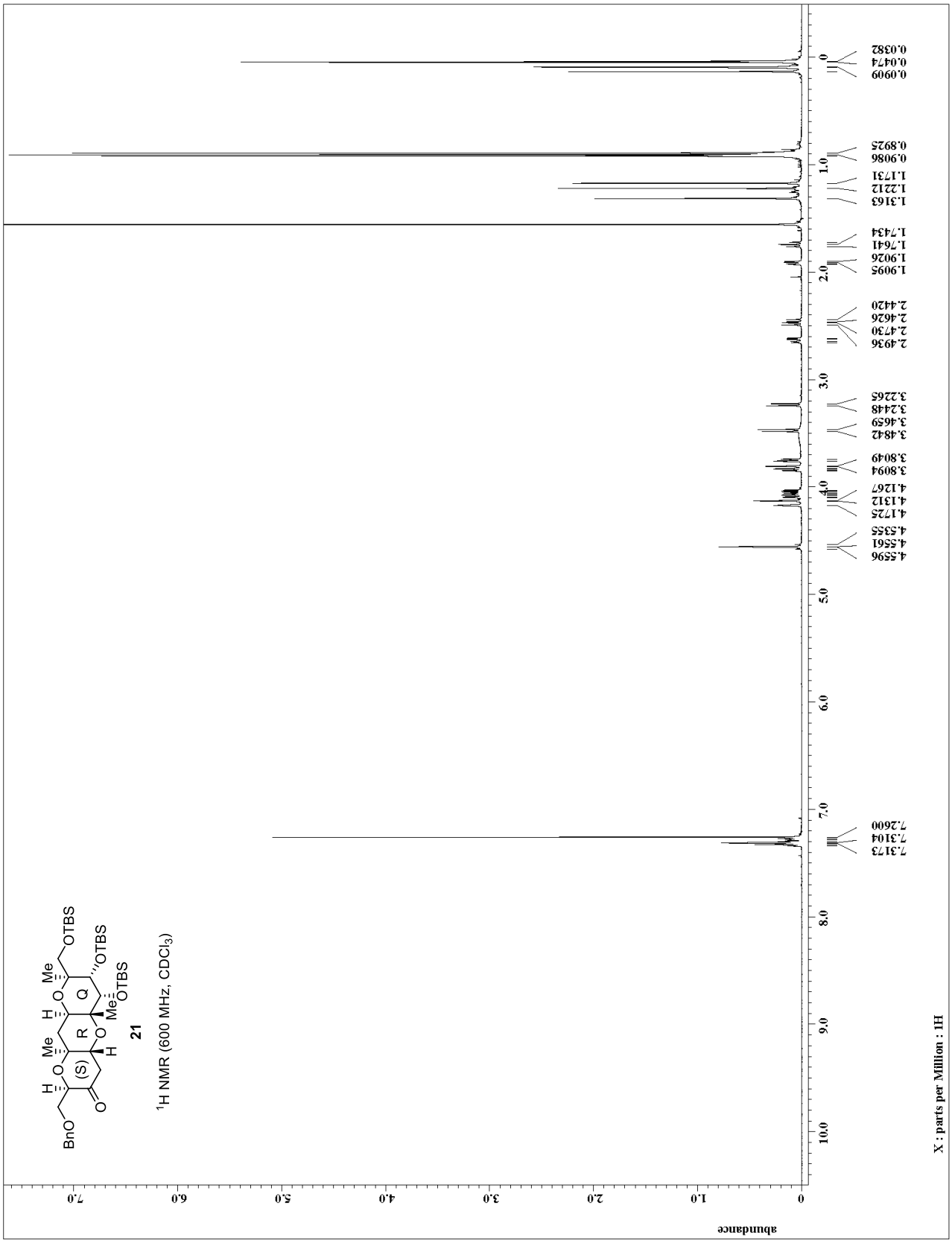

NOE (600 MHz, C_6D_6)
3
X : parts per Million : 1H
(thousandths)
0.030
0.023
0.021
1.038
1.034
1.824
1.804
1.783
3.423
3.417
3.412
3.397
3.391
3.811
3.804
3.798
4.115
4.109
4.102
4.092
4.086

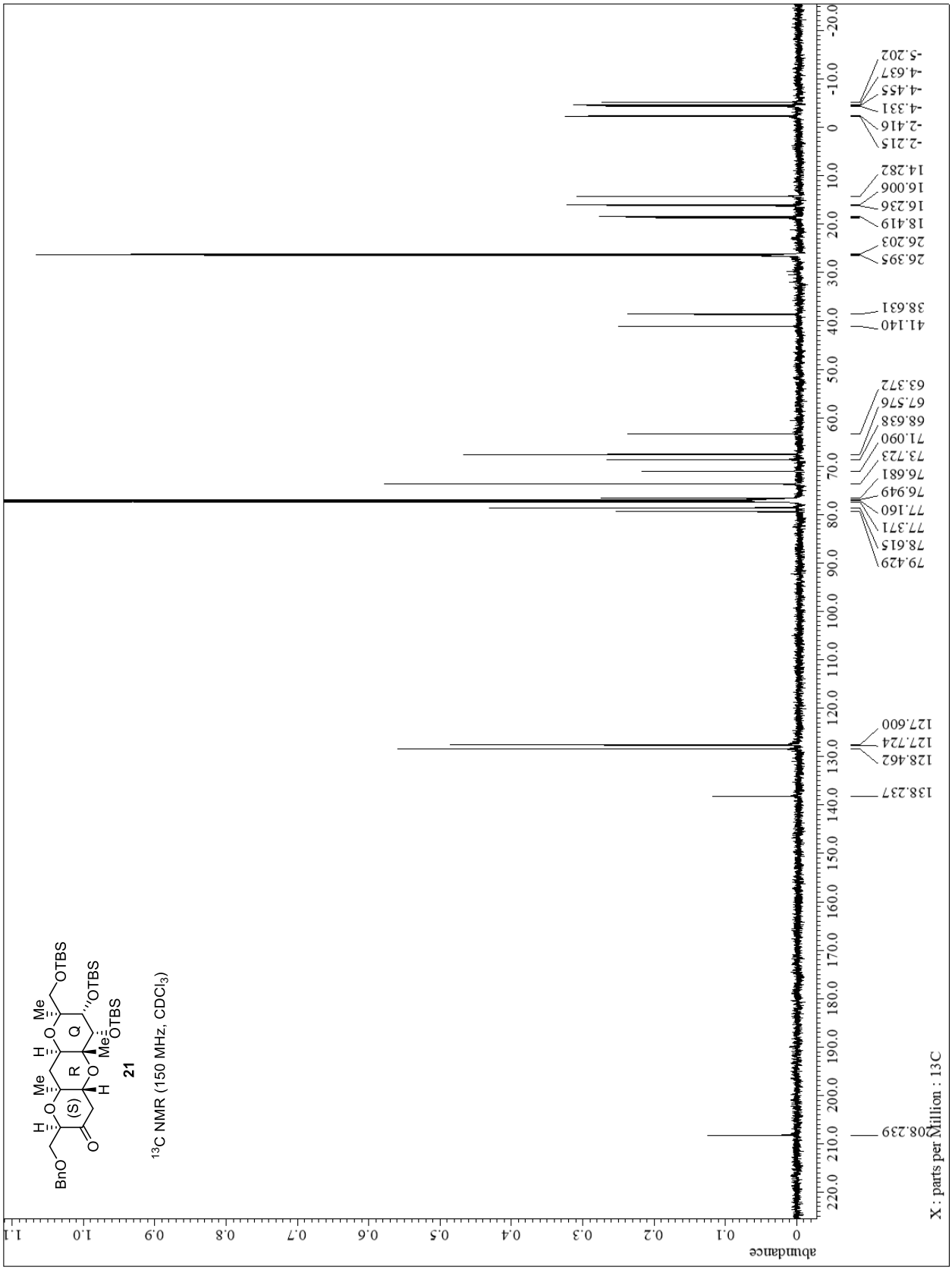

18
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

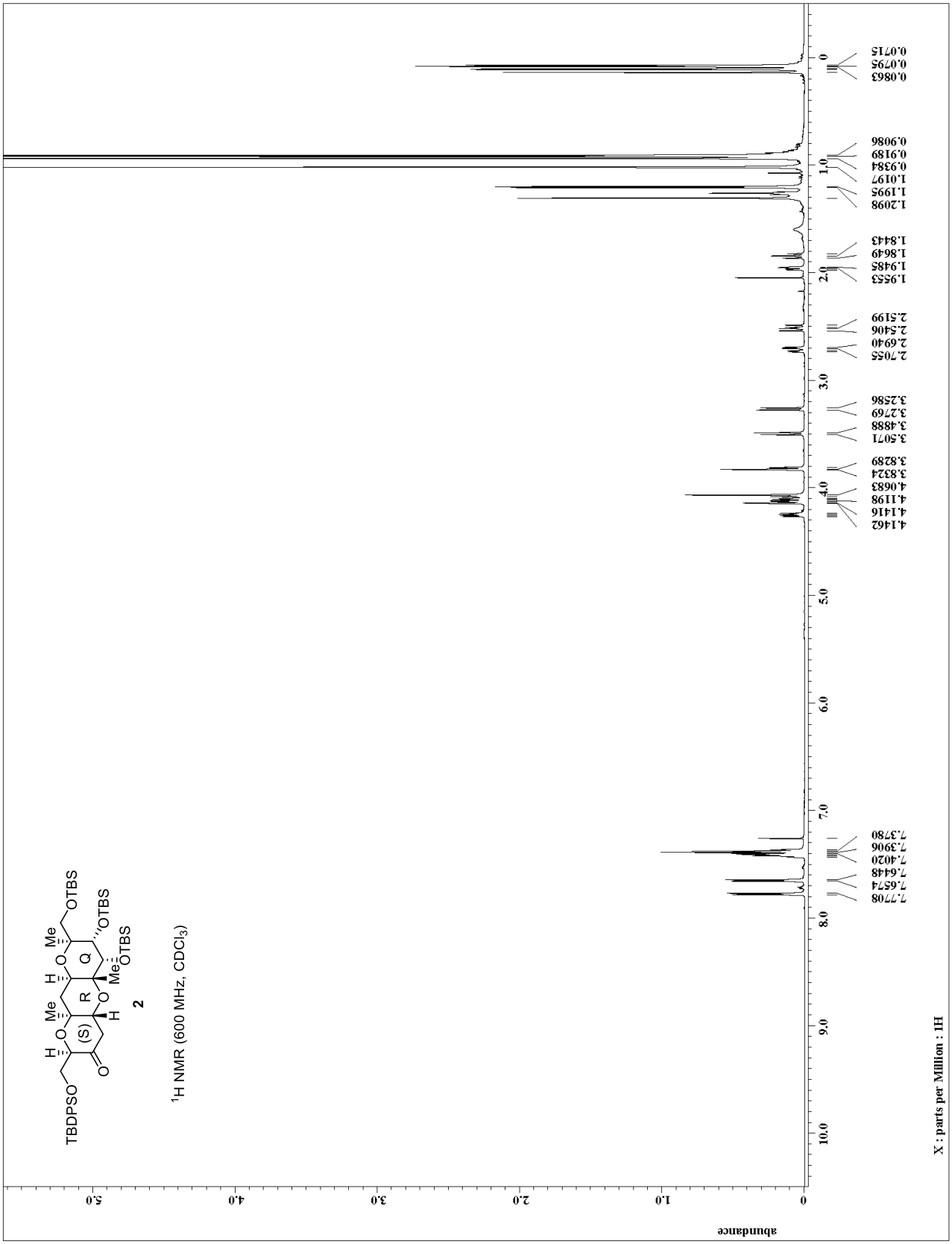

BnO
H
O
Me
H
O
(S)
H
BnO
H
R
O
H
Me
Q
OTBS
OTBS
OTBS
18
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
138.573
138.142
128.529
128.452
128.079
127.897
127.849
127.686
79.314
78.816
77.371
77.160
76.949
74.144
73.828
73.560
72.631
71.099
70.381
69.979
67.604
63.650
39.139
26.548
26.462
26.194
18.658
18.400
16.054
15.987
-2.263
-2.387
-4.465
-4.676
-5.221

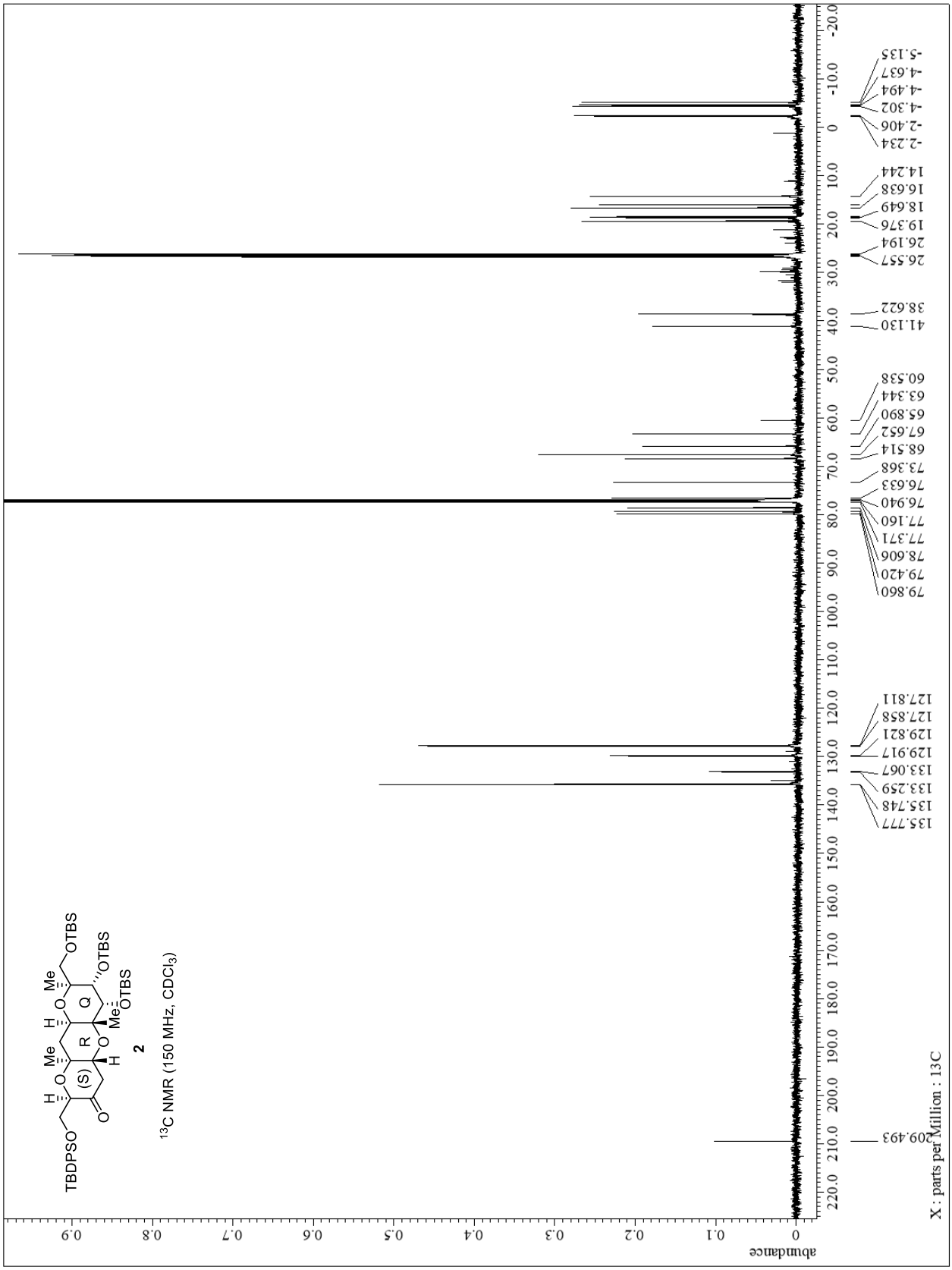

20
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance
7.3562
7.3447
7.3264
4.5733
4.1164
4.1118
4.0774
3.7991
3.7934
3.6858
3.4624
3.4441
3.2196
3.2013
3.1200
2.0103
1.9897
1.7469
1.7354
1.7286
1.5041
1.3174
1.2098
1.1559
0.9040
0.8696
0.0840
0.0176
0.0107

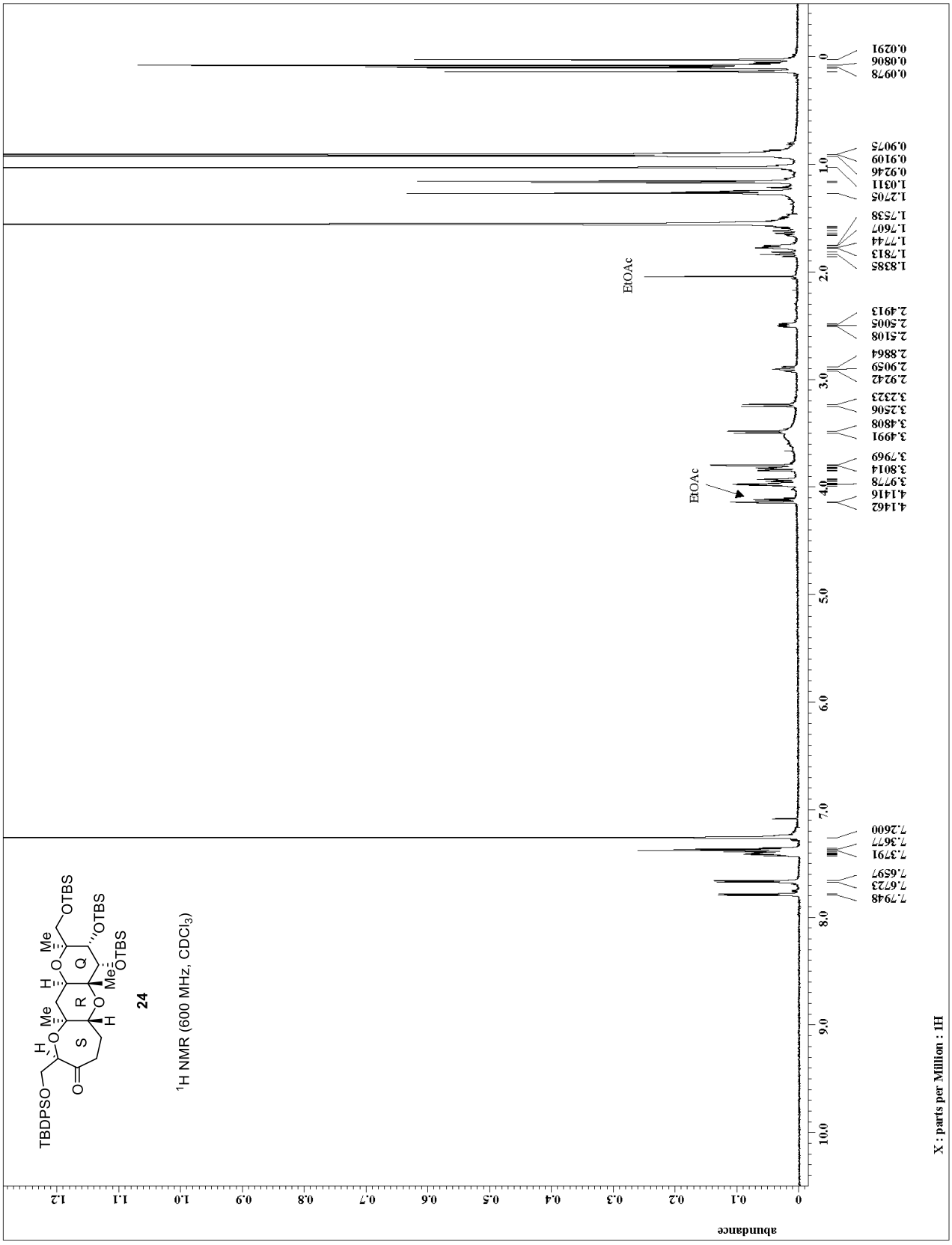

20
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
137.481
128.701
128.165
128.069
79.333
78.682
77.371
77.160
76.949
76.901
74.192
74.029
73.263
71.348
70.199
67.566
67.528
63.602
38.928
32.628
26.519
26.442
26.165
18.629
16.083
15.987
14.417
-2.301
-2.397
-4.503
-4.695
-5.231

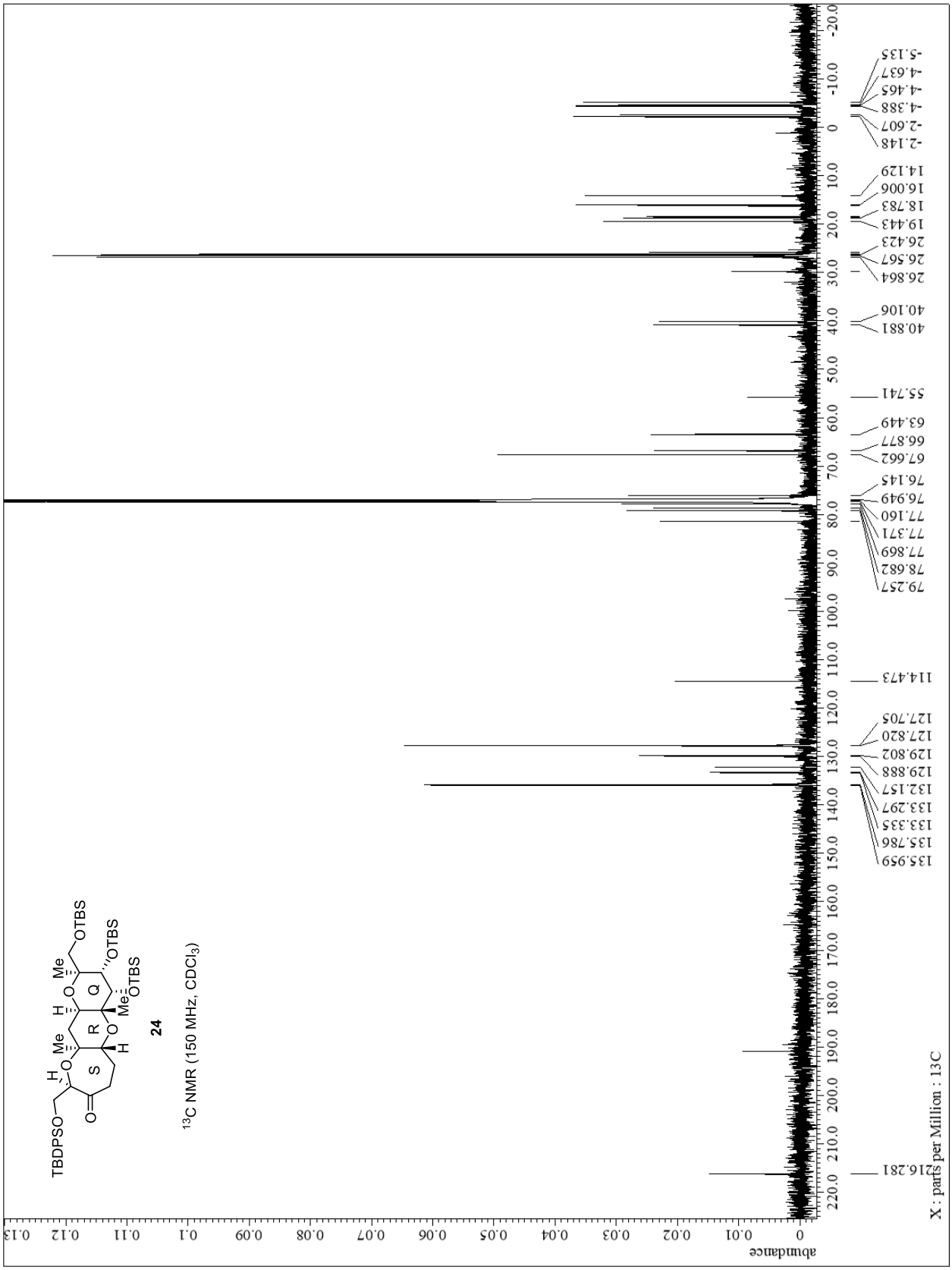

BnO
H
O
Me
H
O
(S)
O
R
O
H
Me
O
Q
OTBS
OTBS
Me
OTBS
21
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.3173
7.3104
7.2600
4.5596
4.5561
4.5355
4.1725
4.1312
4.1267
3.8094
3.8049
3.4842
3.4659
3.2448
3.2265
2.4936
2.4730
2.4626
2.4420
1.9095
1.9026
1.7641
1.7434
1.3163
1.2212
1.1731
0.9086
0.8925
0.0909
0.0474
0.0382

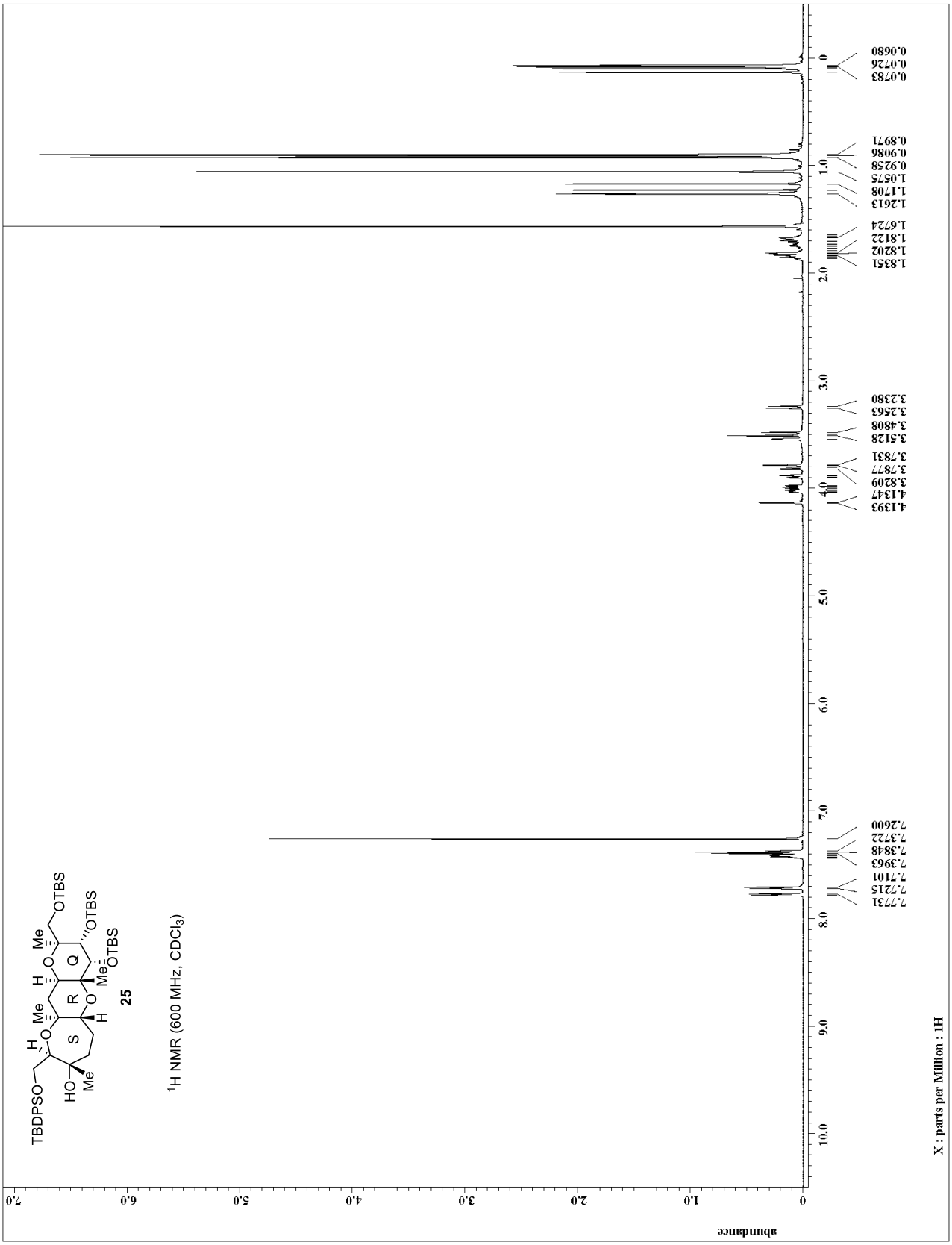

BnO
H
O
Me
(S)
O
H
O
Me
R
O
H
Q
Me
OTBS
OTBS
OTBS
21
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
208.239
138.237
128.462
127.724
127.600
79.429
78.615
77.371
77.160
76.949
76.681
73.723
71.090
68.638
67.576
63.372
41.140
38.631
26.395
26.203
18.419
16.236
16.006
14.282
-2.215
-2.416
-4.331
-4.455
-4.637
-5.202

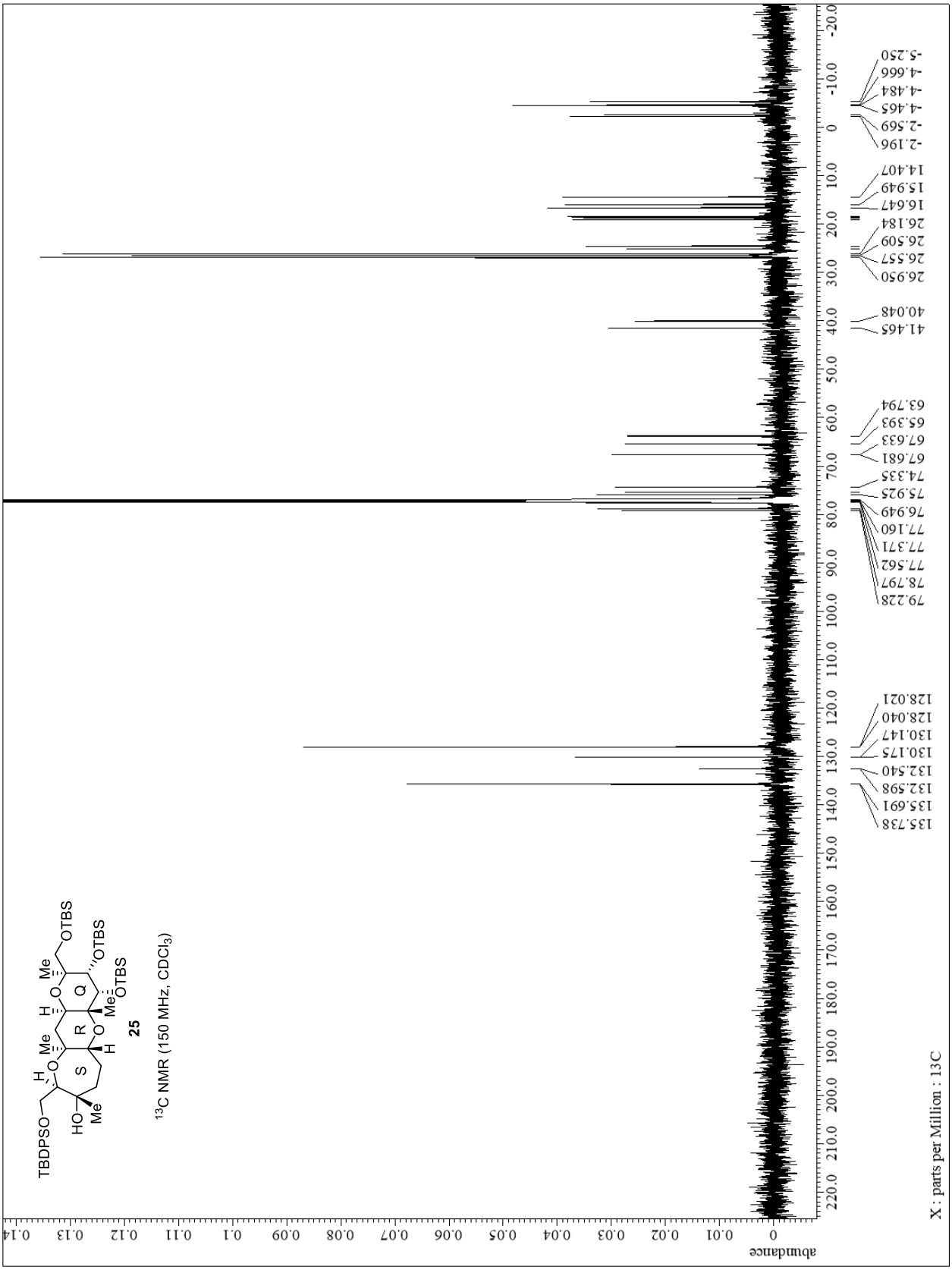

TBDPSO
OTBS
OTBS
OTBS
Me
Me
Me
H
H
H
O
O
O
O
O
(S)
R
Q
2
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.7708
7.6574
7.6448
7.4020
7.3906
7.3780
4.1462
4.1416
4.1198
4.0683
3.8324
3.8289
3.5071
3.4888
3.2769
3.2586
2.7055
2.6940
2.5406
2.5199
1.9553
1.9485
1.8649
1.8443
1.2098
1.1995
1.0197
0.9384
0.9189
0.9086
0.0863
0.0795
0.0715

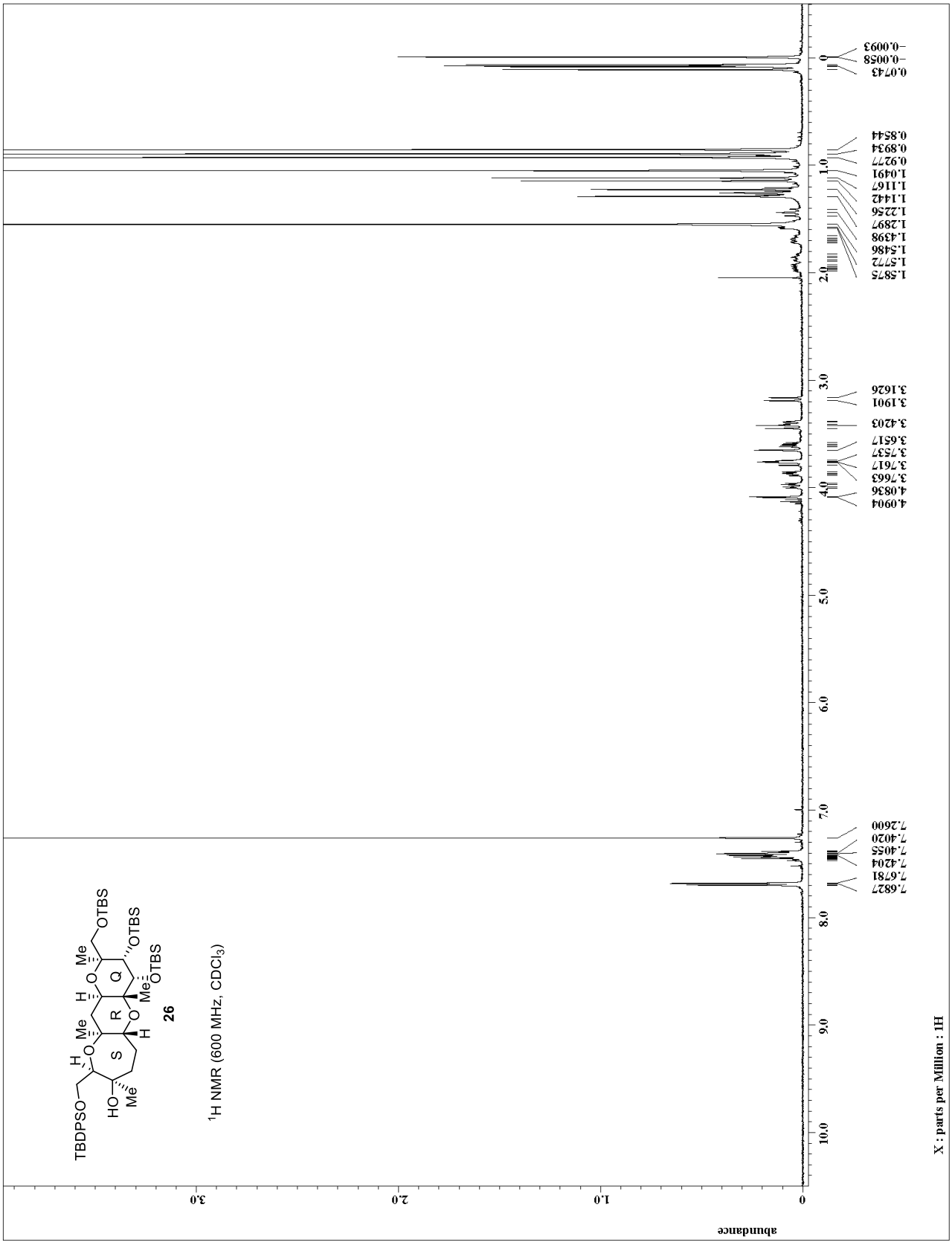

TBDPSO
OTBS
OTBS
OTBS
Me
Me
H
H
(S)
R
Q
2
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
209.493
135.777
135.748
133.259
133.067
129.917
129.821
127.858
127.811
79.860
79.420
78.606
77.371
77.160
76.940
76.633
73.368
68.514
67.652
65.890
63.344
60.538
41.130
38.622
26.557
26.194
19.376
18.649
16.638
14.244
-2.234
-2.406
-4.302
-4.494
-4.637
-5.135

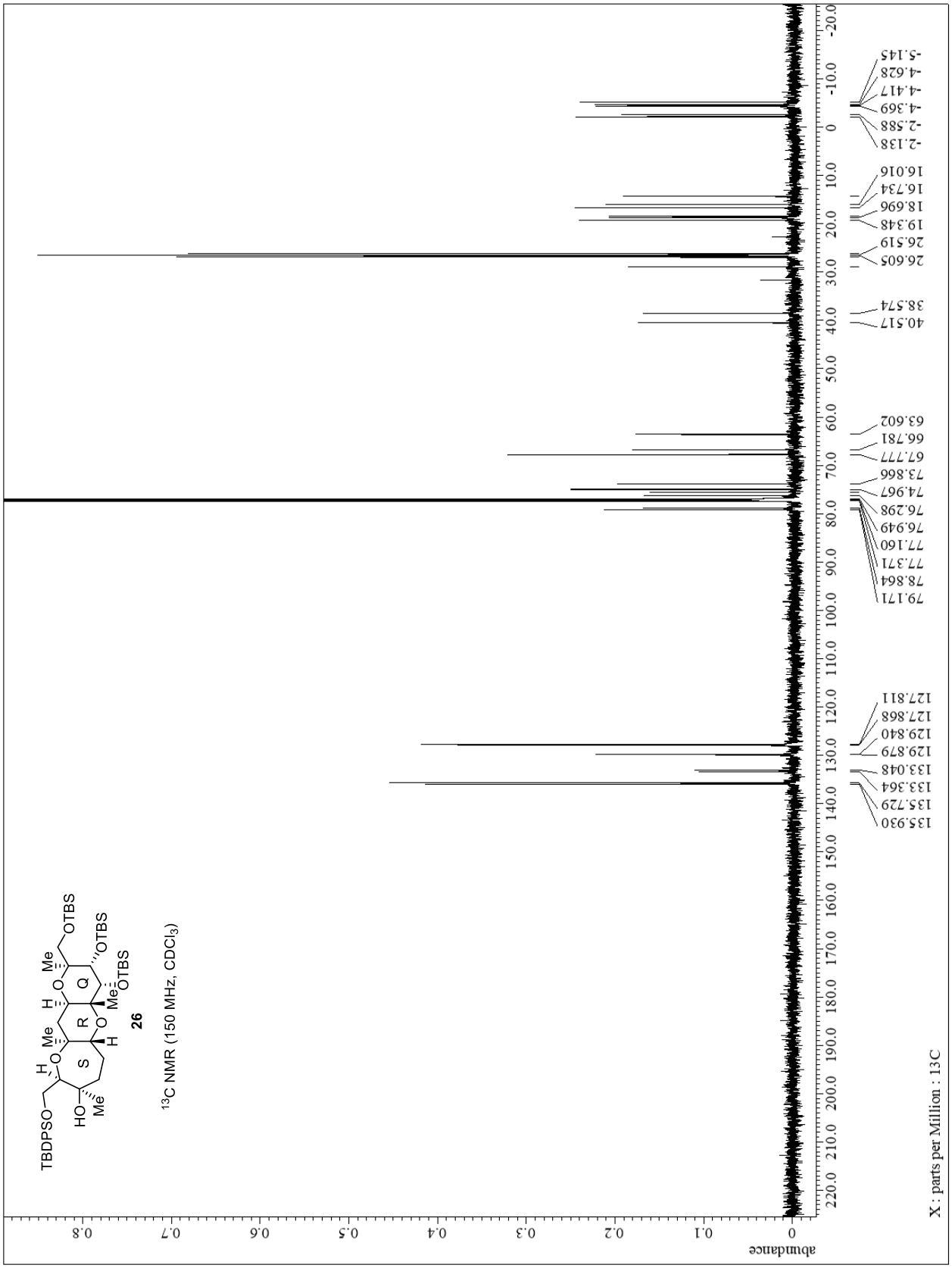

TBDPSO
OTBS
Me
H
O
S
R
Q
OTBS
Me
OTBS
24
^{1}H NMR (600 MHz, CDCl$_3$)
EtOAc
EtOAc
abundance
X : parts per Million : 1H
7.7948
7.6723
7.6597
7.3791
7.3677
7.2600
4.1462
4.1416
3.9778
3.8014
3.7969
3.4991
3.4808
3.2506
3.2323
2.9242
2.9059
2.8864
2.5108
2.5005
2.4913
1.8385
1.7813
1.7744
1.7607
1.7538
1.2705
1.0311
0.9246
0.9109
0.9075
0.0978
0.0806
0.0291

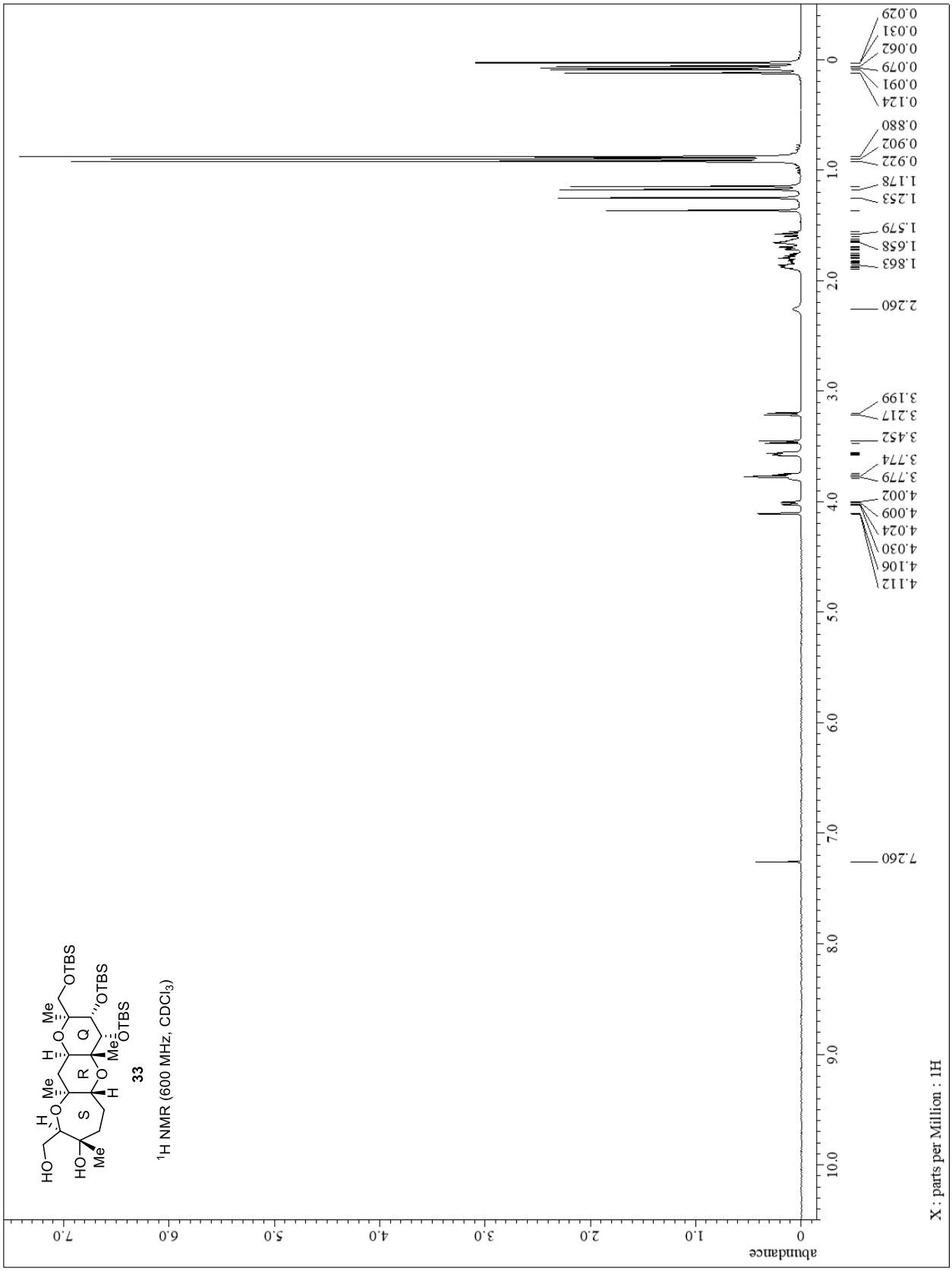

TBDPSO
OTBS
OTBS
OTBS
Me
Me
H
H
O
O
O
O
S
R
Q
O
24
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
216.281
135.959
135.786
133.335
133.297
132.157
129.888
129.802
127.820
127.705
114.473
79.257
78.682
77.869
77.371
77.160
76.949
76.145
67.662
66.877
63.449
55.741
40.881
40.106
26.864
26.567
26.423
19.443
18.783
16.006
14.129
-2.148
-2.607
-4.388
-4.465
-4.637
-5.135

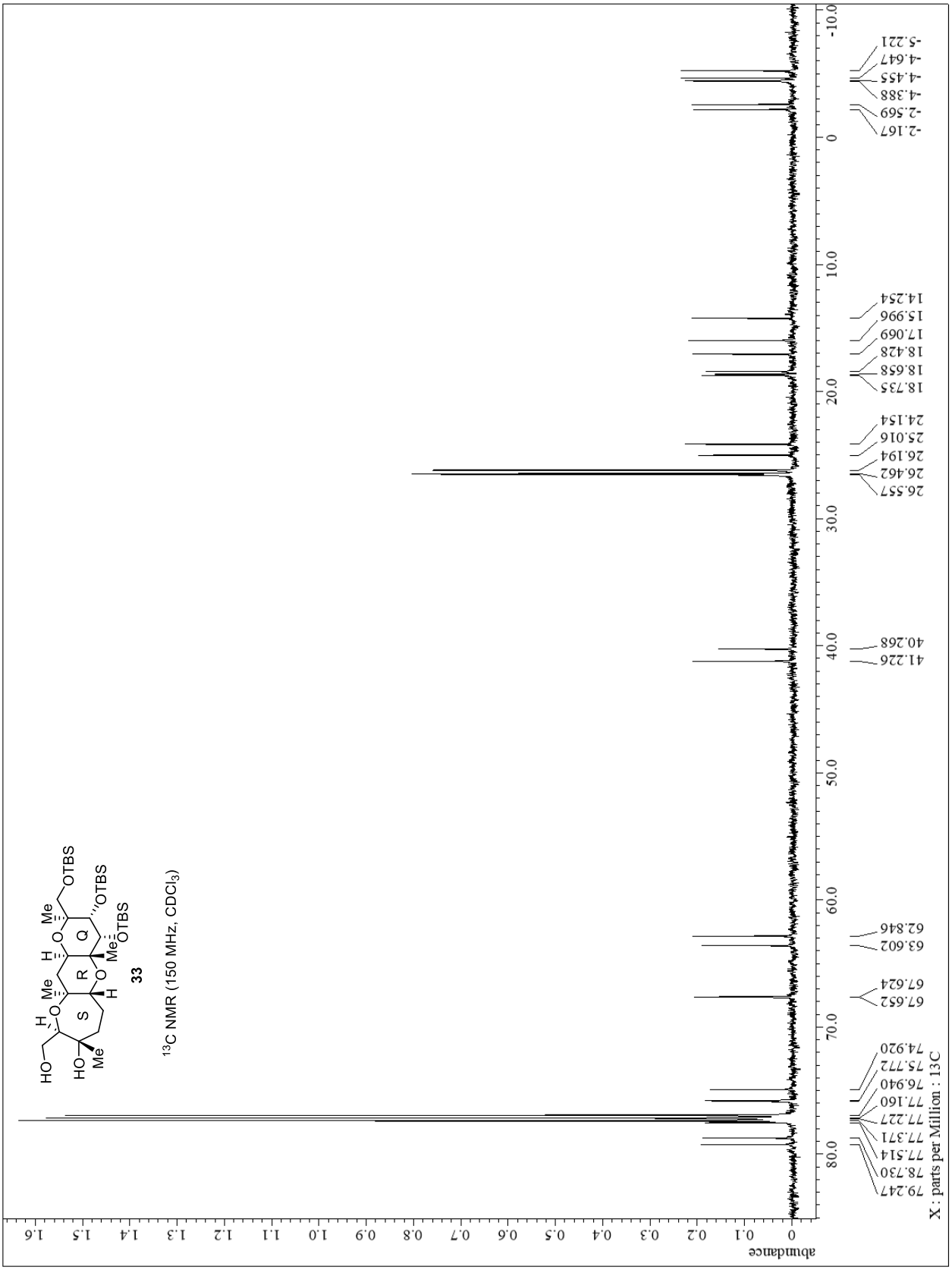

TBDPSO
HO
Me
H
O
Me
S
O
H
Me
H
O
R
O
Me
Q
OTBS
OTBS
OTBS
25
^{1}H NMR (600 MHz, $CDCl_3$)
abundance
X : parts per Million : 1H
7.7731
7.7215
7.7101
7.3963
7.3848
7.3722
7.2600
4.1393
4.1347
3.8209
3.7877
3.7831
3.5128
3.4808
3.2563
3.2380
1.8351
1.8202
1.8122
1.6724
1.2613
1.1708
1.0575
0.9258
0.9086
0.8971
0.0783
0.0726
0.0680

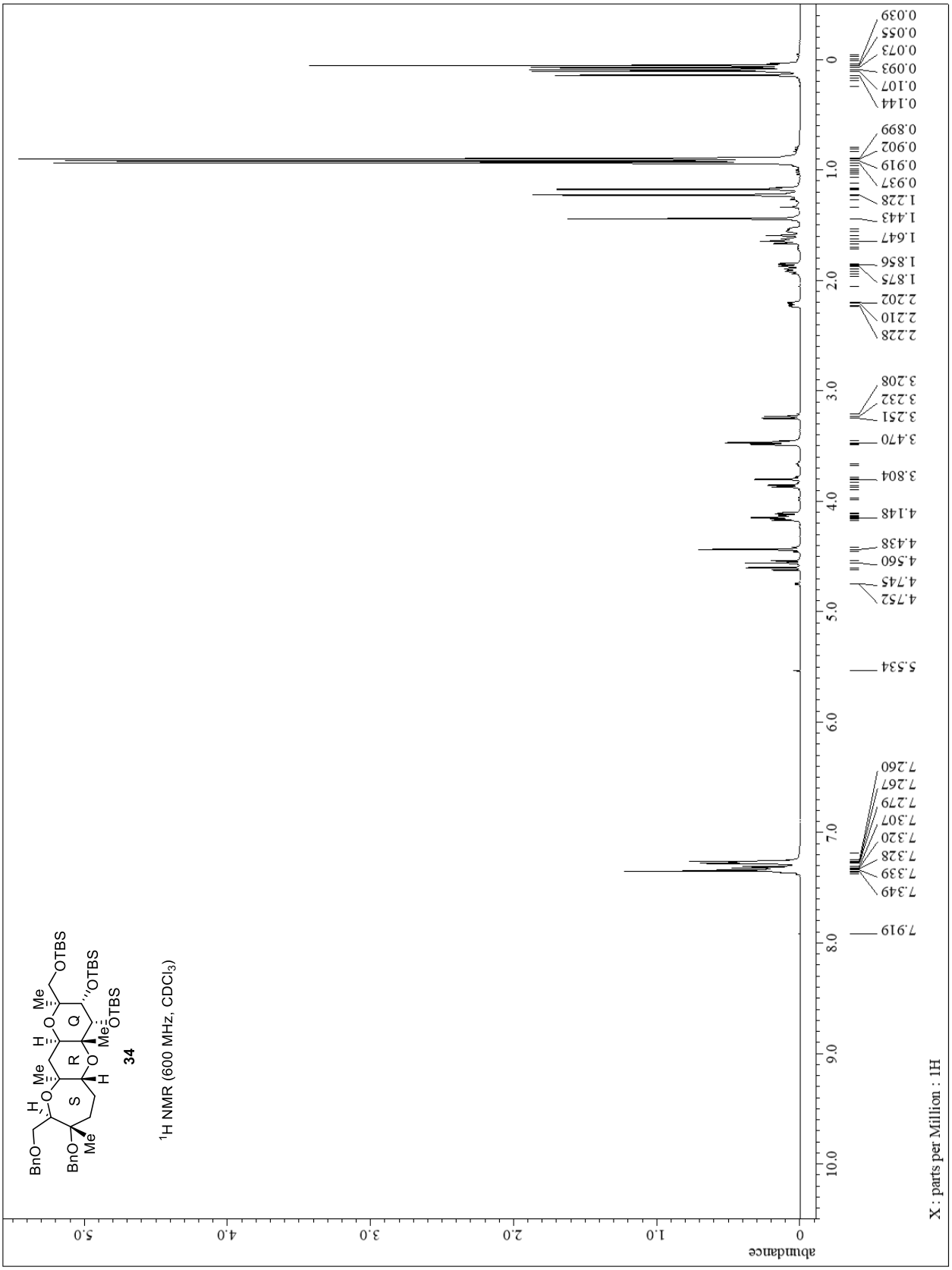

TBDPSO
HO
Me
H
O
Me
S
R
Q
OTBS
OTBS
OTBS
25
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
135.738
135.691
132.598
132.540
130.175
130.147
128.040
128.021
79.228
78.797
77.562
77.371
77.160
76.949
75.925
74.335
67.681
67.633
65.393
63.794
41.465
40.048
26.950
26.557
26.509
26.184
16.647
15.949
14.407
-2.196
-2.569
-4.465
-4.484
-4.666
-5.250

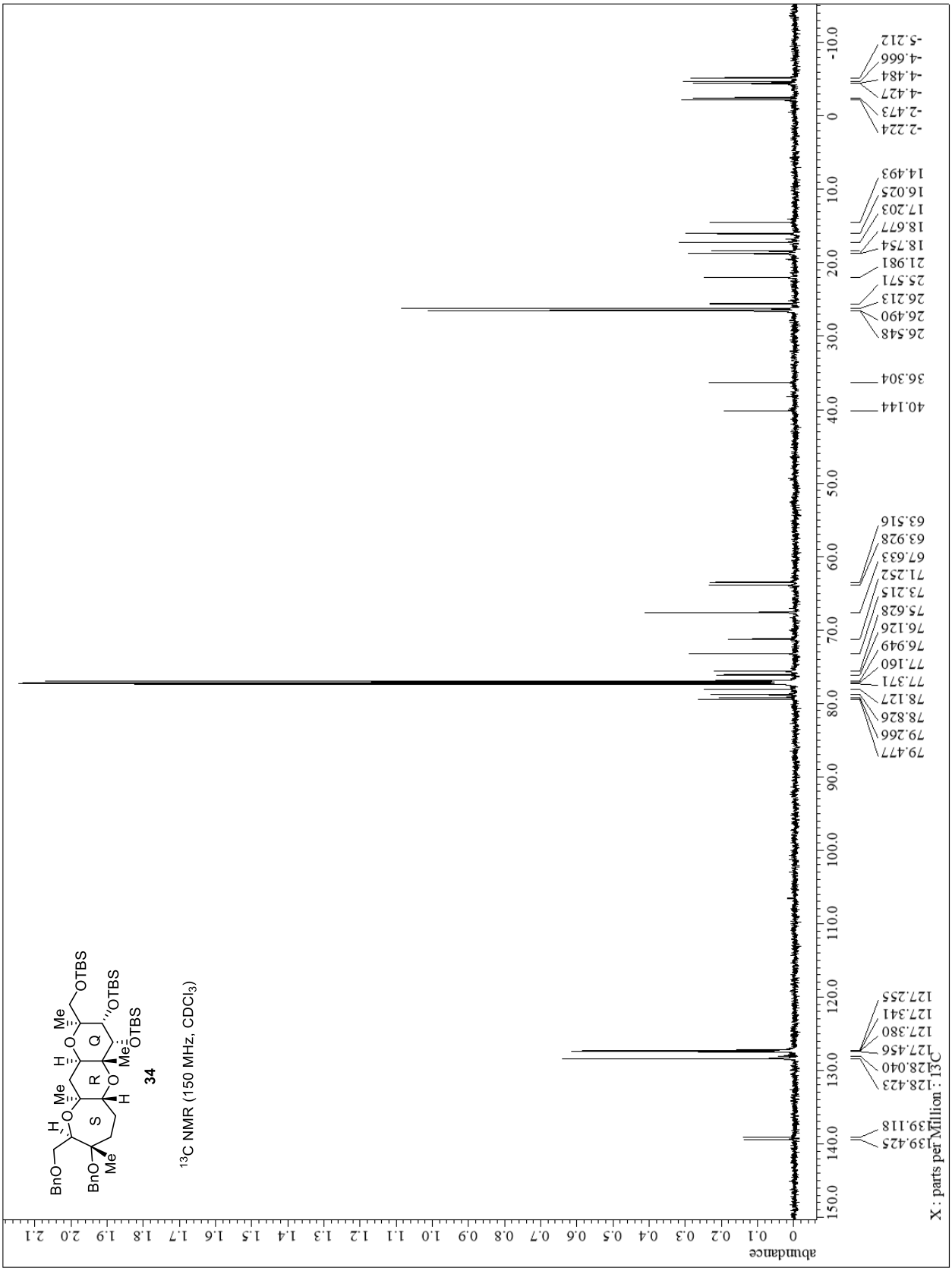

TBDPSO
HO
Me
H
O
Me
S
R
Q
OTBS
OTBS
OTBS
Me
Me
H
26
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.6827
7.6781
7.4204
7.4055
7.4020
7.2600
4.0904
4.0836
3.7663
3.7617
3.7537
3.6517
3.4203
3.1901
3.1626
1.5875
1.5772
1.5486
1.4398
1.2897
1.2256
1.1442
1.1167
1.0491
0.9277
0.8934
0.8544
0.0743
-0.0058
-0.0093

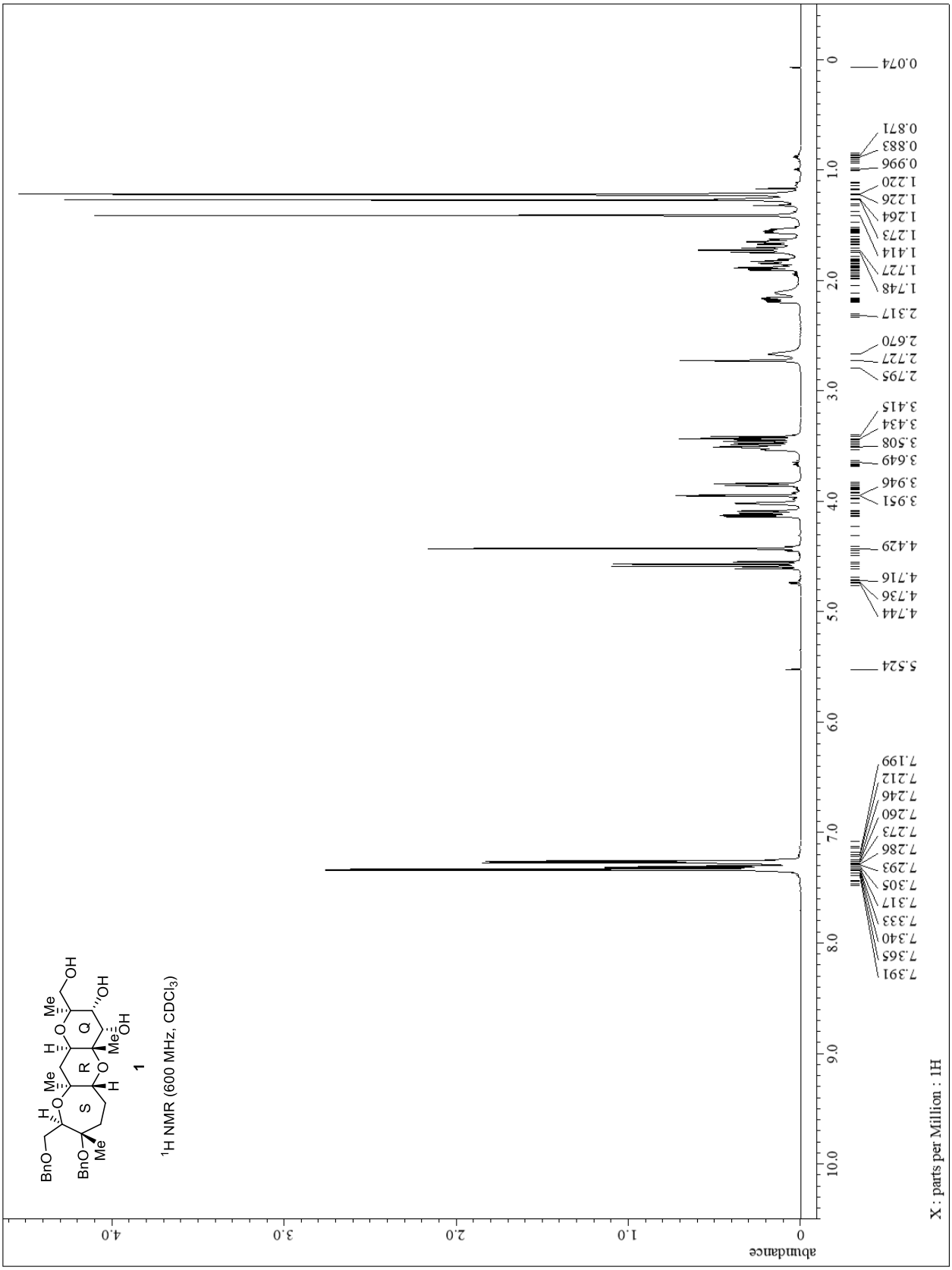

TBDPSO
HO
Me
H
Me
O
S
R
Q
OTBS
OTBS
OTBS
26
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
135.930
135.729
133.364
133.048
129.879
129.840
127.868
127.811
79.171
78.864
77.371
77.160
76.949
76.298
74.967
73.866
67.777
66.781
63.602
40.517
38.574
26.605
26.519
19.348
18.696
16.734
16.016
-2.138
-2.588
-4.369
-4.417
-4.628
-5.145

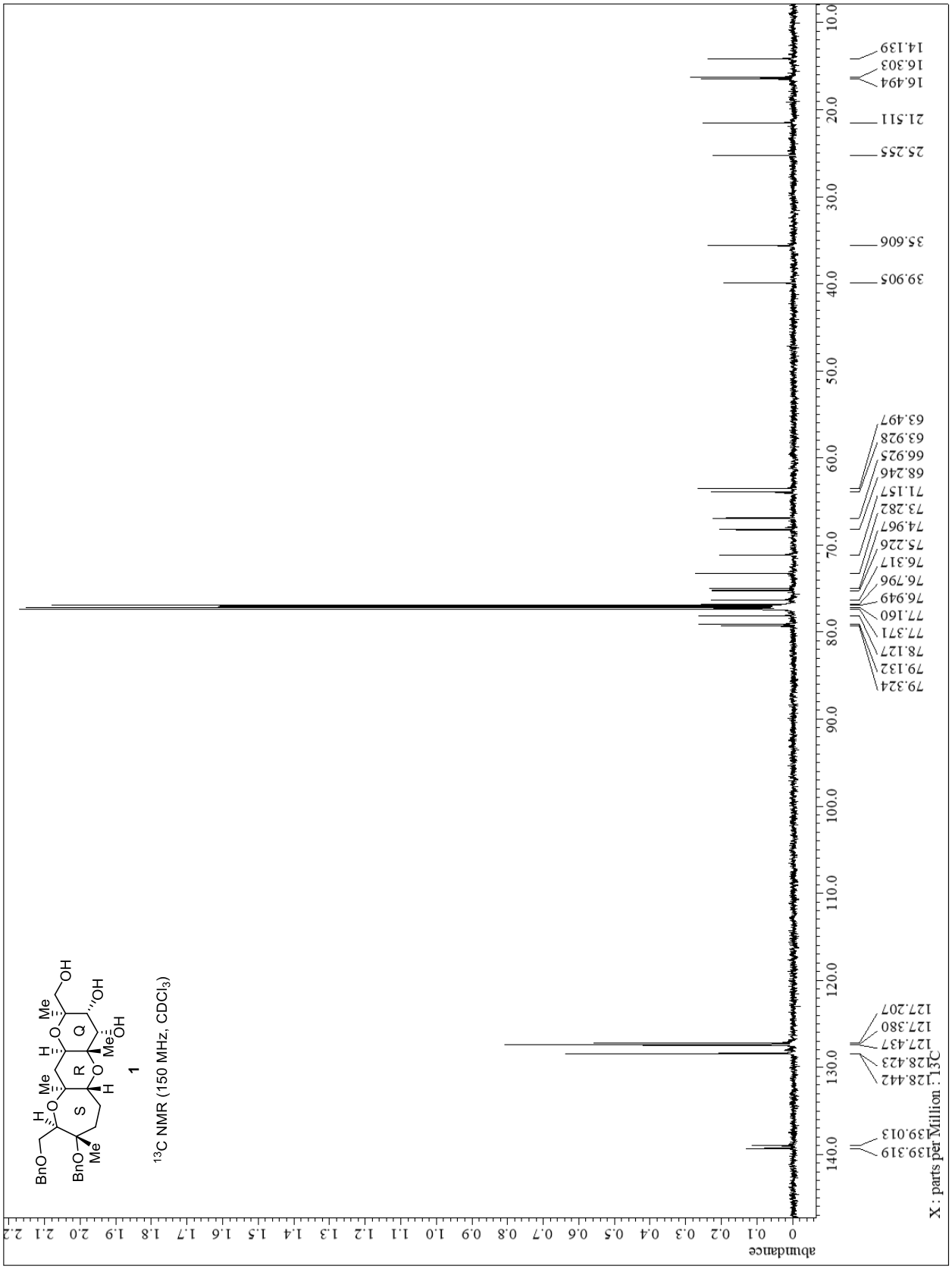

33
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance
7.260
4.112
4.106
4.030
4.024
4.009
4.002
3.779
3.774
3.452
3.217
3.199
2.260
1.863
1.658
1.579
1.253
1.178
0.922
0.902
0.880
0.124
0.091
0.079
0.062
0.031
0.029

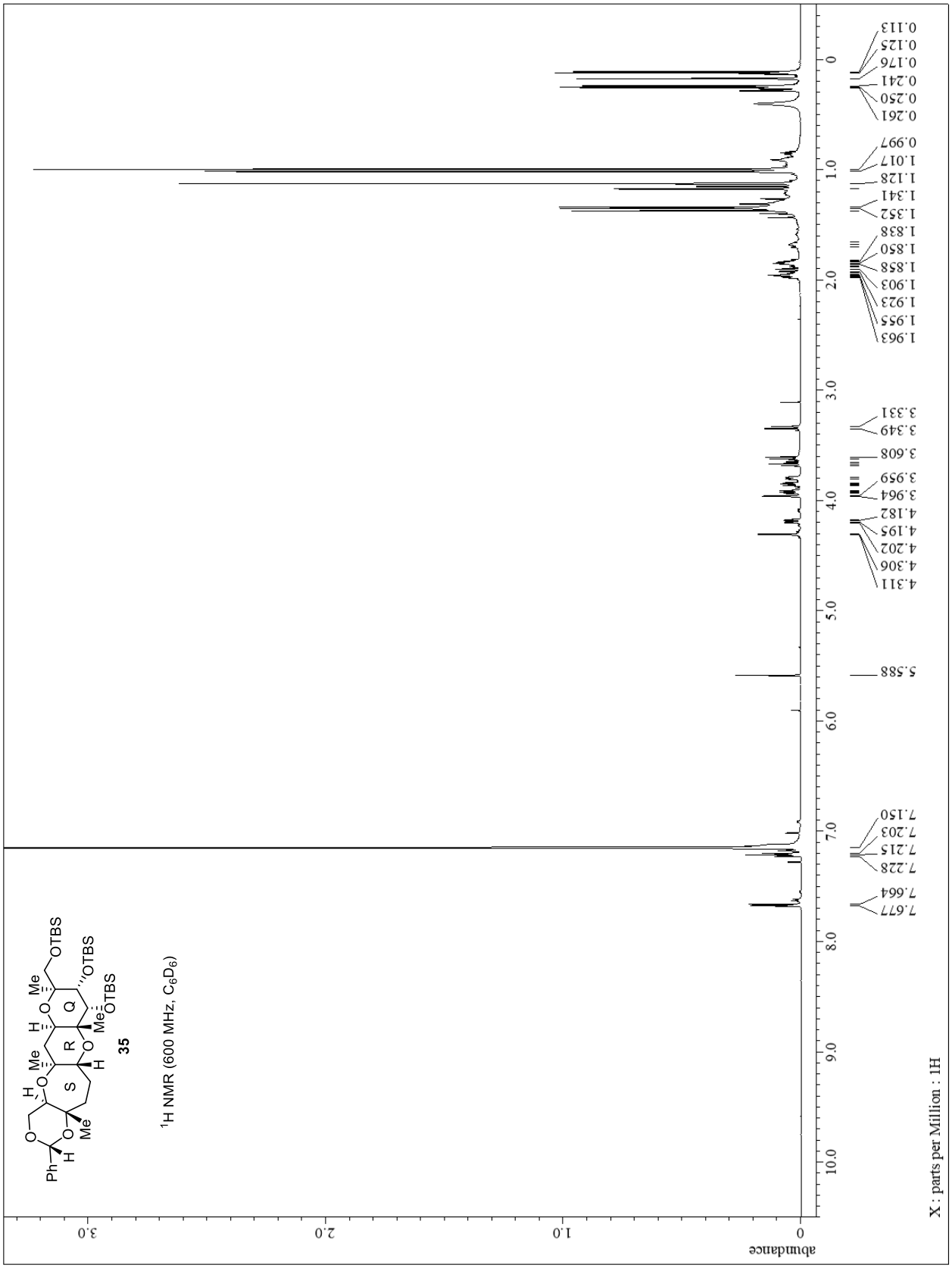

33
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
79.247
78.730
77.514
77.371
77.227
77.160
76.940
75.772
74.920
67.652
67.624
63.602
62.846
41.226
40.268
26.557
26.462
26.194
25.016
24.154
18.735
18.658
18.428
17.069
15.996
14.254
-2.167
-2.569
-4.388
-4.455
-4.647
-5.221

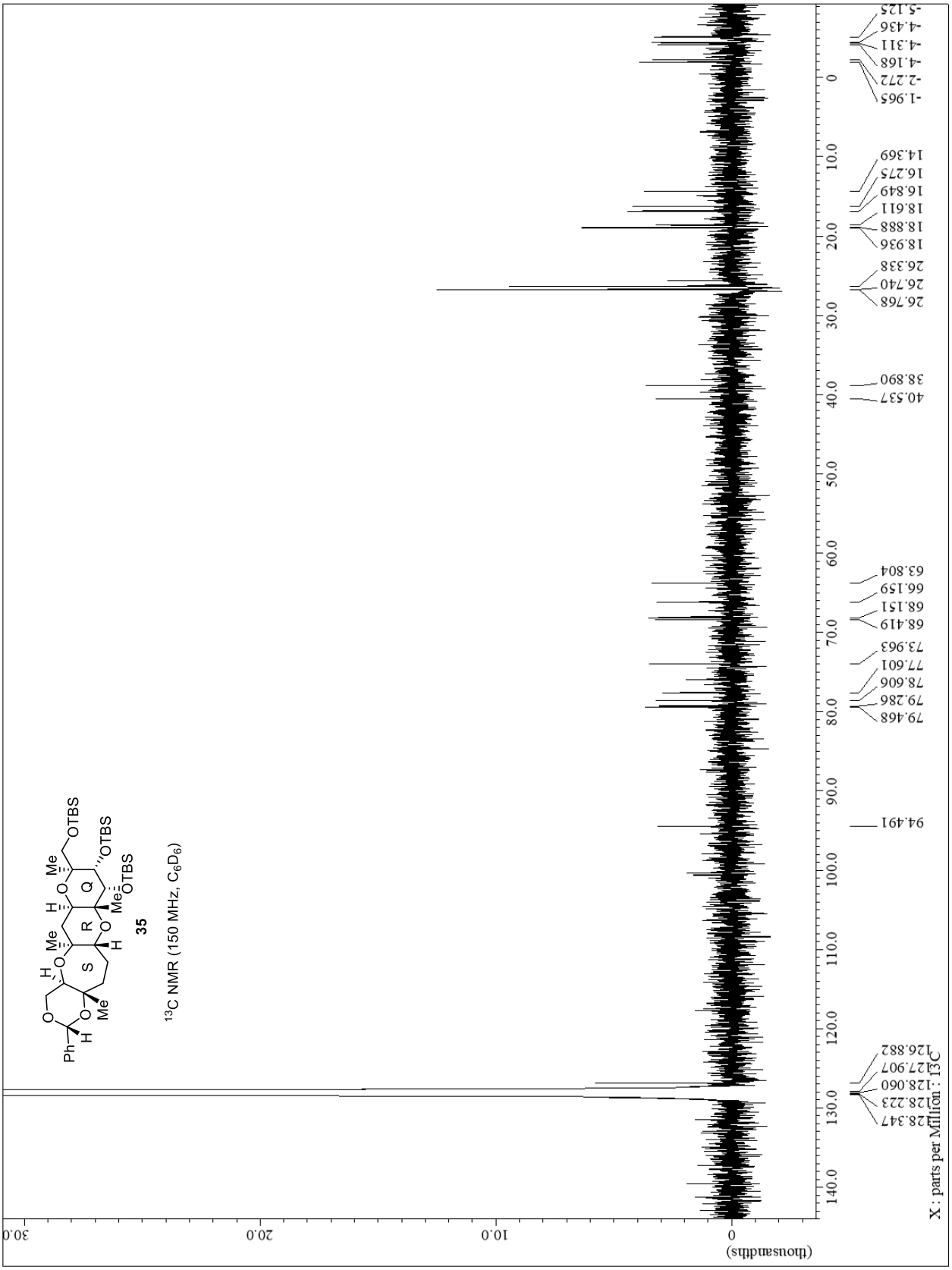

34
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.919
7.349
7.339
7.328
7.320
7.307
7.279
7.267
7.260
5.534
4.752
4.745
4.560
4.438
4.148
3.804
3.470
3.251
3.232
3.208
2.228
2.210
2.202
1.875
1.856
1.647
1.443
1.228
0.937
0.919
0.902
0.899
0.144
0.107
0.093
0.073
0.055
0.039

