Synthetic Studies of Amphidinol 3

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アンフィジノール 3 の合成研究

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Abstract

Amphidinol 3 (AM3) is an amphiphilic polyketide produced by dinoflagellate *Amphidinium klebsii*. AM3 has a potent antifungal activity and hemolytic activity. Although the mode-of-action of AM3 has not fully been elucidated, AM3 is thought to interact directly with lipid membrane and forms barrel-stave or toroidal type pore. Although the absolute configuration of AM3 was determined in 1999 by utilizing NMR analysis, it was dauting task because of the presence of numerous stereogenic centers on the acyclic carbon chain. Therefore, the revisions of the absolute configurations at C2 and C51 were reported in 2008 and 2013 respectively. The unique structural features of AM3 have attracted considerable attention in the synthetic community. Although a number of synthetic studies of AM3 have been reported, the total synthesis of AM3 had not been achieved. In this study, structure revision, total synthesis and structure-activity relationship study were investigated.

The absolute configuration of AM3 was revised to be 32*S*, 33*R*, 34*S*, 35*S*, 36*S*, and 38*S* based on the chemical synthesis of partial structure corresponding to C31–C67 fragment of AM3 in combination with degradation of the natural product. This results revealed that structure of AM3 is unique in that both antipodal tetrahydropyran counterparts exist on a single carbon chain.

Based on the revised structure, the first total synthesis of AM3 was achieved via expeditious assembly of three components; the C1–C29, the C30–C52 and the C53–C67 fragments by using Suzuki–Miyaura coupling and Julia–Kocienski olefination. Comparison of the data between natural product and synthetic specimen confirmed the revised structure of AM3 after more than twenty years since its first discovery.

The established synthetic route would be general strategy for synthesizing amphdinol congeners and artificial analogs. Using the developed strategy, simplified analog corresponding to the C21–C67 part of AM3 was synthesized. The C21–C67 analog elicited antifungal activity comparable to that of AM3. This is the first example of a biologically active artificial analog possessing a shorter polyol moiety. Moreover, the C31–C67 analog did not have antifungal activity suggesting that C21–C30 part of AM3 has an important role for its biological activity.

Contents

Abbreviations

Ac	acetyl
AD	asymmetric dihydroxyation
AM	amphidinol
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
bp	boiling point
Bu	butyl
Bz	benzoyl
calcd	calculated
cat	catalytic or catalyst
COSY	correlation spectroscopy
CS	chemical shift
CSA	(±)-10-camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBB	di-tert-butylbiphenylide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DET	diethyltartrate
DFT	density functional theory
$(DHQ)_2AQN$	hydroquinine (anthraquinone-1,4-diyl) diether
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
(DHQ)MEQ	hydroquinine 4-methyl-2-quinolyl ether
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutyulalminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane

DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphno)propane
dqf-COSY	double quantum filter coherence spectroscopy
dr	diastereomer ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EC	effective concentration
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
ee	enantiomeric excess
eq	equivalent(s)
ESI	electrospray ionization
Et	ethyl
GC	gas chromatography
GIAO	Gauge-independent atomic orbital
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
HR	high-resolution
HSQC	heteronuclear single quantum coherence
i	Iso
IR	infrared
JBCA	*J*-based conformation analysis
KmTx2	karlotoxin 2
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
M	molar
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MIC	minimum inhibitory concentration
MS	mass spectrometry
Ms	methanesulfonyl (mesyl)
MS4A	molecular sieves 4 angstrom
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid

MW	molecular wieght
n	normal
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
o	ortho
p	para
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTSH	1-phenyl-5-mercapto-1*H*-tetrazole
Py	pyridine
quant	quantitative
ROE	rotating frame Overhauser effect
ROESY	rotating frame Overhauser effect spectroscopy
rt	room temperature
SAR	structure–activity relationship
satd	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
sp	species
TAD	Total absolute devitation
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)

TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOCSY	totally correlated spectroscopy
TOF	time-of-filight
TPAP	tetrapropylammonium perruthenate
t_R	retention time
Ts	*para*-toluenesulfonyl (tosyl)
vic	vicinal

Chapter 1. Introduction

1-1. Amphidinol 3 and its congeners

Amphidinol 3 (AM3, Figure 1-1-1) is a natural product isolated from the dinoflagellate *Amphidinium klebsii* in 1996.[1] Among seven amphidinols obtained from the cultured cells of *A. klebsii* at the time, it showed the most potent antifungal (MIC = 4 μg/disk) and hemolytic (EC_{50} = 0.25 μM) activities.[2] Thus, the planar structure of AM3 was elucidated in 1996 to show that AM3 has a characteristic structure with both hydrophilic and hydrophobic moieties in one molecule, namely, long linear polyol chain and polyhydroxy of two tetrahydropyran rings (bis-THP moiety), hydrophobic polyene chain, respectively.

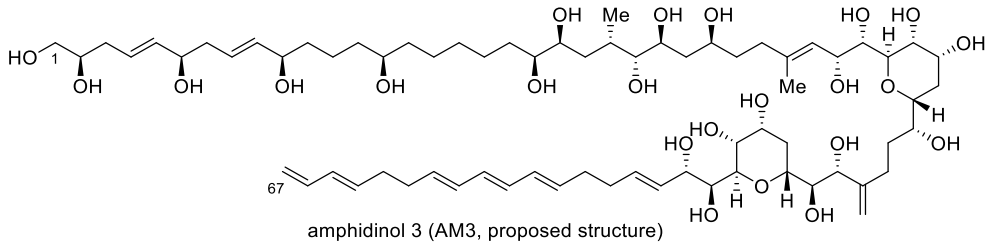


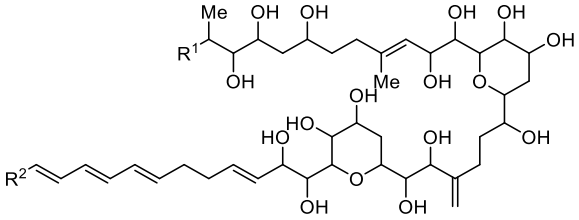
Figure 1-1-1. Structure of amphidinol 3.

Since the first report on the isolation and identification of AM1 in 1991,[3] over twenty-two amphidinol congeners have been reported so far. The central structure comprising two THP rings, part of polyol and polyene moiety is completely conserved among the all analogs. On the other hand, the terminal moiety of polyhydroxy chain has various chain lengths, and the terminal of polyene chain has different unsaturation and oxidation states (Table 1-1-1).[4] The potency of their antifungal and hemolytic activity varies from potent to almost inactive. They seem to have some correlation between structure and biological activities. For example, structural difference of the terminal olefin (R^2) dramatically affects the hemolytic activity. Substitution of the conjugated diene moiety (AM3) to vinyl group (AM4)[2] resulted in the reduction of the hemolytic activity twenty times. AM14[4c] and AM15[4c] elicited no hemolytic activity, which may relate to the hydrophilic 1,2-diol system on the polyene termini. On the other hand, AM20[4g] and AM21[4g] having the longest polyol chain and vinyl group at the end of the polyene chain were isolated, and, they show weak hemolytic activity.

In addition to AM congeners, compounds with similar structures have been isolated from *Amphidinium* species such as luteophanols A–D,[6] lingshuiols A and B,[7] karatungiols A and B,[8] carteraol E,[7] and amdigenol A, E and G.[9] From different genus of dinoflagellates, 15 types of karlotoxins,[10] karmitoxin[11] (from *Karlodinium* sp, respectively), and ostreol A[12]

(from *Ostreopsis* sp.) have also been isolated. Importantly, absolute configurations have been reported only for karlotoxin 2[13] and AM3. Karlotoxin 2 does not have conjugated triene moiety but chlorine atom on the terminal of conjugated diene moiety but shows weak antifungal activity (Figure 1-1-2).[14] These results indicate that antifungal and hemolytic activities can be tuned by changing the polyhydroxy chain length as well as polyene structure.

Table 1-1-1. Structures and biological activities of amphidinol congeners.



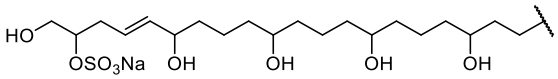
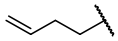
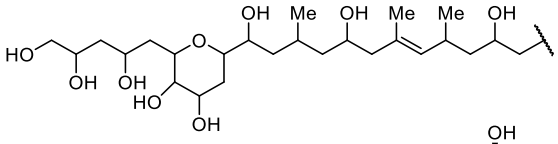
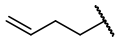
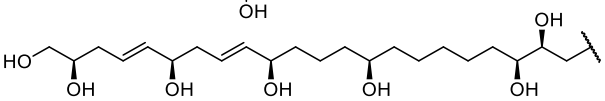
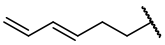
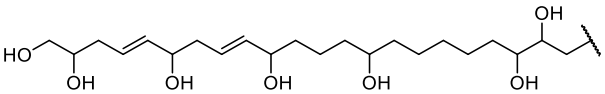
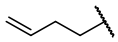
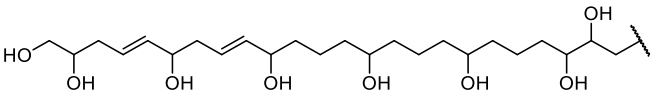
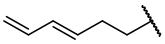
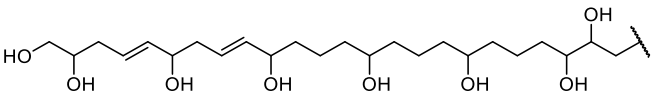
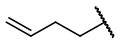
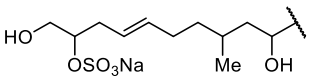
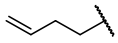
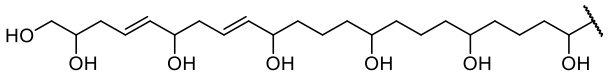
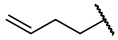
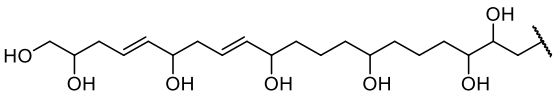
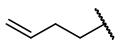
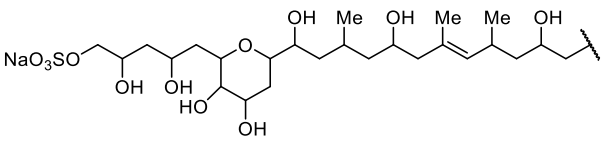
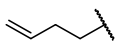
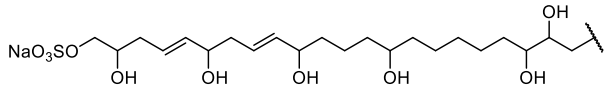
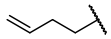
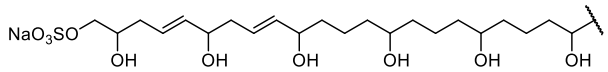
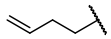
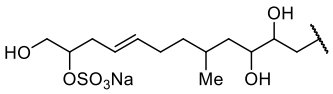
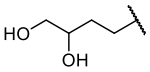
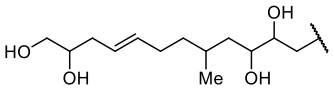
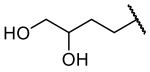
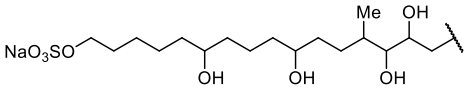
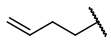
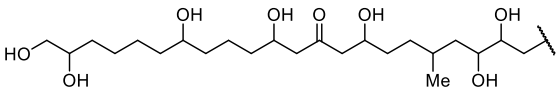
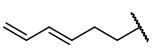
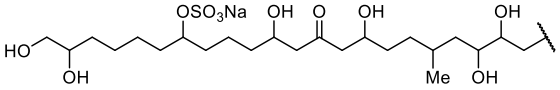
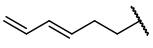
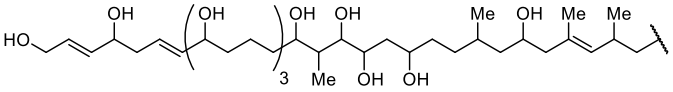
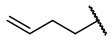
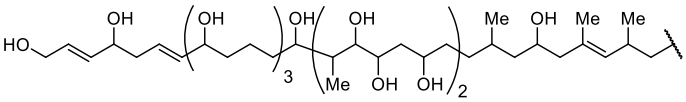
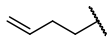
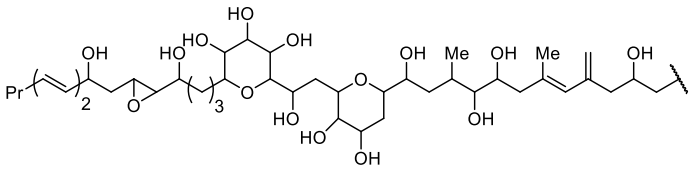
AMs	R^1	R^2	antifungal activity	hemolytic activity
			μg/disk	EC_{50}/ μM
AM1			6	0.05
AM2			6	0.91
AM3			4	0.0094
AM4			6	0.185
AM5			6	0.23
AM6			6	0.58
AM7			10	3.0
AM9			33	0.176
AM10			154	6.53
AM11			256	28.9

Table 1-1-1. Structure and biological activities of amphidinol congeners (continued).

AMs	R^1	R^2	antifungal activity μg/disk	hemolytic activity EC_{50}/μM
AM12			>100	2.99
AM13			132	2.02
AM14			>60	>50
AM15			60	>50
AM17			-	4.9
AM18			9 μg/mL (*Candida albicans*)	
AM19			inactive	inactive
AM20			>15	1.0-3.0
AM21			>15	>10
AM22			64 μg/mL (*Candida albicans*)	

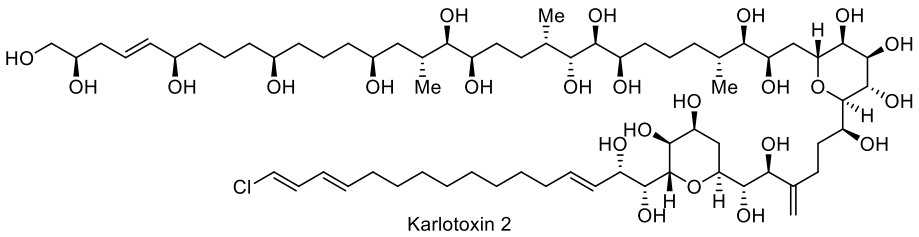


Figure 1-1-2. Structures of karlotoxin 2.

1-2. Structure determination of amphidinol 3

Although it was difficult to determine the absolute configuration of AM3 because of the limited availability of the natural product and the presence of a number of stereogenic centers on the acyclic long carbon chain, the absolute configuration of AM3 was determined in 1999 (Figure 1-2-1).[15] Acyclic parts possessing 1,2-diols and 1,3-diols (C20–C27, C32–C34, C38–C39, C43–C45, and C49–C51) were analyzed by using the *J*-based configuration analysis (JBCA) method.[16] NOE analysis combined with JBCA method was used for two THP rings and tether fragment (C39–C44) between these THP rings (Figure 1-2-2). The modified Mosher method[17] was used to determine the absolute configuration at C6, C10, C14, C23, and C39. HPLC and NMR analyses of degradation products from natural AM3 were used to determine the absolute configuration at C2 (Figure 1-2-3).

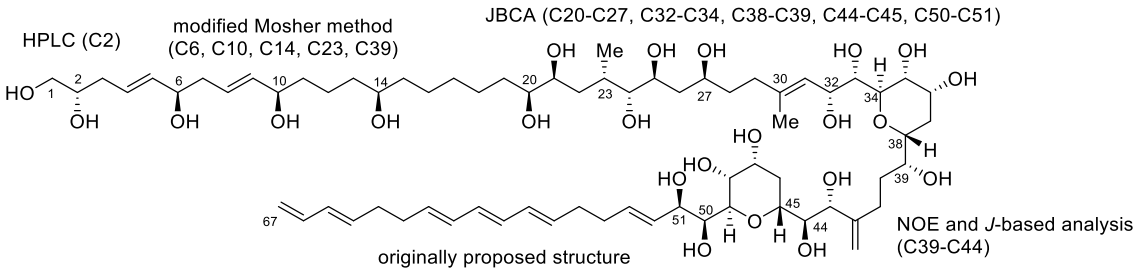


Figure 1-2-1. Originally proposed structure of AM3 and analytical methods for determining the stereochemistry.

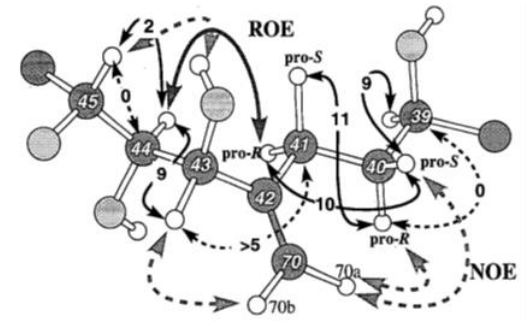


Figure 1-2-2. Observed NOEs and *J*-values in the C39–C45 part.

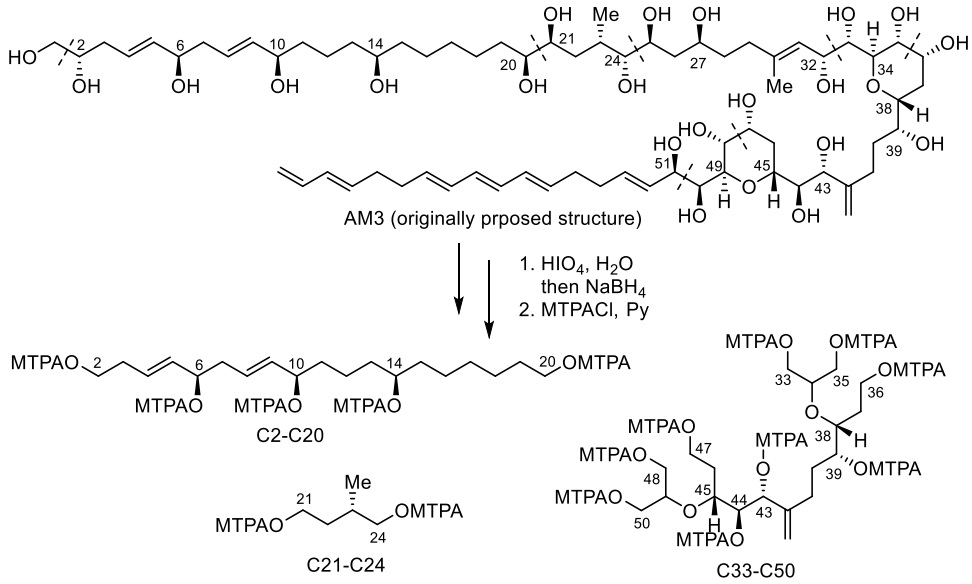


Figure 1-2-3. Degradation products used for determination of the absolute configuration.

1-3. Structure revision of amphidinol 3

In 2008, the absolute configuration at C2 was revised to be *R* by comparing ^{13}C NMR chemical shifts of synthetic diastereomers corresponding to the C1–C14 part of AM3 (Figure 1-3-1) with those of natural AM3. It is also confirmed by chemical degradation of the natural product by cross-metathesis to give the C1–C5 part, which was compared with authentic samples by GC-MS with chiral column.[18] In 2012, absolute configuration at C45 was confirmed to be *R* by comparing ^{1}H NMR chemical shifts of synthetic degradation products corresponding to C44–C50 part of AM3 with those of the degradation product of natural AM3 (Figure 1-3-2).[19] In 2013, configuration at C51 was also revised to be *S* by synthesizing both diastereomers corresponding to the C43–C67 part of AM3 (Figure 1-3-3).[20]

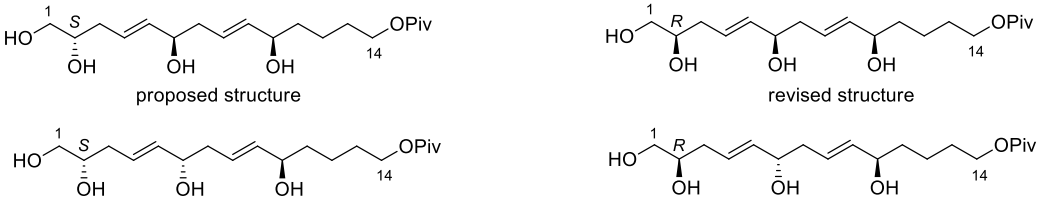


Figure 1-3-1. C1–C14 parts of AM3 used for structure revision.

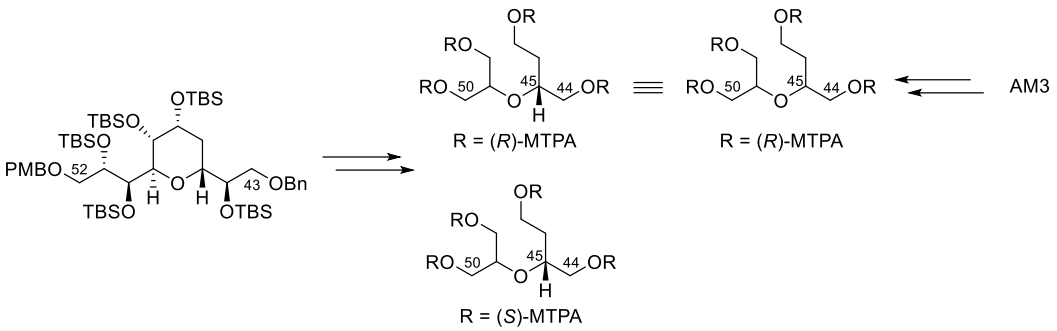


Figure 1-3-2. MTPA esters corresponding to the C44–C50 part used for structure revision.

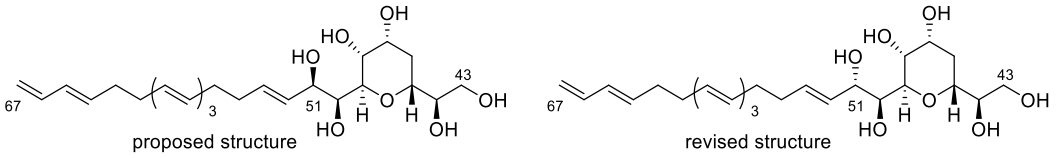


Figure 1-3-3. C43–C67 parts of AM3 used for structure revision.

JBCA method is an effective way to determine the relative configurations of the stereo centers on acyclic carbon chain. In this method, 1,2-diastereomeric relationships between chiral centers are determined by choosing a correct staggered rotamer among six possibilities arising from *syn* and *anti* configurations using spin-coupling constants ($^{3}J_{(H,\ H)}$ and $^{2,3}J_{(C,H)}$, Figure 1-3-4). However, in the case that there is a middle *J* value, it is difficult to determine the relative configuration by JBCA. In the determination of the relative configuration at C50–C51 by JBCA method, there were middle values in $^{3}J_{(H\text{-}50,\ H\text{-}51)}$ and $^{3}J_{(C51,\ H\text{-}50)}$ (Figure 1-3-5 left).[15] It was assumed that these middle vales suggested that this bond undergoes a conformational change. The small value for $^{3}J_{(C49,\ H\text{-}51)}$ indicated gauche C49/H-51 interaction in both conformers. Of the six possible pairs of alternating rotamers arising from *syn* and *anti* configurations, only one pair in Figure 1-3-5 satisfied all of these requirements. However, it was revealed that this assignment was incorrect by the comparison between synthetic partial structure and natural AM3. On the other hand, the relative configuration at the C38–C39 was also determined by JBCA method, and there was middle value in $^{3}J_{(H\text{-}38,\ H\text{-}39)}$. So, the diastereomeric relationships of C38–C39 was assigned in the same manner as C50–C51 (Figure 1-3-5 right).[15] Therefore, there is a possibility that the relative configuration at C38–C39 may also be incorrect. Since the absolute configuration at C39 determined by modified Mosher method was thought to be correct, it was assumed that the absolute configuration at C32–C38 might be opposite (Figure 1-3-6).