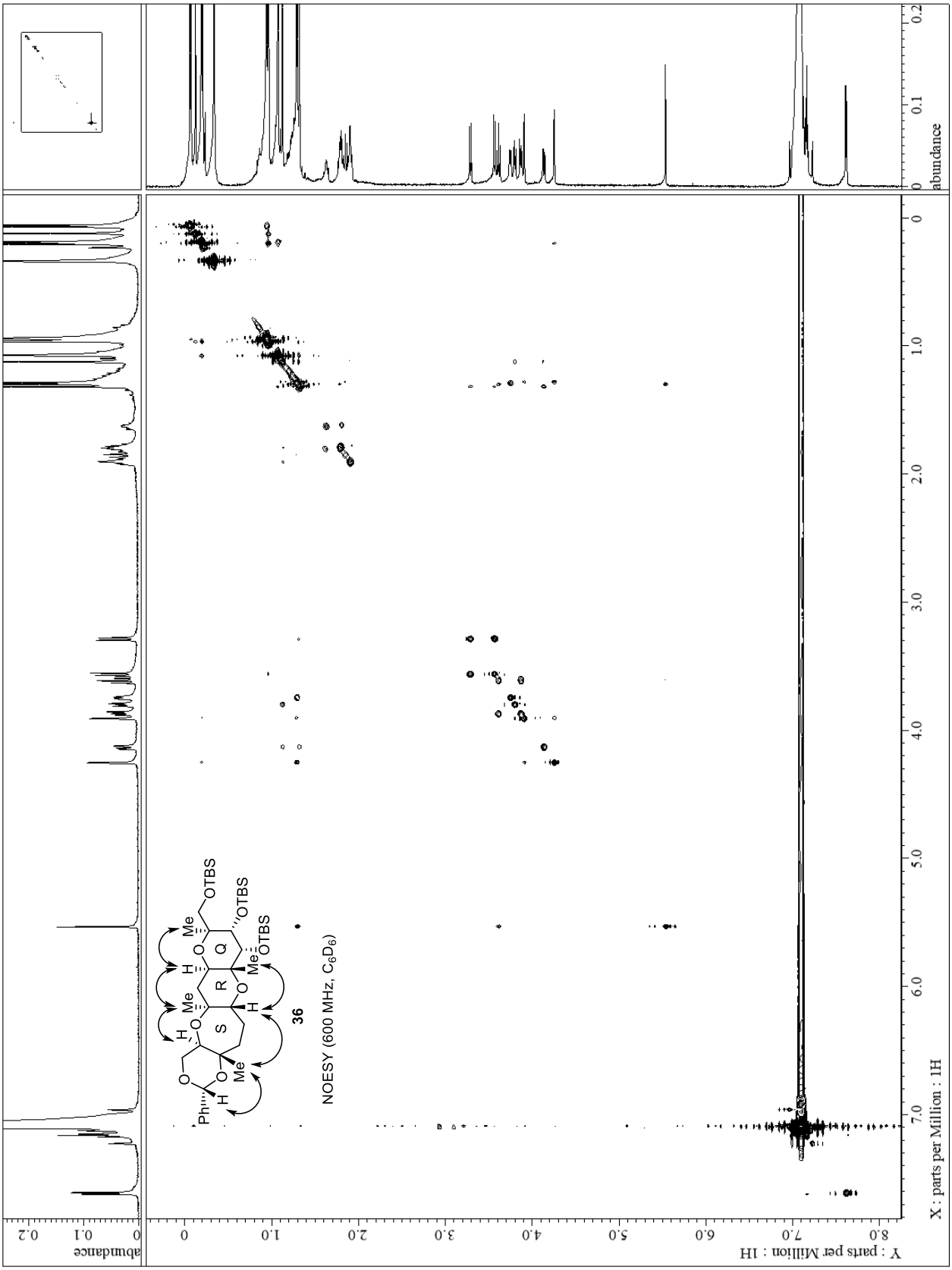

34
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
-5.212
-4.666
-4.484
-4.427
-2.473
-2.224
14.493
16.025
17.203
18.677
18.754
21.981
25.571
26.213
26.490
26.548
36.304
40.144
63.516
63.928
67.633
71.252
73.215
75.628
76.126
76.949
77.160
77.371
78.127
78.826
79.266
79.477
127.255
127.341
127.380
127.456
128.040
128.423
139.118
139.425

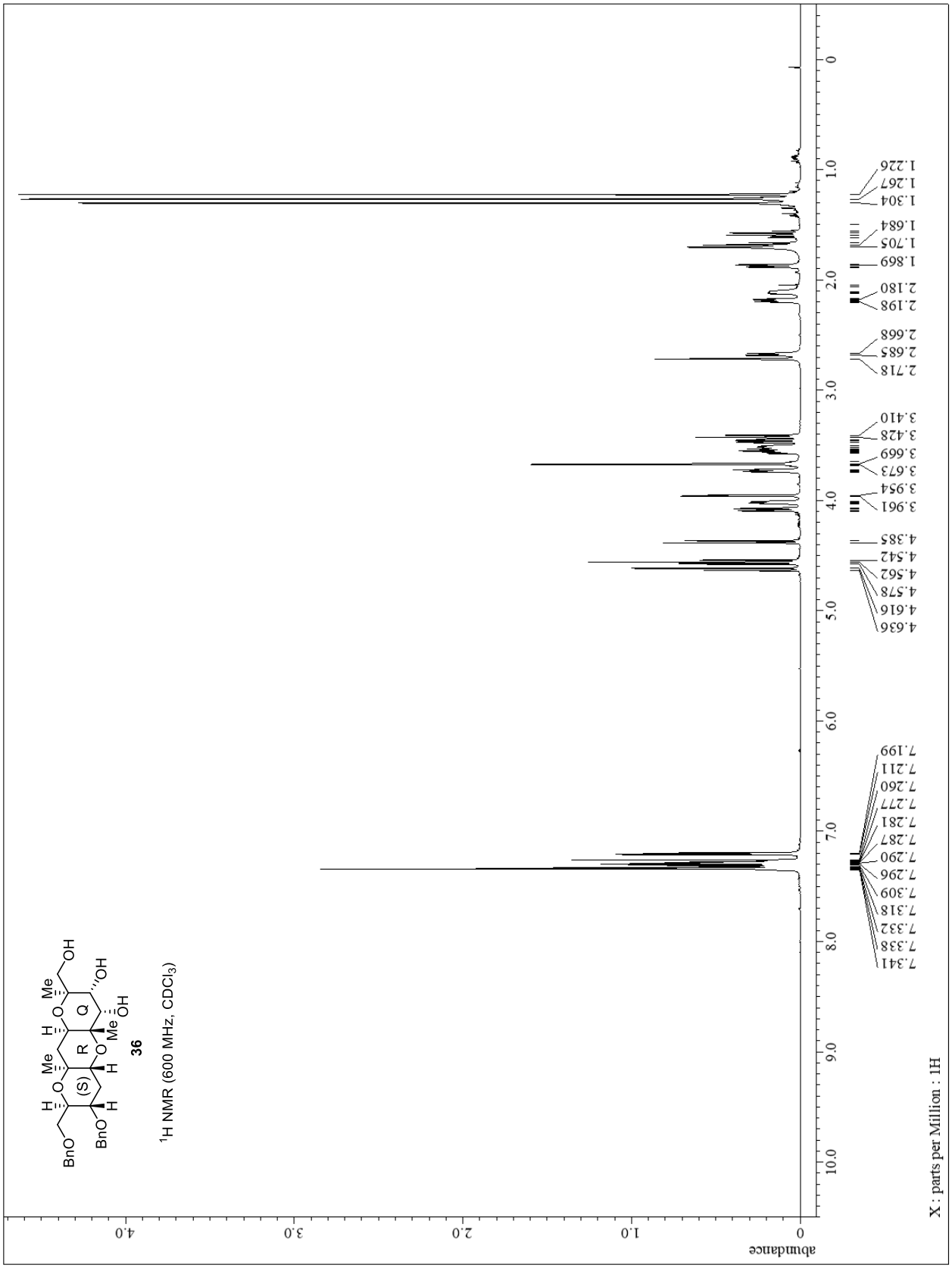

1
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance
0.074
0.871
0.883
0.996
1.220
1.226
1.264
1.273
1.414
1.727
1.748
2.317
2.670
2.727
2.795
3.415
3.434
3.508
3.649
3.946
3.951
4.429
4.716
4.736
4.744
5.524
7.199
7.212
7.246
7.260
7.273
7.286
7.293
7.305
7.317
7.333
7.340
7.365
7.391

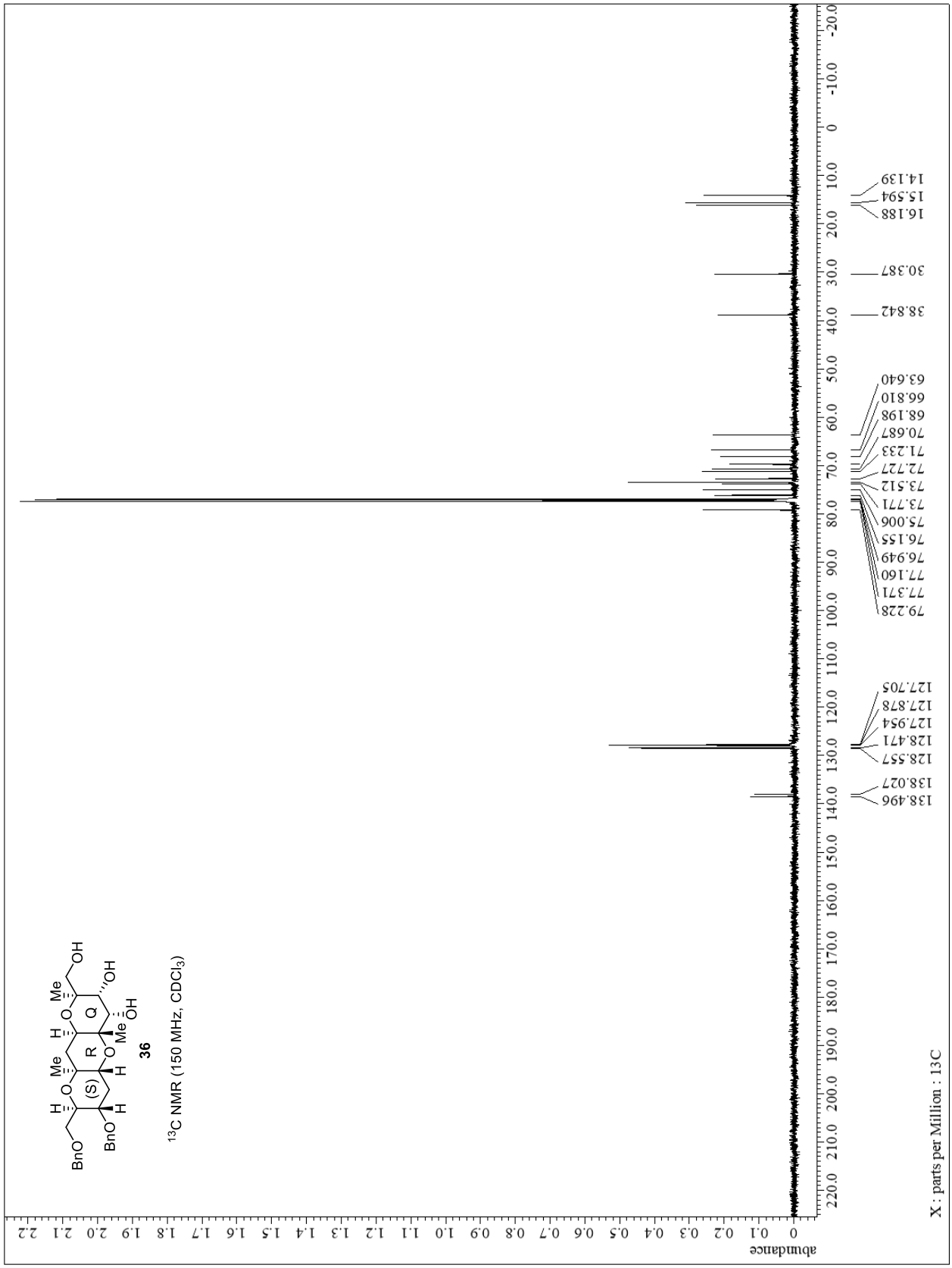

BnO
Me
BnO
Me
H
O
S
Me
H
O
R
O
H
Me
Q
OH
Me
OH
OH
1
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
14.139
16.303
16.494
21.511
25.255
35.606
39.905
63.497
63.928
66.925
68.246
71.157
73.282
74.967
75.226
76.317
76.796
76.949
77.160
77.371
78.127
79.132
79.324
127.207
127.380
127.437
128.423
128.442
139.013
139.319


35
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance
7.677
7.664
7.228
7.215
7.203
7.150
5.588
4.311
4.306
4.202
4.195
4.182
3.964
3.959
3.608
3.349
3.331
1.963
1.955
1.923
1.903
1.858
1.850
1.838
1.352
1.341
1.128
1.017
0.997
0.261
0.250
0.241
0.176
0.125
0.113

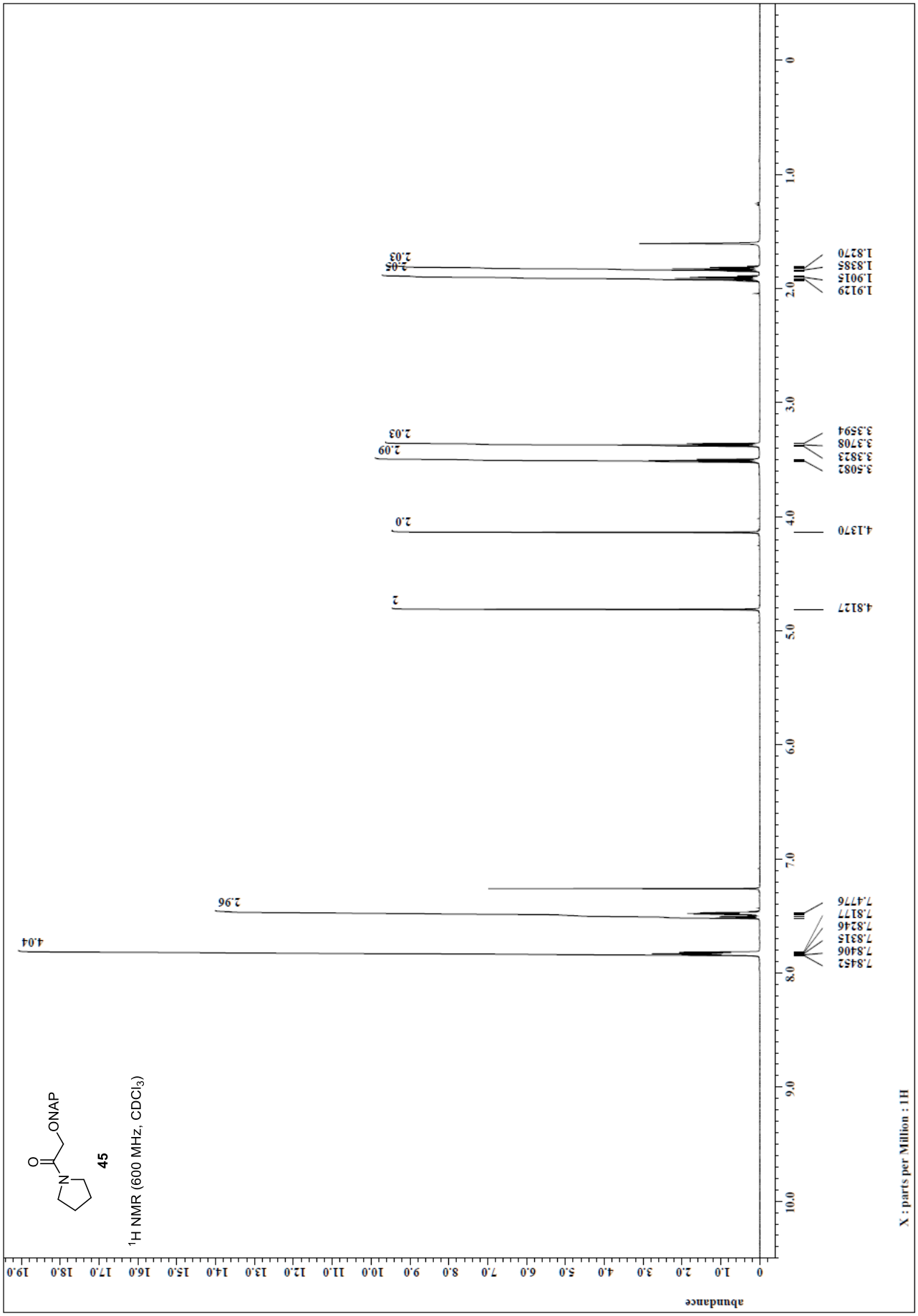

35
^{13}C NMR (150 MHz, C_6D_6)
X : parts per Million : 13C
(thousandths)
-5.125
-4.436
-4.311
-4.168
-2.272
-1.965
14.369
16.275
16.849
18.611
18.888
18.936
26.338
26.740
26.768
38.890
40.537
63.804
66.159
68.151
68.419
73.963
77.601
78.606
79.286
79.468
94.491
126.882
127.907
128.060
128.223
128.347

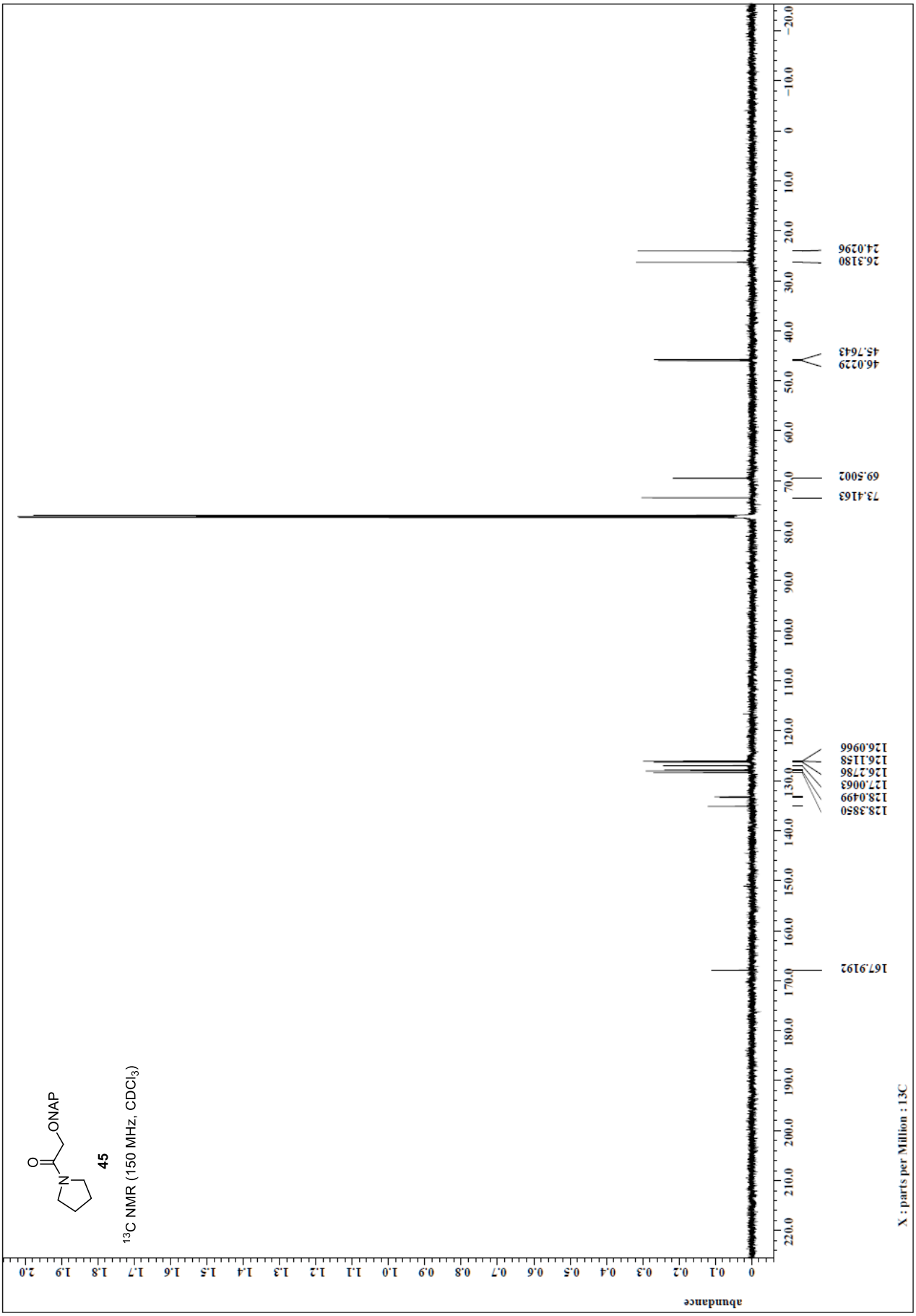

NOESY (600 MHz, C6D6)
36
X : parts per Million : 1H
Y : parts per Million : 1H
abundance

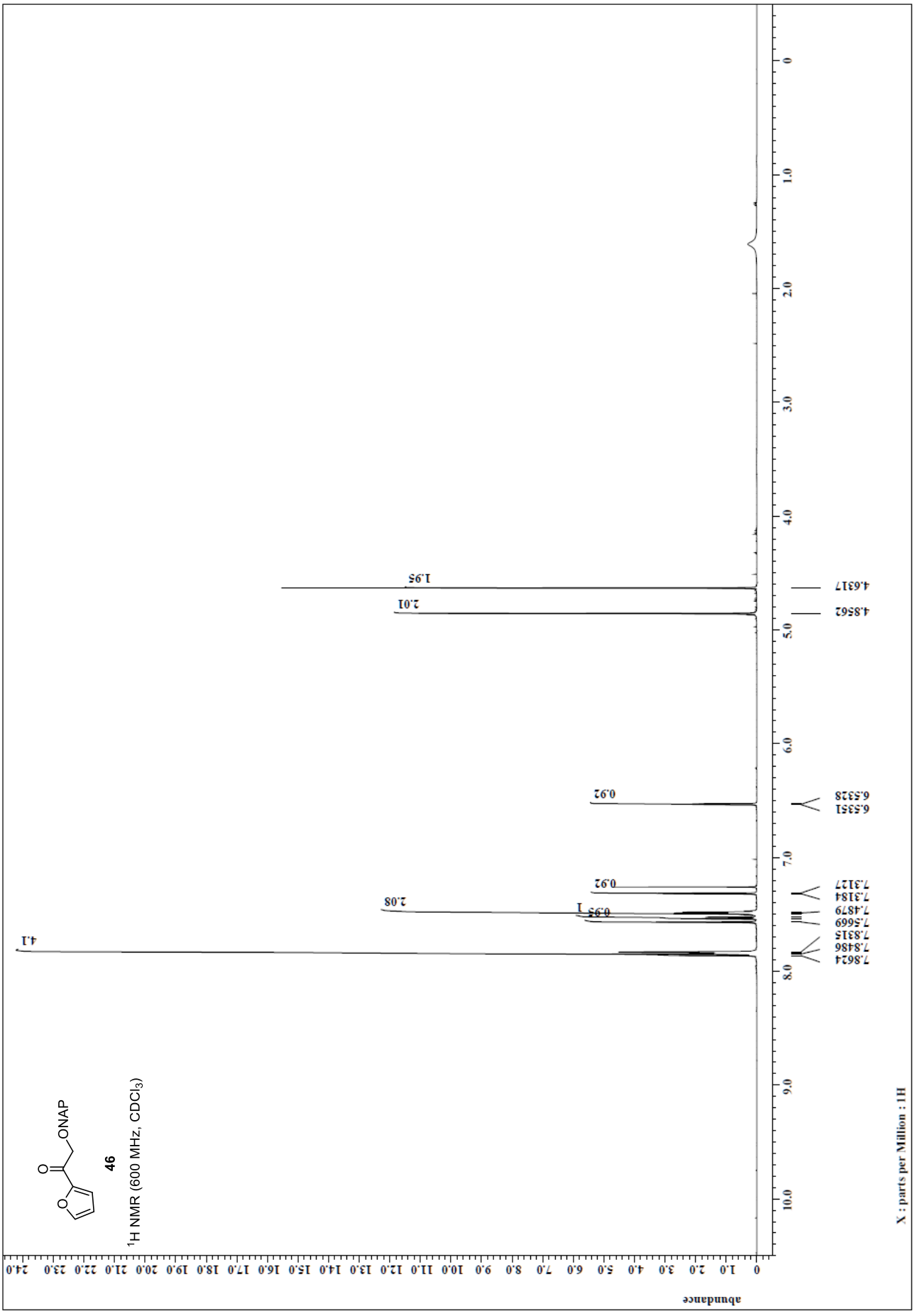

abundance
X : parts per Million : 1H
36
1H NMR (600 MHz, CDCl3)

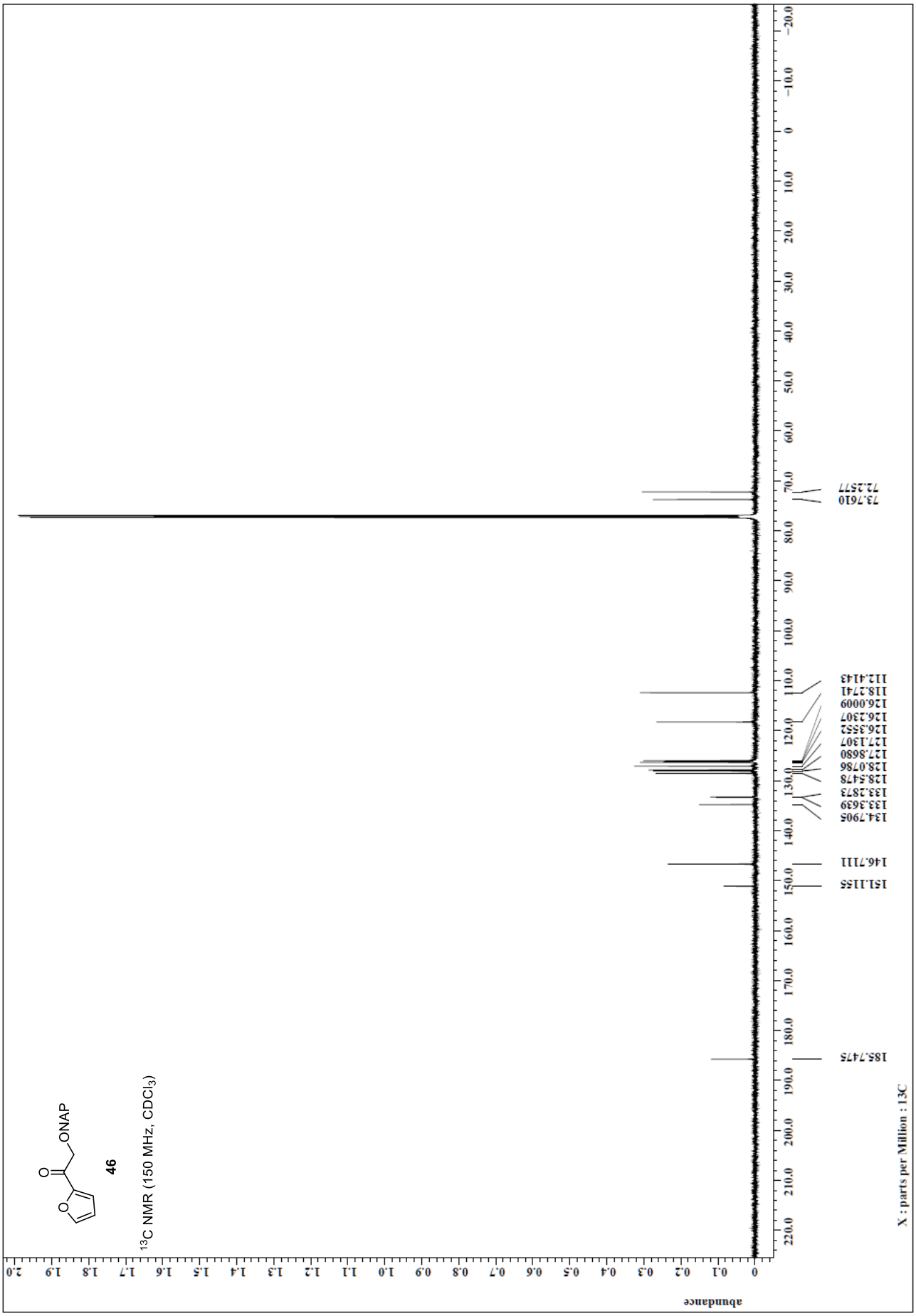

BnO
H
Me
O
(S)
H
O
R
Me
H
Q
OH
OH
Me
OH
36
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
138.496
138.027
128.557
128.471
127.954
127.878
127.705
79.228
77.371
77.160
76.949
76.155
75.006
73.771
73.512
72.727
71.233
70.687
68.198
66.810
63.640
38.842
30.387
16.188
15.594
14.139

Section 2-2

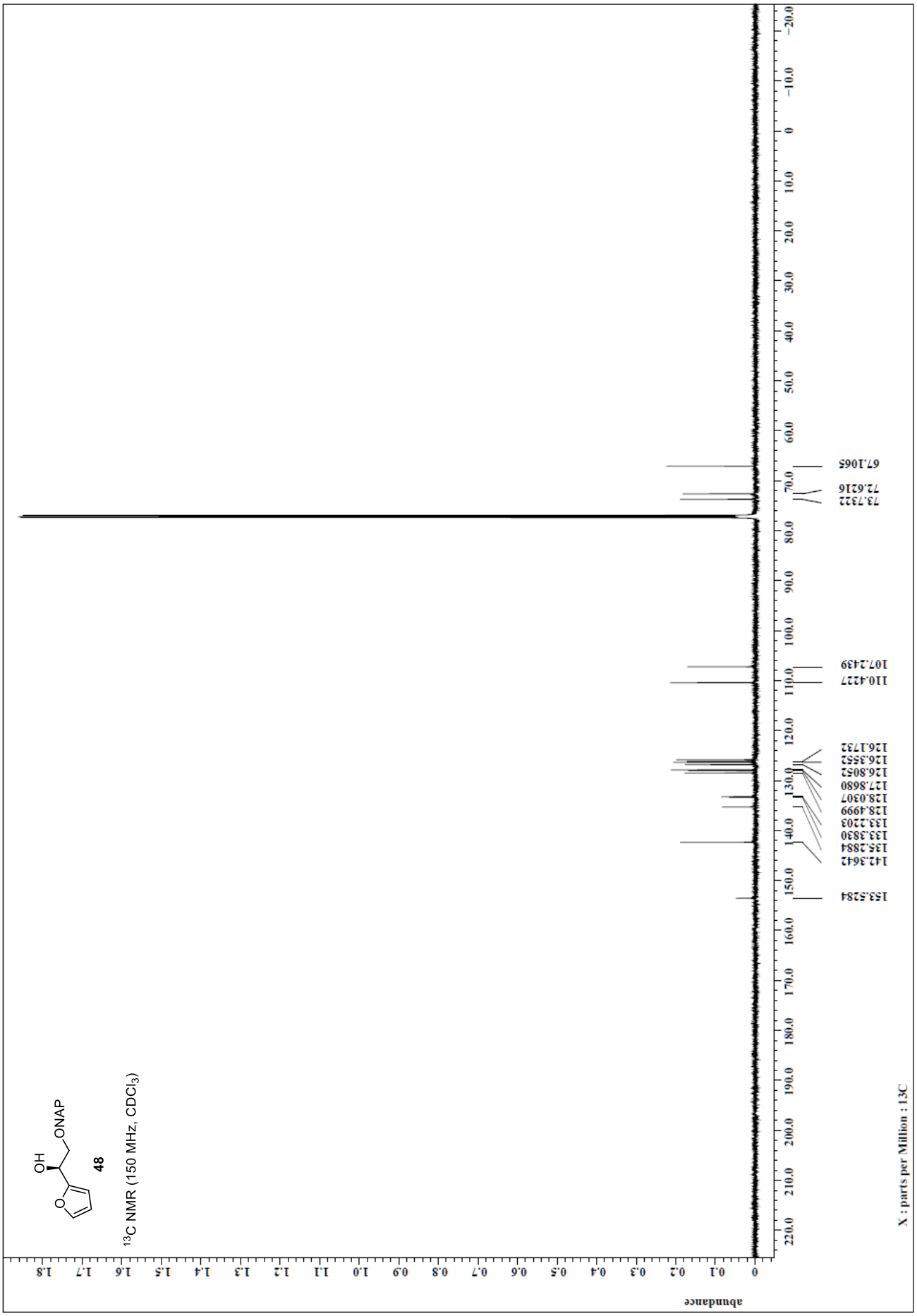

ONAP
45
^{1}H NMR (600 MHz, $CDCl_3$)
4.04
2.96
2
2.0
2.09
2.03
2.05
2.03
7.8452
7.8406
7.8315
7.8246
7.8177
7.4776
4.8127
4.1370
3.5082
3.3823
3.3708
3.3594
1.9129
1.9015
1.8385
1.8270
abundance
X : parts per Million : 1H

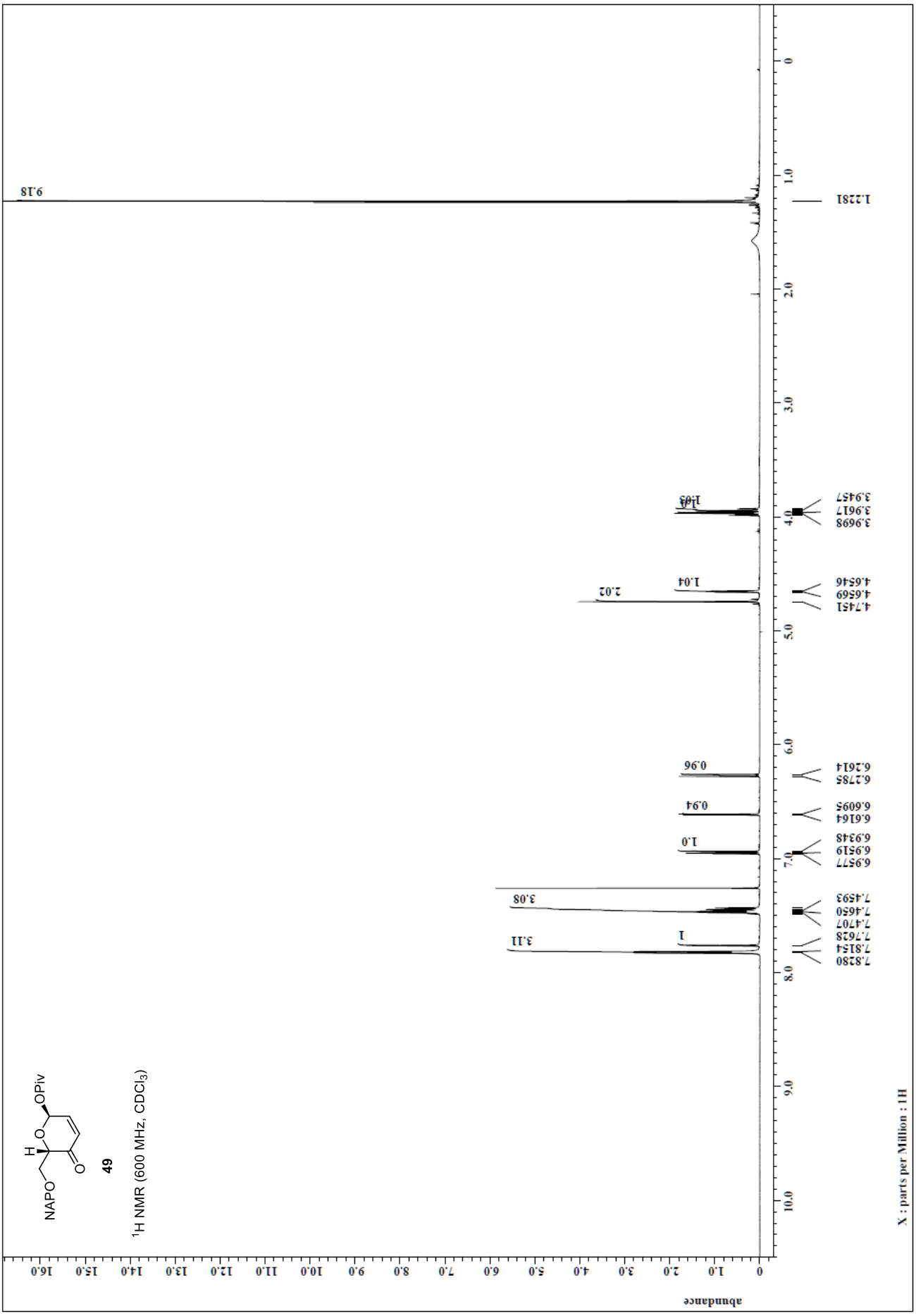

ONAP
O
N
45
^{13}C NMR (150 MHz, $CDCl_3$)
167.9192
128.3850
128.0499
127.0063
126.2786
126.1158
126.0966
73.4163
69.5002
46.0229
45.7643
26.3180
24.0296
X : parts per Million : 13C
abundance

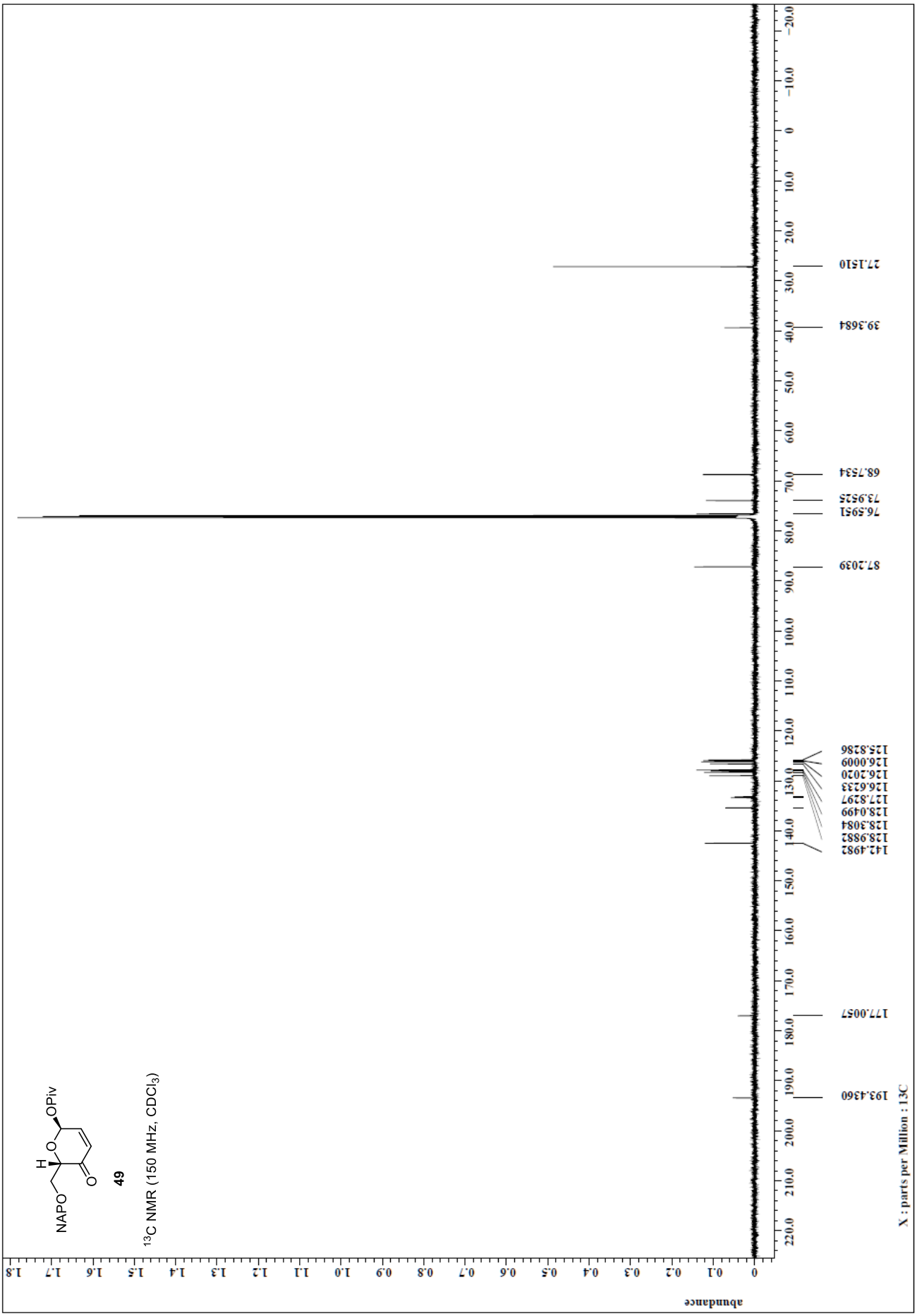

ONAP
O
O
46
^{1}H NMR (600 MHz, $CDCl_3$)
abundance
X : parts per Million : 1 H
4.1
2.08
1
0.95
0.92
0.92
1.95
2.01
7.8624
7.8486
7.8315
7.5669
7.4879
7.3184
7.3127
6.5351
6.5328
4.8562
4.6317

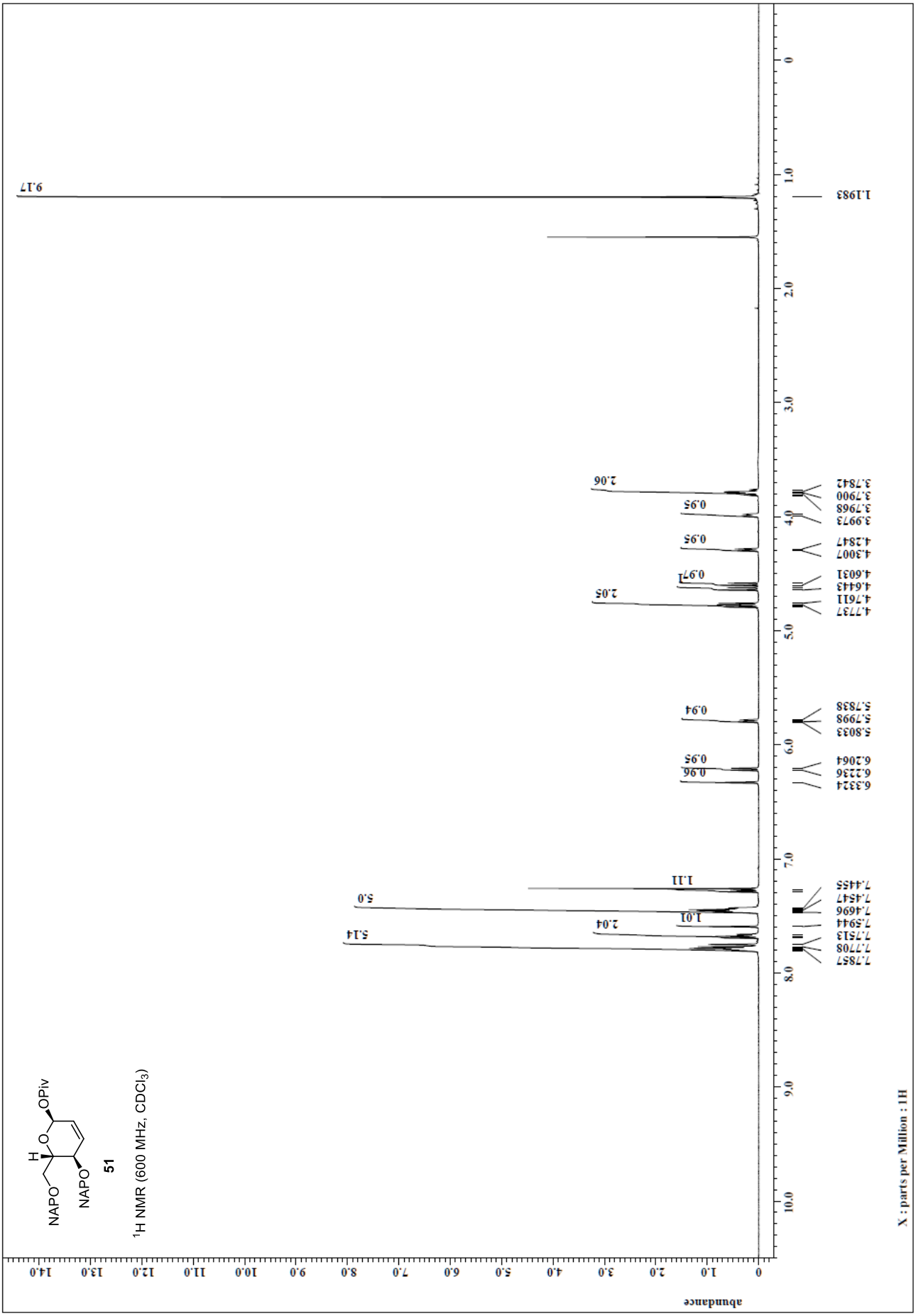

ONAP
46
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
185.7475
151.1155
146.7111
134.7905
133.3639
133.2873
128.5478
128.0786
127.8680
127.1307
126.3552
126.2307
126.0009
118.2741
112.4143
73.7610
72.2577

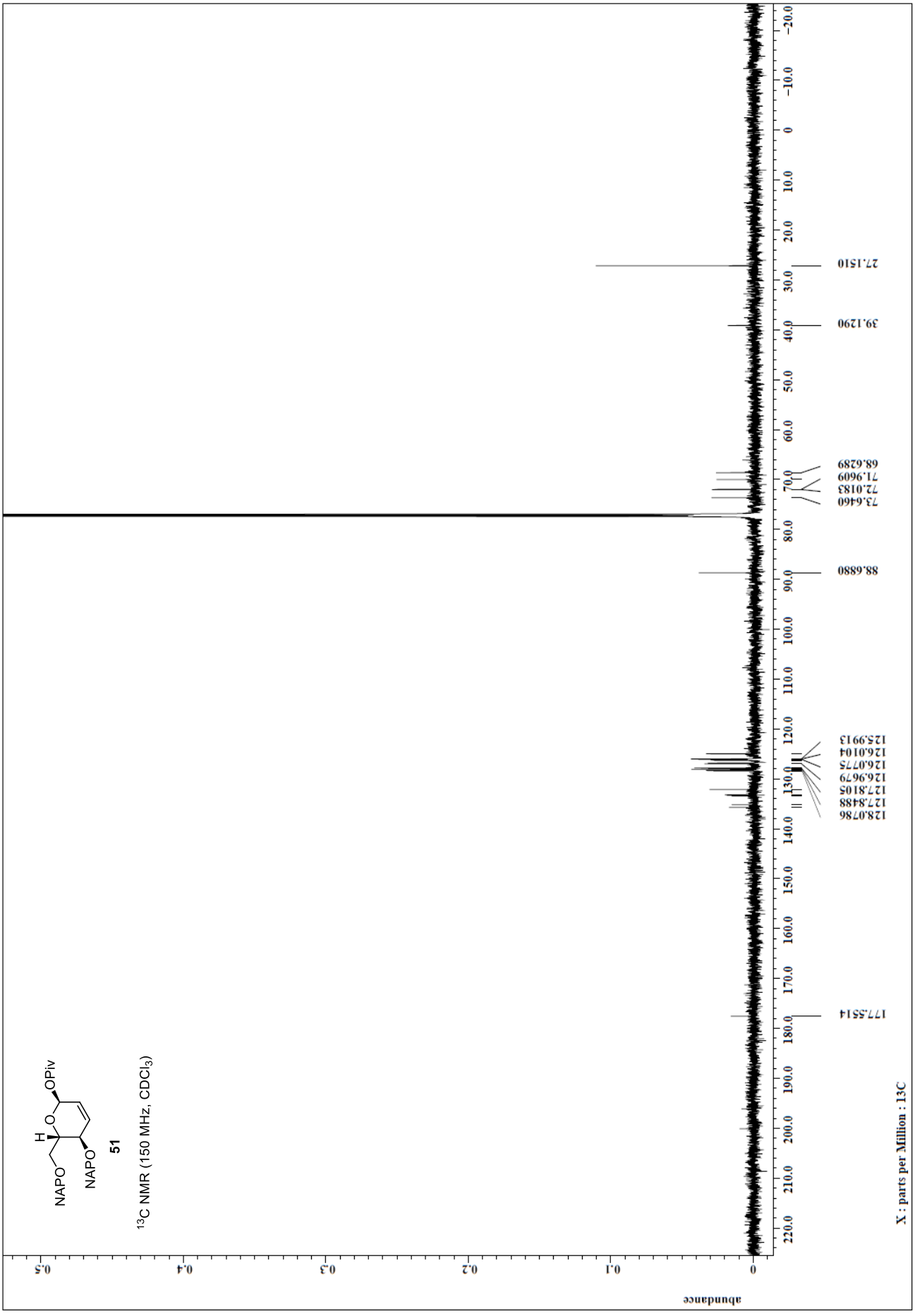
OH
ONAP
O
48
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
7.8509
7.8372
7.7719
7.4913
7.4845
7.4787
7.3745
6.3427
6.3392
6.3232
4.9638
4.9535
4.7772
4.7680
3.8037
3.7934
2.7112
2.7031
3.08
0.99
3.07
0.92
2.05
1
2.01
0.95

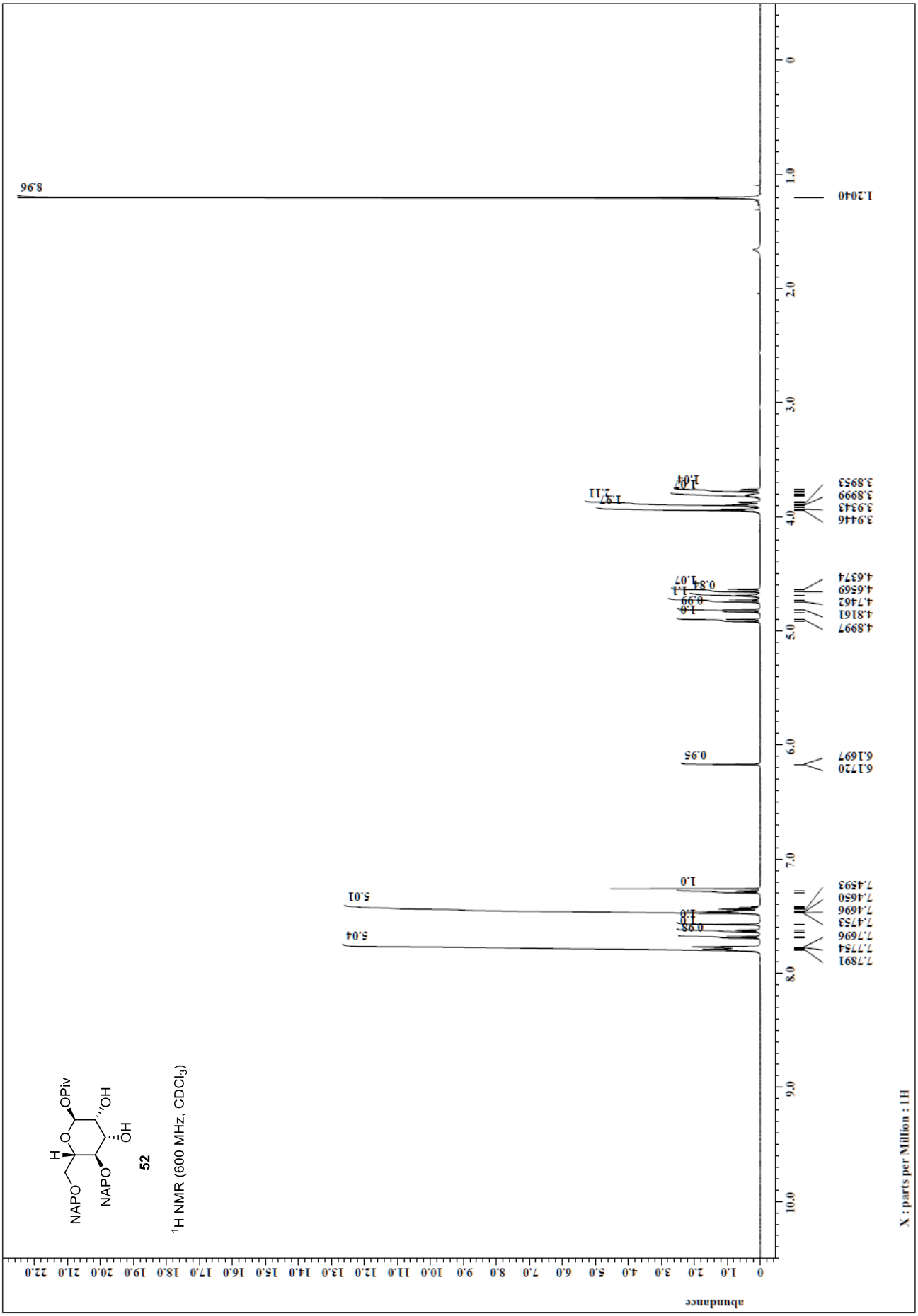

OH
ONAP
O
48
^{13}C NMR (150 MHz, $CDCl_3$)
153.5284
142.3642
135.2884
133.3830
133.2203
128.4999
128.0307
127.8680
126.8052
126.3552
126.1732
110.4227
107.2439
73.7322
72.6216
67.1065
X : parts per Million : 13C
abundance

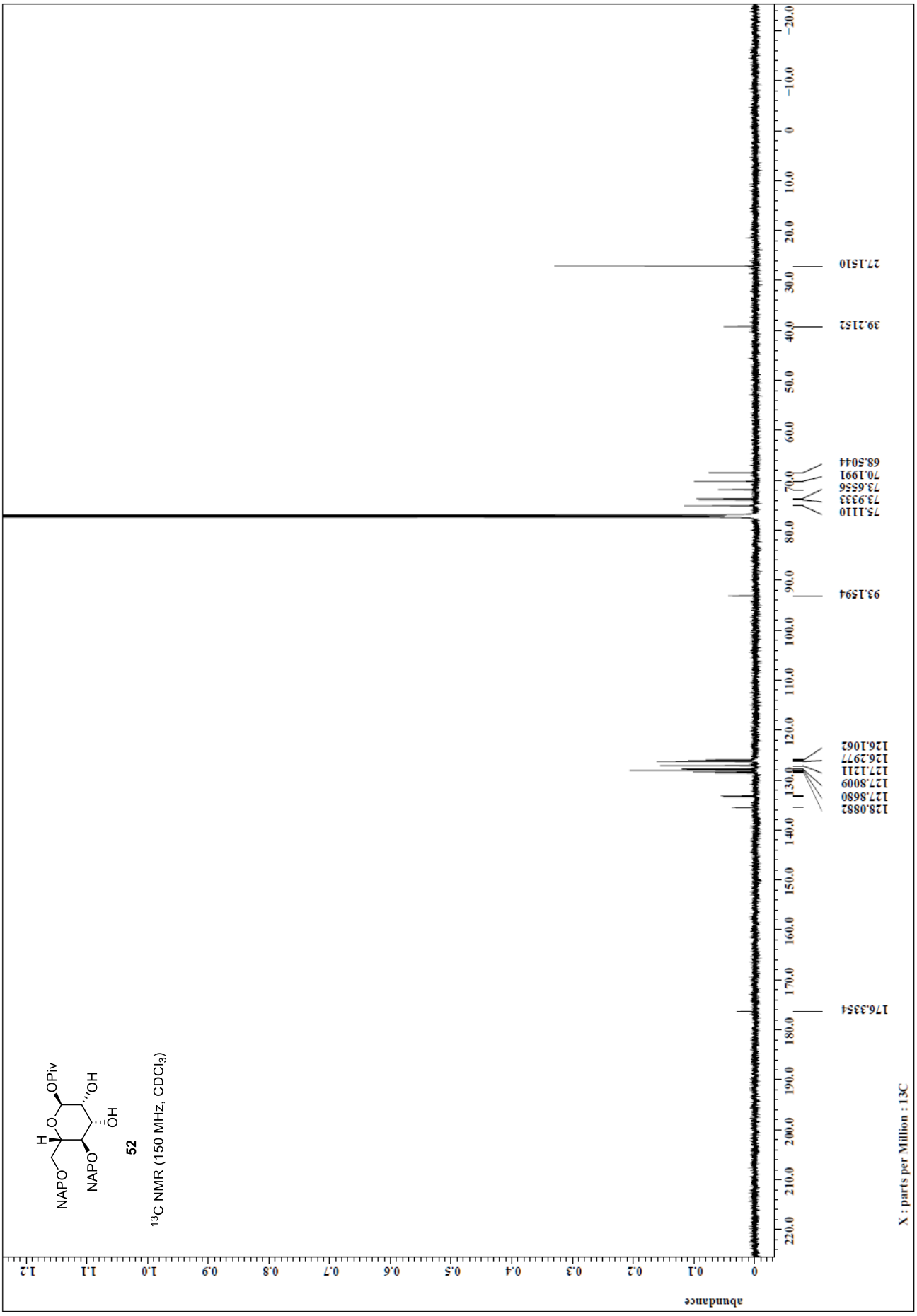

OPiv
O
H
O
NAPO
49
^{1}H NMR (600 MHz, CDCl$_3$)
9.18
7.8280
7.8154
7.7628
7.4707
7.4650
7.4593
6.9577
6.9519
6.9348
6.6164
6.6095
6.2785
6.2614
4.7451
4.6569
4.6546
3.9698
3.9617
3.9457
1.2281
3.11
1
3.08
1.0
0.94
0.96
2.02
1.04
1.03
abundance
X : parts per Million : 1H

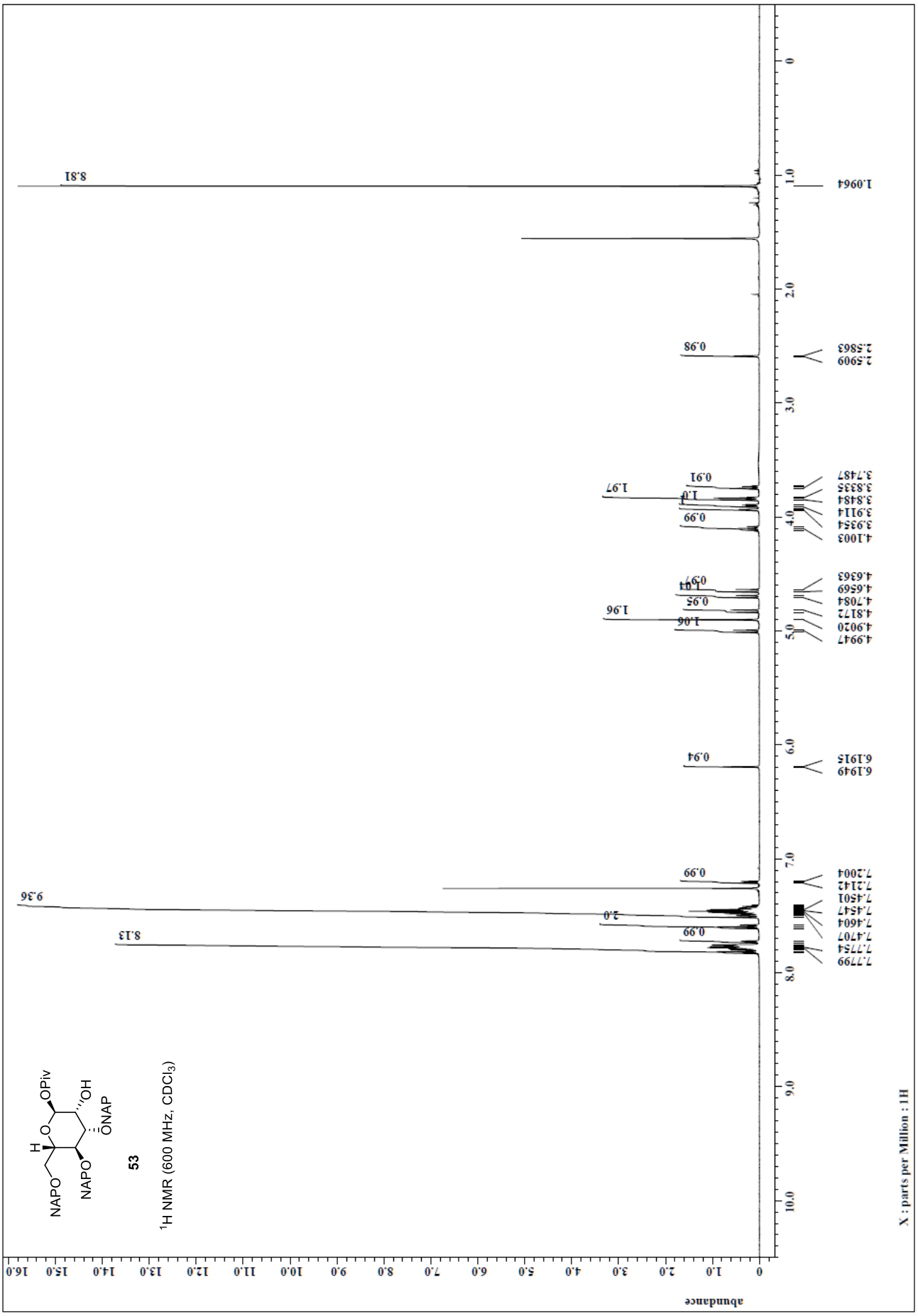

OPiv
O
H
O
NAPO
49
^{13}C NMR (150 MHz, $CDCl_3$)
27.1510
39.3684
68.7534
73.9525
76.5951
87.2039
125.8286
126.0009
126.2020
126.6133
127.8297
128.0499
128.3084
128.9882
142.4982
177.0057
193.4360
X : parts per Million : 13C
abundance

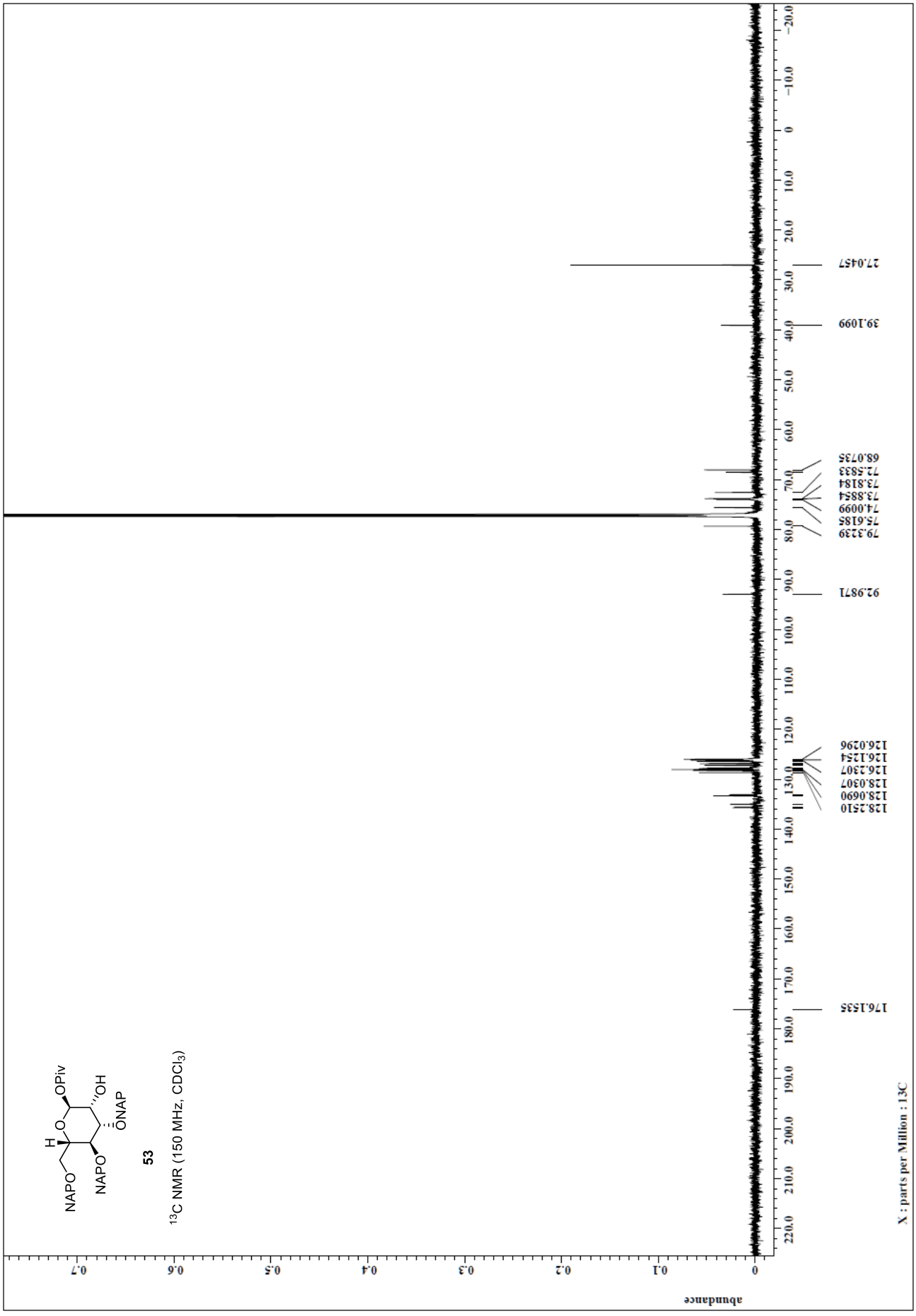

OPiv
H
O
NAPO
NAPO
51
^{1}H NMR (600 MHz, $CDCl_3$)
abundance
X : parts per Million : 1H
9.17
5.14
5.0
2.06
2.05
2.04
1.11
1.01
0.97
0.96
0.95
0.94
1.1983
3.7842
3.7900
3.7968
3.9973
4.2847
4.3007
4.6031
4.6443
4.7611
4.7737
5.7838
5.7998
5.8033
6.2064
6.2236
6.3324
7.4455
7.4547
7.4696
7.5944
7.7513
7.7708
7.7857

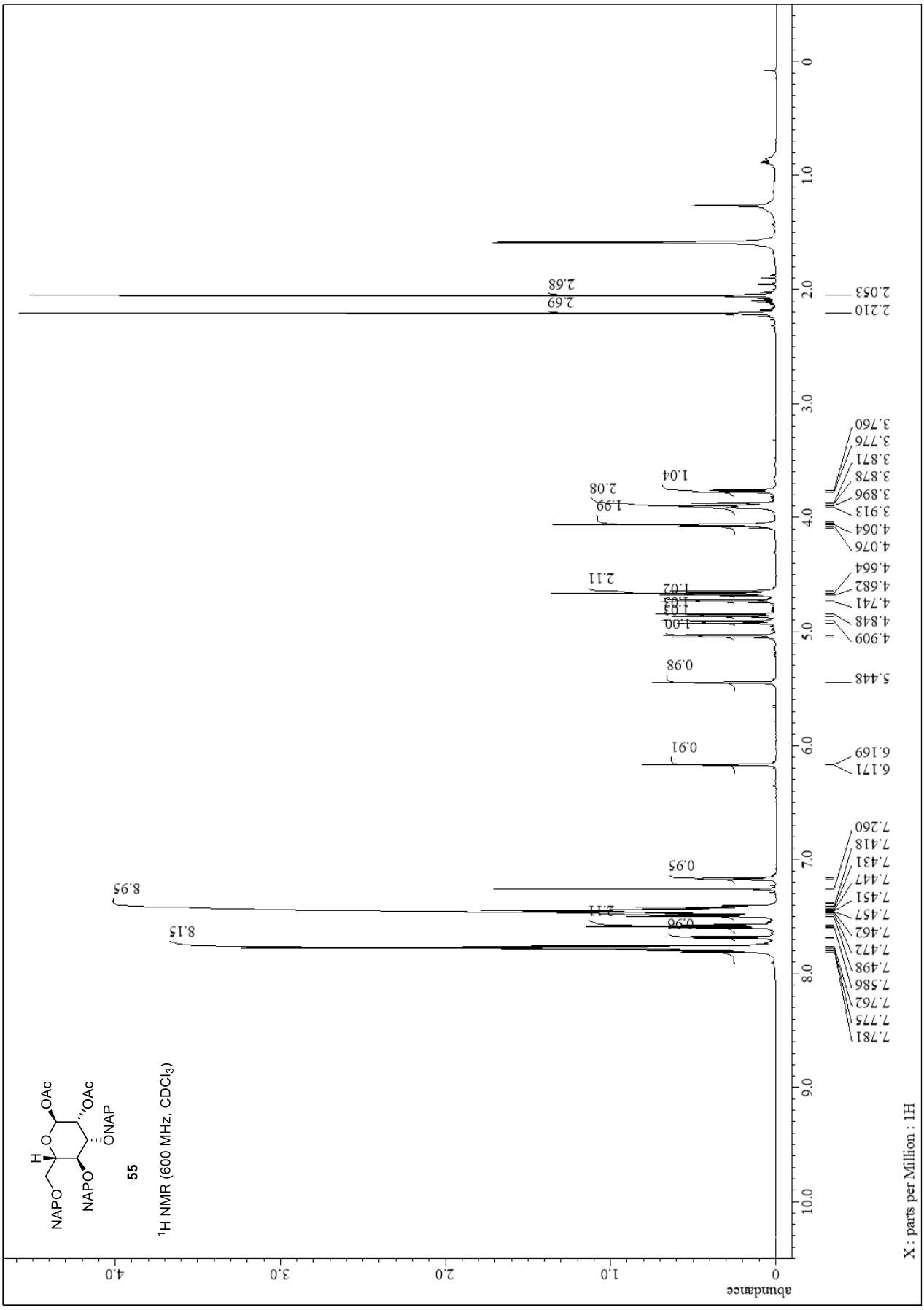

OPiv
O
H
NAPO
NAPO
51
^{13}C NMR (150 MHz, $CDCl_3$)
177.5514
128.0786
127.8488
127.8105
126.9679
126.0775
126.0104
125.9913
88.6880
73.6460
72.0183
71.9609
68.6289
39.1290
27.1510
abundance
X : parts per Million : 13C

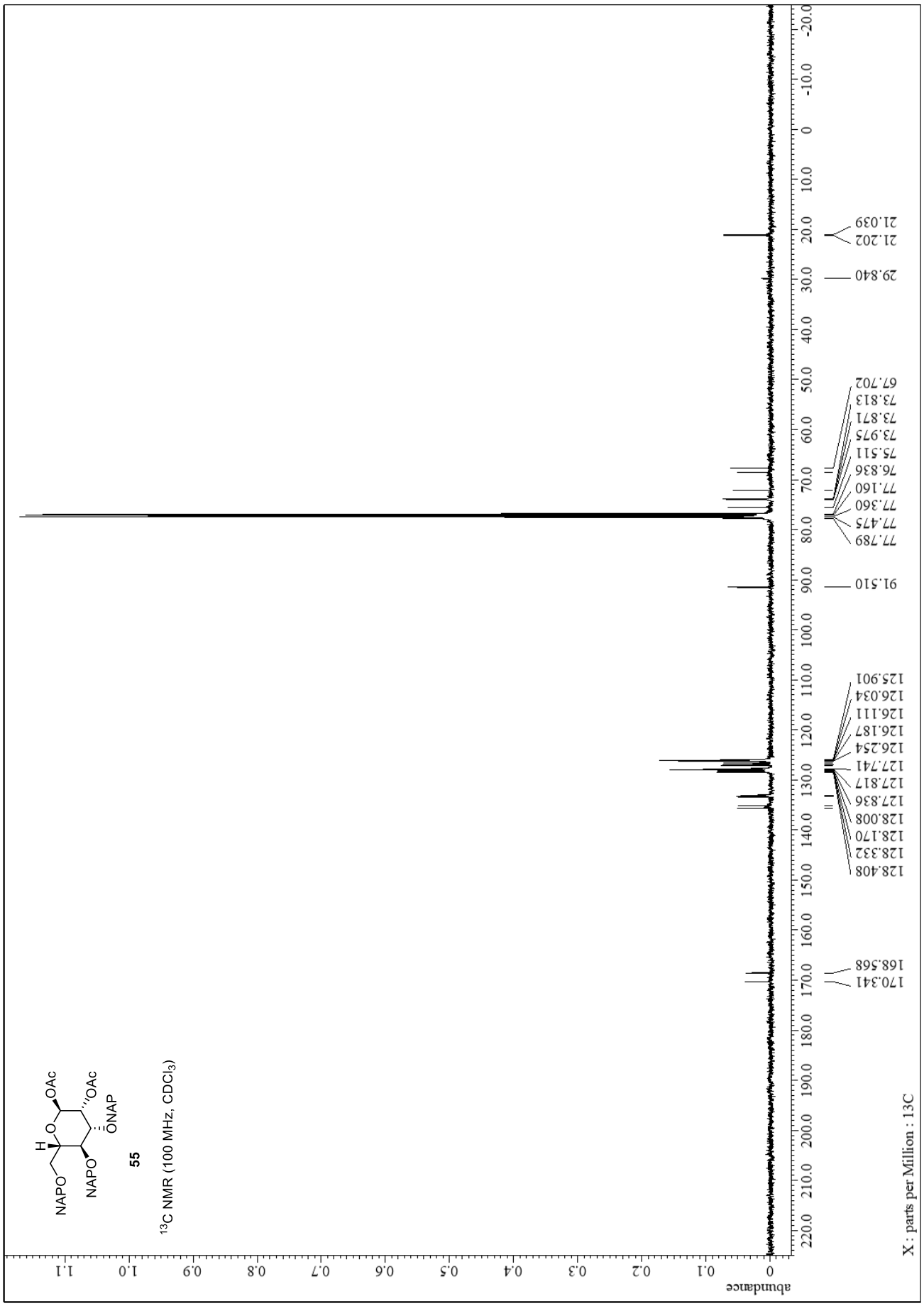

NAPO
O
H
OPiv
NAPO
OH
OH
52
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance
8.96
5.04
5.01
1.20
0.95
1.04
1.97
2.11
1.07
0.84
1.1
0.99
1.0
4.8997
4.8161
4.7462
4.6569
4.6374
3.9446
3.9343
3.8999
3.8953
6.1720
6.1697
7.7891
7.7754
7.7696
7.4753
7.4696
7.4650
7.4593

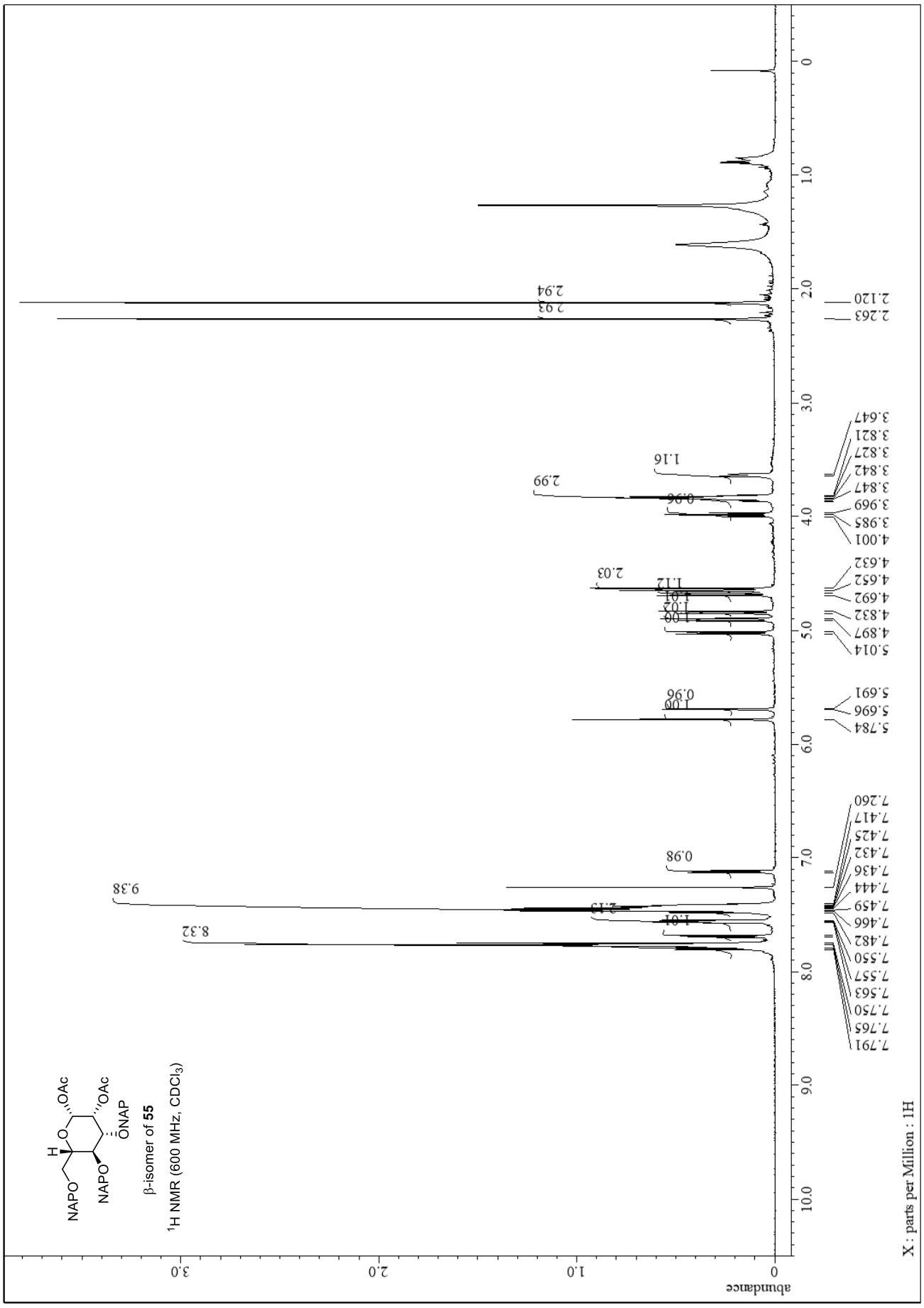

OPiv
OH
OH
NAPO
NAPO
52
^{13}C NMR (150 MHz, $CDCl_3$)
176.3354
128.0882
127.8680
127.8009
127.1211
126.3977
126.1062
93.1594
75.1110
73.9333
73.6556
70.1991
68.5044
39.2152
27.1510
X : parts per Million : 13C
abundance

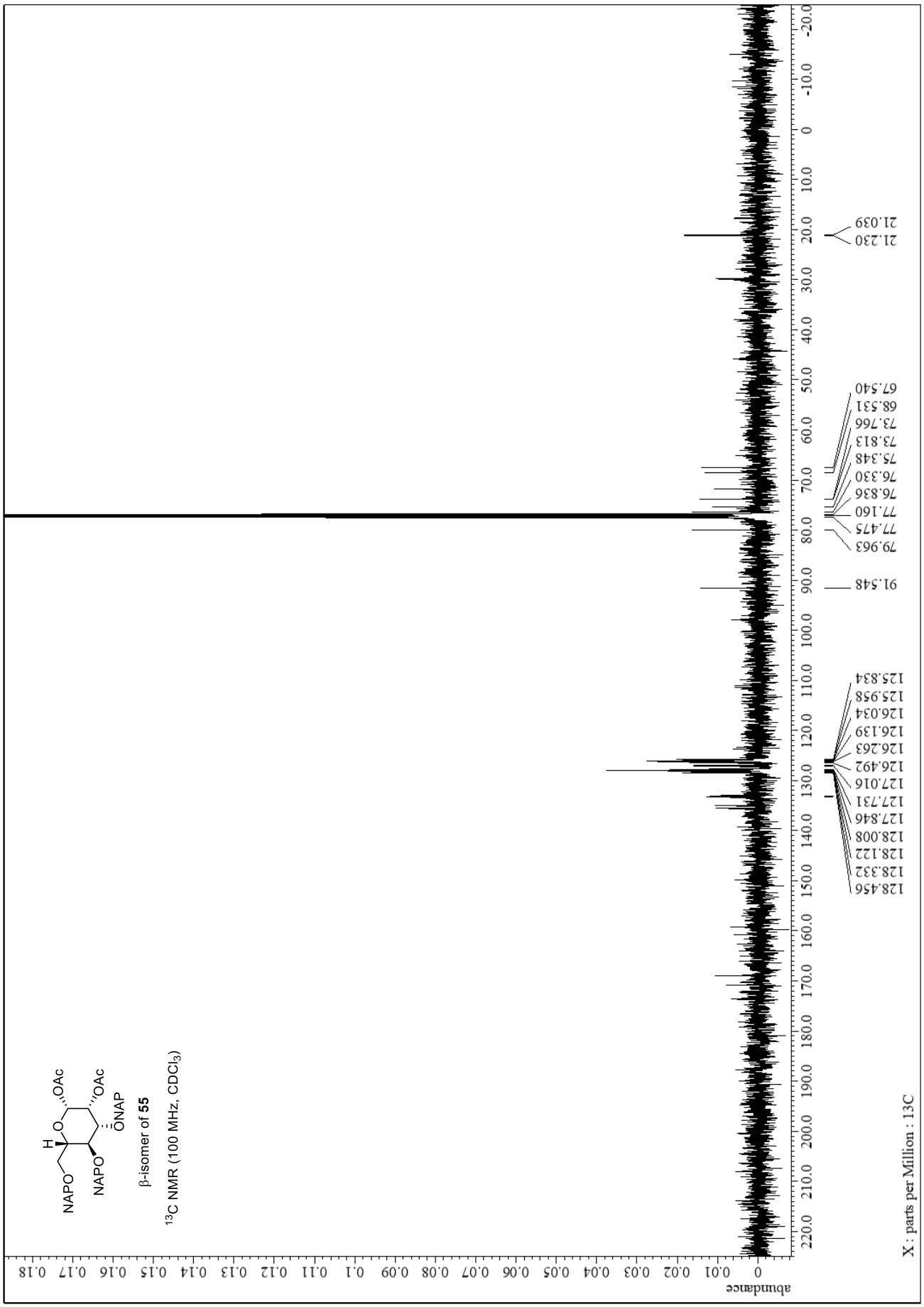

53
^{1}H NMR (600 MHz, CDCl$_3$)
NAPO
NAPO
OPiv
OH
ONAP
abundance
X : parts per Million : 1H
1.0964
2.5909
2.5863
3.7487
3.8335
3.8484
3.9114
3.9354
4.1003
4.6363
4.6569
4.7084
4.8172
4.9020
4.9947
6.1915
6.1949
7.2004
7.2142
7.4501
7.4547
7.4604
7.4707
7.7754
7.7799
8.81
9.36
8.13
0.98
0.91
0.99
1.97
1.0
0.99
0.97
1.04
0.95
1.96
1.06
0.94
0.99
2.0
0.99

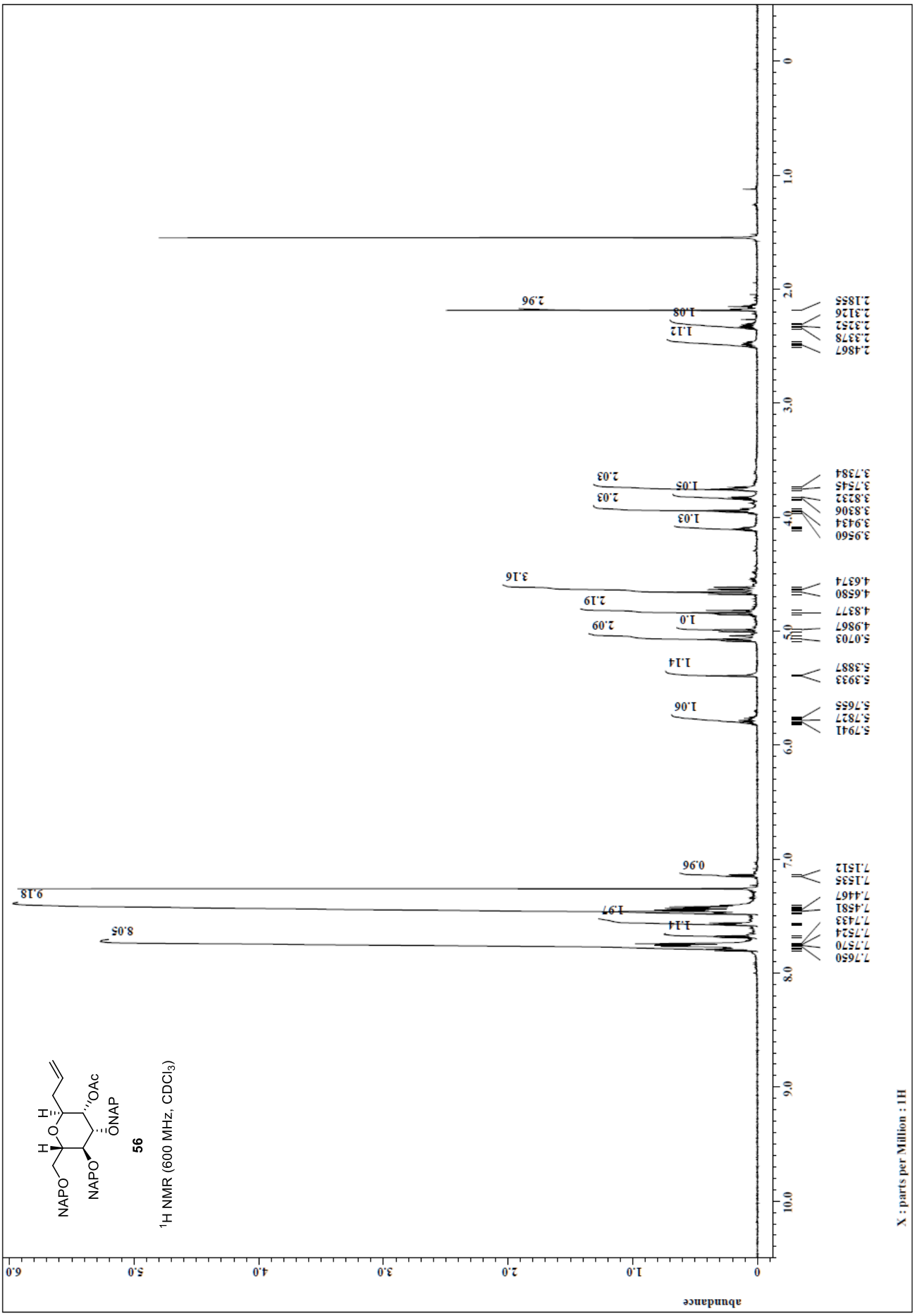

NAPO
NAPO
OPiv
OH
ONAP
H
O
53
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
176.1535
128.2510
128.0690
128.0307
126.2307
126.1254
126.0296
92.9871
79.3239
75.6185
74.0099
73.8854
73.8184
72.5833
68.0735
39.1099
27.0457

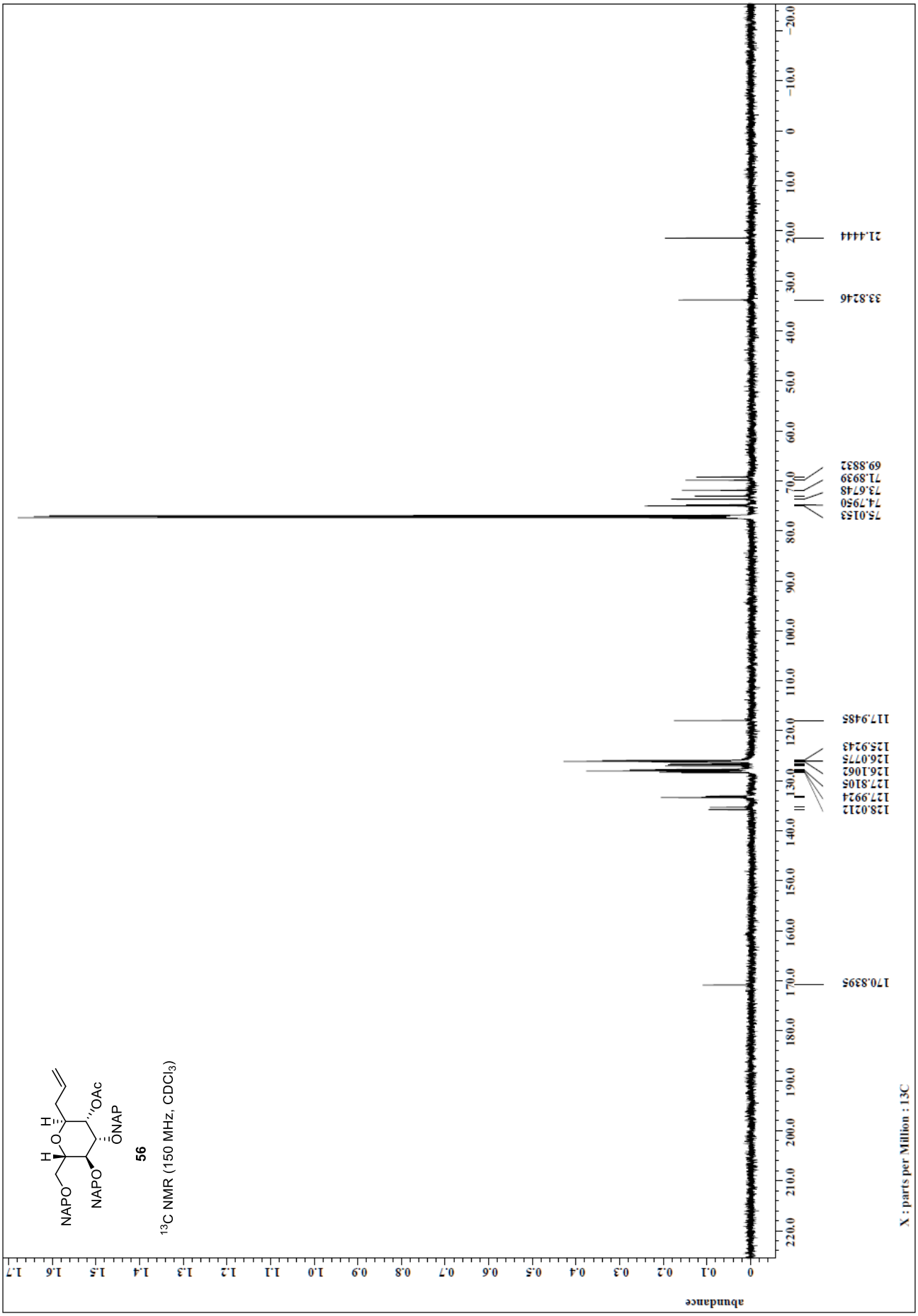

NAPO
OAc
OAc
ONAP
NAPO
H
O
55
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H

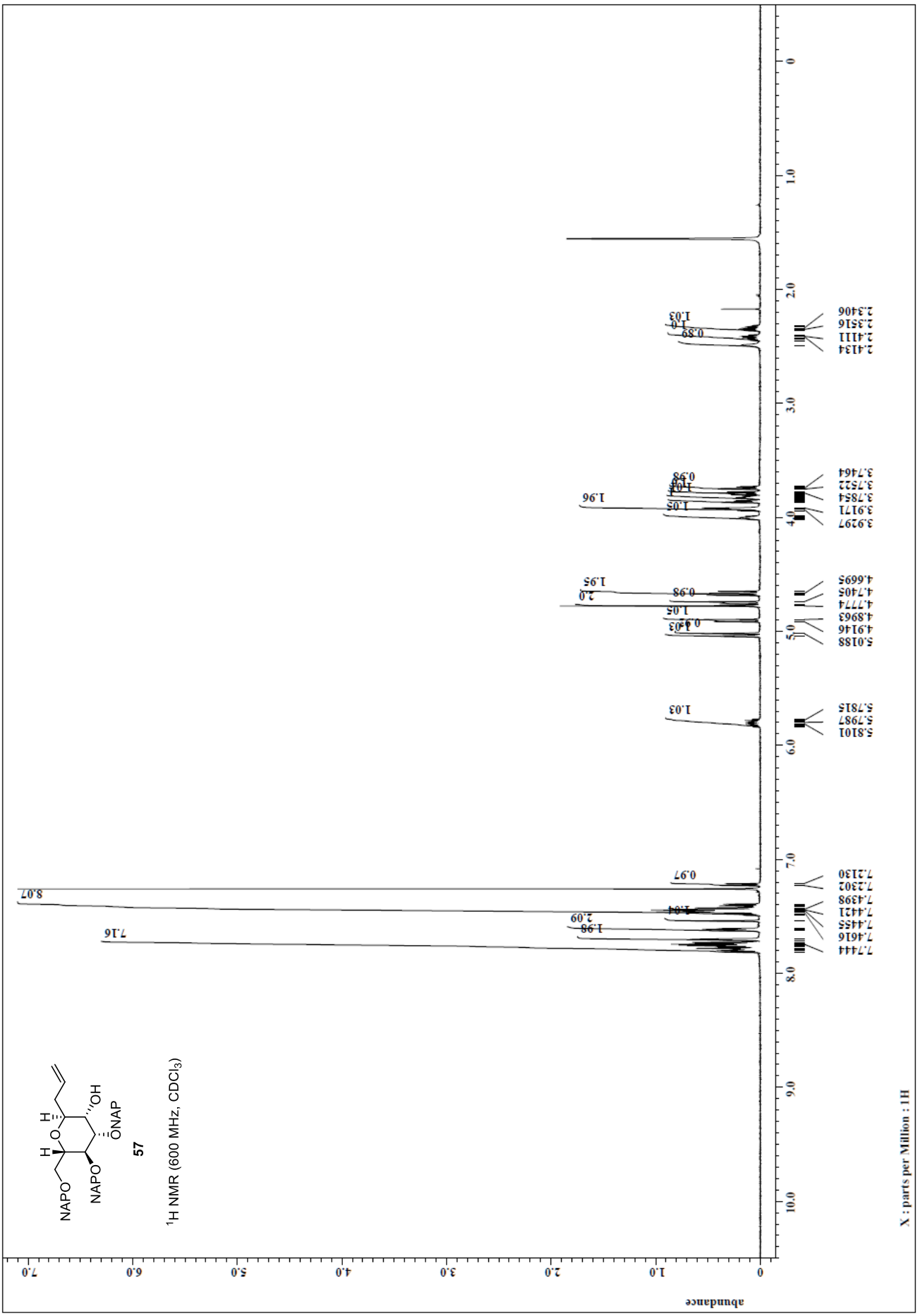

NAPO
O
H
OAc
OAc
ONAP
NAPO
55
^{13}C NMR (100 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
170.341
168.568
128.408
128.332
128.170
128.008
127.836
127.817
127.741
126.254
126.187
126.111
126.034
125.901
91.510
77.789
77.475
77.360
77.160
76.836
75.511
73.975
73.871
73.813
67.702
29.840
21.202
21.039

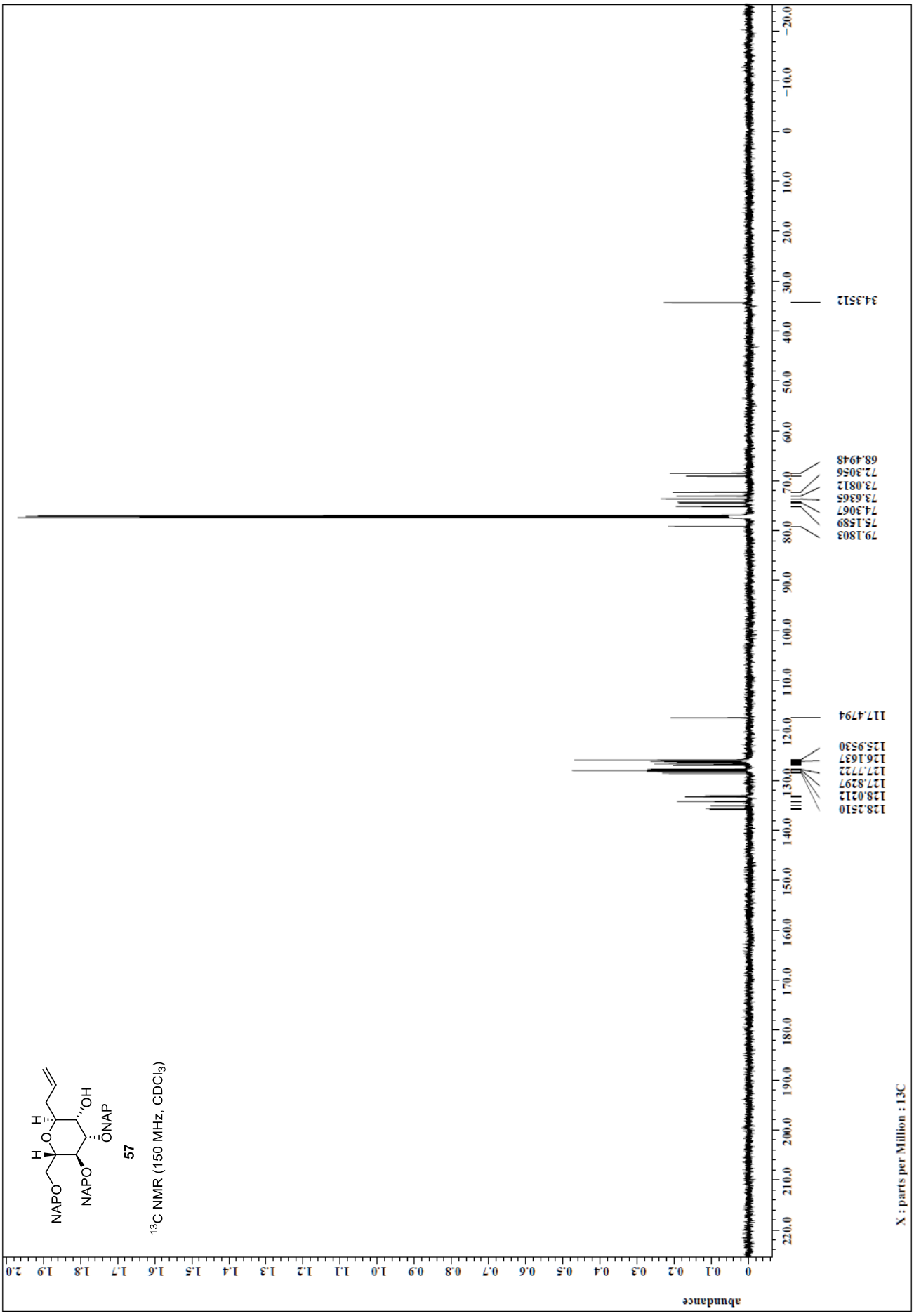

β-isomer of 55
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

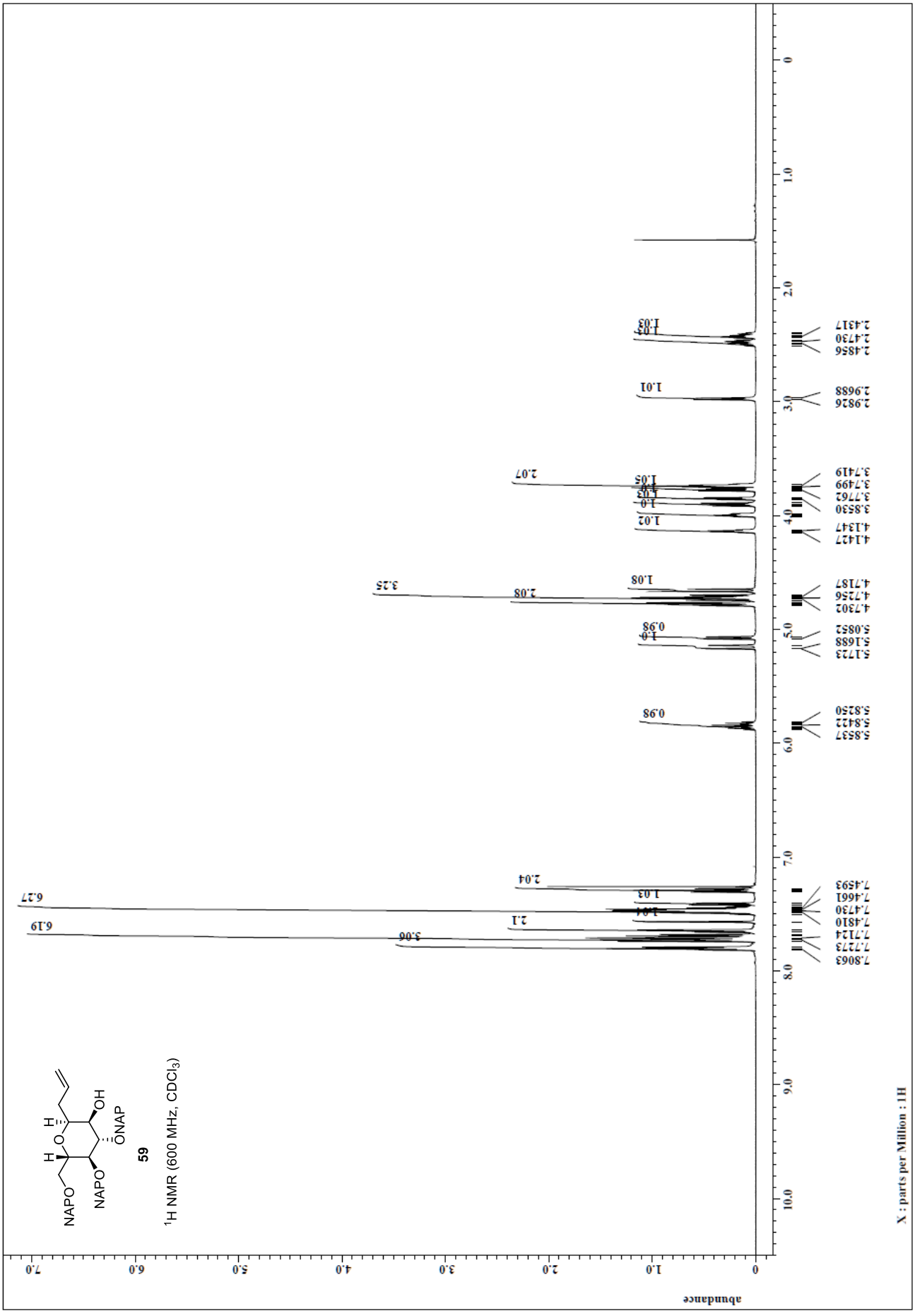

NAPO
OAc
NAPO
OAc
ONAP
H
O
β-isomer of 55
13C NMR (100 MHz, CDCl3)
abundance
X : parts per Million : 13C
21.039
21.230
67.540
68.531
73.766
73.813
75.348
76.330
76.836
77.160
77.475
79.963
91.548
125.834
125.958
126.034
126.139
126.263
126.492
127.016
127.731
127.846
128.008
128.122
128.332
128.456

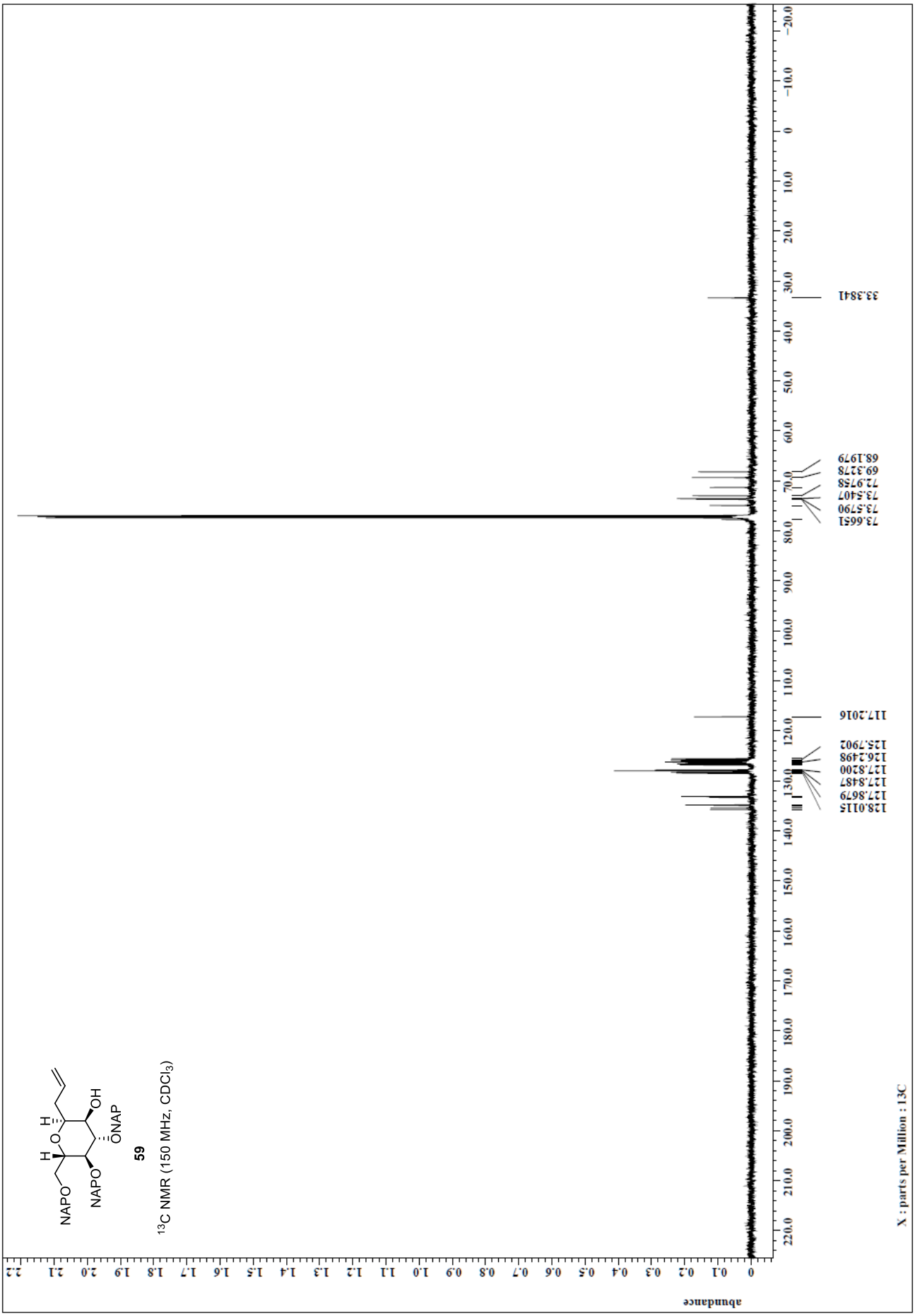

NAPO
NAPO
OAc
ONAP
56
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

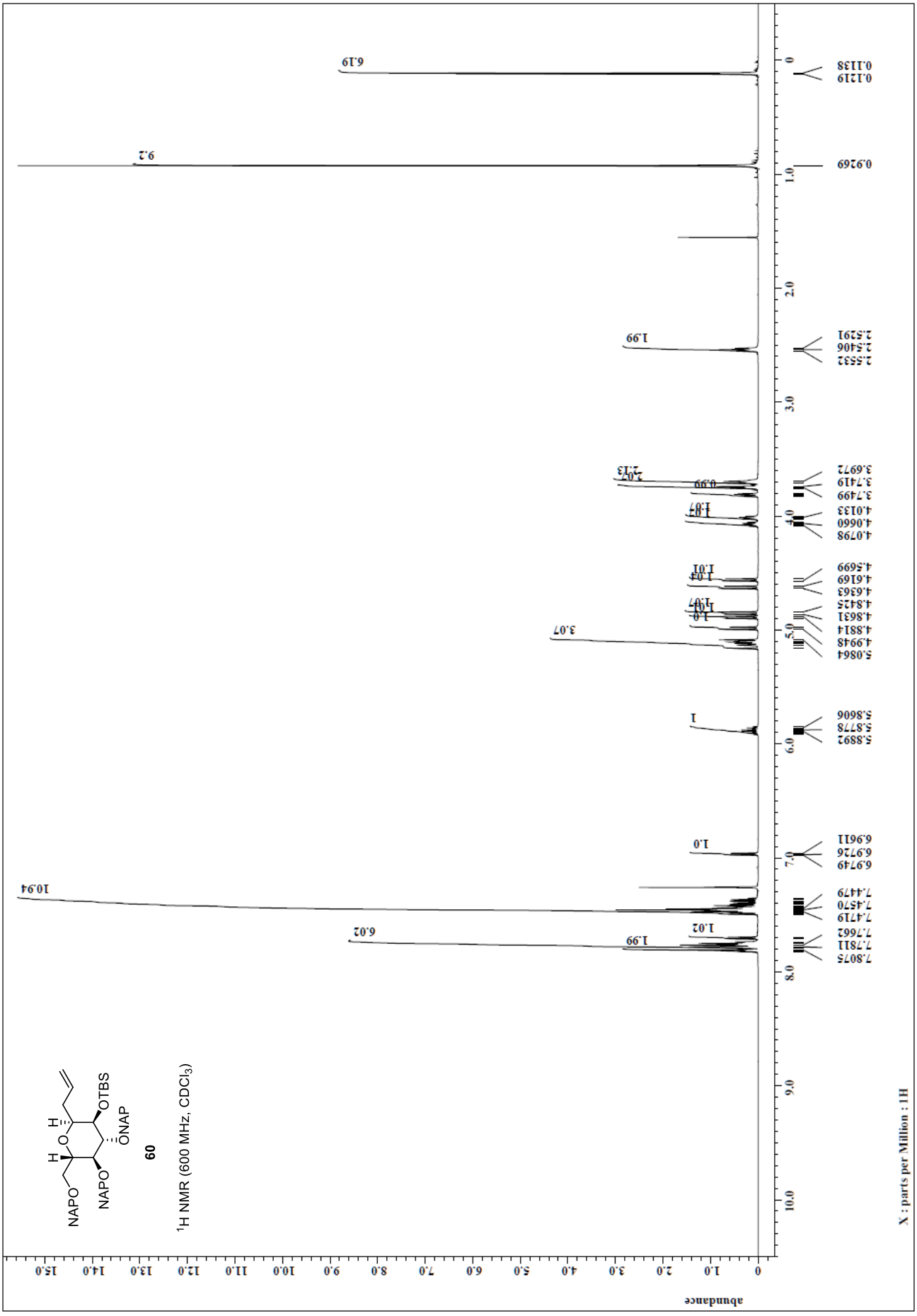

NAPO
NAPO
ONAP
OAc
56
^{13}C NMR (150 MHz, $CDCl_3$)
170.8395
128.0212
127.9924
127.8105
126.1062
126.0775
125.9243
117.9485
75.0153
74.7950
73.6748
71.8939
69.8832
33.8246
21.4444
X : parts per Million : 13C
abundance

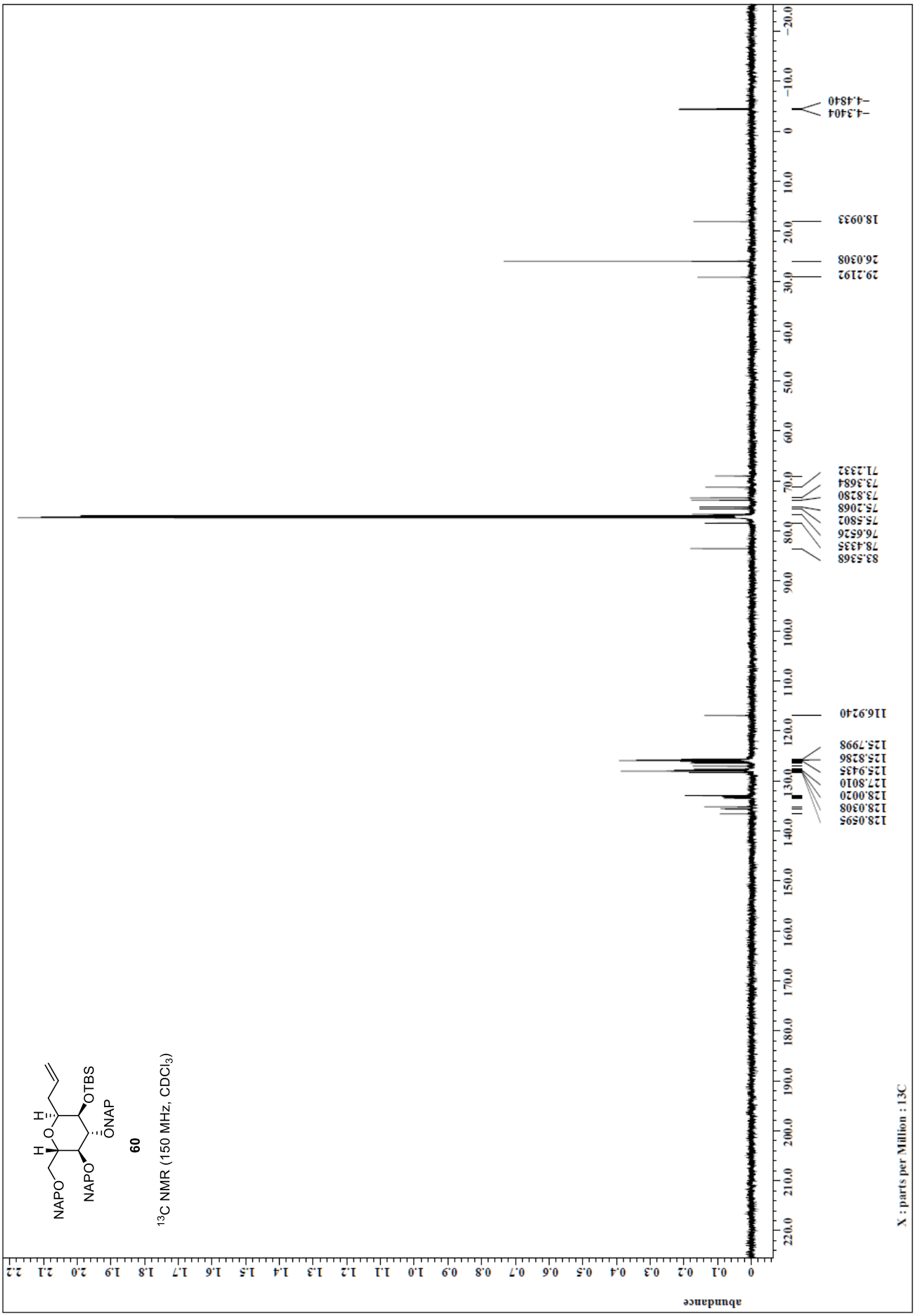

NAPO
NAPO
OH
ONAP
57
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

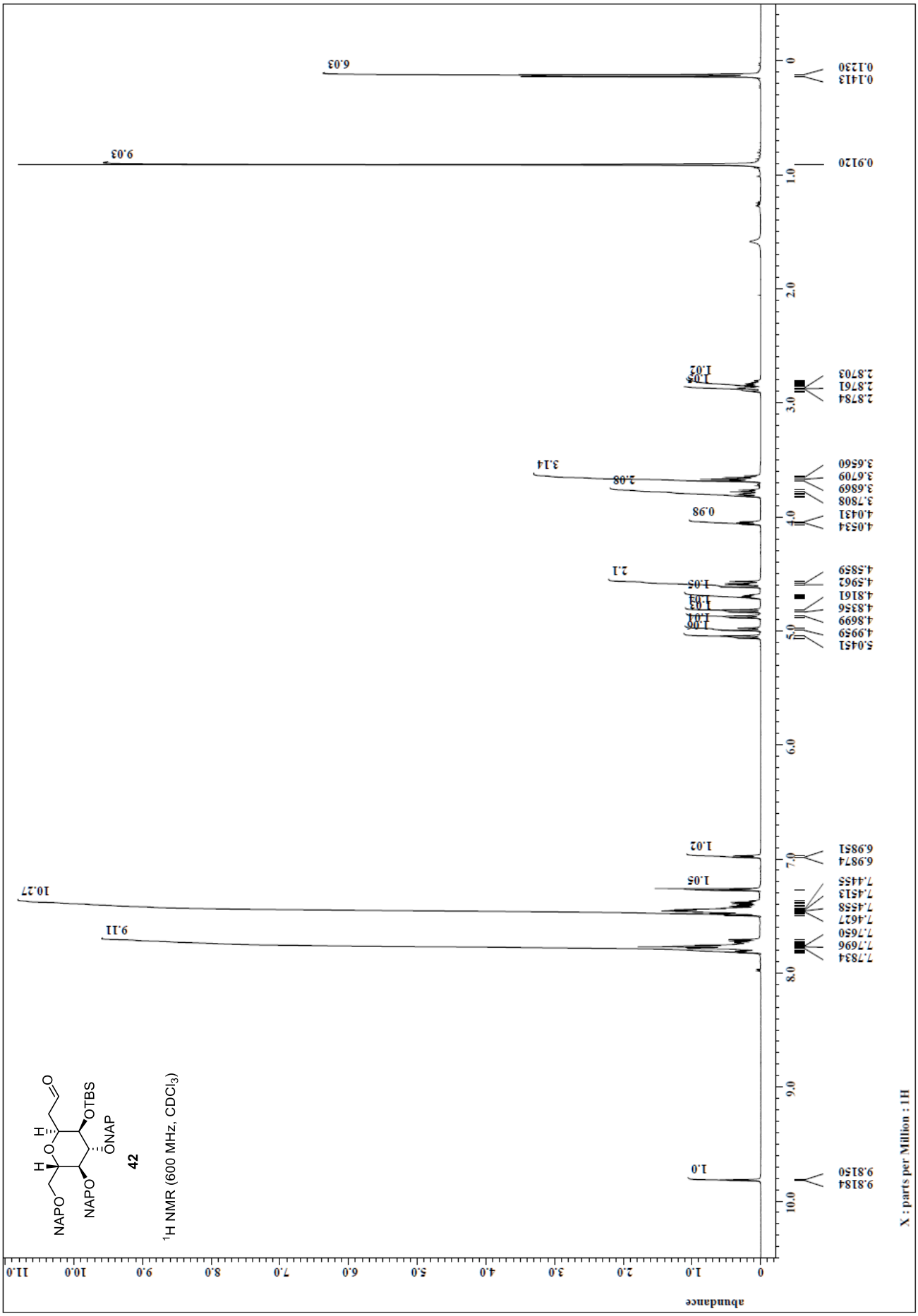

NAPO
NAPO
H
O
H
OH
ONAP
57
^{13}C NMR (150 MHz, CDCl$_3$)
X : parts per Million : 13C
abundance
34.3512
68.4948
72.3056
73.0812
73.6365
74.3067
75.1589
79.1803
117.4794
125.9530
126.1637
127.7722
127.8297
128.0212
128.2510

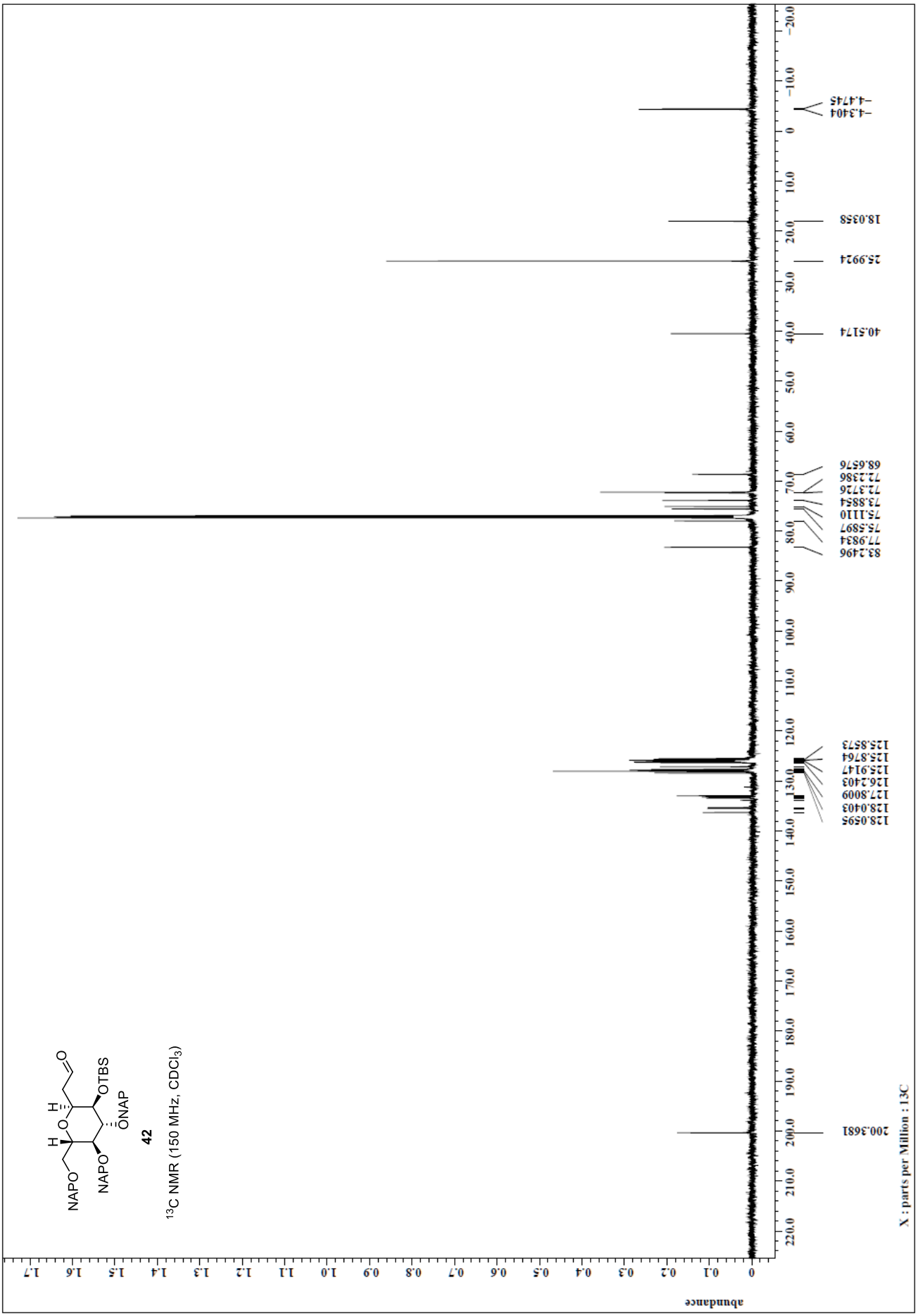

NAPO
NAPO
OH
ONAP
59
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

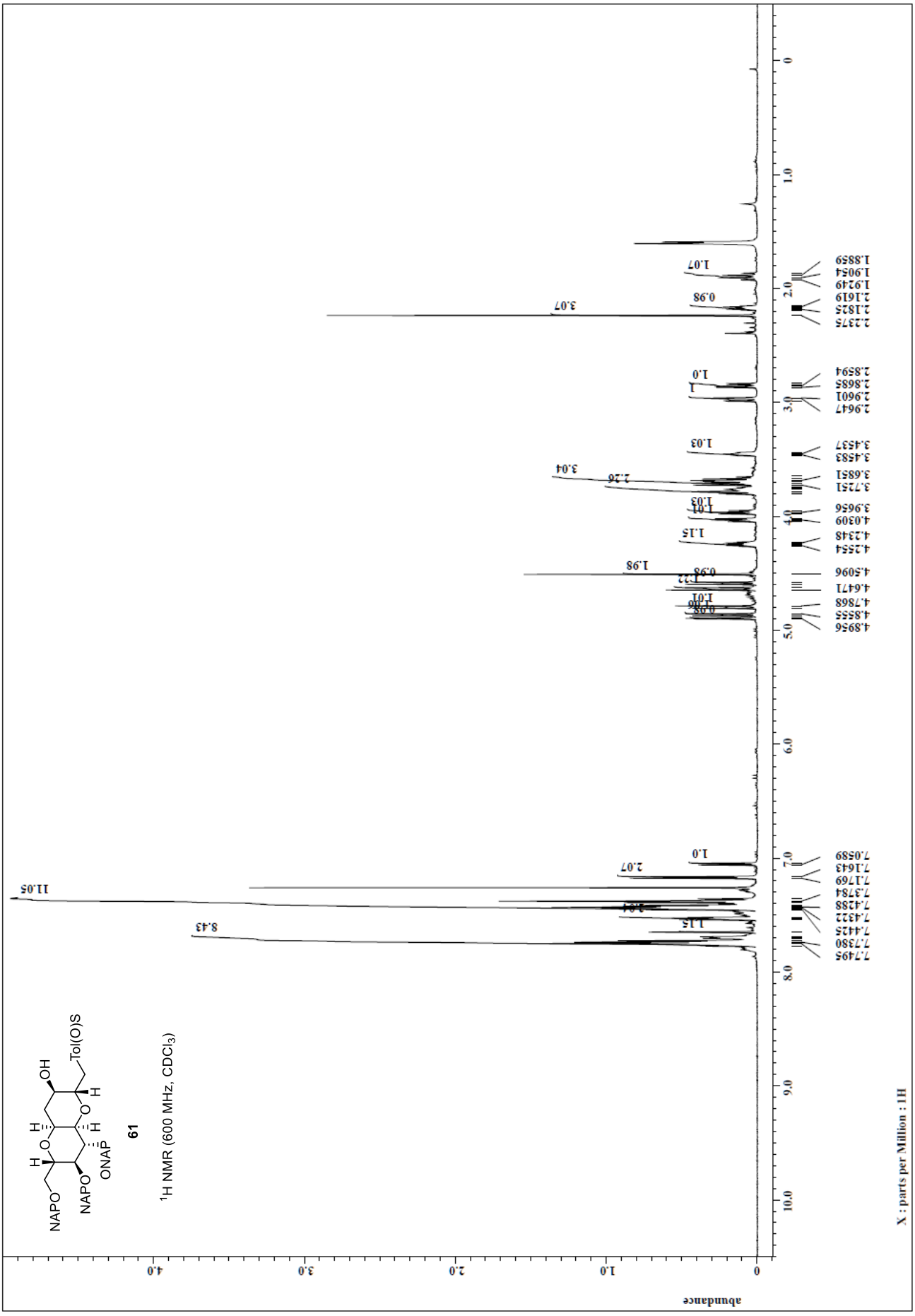

NAPO
NAPO
OH
ONAP
59
^{13}C NMR (150 MHz, $CDCl_3$)
33.3841
68.1979
69.3278
72.9758
73.5407
73.5790
73.6651
117.2016
125.7902
126.2498
127.8200
127.8487
127.8679
128.0115
X : parts per Million : 13C
abundance

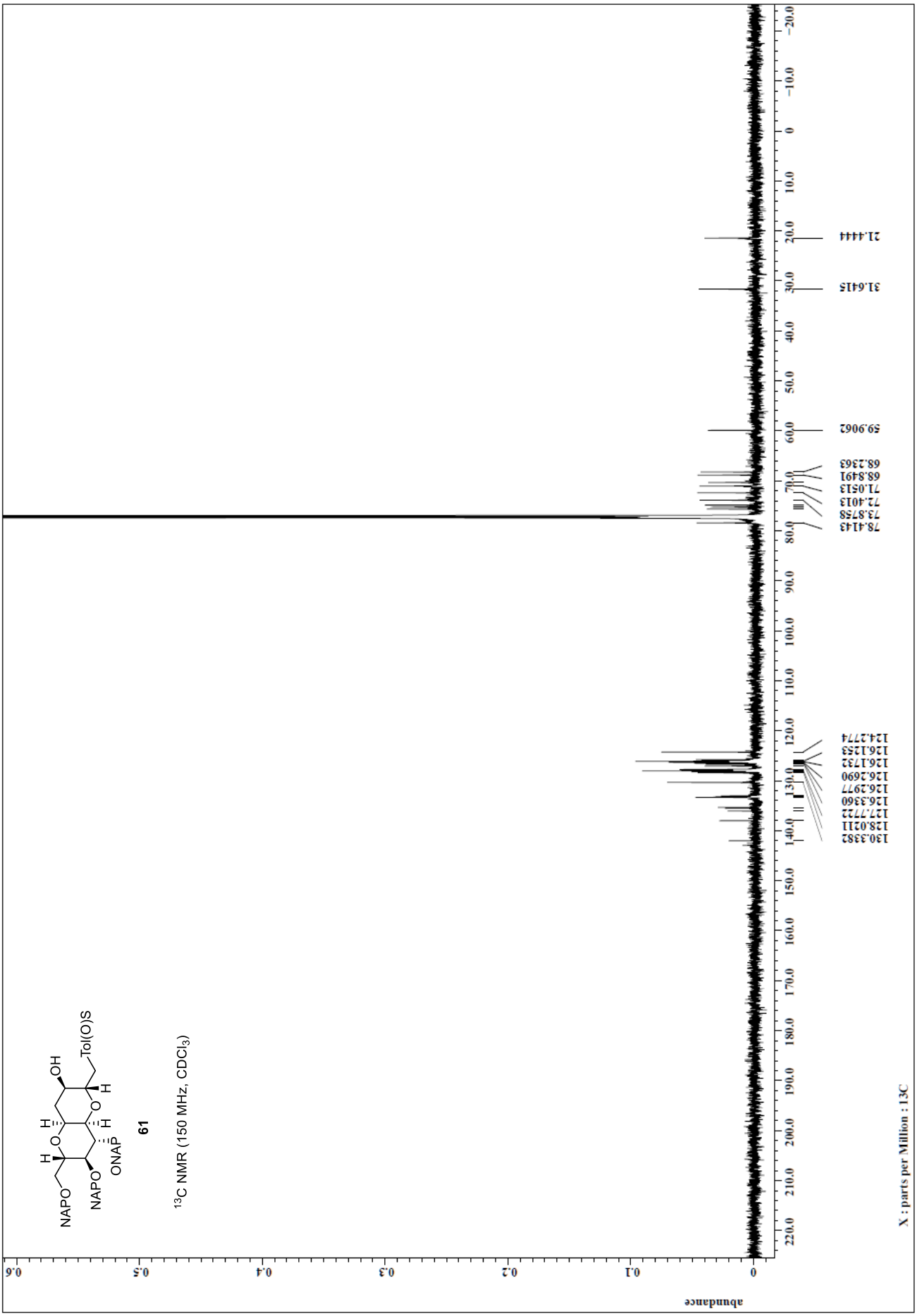

NAPO
NAPO
H
O
H
OTBS
ONAP
60
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

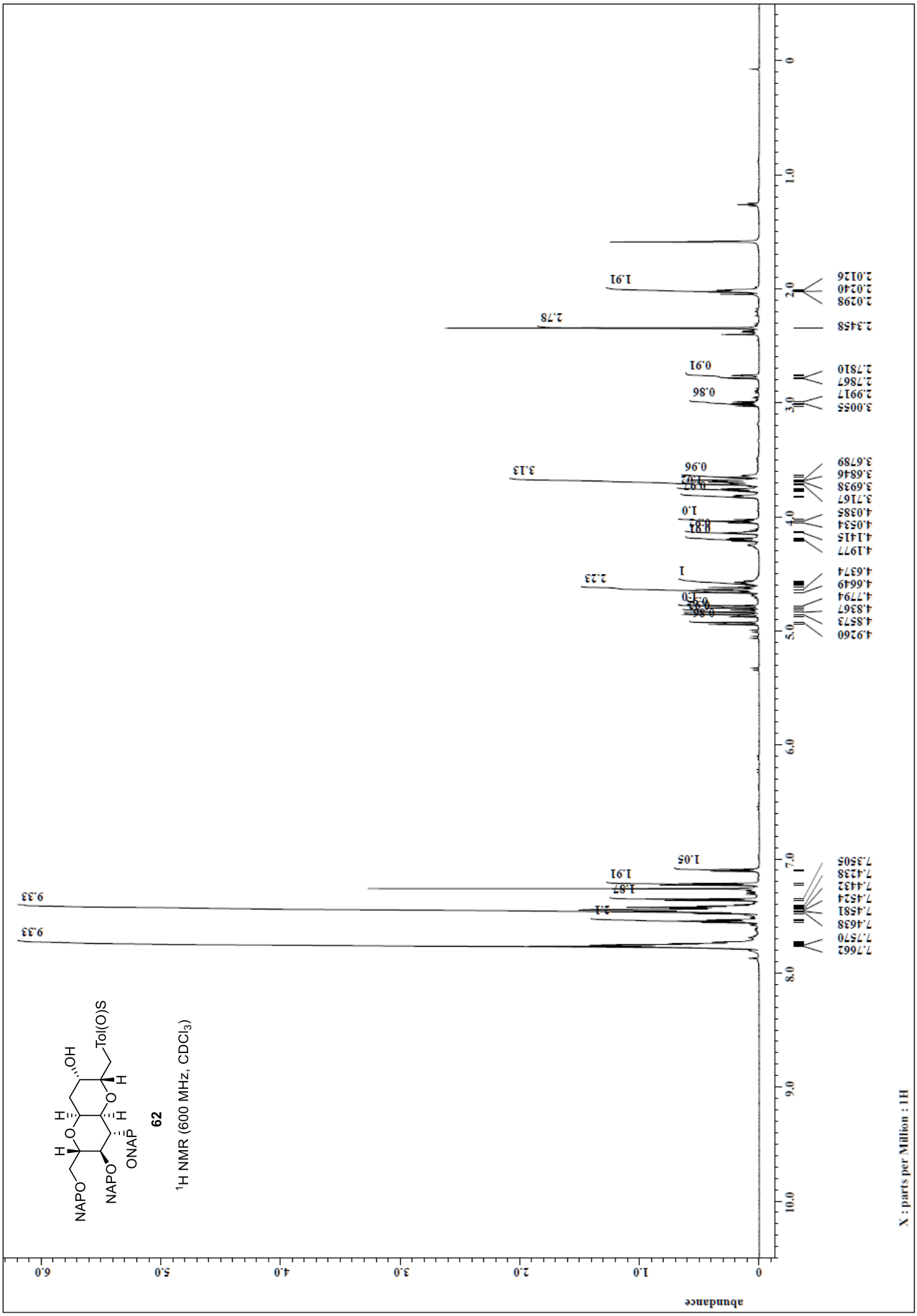

NAPO
NAPO
OTBS
ONAP
60
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
-4.3404
-4.1840
18.0933
26.0308
29.2192
71.2332
73.3684
73.8280
75.2068
75.5802
76.6526
78.4335
83.5368
116.9240
125.7998
125.8286
125.9435
127.8010
128.0020
128.0308
128.0595

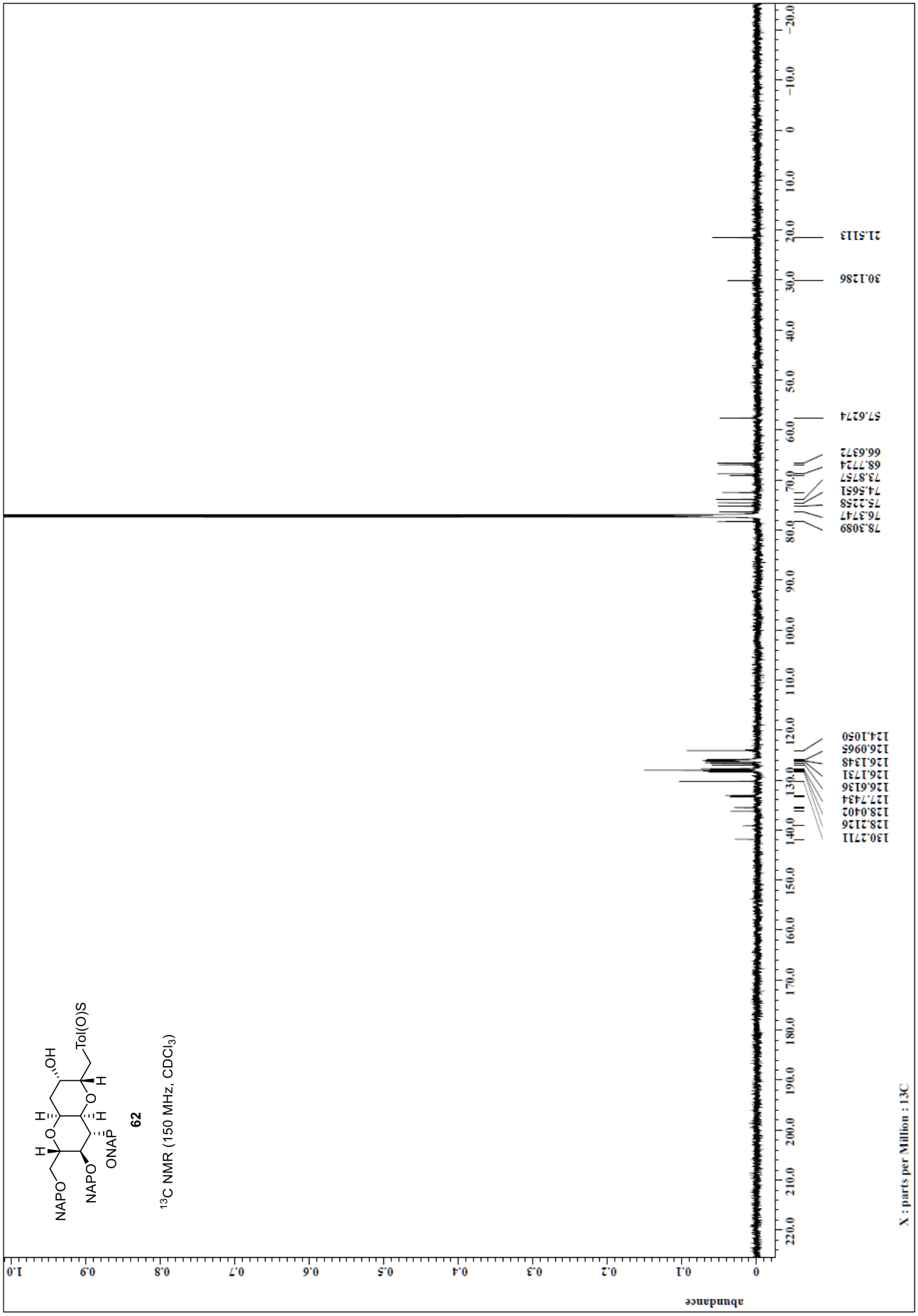

NAPO
NAPO
OTBS
ONAP
42
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

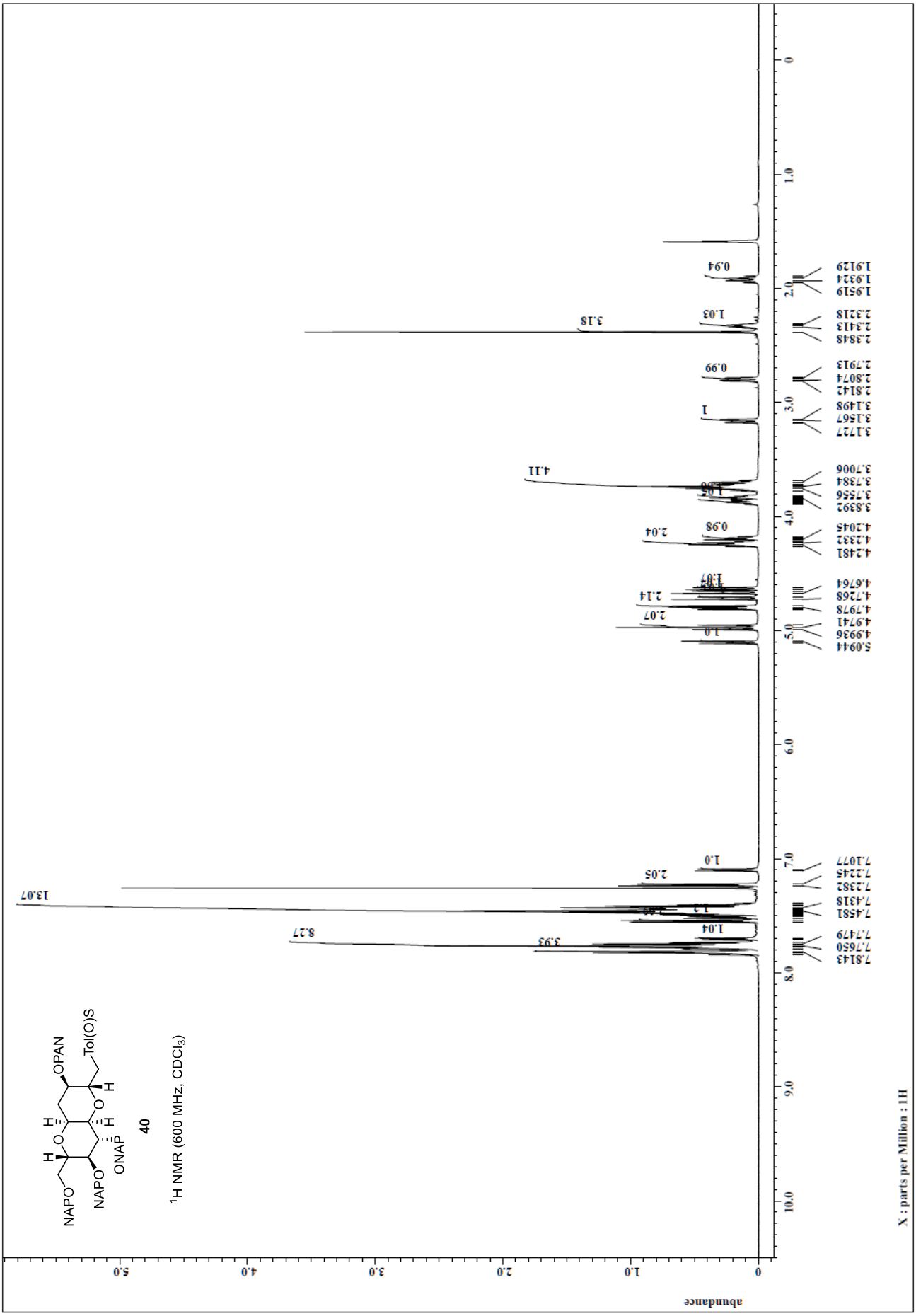

NAPO
NAPO
H
O
H
O
OTBS
ONAP
42
^{13}C NMR (150 MHz, $CDCl_3$)
-4.4745
-4.3404
18.0358
25.9924
40.5174
68.6576
72.2386
72.3726
73.8854
75.1110
75.5897
77.9834
83.2496
125.8573
125.8764
125.9147
126.2403
127.8009
128.0403
128.0595
200.3681
X : parts per Million : 13C
abundance

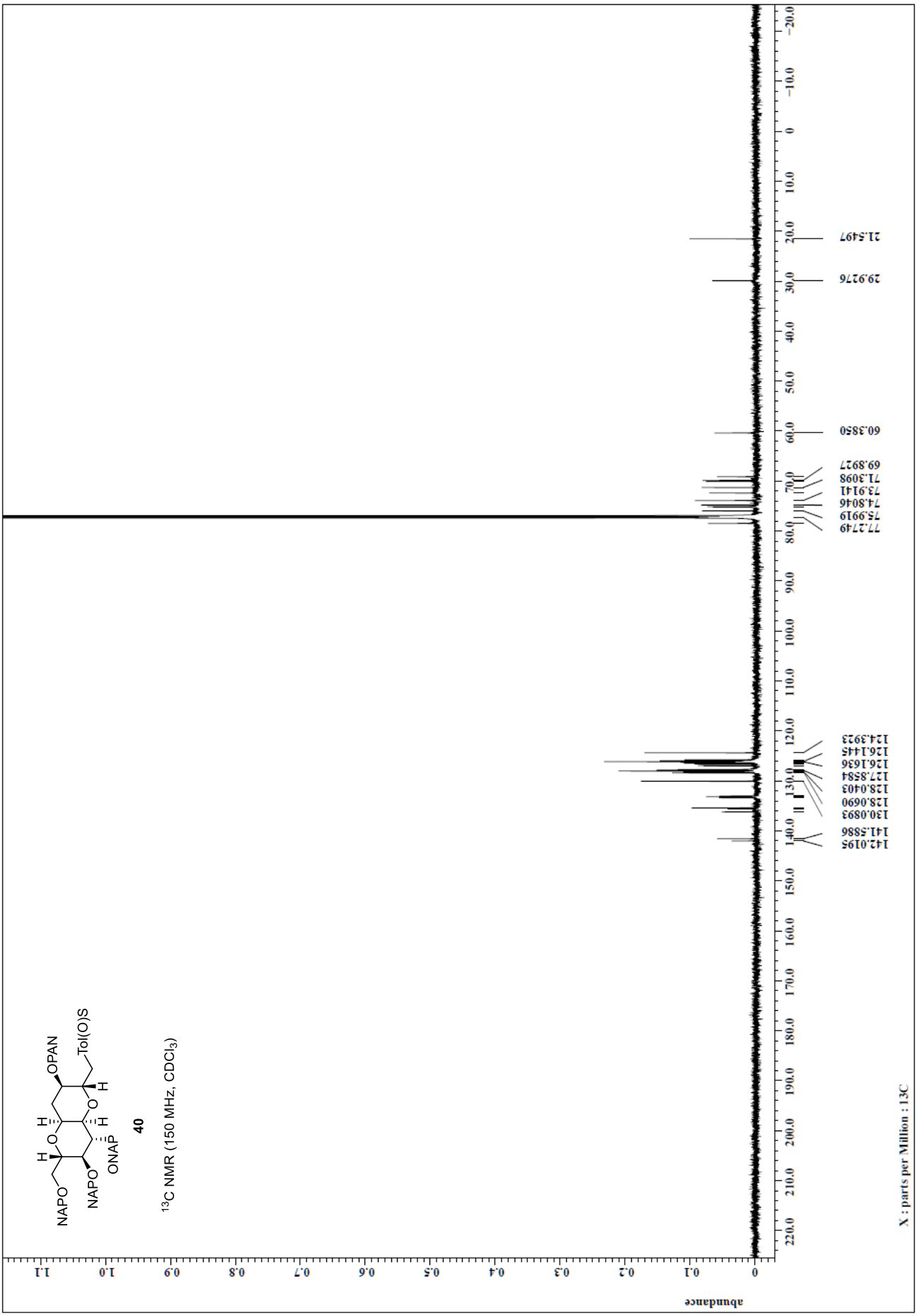

61
^{1}H NMR (600 MHz, CDCl$_3$)
NAPO
NAPO
ONAP
OH
Tol(O)S
abundance
X : parts per Million : 1H

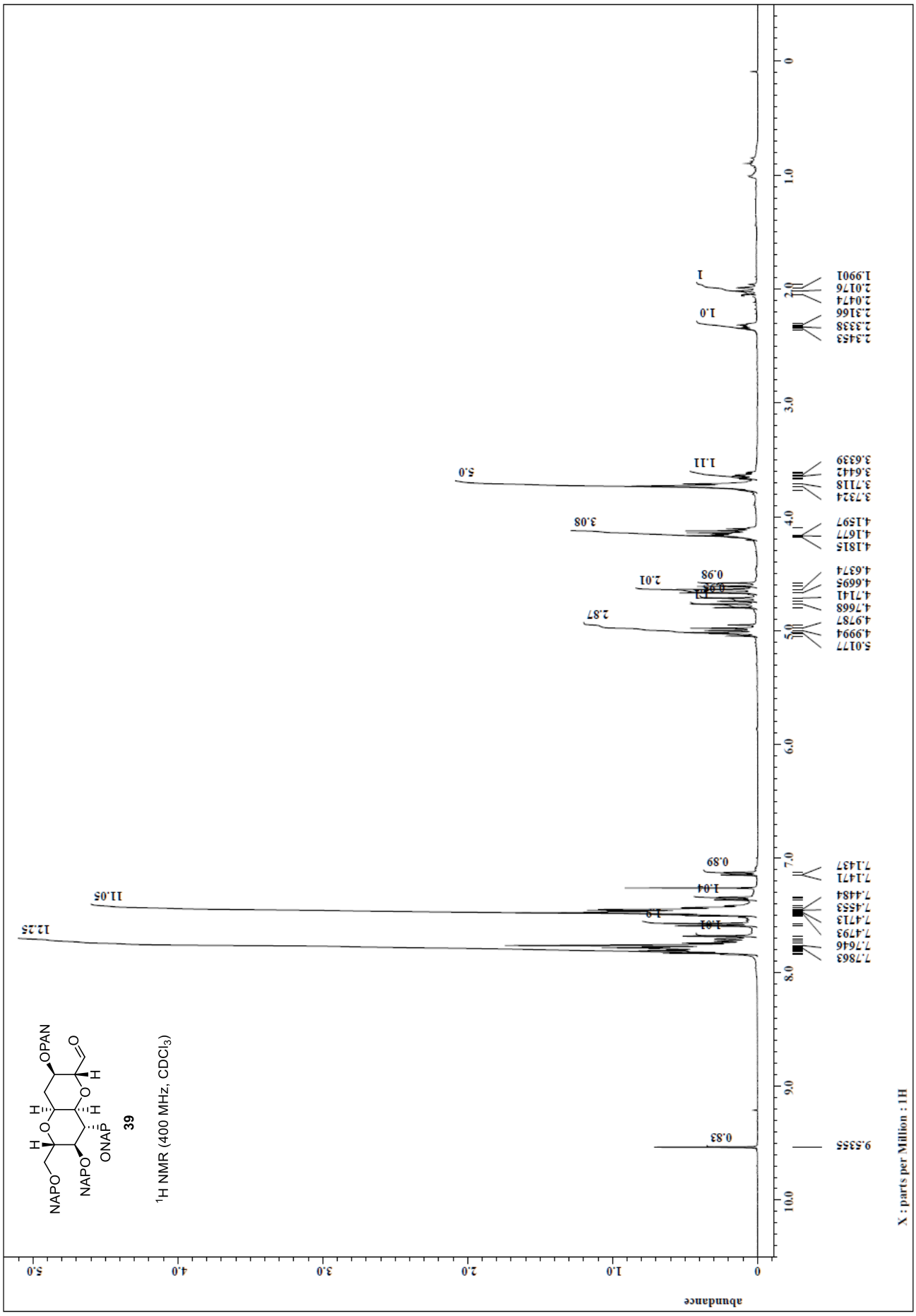

NAPO
NAPO
ONAP
OH
Tol(O)S
61
^{13}C NMR (150 MHz, CDCl$_3$)
21.4444
31.6415
59.9062
68.2363
68.8491
71.0513
72.4013
73.8758
78.4143
124.2774
126.1253
126.1732
126.2690
126.2977
126.3360
127.7722
128.0211
130.3382
X : parts per Million : 13C
abundance