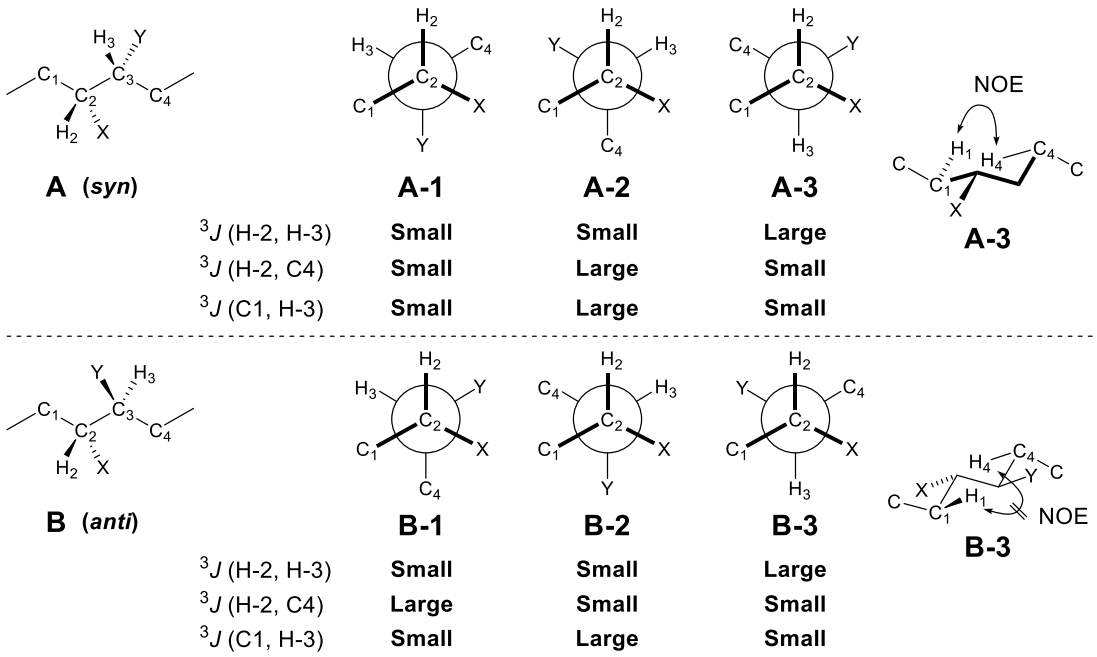


Figure 1-3-4. Six possibilities arising from *syn* and *anti* configurations

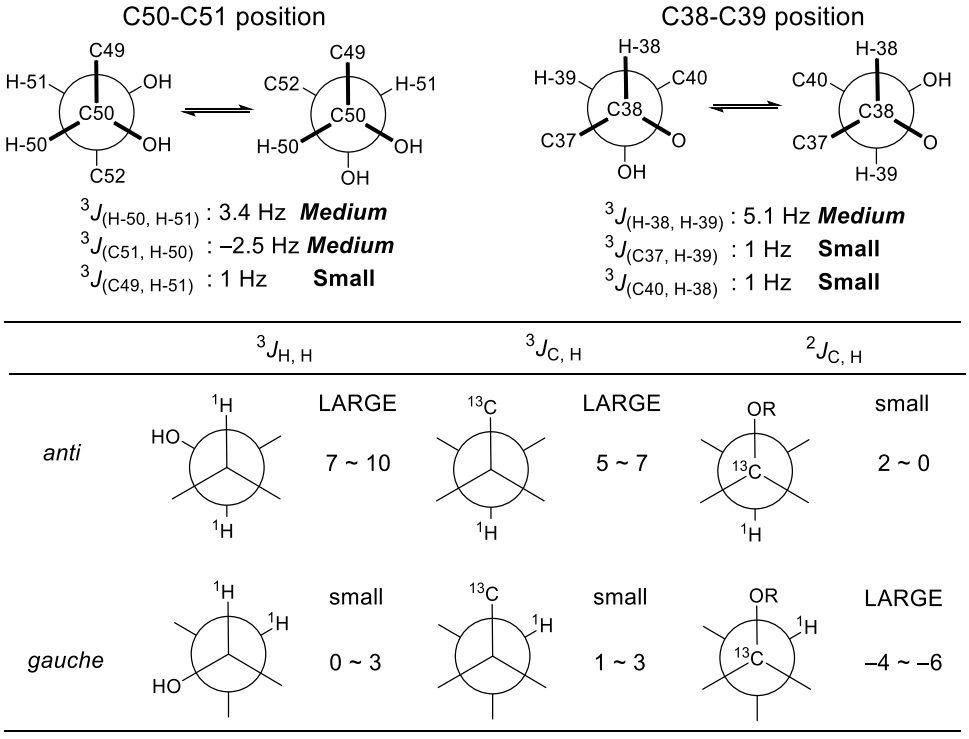


Figure 1-3-5. $^{3}J_{(H, H)}$ and $^{3}J_{(C, H)}$ values used for the determination of relative configurations

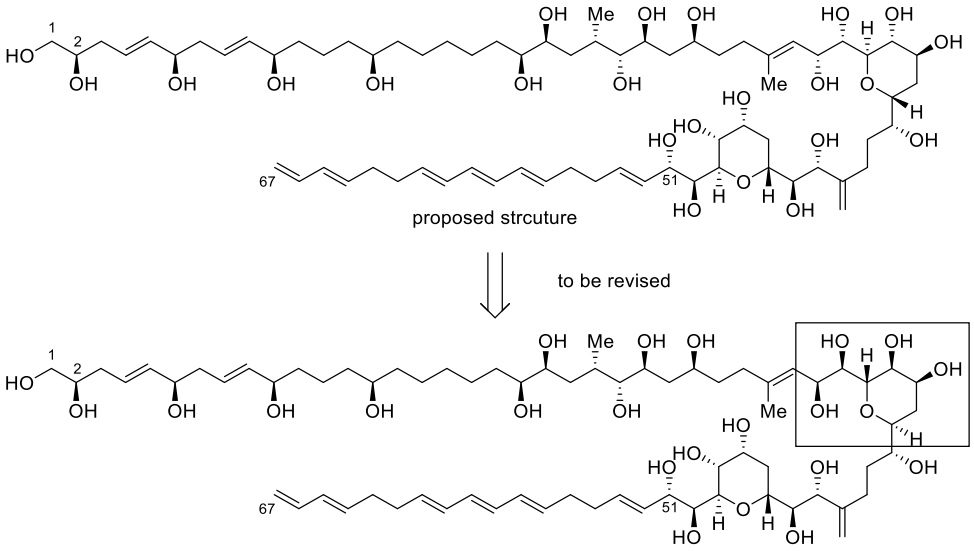


Figure 1-3-6. Plausible structure of AM3.

1-4. Structure determination of karlotoxin 2

Karlotoxin 2 (KmTx2) was isolated from dinoflagellate *Karlodinium veneficum* (Figure 1-4-1).[13] The absolute configuration of karlotoxin 2 was determined in 2010. Acyclic parts possessing 1,2-diol (C14–C18, C21–C24, C28–C27, C41–C49) was analyzed by JBCA method. NOE analysis combined with JBCA method was used for two THP rings and tether fragment (C37–C41) between these THP rings. The modified Mosher method was used to determine the absolute configuration at C6, C10, C14, C21 and C28. Chiral GC-MS analysis of degradation product of natural KmTx2 was used to determine the absolute configuration at C2. Because KmTx2 and AM3 share remarkable structure similarity, it is thought that there is a deep relationship between the stereochemistry of these molecules. In 2013, the absolute configuration AM3 was revised,[20] which gave a question that absolute configuration at C49 of karlotoxin 2 corresponding to C51 of AM3 is correct or not.

In 2015, Hamman *et al.* reported a computational study about the stereochemistry of KmTx2 and AM3. They confirmed the reliability of the structural revision at C51 of AM3 using GIAO NMR CS calculation (Higher DP4 probability indicate the most relevant structure, Figure 1-4-2).[21] The calculation was also applied to KmTx2 and the stereochemistry at C49 of KmTx2 was revised (Figure 1-4-3). Moreover, they showed that the relative configuration at C36–C37 and C28–C29 of the reported structure of KmTx2, both of which showed medium *J* values and was assigned in the same manner as C50–C51 of AM3, were correct (Higher DP4 probability and Lower TAD value indicate the most relevant structure, Figure 1-4-4).[22] Although this result seems to be inconsistent with our hypothesis noted in section 1-3, further investigation about stereochemistry of AM3 is still necessary because substitution pattern in AM3 and KmTx2 are not completely the same.

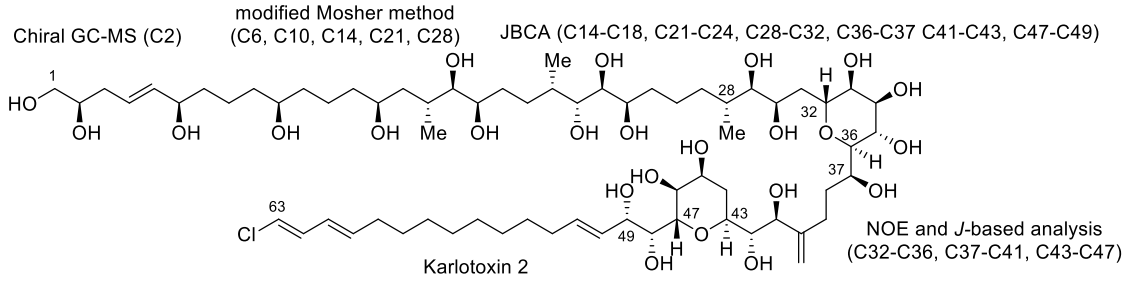


Figure 1-4-1. Proposed structure of karlotoxin 2.

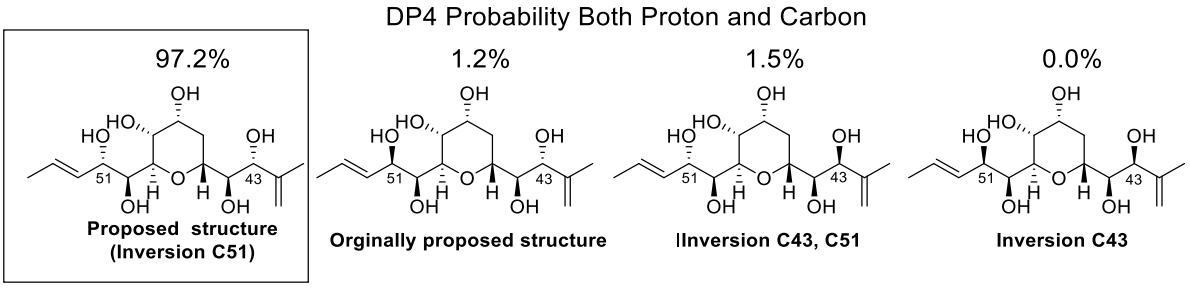


Figure 1-4-2. Confirmation of the structural revision at C51 of AM3 using DP4 calculations.

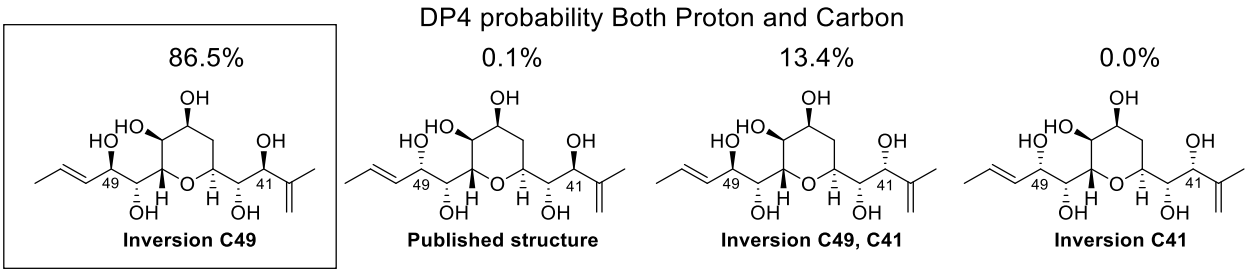


Figure 1-4-3. Structure revision at C49 of karlotoxin 2 using DP4 calculations.

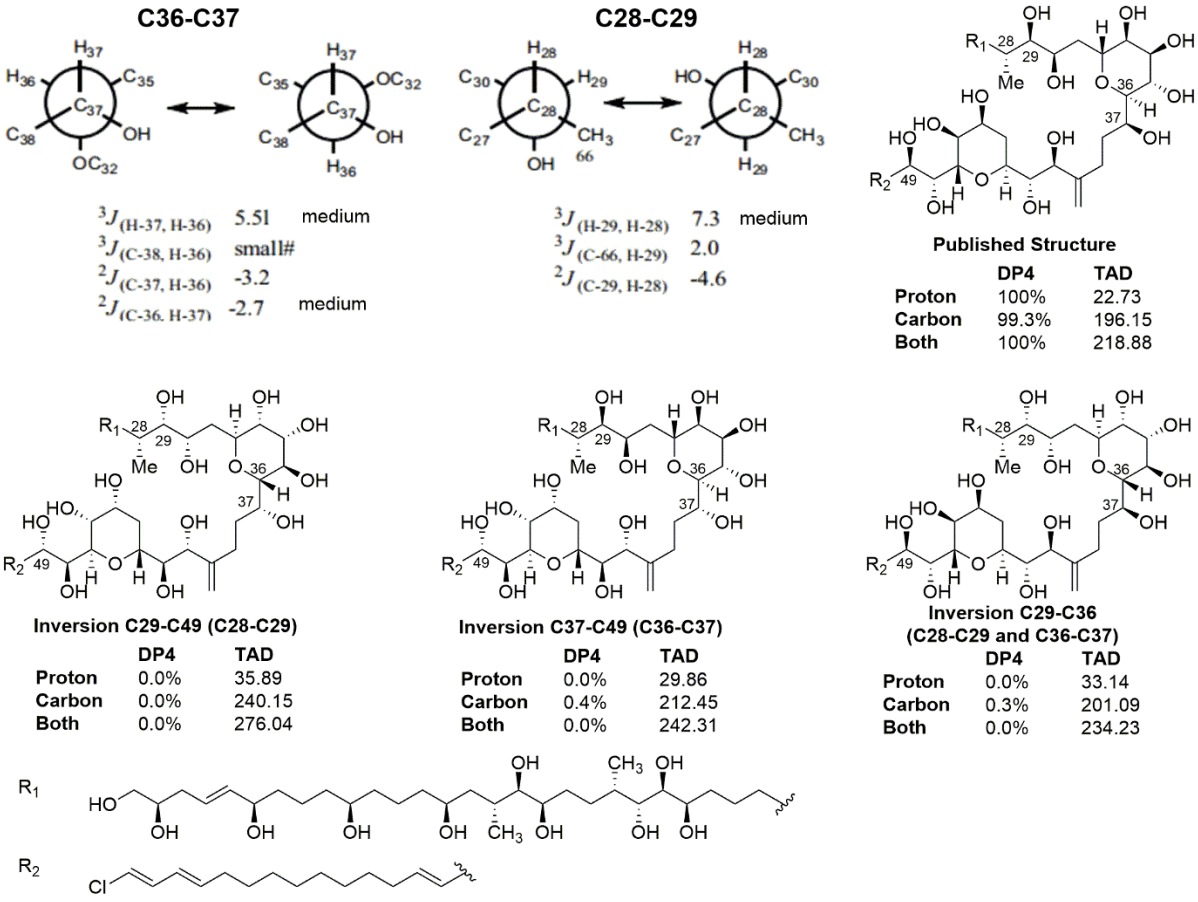


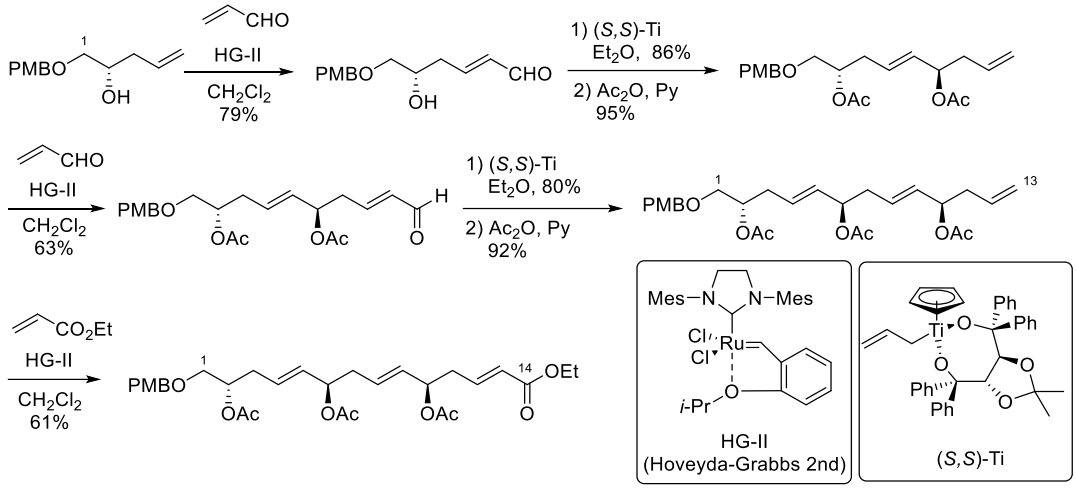
Figure 1-4-4. Four possible diastereomers for GIAO NMR shift analysis of karlotoxin 2.

1-5. Synthetic studies of amphidinol 3

AM3 continues to attract synthetic chemists because of its intriguing bioactivity and structural features. Although a number of synthetic studies of AM3 have been reported by Cossy,[23] Paquette,[24] Roush,[25] Rychnovsky,[26] and Crimmins,[27] all of them were reported before the structure revisions. Recently, Evans[28] and Yadav[29] reported synthesis of the C1–C31 and C1–C28 fragments with correct absolute configuration, respectively. Until now, the total synthesis of AM3, either the originally proposed structure or the revised structure, has not been achieved. In this section, synthetic studies of AM3 would be summarized for each research groups.

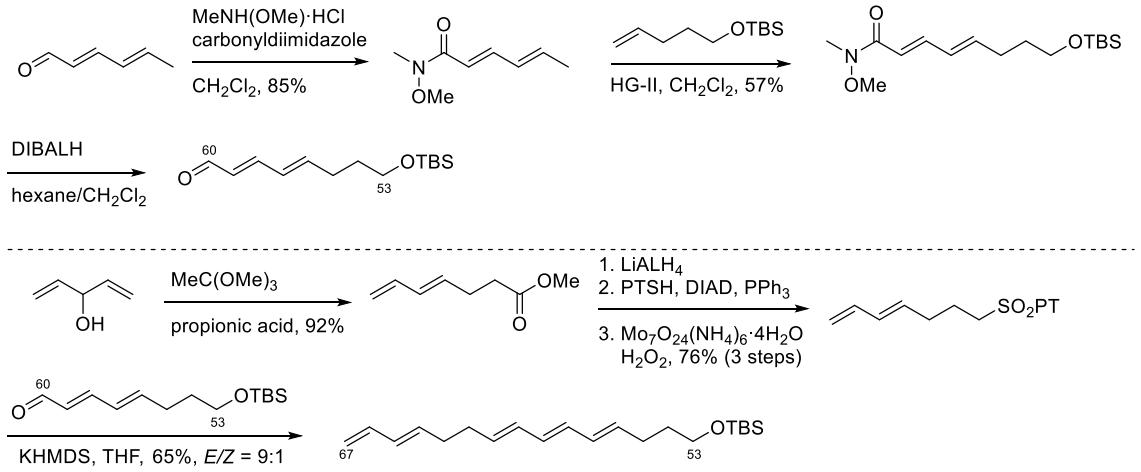
1-5-1. Cossy group

Cossy and Bouz-Bouz reported the first synthetic fragment of AM3, the C1-C14 part, in 2001.[23a] The synthesis is based on chemoselective cross-metathesis reactions and enantioselective allyltitanations (Scheme 1-5-1).



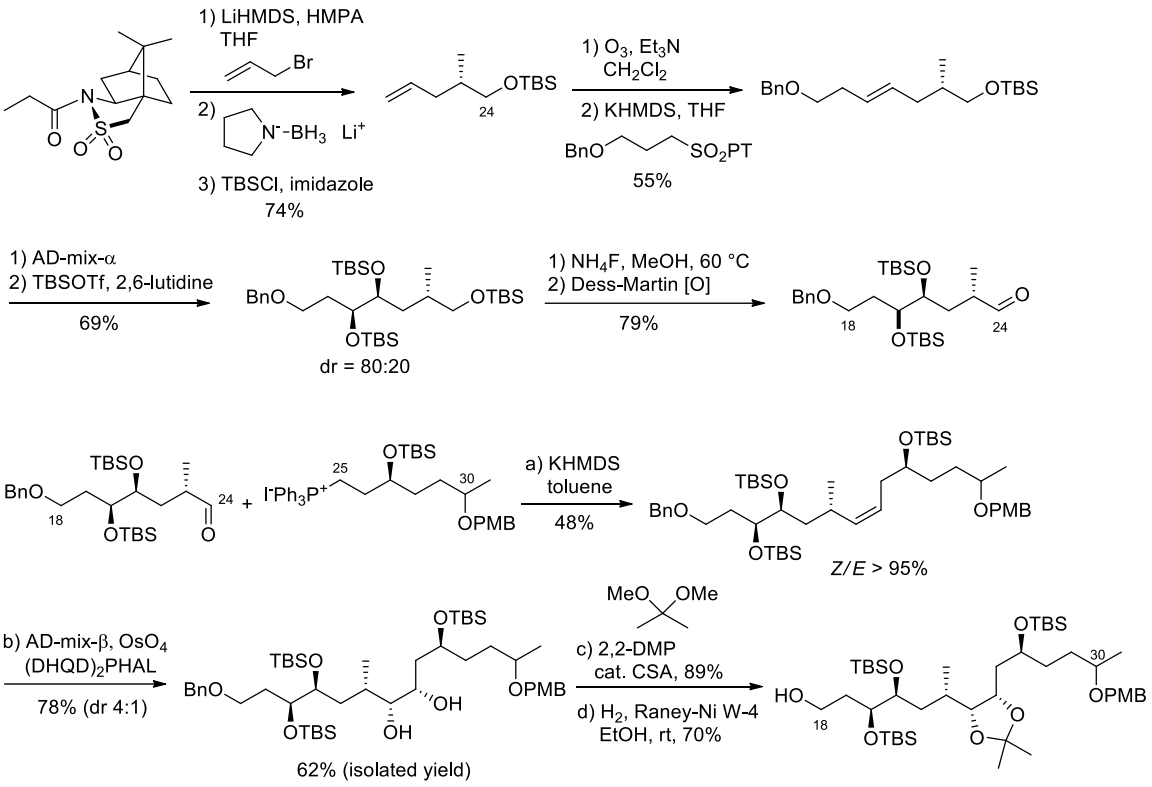
Scheme 1-5-1. Synthesis of the C1–C14 part of AM3.

Synthesis of the C53–C67 part of AM3 was reported by Cossy in 2007 (Scheme 1-5-2).[23b] The C53–C60 part of AM3 was synthesized based on cross-methasesis reaction with sorbic acid and TBS protected propenol. After the C61–C67 section was synthesized via Johonson–Claisen rearrangement and Mitsunobu reaction, two fragments were connected by Julia–Kocienski olefination.



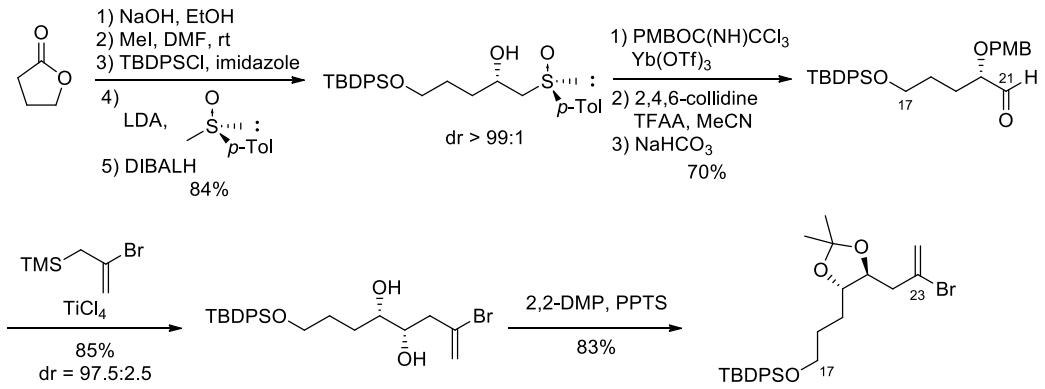
Scheme 1-5-2. Synthesis of the C53–C67 part of AM3.

Cossy and co-worker reported C18-C30 part of AM3 in 2009[23c] by using a diastereoselective alkylation of Oppolzer's chiral sultam, two Sharpless asymmetric dihydroxylations and an enantioselective allyltitanation (Scheme 1-5-3).

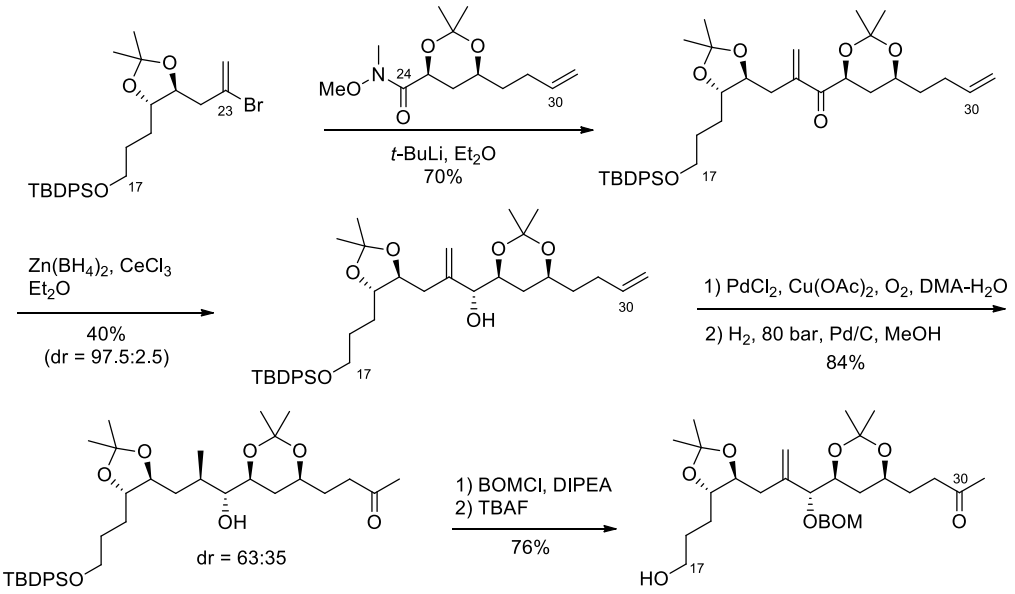


Scheme 1-5-3. Synthesis of the C18–C30 part of AM3.

Cossy also reported the synthesis of the C17-C30 part in 2012 (Scheme 1-5-4, 1-5-5).[23d] The C17-C23 part was synthesized by controlling the absolute configuration of the stereogenic centres by using (+)-*R*-methyl-*p*-tolylsulfoxide as the unique chiral source. The synthesis of the C17-C30 part of AM3 has achieved by constructing the C23-C24 bond with alkylative coupling of the C17-C23 and C24-C30 parts followd by a stereoselective reduction of a ketone and hydrogenation of *exo*-olefin.

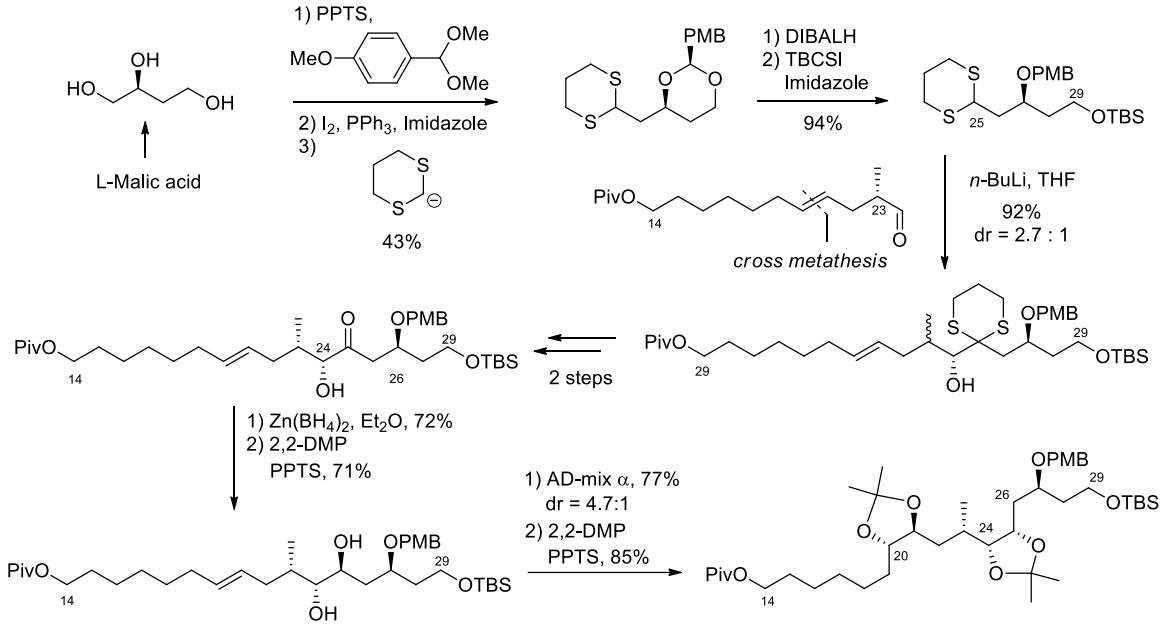


Scheme 1-5-4. Synthesis of C17–C23 of AM3.



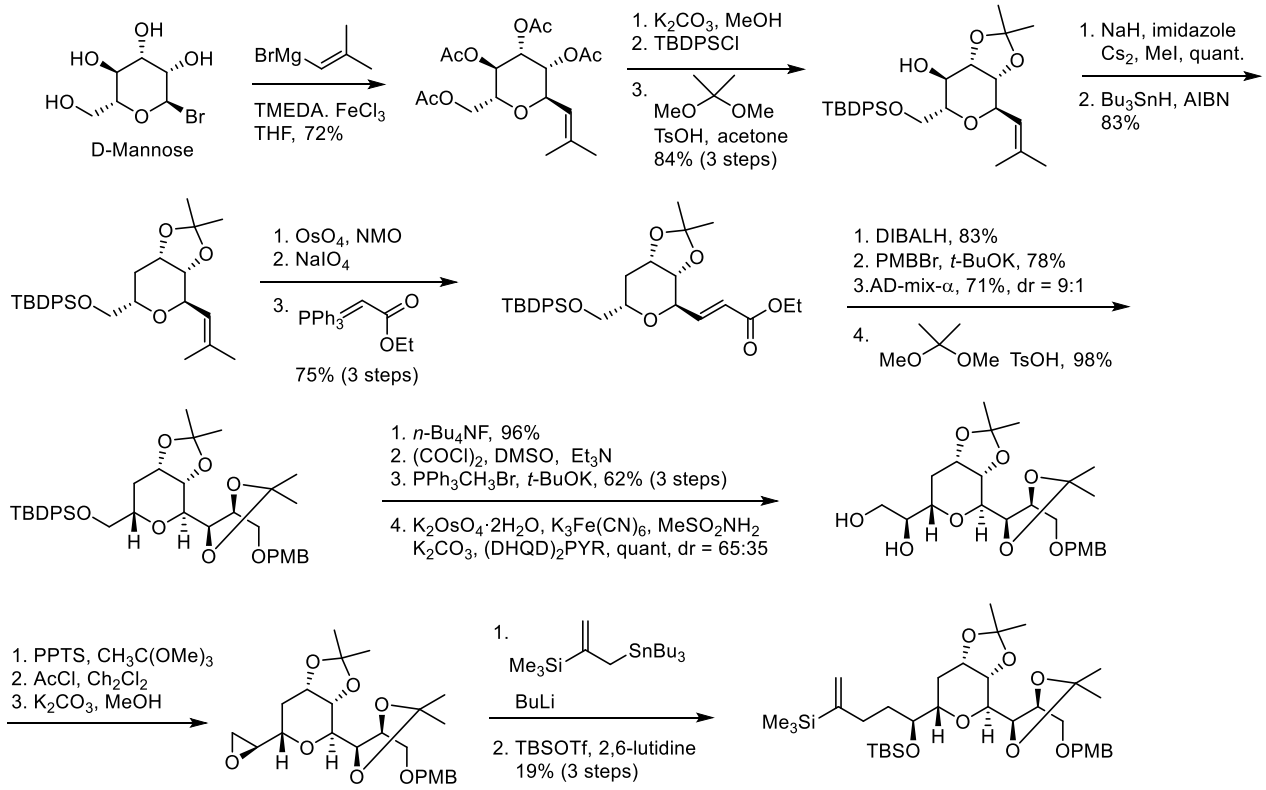
Scheme 1-5-5. Synthesis of the C17–C30 part of AM3.

Cossy reported the C14-C29 part of AM3 which was synthesized by using as key step a cross metathesis to build the C20-C21 bond, and the addition of dithiane to an aldehyde to build the C24-25 bond (Scheme 1-5-6).[23e]



Scheme 1-5-6. Synthesis of the C14–C29 part of AM3.

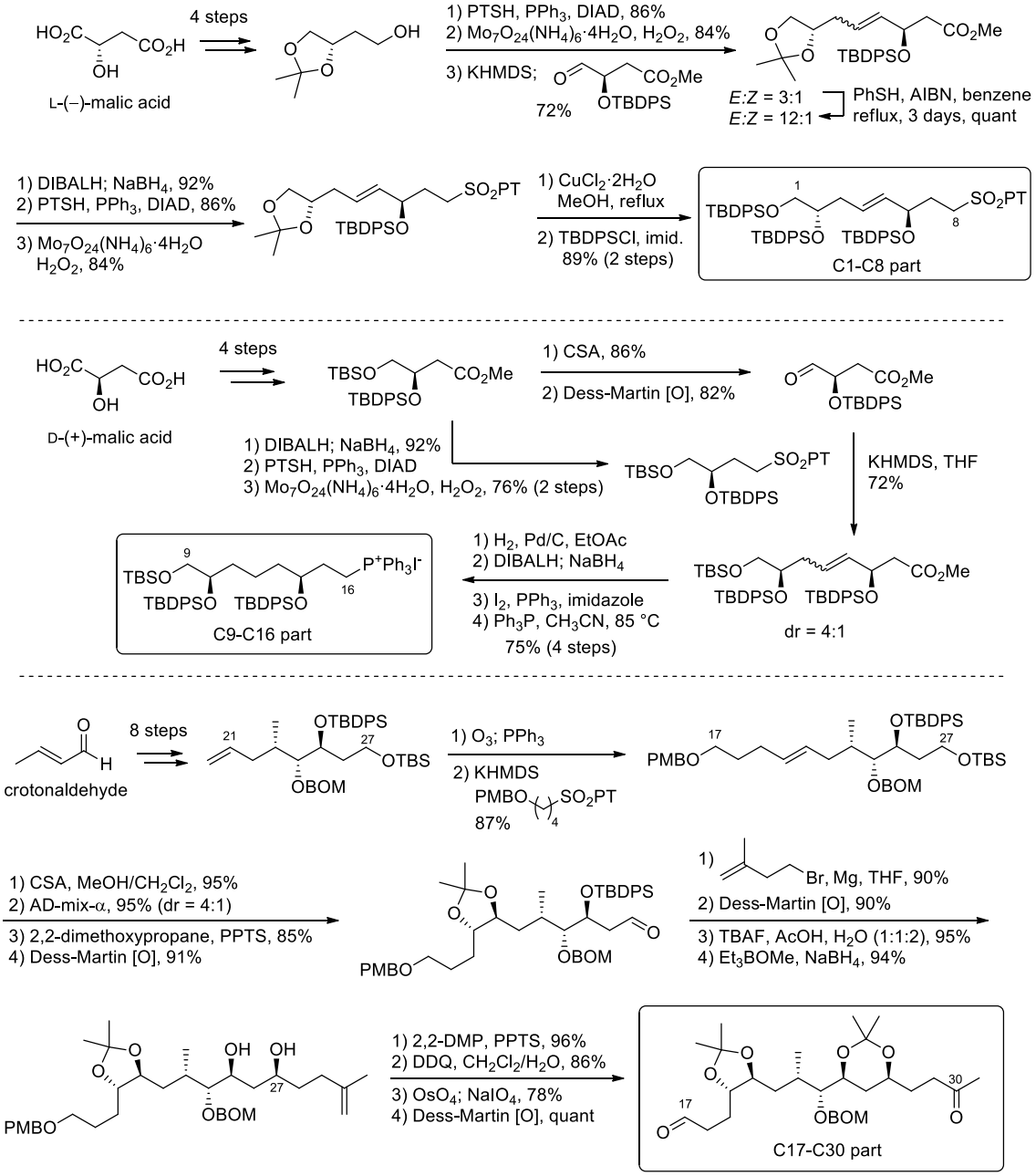
The synthesis of the C31–C42 part was reported in 2013 (Scheme 1-5-7).[23f] Iiron-catalyzed cross-coupling between C-bromo mannnopyranoside derivatives and vinyl Grignard reagent was used as a key step providing trans-tetrahydropyrans.



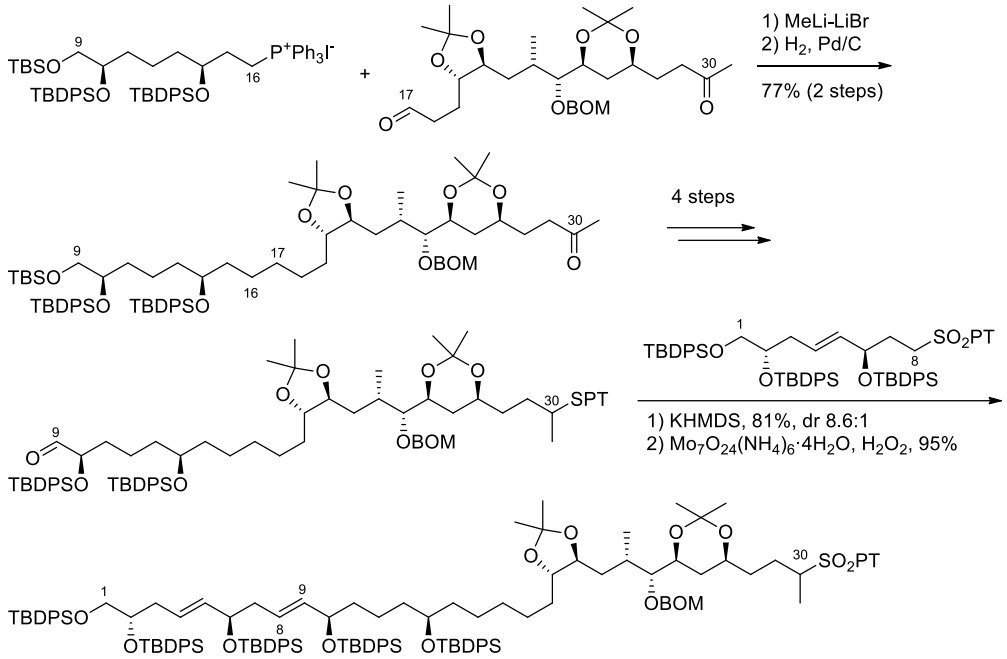
Scheme 1-5-7. Synthesis of the C14–C29 part of AM3.

1-5-2. Paquette group

Paquette et al. achieved the synthesis of the longest polyol moiety. The C1-C30 of AM3 was synthesized of by assembly of the C1-C8, C9-C16, and C17-C30 parts via Julia-Kocienski olefination and Wittig reaction (Scheme 1-5-8, 1-5-9).[24a]

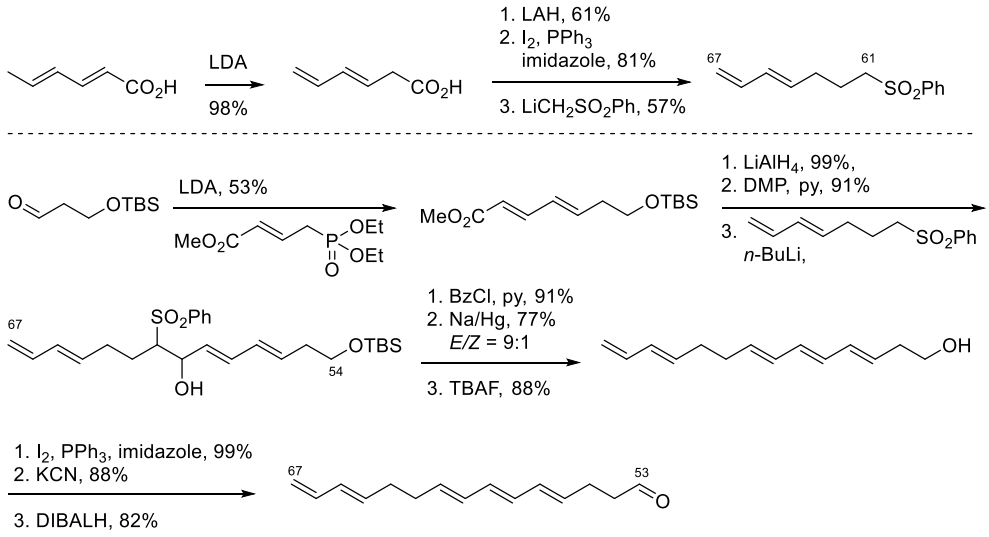


Scheme 1-5-8. Synthesis of the C1–C8, C9–C16 and C17–C30 parts of AM3.

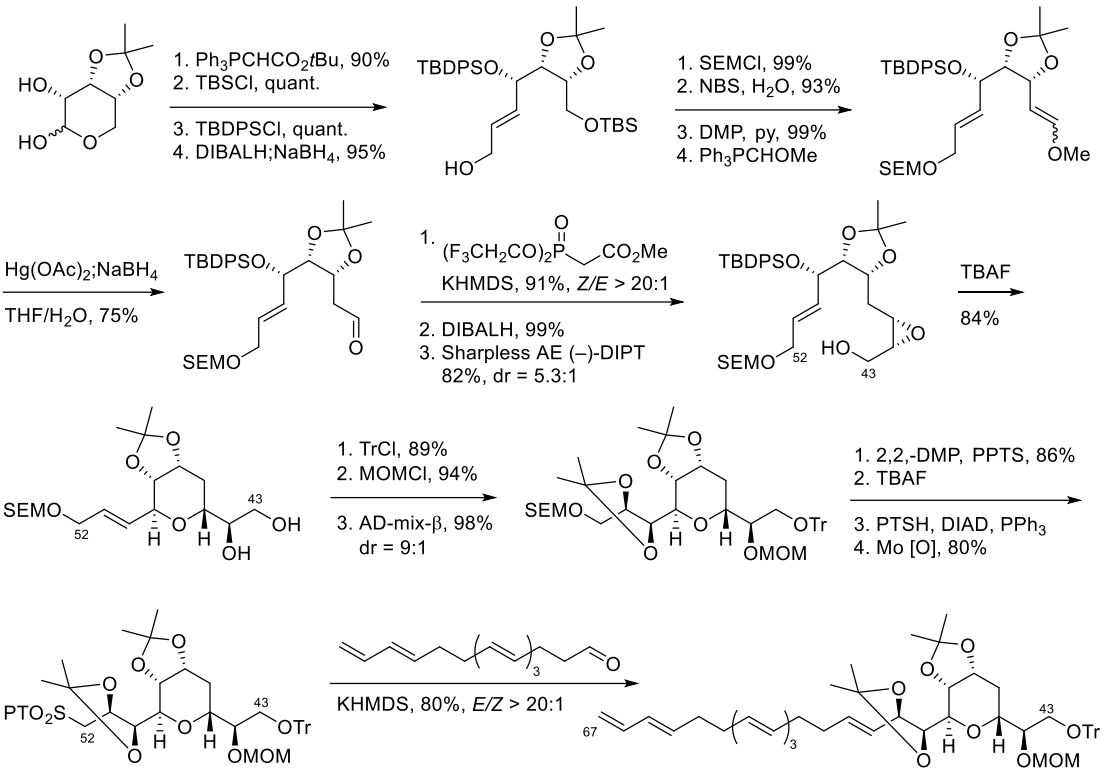


Scheme 1-5-9. Synthesis of the C1–C30 part of AM3.

Paquette reported the synthesis of the C43–C67 part of AM3 (Schemie 1-5-10, 1-5-11).[24b] The C61–C67 section was synthesized from sorbic acid. Synthesis of the C53–C67 part was carried out via Wittig reaction and Julia–Kocienski olefination with C61–C67 part. THP ring was constructed based on intramolecular ring-opening reaction of epoxide. The C43–C67 part of AM3 was synthesized via Julia–Kocienski olefination with C43–C52 and C53–C67 fragments.