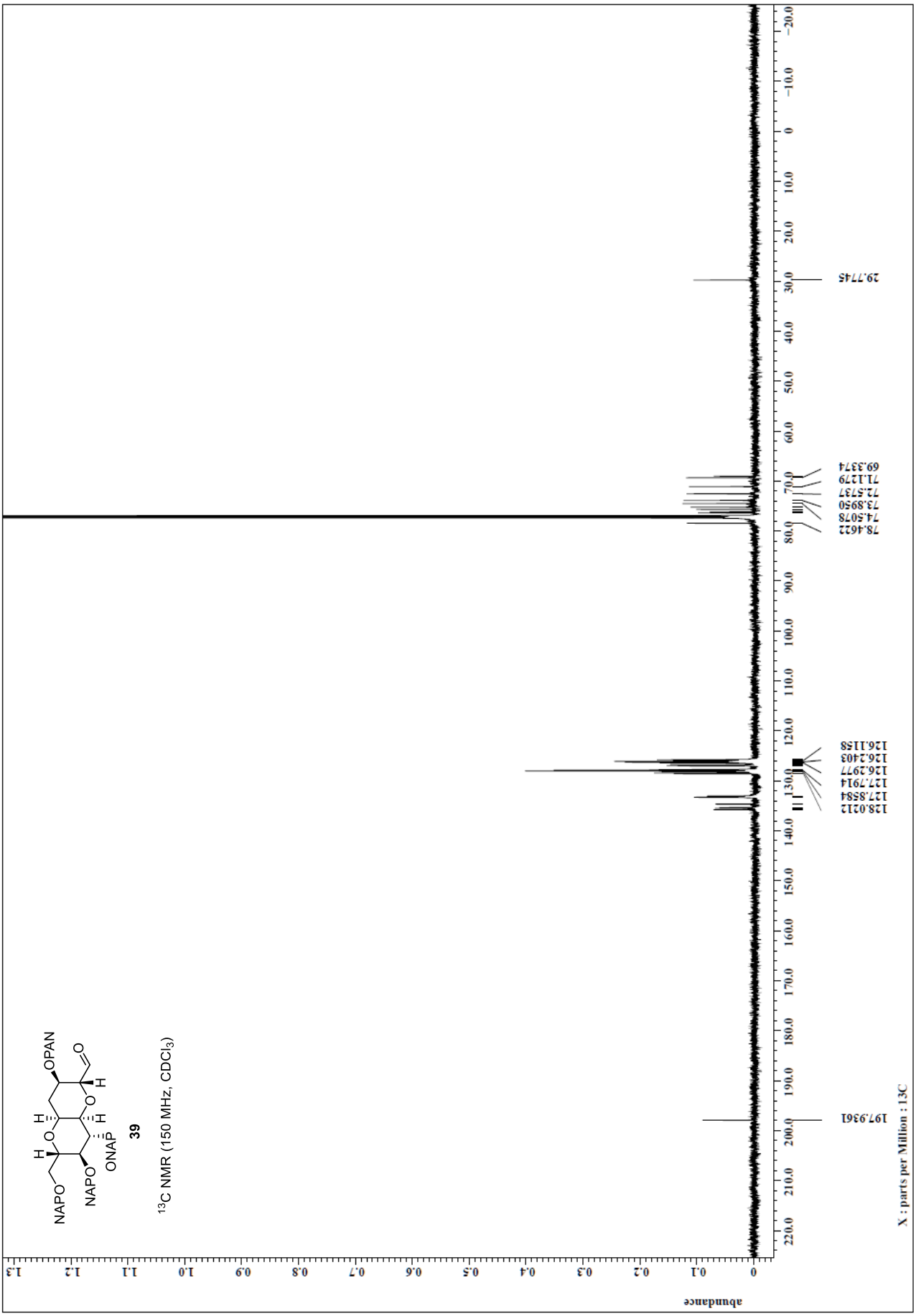

62
^{1}H NMR (600 MHz, $CDCl_3$)
NAPO
NAPO
ONAP
OH
Tol(O)S
abundance
X : parts per Million : 1H

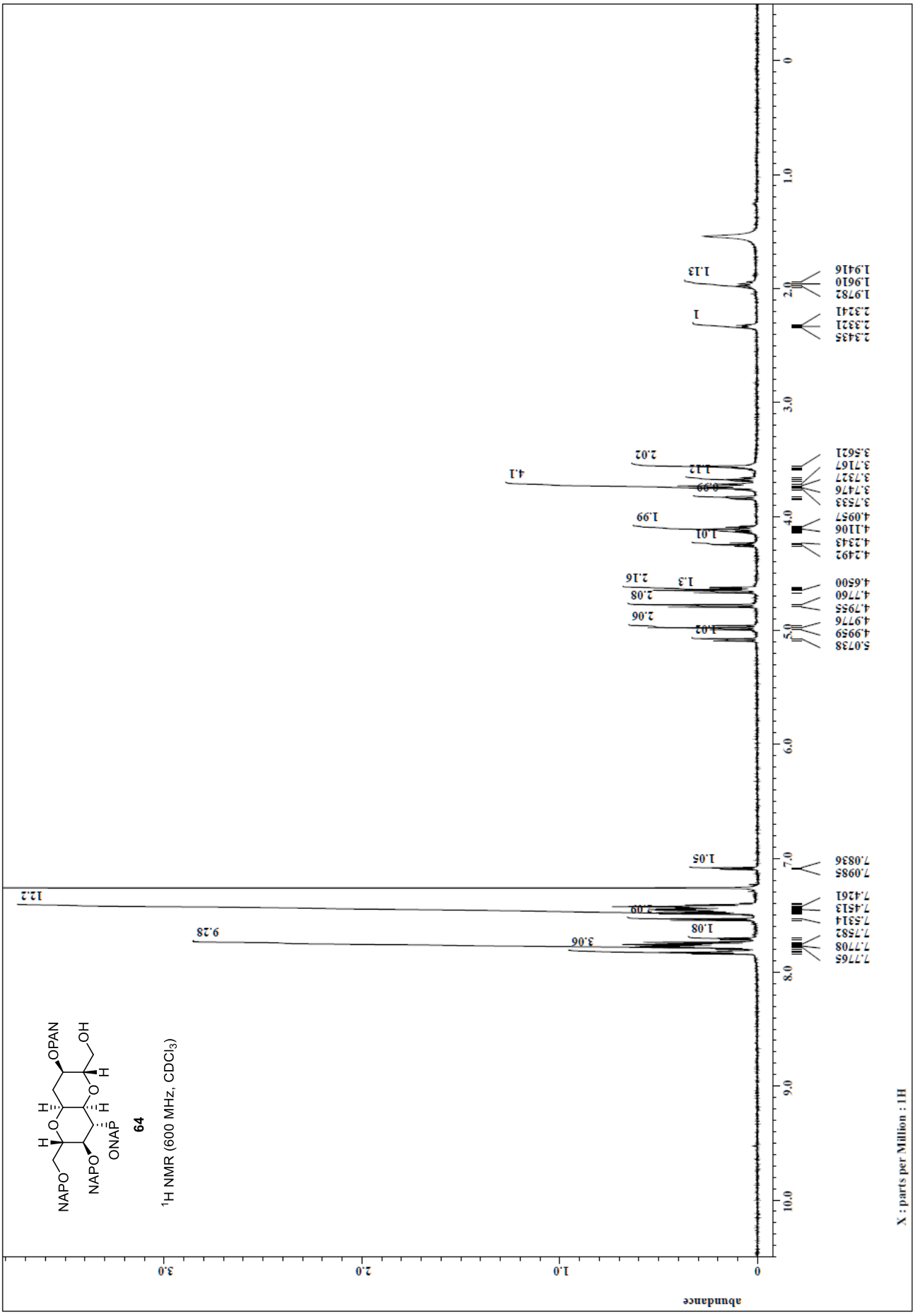

62
^{13}C NMR (150 MHz, $CDCl_3$)
NAPO
NAPO
ONAP
OH
Tol(O)S
abundance
X : parts per Million : 13C
21.5113
30.1286
57.6274
66.6372
68.7724
73.8757
74.6651
75.2258
76.3747
78.3089
124.1050
126.0965
126.1348
126.1731
126.6136
127.7434
128.0402
128.2126
130.2711

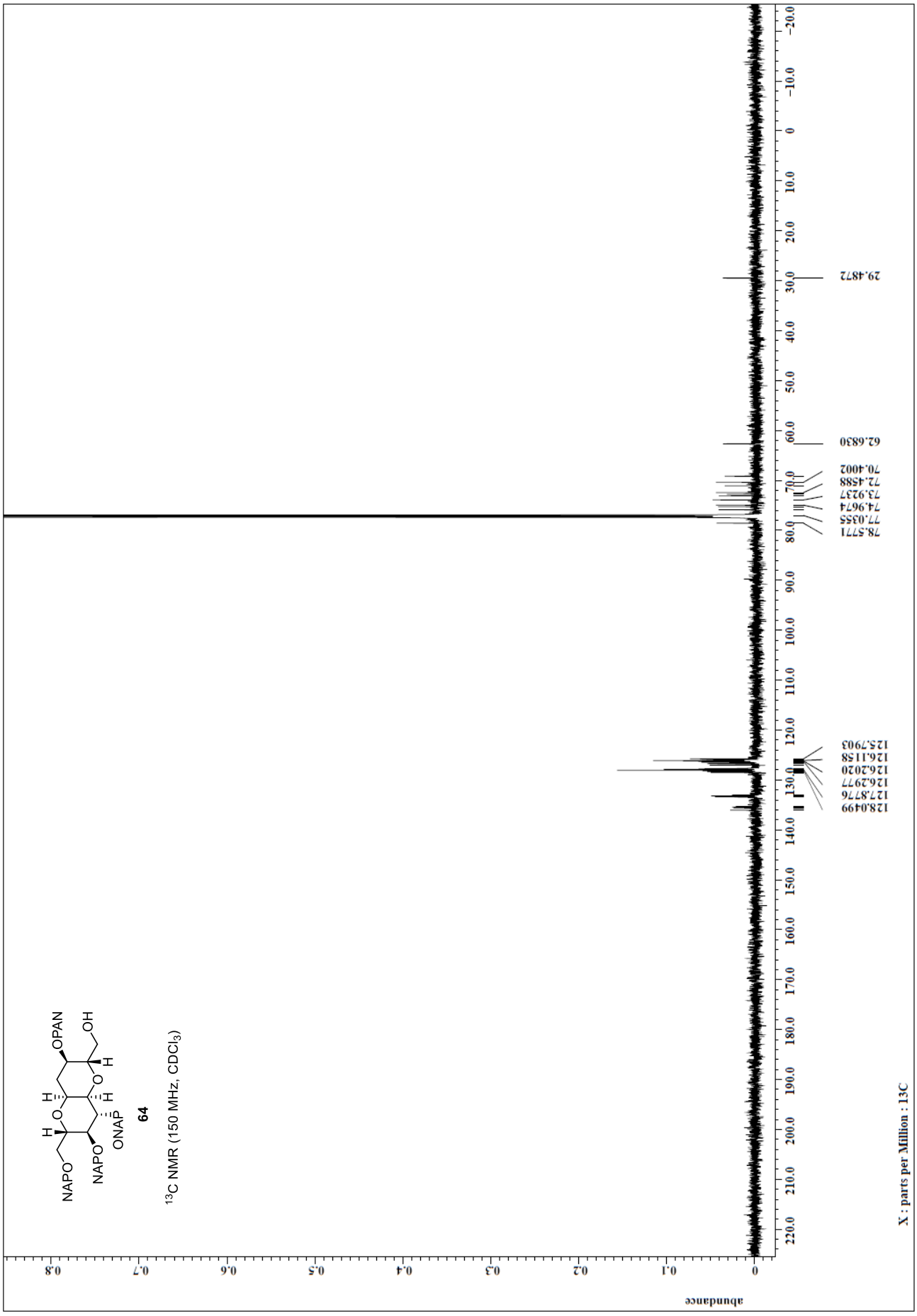

NAPO
NAPO
ONAP
OPAN
Tol(O)S
40
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1 H
abundance


NAPO
NAPO
ONAP
OPAN
Tol(O)S
40
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
142.0195
141.5886
130.0893
128.0690
128.0403
127.8584
126.1636
126.1445
124.3923
77.2749
75.9919
74.8046
73.9141
71.3098
69.8927
60.3850
29.9276
21.5497

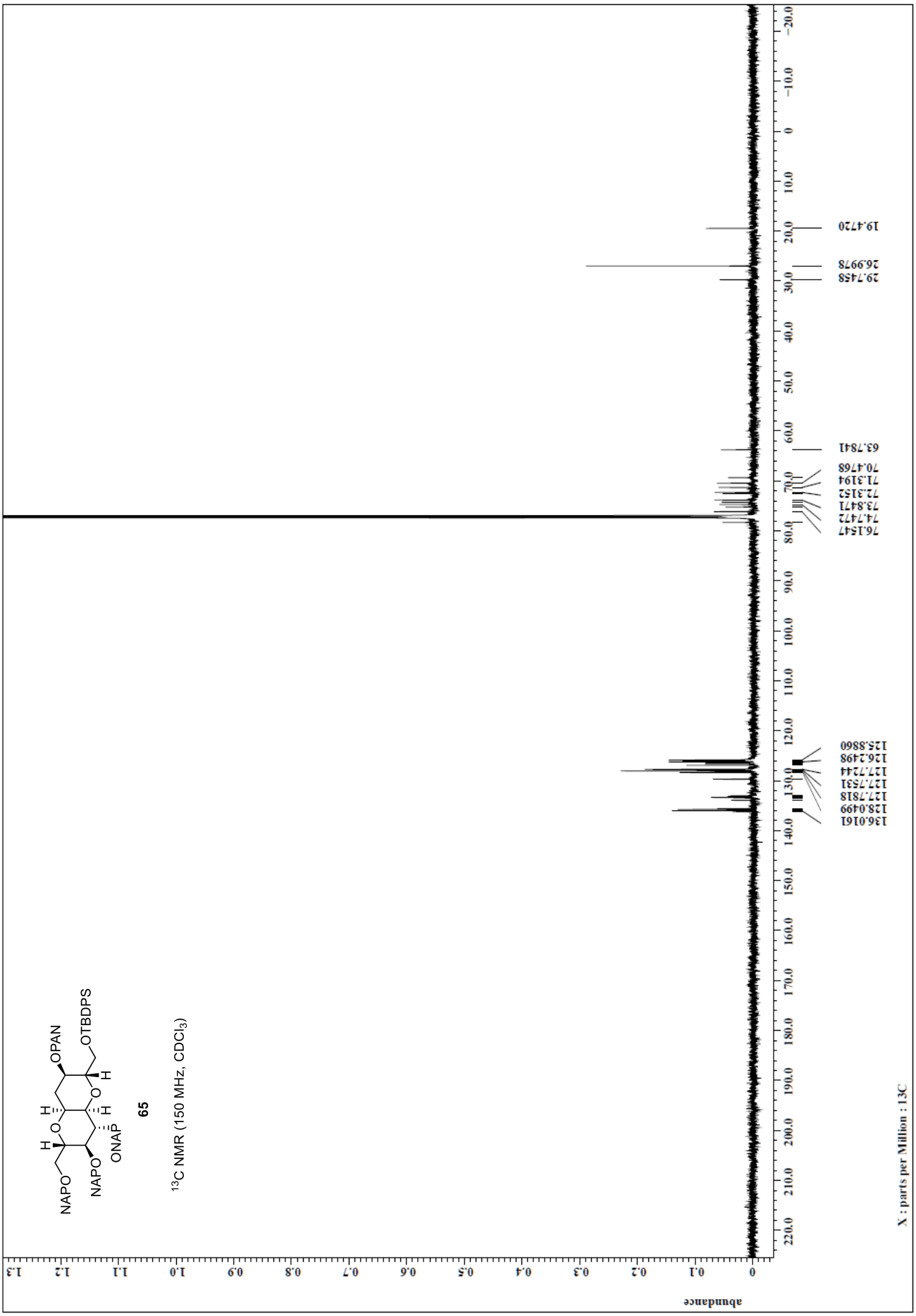

OPAN
NAPO
NAPO
ONAP
39
^{1}H NMR (400 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance


OPAN
NAPO
NAPO
ONAP
H
H
H
H
O
O
O
39
^{13}C NMR (150 MHz, $CDCl_3$)
197.9361
128.0212
127.8584
127.7914
126.2977
126.2403
126.1158
78.4622
74.5078
73.8950
72.5737
71.1279
69.3374
29.7745
X : parts per Million : 13C
abundance

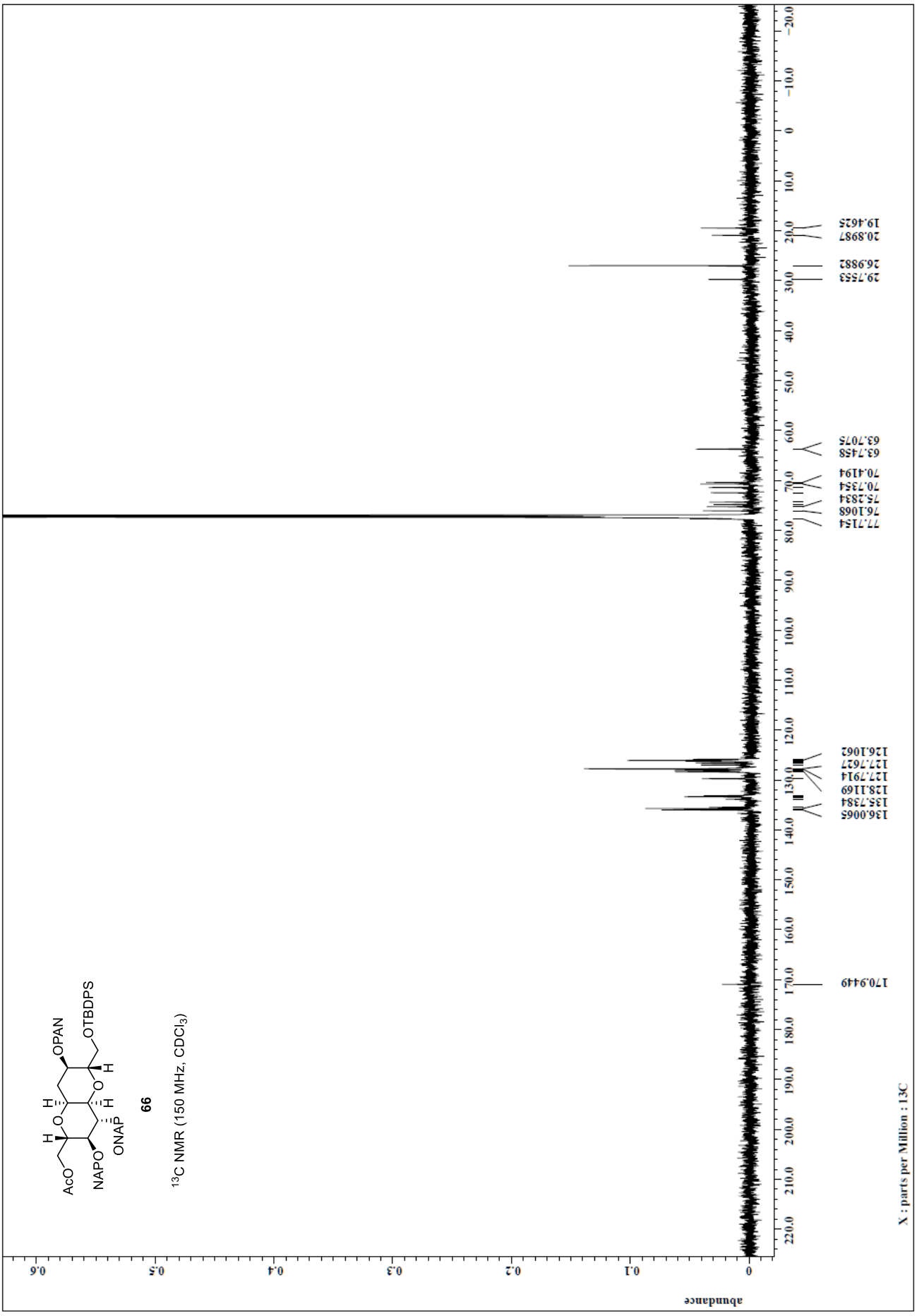

NAPO
NAPO
ONAP
OPAN
OH
64
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

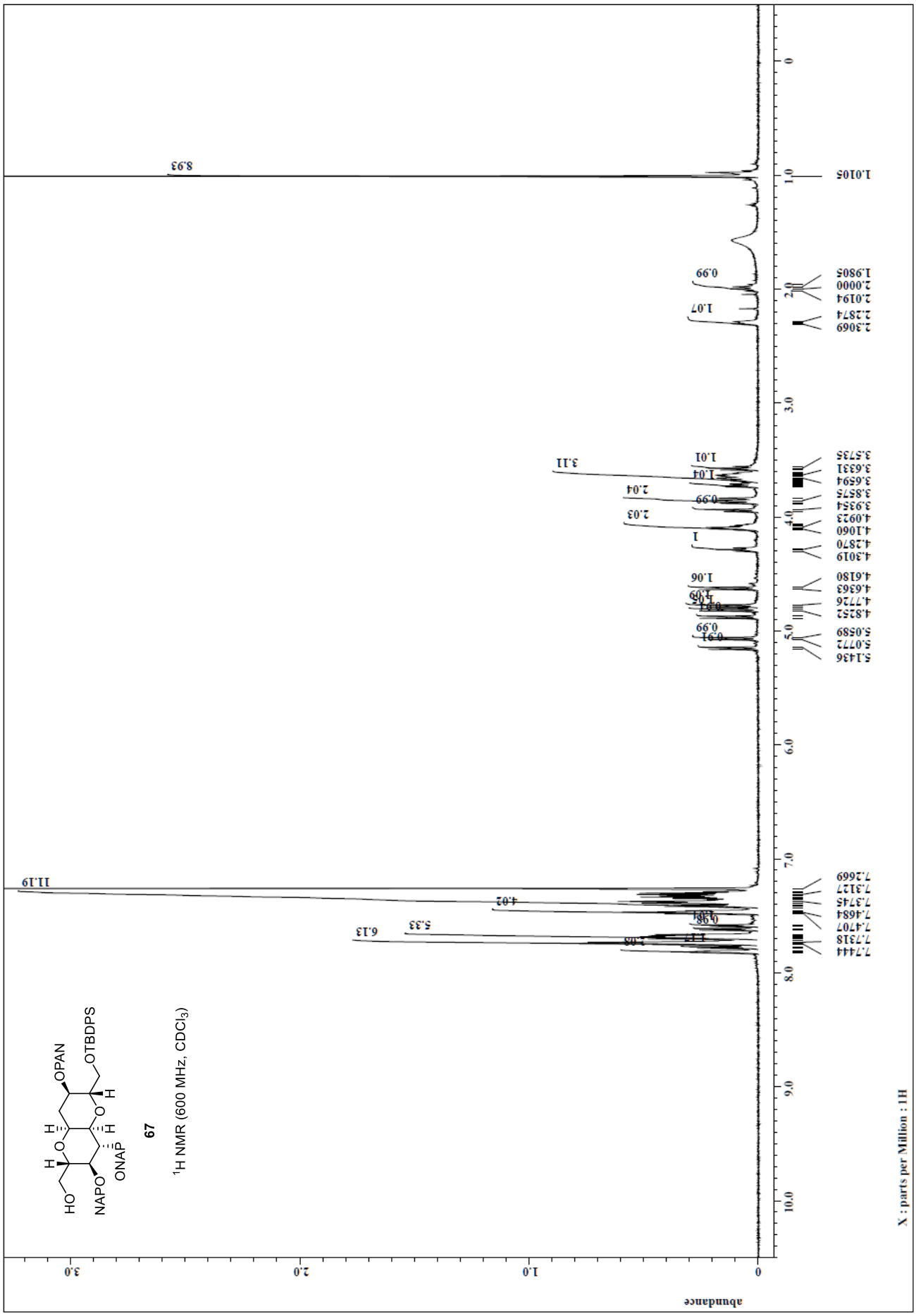

NAPO
NAPO
ONAP
OPAN
OH
64
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
29.4872
62.6830
70.4002
72.4588
73.9237
74.9674
77.0355
78.5771
125.7903
126.1158
126.2020
126.2977
127.8776
128.0499

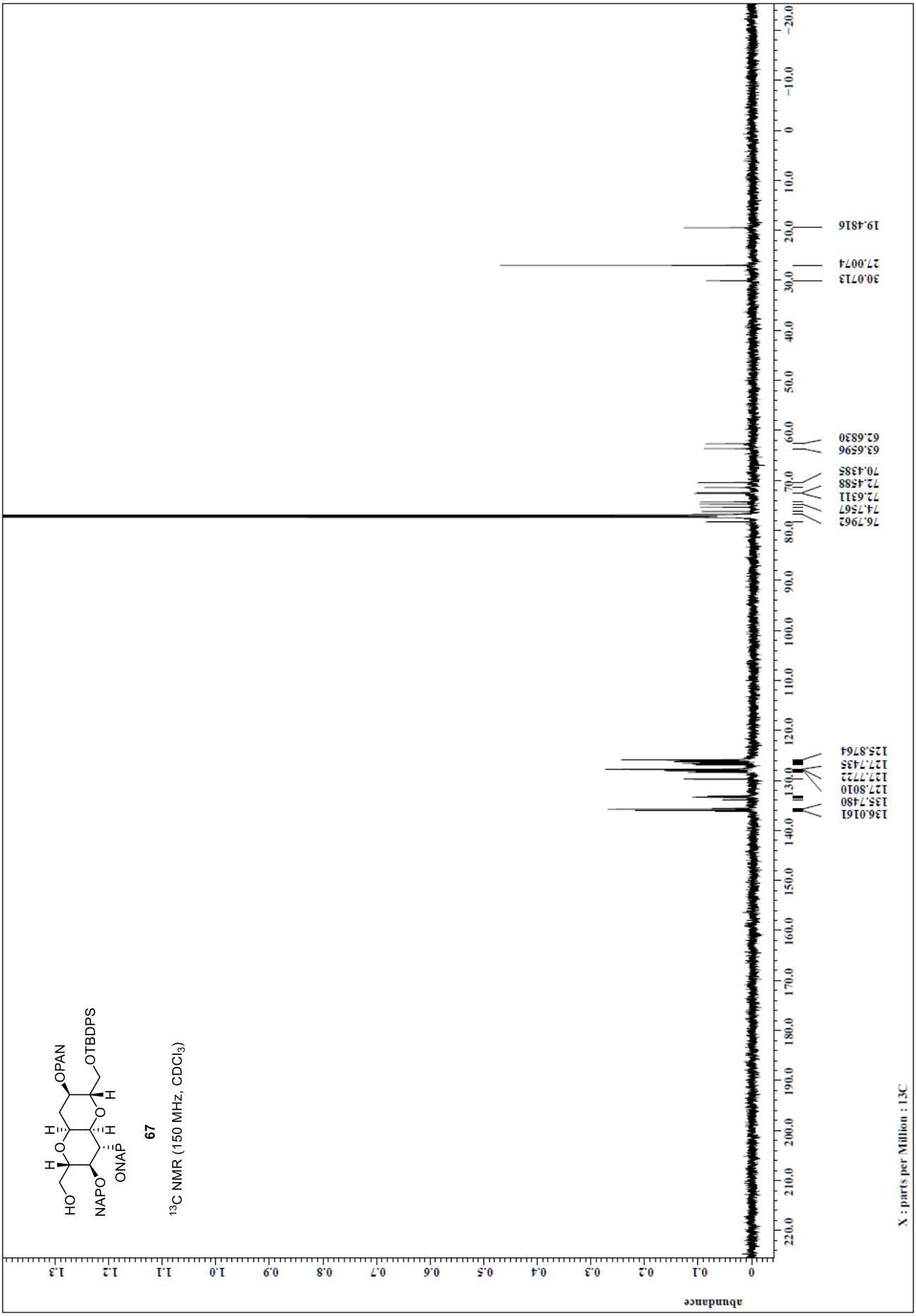
OPAN
OTBDPS
NAPO
NAPO
ONAP
65
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H

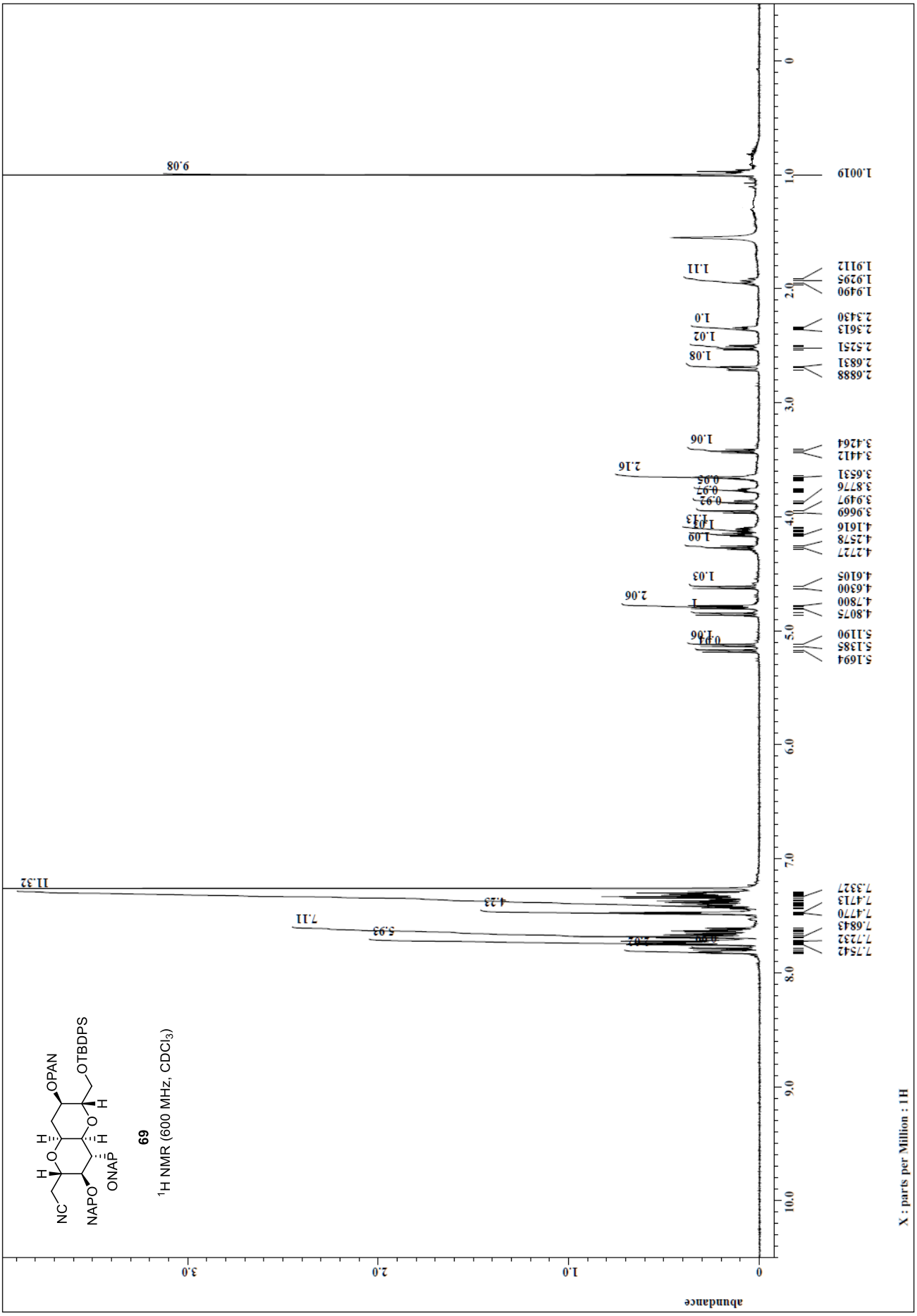

NAPO
NAPO
ONAP
OPAN
OTBDPS
65
^{13}C NMR (150 MHz, $CDCl_3$)
19.4720
26.9978
29.7458
63.7841
70.4768
71.3194
72.3152
73.8471
74.7472
76.1547
125.8860
126.2498
127.7244
127.7531
127.7818
128.0499
136.0161
X : parts per Million : 13C
abundance

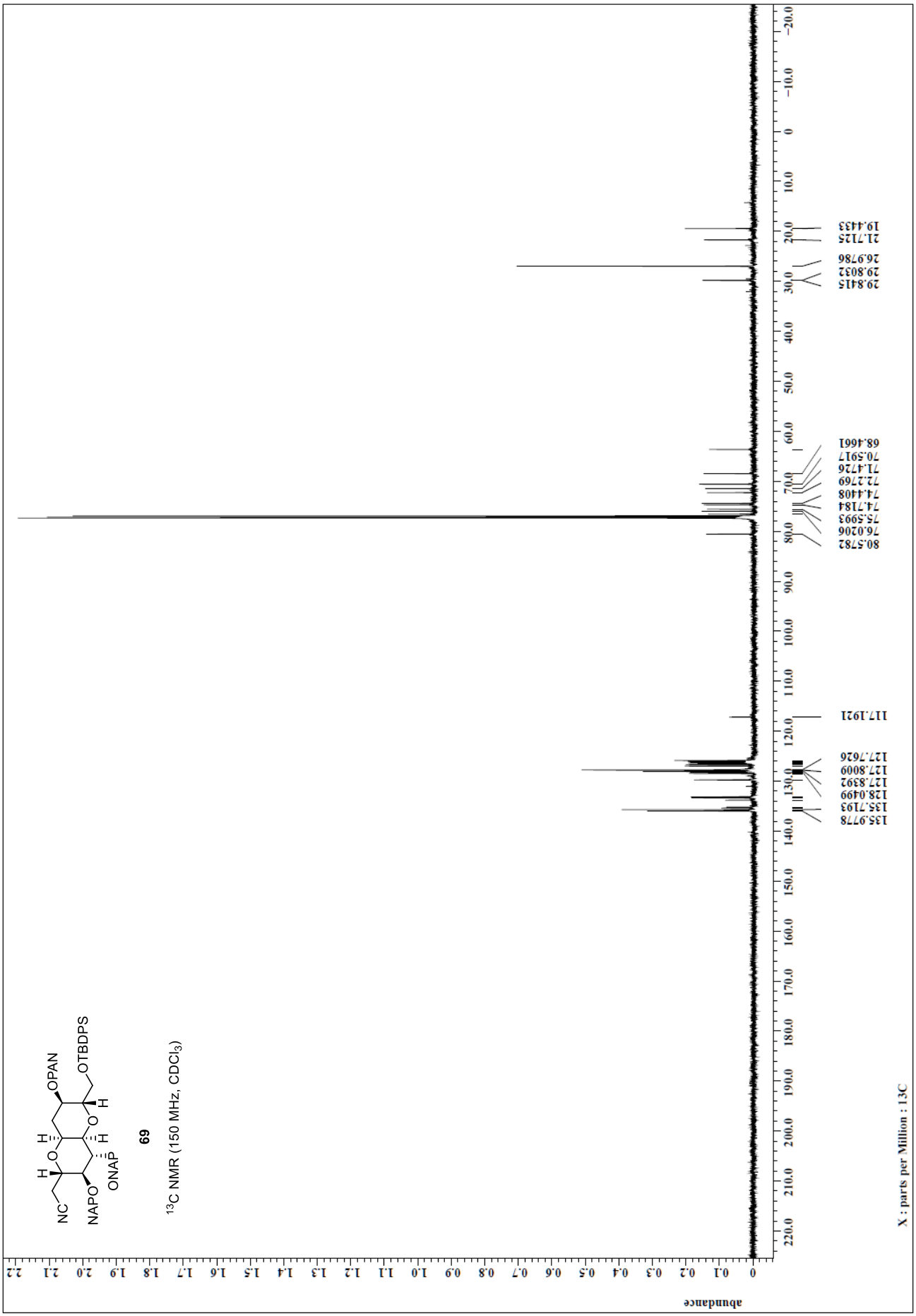
OPAN
OTBDPS
AcO
NAPO
ONAP
99
66
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

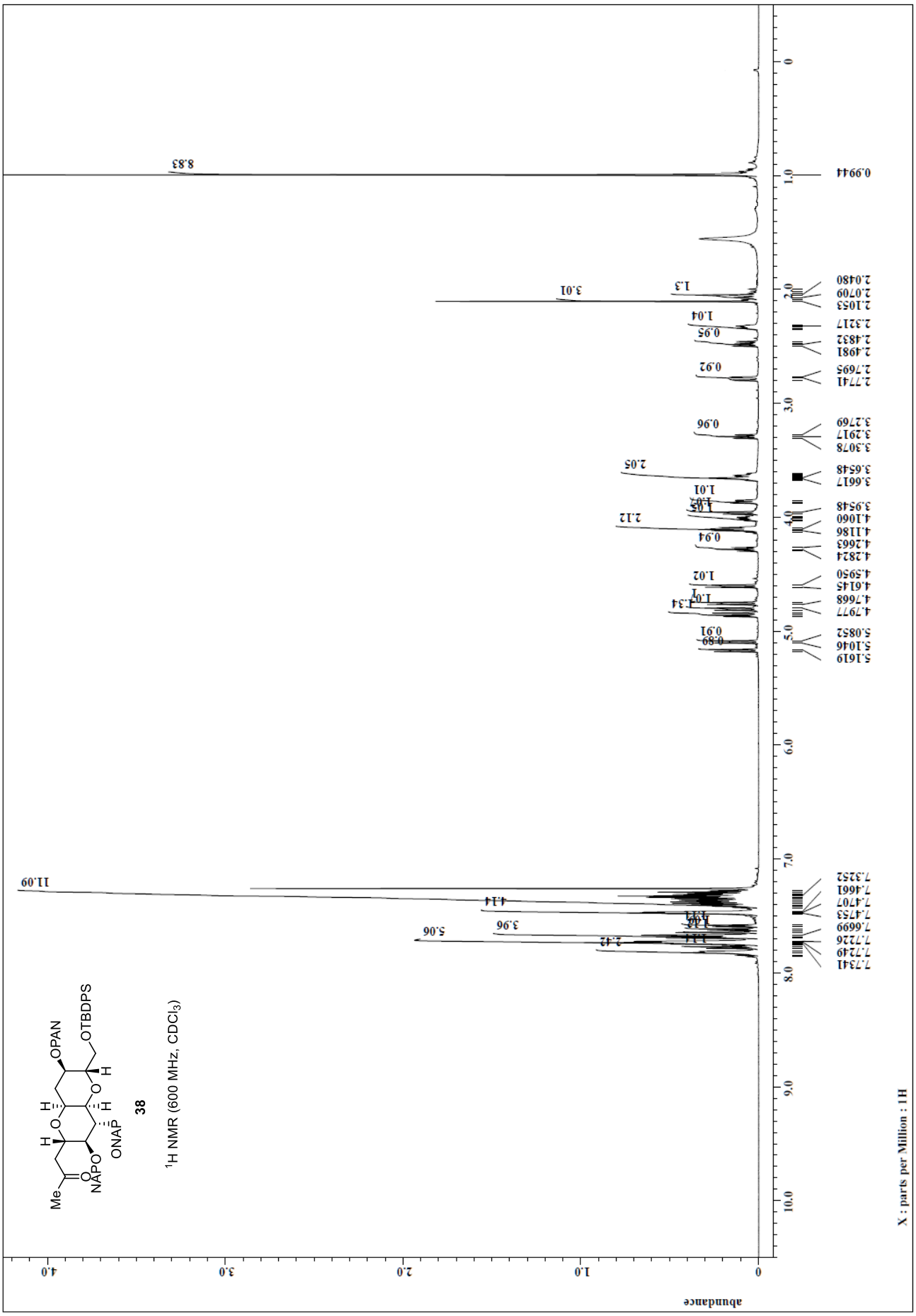

OPAN
OTBDPS
AcO
NAPO
ONAP
66
^{13}C NMR (150 MHz, $CDCl_3$)
170.9449
136.0065
135.7384
128.1169
127.7914
127.7627
126.1062
77.7154
76.1068
75.2834
70.7354
70.4194
63.7458
63.7075
29.7553
26.9882
20.8987
19.4625
X : parts per Million : 13C
abundance

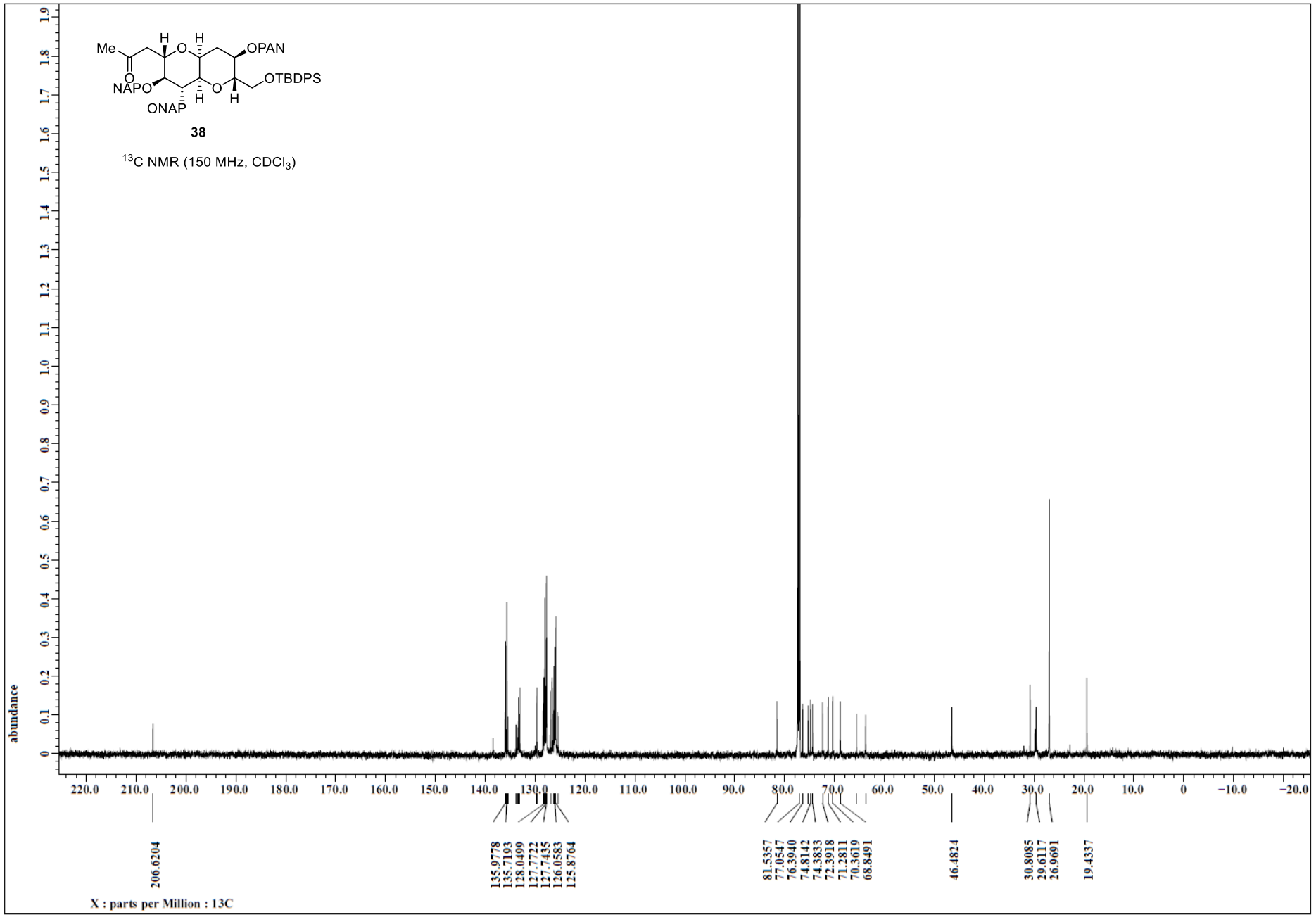

OPAN
OTBDPS
NAPO
ONAP
HO
67
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance

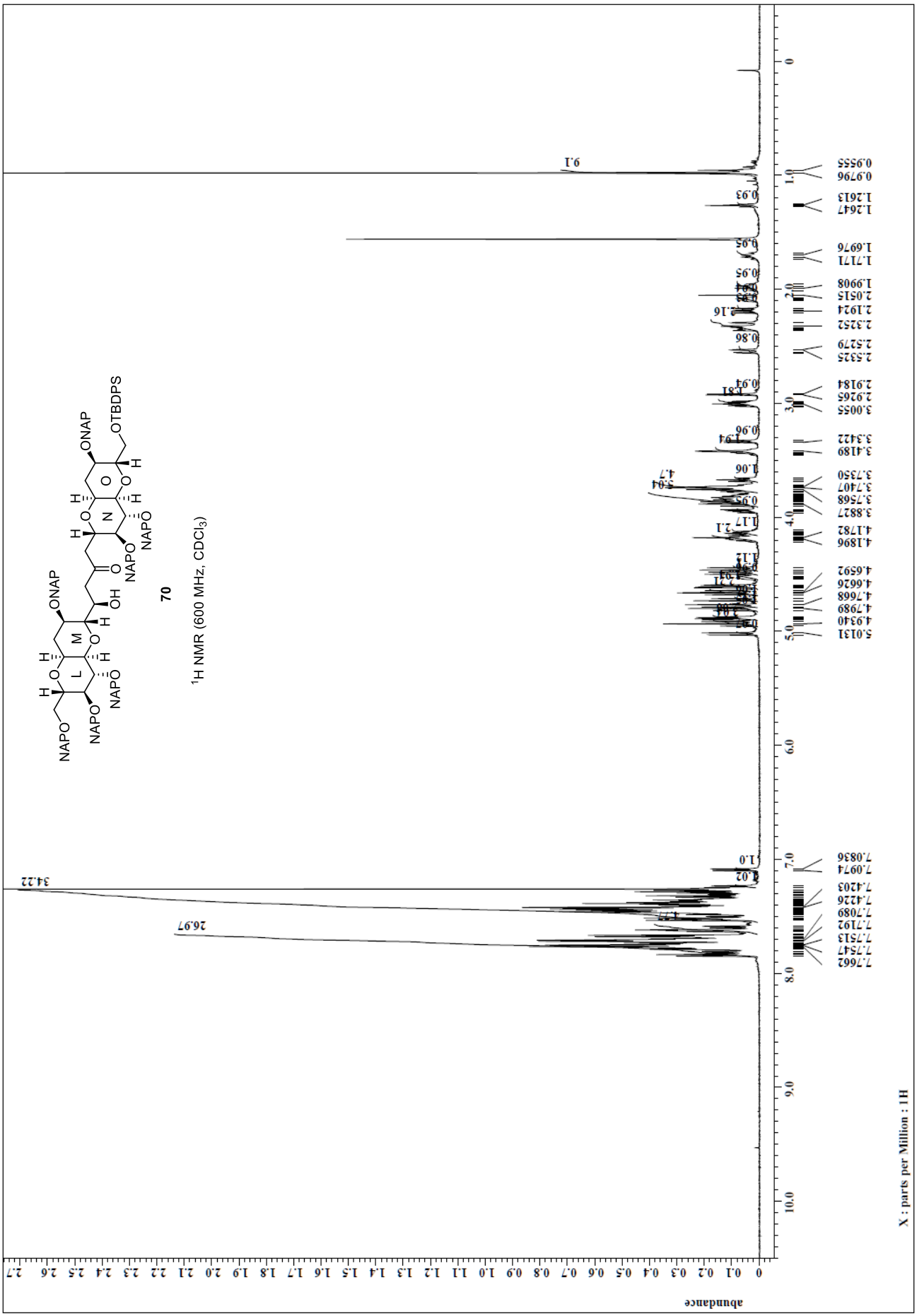

OPAN
OTBDPS
HO
NAPO
ONAP
67
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
136.0161
135.7480
127.8010
127.7722
127.7435
125.8764
76.7962
74.7567
72.6311
72.4588
70.4385
63.6596
62.6830
30.0713
27.0074
19.4816

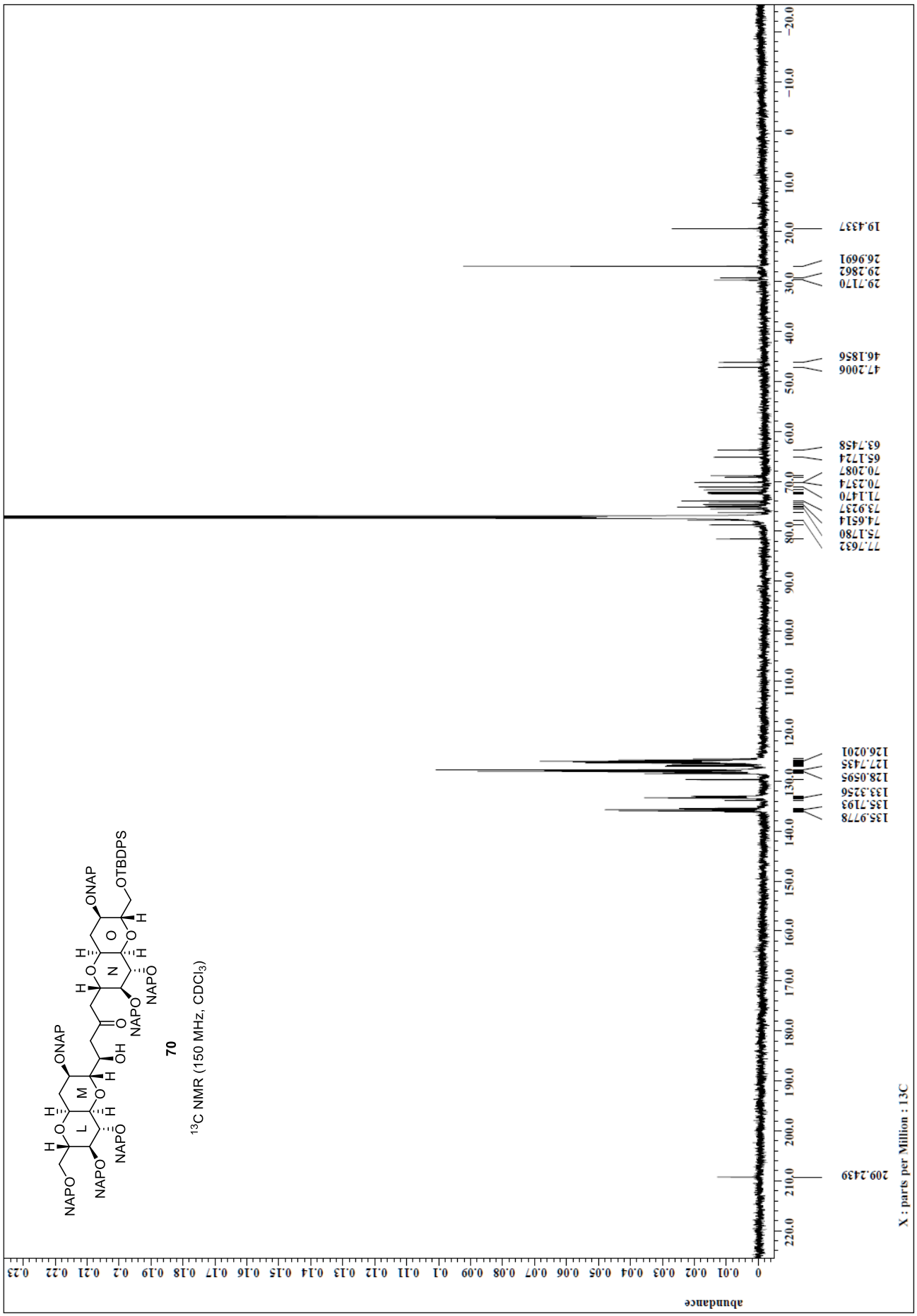

69
^{1}H NMR (600 MHz, $CDCl_3$)
OPAN
OTBDPS
NAPO
ONAP
NC
H
O
abundance
X : parts per Million : 1H

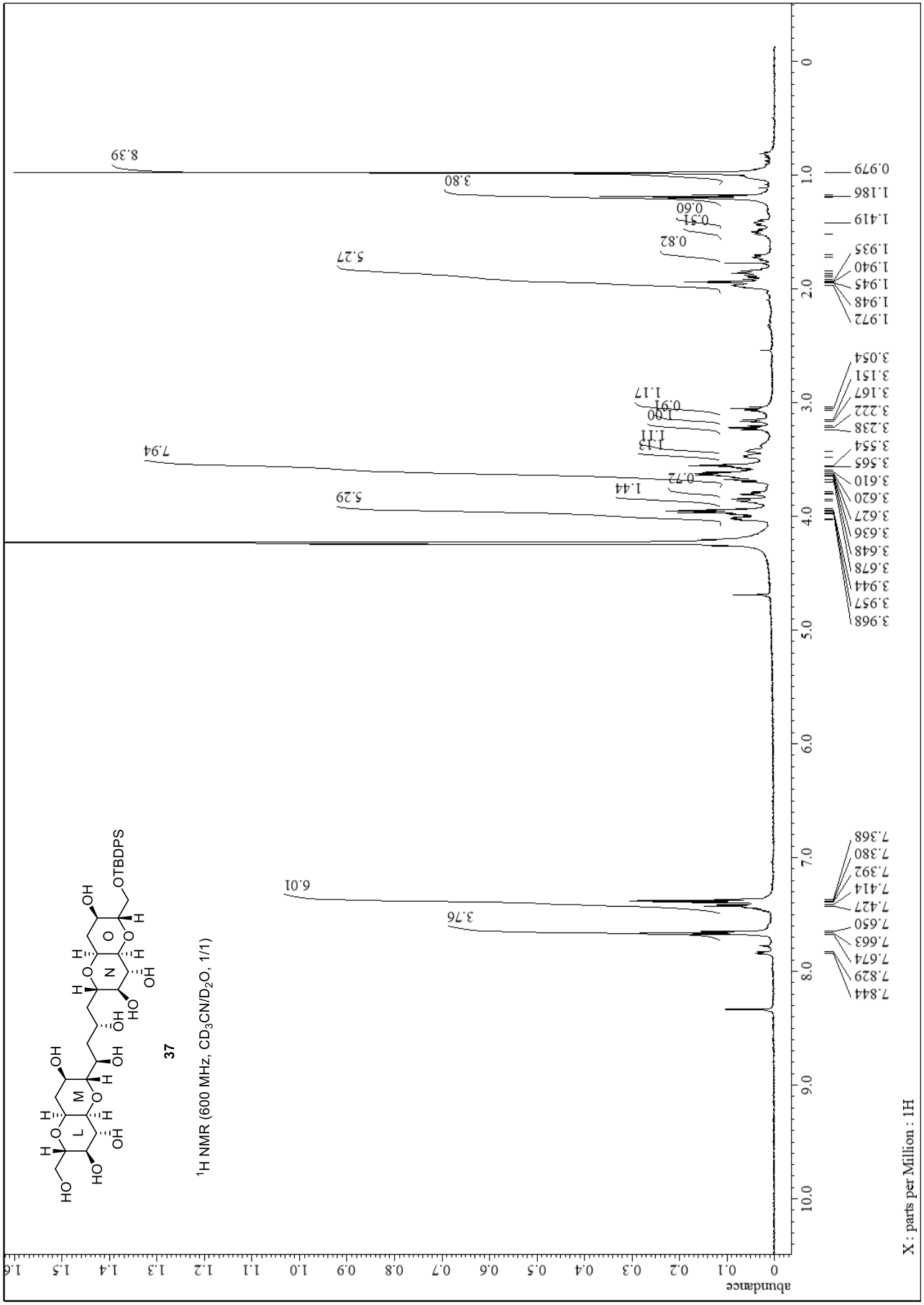

69
^{13}C NMR (150 MHz, $CDCl_3$)
OPAN
OTBDPS
NAPO
ONAP
NC
135.9778
135.7193
128.0499
127.8392
127.8009
127.7626
117.1921
80.5782
76.0206
75.5993
74.7184
74.4408
72.2769
71.4726
70.5917
68.4661
29.8415
29.8032
26.9786
21.7125
19.4433
X : parts per Million : 13C
abundance

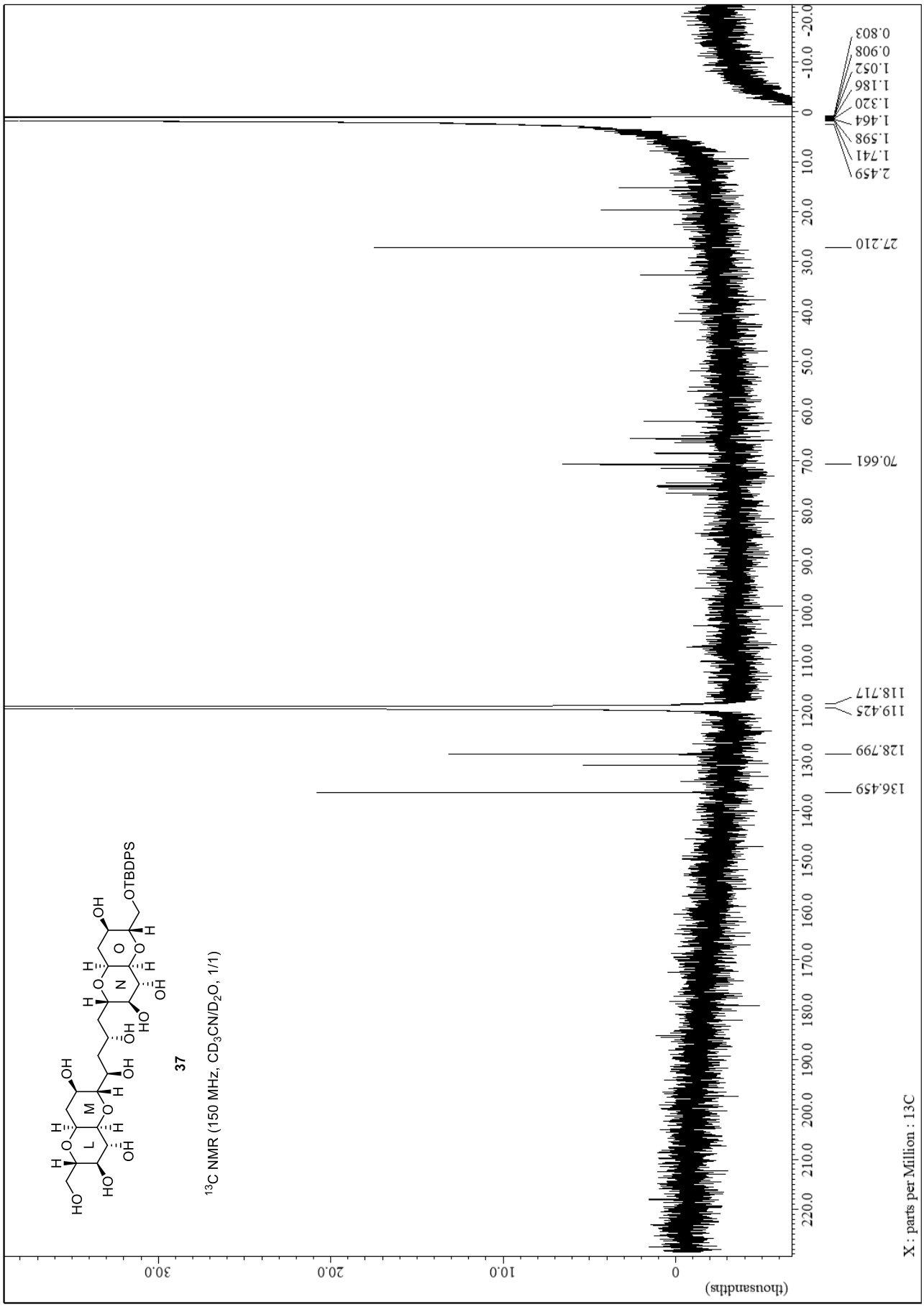

OPAN
OTBDPS
ONAP
NAPO
Me
38
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance


Me
H
O
H
OPAN
O
NAPO
O
OTBDPS
H
H
ONAP
38
13C NMR (150 MHz, CDCl3)
abundance
206.6204
135.9778
135.7193
128.0499
127.7722
127.7435
126.0583
125.8764
81.5357
77.0547
76.3940
74.8142
74.3833
72.3918
71.2811
70.3619
68.8491
46.4824
30.8085
29.6117
26.9691
19.4337
X : parts per Million : 13C

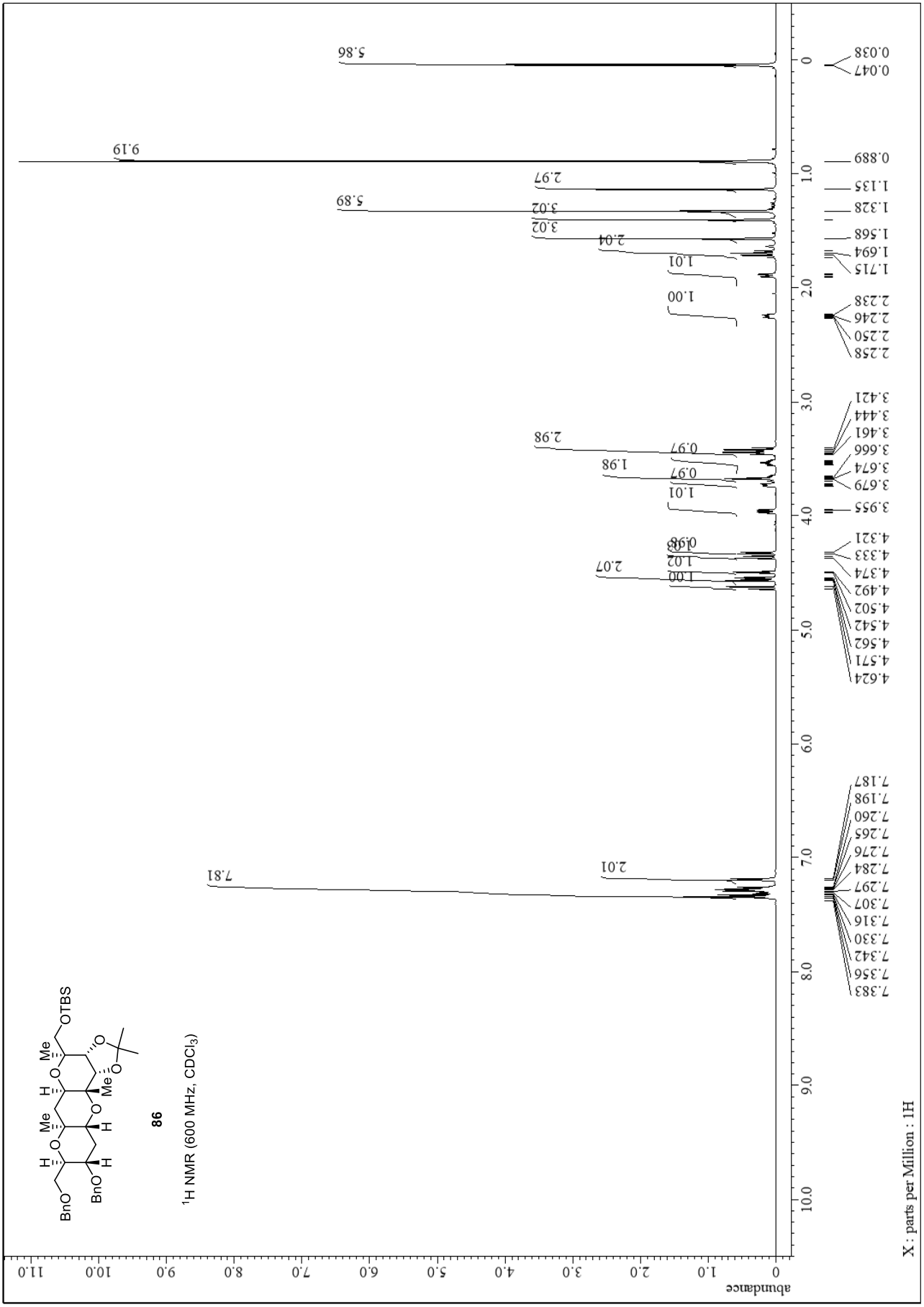

70
^{1}H NMR (600 MHz, CDCl$_3$)
NAPO
ONAP
OTBDPS
X : parts per Million : 1 H
abundance


NAPO
NAPO
NAPO
L
M
N
ONAP
OH
NAPO
NAPO
ONAP
OTBDPS
70
^{13}C NMR (150 MHz, $CDCl_3$)
209.2439
135.9778
135.7193
133.3256
128.0595
127.7435
126.0201
77.7632
75.1780
74.6514
73.9237
71.1470
70.2374
70.2087
65.1724
63.7458
47.2006
46.1856
29.7170
29.2862
26.9691
19.4337
X : parts per Million : 13C
abundance

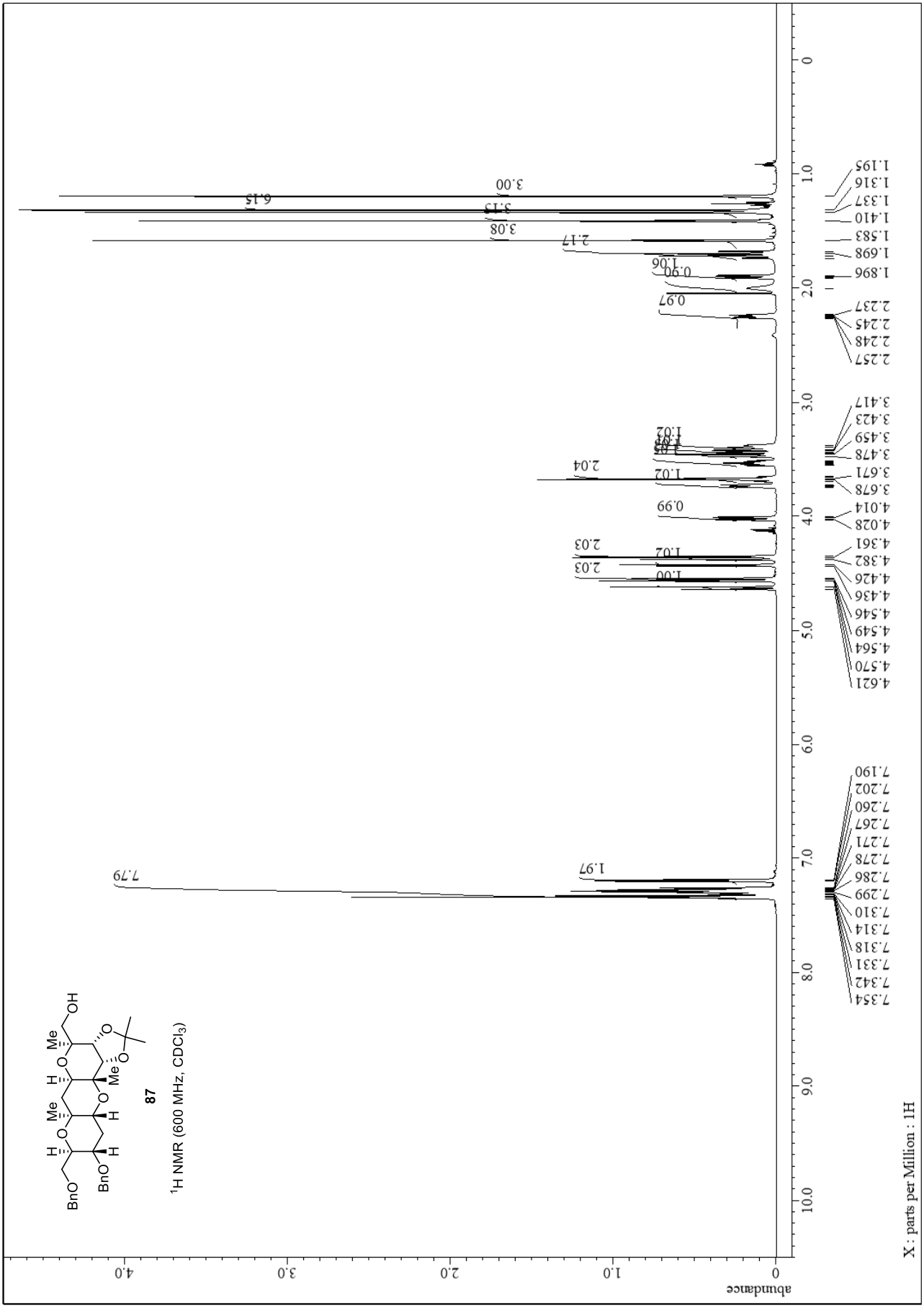

37
^{1}H NMR (600 MHz, CD_3CN/D_2O, 1/1)
X : parts per Million : 1H
abundance

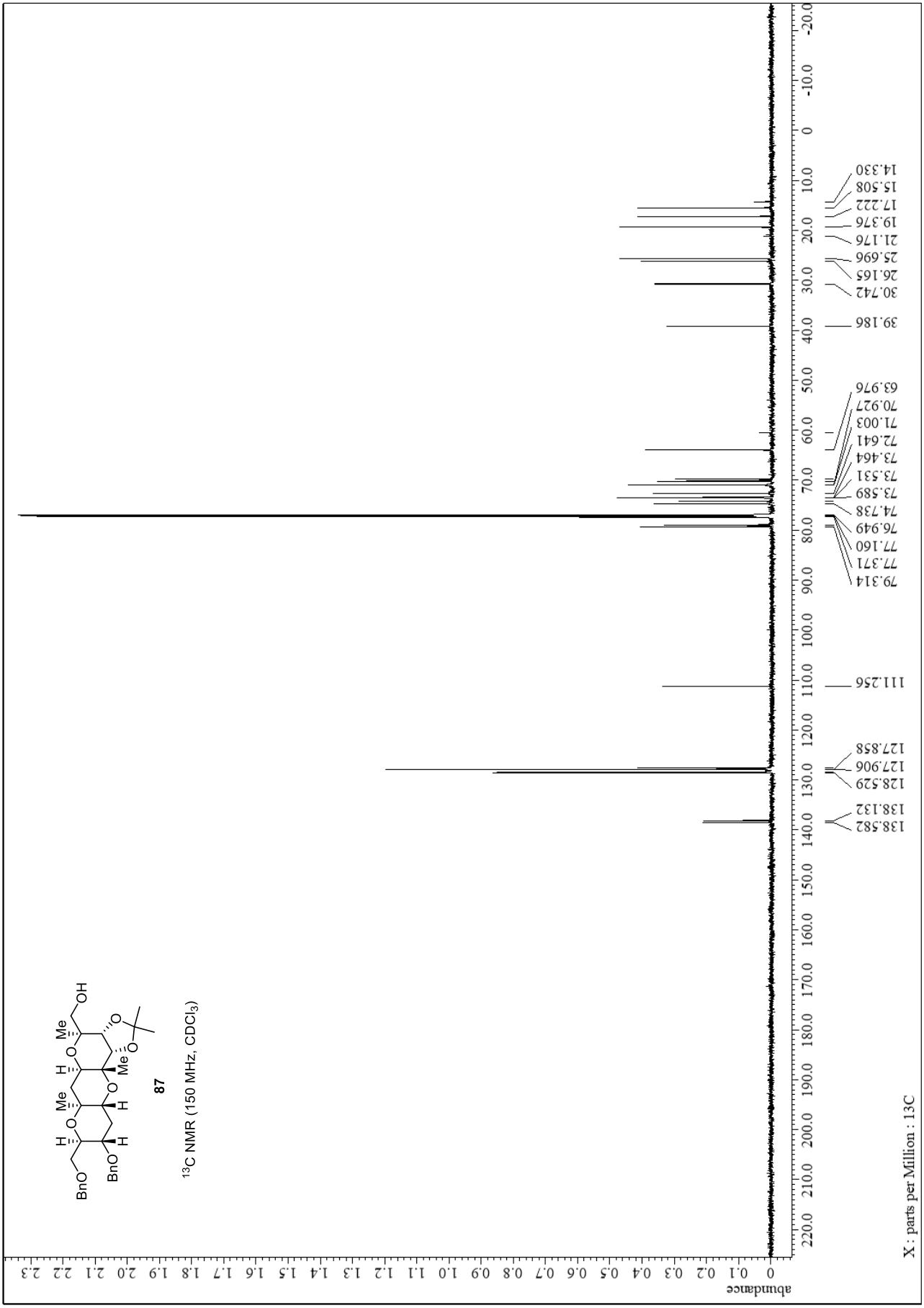

37
^{13}C NMR (150 MHz, CD_3CN/D_2O, 1/1)
X : parts per Million : 13C
(thousandths)
136.459
128.799
119.425
118.717
70.661
27.210
2.459
1.741
1.598
1.464
1.320
1.186
1.052
0.908
0.803