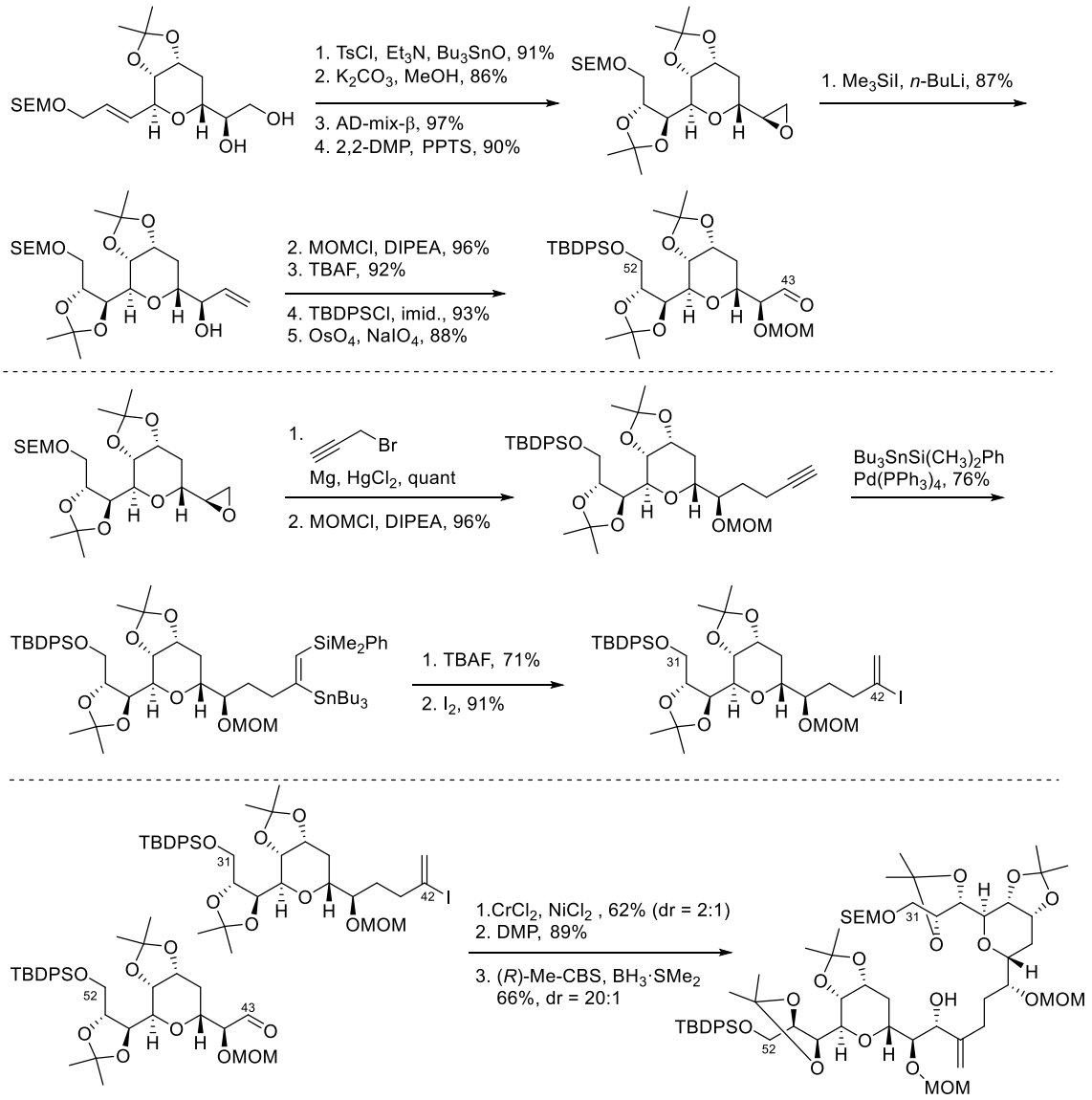


Scheme 1-5-10. Synthesis of the C53–C67 part of AM3.



Scheme 1-5-11. Synthesis of the C43–C67 part of AM3.

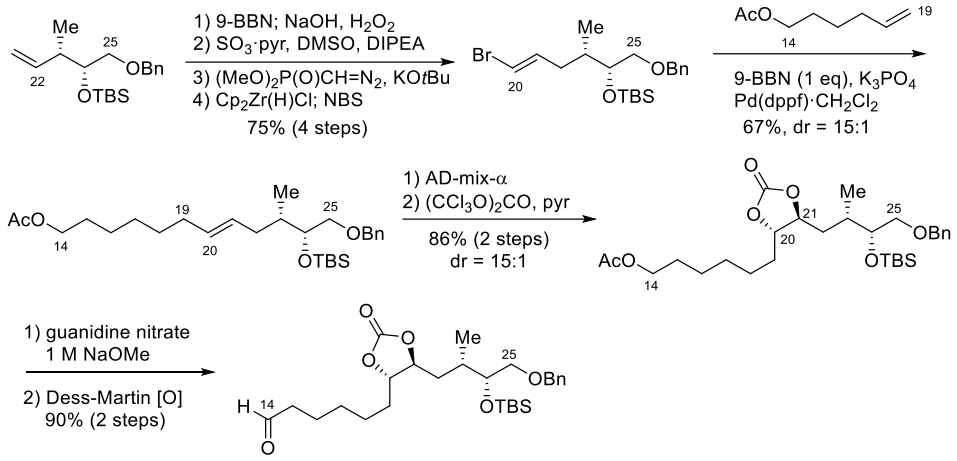
Paquette reported the synthesis of the C31–C52 part of the AM3 in 2007 (Scheme 1-5-12).[24c] Both of the C43–C52 and C31–C42 fragments were synthesized from common epoxide precursor. The coupling of the two THP fragments was achieved via Nozaki–Hiyama–Lishi reaction.



Scheme 1-5-12. Synthesis of the C31–C52 part of AM3.

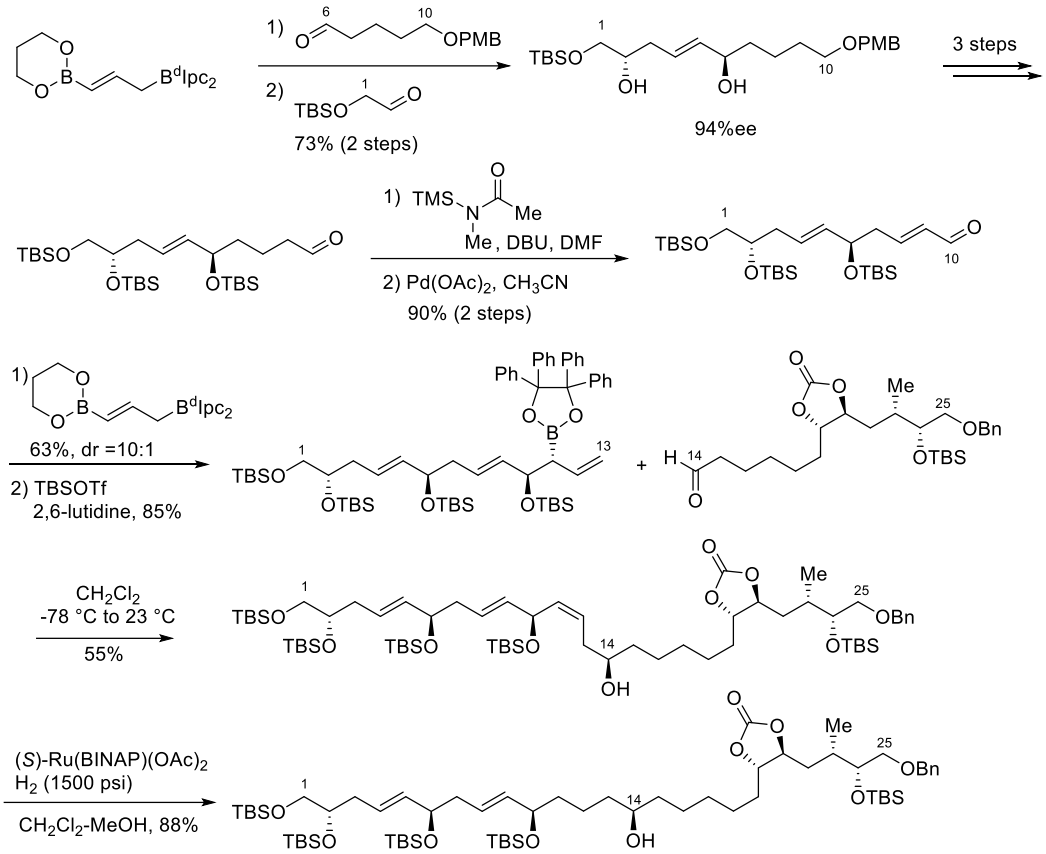
1-5-3. Roush group

Roush *et al.* reported the synthesis of the C1-C25 part of AM3.[25a] The stereochemistry at C20-C21 was controlled by Sharpless asymmetric dihydroxylation (Scheme 1-5-13).



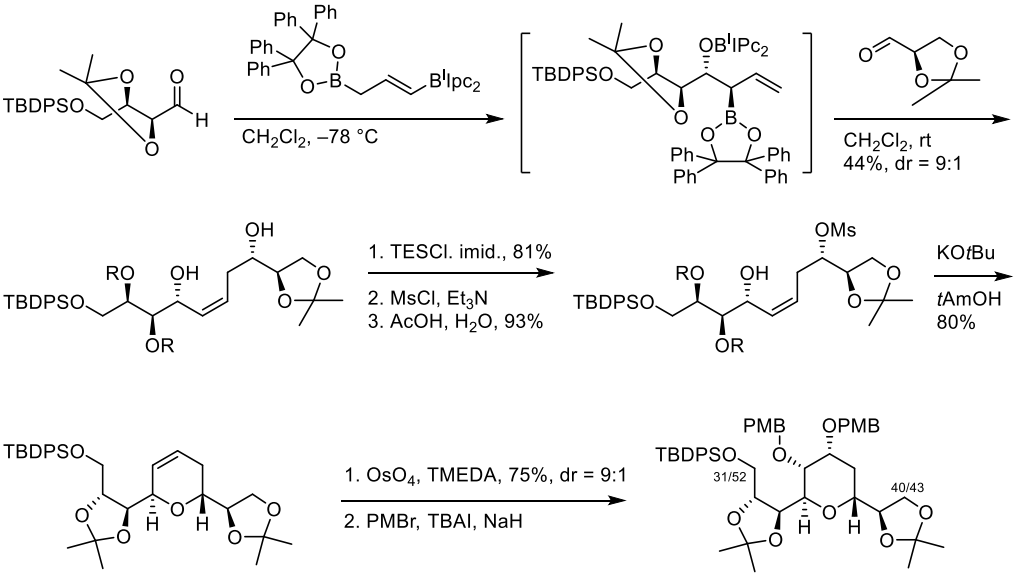
Scheme 1-5-13. Synthesis of the C14–C25 part of AM3.

In order to control the consecutive 1,5-diol units in this part, they used an originally-developed double allylboration reactions.[25b] After that, the C1-C13 allylboronate was coupled with the C14-C25 aldehyde to afford the C1-C25 part (Scheme 1-5-14).



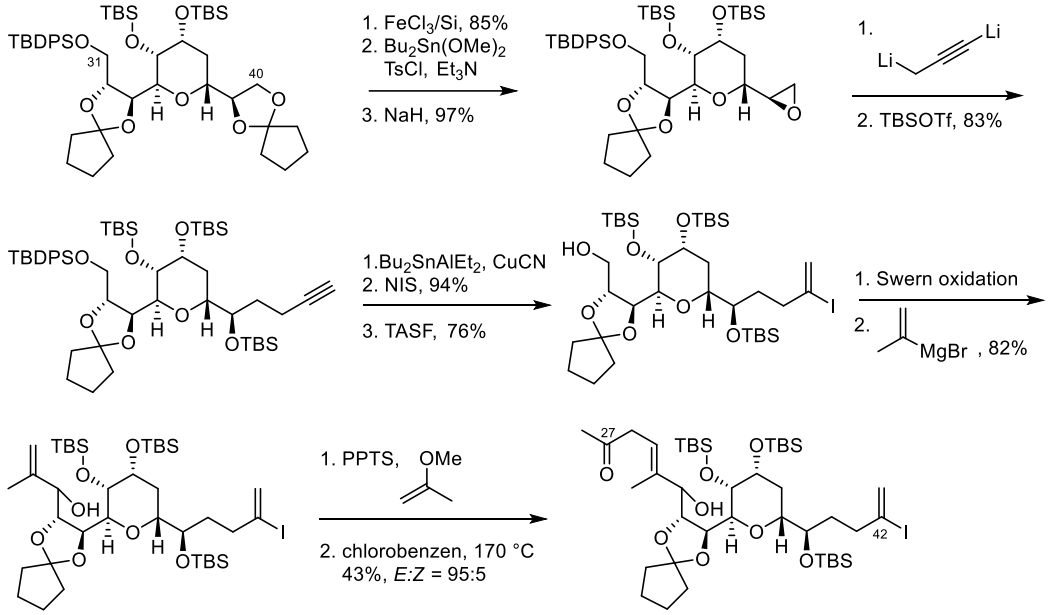
Scheme 1-5-14. Synthesis of the C1–C25 part of AM3.

Roush reported the synthesis of the C31–C40/C43–C52 part of the AM3 in 2005 (Scheme 1-5-15).[25c] Tetrahydro pyran ring was constructed via double-allylboration reaction and the base-mediated cyclization.

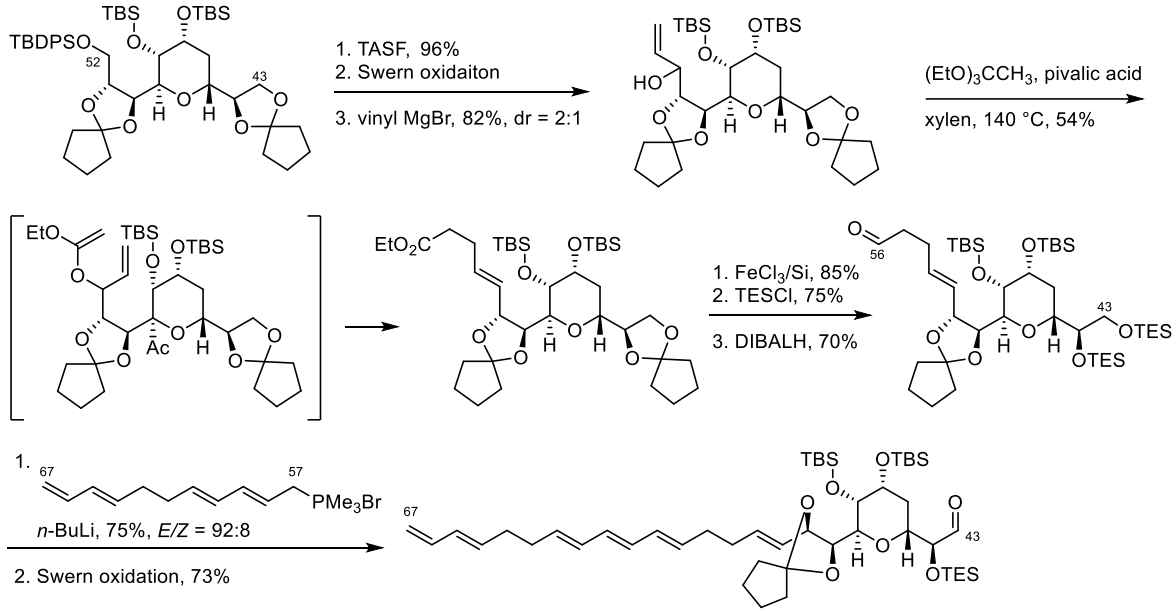


Scheme 1-5-15. Synthesis of the C31–C40/C43–C51 part of AM3.

Roush reported the synthesis of the C27–C42 and C43–C67 part of AM3 in 2008 (Scheme 1-5-16, 1-5-17).[25d] Cyclopentylidene acetal was employed for facilitating deprotection of the alcohol. C27–C42 fragment was synthesized via propargylation using dilithiopropyyne, Stannylalumination and Claisen rearrangement. C43–C56 fragment was synthesized featuring Johonson orthoester Claisen rearrangement. The coupling with polyene fragment was achieved via Horner–Wadsworth–Emmons olefination.



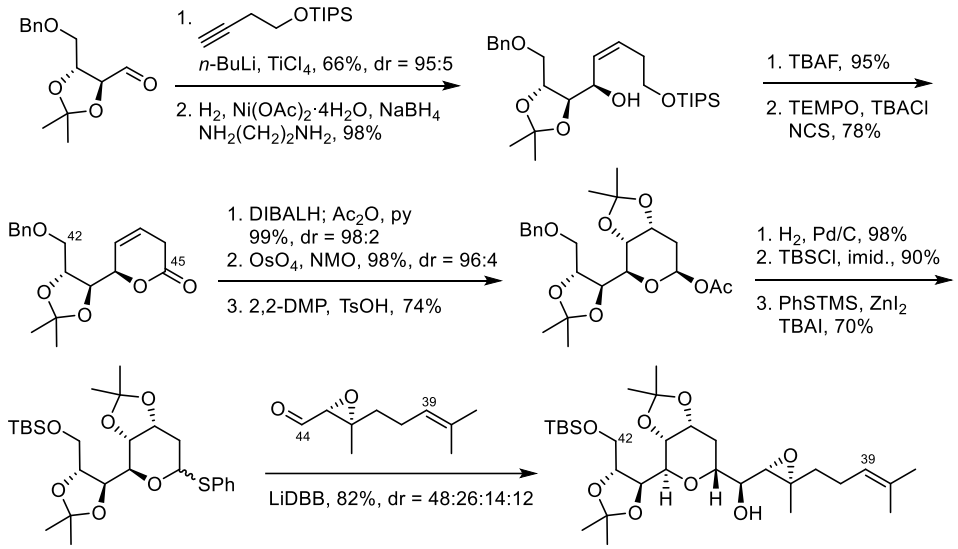
Scheme 1-5-16. Synthesis of the C27–C42 part of AM3.



Scheme 1-5-17. Synthesis of the C43–C67 part of AM3.

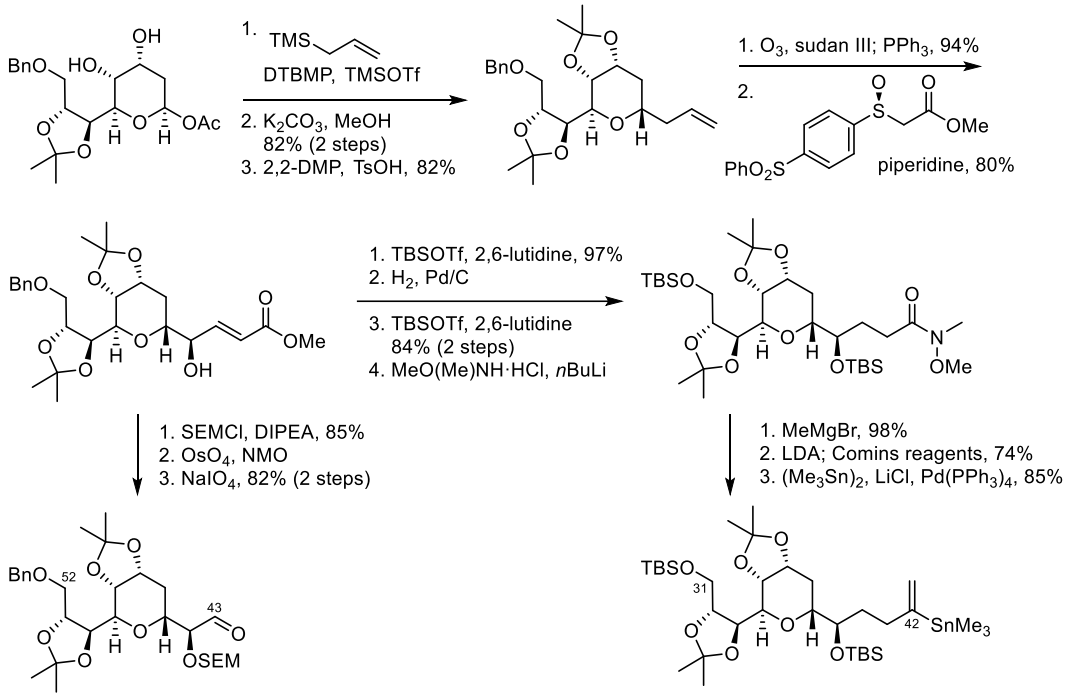
1-5-4. Rychnovsky group

Rychnovsky reported the synthesis of the C39–C42 part of AM3 in 2005 (Scheme 1-5-18).[26a] Tetrahydro pyran ring was constructed via lactone formation and nucleophilic *C*-glycosidation followed by the key coupling with aldehyde.

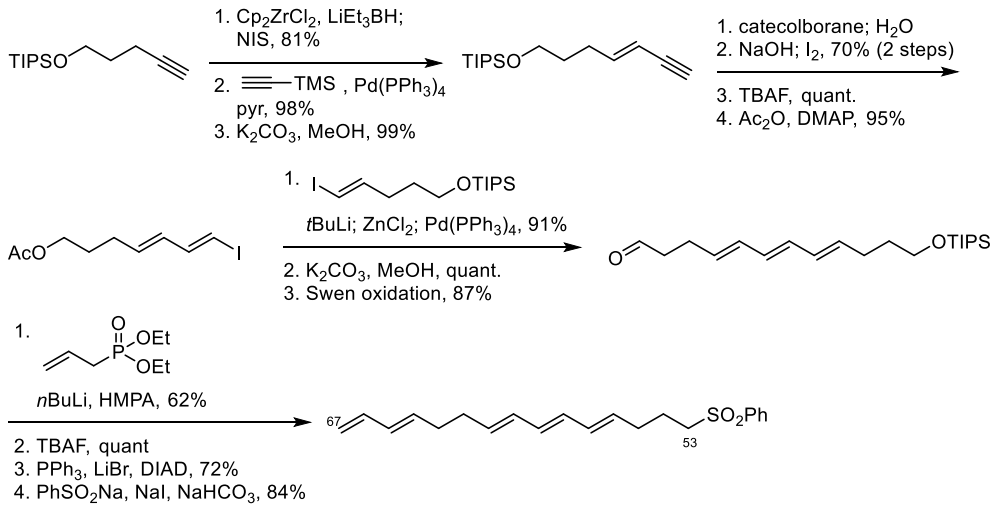


Scheme 1-5-18. Synthesis of the C39–C42 part of AM3.

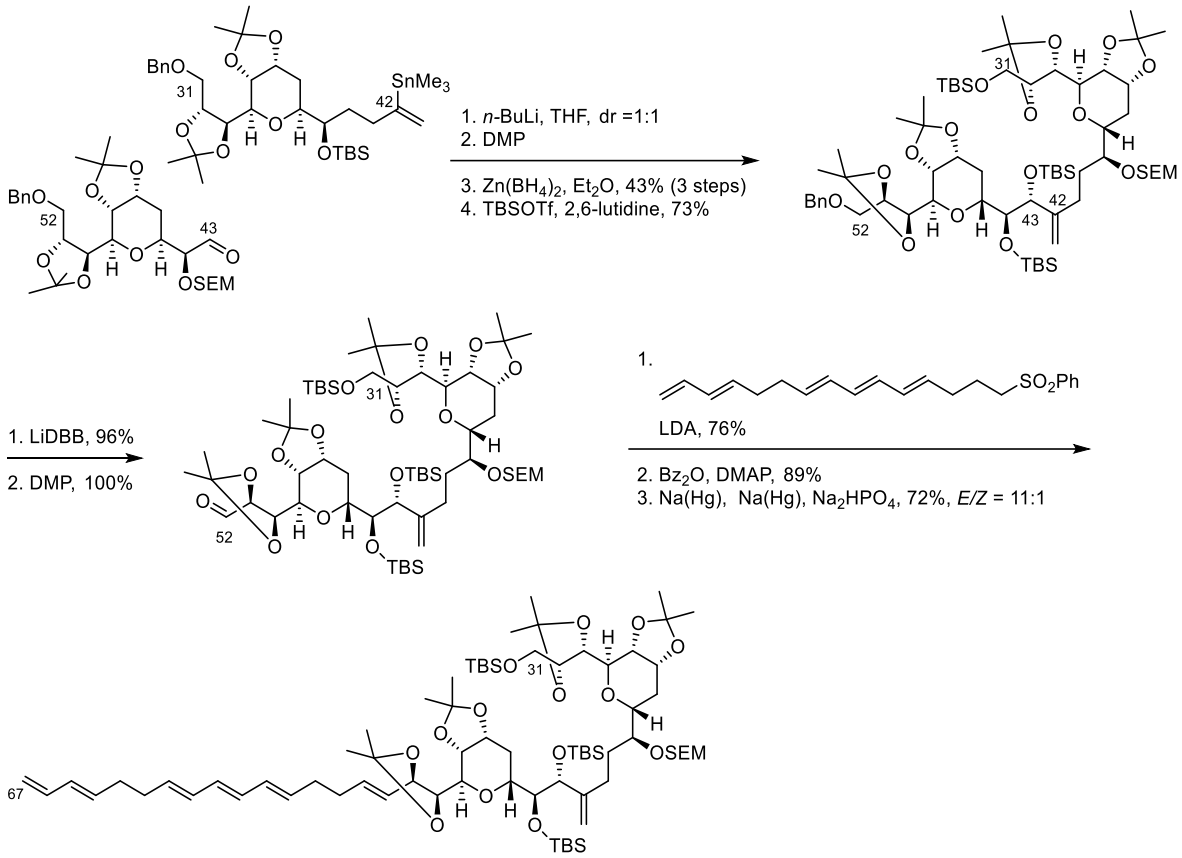
Rychnovsky reported the synthesis of the C31–C67 part of AM3 in 2006 (Scheme 1-5-19, 1-5-20, 1-5-21).[26b] THP common intermediate was constructed via Lewis acid mediated allylation and Knoevenagel condensation. The C31–42 and C43–C52 fragment were synthesized in 7 or 3 steps from the common intermediate respectively. The C53–C67 part was synthesized via hydrozirconation, Hagihara–Sonogashira coupling, Negishi coupling and Wittig reaction. The synthesis of the C31–C67 part of AM3 was achieved by connecting two THP rings via alkenyllithium-aldehyde coupling followed by Julia–Lythgoe olefination with polyene sulfone.



Scheme 1-5-19. Synthesis of the C31–C42 and C43–C52 part of AM3.

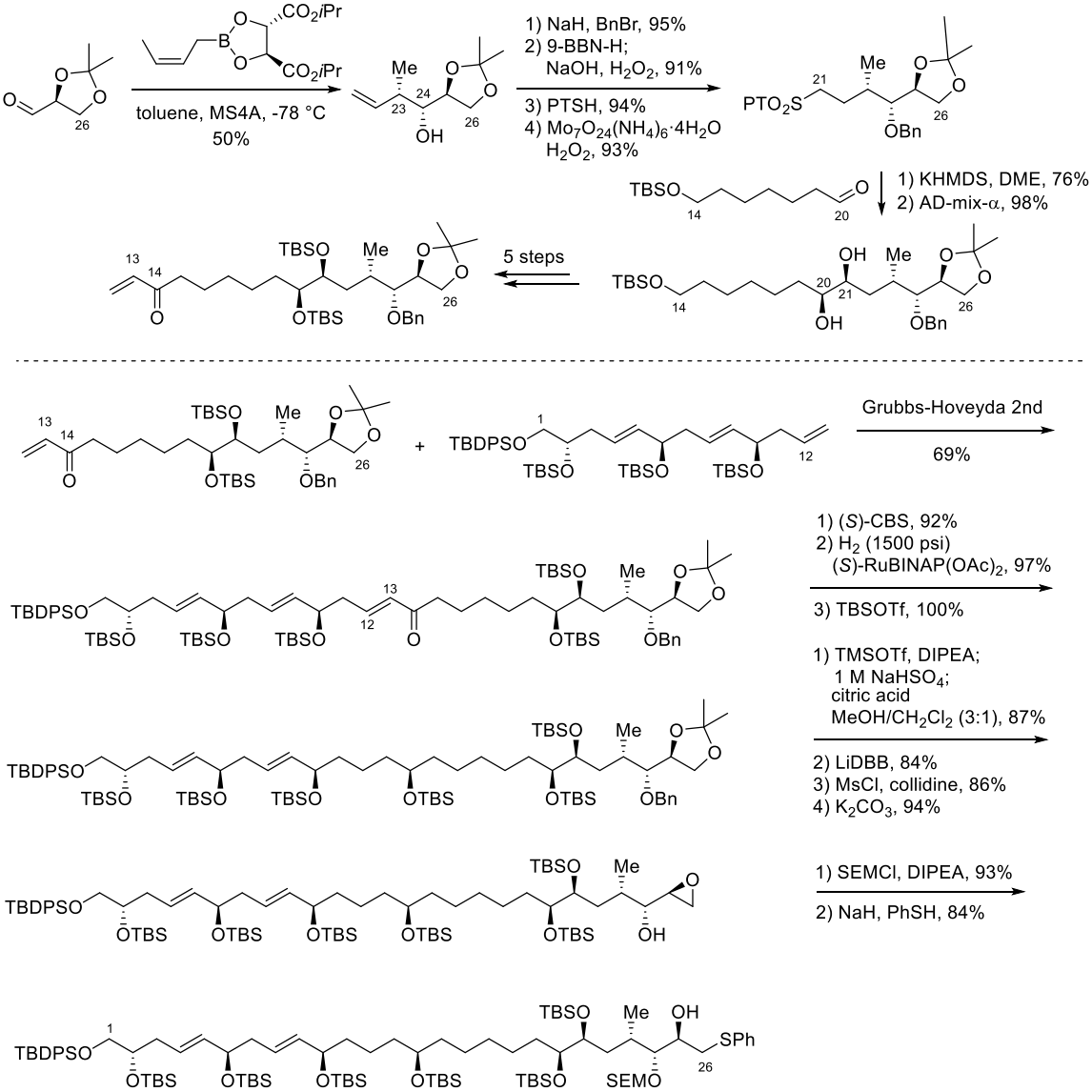


Scheme 1-5-20. Synthesis of the C53–C67 part of AM3.

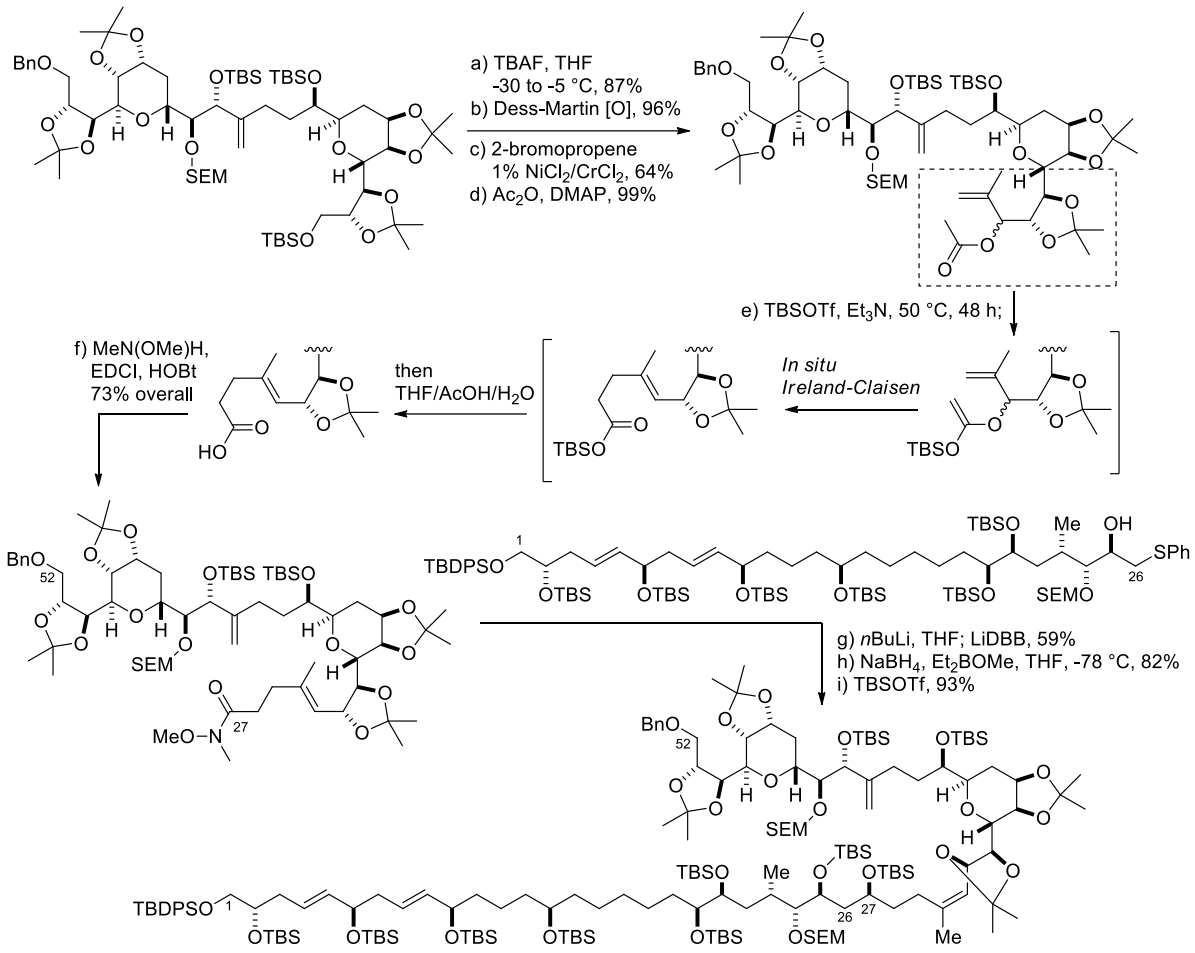


Scheme 1-5-21. Synthesis of the C31–C67 part.

Rychnovsky *et al.* have reported the synthesis of the most advanced fragment, the C1-C52 part of AM3 (Scheme 1-5-22, 1-5-23).[26c] A cross-metathesis reaction was used to couple the C1-C12 and C13-C26 segments. Bis-THP intermediate was converted to Weinreb amide in 7 steps including Nozaki–Hiyama–Kishi reaction and Ireland–Claisen rearrangement. The coupling between polyol and bisTHP segments was carried out by alkyllithium-amide coupling reaction.



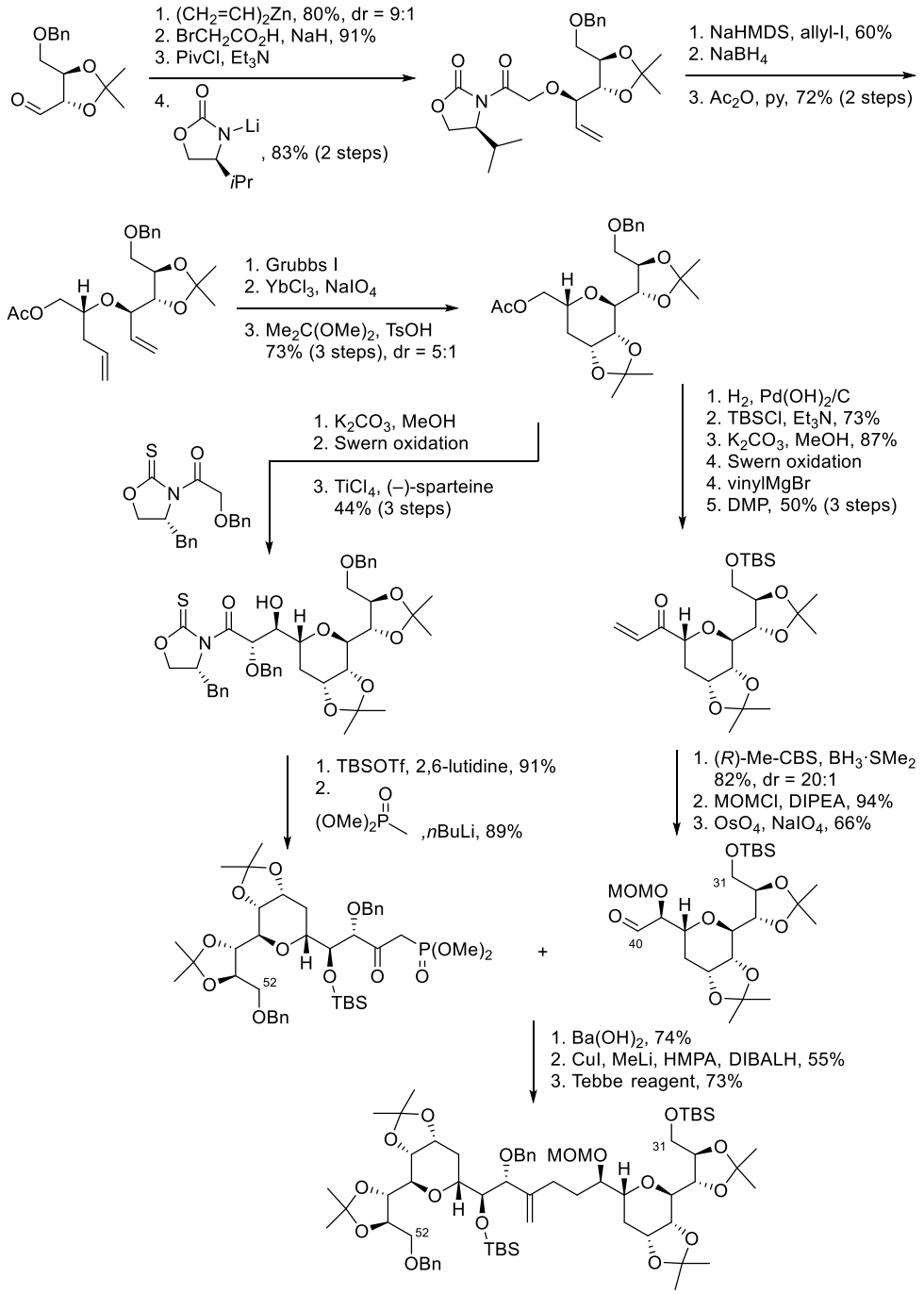
Scheme 1-5-22. Synthesis of the C1–C26 part of AM3.



Scheme 1-5-23. Synthesis of the C1–C52 part.

1-5-5. Crimmins group

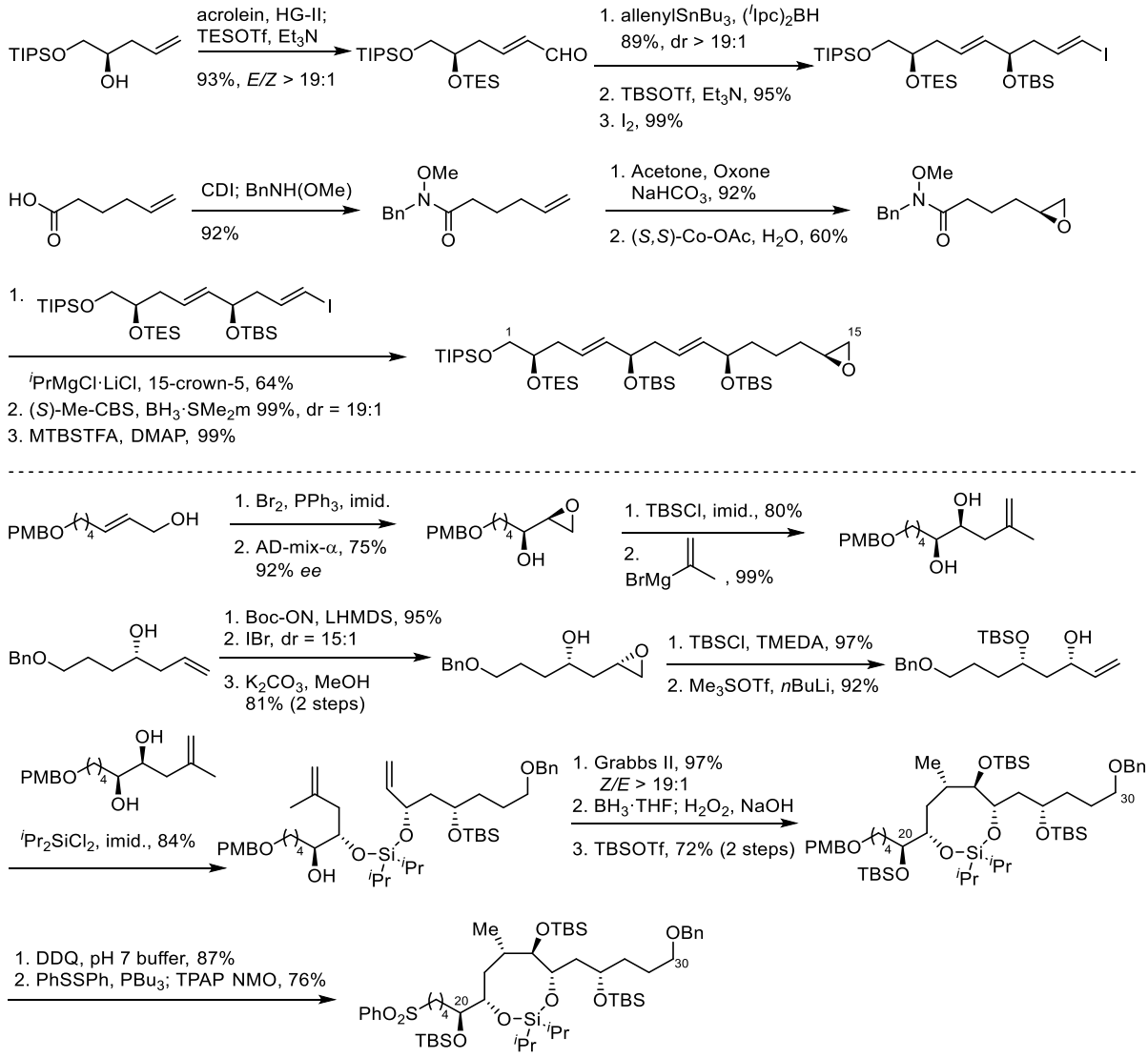
Crimmins reported the synthesis of the C31–C52 part of AM3 in 2010 (Scheme 1-5-24).[27] THP ring was constructed with utilizing asymmetric glycolate alkylation/ring-closing metathesis strategy. The coupling reaction of the two THP fragments was achieved via methylene Wittig reaction.



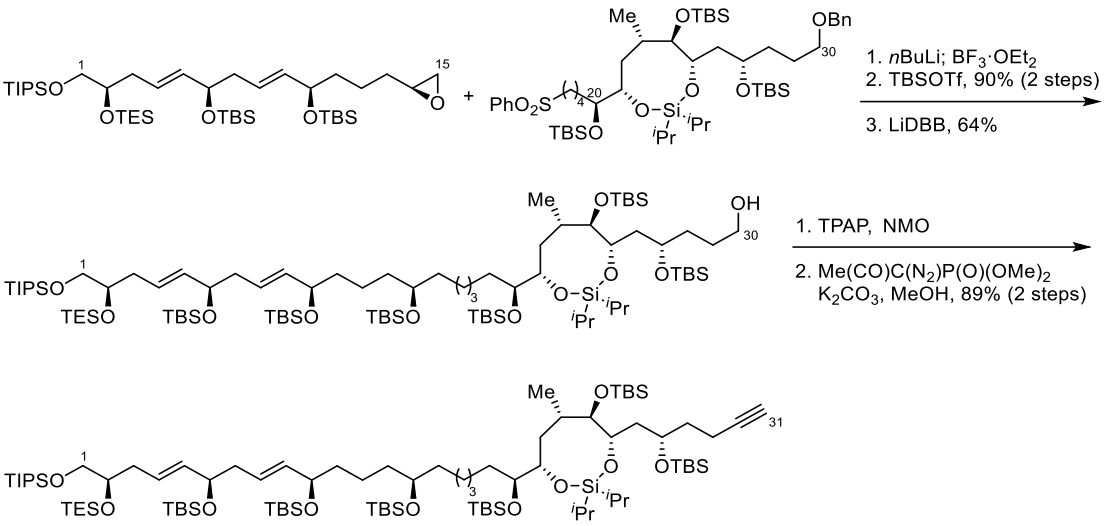
Scheme 1-5-24. Synthesis of the C31–C52 part.

1-5-6. Evans group

Evans reported the synthesis of the C1–C31 part of AM3 in 2015 (Scheme 1-5-25, 1-5-26).[28] The key step is silicon-tethered ring-closing metathesis reaction in combination with diastereoselective hydroboration for the construction of the C16–C31 fragment. The coupling of the C1–C15 and C16–C31 fragments was accomplished by a regioselective ring-opening oh the terminal epoxide with a phenyl sulfone stabilized carbanion.



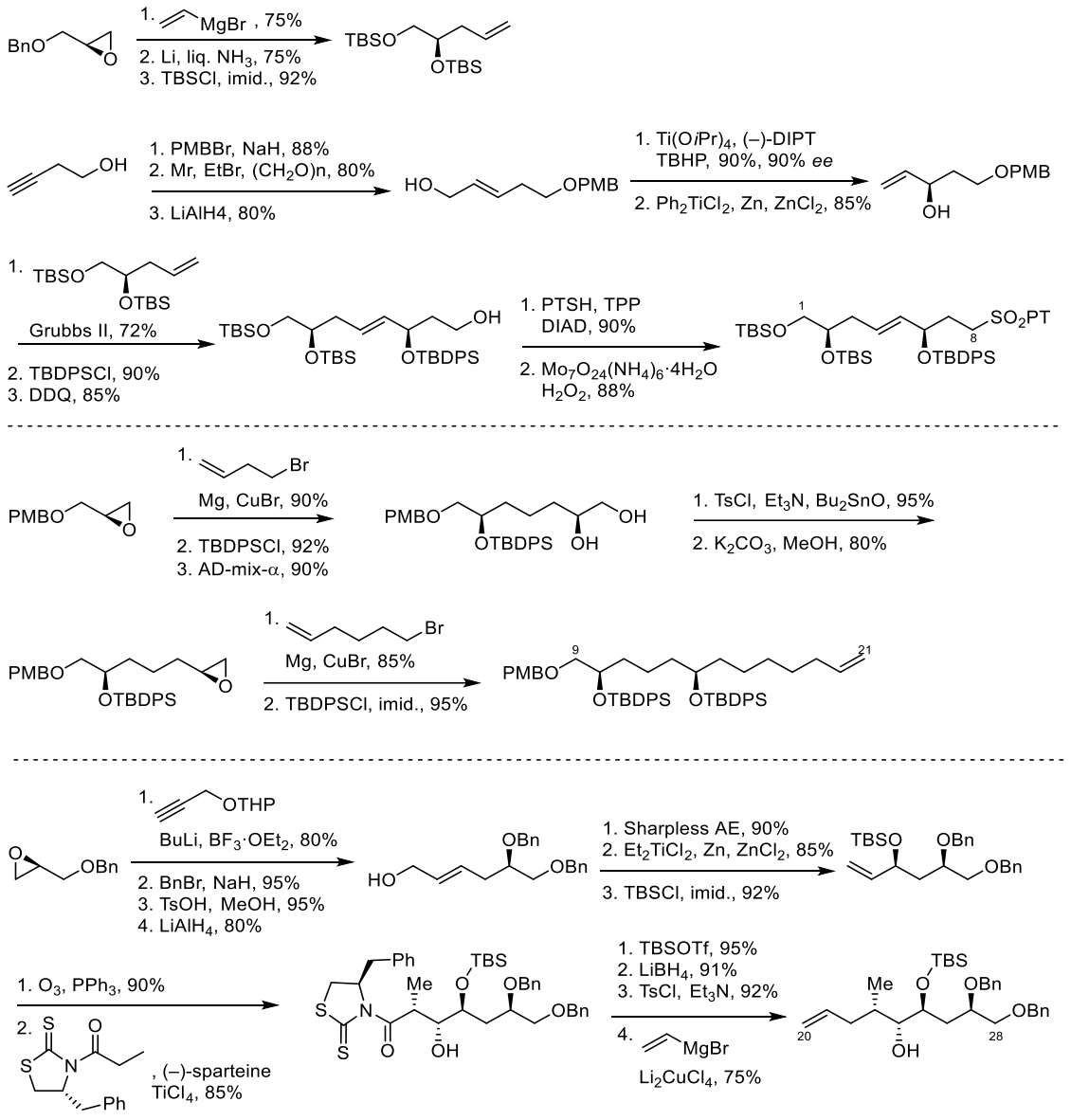
Scheme 1-5-25. Synthesis of the C1–C15 and C16–C30 part of AM3.