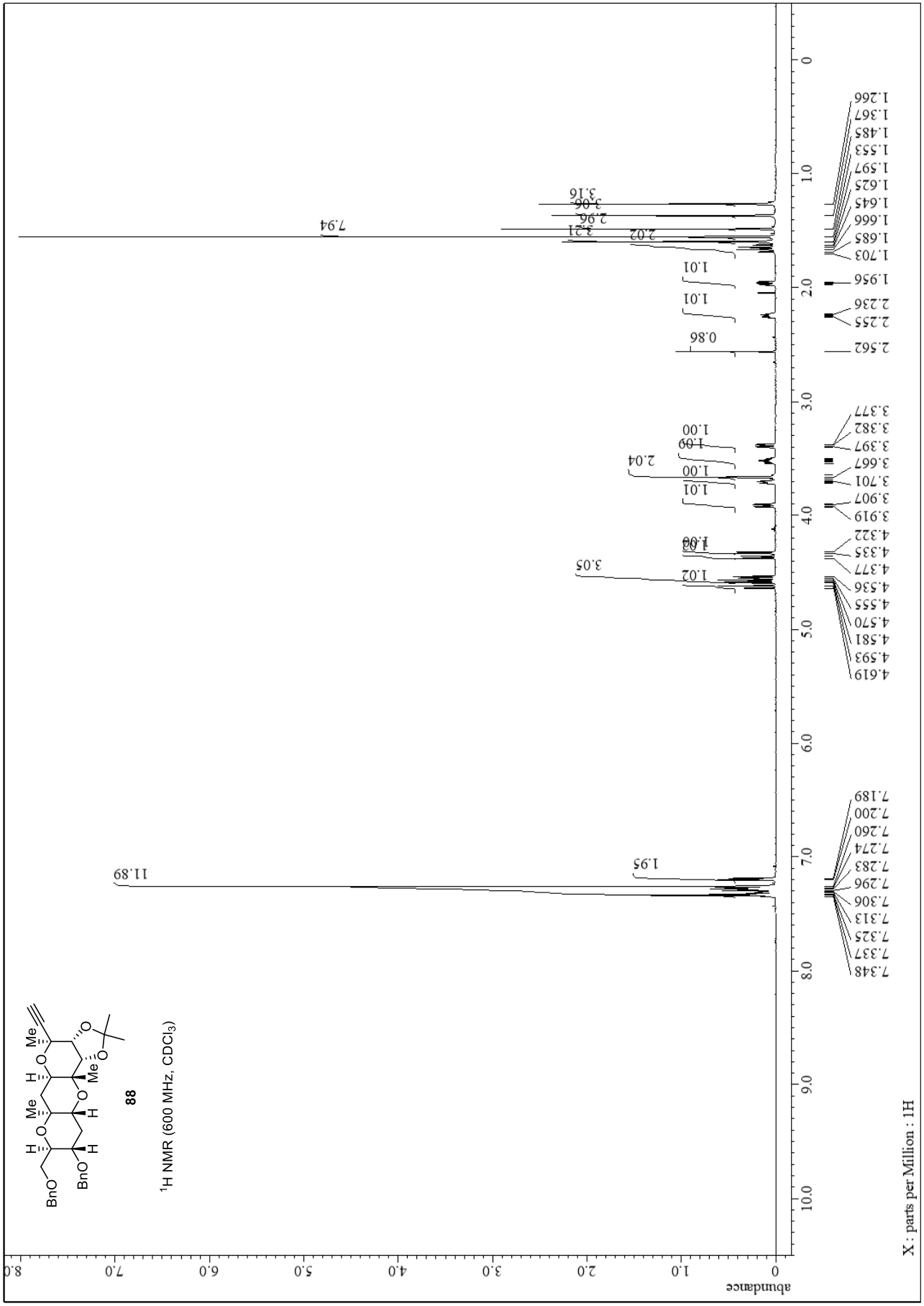
Section 2-3

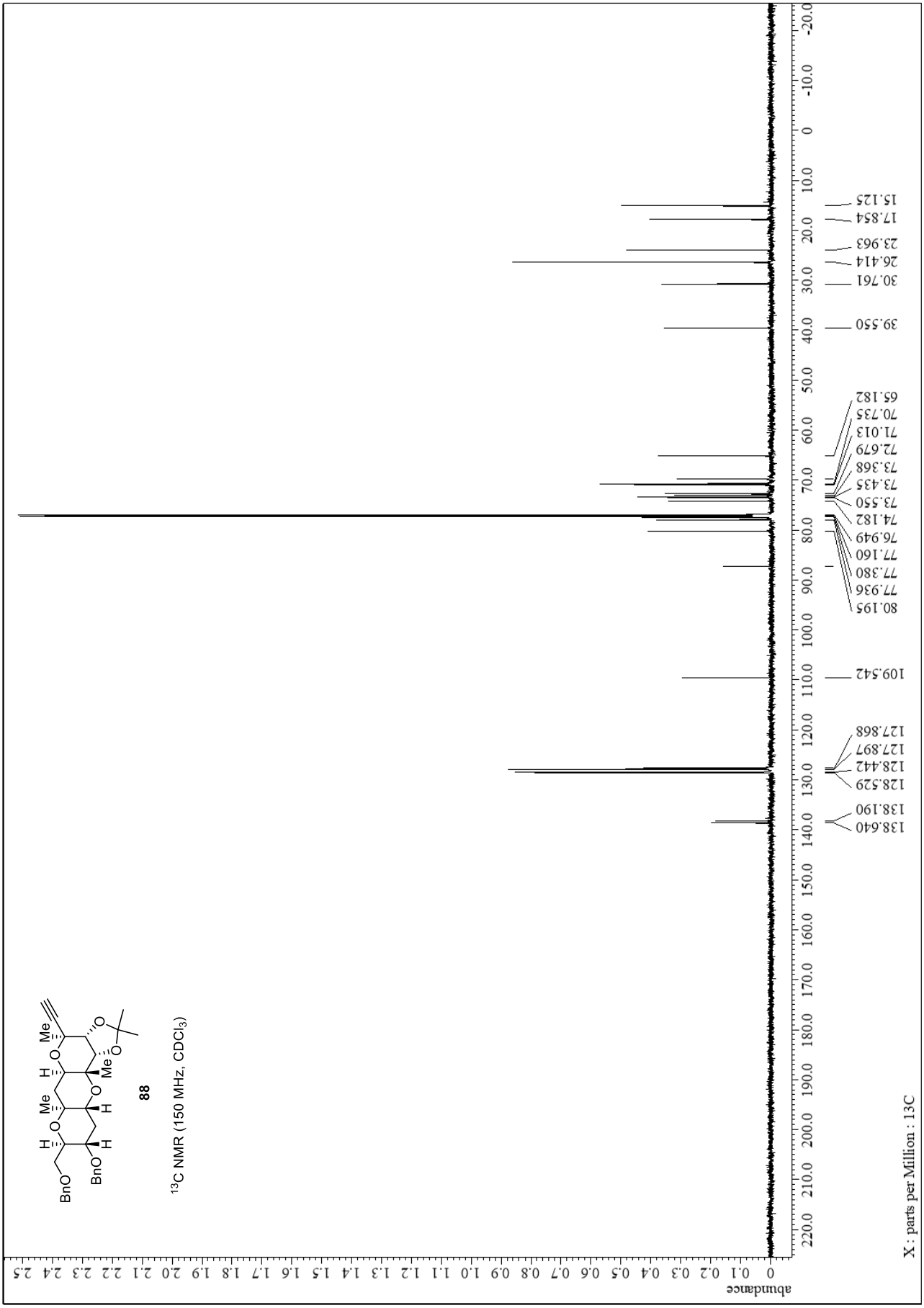

86
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

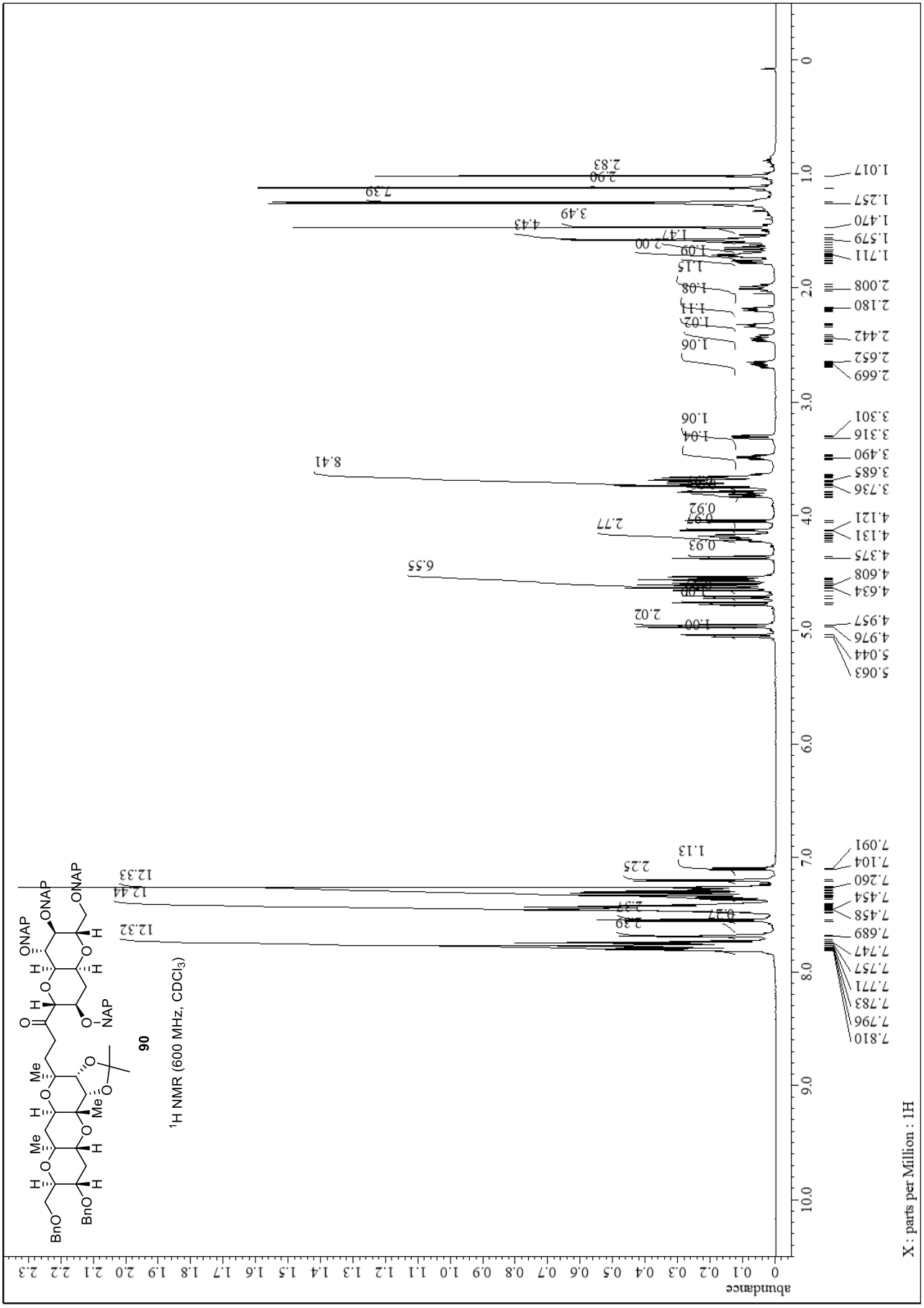
OTBS
Me
H
O
Me
BnO
H
O
Me
O
O
H
O
Me
BnO
H
86
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
X : parts per Million : 13C
138.640
138.190
128.519
128.433
127.945
127.868
110.834
79.535
78.903
77.371
77.160
76.949
74.489
73.636
73.617
73.493
72.612
70.975
70.764
39.321
30.799
26.251
26.079
25.638
19.558
18.572
16.887
15.498
-5.049
-5.298

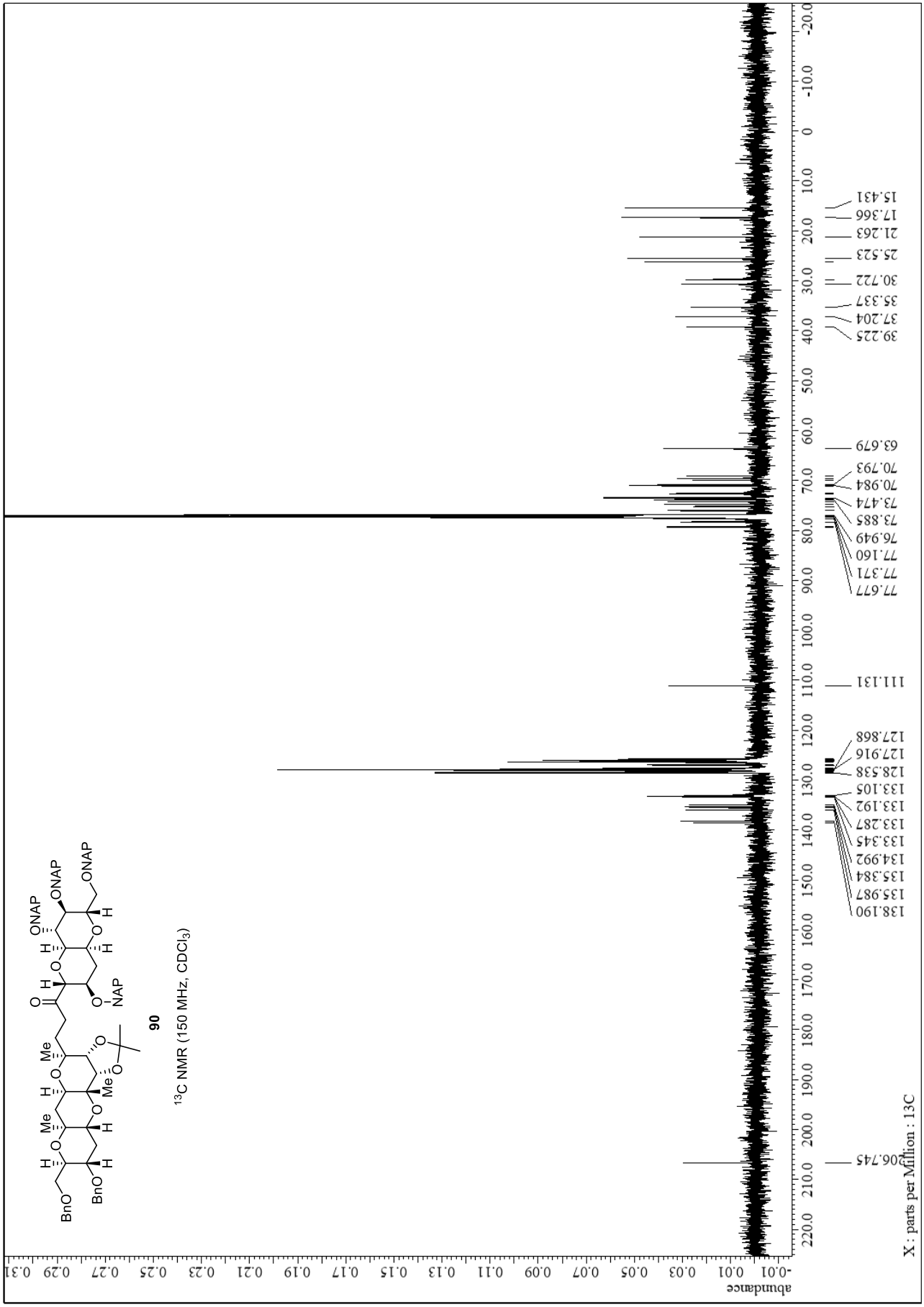

87
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

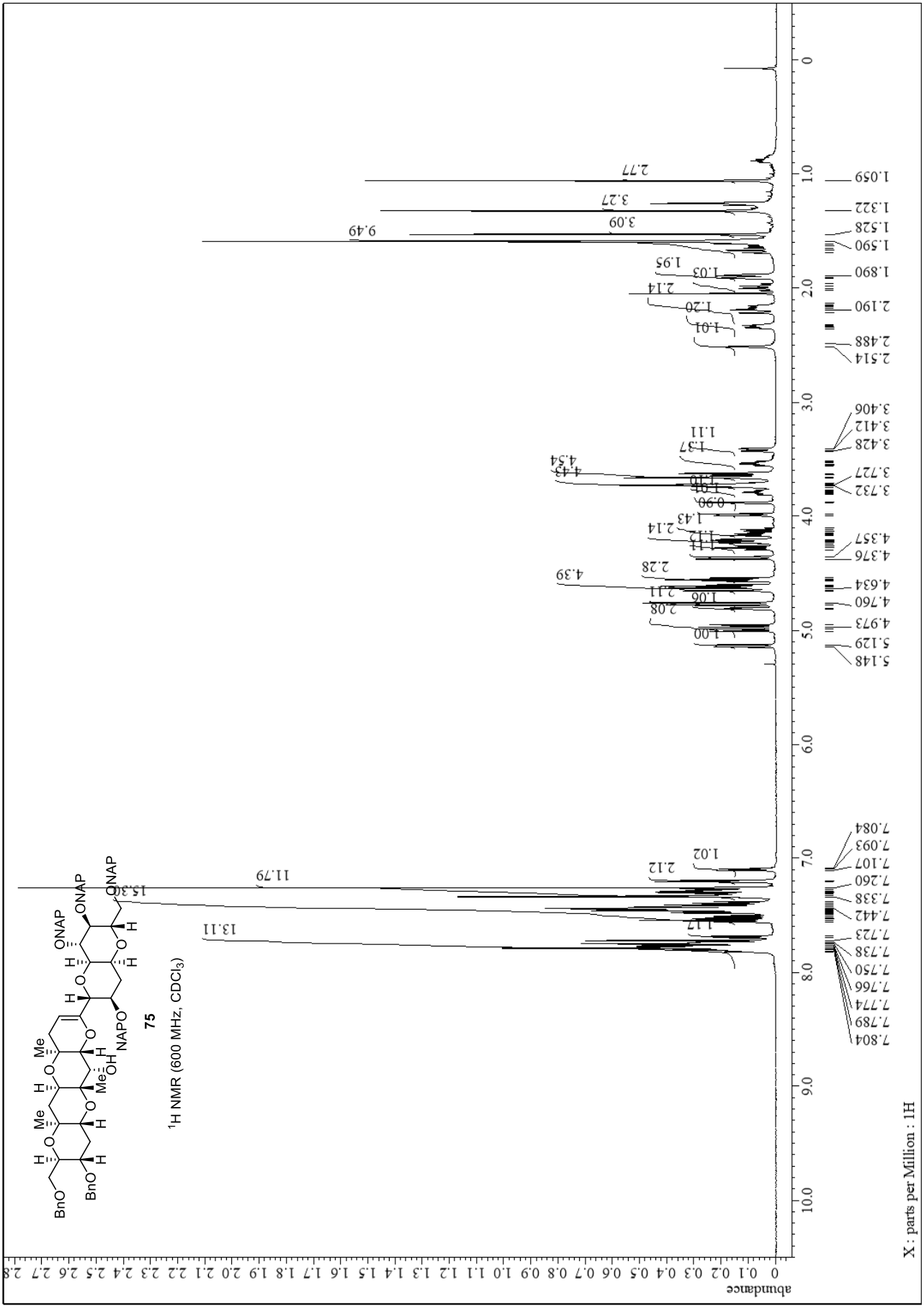

87
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
14.330
15.508
17.222
19.376
21.176
25.696
26.165
30.742
39.186
63.976
70.927
71.003
72.641
73.464
73.531
73.589
74.738
76.949
77.160
77.371
79.314
111.256
127.858
127.906
128.529
138.132
138.582

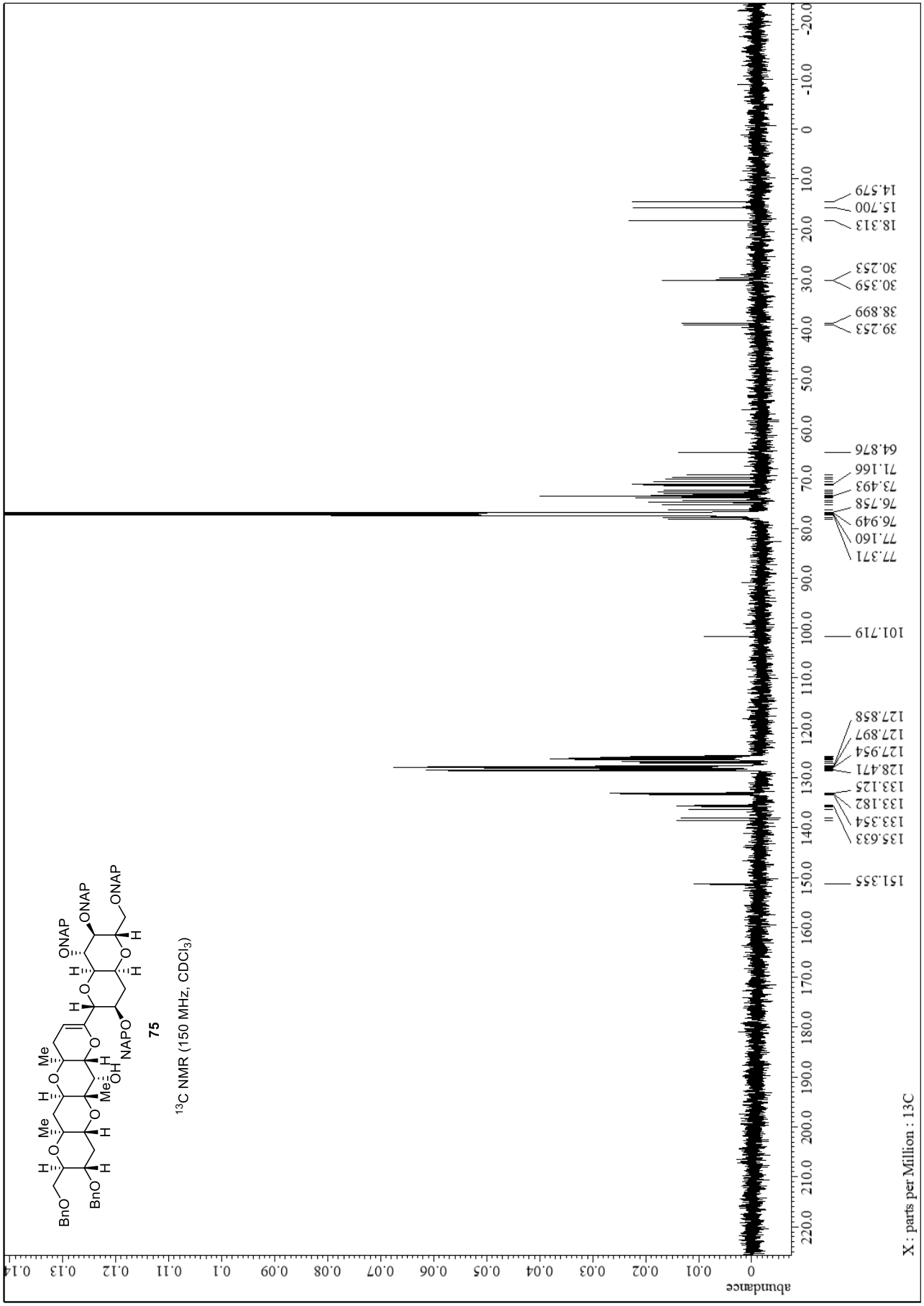

88
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

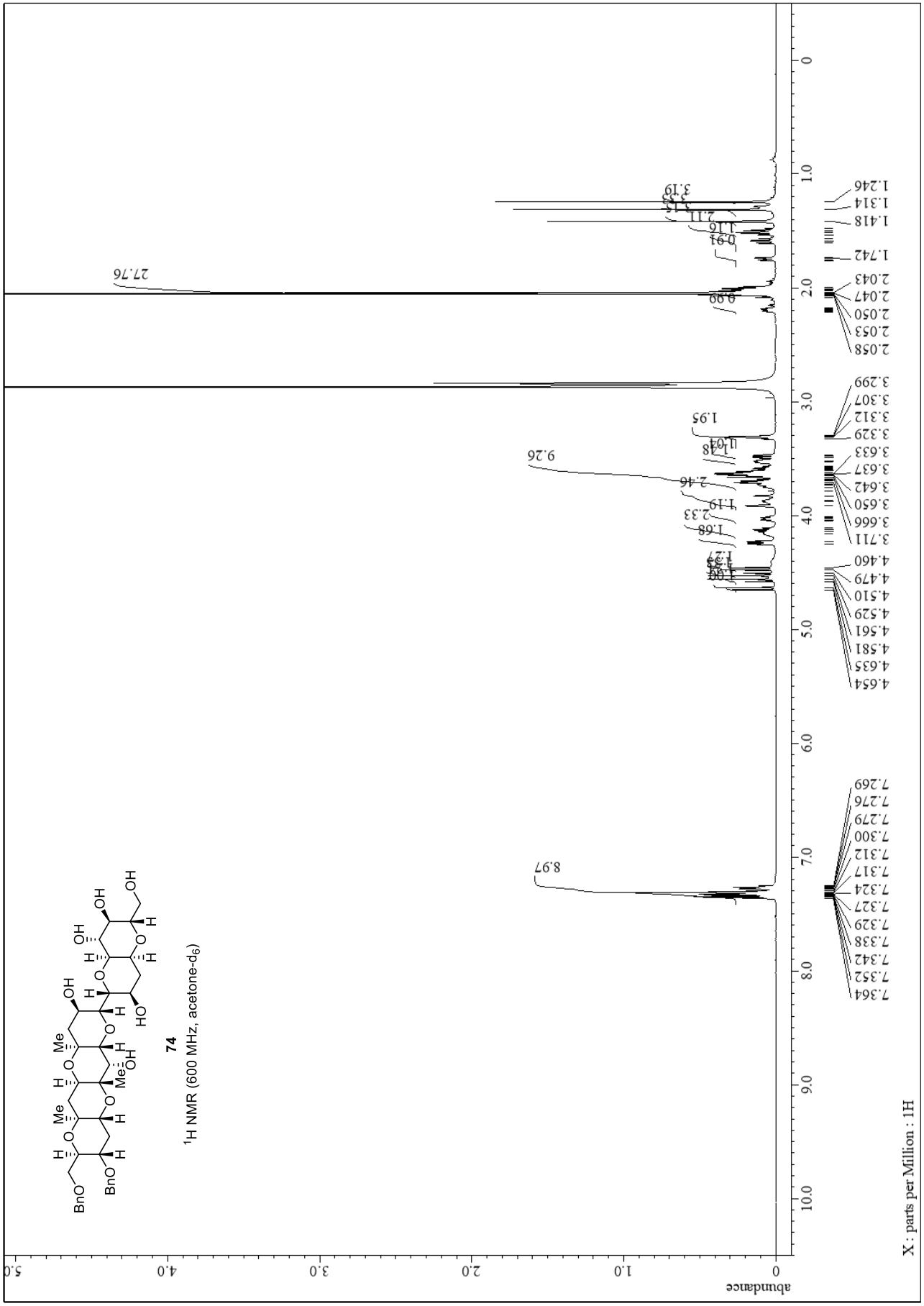

88
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
15.125
17.854
23.963
26.414
30.761
39.550
65.182
70.735
71.013
72.679
73.368
73.435
73.550
74.182
76.949
77.160
77.380
77.936
80.195
109.542
127.868
127.897
128.442
128.529
138.190
138.640

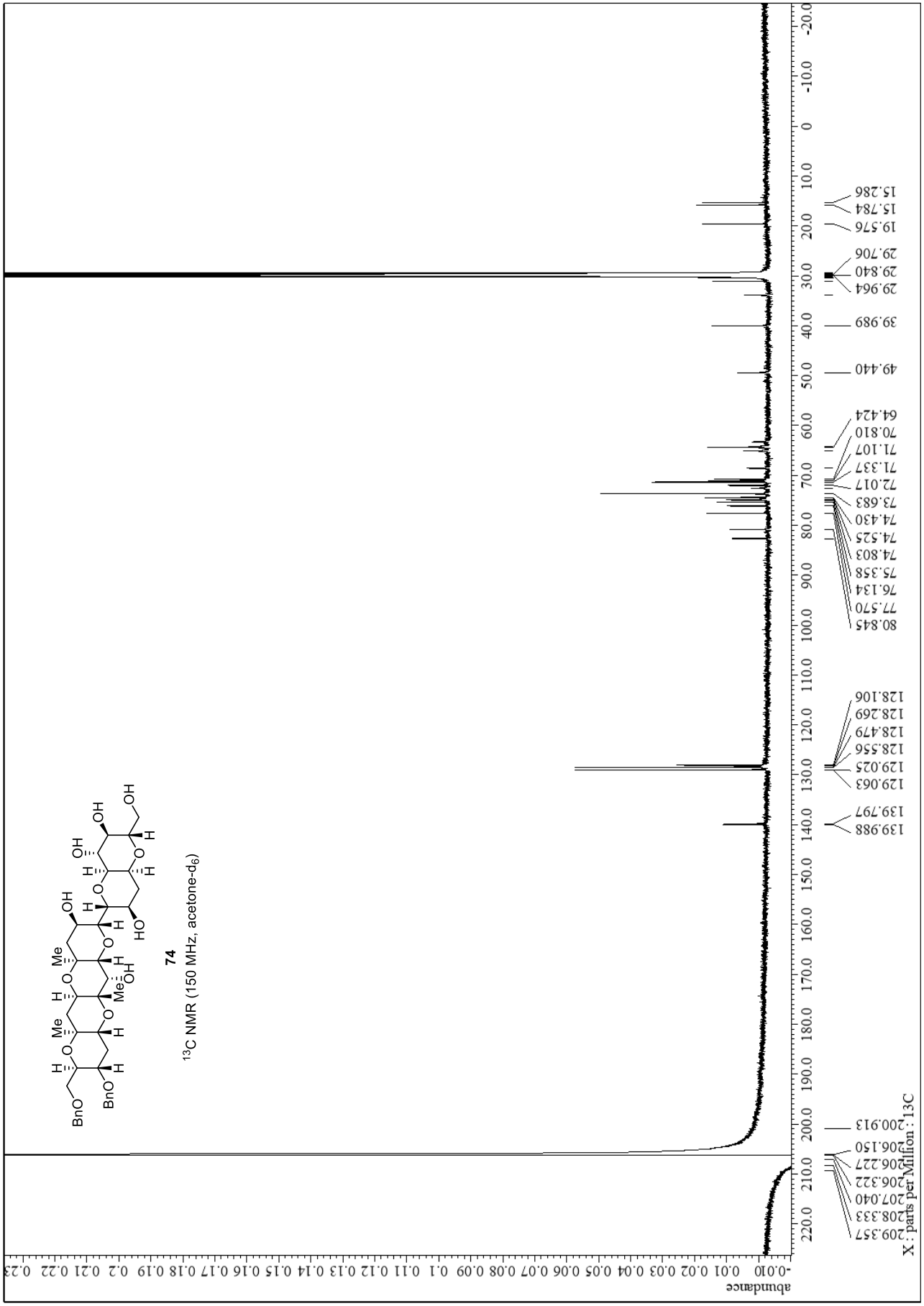

90
^{1}H NMR (600 MHz, $CDCl_3$)
X : parts per Million : 1H
abundance


90
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
206.745
138.190
135.987
135.384
134.992
133.345
133.287
133.192
133.105
128.538
127.916
127.868
111.131
77.677
77.371
77.160
76.949
73.885
73.474
70.984
70.793
63.679
39.225
37.204
35.337
30.722
25.523
21.263
17.366
15.431

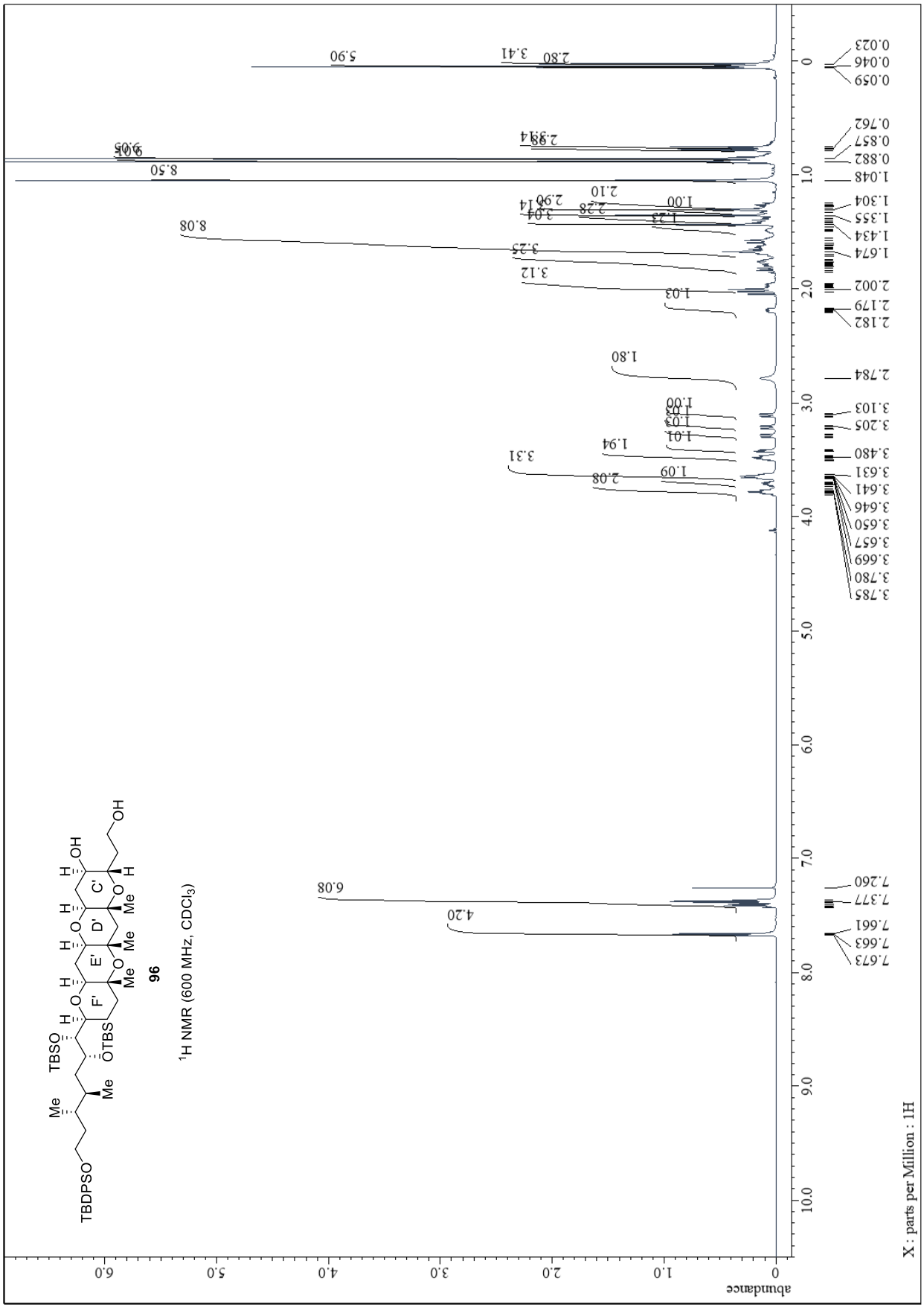

75
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

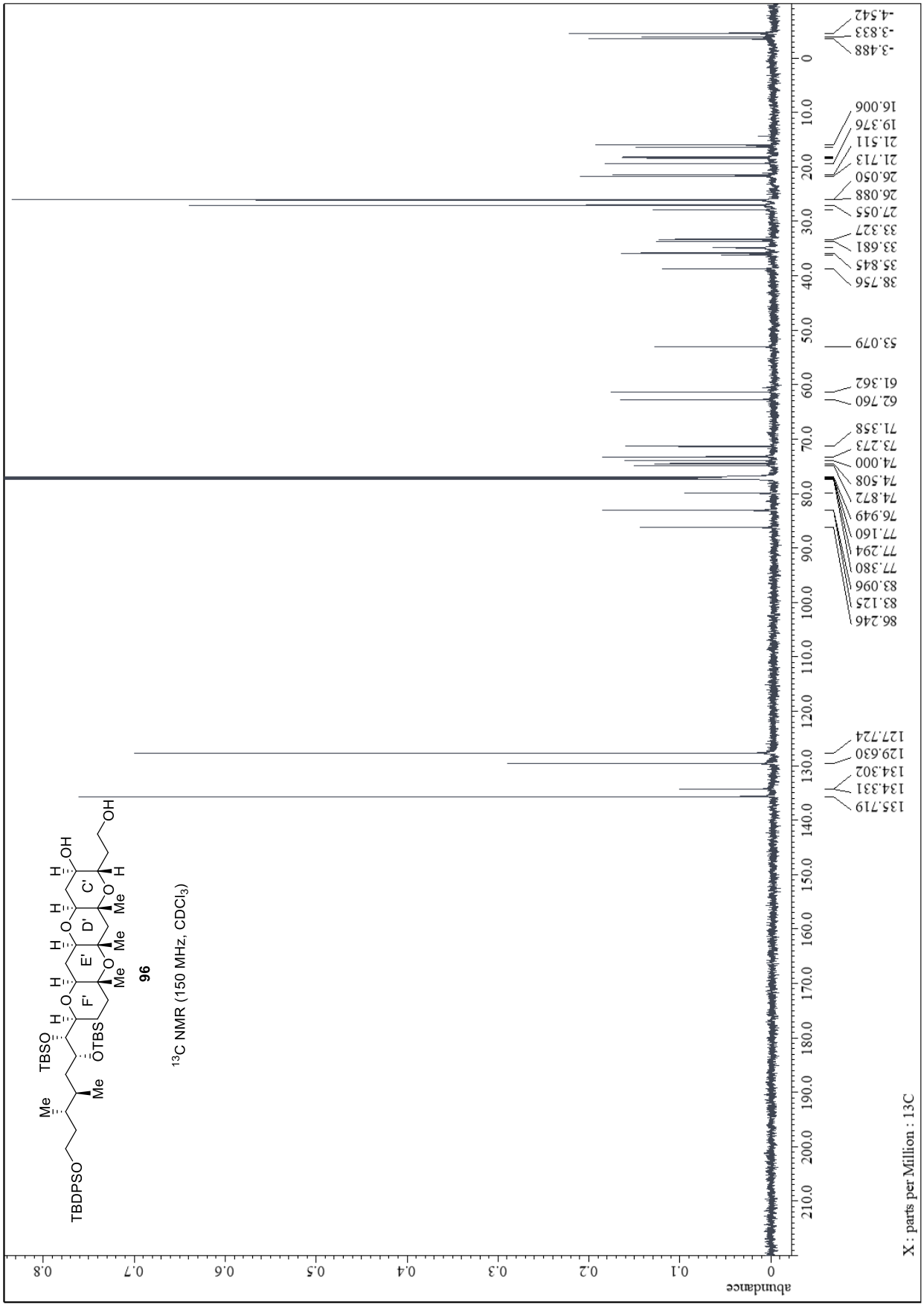

75
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
151.355
135.633
133.354
133.182
133.125
128.471
127.954
127.897
127.858
101.719
77.371
77.160
76.949
76.758
73.493
71.166
64.876
39.253
38.899
30.359
30.253
18.313
15.700
14.579


74
^{1}H NMR (600 MHz, acetone-d_6)
abundance
X : parts per Million : 1H

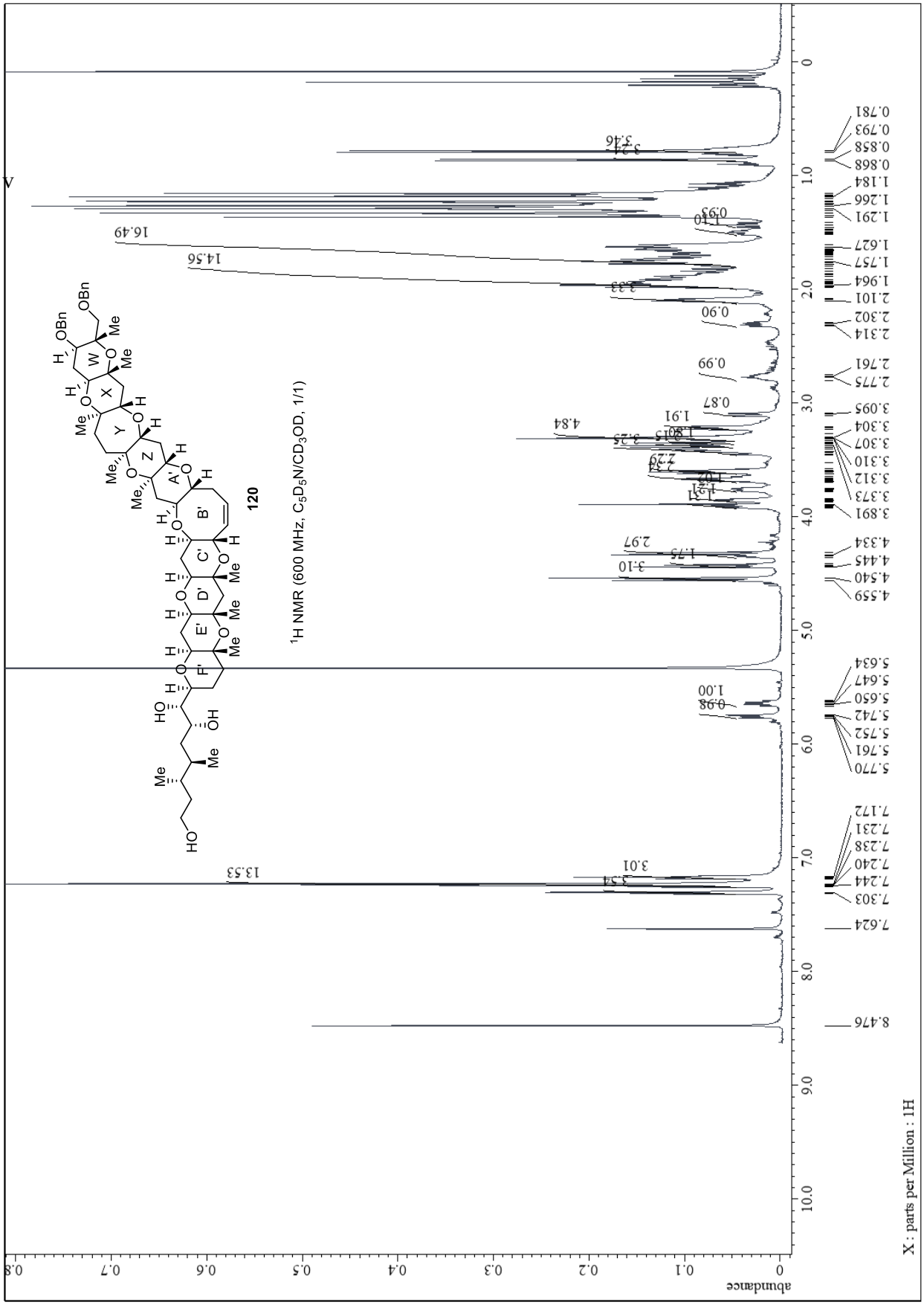

74
^{13}C NMR (150 MHz, acetone-d_6)
abundance
X : parts per Million : 13C

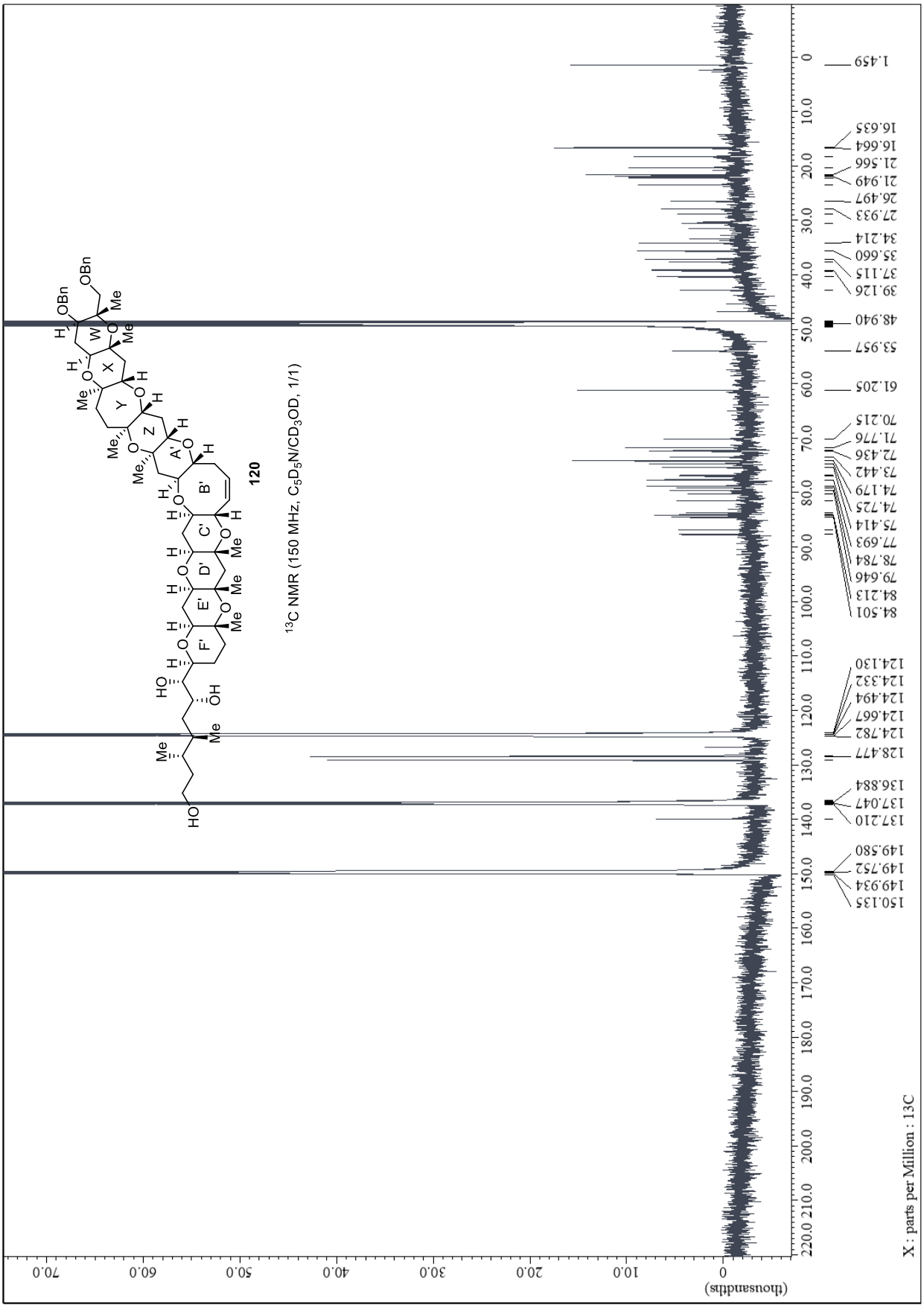
Section 3-2

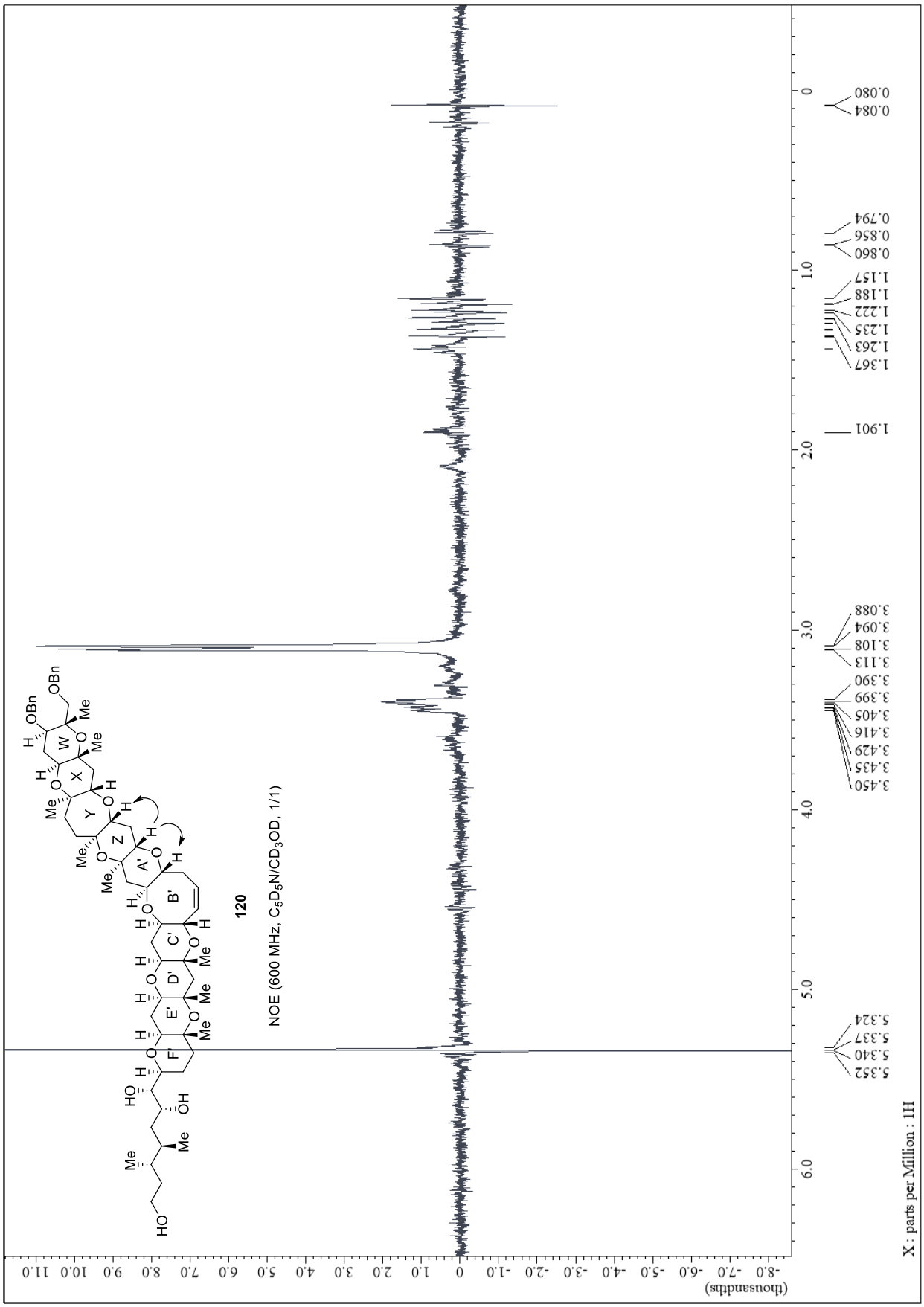

TBDPSO
Me
Me
TBSO
OTBS
F'
E'
D'
C'
Me
Me
Me
OH
96
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

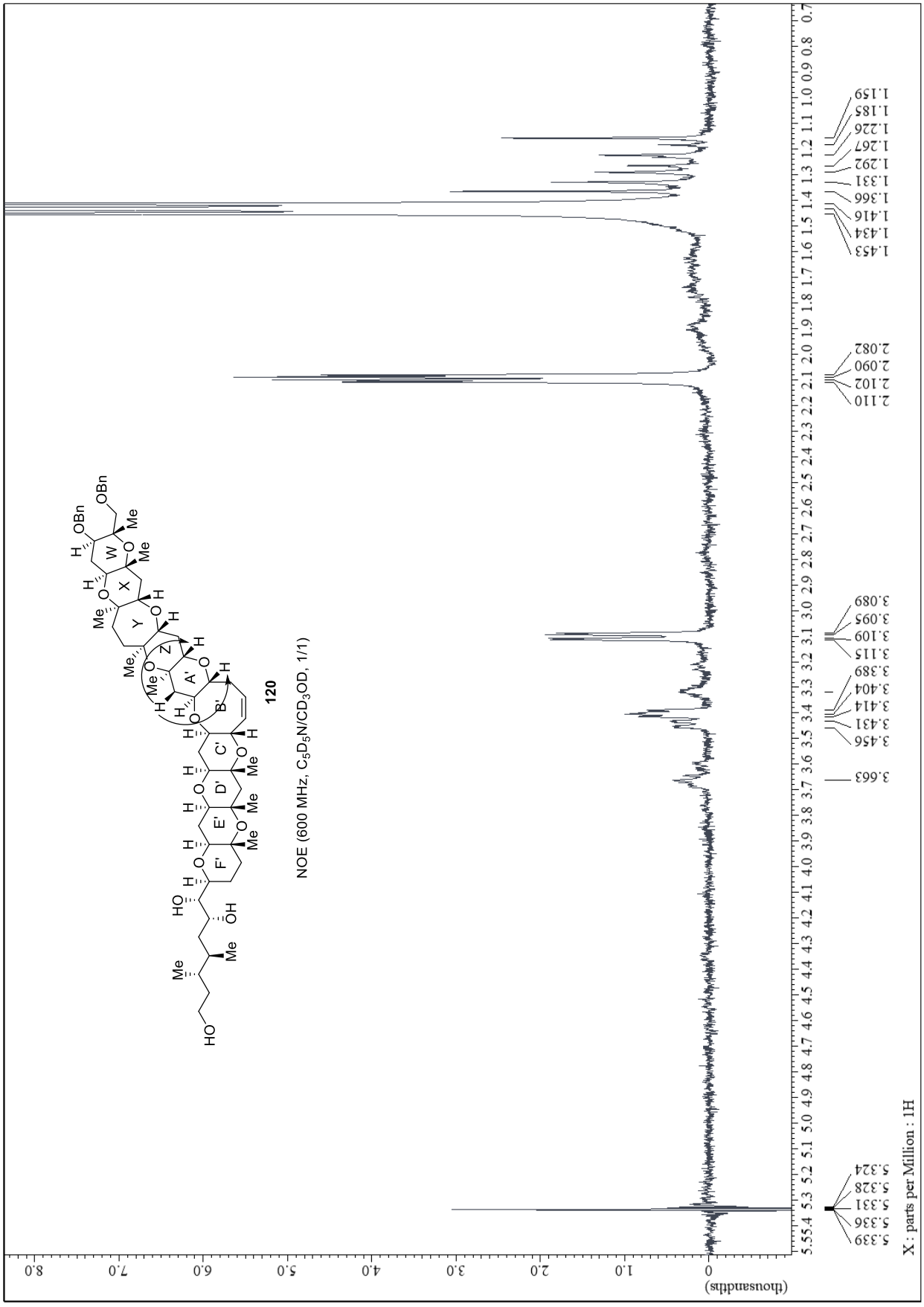

96
^{13}C NMR (150 MHz, $CDCl_3$)
X : parts per Million : 13C
abundance
135.719
134.331
134.302
129.630
127.724
86.246
83.125
83.096
77.380
77.294
77.160
76.949
74.872
74.508
74.000
73.273
71.358
62.760
61.362
53.079
38.756
35.845
33.681
33.327
27.055
26.088
26.050
21.713
21.511
19.376
16.006
-3.488
-3.833
-4.542

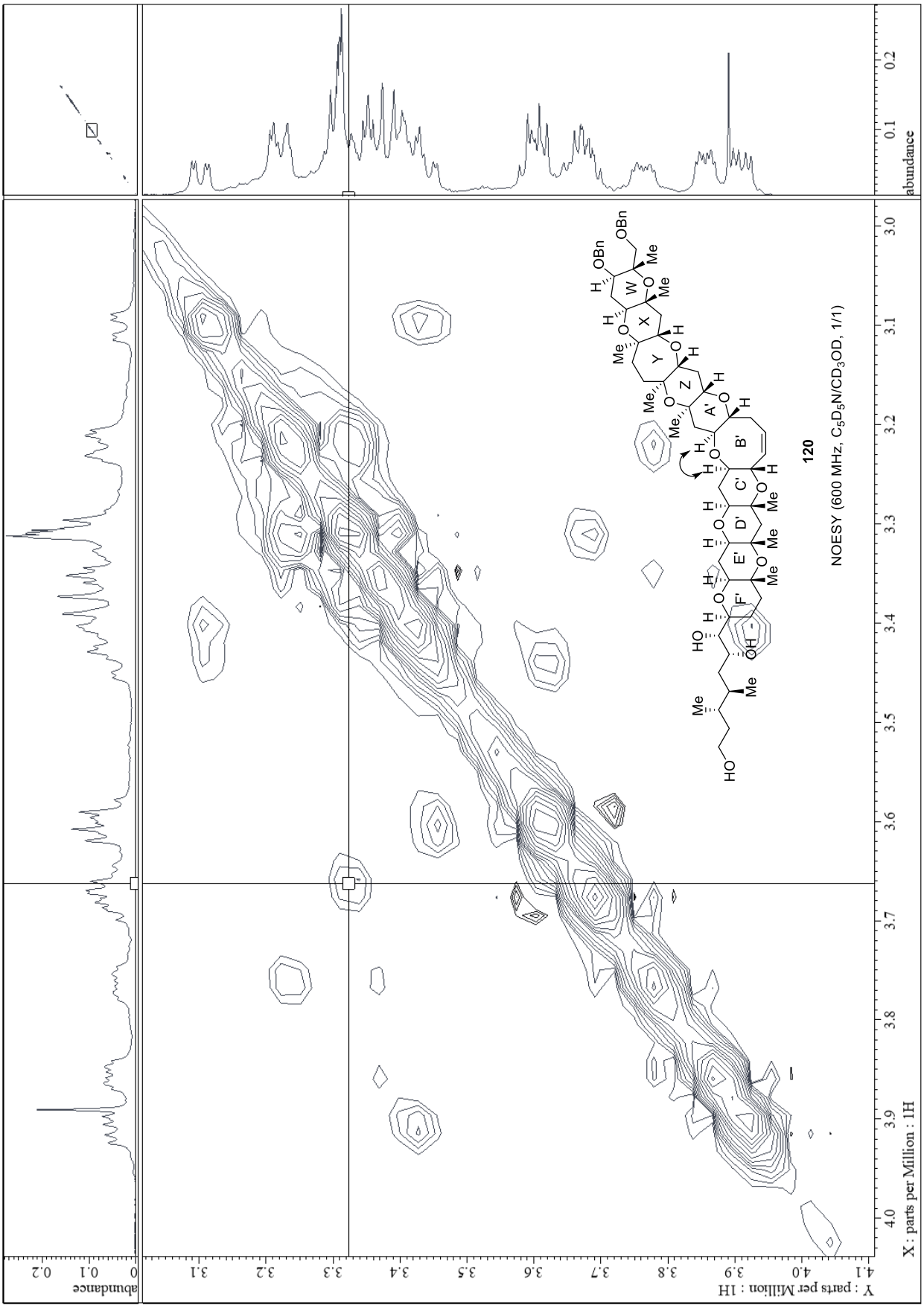
Section 3-3

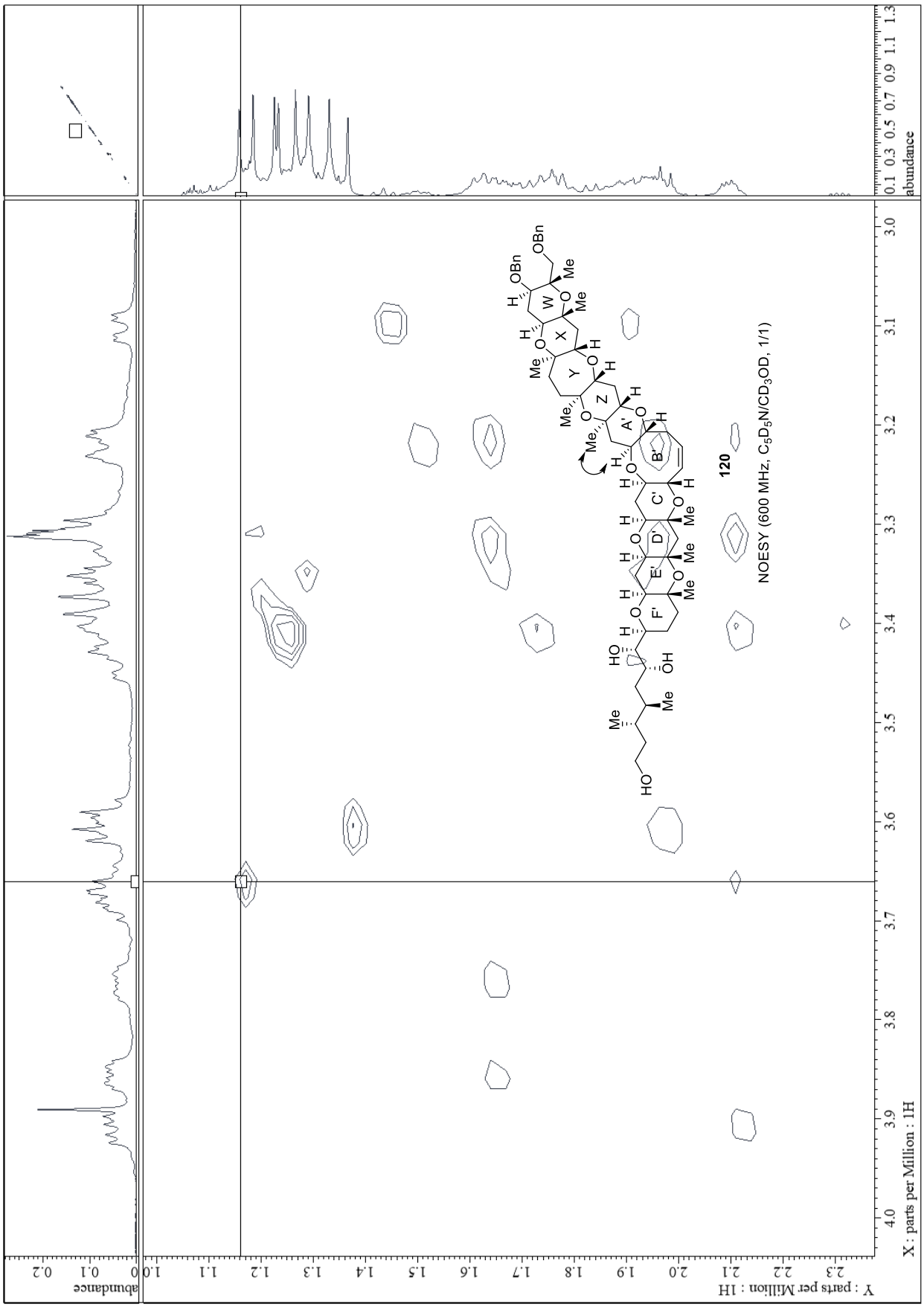

120
^{1}H NMR (600 MHz, C_5D_5N/CD_3OD, 1/1)
X : parts per Million : 1H
abundance


120
^{13}C NMR (150 MHz, C_5D_5N/CD_3OD, 1/1)
X : parts per Million : 13C
(thousandths)
1.459
16.635
16.664
21.566
21.949
26.497
27.933
34.214
35.660
37.115
39.126
48.940
53.957
61.205
70.215
71.776
72.436
73.442
74.179
74.725
75.414
77.693
78.784
79.646
84.213
84.501
124.130
124.332
124.494
124.667
124.782
128.477
136.884
137.047
137.210
149.580
149.752
149.934
150.135


120
NOE (600 MHz, C5D5N/CD3OD, 1/1)
X : parts per Million : 1H
(thousandths)


120
NOE (600 MHz, C5D5N/CD3OD, 1/1)
X : parts per Million : 1H
(thousandths)


NOESY (600 MHz, C5D5N/CD3OD, 1/1)
120
X : parts per Million : 1H
Y : parts per Million : 1H
abundance


NOESY (600 MHz, C5D5N/CD3OD, 1/1)
120
Y : parts per Million : 1H
X : parts per Million : 1H
abundance

Acknowledgments

This research has been carried out under the direction Professor Tohru Oishi at the Department of Chemistry, Graduate school of Science, Kyushu University.

I would first like to thank Professor Tohru Oishi for giving him a chance to study this field, encouragements, guidance and supports on this dissertation for six years. I would also like to thank him for his supports on my thesis.

I would like to thank Dr. Kohei Torikai. He gave me a lot of helpful information and guidance on daily research. I would also like to Dr. Makoto Ebine for providing valuable advice on this study, although it was only for short period from 2013 to 2018.

I would like to thank Associate Professor Keiichi Konoki (Tohoku University). He performed activity evaluations and gave me valuable data.

I would like to thank all members in Oishi's laboratory for their advice and disucussion to this study. Especially, Mr. Hasegawa Taishi, Ms. Tomomi Baba, Ms. Erina Ishikawa, Ms. Riho Marubayashi, Mr. Yoshiki Toma, and Mr. Naoya Osato helped me to provide valuable samples and data. I would also like to thank all members at the Department of Chemistry, Graduate school of Science, Kyushu University. They made my student life meaningful.

Finally, I would like to express to my father, mother, and brother my deepest gratitude. They have always been supportive and no matter what I have ever done they have always been there help me along the way.

To everyone else that I did not mention, thank for making may time at Fukuoka so enjoyable. I wish everyone nothing but the best in future.

Hisaaki Onoue

Fukuoka, Japan
March 2018

List of publications

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Synthesis and Biological Activity of the QRS Ring System of Maitotoxin

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Maitotoxin (MTX) is a ladder-shaped polyether produced by an epiphytic dinoflagellate. As a part of our structure–activity relationship studies using synthetic partial structures of MTX, the QRS ring comprising a 6/6/7 tricyclic system was synthesized through stereoselective construction of five contiguous stereogenic centers on the Q ring via i) coupling of a Weinreb amide and a furyllithium, followed by ii) Noyori asymmetric transfer hydrogenation, iii) the Achmatowicz reaction, iv) chemoselective methylation of a methyl acetal in the presence of a carbonyl group by treatment with Me_2Zn/BF_3·OEt_2, v) highly diastereoselective dihydroxylation, and vi) ring expansion of a six-membered to a seven-membered ring ketone. The synthetic specimen inhibited MTX-induced Ca^{2+} influx with an IC_{50} value of 44 μM.

Maitotoxin (MTX) is one of a series of ladder-shaped polyethers produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*.[1–3] MTX is a highly toxic secondary metabolite, and also causes a profound influx of Ca^{2+} in all cell types examined to date, including rat glioma C6 cells.[4] Although it has been suggested that Ca^{2+} channels or Ca^{2+} pumps are the target proteins of MTX,[5] attempts to identify the target proteins using molecular probes derived from the natural product have been hampered because of nonspecific binding and the limited availability of MTX from natural sources.[6]

We hypothesized that an inhibitor of Ca^{2+} influx activity induced by MTX could bind competitively and act as a molecular probe to identify the target protein. To examine synthetic partial structures of MTX[7,8] as inhibitor candidates, structure–activity relationship studies were carried out, and we found that the W–C′ ring[9] and the C′–F′ ring[10] system, corresponding to the hydrophobic section of MTX (Figure 1), elicited inhibitory activity against MTX-induced Ca^{2+} influx in rat glioma C6 cells with IC_{50} values of 30 μM[6] and 59 μM,[10] respectively. We also found, serendipitously, that an artificial heptacyclic ladder-shaped polyether possessing a 6/6/7 iterative system elicited more potent inhibitory activity than the partial structures (IC_{50} = 2 μM).[11] Based on these results, we focused on the remaining hydrophobic section of MTX, the QRS ring comprising a 6/6/7 ring system. Herein, we report the synthesis of the QRS ring system of MTX (**1**, Figure 1), and provide details of its inhibitory activity against MTX-induced Ca^{2+} influx.

While carrying out synthetic studies of ladder-shaped polyethers, we developed a method for synthesizing a 6/6/6 tricyclic ether corresponding to the ABC ring system of yessotoxin[12] via coupling of a triflate and a furan derivative followed by the Achmatowicz reaction.[13] We planned to extend this method to synthesize the QRS ring system, using Weinreb

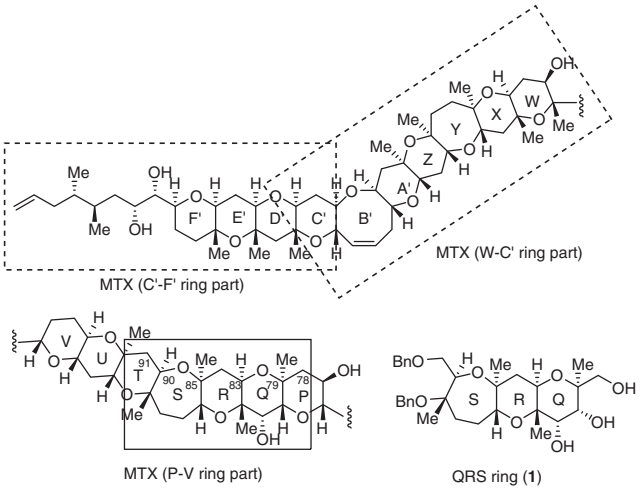
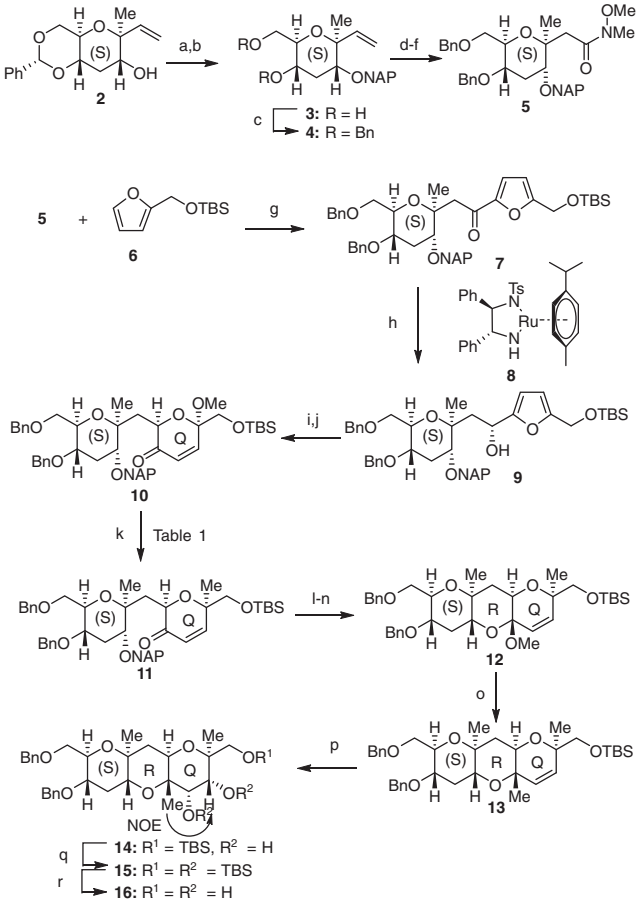


Figure 1. Partial structures of the hydrophobic section of MTX, and structure of the QRS ring system **1**.

amide **5** for coupling with furan **6** instead of a triflate (Scheme 1 and see also Supporting Information (SI)).

Synthesis of Weinreb amide **5** commenced with the protection of the known secondary alcohol **2**[14] as an NAP ether, and hydrolysis of the benzylidene acetal to afford diol **3** (65%, two steps), which was protected as benzyl ether **4** (quant). Hydroboration of olefin **4** with 9-BBN to give a primary alcohol (85%) was followed by TEMPO oxidation using NaOCl and $NaClO_2$ as co-oxidants[15] to furnish a carboxylic acid, which was subjected to condensation with *N*,*O*-dimethylhydroxyamine using EDC to yield Weinreb amide **5** (75%, two steps). Amide **5** was then coupled with 2-furyllithium prepared from furan derivative **6** by treatment with *s*-BuLi in THF at −78 °C to furnish ketone **7** (65%). Noyori asymmetric transfer hydrogenation of **7** using catalyst **8**[16] afforded furfuryl alcohol **9** (77%) as a single diastereomer with recovery of **7** (20%). The Achmatowicz reaction[13] of **9** by treatment with NBS to give a hemiacetal, followed by conversion to methyl acetal by treatment with methyl orthoformate and BF_3·OEt_2 in Et_2O at 0 °C,[17] furnished **10** (93% for two steps) as a major isomer, with an inseparable mixture of its diastereomer (α:β = 2.5:1). Chemoselective methylation of **10** was examined, and the results are summarized in Table 1. When Me_3Al was used as a reagent (Entry 1), methylation occurred selectively at the carbonyl group to give tertiary alcohol **17** (81%) with an inseparable mixture of its C79-diastereomer. Chemoselective methylation of the methyl acetal was achieved in a stereoselective manner by using Me_2Zn instead of Me_3Al in the presence of BF_3·OEt_2[18] as a Lewis acid (Entry 2) to afford enone

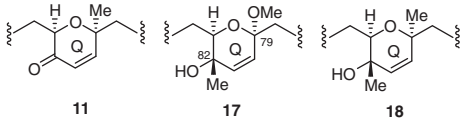


Scheme 1. Synthesis of the precursor of the QRS ring system **16**. (a) NAPBr, NaH, DMF, rt, 1.5 h; (b) *p*-TsOH·H_2O, CH_2Cl_2, MeOH, H_2O, rt, 3.5 h, 65% (two steps); (c) BnBr, NaH, DMF, rt, 80 min, quant; (d) 9-BBN, THF, rt, 3 h; then H_2O_2 aq, NaOH aq, rt, 16 h, 85%; (e) TEMPO, NaOCl, $NaClO_2$, pH 7 buffer, MeCN, 35 °C, 26 h; (f) MeNH(OMe)·HCl, EDC·HCl, DMAP, Et_3N, CH_2Cl_2, rt, 2.5 h, 75% (two steps); (g) **6**, *s*-BuLi, THF, −78 °C, 30 min; then **5**, THF, −78 °C, 1 h, 65%; (h) **8** (20 mol %), HCO_2Na, TBAC, CH_2Cl_2, H_2O, 40 °C, 22 h, 77% (recovery of **7**: 20%); (i) NBS, NaOAc, $NaHCO_3$, THF, H_2O, 0 °C, 1.5 h; (j) $(MeO)_3CH$, BF_3·OEt_2, Et_2O, 0 °C, 1 h, 93% (two steps); (k) Me_2Zn, BF_3·OEt_2, CH_2Cl_2, rt, 3.2 h, 80%; (l) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 1.8 h, 89%; (m) $(MeO)_3CH$, CSA, CH_2Cl_2, MeOH, rt, 1 h; (n) TBSCl, Im, DMF, rt, 40 min, 95%; (o) Me_3Al, BF_3·OEt_2, CH_2Cl_2, −20 °C, 30 min, 77%; (p) OsO_4, NMO, citric acid monohydrate, *t*-BuOH, acetone, H_2O, rt, 23 h, 86%; (q) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 to 40 °C, 15 h, 93%; (r) TBAF, THF, rt to 50 °C, 10 h, 87%.

11 as a single isomer (80%). In contrast, when Me_3Al was used instead of Me_2Zn in the presence of BF_3·OEt_2 (Entry 3), both the carbonyl and methoxy groups reacted, furnishing **18** (67%). Thus, chemoselective and stereoselective methylation was achieved by choosing appropriate reagents.

Next, conversion of ketone **11** to tricyclic ether **15**, corresponding to the QR(S) ring, was carried out (Scheme 1). After removal of the NAP group with DDQ (89%), the resulting hydroxy ketone was converted to methyl acetal **12** by treatment with methyl orthoformate in the presence of CSA. Under the acidic reaction conditions, the TBS group was removed, but the resulting primary alcohol was recovered to give **12** (95%) by treatment with TBSCl and imidazole. Methylation of methyl

Table 1. Chemoselective methylation of methyl acetal **10**

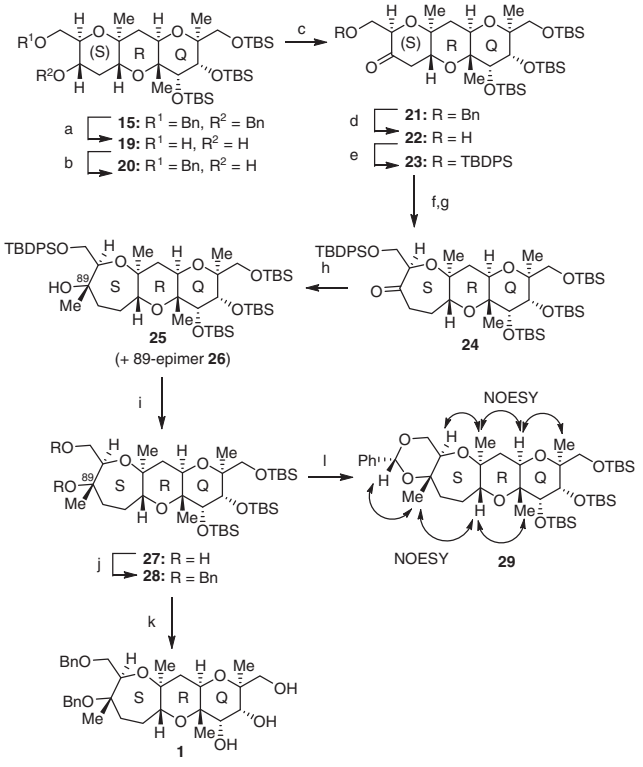


Entry	Reagent	Lewis acid	Temp /°C	Time /min	Yield/%		
					11	**17**	**18**
1	Me_3Al	none	−20	50	—	81	—
2	Me_2Zn	BF_3·OEt_2	rt	190	80	—	—
3	Me_3Al	BF_3·OEt_2	0	30	—	—	67

acetal **12** with Me_3Al and BF_3·OEt_2 at −20 °C proceeded smoothly to afford **13** as a single isomer (77%).

One of the key steps of the synthesis—dihydroxylation of the sterically hindered olefin **13**—was examined. Although dihydroxylation of **13** was too sluggish under the standard catalytic conditions using OsO_4 and NMO,[19] the reaction proceeded stereoselectively in the presence of citric acid[20] to afford **14** (86%) as a single isomer (determined by NOE experiments). The stereochemical outcome may be explained by the hypothesis that the reagent approached from the β-side of the olefin, avoiding the bulky $TBSOCH_2$ group. Protection of the diol by treatment with TBSOTf and 2,6-lutidine gave TBS ether **15** (93%). For the evaluation of biological activity, triol **16** was prepared from **15** by treatment with TBAF (87%).

The remaining task, ring-expansion to give the seven-membered S ring, was achieved as shown in Scheme 2. Hydrogenolysis of benzyl ether **15** gave diol **19**, and selective protection of the primary alcohol as a benzyl ether by treatment with *n*-Bu_2SnO and benzyl bromide furnished **20** (88%, two steps). Oxidation with Dess–Martin periodinane (DMP) furnished ketone **21** (90%). A ring expansion reaction of **21** was carried out using $TMSCHN_2$ in the presence of BF_3·OEt_2,[21] but a complex mixture was formed and none of the desired product was detected, although removal of the benzyl group was observed. Therefore, benzyl ether **21** was converted to TBDPS ether **23** via hydrogenolysis and protection of the resulting primary alcohol **22** (95%, two steps). The ring expansion reaction of **23** was then carried out using $TMSCHN_2$ in the presence of BF_3·OEt_2. Fortunately, the desired seven-membered ring ketone **24** was obtained (52%, two steps) after treatment with PPTS in dichloromethane/methanol. The final stage, stereoselective methylation of the seven-membered ketone **24**, was difficult. Treatment of **24** with methylmagnesium bromide under the conditions reported by Murai[22] using toluene as a solvent resulted in the formation of the desired tertiary alcohol **25** and its 89-epimer **26** in 87% yield in a 1:1.3 ratio. After considerable experimentation, we found that the selectivity of **25** was improved by using a bulky aluminum reagent (MAD), as reported by Yamamoto,[23] to afford **25** (63%) and the C89-epimer **26** (30%). Selective removal of the TBDPS group of **25** under the basic conditions using sodium hydroxide furnished diol **27** (97%), and protection of the resulting diol as a benzyl ether gave **28** (78%). Finally, removal of the TBS groups with TBAF afforded the QRS ring system of MTX (**1**) (86%). The structure of **1** was unambiguously determined by NOESY experiments on benzylidene acetal **29**, which was derived from diol **27** by treatment with $PhCH(OMe)_2$ in the presence of *p*-TsOH (54%).