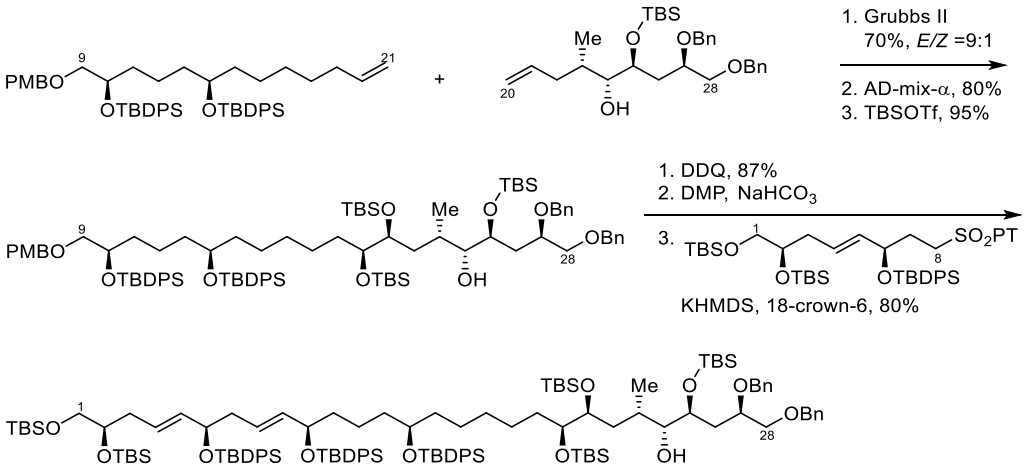
Scheme 1-5-26. Synthesis of the C1–C31 part of AM3.

1-5-7. Yadav group

Yadav reported the synthesis of the C1–C28 part of AM3 in 2016 (Scheme 1-5-27 1-5-28).[29] The synthesis of the C1–C28 was accomplished via Jacobsen hydrolytic kinetic resolution, Sharpless asymmetric epoxidation, Sharpless asymmetric dihydroxylation, Crimmins aldol reaction, cross-metathesis, and Julia–Kocienski olefination.



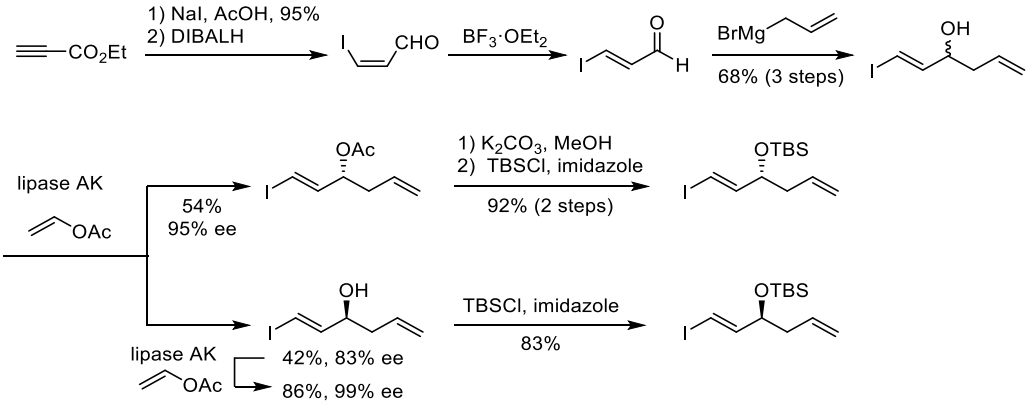
Scheme 1-5-27. Synthesis of the C1–C8, C9–C21 and C20–C28 part of AM3.



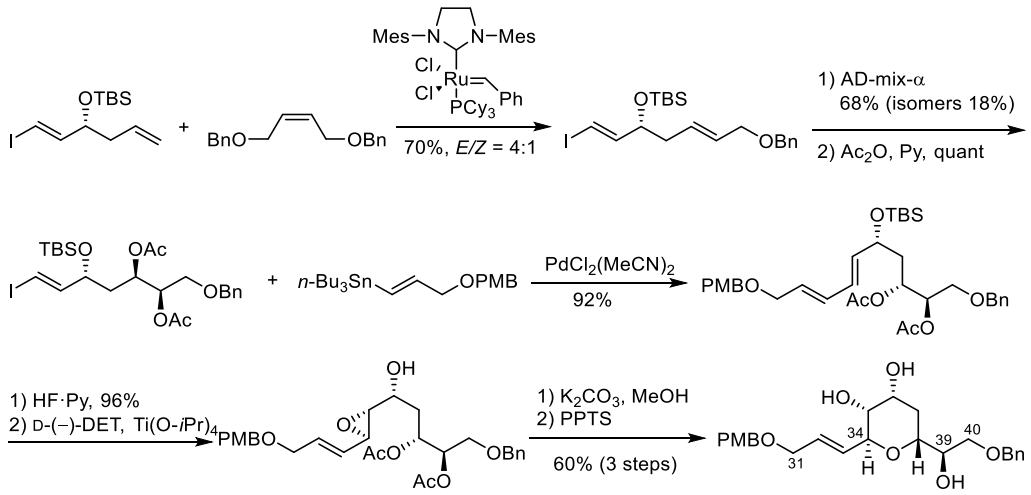
Scheme 1-5-27. Synthesis of the C1–C28 part of AM3.

1-5-8. Oishi group (our laboratory)

In our laboratory, synthesis of the common intermediate corresponding to the THP rings of AM3 has been established.[30] Synthesis of the common THP intermediate was commenced with ethyl propiolate to prepare chiral TBS ether via Grignard reaction and enzymatic kinetic resolution (Scheme 1-5-28).[18] Four stereogenic centers at C34, C35, C38, and C39 on the common THP intermediate were installed via Sharpless asymmetric dihydroxylation and Katsuki–Sharpless asymmetric epoxidation/6-*endo* cyclization sequence (Scheme 1-5-29).

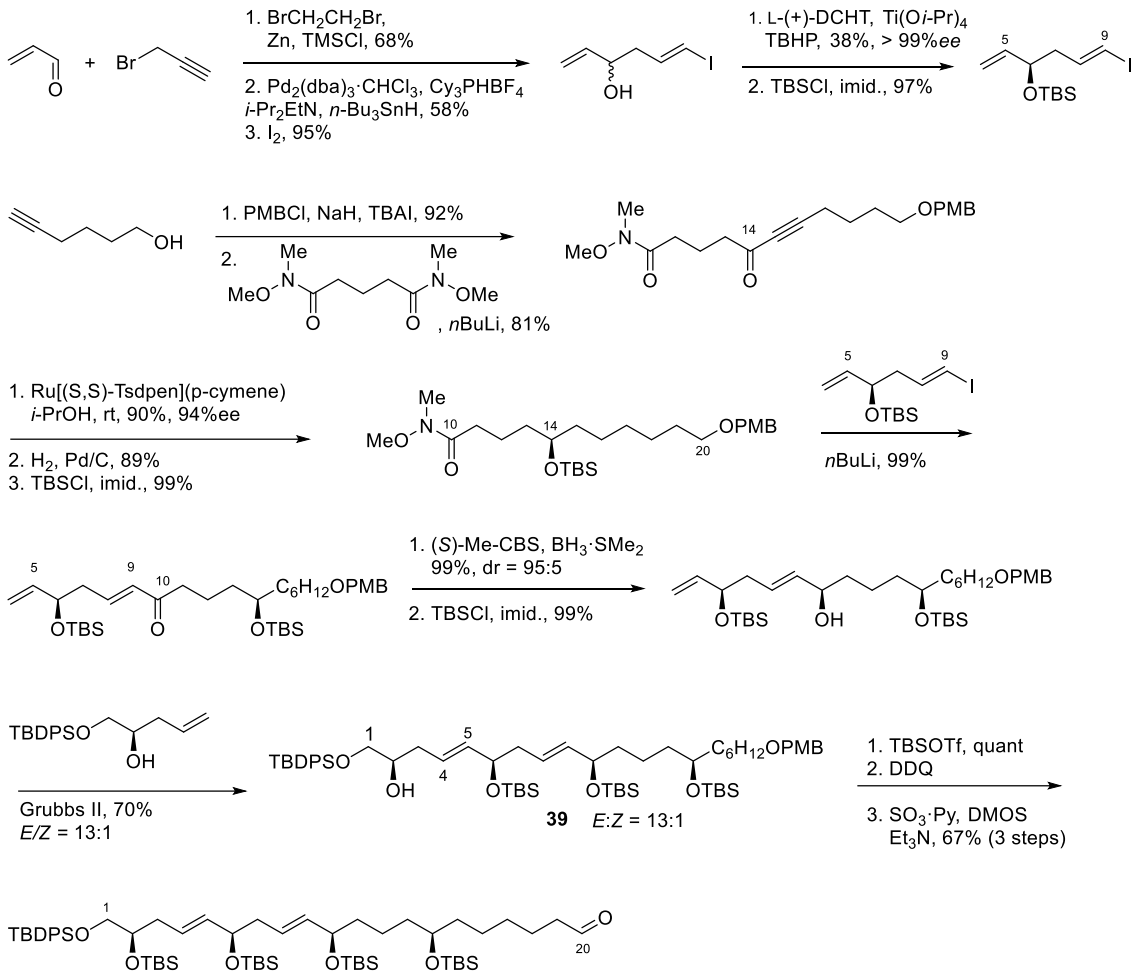


Scheme 1-5-28. Synthesis of the chiral building blocks of common THP intermediate.

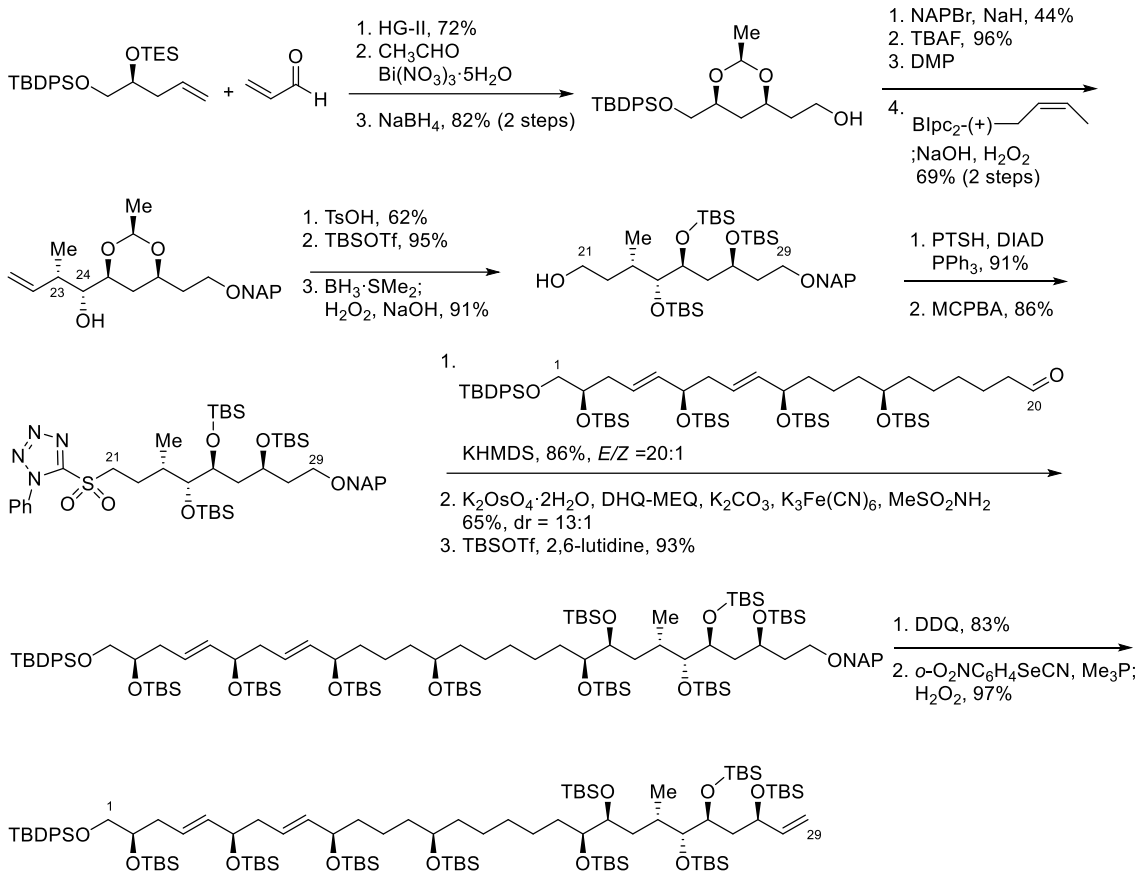


Scheme 1-5-29. Synthesis of the common THP intermediate.

The synthesis of the C1–C31 was reported by our group in 2015 (Scheme 1-5-30, 1-5-31).[31] The C1–C20 fragment was synthesized via regioselective crros-metathesis reaction. The C21–C29 part was constructed via successive cross-metathesis, oxa-Michael addition, Brown asymmetric crotylation. The union of the two fragments was accomplished Julia–Kocienski olefination followed by regio- and stereoselective dihydroxylation.

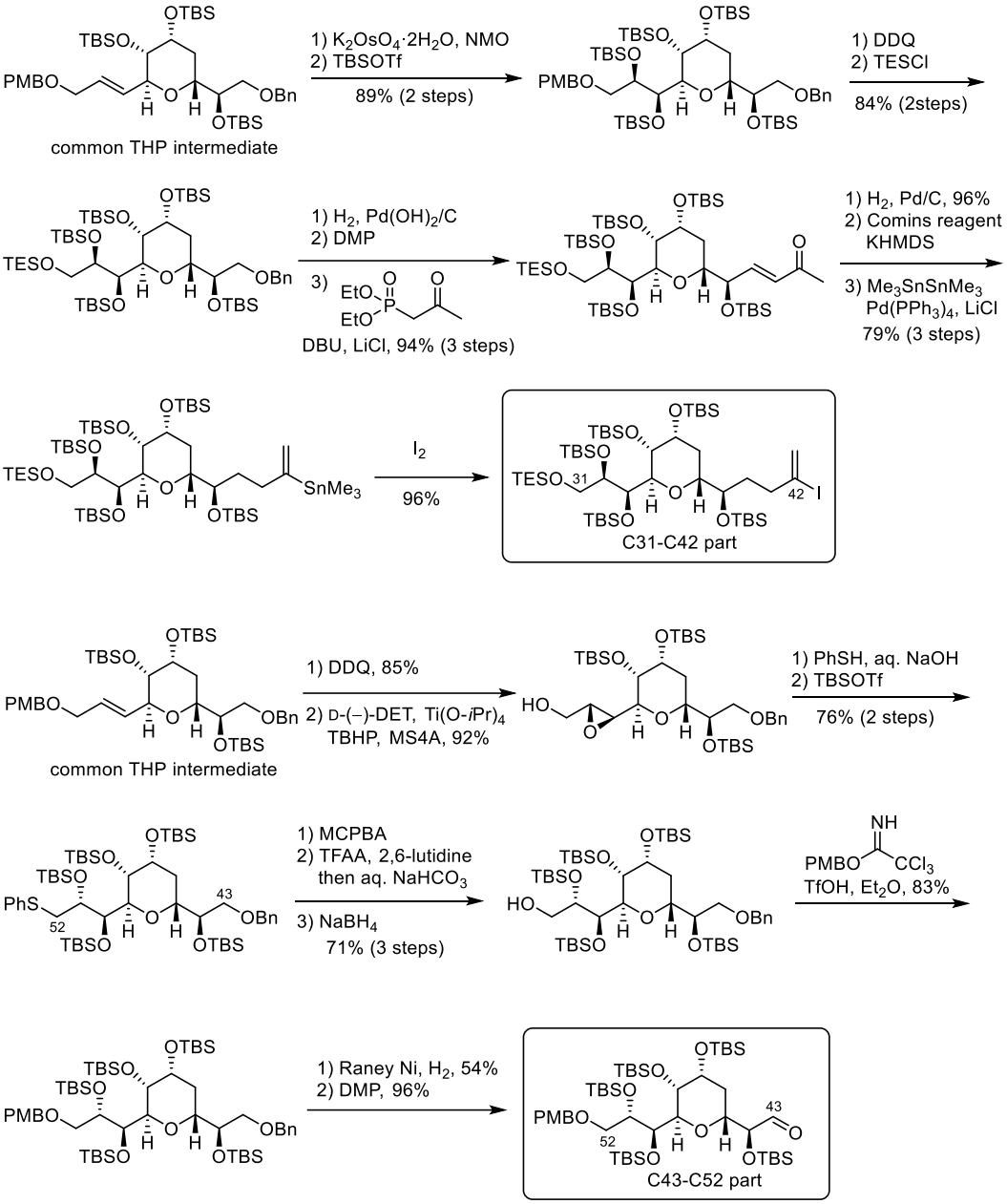


Scheme 1-5-30. Synthesis of the C1–C20 part of AM3 .



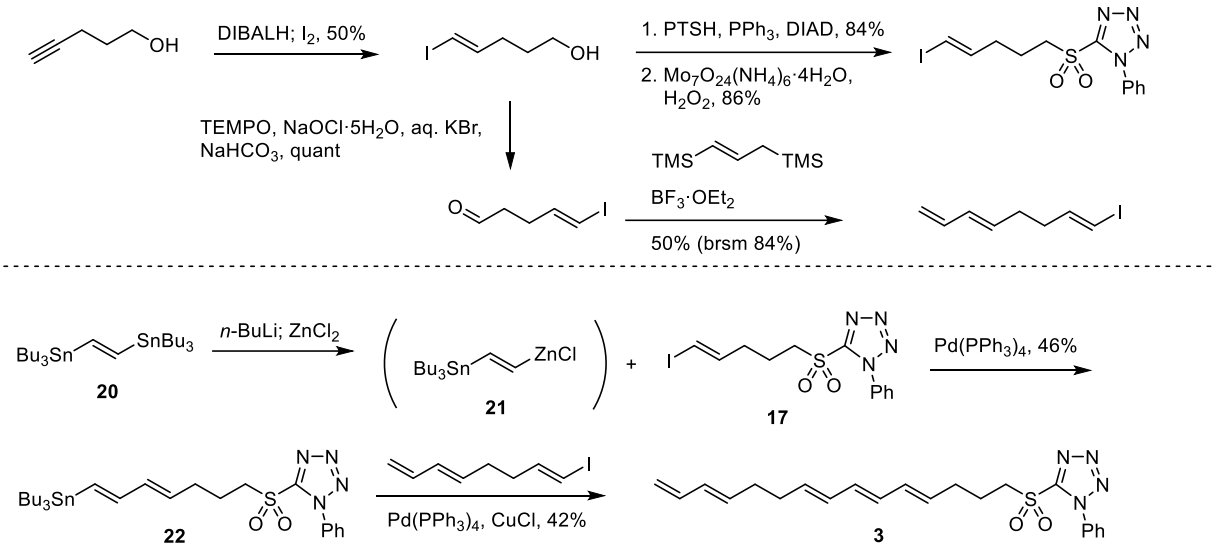
Scheme 1-5-31. Synthesis of the C1–C29 part of AM3 .

Synthesis of the C31–C42 and the C43–C52 part of AM3 were achieved from common THP intermediate in 11 steps and 10 steps, respectively (Scheme 1-5-32).



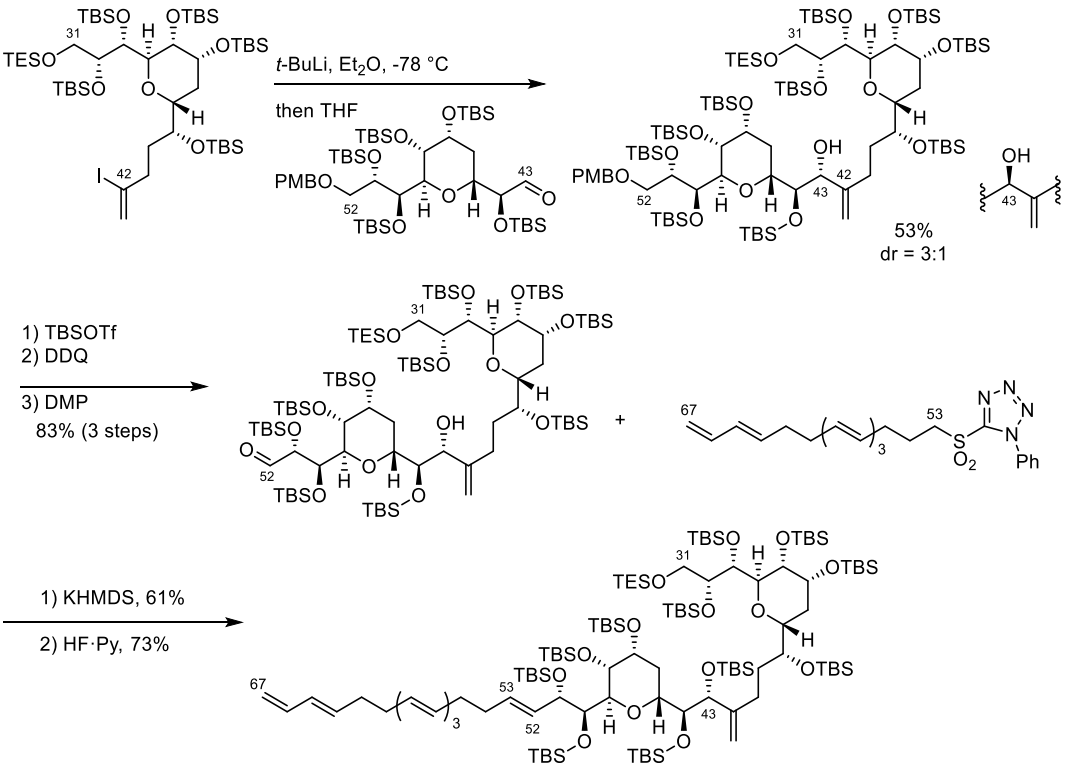
Scheme 1-5-32. Synthesis of the C31–C42 and C43–C52 part.

We reported the synthesis of C53–C67 part of AM3 in 2017 (Scheme 1-5-33).[32] The polyene part of AM3 was synthesized by successive cross coupling via Negishi coupling and Migita–Kosugi–Stille coupling.



Scheme 1-5-33. Synthesis of the C53–C67 part of AM3.

Synthesis of the C31–C67 part of AM3 was achieved via coupling of the C31–C42 alkenyllithium and C43–C52 aldehyde followed by Julia–Kocienski olefination with C53–C67 sulfone (unpublished result, Scheme 1-5-34).



Scheme 1-5-34. Synthesis of the C31–C67 part of AM3.

1-6. Purpose

1-6-1. Structure 5evision of amphidinol 3

As discussed above, the stereochemistry of the C38–C39 portion of AM3 remains ambiguous because the $^{3}J_{(H38,\ H39)}$ value was ‘medium’ in JBCA method. The absolute configuration of C39 was determined using modified Mosher method, therefore, the absolute stereochemistry of C38 seems to be opposite. In addition, the relative stereochemistry on the THP ring is sought to be correct. Thus, the diastereomer C32–C36 and C38 of the proposed structure is to be synthesized. And the comparison of the NMR data between natural product and synthetic partial structures would elucidate correct structure of AM3.

1-6-2. Total synthesis of amphidinol 3

Our structure confirmation of AM3 is based on the synthesis and comparison of the partial structure with natural product. However, total synthesis is the most reliable way to confirm the complete absolute configuration of AM3. Thus, the second objective was set to achieve the first total synthesis of AM3.

1-6-3. Structure-activity relationship study of amphdinol 3

The huge and complex structure of AM3 imposes multi-steps for synthesis and it is hard to supply the large amount of sample. Although the simplification of the structure of AM3 is an important task, only a few structure-activity relationship studies had been reported and the mechanism of AM3 is not fully elucidated. Thus, we decided to perform comprehensive structure-activity relationship study of polyol and bis-THP moiety of AM3 for elucidation of the mechanism and simplification of the structure.

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Chapter 2. Structure Revision of Amphidinol 3

2-1. Synthesis plan of the C31–C67 section

Synthesis plan of the C31–C67 part of AM3 (**1**) is shown in Scheme 2-2-1. The target molecule **1** would be synthesized via Julia–Kocienski olefination of the C53–C67 part (**2**)[1] and the C31–C52 part (**3**). Various coupling reactions between bis-THP fragments were reported by other research groups.[2] In this synthesis, alkenyllithium-aldehyde coupling reaction of the C43–C52 (**4**) and C31–C42 part (**5**) was applied. The C31–C42 part (**5**) was to be constructed through propargylation of epoxide **7**[3] followed by regioselective hydroalumination.[4] Epoxide **7** would be obtained from the known compound (**9**)[5] via asymmetric dihydroxylation followed by epoxide formation via inversion at C39. The syntheses of the C43–C52 (**4**), C53–C67 part (**2**) and C31–C67 section corresponding to the proposed structure have already been achieved in our laboratory (See Chapter 1-5-8)

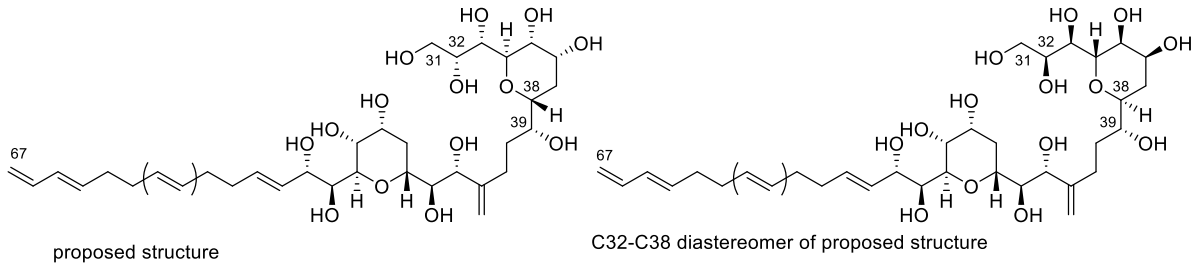
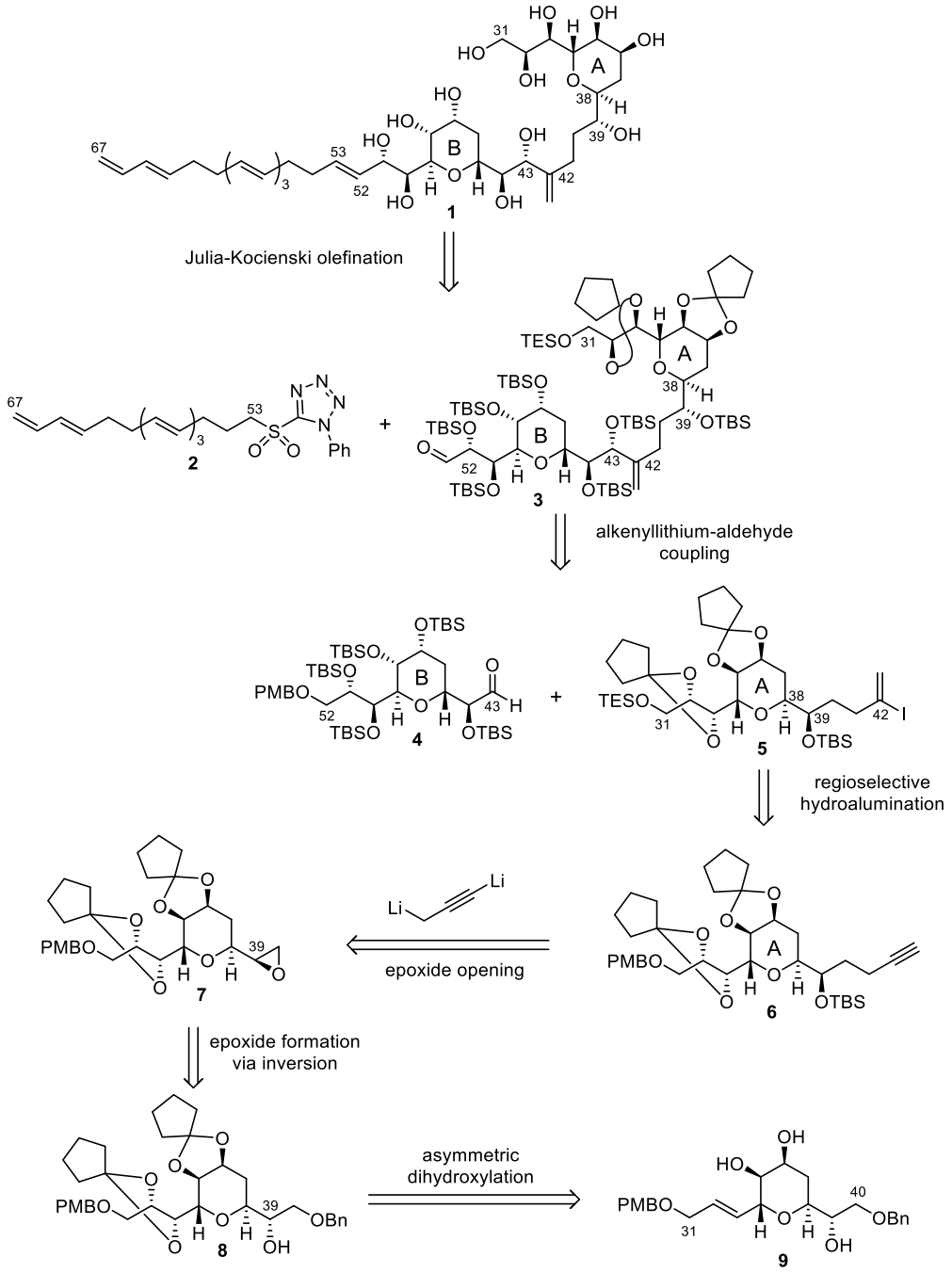


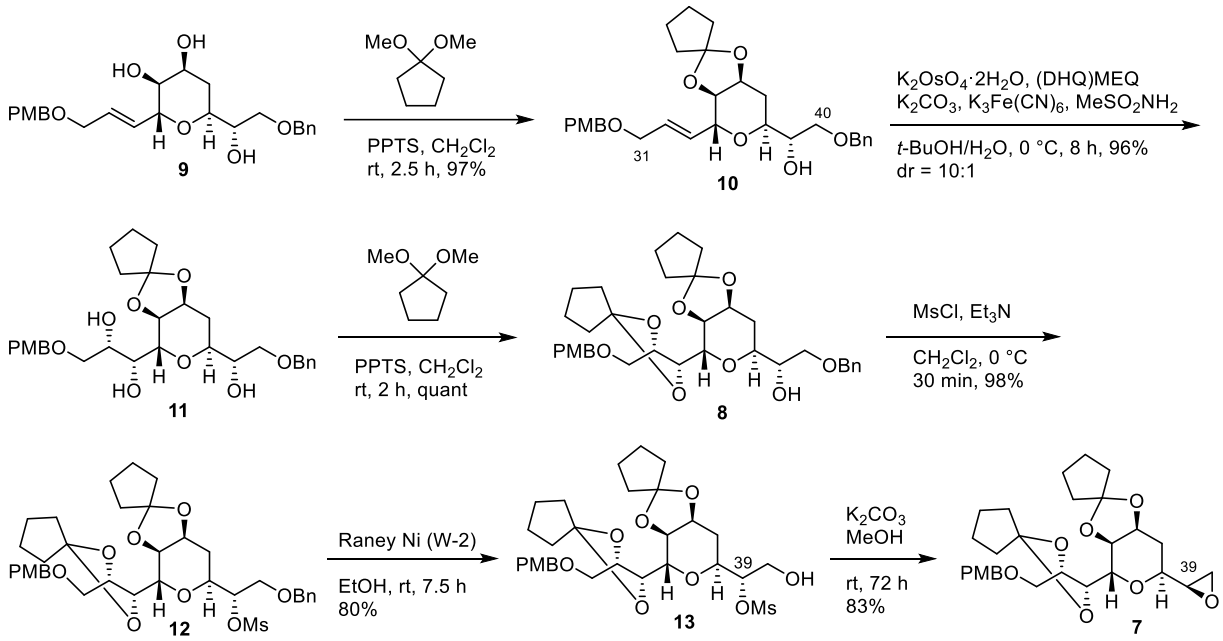
Figure 2-1-1. Structure of both diastereomers of C31–C67 section of AM3.



Scheme 2-1-1. Synthesis plan of the C31–C67 part of AM3.

2-2. Synthesis of the C31–C67 section

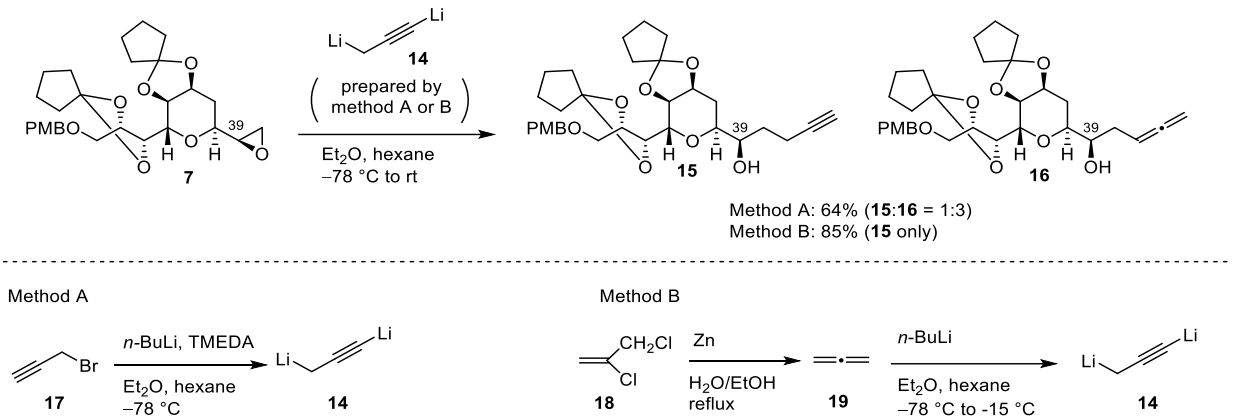
Synthesis of the C31–C42 part of AM3 commenced with the preparation of epoxide **7** (Scheme 2-2-1). Protection of the 1,2-diol moiety of compound **9** as cyclopentylidene acetal with using 1,1-dimethoxycyclopentane and PPTS gave acetal **10** in 97% yield.[6] Sharpless asymmetric dihydroxylation[7] using (DHQ)MEQ[8] as a ligand proceeded successfully to produce 1,2-diol **11** and its diasteromer in 96% yield in a 10:1 ratio. The resulting 1,2-diol moiety was protected as cyclopentylidene acetal to afford bis-cyclopentylidene alcohol **8** quantitatively. Mesylation of the secondary alcohol **8** giving **12** 98% yield, followed by the treatment with Raney Ni (W-2)[9] afforded primary alcohol **13** in 80% yield. Treatment **13** with K_2CO_3 resulted in intramolecular S_N2 reaction with stereoinversion at C39 to afford epoxide **7** in 83% yield.



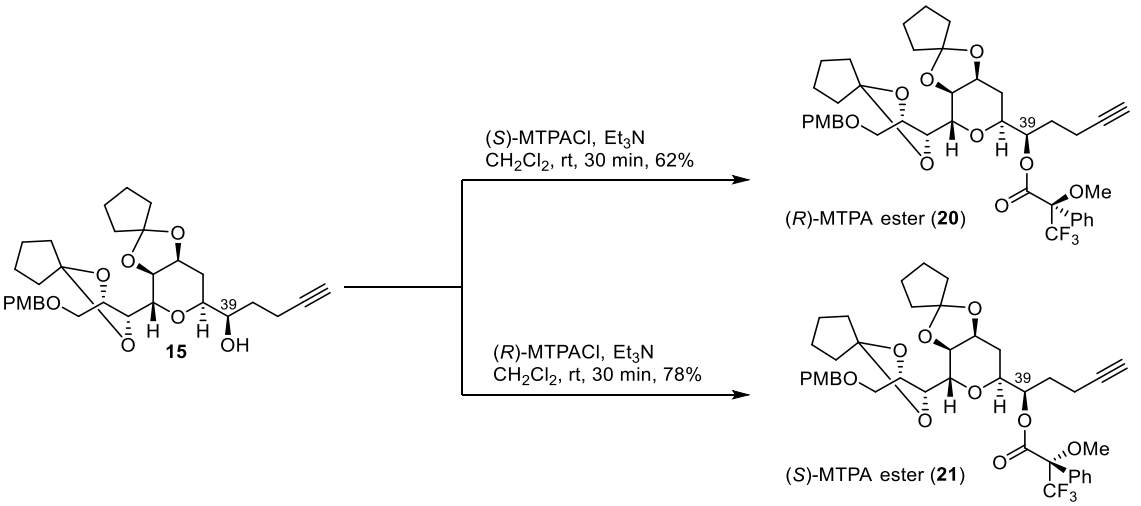
Scheme 2-2-1. Synthesis of the epoxide **7**.

Having obtained epoxide **7**, propargylation using dilithium reagent **14**[10] was carried out (Scheme 2-2-2).[3] Dilithium reagent **14** was prepared by method A,[10a] in which propargyl bromide **17** was treated with *n*-BuLi in the presence of TMEDA. Although the reaction with epoxide **7** proceeded, target molecule **15** was obtained as a minor product with concomitant formation of undesired allene **16.** Next, dilithium reagent **14** was prepared by method B.[10b] Allene **19** was prepared from 2,3-dichloro-1-propene **18** with zinc powder under reflux in advance.[11] Which was treated with *n*-BuLi to afford reagent **14**. In this case, desired compound **15** was obtained successfully in 85% yield. The absolute configuration at C39 was determined by modified Mosher method[12] as shown in Scheme 2-2-1 by using (*R*)-MTPA

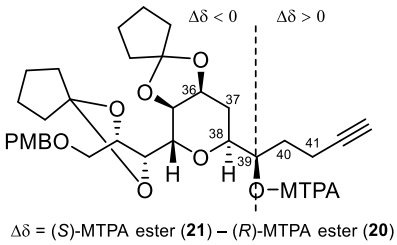
ester **20** and (*S*)-MTPA ester **21** prepared from **15** in 62% and 78% yield, respectively (Scheme 2-2-3).



Scheme 2-2-2. Propargylation of **7** using dilithium reagent **14**.



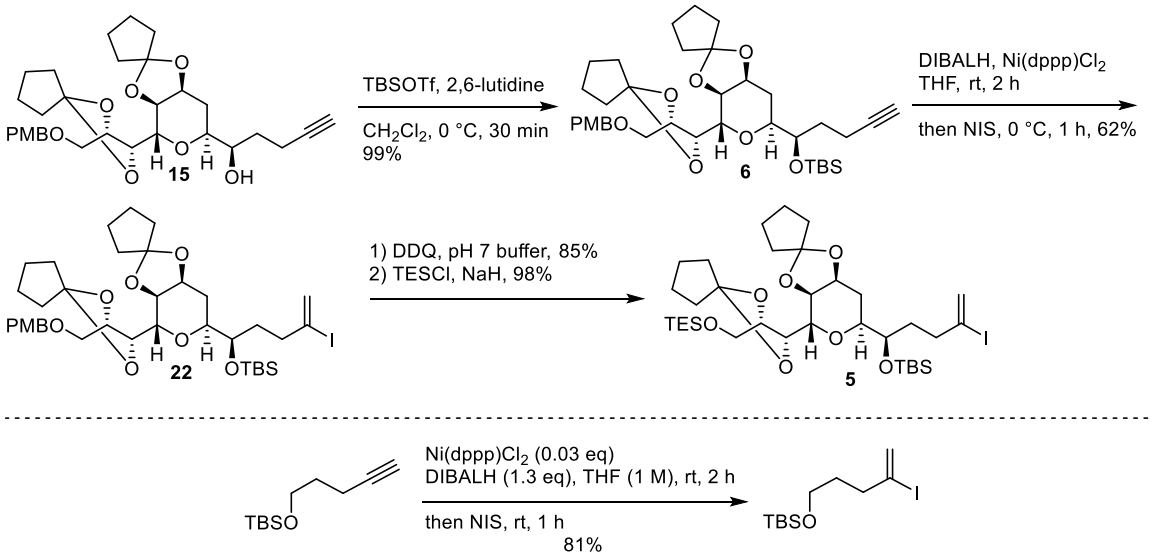
Scheme 2-2-3. Synthesis of (*R*)-and (*S*)-MTPA ester of **15**.



Carbon number	⊿δ (ppm)
41	+0.10
41	+0.14
40	+0.07
38	−0.08
37	−0.01
37	−0.15
36	−0.09

Figure 2-2-1. Determination of the absolute configuration at C39 of **15** by modified Mosher method.

Obtained secondary alcohol **15** was protected as TBS ether to afford terminal alkyne **6** in 99% yield (Scheme 2-2-4). Terminal alkyne **6** was subjected to Ni-catalyzed stereoselective hydroalumination[4] followed by iodination to afford iodoolefin **22** in 62% yield. Removal of the PMB group in compound **22** proceeded in 85% yield, and following TES protection of the resulting primary alcohol furnished the C31–C42 part (**5**) in 98% yield.



Scheme 2-2-4. Synthesis of the iodoolefin **5**.

Investigation of the regioselective hydroalumination of terminal alkyne **6** were summarized in Table 2-2-1. The reaction using excess DIBALH in low substrate concentration gave iodoolefin **22** in 28% yield in a 20:1 ratio (entry 1). In entry 2, the reaction was conducted using 1.3 eq of DIBALH in high substrate concentration to give iodoolefin **22** in 50% yield with slightly decreased regioselectivity (20:1). Increasing the

amount of Ni catalyst resulted in the decreased regioselectivity to 10:1 (entry 3). When the reaction time was reduced to 1 h, both the yield and regioselectivity were increased to 62% yield in a 40:1 ratio (entry 4).

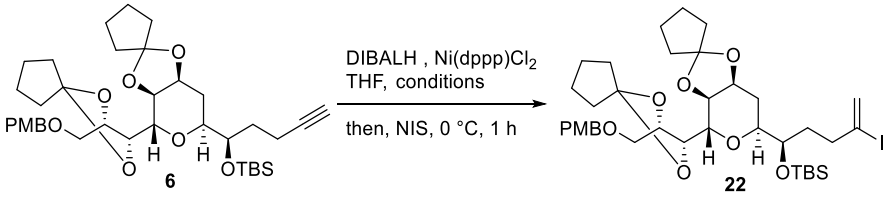


Table 2-2-1. Investigation of the regioselective hydroalumination of terminal alkyne **6**

entry	DIBAL (eq)	Ni(dppp)Cl_2 (eq)	conc/M	temp/°C	time (h)	yield/%	α:β
1	5	0.3	0.05	0 to rt	2	28	1 : 0
2	1.3	0.03	0.6	0 to rt	2	50	20: 1
3	1.3	0.1	0.6	-78 to rt	2	50	10 : 1
4	1.3	0.03	0.6	-78 to rt	1	62	40 : 1

Alkenyllithium–aldehyde coupling reaction of the C43–C52 part (**4**) and the C31–C42 part (**5**) was examined (Table 2-2-1). Iodoolefin **5** was treated with *t*-BuLi (2.0 eq) in Et_2O at −78 °C for 10 min, and then the THF solution of aldehyde **4** was added to the alkenyllithium mixture via cannula to give a mixture of the target compound **23** and its C43-diastereomer **24** in 31% yield in a 1.8:1 ratio (entry 1). The yield was dramatically enhanced to 54% yield by increasing the equivalent of *t*-BuLi to 2.1 (entry 2). When the equivalent of *t*-BuLi was further increased to 2.15, the compound **23** was obtained in 70% yield in a 1.8:1 ratio. To enhance the diastereoselectivity at C43 position, the reaction was attempted in the presence of $BF_3{\cdot}Et_2O$. However, both of the yield and selectivity did not change as that of entry 1 (entry 4). Although, the selectivity was increased to 4:1 in the presence of HMPA, the yield was reduced to 13% (entry 5).