Scheme 2. Synthesis of the QRS ring system **1**. (a) H_2, $Pd(OH)_2/C$, EtOAc, rt, 100 min; (b) BnBr, *n*-Bu_2SnO, TBAI, MS4A, benzene, reflux, 5 h, 88% (two steps); (c) DMP, Py, CH_2Cl_2, rt, 20 min, 90%; (d) H_2, $Pd(OH)_2/C$, EtOAc, rt, 50 min; (e) TBDPSCl, Im, DMF, rt, 1.5 h, 95% (two steps); (f) $TMSCHN_2$, $BF_3 \cdot OEt_2$, MS4A, CH_2Cl_2, −78 °C, 40 min; (g) PPTS, CH_2Cl_2, MeOH, rt, 6 h, 52% (two steps); (h) Me_3Al, BHT, toluene, rt, 1 h; **24**, MeLi, −78 °C, 1.5 h, 63% (89-epimer **26**, 30%); (i) NaOH, MeOH, THF, rt, 3.2 h, 97%; (j) BnBr, NaH, TBAI, MS4A, DMF, rt, 5 h, 78%; (k) TBAF, THF, 50 °C, 5.7 h, 86%; (l) $PhCH(OMe)_2$, *p*-$TsOH \cdot H_2O$, DMF, CH_2Cl_2, rt, 5.5 h, 54%.

The biological activity of 6/6/7 tricyclic ether **1** was evaluated (see SI). A 1 nM solution of MTX induced approximately 10-fold Ca^{2+} influx against rat C6 glioma cells, and this value was defined as 100%. The QRS (tricyclic) ring system blocked Ca^{2+} influx activity in a dose-dependent manner, and the IC_{50} value was estimated to be 44 μM, which is comparable to the values of the W–C′ (heptacyclic) ring and the C′–F′ (tetracyclic) ring system. It is interesting to note that the IC_{50} value of 6/6/6 tricyclic ether **16** (240 μM) was greater than **1**, indicating that the 6/6/7 ring system may be a suitable interacting motif against the target protein of MTX.

In conclusion, stereoselective synthesis of the QRS ring system **1** of MTX was achieved and the QRS ring system inhibited MTX-induced Ca^{2+} influx with an IC_{50} value of 44 μM. The design and synthesis of partial structures of MTX with more potent inhibitory activity against MTX-induced Ca^{2+} influx are currently underway in our laboratory.

We are grateful to Prof. Michio Murata of Osaka University for generous gift of maitotoxin, and Prof. Mari Yotsu-Yamashita of Tohoku University for discussion on the biological activity of the synthetic fragments. This work was supported by a Grant-in-Aid for Scientific Research (A) (No. 24245009) from the JSPS, a Grant-in-Aid for Scientific Research on Innovative Areas (No. 24106735) from MEXT, JST ERATO Lipid Active Structure, and the Asahi Glass Foundation.

Supporting Information is available electronically on J-STAGE.

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Syntheses and Biological Activities of the LMNO, *ent*-LMNO, and NOPQR(S) Ring Systems of Maitotoxin

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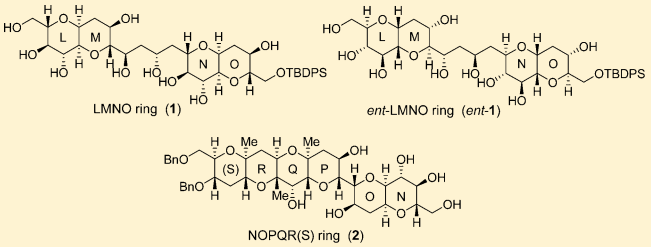
Supporting Information

ABSTRACT: Structure−activity relationship studies of maitotoxin (MTX), a marine natural product produced by an epiphytic dinoflagellate, were conducted using chemically synthesized model compounds corresponding to the partial structures of MTX. Both enantiomers of the LMNO ring system were synthesized via aldol reaction of the LM ring aldehyde and the NO ring ketone. These fragments were derived from a common cis-fused pyranopyran intermediate prepared through a sequence involving Nozaki−Hiyama−Kishi reaction, intramolecular oxa-Michael addition, and Pummerer rearrangement. The NOPQR(S) ring system, in which the original seven-membered S ring was substituted with a six-membered ring, was also synthesized through the coupling of the QR(S) ring alkyne and the NO ring aldehyde and the construction of the P ring via 1,4-reduction, dehydration, and hydroboration. The inhibitory activities of the synthetic specimens against MTX-induced Ca^{2+} influx were evaluated. The LMNO ring system and its enantiomer induced 36 and 18% inhibition, respectively, at 300 μM, whereas the NOPQR(S) ring system elicited no inhibitory activity.



INTRODUCTION

Maitotoxin (MTX) is one of the causative toxins produced by the epiphytic dinoflagellate *Gambierdiscus toxicus* in association with seafood poisoning.[1] MTX exhibits Ca^{2+} influx activity at extremely low concentrations (nM range) in all cell types that have ever been reported.[2,3] The molecular structure of MTX was determined to be a large ladder-shaped polyether that possesses 32 cyclic ethers and 98 stereogenic centers (Figure 1).[4−6] MTX is comprised of two regions, hydrophobic (red) and hydrophilic (blue), that are distinguished by the absence or presence, respectively, of hydroxy groups and sulfate esters. The unique molecular structure of MTX has attracted considerable attention in the synthetic community.[7,8]

In an effort to develop inhibitors against MTX-induced Ca^{2+} ion influx, we hypothesized that the partial structures corresponding to the hydrophobic parts of MTX might competitively bind to the target proteins to inhibit the Ca^{2+} ion influx induced by MTX (Figure 2). To test this hypothesis, we synthesized partial structures corresponding to the hydrophobic regions, including the W−C′ ring,[9,10] the C′D′E′F′ ring,[11] and the QRS ring[12] systems of MTX (Figure 1). We found that these compounds inhibited MTX-induced Ca^{2+} influx with IC_{50} values of 30, 59, and 44 μM, respectively. An analogue of the QRS ring system, the QR(S) ring system in which the original seven-membered S ring was substituted with a six-membered ring, was also synthesized. The simplified tricyclic system was found to elicit inhibitory activity with an IC_{50} value of 240 μM.[12] In addition to finding activity among the partial structures of MTX, we serendipitously found that a hydrophobic artificial ladder-shaped polyether (ALP7B) elicited potent inhibitory activity (IC_{50} = 2 μM).[13]

Similar experiments were carried out by Nicolaou et al., who reported that certain hydrophobic regions of MTX, the Q-A′ ring, and the C′−F′ ring showed inhibitory activity against MTX-induced Ca^{2+} influx with IC_{50} values of 3.2 and 2.3 μM, respectively.[8j] On the other hand, Konoki et al. reported that partial structures corresponding to the hydrophilic region of MTX (the *ent*-LMNO ring and the *ent*-EFGH ring) inhibited Ca^{2+} influx activity, although the activity was much lower than that of the hydrophobic part (Figure 3).[2] It should be noted that these partial structures were antipodal to the natural product; therefore, it would be intriguing to characterize the biological activities of the corresponding natural enantiomers.

Herein, we describe a stereoselective synthesis of the LMNO ring system (**1**) in an effort to elucidate the inhibitory

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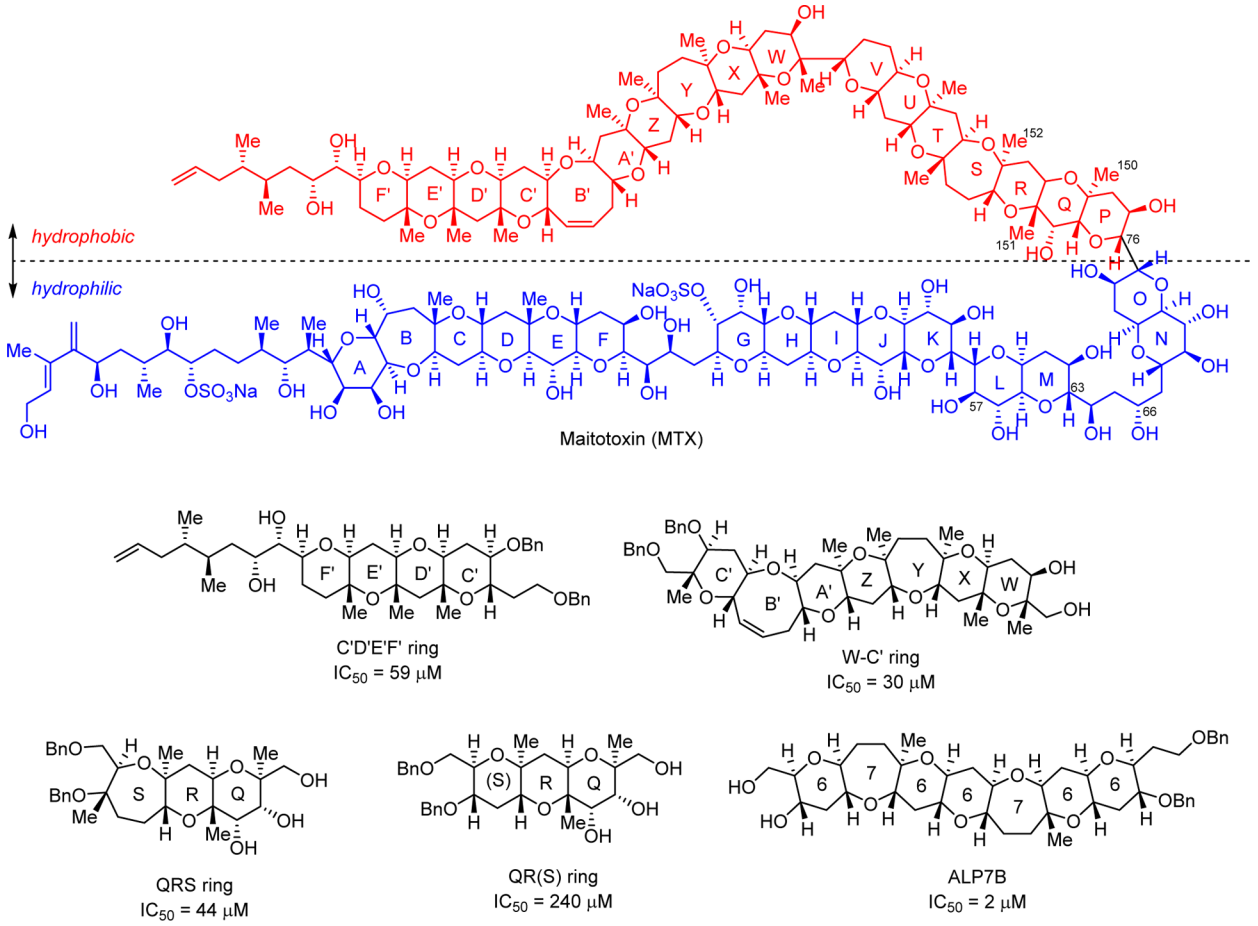

Figure 1. Structure of maitotoxin (MTX), the synthetic partial structures of MTX, and the artificial ladder-shaped polyether.

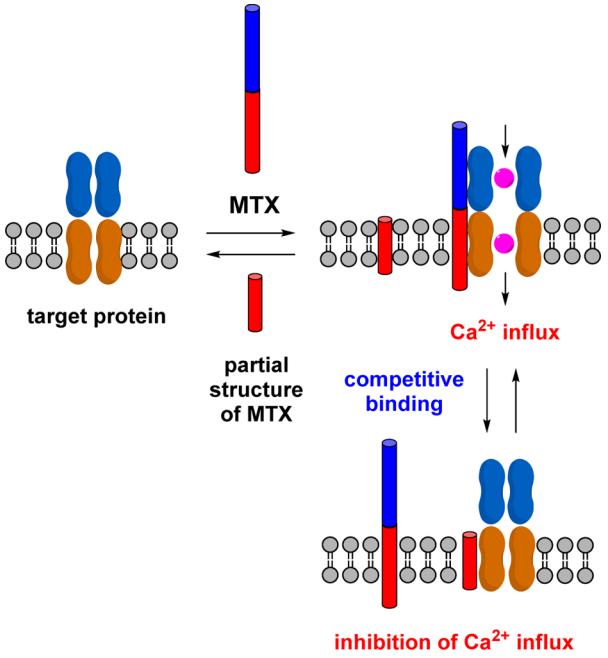

Figure 2. Hypothetical scheme for the inhibition of MTX-induced Ca^{2+} influx activity by partial structures corresponding to the hydrophobic part of MTX.

activities against MTX-induced Ca^{2+} influx because the biological activities of the LMNO ring system were elucidated

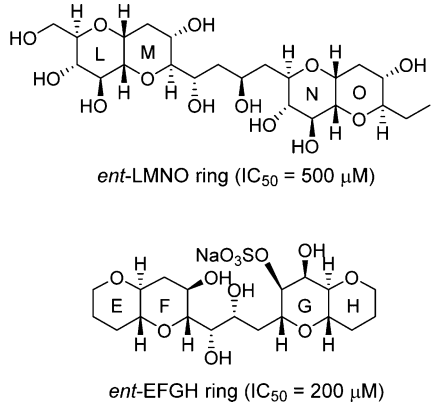

Figure 3. Reported synthetic partial structures of MTX corresponding to the hydrophilic part (*ent*-LMNO and *ent*-EFGH ring system) and their IC_{50} values against MTX-induced Ca^{2+} influx.

only for its enantiomeric synthetic fragment (Figure 4). For elucidating whether the biological activity is due to the specific interaction with the target protein(s), the complete enantiomer of **1** (*ent*-**1**) was also synthesized to permit a comparison with **1**. Although the synthesis of the LMNO ring system of MTX has been reported previously by the Nicolaou group[8e] and its enantiomer has been described by the Tachibana[5b] and Kishi groups,[6a] there is no report to compare the biological activity between the enantiomers. We also report a synthesis of the NOPQR(S) ring system (**2**) corresponding to the border region between the hydrophobic

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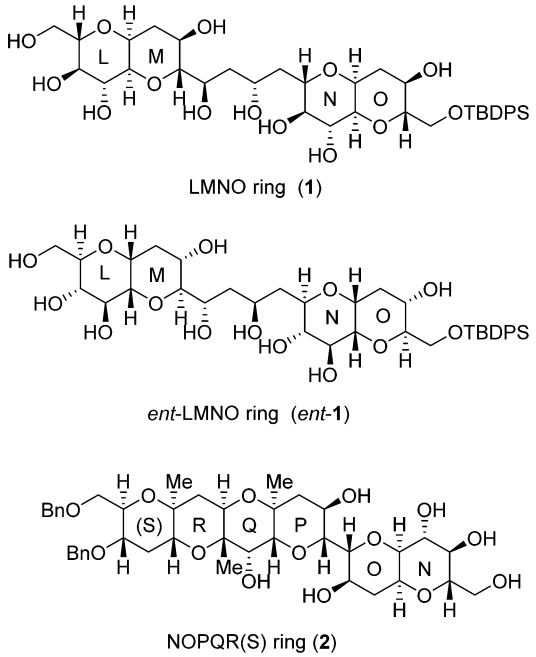


Figure 4. Structures of the LMNO (**1**) and its enantiomer (*ent*-**1**) and the NOPQR(S) ring system (**2**) of MTX.

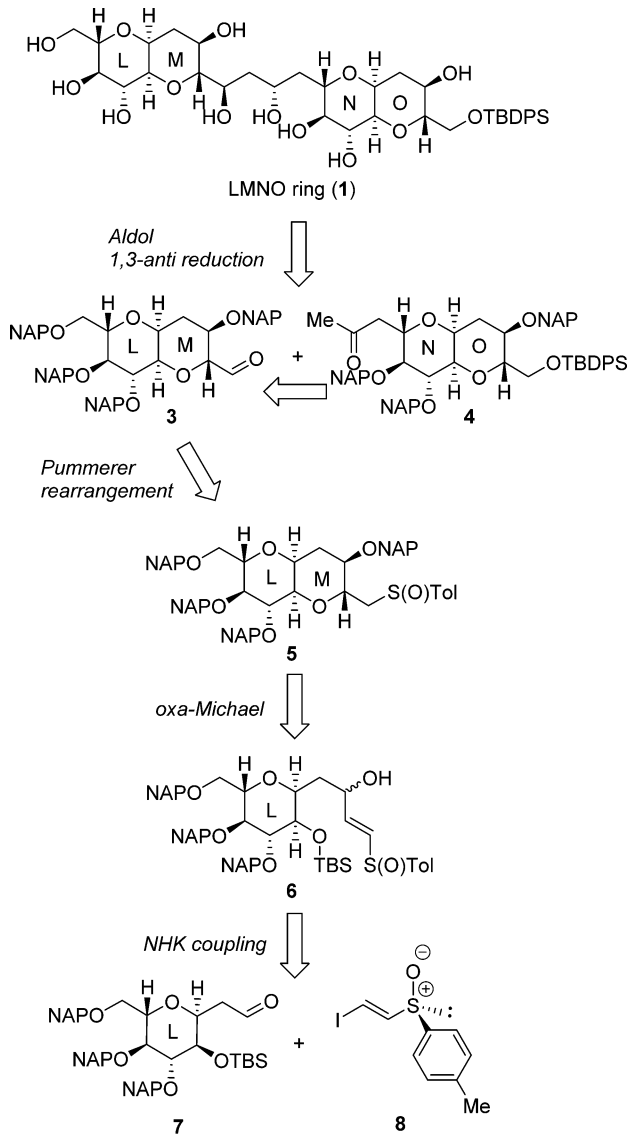
and hydrophilic regions of MTX to investigate the possibility that the combination of both the hydrophobic and hydrophilic regions could elicit biological activity in a synergistic or counteracting manner.

RESULTS AND DISCUSSION

Synthesis Plan. Synthesis plans of the LMNO ring system (**1**) and the NOPQR(S) ring system (**2**) of MTX are shown in Schemes 1 and 2, respectively. Target compound **1** would be derived from the LM ring aldehyde **3** and the NO ring methyl ketone **4** via an aldol reaction, followed by the 1,3-*anti* selective reduction[14] of a β-hydroxy ketone, as reported by Tachibana et al. (Scheme 1),[5b] whereas Nicolaou et al.[8e] used the Horner–Wadsworth–Emmons reaction, and Kishi et al.[6a] used the 1,3-dipolar cycloaddition reaction for the coupling reaction. The LM ring **3**, which was envisaged to be a precursor to the NO ring **4**, could be derived from the L ring aldehyde **7** and known sulfoxide **8**[15] through the successive Nozaki–Hiyama–Kishi (NHK) reaction[16] to give α,β-unsaturated sulfoxide **6** followed by an intramolecular oxa-Michael addition[17] and Pummerer rearrangement.[18,19] Although similar oxa-Michael cyclization (conjugate ester) was reported by Kishi et al.,[6a] an advantage of this strategy is to use the sulfoxide, which acted as both an electron-withdrawing group for the oxa-Michael addition as well as a precursor to the Pummerer rearrangement. This approach could reduce the number of steps needed to construct the M ring; there is no precedent describing the use of sulfoxide **8** for the NHK reaction to our knowledge. The *ent*-LMNO ring system (*ent*-**1**) is to be synthesized in an analogous sequence starting from *ent*-**7**.

On the other hand, it was envisaged that the synthesis of the NOPQR(S) ring system **2** would be achieved via construction of the P ring through the coupling of the QR(S) and NO ring systems (Scheme 2). Dihydropyran **9**, the precursor of **2**, could be derived from ynone **10** through the coupling of the QR(S) ring alkyne **11** derived from

Scheme 1. Synthesis Plans of the LMNO Ring System (1) of MTX



known **12**[12] and the NO ring aldehyde **3** (common intermediate with the LM ring).

Synthesis of the L-Ring. The L-ring **29**, a precursor to aldehyde **7**, was synthesized according to the procedure reported by Nicolaou et al.[8e] with the exception that the secondary hydroxy groups at C57 and C58 were protected with NAP rather than Bn for selective removal of the NAP group in the final step (Scheme 3). The hydroxy group of amide **13**[20] was protected as a NAP ether by treatment with NaH and NAPBr in DMF to afford **14** in 97% yield. Amide **14** was then treated with 2-lithiofuran generated from furan and *n*-BuLi at −78 °C to furnish furylketone **15** in 97% yield. The ketone was converted to chiral secondary alcohol **17** in 99% yield by a Noyori asymmetric hydrogen transfer reaction using ruthenium catalyst (*S*,*S*)-**16** and HCO_2Na as a reductant.[21] An Achmatowicz rearrangement[22,8c] of furfuryl alcohol **17** with NBS, followed by acylation of the resulting hemiacetal with PvCl, afforded pivaloate **18** in 62% yield via two steps with the concomitant formation of its β-anomer in 28% yield. A Luche reduction[23] of enone **18** resulted in the formation of alcohol **19** as a single isomer, which was

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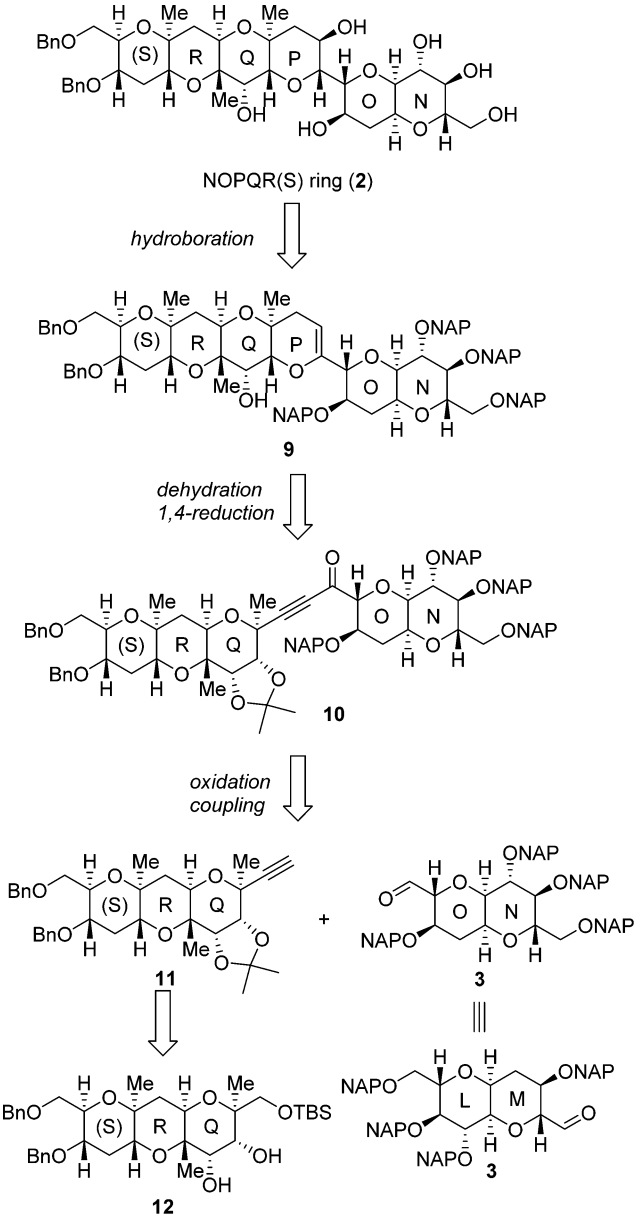
Scheme 2. Synthesis Plans of the NOPQR(S) Ring System (2) of MTX



protected as NAP ether **20** in 86% yield via two steps. Dihydroxylation of olefin **20** furnished α-diol **21** as a single isomer in 95% yield, and the equatorial hydoxy group was selectively protected as a NAP ether via stannylidene to afford **22** in 90% yield with the concomitant formation of its regioisomer in 6% yield.[24] After removing the Pv group, the resulting diol **23** was protected as an acetate by treatment with Ac_2O in pyridine to furnish **24** in 94% yield in two steps. *C*-glycosylation of acetate **24** using allylsilane in the presence of TMSOTf proceeded stereoselectively to afford **25** in 74% yield.[25] In this reaction, conversion of the Pv group to an Ac group was necessary because *C*-glycosylation of the corresponding pivaloate resulted in low yields. Removal of the acetyl group of **25** using K_2CO_3 as a base in methanol afforded **26** in 96% yield. Inversion of secondary alcohol **26** via a Mitsunobu reaction,[26] followed by methanolysis of the resulting 4-nitrobenzoate **27**, gave alcohol **28** in 76% yield via two steps. Protection of the secondary alcohol **28** as a TBS ether furnished key intermediate **29** in quantitative yield.

Synthesis of the LMNO Ring System. The synthesis of the LM ring **3** is illustrated in Scheme 4. Ozonolysis of terminal alkene **29** gave aldehyde **7**, which was subjected to the unprecedented Nozaki–Hiyama–Kishi (NHK) reaction[16] with iodoolefin **8**[15] possessing a *p*-toluenesulfoxide moiety. Fortunately, coupling product **6** was obtained in 77% yield as a mixture of the diastereomers at C62, whereas preliminary attempts to achieve the asymmetric version of the NHK reaction[27] were unsuccessful. Treatment of **6** with TBAF at 50 °C removed the TBS group and concomitantly promoted the intramolecular oxa-Michael addition of the resulting alkoxide to give desired isomer **30** in 43% yield and its C63-epimer **31** in 39% yield, respectively. The structures of these compounds were determined by NOE experiments (Figure 5). The stereochemistry at C63 was presumably controlled by the favored transition state A compared over B, as shown in Figure 6. Epimer **31** was converted to **30** through a Dess–Martin oxidation of the alcohol, followed by reduction of resulting ketone **32** with $NaBH_4$ at −78 °C in 65% yield for two steps. Thus, the M ring was constructed from the L ring **7** in only two steps (four steps, including the conversion of the C63 epimer), and the resulting sulfoxide is directly used as a precursor for the subsequent Pummerer rearrangement.[18,19] After protecting secondary alcohol **30** with the NAP group in 84% yield, treatment of the resulting **5** with trifluoroacetic anhydride in the presence of pyridine,[28] followed by hydrolytic workup, afforded aldehyde **3** in 74% yield, which corresponded to not only the LM ring but also the NO ring system.

We next moved on to the synthesis of methyl ketone **4** and the LMNO ring system (**1**) as shown in Scheme 5. Reduction of aldehyde **3** with $NaBH_4$ furnished alcohol **33** in 98% yield, and the resulting primary hydroxy group was protected as TBDPS ether **34** in 87% yield. Treatment of **34** with $ZnCl_2$ in Ac_2O/AcOH[29] resulted in the selective removal of the primary NAP group with concomitant acetylation to form acetate **35** in 90% yield. Removal of the acetyl group of **35** by methanolysis with K_2CO_3 furnished primary alcohol **36** in 95% yield, which was transformed to nitrile **38** via mesylate **37** in quantitative yield in two steps. Attempts to convert nitrile **38** into methyl ketone **4** by treatment with MeMgBr or MeLi, followed by hydrolytic workup, were unsuccessful. The yields were low with significant decomposition and recovery of the starting material. On the other hand, treatment of **38** with Me_3Al in the presence of $Ni(acac)_2$ as a catalyst provided **4** in 91% yield.[30]

The next transformation was a crucial step in the synthesis: coupling of the LM ring (**3**) and the NO ring (**4**) using an aldol reaction. The yield of a similar transformation was reported to be 37% by Tachibana et al.[5b] Although the aldol reaction was unsuccessful under the reaction conditions reported in the literature, treatment of methylketone **4** with LHMDS, followed by the addition of aldehyde **3**, furnished the desired hydroxy ketone **39** in a low yield (20%) with the concomitant formation of byproducts containing its C64-epimer (10%). Although the yield of the aldol reaction should be improved, alternative approaches were unsuccessful using the Mukaiyama aldol reaction[31] and aldol surrogate approach reported by Trost.[32] The stereoselective reduction of β-hydroxyketone **39** with Saksena–Evans reagent[14] gave 1,3-*anti*-diol **40** as an inseparable mixture with the C66-epimer

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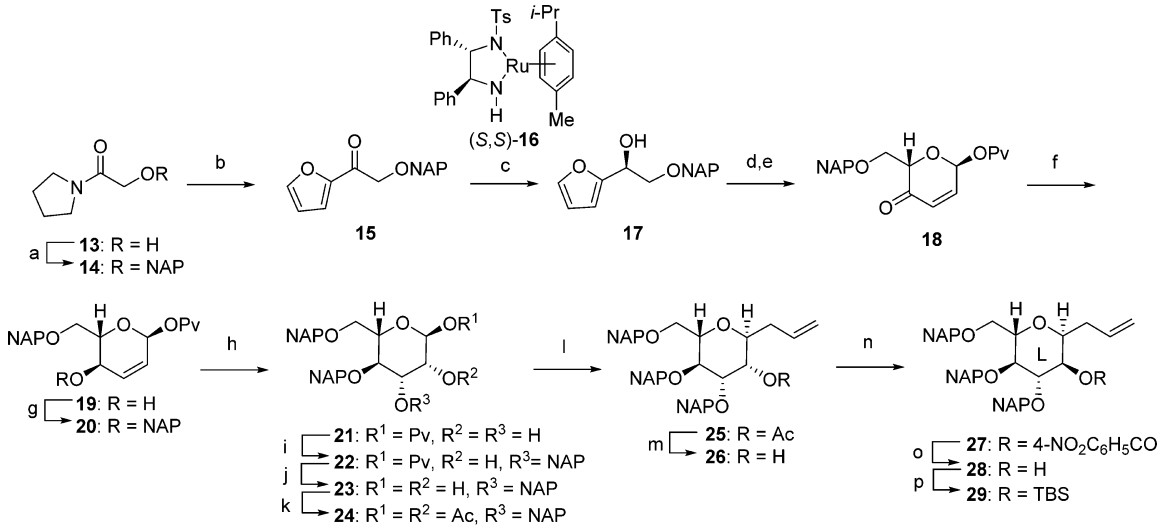
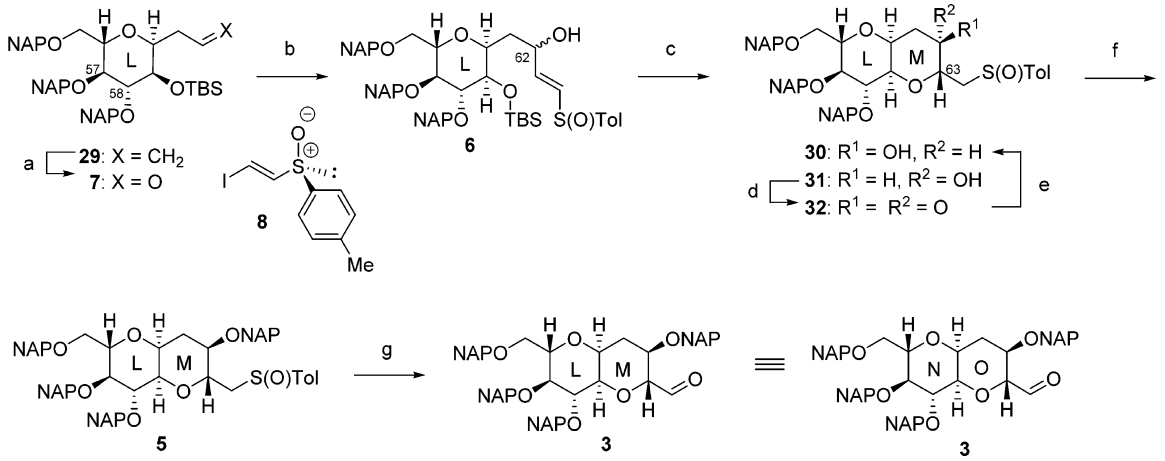
Scheme 3. Synthesis of the L-Ring 29[a]



[a](a) NAPBr, NaH, DMF, rt, 8 h, 97%; (b) furan, *n*-BuLi, THF, 0 °C, 30 min; **14**, −78 °C, 1 h, 97%; (c) (*S*,*S*)-**16**, HCO_2Na, TBAC, CH_2Cl_2, H_2O, rt, 1 h, 99%; (d) NBS, NaOAc, $NaHCO_3$, THF, H_2O, 0 °C, 1 h; (e) PvCl, Et_3N, DMAP, CH_2Cl_2, −78 °C, 30 min, 62% (2 steps); (f) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, CH_2Cl_2, MeOH, −78 °C, 1 h; (g) NAPBr, TBAI, NaOH aq, toluene, rt, 4 h, 86% (2 steps); (h) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone, H_2O, rt, 12 h, 95%; (i) *n*-Bu_2SnO, NAPBr, TBAI, benzene, reflux, 10 h, 90%; (j) NaOMe, THF, MeOH, rt, 2.2 h; (k) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 1.5 h, 94% (2 steps); (l) allylTMS, TMSOTf, CH_3CN, 0 °C, 2.5 h, 74%; (m) K_2CO_3, THF, MeOH, rt, 2 h, 96%; (n) 4-$NO_2C_6H_4CO_2H$, Ph_3P, DIAD, toluene, 70 °C, 1 h; (o) K_2CO_3, THF, MeOH, rt, 1 h, 76% (2 steps); (p) TBSCl, imidazole, DMF, 70 °C, 10.5 h, quant.

Scheme 4. Synthesis of the LM Ring System 3[a]



[a](a) O_3, CH_2Cl_2, MeOH, −78 °C, 11 min; Ph_3P, −78 °C to rt, 3.8 h, 82%; (b) **8**, $CrCl_2$, $NiCl_2$, DMF, THF, rt, 26.5 h, 77%; (c) TBAF, THF, 50 °C, 1 h; **30**: 43%; **31**: 39%; (d) DMP, $NaHCO_3$, CH_2Cl_2, rt, 80 min; (e) $NaBH_4$, THF, MeOH, −78 °C, 1.6 h, 65% (2 steps); (f) NAPBr, NaH, TBAI, DMF, 30 °C, 1 h, 84%; (g) TFAA, Py, CH_2Cl_2, MeCN, 0 °C, 1 h; KOAc, H_2O, rt, 30 min, 74%.

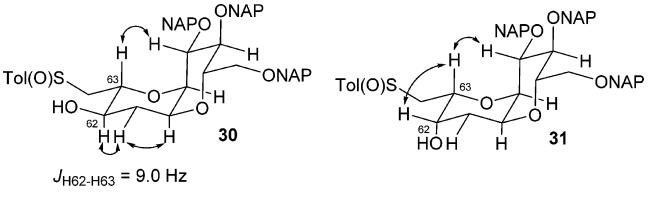


Figure 5. NOE experiments of compounds **30** and **31**.

(**40**:C66-epimer = 4.5:1) in 86% yield. Finally, the global removal of NAP groups from **40** with $Pd(OH)_2/C$ under a hydrogen atmosphere afforded the LMNO ring system **1** in 62% yield as a single isomer after purification using preparative TLC.

Synthesis of the *ent*-LMNO Ring System. In an analogous sequence, the enantiomer of the LMNO ring (*ent*-**1**) was synthesized from *ent*-**29** (Scheme 6), which was prepared from **15** via asymmetric reduction using (*R*,*R*)-**16**. Ozonolysis of terminal alkene *ent*-**29** furnished aldehyde *ent*-**7**. The NHK reaction[16] using iodoolefin **8**[15] furnished secondary alcohol **41** (a diastereomeric compound of **6** with respect to the chirality of the sulfoxide moiety) as a mixture of diastereomers at C62 in 94% yield. Successive removal of the TBAF group from **41** and intramolecular oxa-Michael addition gave desired isomer **42** (43%) and its C63-epimer **43** (39%), which was converted to **42** via an oxidation−reduction sequence (67%, two steps). Protection of the secondary alcohol as a NAP ether giving **44** (84%), followed by a Pummerer rearrangement,[28] furnished aldehyde *ent*-**3** (74%),

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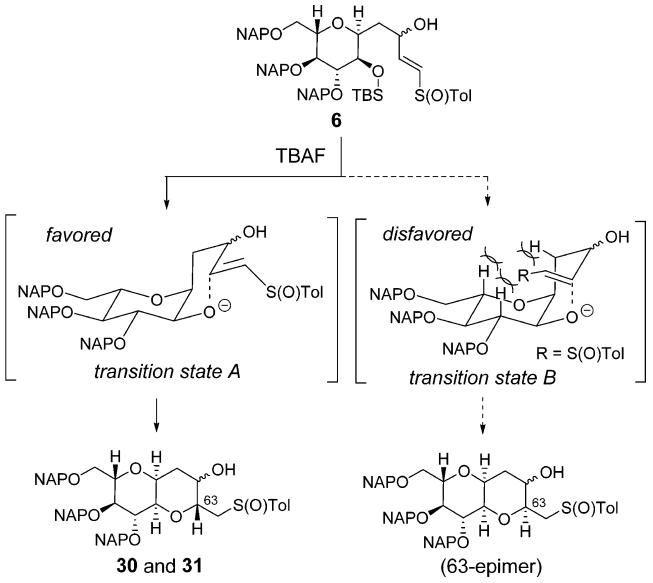


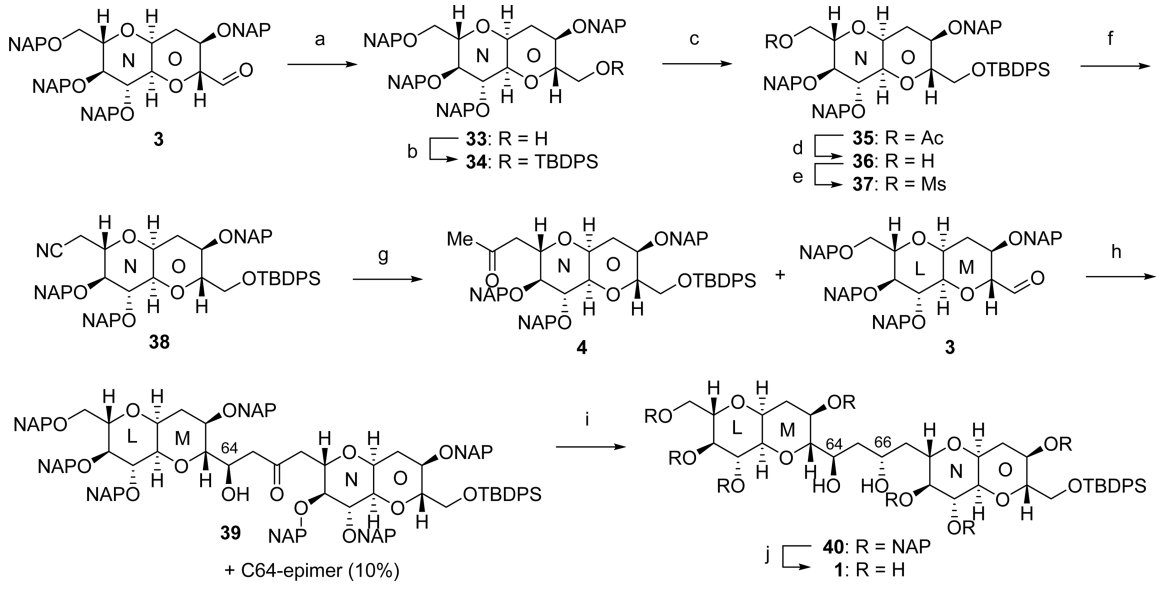
Figure 6. Stereochemical outcome of the intramolecular oxa-Michael reaction of **6**.

which was converted to methyl ketone *ent*-**4** via *ent*-**34**. Aldol reaction of the NO ring methyl ketone (*ent*-**4**) and the LM ring aldehyde (*ent*-**3**) furnished desired *ent*-**39** in 20% yield. Stereoselective reduction of *β*-hydroxyketone *ent*-**39** with Saksena–Evans reagent[14] gave 1,3-diol *ent*-**40**. Finally, global removal of the NAP groups afforded the LMNO ring system *ent*-**1** (62%) after purification using preparative TLC.

Synthesis of the NOPQR(S) Ring System. We next turned our attention to the synthesis of the NOPQR(S) ring system **2** from known compound **12**[12] (Scheme 7). Protection of diol **12** as an acetonide with 2,2-dimethoxypropane (97%), followed by removal of the TBS group of **45** with TBAF gave alcohol **46** in 98% yield. Oxidation of the primary alcohol in the presence of catalytic amounts of AZADOL[33] using $PhI(OAc)_2$ as a co-oxidant afforded an aldehyde, which was then treated with the Ohira–Bestmann reagent $AcC(N_2)P(O)(OMe)_2$[34] in the presence of Cs_2CO_3 as a base to furnish alkyne **11** in 77% yield in two steps. The coupling reaction of the QR(S) ring fragment **11** and the NO ring fragment **3** was then carried out. Treatment of terminal alkyne **11** with *n*-BuLi to generate the corresponding lithium acetylide, followed by the addition of aldehyde **3**, afforded a secondary alcohol as a mixture of diastereomers in a 2:1 ratio, which was then oxidized with MnO_2 to give ynone **10**. 1,4-Reduction of **10** with Stryker reagent $[CuH(PPh_3)]_6$[35] gave saturated ketone **47** in 63% yield in three steps. Methanolysis of acetonide **47** with *p*-TsOH·H_2O resulted in the formation of a mixture of a keto alcohol and a hemiacetal. Although dehydration to obtain dihydropyran derivative **9** by treatment with PPTS or *p*-TsOH·H_2O was unsuccessful, that with Nafion NR-50[36] afforded **9** in 69% yield in two steps. Hydroboration of olefin **9** with $BH_3{\cdot}SMe_2$, followed by an oxidative workup, furnished desired alcohol **48** as a single diastereomer. The stereochemistry of **48** was confirmed by NOE experiments. Finally, the synthesis of the NOPQR(S) ring system **2** was achieved through global removal of the NAP groups with DDQ in 37% yield in two steps.

Biological Activity. The biological activities of the synthetic specimens were evaluated.[2] A solution of 1 nM MTX induced a 10-fold increase in the Ca^{2+} influx compared to the control in rat C6 glioma cells, and this value was defined as 100% Ca^{2+} influx. Because the inhibitory activities of the LMNO, *ent*-LMNO, and NOPQR(S) ring systems were not so potent, the values are listed as inhibition percentages at 300 μM, not IC_{50} values, and the values were compared with those of the QR(S) and QRS ring system[12] (54 and 91% inhibition, respectively) as shown in Table 1.

Scheme 5. Synthesis of the LMNO Ring System 1[a]



[a](a) $NaBH_4$, THF, 0 °C, 30 min, 98%; (b) TBDPSCl, imidazole, DMF, rt, 1 h, 87%; (c) $ZnCl_2$, Ac_2O, AcOH, rt, 3 h, 90%; (d) K_2CO_3, THF, MeOH, rt, 1 h, 95%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (f) NaCN, DMF, MS4A, 80 °C, 17 h, quant (2 steps); (g) Me_3Al, $Ni(acac)_2$, toluene, rt, 91%; (h) **4**, LHMDS, MS4A, THF, −78 °C, 1.1 h; **3**, THF, −78 °C, 1 h, 20% (C64-epimer 10%); (i) $Me_4NHB(OAc)_3$, CH_3CN, AcOH, CH_2Cl_2, 0 °C to rt, 2 h, 86% (**39**:C66-epimer = 4.5:1); (j) H_2, $Pd(OH)_2$/C, EtOAc, MeOH, rt, 24 h, 62%.

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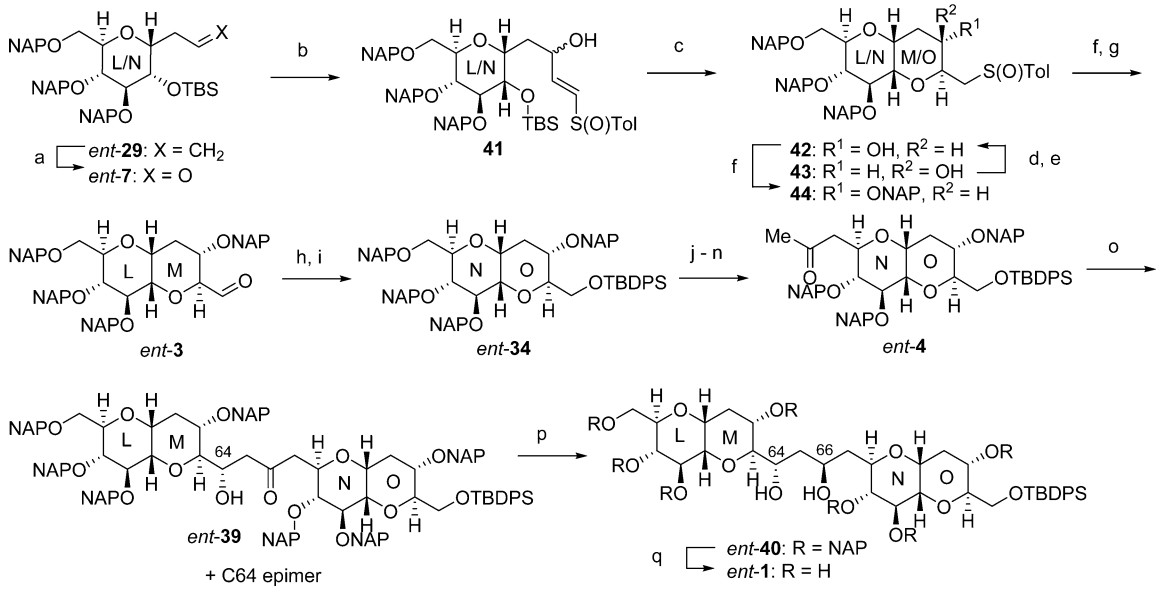
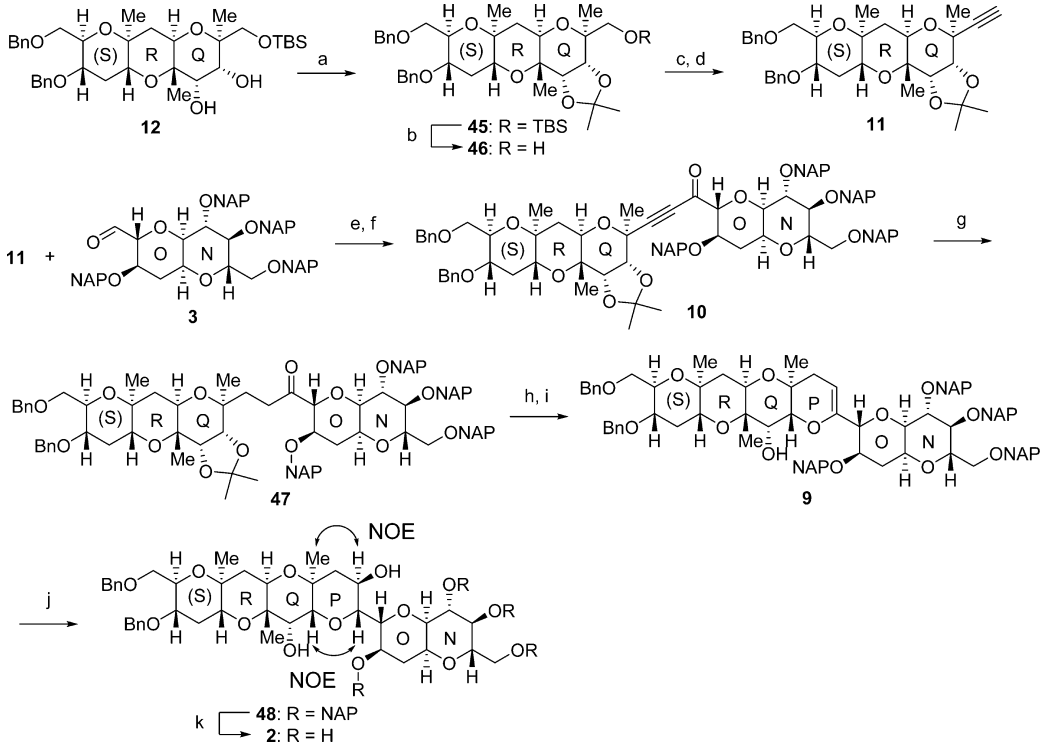
Scheme 6. Synthesis of the *ent*-LM/NO Ring System (*ent*-1)[a]



[a](a) O_3, CH_2Cl_2, MeOH, −78 °C, 3 min; Ph_3P, −78 °C to rt, 1 h, 93%; (b) **8**, $CrCl_2$, $NiCl_2$, DMF, THF, rt, 3 d, 94%; (c) TBAF, THF, 50 °C, 1 h; **42**: 43%; **43**: 39%; (d) DMP, CH_2Cl_2, rt, 30 min, 67%; (e) $NaBH_4$, THF, MeOH, −78 °C, 1 h, quant.; (f) NAPBr, NaH, TBAI, DMF, 30 °C, 1 h, 84%; (g) TFAA, Py, CH_2Cl_2, MeCN, 0 °C, 1 h; KOAc, H_2O, rt, 30 min, 74%; (h) $NaBH_4$, THF, 0 °C, 30 min, 98%; (i) TBDPSCl, imidazole, DMF, rt, 1 h, 87%; (j) $ZnCl_2$, Ac_2O, AcOH, rt, 3 h, 90%; (k) K_2CO_3, THF, MeOH, rt, 1 h, 95%; (l) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (m) NaCN, DMF, MS4A, 80 °C, 17 h, quant (2 steps); (n) Me_3Al, $Ni(acac)_2$, toluene, rt, 91%; (o) *ent*-**4**, LHMDS, MS4A, THF, −78 °C, 1.1 h; *ent*-**3**, THF, −78 °C, 1 h, 20%; (p) $Me_4NHB(OAc)_3$, CH_3CN, AcOH, CH_2Cl_2, 0 °C to rt, 1.9 h, 86% (*ent*-**40**:C66-epimer = 4.5:1); (q) H_2, $Pd(OH)_2/C$, EtOAc, MeOH, rt, 24.2 h, 62%.

Scheme 7. Synthesis of NOPQR(S) Ring System 2[a]



[a](a) 2,2-Dimethoxypropane, *p*-TsOH·H_2O, acetone, rt, 2.3 h, 97%; (b) TBAF, THF, rt, 3.8 h, 98%; (c) AZADOL, $PhI(OAc)_2$, CH_2Cl_2, rt, 5.9 h; (d) $AcC(N_2)P(O)(OMe)_2$, Cs_2CO_3, MeOH, rt, 2 h, 77% (2 steps); (e) **11**, *n*-BuLi, THF, −78 °C, 1 h; **3**, THF, −78 to 0 °C, 1.6 h; (f) MnO_2, CH_2Cl_2, rt, 23.3 h; (g) $[CuH(PPh_3)]_6$, benzene, H_2O, rt, 1 h, 63% (3 steps); (h) *p*-TsOH·H_2O, CH_2Cl_2, MeOH, rt, 14.6 h; (i) Nafion NR-50, MS4A, toluene, reflux, 8.3 h, 69% (2 steps); (j) $BH_3·SMe_2$, THF, rt, 16.8 h; NaOH, H_2O_2, H_2O, rt, 2.3 h; (k) DDQ, CH_2Cl_2, H_2O, 0 °C, 3.4 h, 37% (2 steps).

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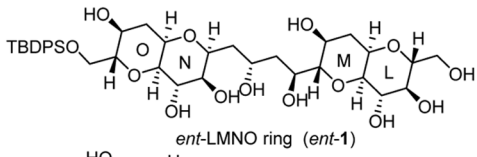
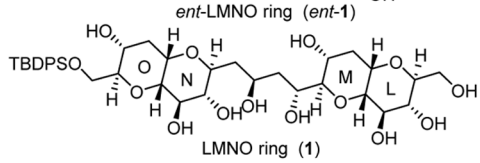
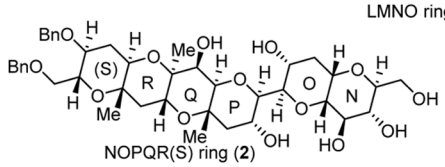
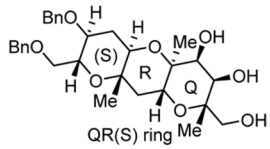
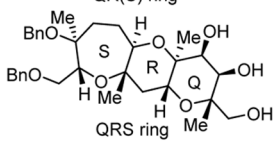
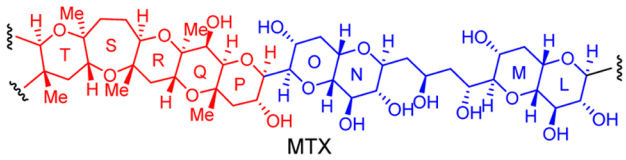
Table 1. Summary of the Inhibitory Activity of the Synthetic Specimens against Ca^{2+} Influx Induced by MTX and Comparison of the Molecular Structures with That of MTX (Colored in Red, Hydrophobic Region; Colored in Blue, Hydrophilic Region)

partial structures of MTX	inhibition (%) at 300 μM
 *ent*-LMNO ring (*ent*-**1**)	18
 LMNO ring (**1**)	36
 NOPQR(S) ring (**2**)	0
 QR(S) ring	54
 QRS ring	91
 MTX	

The inhibitory activity of the LMNO ring system was 36%, whereas that of its enantiomer was slightly less potent (18% inhibition). These results are comparable to those reported by Konoki et al.[2] Thus, the biological activity did not depend significantly on the chirality. The inhibitory activity due to the hydrophilic region may not, therefore, be due to specific binding to the target proteins, and the hydrophilic region may not be a promising inhibitor. These results support our hypothesis: the partial structures corresponding to the hydrophobic region of MTX might bind competitively to the target proteins to inhibit the biological activity due to MTX (Figure 2).

On the other hand, it was surprising that no inhibition was observed with the NOPQR(S) ring system (<300 μM), which possessed hydrophobic and hydrophilic moieties and a large number of rings (hexacyclic) compared with the LMNO (tetracyclic) and QRS (tricyclic) ring systems. Although the mechanism underlying the activity of the NOPQR(S) ring system remains a point of debate, the combination of the hydrophobic and hydrophilic regions influenced the biological activity in contradictory manners.

CONCLUSIONS

In conclusion, the stereoselective synthesis of the LMNO ring system (**1**) of MTX and its enantiomer (*ent*-**1**) was achieved. The LM ring, which is a common precursor to the NO ring, was prepared from the L-ring via the NHK reaction, intramolecular oxa-Michael addition, and Pummerer rearrangement as key steps. Aldol reaction of the LM ring and the NO ring fragments, followed by 1,3-*anti* selective reduction, furnished the LMNO ring system (**1**). The *ent*-LMNO ring system (*ent*-**1**) was also synthesized via an analogous sequence. The NOPQR(S) ring system, in which the original seven-membered S ring was substituted with the six-membered (S) ring, was synthesized via coupling of the QR(S) ring alkyne and the NO ring aldehyde, followed by stereoselective construction of the P-ring through dehydration of the hydroxyketone and hydroboration of the resulting dihydropyran derivative. The inhibitory activities of these synthetic specimens against MTX-induced Ca^{2+} influx into rat C6 glioma cells were evaluated. Although the LMNO ring system and its enantiomer elicited weak inhibitory activities (36 and 18% inhibition at 300 μM, respectively), the NOPQR(S) ring system showed no activity (<300 μM).

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These results suggested guidelines by which an inhibitor could be designed based on the partial structure of MTX. A more potent inhibitor could potentially be developed in light of more detailed structure−activity relationship studies of the hydrophobic region of MTX. Such studies are currently in progress.

EXPERIMENTAL SECTION

General Methods for Organic Synthesis. All reactions sensitive to air or moisture were performed under an argon atmosphere with dry glassware unless otherwise noted. The dehydrated solvents CH_2Cl_2, tetrahydrofuran (THF), toluene, *N*,*N*-dimethylformamide (DMF), Et_2O, and MeOH were used without further dehydration. NMM, BnBr, $BF_3{\cdot}OEt_2$, TBSOTf, 2,6-lutidine, TBDPSCl, and $BH_3{\cdot}SMe_2$ were distilled before use. Molecular sieves (MS4A) were preactivated by heating in vacuo. All other chemicals were obtained from local venders and used as supplied unless otherwise stated. Thin-layer chromatography (TLC) was performed using precoated TLC glass plates (silica gel 60 F_{254}, 0.25 mm thickness) for the reaction analyses. Silica gel was used for column chromatography (spherical, neutral, 100−210 μm) or for flash chromatography (40−50 μm). Optical rotations were recorded on a polarimeter. IR spectra were recorded on FT/IR equipment. ^{1}H NMR spectra were recorded at 600 or 400 MHz, and ^{13}C NMR spectra were recorded at 150 or 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane (TMS) with reference to internal residual solvent [^{1}H NMR $CHCl_3$ (7.26), CD_2HOD (3.31), CD_2HCN (1.94), CD_3COCD_2H (2.05); ^{13}C NMR $CDCl_3$ (77.16), CD_3OD (48.94), CD_3CN (1.32), $(CD_3)_2CO$ (29.84). The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet. High-resolution mass spectra (HRMS) were recorded on ESI-TOF or APCI-TOF equipment.

*2-(Naphthalen-2-ylmethoxy)-1-(pyrrolidin-1-yl)ethanone (**14**).* To a stirred solution of primary alcohol **13** (12.9 g, 100 mmol) in DMF (160 mL) were added NAPBr (22.1 g, 100 mmol) at 0 °C followed by NaH (60% in mineral oil, 4.83 g, 120 mmol), and the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reprecipitation and silica gel column chromatography (hexane/EtOAc = 1:0 → 3:1) to give NAP ether **14** (26.3 g, 97.7 mmol, 97%) as a colorless amorphous solid.

R_f = 0.47 (hexane/EtOAc = 0/1); IR (neat) ν 3053, 2971, 2950, 2872, 1644, 1603, 1508, 1446, 1422, 1337, 1296, 1272, 1253, 1217, 1192, 1171, 1126, 1111, 1160, 1033, 1021, 987, 951, 913, 896, 856, 819 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85−7.81 (m, 4H), 7.53−7.46 (m, 3H), 4.81 (s, 2H), 4.13 (s, 2H), 3.51 (t, J = 6.9 Hz, 2H), 3.37 (t, J = 6.9 Hz, 2H), 1.93 (tt, J = 6.9, 6.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 135.1, 133.4, 133.2, 128.4, 128.0, 127.8, 127.0, 126.3, 126.12, 126.10, 73.4, 69.5, 46.0, 45.8, 26.3, 24.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{19}NO_2Na$ 292.1308, found 292.1312.

*1-(Furan-2-yl)-2-(naphthalen-2-ylmethoxy)ethanone (**15**).* To a stirred solution of furan (2.50 mL, 33.4 mmol) in THF (150 mL) was added a solution of *n*-BuLi (1.73 M in hexane, 16.1 mL, 27.9 mmol) at 0 °C. The resulting solution was allowed to stir for 30 min and then cooled to −78 °C. A solution of amide **14** (5.00 g, 18.6 mmol) in THF (80 mL) was then added, and the resulting mixture was allowed to stir at −78 °C for 1 h, at which time a solution of saturated aqueous NH_4Cl was added. The biphasic mixture was allowed to warm to room temperature and then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reprecipitation and silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1) to give furyl ketone **15** (4.81 g, 18.1 mmol, 97%) as a pale brown amorphous solid.

R_f = 0.63 (hexane/EtOAc = 1/1); IR (neat) ν 3031, 3054, 3020, 2925, 2866, 2360, 1687, 1602, 1570, 1509, 1467, 1393, 1360, 1301, 1267, 1254, 1223, 1170, 1156, 1128, 1083, 1031, 1018, 980, 961, 907, 893, 882, 856, 819 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87−7.82 (m, 4H), 7.57 (d, J = 1.4 Hz, 1H), 7.55−7.46 (m, 3H), 7.32 (d, J = 3.5 Hz, 1H), 6.53 (dd, J = 3.5, 1.4 Hz, 1H), 4.85 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.7, 151.1, 146.7, 134.8, 133.4, 133.3, 128.5, 128.1, 127.9, 127.1, 126.3, 126.2, 126.0, 118.3, 112.4, 73.8, 72.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{14}O_3Na$ 289.0835, found 289.0829.

*(S)-1-(Furan-2-yl)-2-(naphthalen-2-ylmethoxy)ethanol (**17**).* To a stirred solution of furyl ketone **15** (1.60 g, 6.00 mmol) in CH_2Cl_2 (20 mL) were added TBAC (501 mg, 1.80 mmol), a solution of sodium formate (4.08 g, 60.0 mmol) in H_2O (20 mL), and (*S*,*S*)-**16** (18.0 mg, 0.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h, at which time the mixture was diluted with H_2O. The biphasic mixture was then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1) to provide chiral alcohol **17** (1.58 g, 5.89 mmol, 98%) as a colorless solid.

R_f = 0.27 (hexane/EtOAc = 3/1); $[\alpha]_D^{26}$ −8.6 (c 1.00, $CHCl_3$); IR (neat) ν 3559, 3431, 3055, 3017, 2908, 2863, 2372, 2351, 2332, 2321, 1602, 1507, 1470, 1440, 1366, 1348, 1316, 1271, 1215, 1172, 1146, 1124, 1107, 1085, 1068, 1009, 961, 950, 929, 917, 894, 884, 856, 817 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89−7.81 (m, 3H), 7.77 (br s, 1H), 7.51−7.45 (m, 3H), 7.37 (br s, 1H), 6.34 (dd, J = 2.8, 1.4 Hz, 1H), 6.32 (d, J = 2.8 Hz, 1H), 4.96 (dt, J = 11.0, 4.9 Hz, 1H), 4.77 (dd, J = 17.1, 11.6 Hz, 2H), 3.80 (d, J = 8.3 Hz, 2H), 2.71 (d, J = 4.9, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 142.4, 135.3, 133.4, 133.2, 128.5, 128.0, 127.9, 126.8, 126.4, 126.2, 125.8, 110.4, 107.2, 73.7, 72.6, 67.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{16}O_3Na$ 291.0992, found 291.0997.

*(2S,6S)-6-((Naphthalen-2-ylmethoxy)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Pivalate (**18**).* To a stirred solution of chiral furan **17** (3.97 g, 14.8 mmol) in THF (90 mL) and H_2O (36 mL) were added $NaHCO_3$ (2.49 g, 29.6 mmol), NaOAc (1.21 g, 14.8 mmol), and NBS (2.63 g, 14.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, at which time a solution of saturated aqueous $NaHCO_3$ was added. The resulting biphasic mixture was then extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filterd, and concentrated under reduced pressure to give crude enone, which was used in the next step directly without purification.

The crude mixture of hemiacetals was then dissolved in CH_2Cl_2 (65 mL) and cooled to −78 °C. To the stirred solution were added DMAP (90.4 mg, 0.74 mmol), Et_3N (3.0 mL, 29.6 mmol), and PvCl (2.2 mL, 17.8 mmol), and the reaction mixture was stirred at −78 °C for 1 h. The cold mixture was then rapidly poured into a mixed solution of saturated aqueous NH_4Cl and EtOAc. H_2O was added, and the organic layer was removed and then washed with H_2O and saturated aqueous NaCl. The organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 1/0 → 7/1) to afford pyranone **18** (3.36 g, 9.12 mmol, 62% for two steps) as a colorless solid as well as the more polar, undesired β-isomer (1.52 g, 4.12 mmol, 28%) as a colorless syrup.

R_f = 0.47 (hexane/EtOAc = 2/1); $[\alpha]_D^{26}$ +102.8 (c 1.00, $CHCl_3$); IR (neat) ν 3056, 3022, 2975, 2935, 2872, 2363, 1740, 1701, 1636, 1605, 1511, 1480, 1458, 1397, 1370, 1278, 1215, 1125, 1101, 1030, 1003, 930, 857, 817, 748, 668 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84−7.81 (m, 3H), 7.76 (br s, 1H), 7.51−7.42 (m, 3H), 6.95 (dd, J = 10.3, 4.1 Hz, 1H), 6.61 (d, J = 3.4 Hz, 1H), 6.27 (d, J = 10.3 Hz, 1H), 4.74 (s, 2H), 4.66 (dd, J = 4.8, 2.8 Hz, 1H), 3.97 (dd, J = 11.0, 4.8 Hz, 1H), 3.93 (dd, J = 11.0, 2.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.4, 177.0, 142.5, 135.4, 133.4, 133.2, 129.0, 128.3, 128.0, 127.8, 126.6, 126.2, 126.0, 125.8, 87.2, 76.6, 74.0, 68.8, 39.4,

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27.2 (3C); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{22}H_{24}O_5Na$ 391.1516, found 391.1505.

*(2S,5R,6S)-5-Hydroxy-6-((naphthalen-2-ylmethoxy)methyl)-5,6-dihydro-2H-pyran-2-yl Pivalate (**19**).* To a stirred solution of enone **18** (520 mg, 1.41 mmol) in CH_2Cl_2/MeOH (13 mL, 1:1) was added $CeCl_3{\cdot}7H_2O$ (263 mg, 0.71 mmol) at room temperature. The solution was stirred for 15 min and then cooled to −78 °C. To the stirred solution at −78 °C was added $NaBH_4$ (53.4 mg, 1.41 mmol), and the resulting mixture was stirred at −78 °C for 30 min before being quenched with saturated aqueous NH_4Cl. After warming to room temperature, the resulting biphasic mixture was diluted with EtOAc, and the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude allylic alcohol **19** was used in the next step without further purification.

*(2S,5R,6S)-5-(Naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-5,6-dihydro-2H-pyran-2-yl Pivalate (**20**).* To a stirred solution of crude allylic alcohol **19** in toluene (7 mL) were added NAPBr (1.56 g, 7.06 mmol) and TBAI (261 mg, 0.71 mmol) at room temperature. An aqueous solution of NaOH (25%, 7 mL) was added, and the mixture was allowed to stir for 4 h. The reaction mixture was diluted with saturated aqueous NaCl and EtOAc and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 1/0 → 8/1) to give NAP ether **20** (552 mg, 1.08 mmol, 77% yield for two steps) as a colorless syrup.

R_f = 0.55 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −30.7 (c 1.00, $CHCl_3$); IR (neat) ν 3051, 3018, 2973, 2934, 2907, 2870, 1734, 1633, 1600, 1508, 1480, 1459, 1395, 1369, 1275, 1194, 1119, 1094, 1025, 1006, 919, 857, 815, 790, 750, 668 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82−7.76 (m, 4H), 7.75 (br s, 1H), 7.57 (d, J = 1.4 Hz, 1H), 7.71−7.66 (m, 2H), 7.48−7.42 (m, 5H), 7.29 (dd, J = 8.2, 2.0 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 6.21 (d, J = 10.3 Hz, 1H), 5.79 (ddd, J = 10.3, 3.4, 2.0 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.64 (d, J = 12.4 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.29 (dd, J = 9.6, 1.4 Hz, 1H), 3.99 (ddd, J = 9.7, 4.0, 2.0 Hz, 1H), 3.81 (dd, J = 11.0, 4.1 Hz, 1H), 3.77 (dd, J = 11.0, 2.1 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.6, 135.7, 135.2, 133.4, 133.3, 133.19, 133.17, 132.1, 128.4, 128.3, 128.1, 128.0, 127.84, 127.81, 127.0, 126.8, 126.3, 126.24, 126.18, 126.1, 126.01, 125.99, 125.0, 88.7, 73.6, 72.01, 71.96, 70.0, 68.6, 39.1, 27.2 (3C); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{33}H_{34}O_5Na$ 533.2298, found 533.2297.

*(2S,3R,4S,5R,6S)-3,4-Dihydroxy-5-(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2-yl Pivalate (**21**).* To a stirred solution of olefin **20** (2.85 g, 5.59 mmol) in acetone/H_2O (36 mL, 5:1) were added NMO (1.96 g, 16.8 mmol) and $K_2OsO_4{\cdot}2H_2O$ (93.2 mg, 0.25 mmol) at room temperature, and the reaction mixture was allowed to stir for 24 h. The reaction mixture was then quenched with saturated aqueous $Na_2S_2O_3$, and the resulting biphasic mixture was stirred vigorously for 30 min and then extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reprecipitation and flash silica gel column chromatography (hexane/EtOAc = 4/1 → 2/1 → 1/1) to give diol **21** (2.89 g, 5.30 mmol, 95%) as a colorless amorphous solid.

R_f = 0.35 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ −8.5 (c 1.00, $CHCl_3$); IR (neat) ν 3057, 3016, 2976, 2935, 2906, 2872, 2360, 1739, 1603, 1509, 1479, 1461, 1397, 1367, 1275, 1215, 1168, 1114, 1088, 1030, 957, 940, 893, 857, 817, 745, 667 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83−7.77 (m, 5H), 7.69 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.57 (s, 1 H), 7.51−7.41 (m, 5H), 7.29 (dd, J = 8.9, 1.4 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.68 (d, J = 12.4 Hz, 1H), 3.98−3.94 (m, 2H), 3.92 (br s, 1H), 3.88 (dd, J = 11.7, 4.0 Hz, 1H), 3.85−3.81 (m, 1H), 3.78 (dd, J = 11.0, 2.1 Hz, 1H), 2.58 (br s, 1H), 2.43 (br s, 1H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.3, 135.50, 135.45, 133.4, 133.3, 133.21, 133.18, 128.6, 128.4, 128.1 (3C), 127.9, 127.8, 127.1 (2C), 126.3 (3C), 126.2, 126.1, 126.0, 93.2, 75.1, 73.9, 73.6, 71.9, 70.2, 68.5, 39.2, 27.2 (3C); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{33}H_{36}O_7Na$ 567.2353, found 567.2340.

*(2S,3R,4S,5S,6S)-3-Hydroxy-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2-yl Pivalate (**22**).* A stirred solution of diol **21** (2.87 g, 5.30 mmol), n-Bu_2SnO (1.32 g, 5.30 mmol), TBAI (1.96 g, 5.30 mmol), and NAPBr (1.64 g, 7.43 mmol) in benzene (100 mL) was heated at reflux in a flask equipped with a Dean−Stark apparatus for 19 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by reprecipitation and flash silica gel column chromatography (hexane/EtOAc = 6/1 → 3/1) to give NAP ether **22** (3.22 g, 4.71 mmol, 90%) as a colorless amorphous solid.

R_f = 0.28 (hexane/EtOAc = 2/1); $[\alpha]_D^{24}$ −44.1 (c 1.00, $CHCl_3$); IR (neat) ν 3055, 3013, 2974, 2932, 2906, 2871, 2372, 2350, 2324, 1739, 1634, 1602, 1509, 1478, 1461, 1396, 1366, 1344, 1310, 1273, 1216, 1170, 1156, 1122, 1091, 1031, 955, 940, 893, 856, 814, 747, 666 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83−7.75 (m, 8H), 7.73 (d, J = 8.2 Hz, 1H), 7.61 (t, J = 8.9 Hz, 1H), 7.53 (s, 1 H), 7.50−7.40 (m, 8H), 7.22 (dd, J = 8.2, 1.4 Hz, 1H), 6.19 (d, J = 1.3 Hz, 1H), 5.01 (d, J = 11.0 Hz, 1H), 4.90 (s, 2H), 4.82 (d, J = 11.7 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 4.12−3.88 (m, 1H), 3.96−3.93 (m, 1H), 3.90 (dd, J = 9.6, 3.4 Hz, 1H), 3.85 (dd, J = 13.0, 4.1 Hz, 1H), 3.75 (dd, J = 13.0, 2.8 Hz, 1H), 2.60−2.57 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 135.7, 135.6, 135.0, 133.4, 133.34 (2C), 133.29, 133.2, 133.1, 128.7, 128.33, 128.25, 128.1 (2C), 128.0, 127.9, 127.84, 127.75, 127.2, 126.94, 126.86, 126.5, 126.4, 126.23, 126.21, 126.14, 126.13, 126.02 (2C), 125.99, 93.0, 79.3, 75.6, 74.0, 73.9, 73.8, 72.6, 68.5, 68.1, 39.1, 27.0 (3C); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{44}H_{44}O_7Na$ 707.2979, found 707.2965.

*(2R,3R,4S,5S,6S)-4,5-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2,3-diol (**23**).* To a stirred solution of pivalate **22** (5.14 g, 7.51 mmol) in THF (37.0 mL) and MeOH (37.0 mL) was added NaOMe (1.21 g, 22.5 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1.2 h and then quenched with saturated aqueous NH_4Cl. The biphasic mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude diol **23** was used in the next step without further purification.

*(2S,3R,4R,5S,6S)-4,5-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2,3-diyl Diacetate (**24**).* To a stirred solution of crude diol **23** in CH_2Cl_2 (36.1 mL) were added pyridine (4.80 mL, 59.7 mmol), DMAP (58.2 mg, 0.476 mmol), and Ac_2O (2.80 mL, 29.6 mmol) at 0 °C. The reaction mixture was allowed to stir for 80 min, and then H_2O was added. The organic phase was separated, and the aqueous layer was further extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1 → 3/1) to give diacetate **24** (4.46 g, 6.51 mmol, 87% for two steps) and β-isomer (0.624 g, 0.911 mmol, 12% for two steps) as colorless amorphous product.

24: R_f = 0.28 (hexane/EtOAc = 3/1); $[\alpha]_D^{27}$ −10.8 (c 0.58, $CHCl_3$); IR (neat) ν 3055, 3019, 2924, 2856, 1749, 1541, 1508, 1369, 1217, 1155, 1124, 1104, 1028, 963, 899, 856, 819, 753 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82−7.75 (m, 8H), 7.68 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 8.4 Hz, 2H), 7.51−7.40 (m, 9H), 7.17 (d, J = 7.2 Hz, 1H), 6.17 (d, J = 1.2 Hz, 1H), 5.45 (s, 1H), 5.04 (d, J = 11.4 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 12.6 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.67 (d, J = 10.8 Hz, 1H), 4.65 (d, J = 12.6 Hz, 1H), 4.10−4.03 (m, 2H), 3.93−3.87 (m, 2H), 3.77 (d, J = 9.6 Hz, 1H), 2.21 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.6, 135.7, 135.6, 135.2, 133.35, 133.31, 133.1, 133.0, 128.4, 128.3, 128.2, 128.0 (4C), 127.84, 127.82, 127.7, 127.1, 126.9,

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126.6, 126.3 (2C), 126.2, 126.1 (2C), 126.03, 125.97, 125.9, 91.5, 77.8, 75.5, 74.0, 73.9, 73.8, 72.1, 68.5, 67.7, 21.2, 21.0; HRMS (ESI-TOF) calcd for $C_{43}H_{40}O_8Na$ [(M + Na)$^+$] 707.2615, found 707.2611.

β-isomer: R_f = 0.23 (hexane/EtOAc = 3/1); $[\alpha]_D^{27}$ +21.1 (*c* 0.21, $CHCl_3$); IR (neat) *ν* 3053, 2951, 2925, 2856, 1744, 1368, 1240, 1168, 1094, 1059, 962, 894, 857, 820, 752 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.81−7.74 (m, 8H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.56 (dd, *J* = 7.2, 3.6 Hz, 1H), 7.49−7.40 (m, 9H), 7.12 (d, *J* = 7.8 Hz, 1H), 5.78 (s, 1H), 5.69 (d, *J* = 3.0 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H), 4.91 (d, *J* = 11.4 Hz, 1H), 4.84 (d, *J* = 12.6 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 2H), 3.99 (d, *J* = 9.6 Hz, 1H), 3.87−3.80 (m, 3H), 3.66−3.62 (m, 1H), 2.26 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.9, 170.0, 135.6, 135.5, 134.9, 133.34, 133.27, 133.19, 133.16, 133.0, 128.5, 128.3, 128.12, 128.08, 128.0 (2C), 127.84, 127.81, 127.7, 127.1, 127.0, 126.5, 126.3 (2C), 126.22, 126.17, 126.14, 126.10 (2C), 126.03, 125.96, 125.8, 91.5, 80.0, 76.3, 75.3, 73.81, 73.77, 71.8, 68.5, 67.5, 21.2, 21.0; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{43}H_{40}O_8Na$ 707.2615, found 707.2596.

*(2S,3S,4R,5S,6S)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-yl Acetate (**25**).* To a stirred solution of a mixture of acetate **24** and its isomer (5.04 g, 7.36 mmol) and allylTMS (35.0 mL, 221 mmol) in MeCN (38.6 mL), which was predried over MS3A, was added TMSOTf (2.70 mL, 14.9 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2.3 h and then quenched with saturated aqueous $NaHCO_3$. The resulting biphasic mixture was then extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 8/1 → 7/1) to give allylated product **25** (4.11 g, 6.16 mmol, 84%) as a colorless amorphous product.

R_f = 0.43 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −4.5 (*c* 1.03, $CHCl_3$); IR (neat) *ν* 3055, 3017, 2908, 2864, 2360, 1737, 1641, 1602, 1508, 1469, 1440, 1370, 1346, 1270, 1239, 1217, 1170, 1144, 1123, 1098, 1044, 1017, 982, 962, 952, 917, 894, 856, 817 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.80−7.72 (m, 8H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.58−7.55 (m, 1H), 7.49 (s, 1 H), 7.47−7.39 (m, 8H), 7.16 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.82−5.74 (m, 1H), 5.38 (dd, *J* = 2.8, 2.1 Hz, 1H), 5.09−5.03 (m, 2H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.82 (t, *J* = 12.4 Hz, 1H), 4.67−4.61 (m, 2H), 4.11−4.07 (m, 1H), 3.96−3.91(m, 2H), 3.83 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.78−3.72 (m, 2H), 2.52−2.45 (m, 1H), 2.34−2.28 (m, 1H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 170.8, 135.80, 135.76, 135.3, 133.38, 133.35 (2C), 133.3, 133.2, 133.1, 133.0, 128.4, 128.3, 128.2, 128.02 (2C), 127.99, 127.83, 127.81, 127.7, 127.1, 126.8, 126.5, 126.24, 126.20, 126.17, 126.11 (2C), 126.08, 126.0, 125.9 (2C), 117.9, 77.5, 75.0 (2C), 74.8, 73.7, 73.1, 71.9, 69.9, 69.3, 33.8, 21.4; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{42}O_6Na$ 689.2874, found 689.2843.

*(2S,3S,4S,5S,6S)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-ol (**26**).* To a stirred solution of acetate **25** (4.95 g, 7.42 mmol) in THF/MeOH (130 mL, 1:1) was added K_2CO_3 (410 mg, 2.97 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h before being quenched with saturated aqueous NH_4Cl and EtOAc. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1 → 1/1) to give secondary alcohol **26** (4.47 g, 7.15 mmol, 96%) as a colorless oil.

R_f = 0.32 (hexane/EtOAc = 2/1); $[\alpha]_D^{21}$ −21.7 (*c* 0.95, $CHCl_3$); IR (neat) *ν* 3422, 3054, 3013, 2974, 2912, 2864, 2372, 2349, 2333, 2326, 1951, 1914, 1691, 1639, 1602, 1572, 1508, 1468, 1441, 1393, 1365, 1344, 1315, 1271, 1217, 1171, 1146, 1124, 1086, 1008, 960, 951, 915, 894, 884, 856, 816 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.82−7.69 (m, 9H), 7.64−7.61 (m, 2H), 7.55 (s, 1 H), 7.49−7.39 (m, 8H), 7.23 (dd, *J* = 8.9, 1.4 Hz, 1H), 5.83−5.77 (m, 1H), 5.04 (d, *J* = 4.8 Hz, 1H), 5.02 (s, 1H), 4.78 (s, 2H), 4.74 (d, *J* = 12.4 Hz, 1H), 4.69−4.64 (m, 2H), 4.02−3.98 (m, 1H), 3.95−3.91 (m, 2H), 3.86 (dd, *J* = 8.0, 3.4 Hz, 1H), 3.85−3.81 (m, 1H), 3.79 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.74 (dd, *J* = 10.3, 3.4 Hz, 1H), 2.50 (d, *J* = 4.8 Hz, 1H), 2.45−2.41 (m, 1H), 2.37−2.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 135.8, 135.7 135.1, 134.2 (2C), 133.4, 133.3 (2C), 133.2, 133.12, 133.09, 128.6, 128.28, 128.25, 128.0 (2C), 127.9, 127.8, 127.8, 127.0, 126.72, 126.69, 126.4, 126.3, 126.19, 126.16, 126.1, 126.00, 125.95 (2C), 125.9, 117.5, 79.2, 75.2, 74.5, 74.3, 73.6, 73.1, 72.3, 69.1, 68.5, 34.4; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{42}H_{40}O_5Na$ 647.2768, found 647.2784.

*(2S,3R,4R,5S,6S)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-yl 4-Nitrobenzoate (**27**).* To a stirred solution of alcohol **26** (4.94 g, 7.91 mmol) in toluene (76.0 mL) were added Ph_3P (4.73 g, 18.0 mmol), 4-nitrobenzoic acid (2.68 g, 16.0 mmol), and diisopropyl azodicarboxylate (DIAD) (9.40 mL, 17.9 mmol) at room temperature, and the resulting mixture was heated at 70 °C for 1 h. After the cooled reaction mixture was concentrated under reduced pressure, the residue was roughly purified by flash silica gel column chromatography, and the resulting impure nitrobenzoate **27** was used in the next step without further purification.

*(2S,3R,4S,5S,6S)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-ol (**28**).* To a stirred solution of impure nitrobenzoate **27** in THF/MeOH (80.0 mL, 1:1) was added K_2CO_3 (463 mg, 3.35 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h before being quenched with saturated aqueous NH_4Cl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1) to give alcohol **28** (3.77 g, 6.03 mmol, 76% for two steps) as a pale yellow solid.

R_f = 0.28 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −19.5 (*c* 0.70, $CHCl_3$); IR (neat) *ν* 3501, 3054, 3013, 2976, 2925, 2861, 2371, 2351, 2336, 2323, 1953, 1918, 1747, 1641, 1602, 1508, 1469, 1463, 1440, 1414, 1366, 1344, 1271, 1248, 1216, 1171, 1142, 1123, 1079, 961, 952, 915, 893, 855, 816 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.81−7.77 (m, 3H), 7.74−7.67 (m, 6H), 7.76−7.72 (m, 2H), 7.56 (s, 1 H), 7.50−7.39 (m, 7H), 7.30−7.27 (m, 3H), 5.87−5.79 (m, 1H), 5.14 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.06 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.79−4.69 (m, 5H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.14−4.11 (m, 1H), 4.00−3.96 (m, 1H), 3.89 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.89 (dd, *J* = 5.5, 4.8 Hz, 1H), 3.76 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.74−3.70 (m, 2H), 2.98−2.90 (m, 1H), 2.50−2.44 (m, 1H), 2.44−2.37 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 135.7, 135.5, 135.0, 134.8, 133.4, 133.32, 133.29, 133.2, 133.1 (2C), 128.5, 128.4, 128.3, 128.1, 128.0 (2C), 127.9, 127.85, 127.82, 126.8, 126.6, 126.5, 126.4, 126.3, 126.25, 126.20, 126.16, 126.0, 125.9, 125.8, 125.6, 117.2, 77.7, 74.9, 73.7, 73.6, 73.5, 73.0, 71.3, 69.3, 68.2, 33.4; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{42}H_{40}O_5Na$ 647.2768, found 647.2743.

*(((2S,3R,4R,5S,6S)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-yl)oxy)(tert-butyl)dimethylsilane (**29**).* To a stirred solution of alcohol **28** (271 mg, 0.43 mmol) in DMF (0.44 mL) were added imidazole (118 mg, 1.74 mmol) followed by TBSCl (130.8 mg, 0.87 mmol) at 0 °C. The reaction mixture was warmed to 70 °C and stirred for 11 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/0 → 8/1) to give TBS ether **29** (320 mg, 0.43 mmol, quant) as a colorless oil.

R_f = 0.70 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +21.8 (*c* 0.72, $CHCl_3$); IR (neat) *ν* 3055, 3020, 2951, 2927, 2896, 2883, 2856, 2377, 2353, 2321, 1730, 1640, 1603, 1527, 1509, 1470, 1462, 1441, 1406, 1386, 1362, 1343, 1270, 1254, 1126, 1169, 1156, 1142, 1122, 1113, 1088, 1036, 1005, 961, 952, 912, 892, 854, 837, 815 cm^{-1}; ^{1}H NMR (600

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MHz, $CDCl_3$) δ 7.82−7.71 (m, 8H), 7.69 (d, 1H, J = 7.6 Hz), 7.49−7.34 (m, 10H), 7.24 (s, 1 H), 6.95 (dd, J = 8.2, 1.4 Hz, 1H), 5.91−5.83 (m, 1H), 5.13 (dd, J = 17.2, 1.4 Hz, 1H), 5.11−5.07 (m, 2H), 4.97 (d, J = 11.7 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.83 (d, J = 12.4 Hz, 1H), 4.61 (d, J = 12.4 Hz, 1H), 4.54 (d, J = 10.3 Hz, 1H), 4.00 (dd, J = 8.9, 6.2 Hz, 1H), 3.80 (dd, J = 10.3, 3.5 Hz, 1H), 3.76−3.71 (m, 2H), 3.70−3.66 (m, 2H), 2.54−2.51 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 135.7, 135.6, 135.2, 133.5, 133.3, 133.24, 133.16, 133.0 (3C), 128.3, 128.1 (2C), 128.03, 128.00, 127.84, 127.80, 127.6, 127.1, 126.5, 126.3, 126.2, 126.1, 126.0, 125.9 (2C), 125.83 (2C), 125.80, 125.6, 116.9, 83.5, 78.4, 76.7, 75.6, 75.2, 73.8, 73.4, 71.2, 69.0, 29.2, 26.0 (3C), 18.1, −4.3, −4.5; HRMS (ESI-TOF) calcd for $C_{48}H_{54}O_5SiNa$ [(M + Na)$^+$] 761.3633, found 761.3671.

*2-((2S,3R,4R,5S,6S)-3-((tert-Butyldimethylsilyl)oxy)-4,5-bis-(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-tetrahydro-2H-pyran-2-yl)acetaldehyde (**7**).* A stirred solution of terminal olefin **29** (934 mg, 1.26 mmol) in CH_2Cl_2 (14.1 mL) and MeOH (2.6 mL) was cooled to −78 °C. A steam of O_3 was then bubbled through the solution for 11 min, and the O_3 was removed by bubbling O_2 gas. PPh_3 (409 mg, 1.56 mmol) was then added, and the solution was warmed to room temperature over 3.8 h and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 15/1 → 8/1 → 5/1) to afford aldehyde **7** (770 mg, 1.04 μmol, 82%) as a colorless oil.

R_f = 0.25 (hexane/EtOAc = 5/1); $[\alpha]_D^{24}$ +23.6 (c 1.09, $CHCl_3$); IR (neat) ν 3055, 2952, 2927, 2883, 2856, 1727, 1634, 1603, 1509, 1470, 1462, 1386, 1362, 1343, 1254, 1219, 1170, 1155, 1125,1091, 1006, 961, 952, 891, 854, 838, 816, 775, 754, 699, 670 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.82−9.71 (m, 1H), 7.83−7.70 (m, 9H), 7.51−7.36 (m, 10H), 7.27 (s, 1H), 6.98 (dd, J = 8.2, 1.4 Hz, 1H), 5.05 (d, J = 11.7 Hz, 1H), 4.98 (d, J = 11.7 Hz, 1H), 4.87 (d, J = 10.3 Hz, 1H), 4.82 (d, J = 11.7 Hz, 1H), 4.72−4.68 (m, 1H), 4.60 (d, J = 12.4 Hz, 1H), 4.57 (d, J = 11.0 Hz, 1H), 4.04 (dd, J = 8.9, 6.2 Hz, 1H), 3.83−3.75 (m, 2H), 3.70−3.63 (m, 3H), 2.91−2.80 (m, 2H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.4, 136.3, 135.5, 135.3, 133.4, 133.9, 133.3, 133.22, 133.18, 133.0, 128.4, 128.11, 128.06, 128.04 (2C), 127.99, 127.82, 127.80, 127.7, 127.1, 126.4, 126.3, 126.2, 126.13, 126.06, 126.0, 125.91, 125.88, 125.86, 125.7, 125.5, 83.2, 78.0, 75.6, 75.1, 73.9, 72.4, 72.2 (2C), 68.7, 40.5, 26.0 (3C), 18.0, −4.3, −4.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{47}H_{52}O_6SiNa$ 763.3425, found 763.3407.

*(2R,3R,4aS,6S,7S,8R,8aR)-7,8-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)-octahydropyrano[3,2-b]pyran-3-ol (**30**) and (2R,3S,4aS,6S,7S,8-R,8aR)-7,8-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)octahydropyrano[3,2-b]pyran-3-ol (**31**).* To a suspension of CrCl2 (932 mg, 7.58 mmol) and $NiCl_2$ (23.0 mg, 177 μmol) in DMF (8.30 mL) was added a solution of aldehyde **7** (1.09 g, 1.47 mmol) and vinyl iodide **8** (2.17 g, 7.43 mmol) in THF (8.30 mL) under an atmosphere of argon at room temperature, which was then rinsed with THF (4.10 mL) and DMF (3.80 mL). The reaction mixture was stirred for 62.2 h and then filtered through Celite and concentrated under reduced pressure. The residue was roughly purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 → 2/1 → 1/1), and the resulting impure allyl alcohol **6** was used in the next step without further purification.

To a stirred solution of impure allyl alcohol **6** in THF (36.8 mL) was added TBAF (1 M in THF, 3.30 mL, 3.30 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was warmed to 50 °C and stirred for 1 h. The reaction mixture was then quenched with saturated aquous NH_4Cl, and the resulting biphasic mixture was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 1/1 → 2/3 → 1/2 → 1/3) to give bicyclic system **30** (316 mg, 398 μmol, 28% for two steps) as a pale yellow oil and **31** (250 mg, 315 μmol, 22% for two steps) as a pale orange amorphous product.

30: R_f = 0.36 (hexane/EtOAc = 1/2); $[\alpha]_D^{22}$ +10.4 (c 0.37, $CHCl_3$); IR (neat) ν 3377, 3298, 3054, 3011, 2923, 2869, 2373, 2363, 2327, 1634, 1602, 1510, 1494, 1459, 1441, 1398, 1365, 1344, 1303, 1271, 1247, 1217, 1171, 1124, 1085, 1074, 1042 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78−7.72 (m, 8H), 7.71−7.68 (m, 1H), 7.64 (s, 1H), 7.54−7.51 (m, 2H), 7.46−7.36 (m, 11H), 7.17 (d, J = 8.2 Hz, 2H), 7.05 (dd, J = 8.2, 1.4 Hz, 1H), 4.90 (d, J = 2.7 Hz, 1H), 4.86 (d, J = 11.0 Hz, 2H), 4.79 (d, J = 12.4 Hz, 1H), 4.63 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.50 (s, 2H), 4.26−4.21 (m, 1H), 4.03 (dd, J = 10.3, 6.2 Hz, 1H), 3.96 (dd, J = 9.7, 8.2 Hz, 1H), 3.79 (dd, J = 11.0, 4.1 Hz, 1H), 3.78−3.73 (m, 1H), 3.73−3.65 (m, 3H), 3.44 (ddd, J = 9.0, 5.4, 3.0 Hz, 1H), 2.97 (dd, J = 15.0, 3.0 Hz, 1H), 2.84 (dd, J = 15.0, 5.4 Hz, 1H), 2.24 (s, 3H), 2.18−2.14 (m, 1H), 1.89 (dd, J = 23.4, 12.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 138.0, 136.1, 135.5, 135.4, 133.33 (2C), 133.28, 133.2, 133.1, 133.0, 130.3 (2C), 128.4, 128.23, 128.18, 128.0 (2C), 127.9, 127.84, 127.77, 127.7, 127.1, 126.7, 126.5, 126.34, 126.30, 126.27, 126.2, 126.13 (3C), 126.06, 126.0, 125.8, 124.3 (2C), 78.4, 75.7, 75.3, 74.9, 73.9, 72.4, 71.1, 70.3, 68.8, 68.2, 59.9, 31.6, 21.4; HRMS (APCI-TOF) calcd for $C_{50}H_{48}O_7SNa$ [(M + Na)$^+$] 815.3013, found 815.2983.

31: R_f = 0.32 (hexane/EtOAc = 1/2); $[\alpha]_D^{23}$ +13.6 (c 0.31, $CHCl_3$); IR (neat) ν 3378, 3054, 3011, 2924, 2868, 2359, 1634, 1601, 1509, 1494, 1469, 1459, 1449, 1397, 1364, 1344, 1271, 1217, 1171, 1125, 1090, 1043, 1012, 952, 896, 855, 816 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79−7.72 (m, 9H), 7.56−7.52 (m, 2H), 7.48−7.39 (m, 9H), 7.35 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 1H), 4.93 (d, J = 11.0 Hz, 1H), 4.86 (d, J = 12.4 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.60−4.55 (m, 1H), 4.20 (dd, J = 9.7, 6.2 Hz, 1H), 4.16−4.12 (m, 1H), 4.04 (dd, J = 8.9, 8.9 Hz, 1H), 3.83−3.80 (br d, 1H), 3.76 (dd, J = 10.3, 4.1 Hz, 1H), 3.72−3.67 (m, 3H), 3.65 (br d, 1H), 3.01 (dd, J = 13.4, 11.6 Hz, 1H), 2.77 (dd, J = 13.7, 3.4 Hz 1H), 2.35 (s, 3H), 2.03−2.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 139.1, 136.3, 135.55, 135.48, 133.38, 133.36, 133.3 (2C), 133.2, 133.1, 133.0, 130.3, 128.4, 128.3, 128.2, 128.1, 128.0 (3C), 1128.9, 128.8, 127.7, 127.0, 126.7, 126.6, 126.34, 126.27, 126.21, 126.17, 126.13, 126.10, 126.05, 126.01, 125.9, 124.1 (2C), 78.3, 76.4, 75.2, 74.6, 73.9, 72.5, 69.1, 68.8, 67.0, 57.6, 30.1, 21.5; HRMS (APCI-TOF) m/z [M + Na]$^+$ calcd for $C_{50}H_{48}O_7SNa$ 815.3013, found 815.2947

*(2R,4aS,6S,7S,8R,8aR)-7,8-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)-hexahydropyrano[3,2-b]pyran-3(2H)-one (**32**).* To a stirred solution of secondary alcohol **31** (66.6 mg, 84.0 μmol) in CH_2Cl_2 (1.00 mL) at 0 °C were added $NaHCO_3$ (14.1 mg, 168 μmol) and Dess−Martin periodinane (55.0 mg, 130 μmol). After stirring at room temperature for 45 min, $NaHCO_3$ (8.1 mg, 96.4 μmol) and Dess−Martin periodinane (27.7 mg, 65.3 μmol) were added. The reaction mixture was stirred at room temperature for 35 min before being quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and diluted with Et_2O. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude ketone **32** was used in the next step without further purification.

*(2R,3R,4aS,6S,7S,8R,8aR)-7,8-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)-octahydropyrano[3,2-b]pyran-3-ol (**30**).* To a stirred solution of crude ketone **32** in THF/MeOH (1.05 mL, 1:1) was added $NaBH_4$ (20.8 mg, 550 μmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 1.6 h before being quenched with saturated aqueous NH_4Cl. After warming to room temperature, the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc =

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2/1 → 1/2 → 1/3) to give alcohol **30** (43.5 mg, 54.9 μmol, 65% for two steps) as a colorless oil.

*(2S,3S,4R,4aR,6R,7R,8aS)-3,4,7-Tris(naphthalen-2-ylmethoxy)-2-((naphthalen-2-ylmethoxy)methyl)-6-((p-tolylsulfinyl)methyl)-octahydropyrano[3,2-b]pyran (**5**).* To a stirred solution of secondary alcohol **30** (33.9 mg, 42.8 μmol) in DMF (2.0 mL) was added TBAI (4.7 mg, 12.8 μmol), NaH (5.1 mg, 128 μmol), and NAPBr (37.8 mg, 171 μmol) at 0 °C. The reaction mixture was warmed to 30 °C and stirred for 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 2/1 → 1/1) to give naphthylmethyl ether **5** (33.6 mg, 36.0 μmol, 84%) as a colorless oil.

R_f = 0.53 (hexane/EtOAc = 1/1); $[\alpha]_D^{22}$ −9.2 (*c* 0.60, $CHCl_3$); IR (neat) ν 3053, 3013, 2936, 2920, 2866, 2374, 2365, 2359, 2349, 2328, 2319, 2309, 1602, 1509, 1493, 1459, 1441, 1398, 1364, 1343, 1302, 1271, 1246, 1219, 1172, 1141, 1124, 1083, 1044, 1016, 958, 893, 856, 816 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85−7.81 (m, 4H), 7.80−7.73 (m, 8H), 7.70 (brd, *J* = 7.6 Hz, 1H), 7.55 (br d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.50−7.39 (m, 13H), 7.23 (br d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.9 Hz, 1H), 5.10 (d, *J* = 11.6 Hz, 1H), 4.97 (dd, *J* = 11.7, 11.7 Hz, 1H), 4.96 (d, *J* = 11.6 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.63 (d, *J* = 11.0, Hz, 1H), 4.27−4.22 (m, 2H), 4.19 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.87 (ddd, *J* = 10.3, 10.3, 4.1 Hz, 1H), 3.85−3.81 (m, 1H), 3.78−3.68 (m, 4H), 3.16 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.80 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.38 (s, 3H), 2.35−2.31 (m, 1H), 2.92 (dd, *J* = 23.3, 11.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 141.6, 136.2, 135.6, 135.4 (2C), 133.40, 133.37, 133.36, 133.3, 133.2 (2C), 133.1 (2C), 133.0, 130.1, 128.42, 128.40, 128.3, 128.2, 128.1, 128.09, 128.07, 128.0, 127.9, 127.8, 127.7, 127.0, 126.9, 126.7, 126.5, 126.32, 126.29, 126.23, 126.16, 126.14, 126.12, 126.08, 126.0, 125.8, 124.4 (2C), 78.5, 77.3, 76.0, 75.3, 75.1, 74.8, 73.9, 72.4, 71.3, 70.1, 69.9, 69.1, 60.4, 29.9, 21.5; HRMS (APCI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{61}H_{56}O_7SNa$ 955.3639, found 955.3682.

*(2R,3R,4aS,6S,7S,8R,8aR)-3,7,8-Tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)octahydropyrano[3,2-b]pyran-2-carbaldehyde (**3**).* To a solution of sulfoxide **5** (198 mg, 212 μmol) in $MeCN/CH_2Cl_2$/pyridine (4.25 mL, 4/4/1) was added TFAA (290 μL, 2.10 mmol) at 0 °C. After being stirred 30 min at 0 °C, the reaction mixture was added KOAc (679 mg, 6.92 mmol) in H_2O 3.4 mL and stirred at room temperature for 1 h. Then, the mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 2/1 → 1/1) and gave aldehyde **3** (140 mg, 173 μmol, 81%) as a colorless amorphous product.

R_f = 0.10 (hexane/EtOAc = 2/1); $[\alpha]_D^{22}$ −102.1 (*c* 0.75, $CHCl_3$); IR (neat) ν 3465, 3054, 3020, 2930, 2904, 2866, 2360, 2341, 1739, 1634, 1602, 1509, 1460, 1441, 1363, 1344, 1271, 1219, 1170, 1123, 1083, 1018, 961, 952, 893, 855, 817, 771, 754, 705, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.86−7.70 (m, 12H), 7.68 (s, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.52−7.41 (m, 11H), 7.35 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.13 (dd, *J* = 8.6, 1.3, 1H), 5.03 (d, *J* = 11.9 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 12.8 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.21−4.09 (m, 3H), 3.79−3.68 (m, 5H), 3.64 (ddd, *J* = 10.0, 10.0, 4.1 Hz, 1H), 2.37−2.29 (m, 1H), 2.25−1.95 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.9, 135.8, 135.5, 135.3, 134.7, 133.34, 133.31, 133.30, 133.28, 133.23, 133.18, 133.1, 133.0, 128.6, 128.4 (2C), 128.2, 128.1, 128.0 (3C), 127.9 (2C), 127.79, 127.75, 127.02, 126.97, 126.9, 126.5, 126.4, 126.3 (2C), 126.24, 126.15, 126.1 (3C), 126.0, 125.79, 125.75, 78.5, 76.4, 76.2, 75.7, 75.2, 74.5, 73.9, 72.6, 72.5, 71.1, 69.3, 69.0, 29.8; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{54}H_{48}O_7Na$ 831.3292, found 831.3296.

*((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-Tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)octahydropyrano[3,2-b]pyran-2-yl)methanol (**33**).* To a stirred solution of aldehyde **3** (128 mg, 158 μmol) in THF/MeOH (2.0 mL, 1:1) was added $NaBH_4$ (35.7 mg, 944 μmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1.5 h. After addition of $NaBH_4$ (6.8 mg, 180 μmol), the resulting mixture was stirred at 0 °C for 1.4 h before being quenched with saturated aqueous NH_4Cl. After warming to room temperature, the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 4/1 → 2/1) to give primary alcohol **33** (121 mg, 149 μmol, 95%) as a colorless amorphous product.

R_f = 0.52 (hexane/EtOAc = 1/1); $[\alpha]_D^{24}$ −72.0 (*c* 1.00, $CHCl_3$); IR (neat) ν 3482, 3053, 3017, 2918, 2872, 2360, 1922, 1634, 1602, 1509, 1460, 1401, 1362, 1344, 1271, 1219, 1170, 1124, 1088, 1070, 961, 952, 893, 855, 816, 772, 753, 686, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85−7.81 (m, 3H), 7.80−7.73 (m, 9H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.50−7.39 (m, 12H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.97 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 2H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.64 (dd, *J* = 11.0, 4.9 Hz, 2H), 4.25 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.16−4.08 (m, 2H), 3.84 (dd, *J* = 11.7, 2.0 Hz, 1H), 3.77−3.71 (m, 4H), 3.68 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.60−3.54 (m, 2H), 2.36−2.31 (m, 1H), 2.00−1.93 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.1, 135.6, 135.4, 135.3, 133.44, 133.37 (2C), 133.3, 133.21 (2C), 133.15, 133.0, 128.5, 128.43, 138.36, 128.2, 128.1, 128.0 (3C), 127.9 (2C), 127.8, 127.7, 127.0, 126.8, 126.7, 126.5, 126.4, 126.3, 126.20 (2C), 126.17, 126.12 (2C), 126.09, 126.02, 125.97, 125.8 (2C), 78.6, 77.0 75.9, 75.3, 75.0, 73.9, 73.1, 72.8, 72.5, 71.1, 70.4, 69.2, 62.7, 29.5; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{54}H_{50}O_7Na$ 833.3449, found 833.3446.

*tert-Butyldiphenyl(((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-tris-(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-octahydropyrano[3,2-b]pyran-2-yl)methoxy)silane (**34**).* To a stirred solution of primary alcohol **33** (120 mg, 148 μmol) in DMF (740 μL) were added imidazole (42.3 mg, 621 μmol) followed by TBDPSCl (77.0 μL, 297 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.1 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the resulting biphasic mixture was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 → 5/1) to give TBDPS ether **34** (138 mg, 131 μmol, 89%) as a colorless oil.

R_f = 0.23 (hexane/EtOAc = 5/1); $[\alpha]_D^{24}$ −58.3 (*c* 1.00, $CHCl_3$); IR (neat) ν 3053, 3015, 2928, 2878, 2855, 2372, 2351, 2346, 2323, 1717, 1602, 1509, 1470, 1461, 1428, 1388, 1362, 1343, 1271, 1257, 1169, 1080, 1005, 962, 951, 891, 854, 817, 749, 704, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.81 (m, 1H), 7.80−7.72 (m, 10H), 7.71 (s, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.49−7.28 (m, 18H), 7.09 (d, *J* = 8.3 Hz, 1H), 5.16 (d, *J* = 11.0 Hz, 1H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.78 (dd, *J* = 12.4, 6.9 Hz, 2H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.61 (dd, *J* = 11.7, 2.8 Hz, 2H), 4.28 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.19−4.13 (m, 2H), 3.96 (d, *J* = 11.0 Hz, 1H), 3.87 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.78−3.72 (m, 3H), 3.69−3.62 (m, 3H), 2.37−2.32 (m, 1H), 2.04−1.97 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.3, 136.0 (3C), 135.82, 135.76 (3C), 135.6 (2C), 133.9, 133.5, 133.4 (3C), 133.3, 133.2, 133.14, 133.07, 133.0, 129.74, 129.69, 128.4 (2C), 128.1, 128.0 (4C), 127.9, 127.83, 127.78 (2C), 127.75 (2C), 127.7 (2C), 126.9 (2C), 126.59, 126.57, 126.4, 126.2 (2C), 126.1, 126.05 (2C), 126.03, 125.98, 125.9 (2C), 125.85, 125.83, 78.3, 76.2, 75.3, 74.7, 74.3, 73.8, 72.5, 72.3, 71.3, 70.5, 69.4, 63.8, 29.7, 27.0 (3C),

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19.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{70}H_{68}O_7SiNa$ 1071.4627, found 1071.4641.

*((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)-methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)methanol (**36**).* To a stirred solution of tetra-NAP ether **34** (139 mg, 132 μmol) in Ac_2O/AcOH (2.4 mL. 2/1) was added $ZnCl_2$ (361 mg, 2.65 mmol) in Ac_2O/AcOH (2.4 mL; 2/1) at 0 °C. The reaction mixture was stirred at room temperature for 2.4 h. The reaction mixture was then quenched with H_2O, and the resulting biphasic mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous Na_2CO_3 and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 → 5/1 → 4/1) to give acetate **35** (115 mg, 121 μmol, 91%) as a colorless amorphous product.

R_f = 0.12 (hexane/EtOAc = 5/1); $[\alpha]_D^{22}$ −59.6 (c 1.00, $CHCl_3$); IR (neat) ν 3053, 3015, 2929, 2881, 2856, 2371, 2345, 2321, 1739, 1632, 1601, 1589, 1509, 1471, 1461, 1428, 1387, 1363, 1345, 1234, 1218, 1169, 1083, 1053, 893, 855, 818, 752, 703, 666 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84−7.80 (m, 2H), 7.79−7.63 (m, 13H), 7.61 (d, J = 7.6 Hz, 1H), 7.49−7.28 (m, 15H), 5.19 (d, J = 11.0 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 11.7 Hz, 1H), 4.76 (d, J = 11.6, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.36−4.29 (m, 2H), 4.25 (dd, J = 11.7, 4.1 Hz, 1H), 4.15−4.06 (m, 2H), 3.96 (d, J = 11.0, 1H), 3.88 (dd, J = 11.0, 2.8 Hz, 1H), 3.80−3.76 (m, 1H), 3.66 (s, 2H), 3.54 (dd, J = 8.9, 8.9 Hz, 1H), 2.34−2.30 (m, 1H), 2.01−1.95 (m, 1H), 1.95 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 136.1, 136.0 (2C), 135.7 (3C), 135.51, 135.47, 133.9, 133.5, 133.4 (2C), 133.2 (2C), 133.1, 129.8, 129.7, 128.4 (2C), 128.2, 128.12 (2C), 128.08 (2C), 128.0, 127.79 (4C), 127.76 (3C), 127.01, 126.97, 126.62, 126.56, 126.3, 126.2, 126.1 (3C), 125.92, 125.87, 77.7, 76.1, 75.3, 74.8, 74.4, 72.5, 71.5, 70.7, 70.4, 63.75, 63.71, 29.8, 27.0 (3C), 20.9, 19.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{61}H_{62}O_8SiNa$ 973.4106, found 973.4144.

To a stirred solution of acetate **35** (112 mg, 117 μmol) in THF/MeOH (1.8 mL, 1/1) at 0 °C was added K_2CO_3 (7.3 mg, 67.3 μmol) and the mixture was stirred at room temperature for 1 h before being quenched with saturated aqueous NH_4Cl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 2/1) to give primary alcohol **36** (104 mg, 114 μmol, 97%) as a colorless oil.

R_f = 0.17 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −48.3 (c 1.00, $CHCl_3$); IR (neat) ν 3471, 3052, 3013, 2929, 2880, 2857, 2373, 2343, 2334, 2325, 2309, 1633, 1602, 1589, 1509, 1471, 1461, 1427, 1389, 1361, 1344, 1270, 1217, 1187, 1168, 1084, 1058, 1007, 962, 891, 854, 817, 753, 703, 688 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.78 (d, J = 8.3 Hz, 1H), 7.77−7.71 (m, 6H), 7.71−7.65 (m, 5H), 7.62 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.49−7.44 (m, 4H), 7.43−7.28 (m, 11H), 5.15 (d, J = 11.7 Hz, 1H), 5.07 (d, J = 11.0 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 11.0 Hz), 4.28 (dd, J = 8.9, 8.9 Hz, 1H), 4.13−4.06 (m, 2H), 3.94 (d, J = 11.0 Hz, 1H), 3.89−3.83 (m, 2H), 3.73 (dd, J = 11.7, 4.1 Hz, 1H), 3.70−3.60 (m, 3H), 3.57 (dd, J = 8.9, 8.9 Hz,1H), 2.32−2.27 (m, 1H), 2.03−1.95 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 136.0 (3C), 135.7 (3C), 135.6, 133.9, 133.5, 133.42, 133.36 (2C), 133.2, 133.13, 133.09, 129.8, 129.7, 128.4, 128.3, 128.2, 128.11, 128.06 (2C), 127.80 (3C), 127.77 (2C), 127.7 (2C), 126.9, 126.8, 126.6, 126.5, 126.3, 126.2, 126.11, 126.07, 126.02, 125.99, 125.9 (2C), 78.3, 76.8, 76.3, 75.4, 74.8, 74.3, 72.6, 72.5, 71.4, 70.4, 63.7, 62.7, 30.1, 27.0 (3C), 19.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{59}H_{60}O_7SiNa$ 931.4001, found 931.4030.

*((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)-methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)methylmethanesulfonate (**37**).* To a mixture of alcohol **36** (103 mg, 113 μmol) in CH_2Cl_2 (2.0 mL) were added Et_3N (95.0 μL, 682 μmol) and MsCl (26.0 μL, 336 μmol) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with H_2O at 0 °C. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous $KHSO_4$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give crude mesylate **37**, which was used in the next reaction without purification.

*2-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)-methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)acetonitrile (**38**).* To a solution of crude mesylate **37** and powdered MS4A (47.6 mg) in DMF (2.0 mL) was added NaCN (52.3 mg, 1.07 μmol) at 0 °C. After stirring at 70 °C for 17.3 h, the reaction mixture was cooled to 0 °C, diluted with Et_2O, and quenched with saturated aqueous $NaHCO_3$. After filtration through Celite, the aqueous layer was extracted with Et_2O, and the combined organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered. After removal of the solvent in vacuo, the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 → 5/1) to give nitrile **38** (96.7 mg, 105 μmol, 93% for two steps) as a colorless amorphous product.

R_f = 0.58 (hexane/EtOAc = 3/1); $[\alpha]_D^{24}$ −44.5 (c 0.94, $CHCl_3$); IR (neat) ν 3053, 3016, 2954, 2928, 2882, 2856, 2359, 2340, 2253, 1724, 1633, 1602, 1589, 1509, 1488, 1470, 1461, 1428, 1387, 1361, 1346, 1333, 1272, 1217, 1188, 1169, 1142, 1124, 1083, 1008, 961, 952, 893, 855, 819, 770, 756, 704, 669 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84−7.81 (m, 2H), 7.79 (d, J = 8.9 Hz, 1H), 7.77−7.71 (m, 6H), 7.70−7.61 (m, 7H), 7.50−7.47 (m, 4H), 7.45−7.28 (m, 11H), 5.18 (d, J = 11.0 Hz, 1H), 5.13 (d, J = 11.7 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.27 (dd, J = 8.9, 8.9 Hz, 1H), 4,16 (dd, J = 9.6, 1.2 Hz, 1H), 4.14−4.10 (m, 1H), 3.96 (d, J = 10.3 Hz, 1H), 3.87 (dd, J = 11.0, 3.5 Hz, 1H), 3.79−3.75 (m, 1H), 3.69−3.64 (m, 2H), 3.42 (dd, J = 9.3, 9.3 Hz, 1H), 2.70 (dd, J = 17.2, 3.5 Hz, 1H), 2.51 (dd, J = 16.5, 1.2 Hz, 1H), 2.38−2.33 (m, 1H), 1.97−1.91 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0 (2C), 135.9, 135.7 (2C), 135.4, 135.2, 133.8, 133.4, 133.3, 133.2, 133.1, 129.8, 129.7, 128.5, 128.4, 128.3, 128.1, 128.0 (2C), 127.84 (3C), 127.80 (3C), 127.76 (3C), 127.0, 126.9, 126.7, 126.5, 126.4, 126.3, 126.2, 126.13, 126.10, 126.0, 125.89, 125.87, 117.2, 80.6, 76.6, 76.0, 75.6, 74.7, 74.4, 72.3, 71.5, 70.6, 68.5, 63.6, 29.84, 29.80, 27.0 (3C), 21.7, 19.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{60}H_{59}NO_6SiNa$ 940.4004, found 940.4036.

*1-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)-methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)propan-2-one (**4**).* Nitrile **38** (38.5 mg, 41.9 μmol) was dissolved in dry toluene (0.8 mL) and cooled to 0 °C. Me_3Al (1.09 M solution in hexane, 770 μL, 839 μmol) was added followed by the addition of $Ni(acac)_2$ (10 mg/mL of solution in benzene, 220 μL, 8.7 μmol). After stirring at 0 °C for 3.2 h, Me_3Al (1.09 M solution in hexane, 380 μL, 414 μmol) and $Ni(acac)_2$ (10 mg/mL solution in benzene, 110 μL, 4.4 μmol) were added. After stirring at 0 °C for 1.8 h, Me_3Al (1.09 M solution in hexane, 380 μL, 414 μmol) and $Ni(acac)_2$ (10 mg/mL of solution in benzene, 110 μL, 4.4 μmol) were added again. The resulting mixture was stirred at 0 °C for 0.4 h and then quenched with MeOH. After addition of EtOAc and saturated aqueous Rochelle's salt, the resulting mixture was stirred vigorously at room temperature. The biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 → 6/1 → 5/1) to give methyl ketone **4** (25.3 mg, 27.1 μmol, 65%) as a colorless amorphous product.

R_f = 0.35 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −32.2 (c 0.60, $CHCl_3$); IR (neat) ν 3052, 3014, 2955, 2929, 2856, 2360, 2340, 2331, 1716, 1634, 1603, 1589, 1509, 1469, 1462, 1427, 1389, 1360, 1330, 1271, 1239, 1214, 1169, 1143, 1124, 1112, 1104, 1083, 1054, 1020, 1008,

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998, 961, 952, 894, 855, 818, 772, 752, 704, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87−7.80 (m, 2H), 7.78 (d, J = 8.3 Hz, 1H), 7.76−7.71 (m, 5H), 7.70−7.66 (m, 4H), 7.65 (s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.49−7.45 (m, 4H), 7.43−7.28 (m, 11H), 5.17 (d, J = 11.0 Hz, 1H), 5.09 (d, J = 11.6 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H, 4.75 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.28 (dd, J = 8.9, 8.9 Hz), 4.13−4.08 (m, 2H), 4.03−3.99 (m, 1H), 3.96 (d, J = 11.0 Hz, 1H), 3.86 (dd, J = 11.0, 4.1 Hz, 1H), 3.68−3.61 (m, 2H), 3.29 (dd, J = 8.9, 8.9 Hz, 1H), 2.78 (dd, J = 15.8, 2.8 Hz, 1H), 2.48 (dd, J = 15.8, 9.6 Hz, 1H), 2.36−2.31 (m, 1H), 2.10 (s, 3H), 2.08−2.03 (m, 1H), 0.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.6, 136.04, 135.98 (2C), 135.72 (2C), 135.69, 135.5, 133.8, 133.44, 133.37, 133.3, 133.13, 133.07, 129.74, 129.69, 128.5, 128.4, 128.3, 129.2, 128.05 (2C), 128.01, 127.8, 127.8 (2C), 127.7 (2C), 127.0, 126.7, 126.62, 126.57, 126.32, 126.26, 126.2, 126.1, 126.02, 126.00, 125.91, 125.88, 125.6, 125.3, 81.5, 77.1, 76.4, 75.3, 74.8, 74.4, 72.4, 71.3, 70.4, 68.8, 65.6, 63.8, 46.5, 30.8, 29.6, 27.0 (3C), 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{61}H_{62}O_7SiNa$ 957.4157, found 957.4148.

*(R)-1-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)-4-hydroxy-4-((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-octahydropyrano[3,2-b]pyran-2-yl)butan-2-one (**39**).* A flask containing activated MS4A (35.0 mg) and LHMDS (21.0 mg, 126 μmol) was charged with THF (100 μL) and cooled at −78 °C, and a solution of methyl ketone **4** (72.9 mg, 77.9 μmol) in THF (560 μL) was added dropwise precooling along the side of the reaction flask. The reaction mixture was stirred at −78 °C for 1.1 h, and a solution of aldehyde **3** (40.2 mg, 49.7 μmol) in THF (400 μL) was added dropwise precooling along the side of the reaction flask. The mixture was stirred at −78 °C for 1 h and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 4/1 → 2/1 → 1/1) and PTLC (hexane/EtOAc = 3/2 × 4) to give aldol **39** (17.6 mg, 10.1 μmol, 20%) as a colorless oil.

R_f = 0.23 (hexane/EtOAc = 3/2); $[\alpha]_D^{23}$ −29.0 (c 0.44, $CHCl_3$); IR (neat) ν 3054, 3013, 2929, 2881, 2858, 2360, 1172, 1633, 1602, 1509, 1470, 1460, 1427, 1362, 1343, 1271, 1217, 1169, 1124, 1083, 1009, 962, 951, 893, 855, 827, 753, 705, 687, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86−7.66 (m, 23 H), 7.64−7.62 (m, 3H), 7.59 (d, J = 8.3 Hz, 1H), 7.55−7.27 (m, 30 H), 7.24 (dd, J = 8.9, 1.4 Hz, 1H), 7.09 (dd, J = 8.3, 1.4 Hz, 1H), 5.02 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 11.7 Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 4.89 (d, J = 11.6 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.61 (d, J = 11.0 Hz, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.55−4.51 (m, 1H), 4.49 (d, J = 11.0 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.22−4.16 (m, 2H), 4.16−4.11 (m, 1H), 3.95 (dd, J = 10.3, 6.8 Hz, 1H), 3.91−3.79 (m, 5H), 3.79−3.71 (m, 4H), 3.67 (dd, J = 8.9, 8.9 Hz, 1H), 3.46−3.41 (m, 2H), 3.33 (br d, J = 8.9 Hz, 1H), 3.34−2.97 (m, 2H), 2.92 (d, J = 4.9 Hz, 1H), 2.54 (dd, J = 15.1, 2.8 Hz, 1H), 2.37−2.34 (m, 1H), 2.31 (dd, J = 17.8, 2.0 Hz, 1H), 2.19 (dd, J = 15.1, 8.9 Hz, 1H), 2.22−2.27 (m, 1H), 1.98 (dd, J = 23.4, 11.6 Hz, 1H), 1.71 (dd, J = 23.4, 11.7 Hz), 0.98 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 136.2, 136.03, 135.98 (3C), 135.8, 135.72 (3C), 135.65, 135.5 (2C), 135.4, 133.9, 133.5, 133.40 (2C), 133.35, 133.33 (3C), 133.29, 133.22, 133.19, 133.12, 133.11, 133.05 (2C), 133.01, 129.74, 129.68, 128.5 (2C), 128.41, 128.36, 128.3, 128.2 (2C), 128.10 (2C), 128.06 (3C), 128.0, 127.9 (3C), 127.82 (2C), 127.77 (2C), 127.7 (3C), 127.0, 126.92, 126.85, 126.7, 126.5, 126.42, 126.38 (2C), 126.36, 126.3 (2C), 126.21 (2C), 126.16 (2C), 126.13 (2C), 126.08, 126.02 (3C), 125.99, 125.97, 125.9, 125.85, 125.77 (2C), 125.5, 81.5, 78.7, 77.8, 76.3, 75.6, 75.2 (2C), 75.0, 74.9, 74.7, 74.3, 73.9 (2C), 72.5, 72.3, 72.2, 71.7, 71.1, 70.23, 70.21, 69.2, 68.9, 65.2, 63.4, 47.2, 46.2, 29.7, 29.3, 27.0 (3C), 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{115}H_{110}O_{14}SiNa$ 1766.7589, found 1766.7579.

*(1R,3R)-4-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)-oxy)methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano-[3,2-b]pyran-2-yl)-1-((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-tris-(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-octahydropyrano[3,2-b]pyran-2-yl)butane-1,3-diol (**40**).* To a solution of β-hydroxy ketone **39** (9.9 mg, 5.7 μmol) in MeCN (680 μL), AcOH (340 μL), and CH_2Cl_2 (100 μL) was added $Me_4NHB(OAc)_3$ (9.4 mg, 30.4 μmol) at 0 °C. After stirring at 0 °C for 1.3 h, the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 0.6 h and then quenched with saturated aqueous solution of Rochelle's salt. The resulting biphasic mixture was stirred vigorously for 1.3 h. The biphasic mixture was then extracted with EtOAc, and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash silica gel column chromatography (hexane/EtOAc = 2/1 → 3/2 → 1/1), and the resulting impure diol **40** was used in the next step without further purification.

*(2S,3R,4R,4aS,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-((2R,4R)-2,4-dihydroxy-4-((2S,3R,4aS,6S,7R,8R,8aS)-3,7,8-trihydroxy-6-(hydroxymethyl)octahydropyrano[3,2-b]pyran-2-yl)butyl)-octahydropyrano[3,2-b]pyran-3,4,7-triol (**1**).* To a stirred solution of antidiol **40** in EtOAc (500 μL) and MeOH (500 μL) was added $Pd(OH)_2/C$ (20% Pd, 4.1 mg, 48 wt %) at room temperature, and the solution was purged with H_2 and then stirred for 19.4 h under an atmosphere of H_2 (baloon). The reaction mixture was filtered through a short pad of Celite and then concentrated. The residue was purified by reverse phase preparative TLC ($MeOH/H_2O$ = 2/1) to give the LMNO ring system **1** (2.3 mg, 3.0 μmol, 53% for two steps) as a colorless oil.

R_f = 0.20 ($MeOH/H_2O$ = 2/1); $[\alpha]_D^{22}$ −26.7 (c 0.10, MeOH); IR (neat) ν 3360, 2947, 2872, 2832, 1725, 1637, 1601, 1459, 1450, 1397, 1384, 1365, 1319, 1285, 1162, 1108, 1064, 1028 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66 (t, J = 7.2 Hz, 4H), 7.47−7.36 (m, 6H), 4.05−3.93 (m, 5H), 3.90−3.84 (m, 1H), 3.80 (dd, J = 10.8, 6.0 Hz, 1H), 3.71−3.54 (m, 8H), 3.49−3.45 (m, 1H), 3.45−3.41 (m, 1H), 3.22 (t, J = 9.6 Hz, 1H), 3.16 (d, J = 9.6 Hz, 1H), 3.05 (t, J = 9.6 Hz, 1H), 2.01−1.82 (m, 4H), 1.76−1.70 (m, 1H), 1.54−1.46 (m, 1H), 1.46−1.39 (m, 1H), 1.24−1.16 (m, 4H), 0.98 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5 (6C), 130.9 (2C), 128.8 (4C), 76.4, 75.6, 75.2, 75.1, 74.9, 74.4, 71.5, 70.71 (2C), 70.66 (2C), 68.5, 68.4, 66.3, 66.0, 65.6, 65.5, 62.1, 41.9, 40.4, 32.7, 27.2 (3C), 19.7, 15.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{38}H_{56}O_{14}SiNa$ 787.3332, found 787.3336.

*(R)-1-(Furan-2-yl)-2-(naphthalen-2-ylmethoxy)ethan-1-ol (ent-**17**).* To a stirred solution of furyl ketone **15** (8.51 g, 31.9 mmol) in CH_2Cl_2 (106 mL) were added TBAC (2.66 g, 9.58 mmol), a solution of sodium formate (21.8 g, 319 mmol) in H_2O (106 mL), and (*R*,*R*)-**16** (95.8 mg, 0.160 mmol). The resulting mixture was stirred at room temperature for 4 h, at which time the mixture was diluted with H_2O. The biphasic mixture was then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 → 7/1) to provide chiral alcohol *ent*-**17** (8.57 mg, 31.9 mmol, quant) as a pale yellow solid.

R_f = 0.41 (hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ +8.3 (c 1.1, $CHCl_3$); IR (neat) ν 3357, 3421, 3147, 3116, 3053, 3022, 2914, 2863, 2372, 2349, 2322, 1723, 1631, 1600, 1507, 1469, 1439, 1364, 1344, 1316, 1269, 1253, 1217, 1172, 1144, 1123, 1107, 1087, 1069, 1008, 948, 890, 856, 816, 771, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85−7.82 (m, 3H), 7.77 (s, 1H), 7.51−7.48 (m, 2H), 7.46 (dd, J = 7.8, 1.2 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 6.34 (dd, J = 2.8, 1.8 Hz, 1H), 6.32 (d, J = 2.8 Hz, 1H), 4.96 (dd, J = 11.0, 4.8 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 3.82−3.78 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 142.3, 135.3, 133.4, 133.2, 128.5, 128.0, 127.8, 126.8, 126.3, 126.1, 125.8, 110.4, 107.2, 73.7, 72.6, 67.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{16}O_3Na$ 291.0992, found 291.0991.

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*(2R,6R)-6-((Naphthalen-2-ylmethoxy)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Pivalate (ent-**18**).* To a stirred solution of chiral furan *ent*-**17** (8.57 g, 31.94 mmol) in THF (228 mL) and H_2O (90 mL) at 0 °C were added $NaHCO_3$ (5.37 g, 63.9 mmol), NaOAc (2.62 g, 31.94 mmol), and NBS (5.69 g, 31.9 mmol). The reaction mixture was stirred at 0 °C for 30 min at which time a solution of saturated aqueous $NaHCO_3$ was added. The resulting biphasic mixture was then extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give crude hemiacetal, which was used in the next step directly without purification.

The crude mixture of hemiacetals was then dissolved in CH_2Cl_2 (160 mL) and cooled to −78 °C. To the stirred solution were added DMAP (195 mg, 1.60 mmol), Et_3N (6.6 mL, 63.9 mmol), and PvCl (4.7 mL, 38.3 mmol), and the reaction mixture was stirred at −78 °C for 1 h. The cold mixture was then rapidly poured into a mixed solution of saturated aqueous NH_4Cl and EtOAc. H_2O was added, and the resulting biphasic mixture was then extracted with EtOAc. The combined organic was washed with H_2O and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 → 8/1 → 7/1 → 5/1) to afford pyranone *ent*-**18** (7.05 g, 19.1 mmol, 60% for two steps) as a colorless solid and α-anomer (2.89 g, 7.84 mmol, 25% for two steps) as a colorless solid.

R_f = 0.65 (hexane/EtOAc = 2/1); $[\alpha]_D^{25}$ −101.6 (*c* 0.91, $CHCl_3$); IR (neat) ν 3053, 2972, 2930, 2870, 2365, 2338, 2098, 1739, 1699, 1631, 1604, 1509, 1480, 1459, 1398, 1367, 1273, 1232, 1123, 1096, 1029, 999, 930, 856, 816, 768, 751, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.76 (s, 1H), 7.49−7.46 (m, 2H), 7.44 (dd, *J* = 9.0, 1.2 Hz, 1H), 6.95 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 6.27 (d, *J* = 10.2, 1H), 4.75 (s, 2H), 4.65 (dd, *J* = 4.2, 2.4 Hz, 1H), 3.97 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.93 (dd, *J* = 10.8, 3.0 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.4, 177.0, 142.5, 135.4, 133.4, 133.2, 129.0, 128.3, 128.0, 127.8, 126.6, 126.2, 126.0, 125.8, 87.2, 76.6, 73.9, 68.7, 39.3, 27.1; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{24}O_5Na$ 391.1516, found 391.1499.

*(2R,5S,6R)-5-Hydroxy-6-((naphthalen-2-ylmethoxy)methyl)-5,6-dihydro-2H-pyran-2-yl Pivalate (ent-**19**).* To a stirred solution of *ent*-**18** (4.68 g, 12.7 mmol) in CH_2Cl_2/MeOH (116 mL, 1:1) at room temperature was added $CeCl_3{\cdot}7H_2O$ (2.36 g, 6.34 mmol). The solution was stirred for 15 min and then cooled to −78 °C. To the stirred solution at −78 °C was added $NaBH_4$ (576 mg, 15.2 mmol), and the resulting mixture was stirred at −78 °C for 30 min before being quenched with saturated aqueous NH_4Cl. After warming to rt, the resulting biphasic mixture was diluted with EtOAc, and the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting crude allylic alcohol *ent*-**19** was used in the next step without further purification.

*(2R,5S,6R)-5-(Naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-5,6-dihydro-2H-pyran-2-yl Pivalate (ent-**20**).* To a stirred solution of crude allylic alcohol *ent*-**19** in toluene (63 mL) at room temperature were added NAPBr (14.0 g, 63.5 mmol) and TBAI (2.31 g, 6.35 mmol). An aqueous solution of NaOH (25%, 63 mL) was added, and the mixture was allowed to stir for 4 h. The reaction mixture was diluted with saturated aqueous NaCl and EtOAc and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 → 9/1 → 8/1 → 7/1 → 5/1) to give naphthylmethyl ether *ent*-**20** (5.36 mg, 10.5 mmol, 83% yield for two steps) as a yellow oil.

R_f = 0.6 (hexane/EtOAc = 3/1); $[\alpha]_D^{25}$ +30.0 (*c* 0.89, $CHCl_3$); IR (neat) ν 3053, 2968, 2927, 2907, 2867, 2359, 1737, 1601, 1509, 1479, 1394, 1367, 1276, 1195, 1120, 1096, 1029, 1006, 921, 853, 816, 771, 751 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.75 (m, 5H), 7.70−7.66 (m, 2H), 7.60 (s, 1H), 7.48−7.43 (m, 5H), 7.28 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.33 (s, 1H), 6.21 (d, *J* = 10.2 Hz, 1H), 5.79 (ddd, *J* = 10.2, 3.0, 1.8 Hz, 1H), 4.79 (d, *J* = 12.6 Hz, 1H), 4.77 (d, *J* = 11.4 Hz, 1H) 4.64 (d, *J* = 12.6 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.30 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.01−3.98 (m, 1H), 3.81 (dd, *J* = 10.8, 2.4, Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5, 135.7, 135.2, 133.4, 133.3, 133.2, 133.1, 132.1, 128.4, 128.3, 128.1, 128.0, 127.8, 127.8, 126.9, 126.8, 126.3, 126.2, 126.2, 126.0, 126.0, 126.0, 124.9, 88.7, 73.6, 72.0, 71.9, 70.0, 68.6, 39.1, 27.1; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{34}O_5Na$ 533.2298, found 533.2303.

*(2R,3S,4R,5S,6R)-3,4-Dihydroxy-5-(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2-yl Pivalate (ent-**21**).* To a stirred solution of naphthylmethyl ether *ent*-**20** (5.07 g, 9.92 mmol) in acetone/H_2O (102 mL, 5:1) at room temperature were added NMO (3.49 g, 29.8 mmol) and $K_2OsO_4{\cdot}2H_2O$ (183 mg, 0.496 mmol), and the reaction mixture was allowed to stir for 15 h. The reaction was then quenched with saturated aqueous $Na_2S_2O_3$ (32 mL), and the resulting biphasic mixture was stirred vigorously for 30 min and then extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by reprecipitation and flash silica gel column chromatography (hexane/EtOAc = 1/1) to give diol *ent*-**21** (5.23 g, 9.61 mmol, 97%) as a colorless amorphous solid.

R_f = 0.15 (hexane/EtOAc = 2/1); $[\alpha]_D^{26}$ +59.8 (*c* 0.95, $CHCl_3$); IR (neat) ν 3394, 3054, 2928, 2859, 2360, 2341, 2102, 1740, 1602, 1508, 1478, 1366, 1343, 1277, 1253, 1220, 1119, 1087, 1029, 969, 897, 857, 818, 773, 752, 674 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.77 (m, 5H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.56 (s, 1H), 7.5−7.41 (m, 5H), 7.29 (d, *J* = 6.8 Hz, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 2H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 3.96−3.92 (m, 3H), 3.89 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.85−3.81 (m, 1H), 3.78 (dd, *J* = 10.8, 1.8 Hz, 1H), 2.50 (s, 1H), 2.39 (s, 1H), 1.19 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.4, 135.5, 135.4, 133.4, 133.3, 133.2, 133.2, 128.5, 128.4, 128.1, 127.8, 127.8, 127.1, 127.0, 126.3, 126.2, 126.1, 126.0, 93.2, 75.2, 75.1, 73.9, 73.36, 71.9, 70.2, 68.5, 39.2, 27.1; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{36}O_7Na$ 567.2353, found 567.2354.

*(2R,3S,4R,5R,6R)-3-Hydroxy-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2-yl Pivalate (ent-**22**).* A stirred solution of diol *ent*-**21** (5.23 g, 9.61 mmol), *n*-Bu_2SnO (2.39 g, 9.61 mmol), TBAI (1.14 g, 3.09 mmol), and NAPBr (2.97 g, 13.5 mmol) in benzene (181 mL) was heated at reflux in a flask equipped with a Dean−Stark apparatus for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by reprecipitation and flash silica gel column chromatography (hexane/EtOAc = 5/1 → 4/1) to give naphthylmethyl ether *ent*-**22** (5.19 g, 7.58 mmol, 79%) as a colorless amorphous solid.

R_f = 0.38 (hexane/EtOAc = 2/1); $[\alpha]_D^{26}$ +65.2 (*c* 0.97, $CHCl_3$); IR (neat) ν 3727, 3440, 3055, 2961, 2930, 2867, 2359, 2341, 2102, 1742, 1602, 1509, 1461, 1366, 1274, 1255, 1219, 1168, 1123, 1032, 957, 892, 856, 815, 776, 770, 754, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.83−7.72 (m, 9H), 7.60 (t, 2H), 7.52−7.40 (m, 9H), 6.19 (s, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.90 (s, 2H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.6 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 4.10 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.94 (d, *J* = 1.8 Hz, 1H), 3.90 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.84 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.74 (dd, *J* = 12.6, 3.6 Hz, 2H), 2.62 (d, *J* = 2.4 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 135.7, 135.6, 135.0, 133.4, 133.3, 133.3, 133.1, 133.1, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.2, 126.9, 126.8, 126.4, 126.3, 126.2, 126.2, 126.1, 126.1, 126.0, 126.0, 93.0, 79.3, 75.6, 74.0, 73.9, 73.8, 72.5, 68.5, 68.0, 39.1, 27.0; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{44}H_{44}O_7Na$ 707.2979, found 707.2981.

*(2S,3S,4R,5R,6R)-4,5-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2,3-diol (ent-**23**).* To a stirred solution of benzyl ether *ent*-**22** (50.3 mg, 69.2 μmol) in THF/MeOH (1 mL, 1:1) at 0 °C was added NaOMe (14.0 mg, 259 μmol). The reaction mixture was allowed to stir at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The

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organic phase was separated, and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residual crude diol *ent*-**23** was immediately used in the next reaction without further purification.

*(2R,3S,4S,5R,6R)-4,5-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-2,3-diyl Diacetate (ent-**24**).* To a solution of the above crude acetate *ent*-**23** in CH_2Cl_2 (1 mL) at room temperature were added pyridine (0.1 mL, 1.24 mmol), DMAP (3.0 mg, 24.6 μmol), and Ac_2O (0.1 mL, 1.06 mmol). The reaction mixture was allowed to stir for 30 min, and then H_2O was added. The organic phase was separated, and the aqueous layer was further extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 → 7/1 → 5/1 → 3/1) to give acetate *ent*-**24** (46.2 mg, 67.5 μmol, 97% for two steps) as a colorless oil.

R_f = 0.37 (hexane/EtOAc = 3/1); $[\alpha]_D^{18}$ +10.4 (*c* 1.7, $CHCl_3$); IR (neat) ν 3054, 2864, 2372, 2321, 1750, 1602, 1509, 1368, 1217, 1155, 1124, 1104, 1029, 963, 857, 818, 771, 753, 662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.75 (m, 8H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.50−7.40 (m, 9H), 7.17 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.16 (d, *J* = 1.8 Hz, 1H), 5.45−5.44 (m, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.09−4.04 (m, 2H), 3.91−3.89 (m, 2H), 3.76 (d, *J* = 9.0 Hz, 1H), 2.20 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 168.5, 135.7, 135.7, 135.3, 133.39, 133.36, 133.3, 133.19, 133.15, 133.1, 128.4, 128.3, 128.2, 128.04, 128.01 (2C), 127.83, 127.82, 127.7, 127.1, 126.8, 126.5, 126.24 (2C), 126.18, 126.1 (2C), 126.01, 125.96, 125.9, 91.5, 77.8, 75.5, 74.0, 73.9, 73.8 (2C), 72.1, 68.6, 67.7, 21.2, 21.0; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{43}H_{40}O_8Na$ 707.2615, found 707.2619.

*(2R,3R,4S,5R,6R)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-yl Acetate (ent-**25**).* To a stirred solution of acetate *ent*-**24** (249 mg, 0.363 mmol) in MeCN (2.8 mL) at room temperature were added allyltrimethylsilane (0.87 mL, 5.44 mmol) and 3Å powdered molecular sieves (120 mg). The mixture was cooled to 0 °C, and TMSOTf (0.13 mL, 0.726 mmol) was added. The resulting solution was stirred at room temperature for 1 h before being poured into saturated aqueous $NaHCO_3$. The resulting biphasic mixture was then filtrated through Celite and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 8/1 → 7/1 → 5/1 → 3/1) to give olefin *ent*-**25** (197 mg, 0.295 mmol, 81%) as a colorless oil.

R_f = 0.50 (hexane/EtOAc = 3/1); $[\alpha]_D^{27}$ +6.5 (*c* 1.2, $CHCl_3$); IR (neat) ν 3054, 2864, 2359, 1737, 1641, 1602, 1509, 1440, 1372, 1240, 1170, 1123, 1099, 1044, 918, 856, 818, 771, 752, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.73 (m, 8H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 8.4, 4.2 Hz, 2H), 7.49−7.40 (m, 9H), 7.16 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.79 (dddd, *J* = 17.4, 10.8, 6.6, 6.6 Hz, 1H), 5.39 (dd, *J* = 3.0, 1.8 Hz, 1H), 5.08 (d, *J* = 9.6 Hz, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 5.00 (d, *J* = 11.6 Hz, 1H), 4.83 (dd, *J* = 12.6, 11.4 Hz, 2H), 4.68−4.62 (m, 3H), 4.15−4.09 (m, 1H), 3.97−3.92 (m, 2H), 3.84 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.77−3.74 (m, 2H), 2.51−2.46 (m, 1H), 2.35−2.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 135.8, 135.7, 135.3, 133.4, 133.35, 133.31, 133.2, 133.1, 133.0, 128.4, 128.3, 128.1, 128.02, 127.99, 127.83, 127.81, 127.7, 127.1, 126.8, 126.5, 126.24, 126.20, 126.17, 126.11, 126.07, 126.0, 125.9, 117.9, 77.5, 75.0, 74.8, 73.7, 73.0, 71.9, 69.9, 69.2, 33.8, 21.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{44}H_{42}O_6Na$ 689.2874, found 689.2854.

*(2R,3R,4R,5R,6R)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-ol (ent-**26**).* To a stirred solution of acetate *ent*-**25** (742 mg, 1.11 mmol) in THF/MeOH (20 mL, 1:1) at 0 °C was added K_2CO_3 (61.5 mg, 0.445 mmol), and the mixture was stirred at room temperature for 2 h before being quenched with saturated aqueous NH_4Cl and EtOAc. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1) to give alcohol *ent*-**26** (683 mg, 1.09 mmol, 98%) as a colorless oil.

R_f = 0.11 (hexane/EtOAc = 3/1); $[\alpha]_D^{19}$ +23.5 (*c* 1.2, $CHCl_3$); IR (neat) ν 3449, 3054, 2867, 1749, 1639, 1602, 1508, 1440, 1366, 1271, 1218, 1170, 1124, 1091, 895, 856, 817, 770, 752, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.70 (m, 9H), 7.62 (dd, *J* = 8.4, 4.2 Hz, 2H), 7.55 (s, 1H), 7.49−7.39 (m, 8H), 7.22 (dd, *J* = 9.0, 1.2 Hz, 1H), 5.81 (dddd, *J* = 17.4, 9.6, 6.6, 6.6 Hz, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 5.03 (d, *J* = 9.6 Hz, 1H), 4.89 (d, *J* = 11.4 Hz, 1H), 4.78−4.74 (m, 3H), 4.67 (dd, *J* = 12.6, 11.4 Hz, 2H), 4.02−3.98 (m, 1H), 3.95−3.92 (m, 2H), 3.86 (dd, *J* = 7.2, 3.0 Hz, 1H), 3.85−3.81 (m, 1H), 3.79 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.74 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.42 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 2.34 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.9 135.7, 135.1, 134.3 (2C), 133.4, 133.3, 133.2, 133.13, 133.11, 128.6, 128.3, 128.0 (2C), 127.9, 127.83, 127.77, 127.0, 126.7 (2C), 126.4, 126.3, 126.18, 126.16, 126.05, 126.00, 125.95 (2C), 125.9, 117.5, 79.2 (2C), 75.1, 74.4, 74.3, 73.6 (2C), 73.1, 72.3, 69.1, 68.5, 34.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{42}H_{40}O_5Na$ 647.2768, found 647.2767.

*(2R,3S,4S,5R,6R)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-yl 4-Nitrobenzoate (ent-**27**).* To a stirred solution of alcohol *ent*-**26** (684 mg, 1.09 mmol) in toluene (10 mL) at room temperature were added Ph_3P (655 mg, 2.64 mmol), 4-nitrobenzoic acid (366 mg, 2.19 mmol), and DIAD (1.3 mL, 2.46 mmol), and the resulting mixture was heated at 70 °C for 1.5 h. The cooled reaction mixture was concentrated, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 → 7/1) to give 4-nitrobenzoate *ent*-**27** (632 mg, 0.816 mmol, 75%) as a pale yellow oil.

R_f = 0.53 (hexane/EtOAc = 3/1); $[\alpha]_D^{27}$ +89.4 (*c* 1.0, $CHCl_3$); IR (neat) ν 3054, 2925, 2360, 2327, 2308, 1727, 1603, 1525, 1347, 1270, 1095, 1014, 855, 818, 718, 686, 673 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.80 (dd, *J* = 7.8, 7.8 Hz, 6H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.45−7.54 (m, 6H), 7.50−7.38 (m, 8H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 1H), 5.76 (dddd, *J* = 17.4, 9.6, 6.6, 6.6 Hz, 1H), 5.37 (dd, *J* = 7.8, 5.4 Hz, 1H), 5.09 (d, *J* = 16.2 Hz, 1H), 5.04 (d, *J* = 11.4 Hz, 1H), 5.02 (d, *J* = 12.6 Hz, 1H), 4.88−4.81 (m, 3H), 4.68 (dd, *J* = 9.6, 9.6 Hz, 2H), 4.31 (ddd, *J* = 10.2, 4.8, 4.8 Hz, 1H), 4.07 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.93−3.85 (m, 3H), 3.77 (dd, *J* = 10.2, 1.2 Hz, 1H), 2.58 (ddd, *J* = 16.2, 8.4, 8.4 Hz, 1H), 2.32−2.27 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.8, 150.4, 135.7, 135.6, 135.3, 134.7, 133.6, 133.4, 133.25, 133.20, 133.1, 132.9, 130.5 (3C), 128.4, 128.35, 128.25, 128.04, 127.97, 127.91, 127.87, 127.73, 127.71, 126.9, 126.8, 126.6, 126.32, 126.30, 126.2, 126.14, 126.11, 126.0, 126.0, 125.9, 123.2 (3C), 117.8, 79.7, 77.5, 75.0, 74.7, 73.8, 73.0, 72.6, 71.6, 68.7, 32.0; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{49}H_{43}O_8NNa$ 796.2881, found 796.2877.

*(2R,3S,4R,5R,6R)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-ol (ent-**28**).* To a stirred solution of 4-nitrobenzoate *ent*-**27** (628 mg, 0.811 mmol) in THF/MeOH (16 mL, 1:1) at 0 °C was added K_2CO_3 (44.8 mg, 0.324 mmol), and the mixture was stirred at room temperature for 30 min before being quenched with saturated aqueous NH_4Cl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 6/1 → 4/1) to give alcohol *ent*-**28** (492 mg, 0.787 mmol, 97%) as a colorless oil.

R_f = 0.48 (hexane/EtOAc = 2/1); $[\alpha]_D^{22}$ +24.5 (*c* 1.0, $CHCl_3$); IR (neat) ν 3495, 3053, 3019, 2924, 2856, 2359, 2342, 2295, 1712, 1638, 1604, 1506, 1466, 1439, 1364, 1340, 1269, 1253, 1219, 1172,

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1141, 1123, 1080, 1006, 951, 910, 894, 853, 816, 771, 681 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.82 (m, 4H), 7.74−7.63 (m, 7H), 7.57 (s, 1H), 7.50−7.42 (m, 7H), 7.40 (dd, J = 8.4, 1.2 Hz, 1H), 7.30−7.27 (m, 2H), 5.84 (dddd, J = 16.8, 10.2, 7.2, 7.2 Hz, 1H), 5.13 (dd, J = 16.8, 1.2 Hz, 1H), 5.06 (dd, J = 9.0, 1.2 Hz, 1H), 4.13 (dd, J = 10.2, 5.4 Hz, 1H), 4.00−6.96 (m, 1H), 3.89 (dd, J = 10.2, 6.6 Hz, 1H), 3.84 (dd, J = 5.4, 5.4 Hz, 1H), 3.77 (dd, J = 10.2, 4.8 Hz, 1H), 3.74−3.71 (m, 2H), 2.96 (d, J = 7.2 Hz, 1H), 2.47 (ddd, J = 14.4, 7.2, 7.2 Hz, 1H), 2.41 (ddd, J = 14.4, 7.2, 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.8, 135.5, 135.0,134.8 (2C), 133.4, 133.33, 133.30, 133.2, 133.1 (2C), 128.5, 128.4, 128.3, 128.1, 128.0 (2C), 127.9, 127.84, 127.82, 126.8, 126.6, 126.5, 126.4, 126.3, 126.24, 126.19, 126.15, 126.0, 125.9, 125.8, 125.6, 117.2, 77.8, 74.9, 73.7, 73.6, 73.5, 73.0, 69.3, 68.2, 33.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{42}H_{40}O_5Na$ 647.2768, found 647.2763.

*(((2R,3S,4S,5R,6R)-2-Allyl-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)tetrahydro-2H-pyran-3-yl)oxy)-(tert-butyl)dimethylsilane (ent-**29**).* To a stirred solution of alcohol *ent*-**28** (488 mg, 0.782 mmol) in DMF (1.0 mL) at 0 °C were added imidazole (213 mg, 3.13 mmol) followed by TBSCl (236 mg, 1.56 mmol). The reaction mixture was warmed to 70 °C and stirred for 14 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/0 → 9/1) to give TBS ether *ent*-**29** (574 mg, 0.777 mmol, 99%) as a colorless oil.

R_f = 0.58 (hexane/EtOAc = 5/1); $[\alpha]_D^{22}$ +21.5 (c 1.0, $CHCl_3$); IR (neat) ν 3053, 2951, 2927, 2890, 2856, 2372, 2349, 2322, 1641, 1601, 1506, 1469, 1439, 1361, 1340, 1253, 1219, 1087, 1006, 955, 910, 890, 853, 836, 813, 771, 677 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.68 (m, 9H), 7.48−7.34 (m, 10H), 6.96 (dd, J = 9.0, 2.4 Hz, 1H), 5.87 (dddd, J = 17.4, 10.8, 6.6, 6.6 Hz, 1H), 5.12 (dd, J = 17.4, 1.2 Hz, 1H), 5.10−5.07 (m, 2H), 4.97 (d, J = 12.0 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.50 (ddd, J = 8.4, 6.0, 6.0 Hz, 1H), 4.01−3.98 (m, 1H), 3.80 (dd, J = 10.2, 3.6 Hz, 1H), 3.75−3.68 (m, 4H), 2.54−2.51 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 135.7, 135.6, 135.2, 133.5, 133.4, 133.2, 133.2, 133.0, 128.3, 128.1, 128.0, 128.0, 127.8, 127.8, 127.6, 127.1, 126.5, 126.3, 126.2, 126.1, 126.0, 125.9, 125.8, 125.8, 125.7, 116.9, 83.5, 78.5, 76.7, 75.6, 75.2, 73.8, 73.4, 71.3, 69.0, 29.2, 26.0, 18.1, −4.3, −4.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{48}H_{54}O_5SiNa$ 761.3633, found 761.3633.

*2-((2R,3S,4S,5R,6R)-3-((tert-Butyldimethylsilyl)oxy)-4,5-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-tetrahydro-2H-pyran-2-yl)acetaldehyde (ent-**7**).* A stirred solution of TBS ether *ent*-**29** (574 mg, 0.777 mmol) in CH_2Cl_2/MeOH (7.8 mL, 5:1) was cooled to −78 °C. A steam of O_3 was then bubbled through the solution for 8 min, and the O_3 was removed by O_2 bubbling. PPh_3 (234 mg, 0.894 mmol) was then added, and the solution was warmed to room temperature over 3 h and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 8/1 → 5/1 → 2/1) to afford aldehyde *ent*-**7** (532 mg, 0.719 mmol, 93%) as a colorless amorphous product.

R_f = 0.29 (hexane/EtOAc = 5/1); $[\alpha]_D^{22}$ +31.8 (c 1.0, $CHCl_3$); IR (neat) ν 3054, 2953, 2926, 2887, 2855, 1727, 1633, 1602, 1509, 1471, 1464, 1386, 1364, 1345, 1254, 1219, 1159, 1123, 1092, 1004, 959, 953, 892, 851, 838, 816, 774, 753, 696, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.80 (d, J = 1.8 Hz, 1H), 7.81−7.69 (m, 9H), 7.49−7.35 (m, 10H), 7.27 (s, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.03 (d, J = 11.4 Hz, 1H), 4.96 (d, J = 12.0 Hz, 1H), 4.86 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.68 (ddd, J = 10.2, 4.8, 4.8 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.04 (dd, J = 9.0, 6.0 Hz, 1H), 3.80 (dd, J = 11.4, 3.0 Hz, 1H), 3.76 (t, J = 9.6 Hz, 1H), 3.68−3.62 (m, 3H), 2.89−2.79 (m, 2H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.4, 136.3, 135.5, 135.3, 133.5, 133.3, 133.2, 133.2, 133.0, 128.4, 128.1, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.1, 126.4, 126.3, 126.2, 126.1, 126.1, 126.0, 125.9, 125.9, 125.9, 125.7, 125.5, 83.3, 78.0, 75.6, 75.1, 73.9, 72.4, 72.2, 68.7, 40.5, 26.0, 18.0, −4.3, −4.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{47}H_{52}O_6SiNa$ 763.3425, found 763.3426.

*(E)-1-((2R,3S,4S,5R,6R)-3-((tert-Butyldimethylsilyl)oxy)-4,5-bis-(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-tetrahydro-2H-pyran-2-yl)-4-(p-tolylsulfinyl)but-3-en-2-ol (**41**).* To a suspension of CrCl2 (940 mg, 7.67 mmol) and $NiCl_2$ (22 mg, 0.170 mmol) in DMF (6.0 mL) were added a solution of aldehyde *ent*-**7** (1.12 g, 1.52 mmol) and vinyl iodide **8** (2.23 g, 7.62 mmol) in THF (6.0 mL) under an atmosphere of argon, which was then rinsed with THF (3.0 mL × 2). The reaction mixture was stirred for 38.5 h and then concentrated. The residue was roughly purified by silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1 → 3/1 → 1/1) to give mixture allylic alcohol **41**, which was used in the next step.

*(2R,3R,4aS,6S,7S,8R,8aR)-7,8-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)-octahydropyrano[3,2-b]pyran-3-ol (**42**) and (2R,3S,4aS,6S,7S,8-R,8aR)-7,8-bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)octahydropyrano[3,2-b]pyran-3-ol (**43**).* To a stirred solution of allylic alcohol **41** in THF (34.6 mL) at 0 °C was added TBAF (3.1 mL, 3.1 mmol). The solution was stirred for 30 min and then warmed to 50 °C and stirred for 2.2 h. The reaction mixture was then quenched with saturated aquous NH_4Cl, and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1 → 1/2) to give bicyclic system **42** (219 mg, 0.276 mmol, 18% for two steps) and **43** (332 mg, 0.418 mmol, 28% for two steps) as a pale yellow amorphous product.

42: R_f = 0.48, (hexane/EtOAc = 4/1 × 2); $[\alpha]_D^{23}$ +58.5 (c 0.83, $CHCl_3$); IR (neat) ν 3346, 3053, 2923, 2360, 2334, 1602, 1509, 1457, 1344, 1220, 1171, 1080, 1041, 1012, 894, 856, 817, 673 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.80−7.25 (m, 8H), 7.56−7.52 (m, 3H), 7.46−7.38 (m, 10H), 7.29−7.26 (m, 2H), 7.11−7.09 (m, 1H), 5.24 (d, J = 11.4 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 4.99 (d, J = 10.8 Hz, 1H), 4.77 (m, 1H), 4.65−4.61 (m, 2H), 4.28−4.25 (m, 1H), 4.21 (ddd, J = 11.4, 4.8, 4.8 Hz, 1H), 4.10 (dd, J = 9.0, 6.0 Hz, 1H), 3.95−3.93 (m, 1H), 3.76−3.69 (m, 4H), 3.53−3.48 (m, 1H), 3.20−3.15 (m, 1H), 2.69 (dd, J = 13.8, 7.8 Hz, 1H), 2.39 (s, 3H), 2.17 (ddd, J = 12.0, 4.8, 4.8 Hz, 1H), 2.01 (q, J = 10.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 140.4, 136.5, 135.6, 135.4, 133.5, 133.3, 133.25, 133.15, 133.1, 133.0, 130.2 (2C), 128.4, 128.2 (2C), 128.1, 128.0 (2C), 127.84, 127.79, 127.7, 127.0, 126.5 (2C), 126.3, 126.2, 126.15, 126.08, 126.05 (2C), 125.91, 125.87 (2C), 124.2 (2C), 78.3, 77.8, 76.0, 75.2, 75.1, 73.8, 72.4, 70.5, 70.2, 69.5, 69.0, 62.4, 32.6, 21.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{50}H_{48}O_7SNa$ 815.3013, found 815.3012.

43: R_f = 0.30, (hexane/EtOAc = 4/1 × 2); $[\alpha]_D^{17}$ +46.9 (c 0.595, $CHCl_3$); IR (neat) ν 3383, 3054, 2924, 2360, 1602, 1508, 1343, 1219, 1125, 1094, 1041, 953, 912, 855, 817, 770, 754, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H). 7.79−7.72 (m, 9H), 7.58−7.53 (m, 3H), 7.47−7.39 (m, 10H), 7.29 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 9.0 Hz, 1H), 5.33 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 10.8 Hz, 1H), 5.01 (d, J = 10.8 Hz, 1H), 4.78 (d, J = 12.6 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.55−4.53 (m, 1H), 4.29−4.24 (m, 3H), 4.03 (s, 1H), 3.78−3.69 (m, 5H), 2.97 (dd, J = 13.8, 3.6 Hz, 1H), 2.91 (dd, J = 13.2, 8.4 Hz, 1H), 2.39 (s, 3H), 2.19 (dd, J = 13.2, 13.2 Hz, 1H), 2.05−2.01 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 140.7, 136.5, 135.5, 135.4, 133.4, 133.3, 133.2, 133.1, 133.02, 132.98, 130.2 (2C), 128.4, 128.14, 128.10 (2C), 128.0 (2C), 127.8, 127.72, 127.68, 127.0, 126.5 (2C), 126.3 (2C), 126.1, 126.04 (2C), 126.01, 125.9, 125.8 (2C), 123.9 (2C), 78.4, 77.3, 76.6, 75.2, 75.0, 73.8, 72.2, 69.1, 68.4, 67.1, 66.6, 61.0, 30.5, 21.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{50}H_{48}O_7SNa$ 815.3013, found 815.3015.

(2R,3R,4aS,6S,7S,8R,8aR)-7,8-Bis(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-2-((p-tolylsulfinyl)methyl)-

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*octahydropyrano[3,2-b]pyran-3-ol (**42**).* To a stirred solution of secondary alcohol **43** (116 mg, 0.149 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added Dess−Martin periodinane (126 mg, 0.297 mmol). The reaction mixture was stirred for 1.5 h before being quenched with saturated aqueous $NaHCO_3/Na_2S_2O_3$ (1/1). The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting crude of ketone **44** was used in the next step without further purification.

To a stirred solution of ketone **44** (59.8 mg, 75.6 μmol) in THF/MeOH (0.8 mL, 1:1) at −78 °C was added $NaBH_4$ (28.6 mg, 0.756 mmol), and the resulting mixture was stirred at −78 °C for 1 h before being quenched with saturated aqueous NH_4Cl. After warming to room temperature, the resulting biphasic mixture was diluted with EtOAc, and the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1 → 1/2 → 1/4) to give alcohol **42** (36.4 mg, 45.9 μmol, 65% for two steps) as a colorless solid.

*tert-Butyldiphenyl(((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)octahydropyrano[3,2-b]pyran-2-yl)methoxy)silane (ent-**34**).* To a stirred solution of aldehyde *ent*-**3** (129 mg, 160 μmol) in THF/MeOH (3.0 mL, 1:1) was added $NaBH_4$ (30.5 mg, 80.6 μmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h before being quenched with saturated aqueous NH_4Cl. After warming to room temperature, the resulting biphasic mixture was diluted with EtOAc, and the organic phase was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 4/1 → 2/1 → 1/1) to give alcohol *ent*-**33** (110 mg, 135 μmol, 85%) as a colorless amorphous product.

R_f = 0.33 (hexane/EtOAc = 1/1); $[\alpha]_D^{25}$ +74.3 (*c* 1.23, $CHCl_3$); IR (neat) ν 3482, 3054, 3013, 2873, 1633, 1602, 1508, 1458, 1344, 1271, 1216, 1169, 1124, 1087, 1068, 953, 893, 855, 816, 751, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85−7.72 (m, 13H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.51−7.41 (m, 12H), 7.11 (d, *J* = 8.4 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* = 12.6 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.69−4.64 (m, 3H), 4.27 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.17−4.11 (m, 2H), 3.86 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.78−3.74 (m, 4H), 3.69 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.60−3.57 (m, 2H), 2.36−2.34 (m, 1H), 2.04−1.96 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.1, 135.6, 135.4, 135.3, 133.43, 133.36 (2C), 133.3, 133.2 (2C), 133.1, 133.0, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0 (3C), 127.9 (2C), 127.8, 127.7, 127.0, 126.72, 126.66, 126.5, 126.4, 126.3, 126.19 (2C), 126.15, 126.11 (2C), 126.08, 126.01, 125.95, 125.8 (2C), 78.6, 77.0, 75.9, 75.3, 74.9, 73.9, 73.1, 72.8, 72.4, 71.1, 70.4, 69.2, 62.7, 29.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{54}H_{50}O_7Na$ 833.3449, found 833.3452.

To a stirred solution of primary alcohol *ent*-**33** (23.8 mg, 29.4 μmol) in DMF (0.3 mL) were added imidazole (20.0 mg, 0.293 mmol) followed by TBDPSCl (38 μL, 147 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the resulting biphasic mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1 → 3/1) to give TBDPS ether *ent*-**34** (28.5 mg, 27.2 μmol, 93%) as a colorless amorphous product.

R_f = 0.33 (hexane/EtOAc = 4/1); $[\alpha]_D^{25}$ +56.8 (*c* 0.89, $CHCl_3$); IR (neat) ν 3053, 2929, 2856, 1602, 1509, 1470, 1427, 1361, 1343, 1271, 1219, 1170, 1124, 1082, 1008, 952, 893, 855, 818, 771, 755, 704, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.68 (m, 15H), 7.63−7.54 (m, 4H), 7.48−7.31 (m, 18H), 7.11 (d, *J* = 9.0 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 12.6 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 12.6 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.29 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.20−4.14 (m, 2H), 3.96 (d, *J* = 11.4 Hz, 1H), 3.88 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.78−3.74 (m, 3H), 3.70−3.63 (m, 3H), 2.36−2.34 (m, 1H), 2.01 (q, *J* = 12.0 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 136.0 (3C), 135.8, 135.7 (3C), 135.6, 133.9, 133.5, 133.4 (3C), 133.3, 133.2, 133.13, 133.07, 133.0, 129.75, 129.68, 128.4 (2C), 128.15, 128.09, 128.0 (3C), 127.85, 127.82, 127.77 (2C), 127.74 (2C), 127.72 (2C), 126.9 (2C), 126.59, 126.56, 126.4, 126.2 (2C), 126.1, 126.05 (2C), 126.02, 125.96, 125.9 (2C), 125.85, 125.82, 78.3, 77.0, 76.1, 75.3, 74.7, 74.3, 73.8, 72.5, 72.3, 71.3, 70.5, 69.4, 63.8, 29.7, 27.0 (3C), 19.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{70}H_{68}O_7SiNa$ 1071.4632, found 1071.4651.

*1-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)propan-2-one (ent-**4**).* To a stirred solution of tetra-NAP ether *ent*-**34** (126 mg, 120 μmol) in Ac_2O/AcOH (1.2 mL, 2/1) was added $ZnCl_2$ (327 mg, 2.4 mmol) in Ac_2O/AcOH (1.2 mL, 2/1) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$, and the resulting biphasic mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 8/1 → 5/1 → 3/1) to give acetate *ent*-**35** (107 mg, 112 μmol, 94%) as a colorless amorphous product.

R_f = 0.43 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +60.5 (*c* 1.11, $CHCl_3$); IR (neat) ν 3460, 3055, 2931, 2858, 1740, 1602, 1508, 1455, 1428, 1364, 1236, 1086, 1054, 1028, 856, 818, 771, 755, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.62 (m, 16 H), 7.50−7.30 (m, 15H), 5.20 (d, *J* = 11.4 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.90 (d, *J* = 11.4 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.37 (dd, *J* = 11.4, 2.4 Hz, 1H), 4.33 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.27 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.17−4.09 (m, 2H), 3.98 (d, *J* = 10.8 Hz, 1H), 3.89 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.81−3.79 (m, 1H), 3.68−3.66 (m, 2H), 3.56 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.35−2.32 (m, 1H), 2.03−1.96 (m, 4H), 1.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 136.05, 136.00 (3C), 135.7 (3C), 135.50, 135.46, 133.9, 133.44, 133.36 (2C), 133.2, 133.1, 129.8, 129.7, 128.40, 128.38, 128.2, 128.11, 128.07, 128.0, 127.83, 127.79 (3C), 127.75 (3C), 127.01, 126.97, 126.61, 126.57, 126.3, 126.2, 126.1 (2C), 126.0, 125.92, 125.86, 77.7, 77.1, 76.1, 75.3, 74.8, 74.3, 72.5, 71.4, 70.7, 70.4, 63.74, 63.70, 29.7, 27.0 (3C), 20.9, 19.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{61}H_{62}O_8SiNa$ 973.4106, found 973.4106.

To a stirred solution of acetate *ent*-**35** (107.3 mg, 133 μmol) in THF/MeOH (1.4 mL, 1/1) at 0 °C was added K_2CO_3 (47.5 mg, 344 μmol), and the mixture was stirred at room temperature for 1 h before being quenched with saturated aqueous NH_4Cl and EtOAc. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residure was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1 → 2/1) to give primary alcohol *ent*-**36** (93.4 mg, 102 μmol, 91%) as a colorless product.

R_f = 0.30 (hexane/EtOAc = 2/1); $[\alpha]_D^{19}$ +45.5 (*c* 1.17, $CHCl_3$); IR (neat) ν 3453, 3053, 2928, 2856, 1602, 1509, 1462, 1427, 1343, 1271, 1219, 1085, 1058, 855, 819, 704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.79−7.66 (m, 12H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.48−7.45 (m, 4H), 7.43−7.29 (m, 11H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.23 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.11−4.06 (m, 2H), 3.94 (d, *J* = 10.2 Hz, 1H), 3.88−3.83 (m, 2H), 3.73−3.61 (m, 4H), 3.57 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.31−2.27 (m,

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1H), 1.99 (q, J = 11.4 Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 136.0 (3C), 135.7 (3C), 135.6, 133.9, 133.5, 133.41, 133.35 (2C), 133.2, 133.13, 133.08, 129.8, 129.7, 128.4, 128.3, 128.2, 128.10, 128.05 (2C), 127.80 (3C), 127.76 (2C), 127.7 (2C), 126.9, 126.7, 126.6, 126.5, 126.3, 126.2, 126.1, 126.05, 126.00, 125.98, 125.9 (2C), 78.3, 76.8, 76.2, 75.4, 74.7, 74.3, 72.6, 72.5, 71.4, 70.4, 63.7, 62.7, 30.1, 27.0 (3C), 19.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{59}H_{60}O_7SiNa$ 931.4001, found 931.4003.

To a mixture of alcohol *ent*-**36** (93.4 mg, 103 μmol) and Et_3N (86 μL, 616 μmol) in CH_2Cl_2 was added MsCl (25 μL, 308 μmol) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with H_2O at 0 °C. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with saturated aqueous $KHSO_4$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude mesylate *ent*-**37**, which was used in the next reaction without purification.

To a solution of crude mesylate *ent*-**37** in DMF (1.0 mL) were added powdered 4Å molecular sieves (33 mg) and NaCN (52.6 mg, 1.07 mmol) at room temperature. After stirring at 70 °C for 13 h, H_2O was added to the reaction mixture, which was then diluted with ether followed by the addition of saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and filtered. After removal of the solvent in vacuo, the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1 → 3/1) to give nitrile *ent*-**38** (86.3 mg, 93 μmol, 92% for two steps) as a colorless amorphous product.

R_f = 0.40 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +49.1 (c 1.76, $CHCl_3$); IR (neat) ν 3053, 2929, 2856, 1602, 1509, 1471, 1427, 1361, 1271, 1219, 1083, 1008, 894, 856, 819, 771, 756, 704 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86–7.81 (m, 3H), 7.78–7.64 (m, 13H), 7.51–7.49 (m, 4H), 7.47–7.32 (m, 11H), 5.21 (d, J = 11.4 Hz, 1H), 5.16 (d, J = 11.4 Hz, 1H), 4.89 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.30 (dd, J = 9.6, 9.6 Hz, 1H), 4.15 (dd, J = 12.0, 2.4 Hz, 1H) 3.99 (d, J = 10.8 Hz, 1H), 3.91–3.89 (m, 1H), 3.81–3.78 (m, 1H), 3.70–3.66 (m, 2H), 3.45 (dd, J = 9.6, 9.6 Hz, 1H), 2.72 (dd, J = 16.8, 3.0 Hz, 1H), 2.54 (dd, J = 17.4, 6.0 Hz, 1H), 2.39–2.37 (m, 1H), 2.00–1.94 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0 (2C), 135.8, 135.7 (2C), 135.3, 135.2, 133.8, 133.3 (2C), 133.13, 133.09, 129.8, 129.7, 128.5, 128.4, 128.2, 128.1, 128.0 (2C), 127.82 (3C), 127.79 (3C), 127.76 (3C), 127.0, 126.9, 126.7, 126.5, 126.4, 126.3, 126.2, 126.13, 126.09, 126.0, 125.89, 125.86, 117.2, 80.5, 76.6, 76.0, 75.6, 74.7, 74.4, 72.2, 71.5, 70.6, 68.4, 63.6, 29.8, 27.0 (3C), 21.7, 19.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{60}H_{59}O_6NSiNa$ 940.4009, found 940.4017.

Nitrile *ent*-**38** (86.3 mg, 94.0 μmol) was dissolved in dry toluene (0.94 mL) and cooled to 0 °C. Me_3Al (1.07 M solution in hexane, 0.88 mL, 0.94 mmol) and $Ni(acac)_2$ (10 mg/mL solution in benzene, 0.24 mL, 9.4 μmol) was added, and the brown reaction mixture was allowed to stir at room temperature for 1.5 h. This operation was repeated twice, after which 1 M HCl was added. The biphasic mixture was stirred at room temperature for 15 min and subsequently extracted with ether. The combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1) to give methyl ketone *ent*-**4** (73.1 mg, 78.2 μmol, 83%).

R_f = 0.40 (hexane/EtOAc = 2/1); $[\alpha]_D^{20}$ +36.9 (c 0.57, $CHCl_3$); IR (neat) ν 3051, 2929, 2359, 1716, 1508, 1428, 1359, 1220, 1085, 855, 819, 772, 704, 672 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.79–7.73 (m, 6H), 7.70–7.77 (m, 4H), 7.65 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.49–7.47 (m, 4H), 7.44–7.28 (m, 11H), 5.18 (d, J = 10.8 Hz, 1H), 5.10 (d, J = 11.4 Hz, 1H), 4.86 (d, J = 11.4 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.76 (d, J = 10.8 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.29 (dd, J = 8.4, 8.4 Hz, 1H), 4.13–4.09 (m, 2H), 4.04–4.00 (m, 1H), 3.97 (d, J = 10.8 Hz, 1H), 3.87 (dd, J = 10.8, 4.2 Hz, 1H), 3.69–3.62 (m, 2H), 3.30 (dd, J = 9.6, 9.6 Hz, 1H), 2.79 (dd, J = 16.2, 3.6 Hz, 1H), 2.48 (d, J = 15.6, 9.0 Hz, 1H), 2.36–2.32 (m, 1H), 2.11 (s, 3H), 2.10–2.03 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.6, 136.06, 136.0 (2C), 135.74 (2C), 135.71, 135.5, 133.9, 133.5, 133.39, 133.35, 133.2, 133.1, 129.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.1 (2C), 128.0, 127.81 (3C), 127.79 (2C), 127.76 (2C), 127.73 (2C), 127.0, 126.7, 126.64, 126.58, 126.35, 126.28, 126.2, 126.1, 126.0, 125.93, 125.90, 81.5, 77.1, 76.4, 75.3, 74.8, 74.4, 72.4, 71.3, 70.4, 68.9, 63.8, 46.5, 30.8, 29.6, 27.0 (3C), 19.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{61}H_{62}O_7SiNa$ 957.4157, found 957.4163.

*(R)-1-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano[3,2-b]pyran-2-yl)-4-hydroxy-4-((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-octahydropyrano[3,2-b]pyran-2-yl)butan-2-one (ent-**39**).* A flask containing 184 μM LHMDS solution (1.3 M in THF, 239 μmol) was cooled at −78 °C, and a solution of methyl ketone *ent*-**4** (149 mg, 159 μmol) in 0.8 mL of THF was added dropwise precooling along the side of the reaction flask (0.3 mL THF rinse). The reaction mixture was stirred at −78 °C for 1 h, and a solution of aldehyde *ent*-**3** (37.2 mg, 46.0 μmol) in 0.3 mL of THF was added dropwise precooling along the side of reaction flask (0.2 mL of THF rinse). The mixture was stirred at −78 °C for 1 h; the temperature of the mixture was increased from −78 to −20 °C gradually over 3 h and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc. The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 3/1 → 2/1) and PTLC to give β-hydroxy ketone *ent*-**39** (15.6 mg, 8.94 μmol, 19%) and its epimer (13.3 mg, 7.63 μmol, 17%) as colorless oils.

R_f = 0.40 (hexane/EtOAc = 1/1); $[\alpha]_D^{18}$ +27.8 (c 0.63, $CHCl_3$); IR (neat) ν 3052, 2927, 2362, 1714, 1602, 1509, 1343, 1271, 1220, 1125, 1052, 948, 855, 818, 772, 708, 687, 674 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85–7.67 (m, 24H), 7.64–7.62 (m, 3H), 7.60 (d, J = 8.4 Hz, 1H), 7.54–7.50 (m, 3H), 7.49–7.27 (m, 26H), 7.25–7.23 (m, 1H), 7.10 (dd, J = 8.3, 1.4 Hz, 1H), 5.03 (d, J = 11.0 Hz, 1H), 4.95 (d, J = 11.7 Hz, 1H), 4.93 (d, J = 12.4 Hz, 1H), 4.894 (d, J = 11.0 Hz, 1H), 4.885 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 4.67 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 4.613 (d, J = 11.0 Hz, 1H), 4.609 (d, J = 11.0 Hz, 1H), 4.54–4.52 (m, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.22–4.17 (m, 2H), 4.15 (dd, J = 8.9, 8.9 Hz, 1H), 3.95 (dd, J = 10.3, 6.9 Hz, 1H), 3.91–3.80 (m, 5H), 3.79–3.71 (m, 4H), 3.68 (dd, J = 8.9 Hz, 1H), 3.46–3.41 (m, 2H), 3.34 (d, J = 9.6 Hz, 1H), 3.03–2.98 (m, 2H), 2.93 (d, J = 4.1 Hz, 1H), 2.55 (dd, J = 15.1, 3.4 Hz, 1H), 2.36–2.29 (m, 2H), 2.19 (dd, J = 15.1, 8.9 Hz, 1H), 1.99 (q, J = 11.0 Hz, 1H), 1.71 (q, J = 11.0 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 136.2, 136.04, 135.97 (3C), 135.8, 135.72 (3C), 135.66, 135.5 (2C), 135.4, 133.9, 133.5, 133.41 (2C), 133.36, 133.33 (3C), 133.30, 133.22, 133.19, 133.13, 133.11, 133.04 (2C), 133.02, 129.74, 129.68, 128.5 (2C), 128.41, 128.36, 128.3, 128.2 (2C), 128.10 (2C), 128.06 (3C), 128.02 (2C), 128.0, 127.9 (2C), 127.82, 127.77 (2C), 127.7 (3C), 127.0, 126.92, 126.85, 126.7, 126.5, 126.42, 126.38 (2C), 126.36, 126.3 (2C), 126.22 (2C), 126.16 (2C), 126.14 (2C), 126.08, 126.02 (3C), 125.99, 125.97, 125.9, 125.85, 125.77 (2C), 125.6, 81.5, 78.7, 77.8, 76.3, 75.6, 75.2 (2C), 75.0, 74.9, 74.7, 74.2, 73.9 (2C), 72.5, 72.3, 72.2, 71.7, 71.2, 70.23, 70.22, 69.2, 68.9, 65.2, 63.7, 47.2, 46.2, 29.7, 29.3, 27.0 (3C), 19.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{115}H_{110}O_{14}SiNa$ 1766.7589, found 1766.7591.

*(1R,3R)-4-((2S,3S,4R,4aR,6S,7R,8aS)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3,4,7-tris(naphthalen-2-ylmethoxy)octahydropyrano-[3,2-b]pyran-2-yl)-1-((2S,3R,4aS,6S,7S,8R,8aR)-3,7,8-tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)-octahydropyrano[3,2-b]pyran-2-yl)butane-1,3-diol (ent-**40**).* To a solution of β-hydroxy ketone *ent*-**39** (15.6 mg, 8.94 μmol) in MeCN/AcOH/CH_2Cl_2 (1.0 mL, 6/3/1) was added $Me_4NHB(OAc)_3$ (14.1 mg, 53.6 μmol) at −20 °C. After stirring at −20 °C for 1.5 h, the reaction mixture was stirred at 0 °C for 1 h. After stirring at room temperature for 45 min, $Me_4NHB(OAc)_3$ (11.1 mg, 42.2 μmol) was added. The reaction mixture was stirred at room temperature for 15 min and then quenched with a saturated aqueous

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solution of Rochelle's salt. The resulting biphasic mixture was stirred vigorously for 20 h. The biphasic mixture was then extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by PTLC to give diol *ent*-**40** (7.7 mg, 4.36 μmol, 49%) as a colorless oil.

R_f = 0.23 (hexane/EtOAc = 1/1); $[\alpha]_D^{16}$ +35.0 (*c* 0.39, $CHCl_3$); IR (neat) ν 3468, 3053, 2927, 2359, 1602, 1509, 1461, 1427, 1362, 1250, 1219, 1080, 893, 854, 817, 706, 671, 662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82−7.74 (m, 10H), 7.72−7.62 (m, 17H), 7.61−7.57 (m, 2H), 7.52−7.48 (m, 2H), 7.47−7.39 (m, 14H), 7.38−7.27 (m, 13H), 7.07 (d, *J* = 8.3 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.92 (d, *J* = 10.3 Hz, 1H), 4.91 (d, *J* = 11.7 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.77 (d, *J* = 12.4 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.35 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.22 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.16−4.14 (m, 3H), 3.98 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.93 (ddd, *J* = 13.6, 4.8, 4.8 Hz, 1H), 3.87 (d, *J* = 10.3 Hz, 1H), 3.82 (d, *J* = 8.9 Hz, 1H), 3.79−3.70 (m, 6H), 3.67 (dd, *J* = 8.9 Hz, 1H), 3.52 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.49 (d, *J* = 9.6 Hz, 1H), 3.36 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.19 (dd, *J* = 8.9, 8.9 Hz, 1H), 2.82 (d, *J* = 4.1 Hz, 1H), 2.36−2.33 (m, 1H), 2.15−2.00 (m, 2H), 1.93−1.86 (m, 2H), 1.72 (q, *J* = 12.4 Hz, 1H), 1.60−1.54 (m, 1H), 1.49−1.45 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.3, 136.0 (3C), 135.89, 135.87, 135.72 (3C), 135.67, 135.5, 135.4 (2C), 133.9, 133.5, 133.39, 133.36 (3C), 133.34 (2C), 133.29, 133.20 (2C), 133.15, 133.03, 133.06 (2C), 133.0, 129.75, 129.69, 128.6, 128.5, 128.4 (2C), 128.22, 128.16 (2C), 128.1 (3C), 128.0 (3C), 127.90, 127.87 (2C), 127.84 (2C), 127.77 (2C), 127.7 (3C), 127.0, 126.9, 126.8, 126.6 (2C), 126.5, 126.4, 126.34, 126.28, 126.21 (3C), 126.15 (2C), 126.10, 126.07 (3C), 126.04 (2C), 125.98 (3C), 125.94, 125.91 (2C), 125.83, 125.78, 81.5, 78.6, 77.2, 76.1, 75.8, 75.6, 75.2 (2C), 74.7, 74.2, 73.9 (2C), 72.7, 72.5, 72.3, 71.6, 71.3, 70.4, 70.3, 70.2, 69.2, 66.6, 65.9, 63.6, 41.6, 38.5, 29.9, 29.7, 29.5, 27.0 (3C), 19.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{115}H_{112}O_{14}SiNa$ 1768.7746, found 1768.7747.

*(2S,3R,4R,4aS,6S,7R,8aS)-6-((1R,3R)-1,3-Dihydroxy-4-((2S,3R,4R,4aS,6S,7R,8aS)-3,4,7-trihydroxy-6-(hydroxymethyl)-octahydropyrano[3,2-b]pyran-2-yl)butyl)-2-(hydroxymethyl)-octahydropyrano[3,2-b]pyran-3,4,7-triol (ent-**1**).* To a solution of antidiol *ent*-**40** (7.7 mg, 4.36 μmol) in EtOAc/MeOH (1 mL, 1/1) was added $Pd(OH)_2/C$ (20% Pd, 9.2 mg, 13.1 μmol) at room temperature, and the solution was purged with H_2 and then stirred for 26 h under an atmosphere of H_2 (ballon). The reaction mixture was filtered through a short pad of Celite and then concentrated. The residue was purified by preparative TLC to give *ent*-LMNO ring *ent*-**1** (2.2 mg, 2.88 μmol, 65%) as a colorless oil.

R_f = 0.37 ($CHCl_3$/MeOH = 7/3); $[\alpha]_D^{18}$ +52.4 (*c* 0.11, MeOH); IR (neat) ν 3389, 3181, 2973, 2372, 2321, 1659, 1339, 1054, 1033, 1009, 756, 695, 659 cm^{-1}; ^1H NMR (600 MHz, CD_3OD/C_5D_5N) δ 7.76−7.74 (m, 4H), 7.35−7.31 (m, 6H), 4.50 (ddd, *J* = 8.9, 4.1, 2.1 Hz, 1H), 4.32−4.24 (m, 3H), 4.14−4.10 (m, 1H), 4.04−3.93 (m, 5H), 3.90−3.82 (m, 4H), 3.70−3.67 (m, 1H), 3.56−3.53 (m, 3H), 3.28−3.25 (m, 1H), 2.23−2.05 (m, 6H), 1.89 (ddd, *J* = 14.4, 8.9, 4.1 Hz, 1H), 1.59 (ddd, *J* = 14.4, 8.9, 2.8 Hz), 1.19−1.16 (m, 2H), 0.98 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.0 (2C), 134.9 (2C), 130.6 (2C), 128.7 (6C), 77.2, 76.72, 76.66, 76.4, 76.0, 75.6, 72.8, 71.6, 71.5, 71.4, 69.31, 69.26, 67.8, 66.25 (2C), 66.21, 64.9, 63.3, 43.2, 42.5, 34.2, 34.1, 30.6, 27.4 (3C), 20.2; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{56}O_{14}SiNa$ 787.3332, found 787.3338.

*Acetonide (**45**).* *p*-TsOH·H_2O (55.9 mg, 294 μmol) was added to a solution of diol **12** (1.87 g, 2.91 mmol) in acetone/2,2-dimethylpropane (1/1, v/v, 14.6 mL) at 0 °C. After stirring at room temperature for 2.3 h, the reaction mixture was quenched with Et_3N (2.00 mL, 14.3 mmol) and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 12/1 → 8/1) to give acetonide **45** (1.93 g, 2.82 mmol, 97%) as a colorless amorphous product.

R_f = 0.65 (hexane/EtOAc = 2/1); $[\alpha]_D^{20}$ + 58.1 (*c* 1.25, $CHCl_3$); IR (neat) 2987, 2951, 2883, 2857, 1463, 1454, 1381, 1277, 1249, 1098, 1066, 1044, 991, 882, 837, 734, 697, 679, 668, 660 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35−7.26 (m, 8H), 7.19 (d, *J* = 6.6 Hz, 2H), 4.63 (d, *J* = 13.2 Hz, 1H), 4.56 (d, *J* = 13.2 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 1H), 3.95 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.74−3.70 (m, 2H), 3.53 (dt, *J* = 12.0, 4.8 Hz, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.44 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 2.24 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.89 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.70 (q, *J* = 12.0 Hz, 2H), 1.56 (s, 3H), 1.40 (s, 3H), 1.32 (s, 6H), 1.13 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.2, 128.5 (2C), 128.4 (2C), 127.95 (2C), 127.87 (2C), 127.8, 127.6, 110.8, 79.5, 78.9, 74.6, 74.5, 73.64, 73.62, 73.5, 72.6, 71.0, 70.8, 70.4, 70.0, 63.8, 39.3, 30.8, 26.3, 26.1 (3C), 25.6, 19.6, 18.6, 16.9, 15.5, −5.0, −5.3; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{58}O_8Na$ 705.3793, found 705.3798.

*Alcohol (**46**).* TBAF (1.0 M in THF, 5.50 mL, 5.50 mmol) was added to a solution of TBS ether **45** (1.88 g, 2.75 mmol) in THF (28.8 mL) at 0 °C. After stirring at room temperature for 3.2 h, TBAF (1.0 M in THF, 1.40 mL, 1.40 mmol) was added to the solution at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 3/1 → 1/1) to give alcohol **46** (1.54 g, 2.70 mmol, 98%) as a colorless amorphous product.

R_f = 0.23 (hexane/EtOAc = 1/1); $[\alpha]_D^{22}$ + 67.8 (*c* 1.13, $CHCl_3$); IR (neat) 3501, 2988, 2944, 2881, 1496, 1455, 1382, 1248, 1209, 1137, 1095, 1063, 1029, 988, 908, 876, 736, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36−7.26 (m, 8H), 7.19 (d, *J* = 7.8 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 6.6 Hz, 1H), 4.02 (dd, *J* = 12.0 Hz, 1H), 3.73 (ddd, *J* = 10.2, 4.8, 2.4 Hz, 1H), 3.70−3.64 (m, 2H), 3.53 (dt, *J* = 12.0, 4.8 Hz, 1H), 3.47 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.43 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.39 (dd, *J* = 11.4, 9.0 Hz, 1H), 2.24 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.94 (dd, *J* = 9.0, 4.2 Hz, 1H), 1.90 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.70 (q, *J* = 12.0 Hz, 1H), 1.58 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 128.6 (2C), 128.4 (2C), 127.91 (2C), 127.86 (3C), 127.6, 111.3, 79.3, 79.0, 74.7, 74.3, 73.6, 73.53, 73.46, 72.6, 71.0, 70.9, 70.2, 69.8, 64.0, 39.2, 30.7, 26.2, 25.7, 19.4, 17.2, 15.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{44}O_8Na$ 591.2928, found 591.2927.

*Alkyne (**11**).* AZADOL (2.8 mg, 18.3 μmol) and (diacetoxyiodo)-benzene (83.6 mg, 260 μmol) were added to a solution of alcohol **46** (99.4 mg, 175 μmol) in CH_2Cl_2 (1.70 mL) at 0 °C. After stirring at room temperature for 5.9 h, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual crude aldehyde was immediately used in the next reaction without further purification.

Cs_2CO_3 (177 mg, 543 μmol) was added to a solution of the above crude aldehyde and Ohira−Bestmann reagent (177 mg, 921 μmol) in MeOH (3.50 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1) to give alkyne **11** (75.3 mg, 134 μmol, 77% for two steps) as a colorless solid.

R_f = 0.46 (hexane/EtOAc = 2/1); $[\alpha]_D^{20}$ +111.8 (*c* 1.01, $CHCl_3$); IR (neat) 2988, 2934, 2880, 1462, 1448, 1383, 1266, 1249, 1213, 1092, 1065, 1046, 910, 883, 822, 746, 698, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35−7.26 (m, 8H), 7.20 (d, *J* = 7.2 Hz,

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2H), 4.63 (d, J = 12.6 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 4.56 (d, J = 12.6 Hz, 1H), 4.55 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.33 (d, J = 6.6 Hz, 1H), 3.92 (dd, J = 12.0, 6.0 Hz, 1H), 3.71 (dt, J = 12.0, 1.8 Hz, 1H), 3.67 (d, J = 3.0 Hz, 2H), 3.52 (dt, J = 12.0, 6.0 Hz, 1H), 3.39 (dd, J = 12.0, 4.2 Hz, 1H), 2.56 (s, 1H), 2.25 (dt, J = 12.0, 4.8 Hz, 1H), 1.96 (dd, J = 12.0, 4.8 Hz, 1H), 1.66 (q, J = 12.0 Hz, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.2, 128.5 (2C), 128.4 (2C), 127.90 (2C), 127.87 (2C), 127.8, 127.6, 109.5, 87.2, 80.2, 77.9, 74.2, 73.6, 73.44, 73.37, 73.0, 72.7, 71.0, 70.7 (2C), 69.8, 65.2, 39.6, 30.8, 26.4 (2C), 24.0, 17.9, 15.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{34}H_{42}O_7Na$ 585.2823, found 585.2840.

*Ketone (**47**).* n-BuLi (1.6 M in n-hexane, 390 μL, 624 μmol) was added to a solution of alkyne **11** (375.2 mg, 667 μmol, predried with MS4A) in THF (6.7 mL) at −78 °C. After the resultant mixture was stirred at −78 °C for 1 h, a solution of aldehyde **3** (71.4 mg, 88.3 μmol, predried with MS4A) in THF (0.88 mL) was added via cannula. After stirring at −78 °C for 35 min and at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 5/1 → 3/1) to give alcohol as a diastereomixture including a small amount of unreacted aldehyde **3**, which was immediately used in the next reaction without further purification.

MnO_2 (732.5 mg, 8.43 mmol) was added to a soluion of secondary alcohol in CH_2Cl_2 (900 μL) at 0 °C. After stirring at room temperature for 2 h, MnO_2 (806.1 mg, 9.27 mmol) was added to the reaction mixture. After stirring at room temperature for 19 h, MnO_2 (224.8 mg, 2.59 mmol) was added to the reaction mixture. After stirring at room temperature for 2.3 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. Residual crude ynone **10** was immediately used in the next reaction without further purification.

A solution of the above crude ynone **10** in degassed benzene (3.3 mL) and degassed H_2O (33 μL) were added to Stryker's reagent (214 mg, 98.2 μmol) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ and Et_2O. After stirring under air at room temperature for 1 h, the reaction mixture was extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 2/1 → 3/2) to give ketone **47** (76.2 mg, 55.5 μmol, 63% for three steps) as a colorless oil.

R_f = 0.55 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ −5.6 (c 0.49, $CHCl_3$); IR (neat) 3056, 2989, 2937, 1731, 1508, 1456, 1381, 1273, 1247, 1210, 1124, 1067, 954, 889, 856, 818, 753, 697, 681, 668 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82−7.72 (m, 11H), 7.68 (d, J = 4.2 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.49−7.39 (m, 12H), 7.37−7.26 (m, 8H), 7.19 (d, J = 6.6 Hz, 2H), 7.09 (d, J = 9.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 4.96 (d, J = 12.0 Hz, 2H), 4.77 (d, J = 12.6 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.6 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 11.4 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.23−4.15 (m, 3H), 4.12 (q, J = 12.6 Hz, 1H), 4.04 (d, J = 9.0 Hz, 1H), 3.82 (dd, J = 12.0, 4.2 Hz, 1H), 3.79 (d, J = 6.0 Hz, 1H), 3.75−3.62 (m, 8H), 3.48 (dt, J = 11.4, 4.8 Hz, 1H), 3.30 (dd, J = 11.4, 4.8 Hz, 1H), 2.69−2.63 (m, 1H), 2.47−2.40 (m, 1H), 2.35−2.30 (m, 1H), 2.19 (dt, J = 11.4, 4.8 Hz, 1H), 1.99 (q, J = 12.0 Hz, 1H), 1.76 (dd, J = 12.0, 4.2 Hz, 1H), 1.71 (quintet, J = 4.8 Hz, 2H), 1.65 (q, J = 11.4 Hz, 1H), 1.57 (t, J = 12.0 Hz, 1H), 1.46 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 138.6, 138.2, 136.0, 135.6, 135.4, 135.0, 133.4, 133.35, 133.29, 133.2, 133.1, 133.0, 128.54 (3C), 128.51, 128.45 (3C), 128.4, 128.3, 128.2, 128.1, 128.0 (3C), 127.92 (3C), 127.87 (4C), 127.8, 127.7, 127.6, 127.0, 126.9, 126.5, 126.4 (2C), 126.3, 126.2, 126.13 (2C), 126.09 (2C), 126.02, 125.97, 125.9, 125.83, 125.78, 111.1, 79.4, 79.2, 78.3, 77.7, 76.0, 75.2, 74.8, 74.3, 73.9, 73.7, 73.6, 73.50, 73.47 (2C), 72.6, 72.5, 71.2, 71.0, 70.8, 69.9, 69.6, 69.1, 39.2, 37.2, 35.3, 30.7, 29.7, 26.2, 25.5, 21.3, 17.4, 15.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{88}H_{92}O_{14}Na$ 1395.6379, found 1395.6485.

*(2R,3S,4aR,5aS,6S,6aR,10aS,11aR,12aS)-3-(Benzyloxy)-2-((benzyloxy)methyl)-5a,10a,12a-trimethyl-8-((2R,3R,4aS,6S,7S,8-R,8aR)-3,7,8-tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)octahydropyrano[3,2-b]pyran-2-yl)-2,3,4,4a,5a,6,6a,10,10a,11a,12,12a-dodecahydropyrano[3,2-b]-pyrano[2′,3′:5,6]pyrano[2,3-e]pyran-6-ol (**9**).* p-TsOH·H_2O (7.0 mg, 36.8 μmol) was added to a solution of ketone **47** (74.6 mg, 54.3 μmol) in CH_2Cl_2/MeOH (1/2, v/v, 2.7 mL) at 0 °C. After stirring at room temperature for 14.6 h, the reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was roughly purified by flash silica gel column chromatography (hexane/EtOAc = 3/1 → 1/1) to give an inseparable mixture of hemiacetal and dihydropyran **9**, which was immediately used in the next reaction without further purification.

Nafion NR-50 (1.11 g) was added to a solution of the above mixture and powdered MS4A (664 mg) in toluene (1.0 mL) at room temperature. After stirring at 120 °C for 4.7 h, Nafion NR-50 (614 mg) was added to the solution at room temperature. After stirring at 120 °C for 3.6 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 2/1 → 1/1) to give dihydropyran **9** (49.5 mg, 37.6 μmol, 69% for two steps) as a colorless amorphous product.

R_f = 0.38 (hexane/EtOAc = 1/1); $[\alpha]_D^{26}$ +26.1 (c 0.24, $CHCl_3$); IR (neat) 3055, 3026, 2922, 2857, 1508, 1455, 1364, 1346, 1273, 1166, 1124, 1083, 1056, 953, 855, 817, 752, 698, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83−7.68 (m, 13H), 7.57−7.37 (m, 14H), 7.35−7.25 (m, 8H), 7.20 (d, J = 6.6 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 5.13 (d, J = 10.8 Hz, 1H), 5.00 (d, J = 10.8 Hz, 1H), 4.96 (d, J = 11.4 Hz, 1H), 4.81 (dd, J = 5.4, 2.4 Hz, 1H), 4.77 (d, J = 12.0 Hz, 2H), 4.66−4.60 (m, 4H), 4.56 (d, J = 12.0 Hz, 1H), 4.55 (f, J = 12.0 Hz, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.28 (t, J = 9.6 Hz, 1H), 4.22 (dd, J = 13.2, 4.2 Hz, 2H), 4.15 (dd, J = 9.6, 6.6 Hz, 1H), 3.98 (d, J = 10.8 Hz, 1H), 3.88 (d, J = 3.0 Hz, 1H), 3.79 (dt, J = 10.8, 4.2 Hz, 1H), 3.76−3.70 (m, 4H), 3.68−3.61 (m, 4H), 3.54 (dt, J = 10.2, 5.4 Hz, 1H), 3.41 (dd, J = 12.6, 3.6 Hz, 1H), 2.54 (s, 1H), 2.36−2.31 (m, 1H), 2.22−2.13 (m, 2H), 1.99 (q, J = 10.8 Hz, 1H), 1.90 (d, J = 9.6 Hz, 2H), 1.70−1.58 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 136.4, 135.8, 135.6, 135.5, 133.43, 133.35 (2C), 133.3, 133.2, 133.1 (2C), 128.6 (2C), 128.5 (2C), 128.4, 128.3, 128.2, 128.13, 128.11, 128.05 (2C), 127.98, 127.95 (2C), 127.92, 127.90 (2C), 127.86 (2C), 127.8, 127.73, 127.69, 127.0, 126.7, 126.44, 126.41, 126.38, 126.35, 126.26, 126.2 (2C), 126.12, 126.09, 126.0, 125.94, 125.92, 125.8, 125.6, 78.2, 77.8, 76.8, 76.3, 75.3, 74.8, 74.4, 73.9, 73.8, 73.6, 73.5 (2C), 73.4, 73.1, 72.8, 72.4, 71.4, 71.2, 70.7, 70.1, 69.8, 69.3, 64.9, 39.3, 38.9, 30.4, 30.3, 18.3, 15.7, 14.6 (a signal of ethereal region is overlapped with solvent); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{85}H_{86}O_{13}Na$ 1337.5961, found 1337.6094.

*(2R,3R,4aS,5aR,6aS,8R,9S,10aR,11aS,12S,12aR)-9-(Benzyloxy)-8-((benzyloxy)methyl)-4a,6a,11a-trimethyl-2-((2R,3R,4aS,6S,7S,8-R,8aR)-3,7,8-tris(naphthalen-2-ylmethoxy)-6-((naphthalen-2-ylmethoxy)methyl)octahydropyrano[3,2-b]pyran-2-yl)-tetradecahydropyrano[3,2-b]pyrano[2′,3′:5,6]pyrano[2,3-e]pyran-3,12-diol (**48**).* BH_3·SMe_2 (210 μL, 2.21 mmol) was added to a solution of dihydropyran **9** (11.6 mg, 8.8 μmol) in THF (670 μL) at 0 °C. After the resultant mixture was stirred at room temperature for 16.8 h, NaOH (3 M in H_2O, 3.67 mL, 11.0 mmol) and H_2O_2 (30% in H_2O, 1.12 mL, 11.0 mmol) were added to the reaction solution at 0 °C. After stirring at room temperature for 2.3 h, the reaction mixture was diluted with H_2O and THF, quenched with $Na_2S_2O_3$ (7.03 g, 44.5 mmol), and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography

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(hexane/EtOAc = 2/1 → 3/2 → 1/1) to give alcohol **48** as an impure mixture including inseparable compound, and it was immediately used in the next reaction without further purification.

R_f = 0.35 (hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85−7.72 (m, 13H), 7.52 (d, J = 7.8 Hz, 2H), 7.50−7.38 (m, 12H), 7.35−7.26 (m, 8H), 7.21 (d, J = 6.0 Hz, 2H), 7.07 (dd, J = 7.8, 1.2 Hz, 1H), 5.05 (s, 2H), 4.92 (d, J = 11.4 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.6 Hz, 1H), 4.67 (d, J = 12.6 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.31−4.24 (m, 2H), 4.19−4.11 (m, 2H), 4.09−4.02 (m, 2H), 3.95 (dt, J = 9.6, 4.2 Hz, 1H), 3.89 (d, J = 9.6 Hz, 1H), 3.79 (d, J = 2.4 Hz, 1H), 3.79−3.65 (m, 7H), 3.59−3.52 (m, 2H), 3.44 (dd, J = 12.6, 4.2 Hz, 1H), 3.16 (d, J = 2.4 Hz, 1H), 2.99 (s, 1H, + contamination), 2.32 (dt, J = 11.4, 4.2 Hz, 1H), 2.16 (dt, J = 11.4, 4.2 Hz, 1H), 2.02 (q, J = 11.4 Hz, 1H), 1.85 (dt, J = 11.4, 6.0 Hz, 2H), 1.68−1.59 (m, 2H), 1.38 (s, 3H), 1.35 (t, J = 11.4 Hz, 1H), 1.31 (s, 3H), 1.17 (s, 3H), 1.08 (d, J = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 136.8, 135.8, 135.6, 135.5, 133.5, 133.4 (2C), 133.3, 133.2, 133.1, 133.0 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3, 128.14, 128.05 (4C), 127.94 (3C), 127.90 (2C), 127.85 (3C), 127.71, 127.68, 127.0, 126.6, 126.5, 126.4, 126.31, 126.26, 126.2 (2C), 126.07, 126.05, 126.0, 125.93, 125.87, 125.8, 125.5, 125.2, 82.0, 80.4, 78.8, 77.8, 76.7, 75.3, 75.0, 74.7, 74.4, 74.2, 73.9 (2C), 73.6, 73.5, 72.8, 72.4, 72.0, 71.7, 71.2, 70.8, 70.21, 70.17, 69.8, 69.3, 63.9, 63.8, 48.9, 38.8, 30.4, 30.3, 18.9, 15.7, 15.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{85}H_{88}O_{14}Na$ 1355.6066, found 1355.6121.

(2S,3R,4R,4aS,6R,7R,8aS)-6-((2R,3R,4aS,5aR,6aS,8R,9S,10aR,11-aS,12S,12aR)-9-(Benzyloxy)-8-((benzyloxy)methyl)-3,12-dihydroxy-4a,6a,11a-trimethyltetradecahydropyrano[3,2-b]pyrano[2′,3′:5,6]-pyrano[2,3-e]pyran-2-yl)-2-(hydroxymethyl)octahydropyrano[3,2-b]pyran-3,4,7-triol (**2**). DDQ (23.0 mg, 101 μmol) was added to a solution of the diol **48** in CH_2Cl_2 (880 μL) and H_2O (440 μL) at 0 °C. After stirring at 0 °C for 2.1 h, DDQ (23.6 mg, 104 μmol) was added to the solution at 0 °C. After stirring at 0 °C for 1.3 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase silica gel column chromatography (MeOH/H_2O = 1/1 → 3/2) to give NOPQRS ring analogue **2** (2.5 mg, 3.2 μmol, 37% for two steps) as a pale yellow oil.

R_f = 0.47 (MeOH/EtOAc = 1/6); $[\alpha]_D^{26}$ +25.7 (c 0.22, $CHCl_3$); IR (neat) 3358, 2943, 2870, 1456, 1385, 1273, 1092, 1060, 1040, 789, 754, 699 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.37−7.25 (m, 10H), 4.65 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 12.6 Hz, 1 H), 4.52 (d, J = 12.6 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.24 (dd, J = 13.2, 4.2 Hz, 1H), 4.20−4.07 (m, 4H), 4.03 (dt, J = 12.6, 6.0 Hz, 1H), 3.91 (br s, 1H), 3.90−3.85 (m, 1H), 3.77−3.56 (m, 12H), 3.52−3.44 (m, 3H), 3.34−3.29 (m, 2H), 2.22−2.17 (m, 1H), 2.10−1.94 (m, 3H), 1.75 (dd, J = 11.4, 4.2 Hz, 1H), 1.58 (t, J = 12.0 Hz, 1H), 1.55−1.47 (m, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 140.0, 139.8, 129.1 (2C), 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.3, 128.1, 82.7, 80.8, 77.6, 76.1, 75.4, 75.0, 74.9, 74.8, 74.5, 74.4, 73.7 (2C), 72.6, 72.0, 71.3 (2C), 71.1, 70.8, 68.6, 65.1, 64.4, 63.3, 49.4, 40.0, 33.9, 31.1, 19.6, 15.8, 15.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{41}H_{56}O_{14}Na$ 795.3562, found 795.3565.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01658.

Spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the late Dr. Kazuo Tachibana, Emeritus Professor of The University of Tokyo.

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Convergent Syntheses of the WXYZ Ring of Maitotoxin and the HIJK Ring of Brevisulcenal-F

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A convergent method to construct the 6/7/6/6-tetracyclic ether system possessing contiguous angular methyl groups was developed. The key steps of the synthesis involve coupling of a lithium acetylide and an aldehyde, cyclodehydration of a hydroxy ketone to form a dihydropyran, ring expansion of a six-membered ring ketone into a seven-membered one, and methylation of a mixed-thioacetal. Based on this strategy, syntheses of the WXYZ ring of maitotoxin and the HIJK ring of brevisulcenal-F were achieved, and the stereochemistry of the HIJK ring of brevisulcenal-F was confirmed.

Keywords: Ladder-shaped polyether | Tetracyclic ether | Brevisulcenal-F

Epiphytic dinoflagellates produce highly toxic secondary metabolites, so-called ladder-shaped polyethers.[1] Maitotoxin (MTX)[2] and brevisulcenal-F (KBT-F),[3] in particular, are outstanding in their large molecular weights. Their unique structures and potent biological activities have attracted much interest in the synthetic community.[4] Despite development of a number of convergent methods to synthesize ladder-shaped polyethers, it is a daunting task to construct polycyclic ether frameworks possessing contiguous angular methyl groups such as the WXYZ ring system of MTX and the HIJK ring system of KBT-F (Figure 1) because of the severe steric repulsion existing within them. Thus, there are only three precedents to construct the polycyclic ether system containing the WXYZ ring system of MTX. The WXYZA′ ring of MTX was synthesized by Nakata[5] in a linear manner via SmI_2-induced reductive cyclization and 6-endo cyclization of a vinyl epoxide, whereas a convergent synthesis of the WXYZA′ ring of MTX was reported by Nicolaou[6] via Takai olefination and ring-closing metathesis.

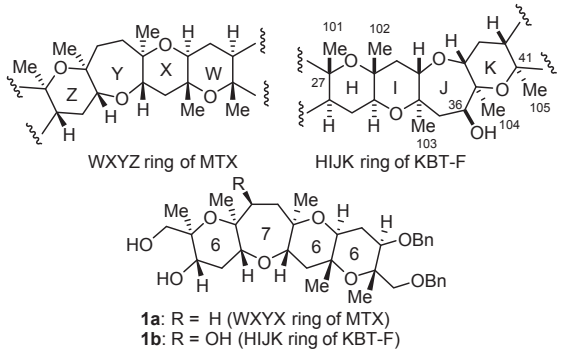


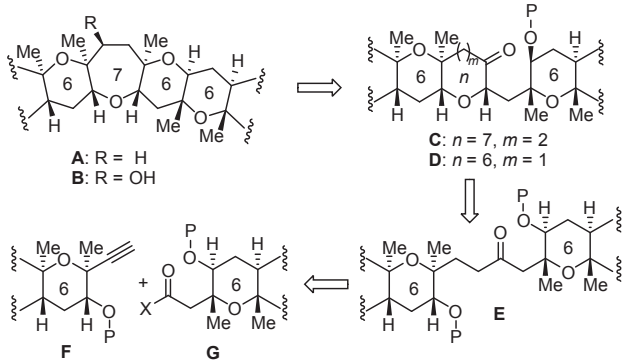
Figure 1. Partial structures of the WXYZ ring of MTX, the HIJK ring of KBT-F, and structures of the 6/7/6/6-tetracyclic ethers (**1a** and **1b**).

We reported a highly convergent synthesis of the WXYZA′B′C′ ring[7] of MTX based on the α-cyano ether method[8] developed in our laboratory as part of a structure–activity relationship study.[9]

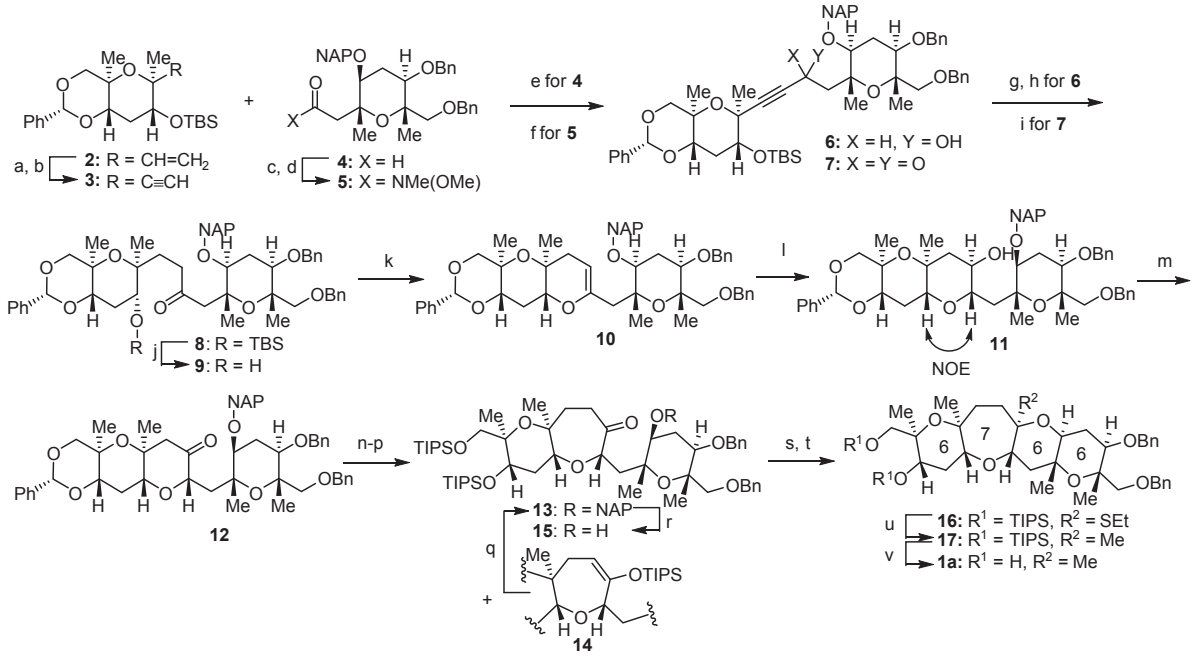
However, there are no reports on the synthesis of the HIJK ring system of KBT-F possessing a β-hydroxy group on the seven-membered ring. Herein, we describe an alternative convergent strategy via two-ring construction[4c] for synthesizing the 6/7/6/6-tetracyclic ether system possessing contiguous angular methyl groups corresponding not only to the WXYZ ring system of MTX (**1a**) but also the HIJK ring system of KBT-F (**1b**).

Our synthetic strategy is shown in Scheme 1. The 6/7/6/6-tetracyclic ether system **A** corresponding to the WXYZ ring of MTX is to be derived from **C** through the construction of the tetrahydropyran ring via methylation of a mixed-thioacetal reported by Nicolaou[10] in an analogous manner as previously reported.[7] The seven-membered ring ketone **C** could be derived from six-membered **D** by the ring-expansion reaction reported by Mori,[11] and the cyclic ketone **D** can be traced back to an acyclic saturated ketone **E** via cyclodehydration giving a dihydropyran followed by hydroboration as reported by Crimmins[12] and Nakata.[13] Although a related synthetic method of the ketone **E** was reported by Crimmins via Horner–Wadsworth–Emmons reaction followed by 1,4-reduction,[12] we envisaged that the ketone **E** would be obtained by coupling of a terminal alkyne **F** and a carbonyl compound **G** followed by hydrogenation of the alkyne. The 6/7/6/6-tetracyclic ether system **B** corresponding to the HIJK ring of KBT-F is to be synthesized in a similar manner from the common intermediate **C**, where regio- and stereoselective installation of the hydroxy group of the seven-membered ring is required.

Synthesis of the 6/7/6/6-tetracyclic ether **1a** via seven-membered ring ketone **13** is shown in Scheme 2.



Scheme 1. Synthetic strategy for synthesizing the 6/7/6/6-tetracyclic ethers (P = protecting group).

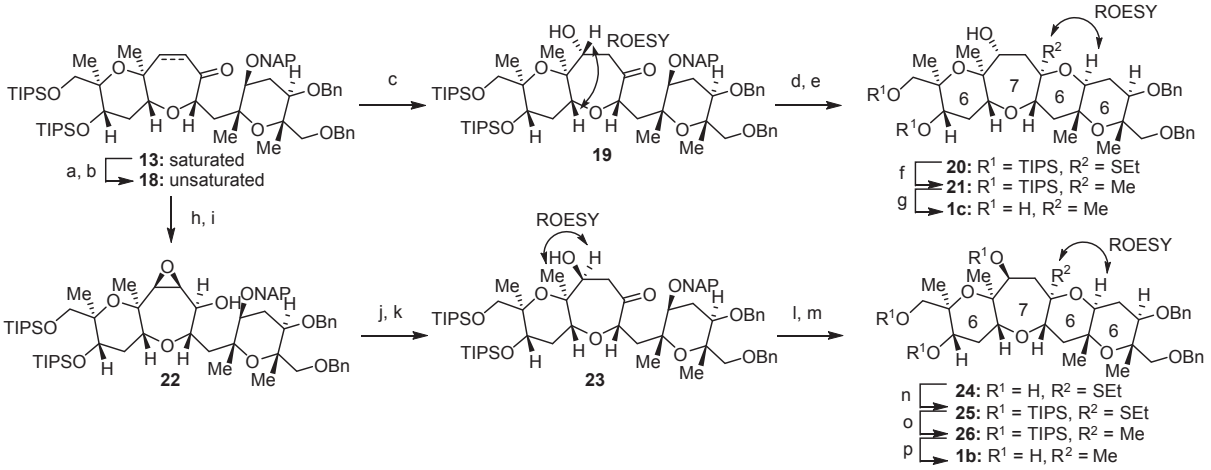


Scheme 2. Synthesis of the 6/7/6/6-tetracyclic ether **1a**. (a) O_3, CH_2Cl_2, MeOH, −78 °C, 3.5 h, then PPh_3, −78 °C to rt, 3.6 h; (b) $MeCOCN_2PO(OMe)_2$, Cs_2CO_3, MeOH, rt, 1.4 h, 83% (two steps); (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, rt, 1 h, 90%; (d) Me(OMe)NH·HCl, DCC, DMAP, Et_3N, CH_2Cl_2, rt, 25.5 h, 97%; (e) **3**, *n*-BuLi, THF, 0 °C, 1 h; then **4**, THF, −78 °C, 1 h, 88%; (f) **3**, *n*-BuLi, THF, 0 °C, 1 h; then **5**, THF, 0 °C to rt, 2 h, 49%; (g) PtO_2, H_2, EtOAc, rt, 7.7 h; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 1.1 h, 87% (two steps); (i) $[CuH(PPh_3)]_6$, phenylsilane, H_2O, benzene, 0 °C, 2 h, 76%; (j) TBAF, THF, rt, 1 h, **9** (54%), recovery of **8** (40%); (k) Nafion NR-50, MS4A, toluene, reflux, 30 min, 76%; (l) BH_3·SMe_2, THF, 0 °C, then H_2O_2, NaOH rt, 1.5 h, 98%; (m) TPAP, NMO, MS4A, CH_2Cl_2, rt, 1.4 h, 97%; (n) $TMSCHN_2$, BF_3·OEt_2, CH_2Cl_2, −78 °C, 1.9 h; (o) *p*-TsOH·H_2O, CH_2Cl_2/MeOH, rt, 21.2 h, 63% (two steps); (p) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 14.5 h, **13** (64%), **14** (34%); (q) TBAF, THF, −20 °C, 4 min, 86%; (r) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C to rt, 50 min, 85%; (s) EtSH, TfOH, MS4A, CH_2Cl_2, 0 °C, 1.6 h; (t) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 30 min, 74% (two steps); (u) MCPBA, CH_2Cl_2, −78 °C to −40 °C, 1 h; then Me_3Al, −40 °C to 0 °C, 1.5 h, 73%; (v) TBAF, THF, rt, 1 h, 87%.

Terminal alkyne **3** was prepared from known alkene **2**[14] by ozonolysis followed by treatment with Ohira-Bestmann reagent[15] in the presence of Cs_2CO_3 in 83% yield for two steps.

Alkyne **3** was treated with *n*-BuLi and the resulting lithium acetylide was reacted with known aldehyde **4**[7] to furnish propargylic alcohol **6** in 88% yield as a mixture of diastereomers in a 2.5:1 ratio. Hydrogenation of alkyne **6** with PtO_2 under a hydrogen atmosphere, followed by Dess–Martin oxidation of the resulting saturated alcohol gave ketone **8** in 87% yield over two steps. Although the ketone **8** was alternatively obtained from the Weinreb amide **5** derived from **4** (87%, two steps) via coupling with **3** (49%) and 1,4-reduction of the resulting ynone **7** with Stryker reagent[16] (76%), the former route (77% for three steps from **4**) was more practical than the latter one (33% for four steps from **4**) both in yield and reagent economy. Removal of the TBS group of **8** with TBAF resulted in the formation of hydroxy ketone **9** in 54% yield as a mixture of its hemiacetal in a 1:1 ratio with 40% recovery of **8** (prolonged reaction time resulted in low yield of **9**). Treatment of **9** with Nafion NR-50[17] in toluene under reflux afforded dihydropyran derivative **10** in 76% yield. Hydroboration of **10** with BH_3·SMe_2 proceeded stereoselectively to yield secondary alcohol **11** in 98% yield as a single isomer. Ley oxidation of alcohol **11** with TPAP and NMO[18] furnished ketone **11** in 97% yield. The next task, ring-expansion of the six-membered ring ketone into the seven-membered one, was carried out as reported by Mori.[11] Thus, treatment of **12** with $TMSCHN_2$ in the presence of BF_3·OEt_2 resulted in the formation of a seven-membered ring ketone as a mixture with α-TMS ketone, which was subjected to hydrolytic conditions with *p*-TsOH in CH_2Cl_2/MeOH resulting in concomitant removal of the TMS group and benzylidene acetal to afford the diol in 60% yield for two steps. Protection of the resulting diol as TIPS ethers gave **13** (64%) with concomitant formation of silyl enol ether **14** (34%), which was recovered to form **13** (86%) by treatment with TBAF at −20 °C for 4 min.

Having the key intermediate **13** in hand, the WXYZ ring of MTX was synthesized as previously reported but with modification of the mixed-thioacetal formation.[7] After removal of the NAP group of **13** with DDQ giving hydroxy ketone **15** in 85% yield, the mixed-thioacetal formation was examined. As reported,[7] treatment of the hydroxy ketone with EtSH in the presence of $Zn(OTf)_2$ afforded the desired mixed-thioacetal **16** (42%) with concomitant formation of dithioacetal (8%). Recovery of the starting material (42%), and recycling of the recovered **15** gave **16** in 64% total yield. After considerable experimentation with various Lewis acids, such as $Sc(OTf)_3$ and $In(OTf)_3$, we finally found that not metal triflates but TfOH in the presence of MS4A gave better results, and **16** was obtained in 74% yield as a mixture of diastereomers (α:β = 4.8:1) after protection of the partially desilylated products. Next, introduction of the angular methyl group was achieved by treatment with MCPBA followed by Me_3Al to afford **17** in 73% yield.



Scheme 3. Syntheses of the 6/7/6/6-tetracyclic ether **1b** and **1c**. (a) LHMDS, TMSCl, Et_3N, THF, −78 °C, 1 h; (b) $Pd(OAc)_2$, *p*-benzoquinone, CH_3CN, rt, 15.5 h, 95% (two steps); (c) $B_2(pin)_2$, CuCl, *n*-Bu_3P, DMF, rt, 4.5 h; H_2O_2, NaOH, rt, 30 min, 84%; (d) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C, 2 h, 93%; (e) EtSH, TfOH, MS4A, CH_2Cl_2, 0 °C, 4 h, 74% (α:β = 2.9:1); (f) MCPBA, CH_2Cl_2, −78 °C to −40 °C, 1 h, then Me_3Al, −40 °C to 0 °C, 1 h, 42%; (g) TBAF, THF, rt, 2.5 h, 87%; (h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2, MeOH, 0 °C, 20 min, 81%; (i) MCPBA, CH_2Cl_2, rt, 2 h, 87%; (j) TPAP, NMO, MS4A, CH_2Cl_2, rt, 30 min, 95%; (k) $Na[PhSeB(OEt)_3]$, AcOH, EtOH, rt, 1.5 h, 90%; (l) DDQ, pH 7 buffer, CH_2Cl_2, rt, 1 h, 89%; (m) EtSH, TfOH, MS4A, CH_2Cl_2, 0 °C, 4 h, 69% (30% recovery); (n) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 6.5 h, 91%; (o) MCPBA, CH_2Cl_2, −78 °C to −40 °C, 1 h; then Me_3Al, −40 °C to 0 °C, 3 h, 94%; (p) TBAF, THF, rt, 27 h, 84%.

Although direct methylation of the mixed thioacetal **16** was carried out with Me_2Zn and $Zn(OTf)_2$ as reported by Kadota,[19] no reaction occurred in CH_2Cl_2 at room temperature, and that in $ClCH_2CH_2Cl$ under reflux afforded **17** with concomitant formation of an enol ether formed via elimination of the ethylthio group as an inseparable mixture in a 1.2:1 ratio. Removal of the TIPS group with TBAF furnished the 6/7/6/6-tetracyclic ether **1a** corresponding to the WXYZ ring of MTX in 87% yield.

Next, we moved on to the synthesis of the HIJK ring of KBT-F as shown in Scheme 3. The seven-membered ring ketone **13** was converted to α,β-unsaturated ketone **18** in 95% yield for two steps via silyl enol ether formation by successive treatment with LHMDS, TMSCl, and Et_3N,[20] followed by the Ito–Saegusa reaction with $Pd(OAc)_2$ and *p*-benzoquinone.[21] The next crucial step, regio- and stereoselective introduction of the β-hydroxy group at the C36 position of KBT-F to form the secondary alcohol **19**, was examined using a copper-catalyzed borylation-oxidation sequence reported by Hosomi.[22] Thus, treatment of the enone **18** with bispinacolborane in the presence of CuCl and *n*-Bu_3P followed by oxidative work-up resulted in the formation of **19** in 84% yield as a single isomer. Unfortunately, the stereochemistry of **19** turned out to be opposite to that of the HIJK ring system of KBT-F.[23] Although attempts to invert the secondary alcohol by Mitsunobu reaction modified by Tsunoda[24] were unsuccessful, producing **18** via β-elimination, we proceeded to the next transformation with the expectation of inverting the stereochemistry after constructing the tetracyclic system. Thus, **19** was converted to **1c** in an analogous sequence with **1a**: 1) removal of the NAP group (93%); 2) mixed-thioacetal formation giving **20** (74%, α:β = 2.9:1); and 3) introduction of the angular methyl group to afford **21** (42%)[23] with a byproduct formed via β-elimination of ethylthio group (38%). Although the low yield of **21** was considered to be due to the presence of the free hydroxy group, and the reactions were carried out after protecting the alcohol as a TIPS ether, the desired product was obtained as an inseparable mixture with unidentified by-products. Inversion of the secondary alcohol of **21** was unsuccessful, oxidation of **21** and reduction of the resulting ketone gave **21** as a single isomer, and Mitsunobu inversion of **21** did not occur. Finally, removal of the TIPS groups of **21** with TBAF afforded **1c** in 87% yield.

Since direct introduction of the β-hydroxy group to the enone **18** and inversion of the secondary alcohol of **21** were unsuccessful, we next examined the method applied for the synthesis of gymnocin-A reported by Sasaki.[20,25] Luche reduction[26] of the enone **18** resulted in the formation of an allylic alcohol as a single isomer in 81% yield, which was oxidized with MCPBA to afford β-epoxide **22** in 87% yield as a single isomer. Ley oxidation of the alcohol **22** with TPAP/NMO furnished an epoxy ketone, which was treated with $Na[PhSeB(OEt)_3]$ developed by Miyashita–Yoshikoshi[27] to afford β-hydroxy ketone **23** in 90% yield. Formation of the six-membered ring was achieved in an analogous sequence: 1) removal of the NAP group with DDQ (89%) giving a hydroxy ketone; 2) mixed-thioacetal formation with EtSH and TfOH to give **24** (69%, 30% recovery of the hydroxy ketone); 3) protection of the hydroxy group as TIPS ether **25** (91%); 4) introduction of the angular methyl group to afford **26** (94%);[23] and 5) removal of all TIPS groups with TBAF to provide **1b** corresponding to the HIJK ring of KBT-F (84%).

The NMR spectra of **1b** and **1c** were compared with those of KBT-F. The differences in the chemical shifts between KBT-F, **1b** and **1c** are shown in Figure 2: (a) ^1H NMR (600 MHz, C_5D_5N), (b) ^{13}C NMR (150 MHz, C_5D_5N). The *x*- and *y*-axes represent carbon number and Δδ (Δδ = δKBT-F − δsynthetic **1b** and **1c** in ppm), respectively (The carbon numbering of KBT-F is shown in Figure 1). For both diastereomers, ^1H NMR chemical shifts at both termini deviated because the structures are different from the natural product. However, for other parts, chemical shifts of **1b** are identical with those of KBT-F, while

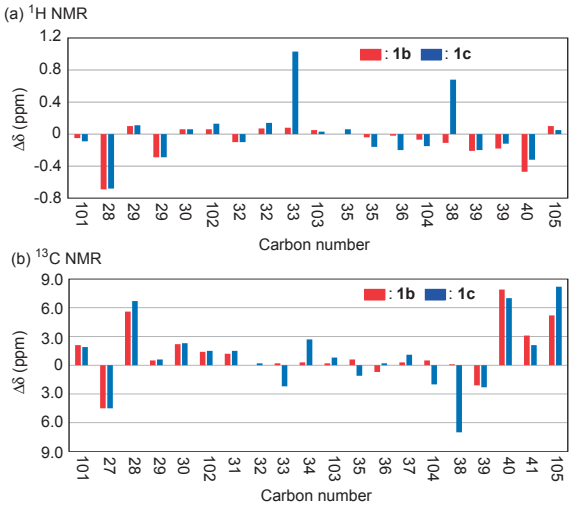


Figure 2. Differences in chemical shifts between KBT-F and the synthetic fragments **1b** and **1c**. (a) ^{1}H NMR (600 MHz, C_5D_5N), (b) ^{13}C NMR (150 MHz, C_5D_5N). The *x*- and *y*-axes represent carbon number and Δδ in ppm. Red and blue bars represent Δδ = δ KBT-F − δsynthetic **1b** and **1c**, respectively.

those of **1c** at C33 and C38 deviate by 1.03 and 0.68 ppm, respectively. Analogously, ^{13}C NMR chemical shifts at both termini deviate for both diastereomers, and chemical shifts of **1b** for other parts are identical with those of KBT-F, while those of **1c** at C33, C34, C104, and C38 deviate by more than 2.0 ppm. Therefore, the structure of the HIJK ring system of KBT-F has been confirmed, whereas previously its absolute configuration was unknown.[3]

In conclusion, a convergent method for synthesizing the 6/7/6/6-tetracyclic ether system was developed via acetylide-aldehyde coupling, dehydrative cyclization, and ring-expansion as key steps. The advantages of this strategy are its applicability to ring systems possessing contiguous angular methyl groups, and the use of the highly nucleophilic acetylide as a coupling partner, which can be easily recovered after the coupling reaction if an excess amount of the acetylide was used. Based on this strategy, stereoselective syntheses of the WXYZ ring of MTX (**1a**), the HIJK ring of KBT-F (**1b**), and its C36 epimer (**1c**), have been achieved from the key intermediate **13**, and the stereochemistry of the HIJK ring of KBT-F was confirmed. Applications of this method to synthesize other ladder-shaped polyethers are currently underway in our laboratory.

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