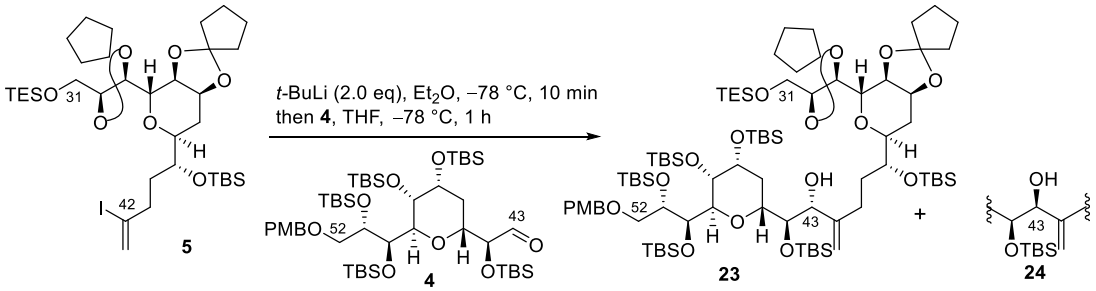
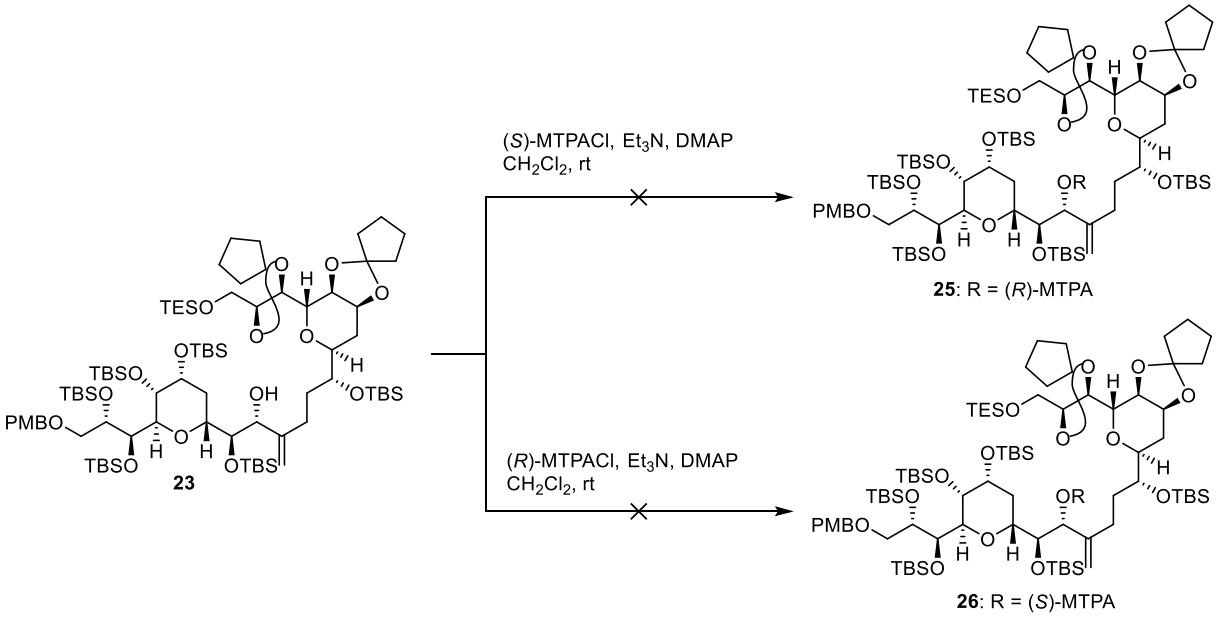


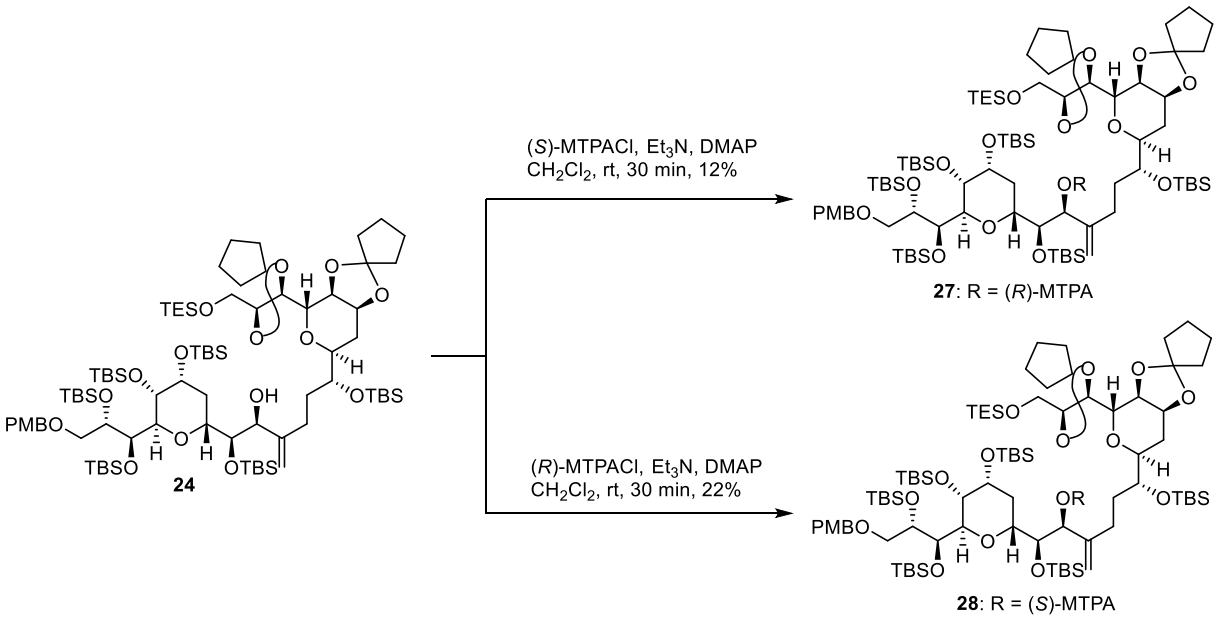
Table 2-2-1. Coupling reaction of **4** and **5** using lithium reagent.

entry	**5** (mg)	**4** (eq)	*t*-BuLi (eq)	additive	yield/%	ratio (**23**:**24**)
1	51	1.05	2.0	-	31	1.8:1
2	72	1.10	2.1	-	54	1.8:1
3	152	1.12	2.15	-	70	1.8:1
4	16	1.23	2.0	$BF_3{\cdot}Et_2O$	30	1.8:1
5	22	1.14	2.0	HMPA	13	4:1

To determine the absolute configuration at C43 of compound **23** by modified Mosher method,[12] conversion of **23** to (*R*)- and (*S*)-MTPA esters was attempted (Scheme 2-2-5). However, the reaction did not proceed, probably because of the steric hindrance at C43. On the other hand, conversion of diastereomer **24** proceeded slightly to afford (*R*)- and (*S*)-MTPA ester **27**, **28** in 12% and 22% yiled, respectively (Scheme 2-2-6). Thus, the absolute configuration at C43 of minor diasteremoer **24** was determined to be *S* by the modified Mosher method (Figure 2-2-2). Therefore, the absolute configuration at C43 of major product is to be *R*.



Scheme 2-2-5. Synthesis of the (*R*)-and (*S*)-MTPA ester of **23**.



Scheme 2-2-6. Synthesis of the (*R*)-and (*S*)-MTPA ester of **24**.

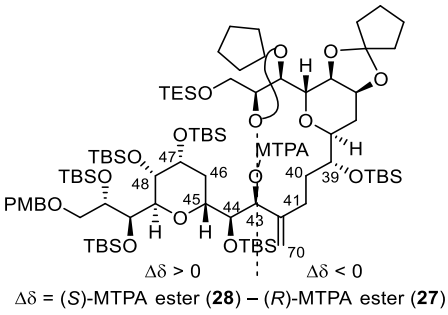


Figure 2-2-2. Determination of the absolute configuration at C43 of minor compound **24** by modified Mosher method.

Carbon number	⊿δ (ppm)
C39	−0.005
C40	−0.042
C40	−0.009
C41	−0.030
C41	−0.042
C70	−0.355
C70	−0.267
C44	+0.051
C45	+0.071
C46	−0.004
C46	+0.104
C47	+0.034
C48	+0.087

Oxidation/reduction sequence to invert the C43 stereochemistry of the **24** was carried out to obtain desired product **23** (Table 2-2-2). Although Dess–Martin oxidation of **24** proceeded successfully in 91% yield, stereoselective reduction of the enone was difficult. $NaBH_4$ reduction resulted in decomposition (entry 1). CBS reduction[13] did not proceed (entry 2). Reduction with DIBALH proceeded smoothly but gave undesired diastereomer **24** as a single isomer (entry 3).

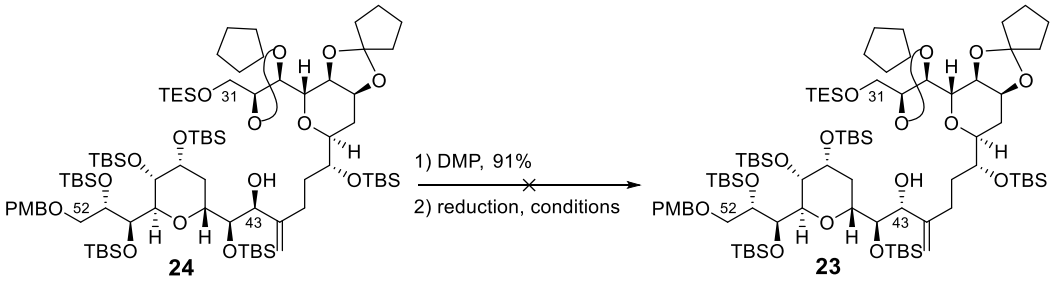
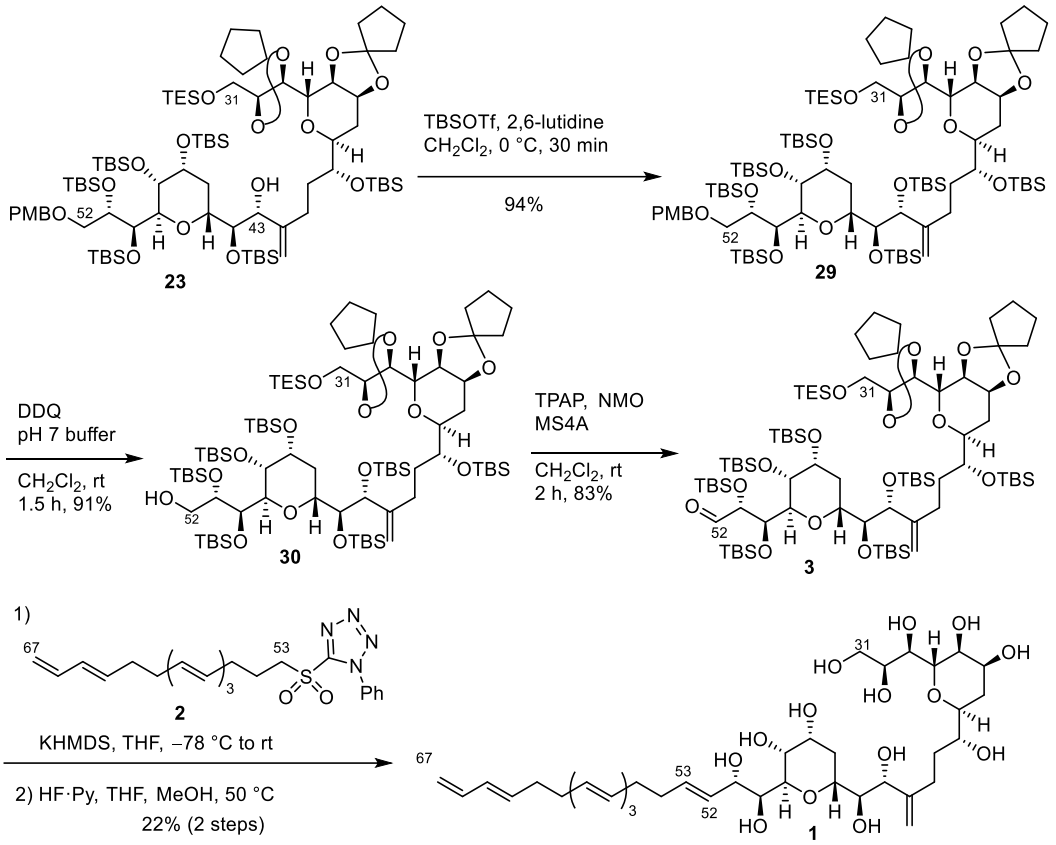


Table 2-2-2. Oxidation and reduction of **24**.

entry	reagent	temperature/°C	time/h	yield/%	ratio (**24**:**23**)
1	$NaBH_4$	rt	1	decompose.	-
2	(*R*)-Me-CBS $BH_3 \cdot Me_2S$	rt	17	trace	-
3	DIABLH	−78	0.15	85	1 : 0

Having obtained the desired C31–C52 part **23**, secondary hydroxy group was protected as TBS ether to afford compound **29** in 94% yield. Removal of the PMB group of compound **29** gave primary alcohol **30** in 91% yield. TPAP oxidation[14] of primary alcohol **28** furnished aldehyde **3** in 83% yield. Finally, the C31–C67 part of AM3 (**1**) was synthesized via Julia–Kocienski olefination[15] of aldehyde **3** and sulfone **2**[1] followed by removal of all protecting groups in 22% yield for the two steps after purification by HPLC.



Scheme 2-2-7. Synthesis of the C31-C67 part of amphidinol 3.

2-3. Comparison of the NMR data with the natural product

^{1}H NMR data of the synthetic products **31** and diastereomer at C32–C36 and C38 **1** were compared with those of the natural product (Figure 2-3-1(a)). The horizontal axis of the graph represents carbon number, and the vertical axis indicates the differences of the data between the natural product and synthetic partial structures. As a result, larger differences of chemical shifts were observed in compound **31** corresponding to proposed structure than the compound **1** corresponding to the C32–C36 and C38 diastereomer. Particularly, the largest difference was observed at C37 of compound **31**. ^{13}C NMR data of the synthetic products were also compared with those of natural product (Figure 2-3-1(b)). As a result, larger differences were also observed in compound **31** and the difference at C37 was the largest. However, even in compound **1**, significant differences of the chemical shifts were observed around at C38–C41. Therefore, further investigation was necessary for the structure confirmation of amphidinol 3.

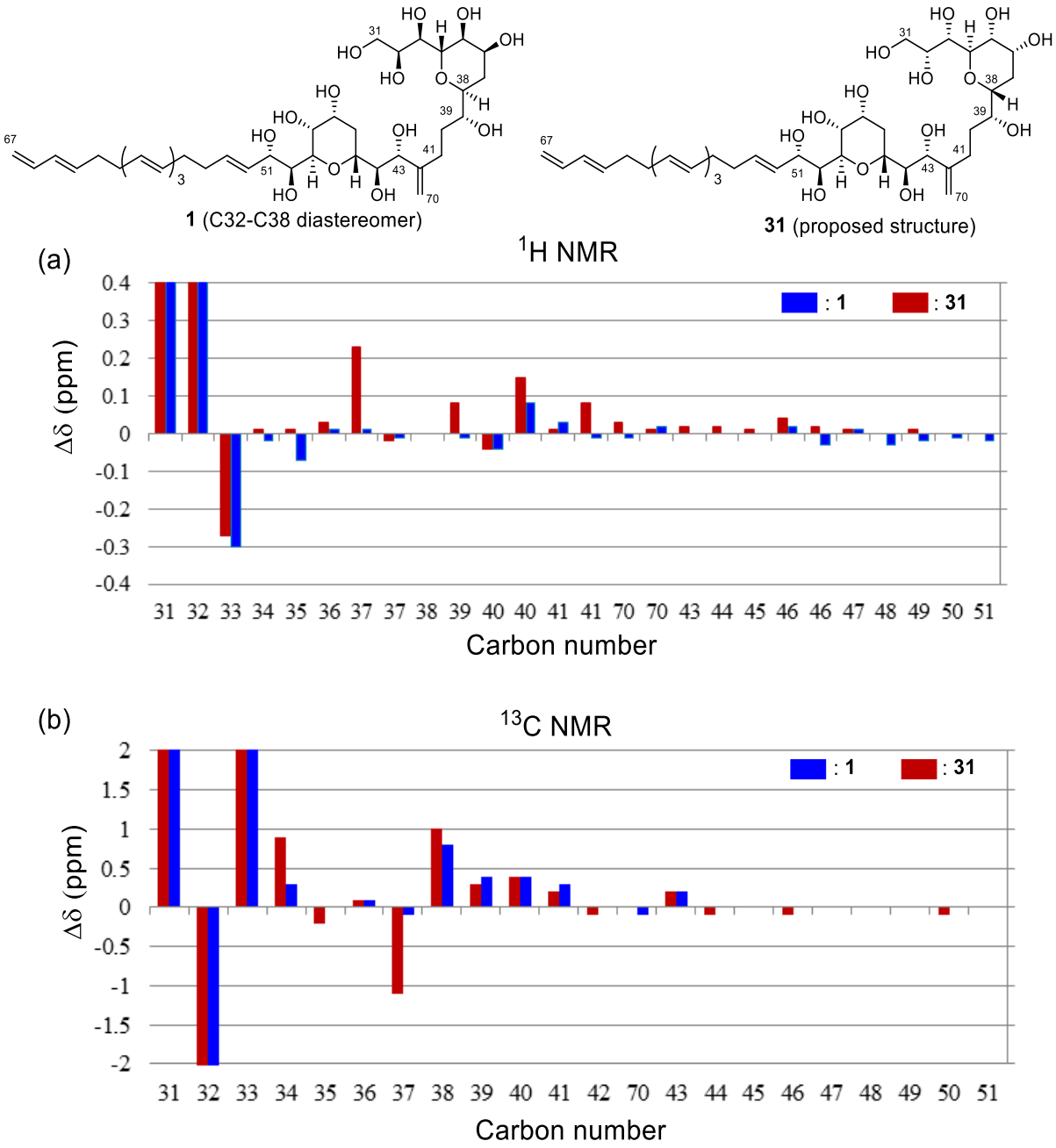
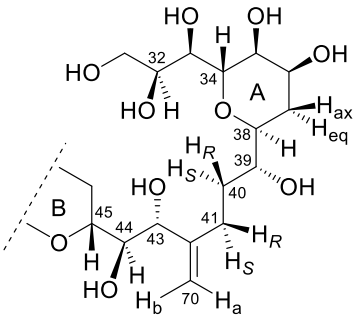


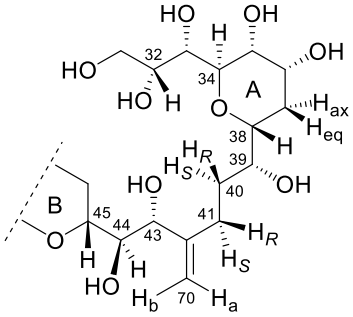
Figure 2-3-1. Differences in chemicalshifts between AM3 and synthetic partial structures **1** and **31**. (a) ^{1}H NMR data (600 MHz, 1:2 C_5D_5N/CD_3OD). (b) ^{13}C NMR data (150 MHz, 1:2 C_5D_5N/CD_3OD1:2 C_5D_5N/CD_3OD). The *x*- and *y*-axes represent carbon number and △δ in ppm, respectively. Red and blue bars represent △δ = δAM3 – δ**1** and **31**, respectively

Comparison of ^{1}H NMR coupling constants of **1** and **31** with those of natural product was performed to investigate the conformation of synthesized partial structures. As a result, it was revealed that almost all coupling constants of partial structures were similar to those of

natural product. As a noteworthy point, similar coupling constants were also observed at (H38, H39) position where medium *J* value was observed in natural product. This result suggested that the conformation of both partial structures is similar to that of natural product.



1



31

position	AM3	**1** (revised)	**31** (proposed)
H32,H33	1.6	ca 0	ca 0
H33,H34	9.5	10.2	10.1
H34,H35	nd	1.9	1.9
H35,H36	3.1	3.1	3.2
H36,H37$_{ax}$	nd	9.6	10.6
H36,H37$_{eq}$	nd	4.6	4.1
H37$_{ax}$,H38	nd	10.6	10.5
H37$_{eq}$,H38	nd	2.5	2.8
H38,H39	5.1	5.4	4.6
H39,H40$_S$	9.4	8.6	8.5
H39,H40$_R$	3.4	3.1	4.2
H40$_S$,H41$_R$	10.2	9.6	10.0
H40$_R$,H41$_S$	11.1	10.8	10.6
H43,H44	9.0	8.4	8.7
H44,H45	1.7	ca 0	ca 0

[Hz]

Figure 2-3-2. Comparison of ^{1}H NMR coupling constants of **1** and **31** with those of natural product.

The plausible reason why such deviations were observed can be explained as illustrated in Figure 2-3-3. In the ^{1}H NMR, NOE correlation was observed between C69 methyl group and C70 methylene group.[16] Therefore, olefin moieties C30–C31 and C42–C70 are close to each other. On the other hand, synthetic products corresponding to C31–C67 is lacking the C30–C31 olefin group. The presence of the magnetic anisotropic effect of olefin at C30–C31 position possibly cause the low field shifts around at C38–C41 of the natural product. Thus, it is difficult to conclude the accurate structure by comparing partial structures corresponding to the C31–C67 section with the natural product.

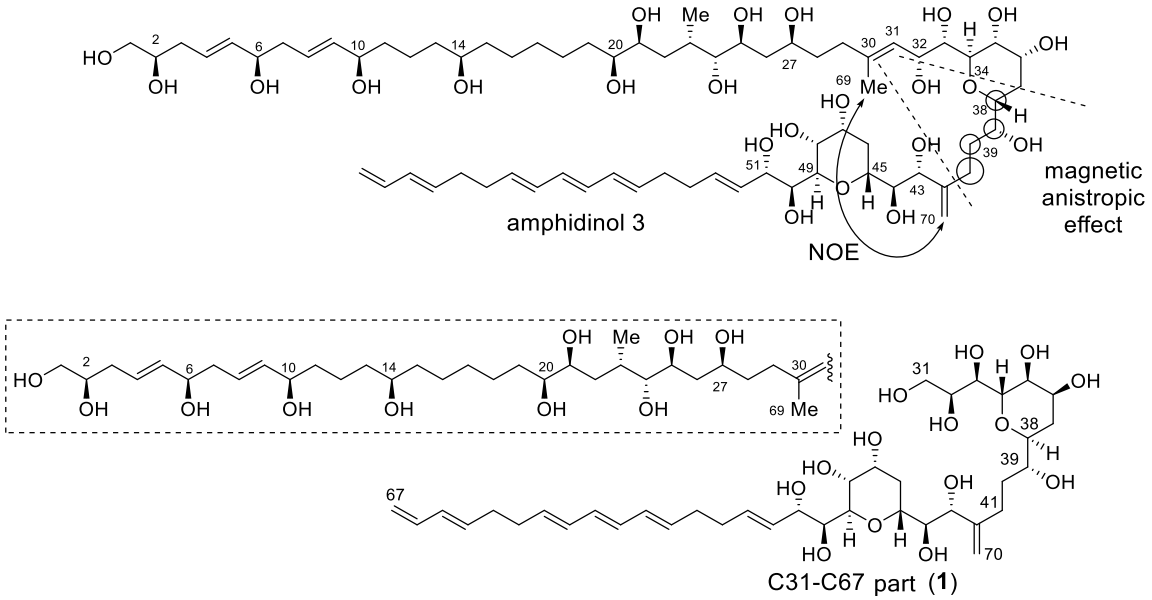


Figure 2-3-3. Plausible reason of the deviation of the chemical shifts.

2-4. Degradation studies and comparison of the NMR data

As discussed in section 2-3, it was controversial to determine the absolute configuration of AM3 by comparing NMR data of synthetic partial structures with those of the natural product. To solve this problem, as shown in Figure 2-4-1, a strategy was proposed to convert synthetic partial structures into MTPA esters (**32**–**34**) which lack the C30–C31 double bond, but retain the C38–C39 portion.[17] And the comparison of NMR data between authentic samples **32**, **34** and degradation product of AM3 **33** would elucidate accurate absolute configuration.

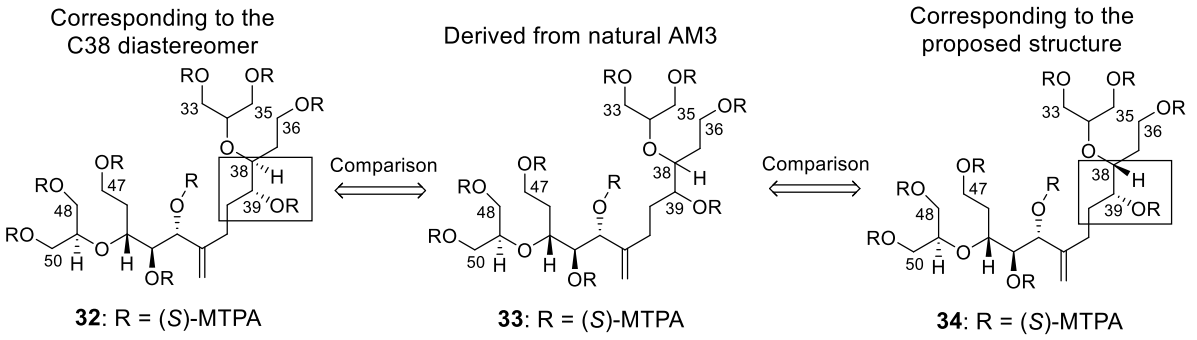
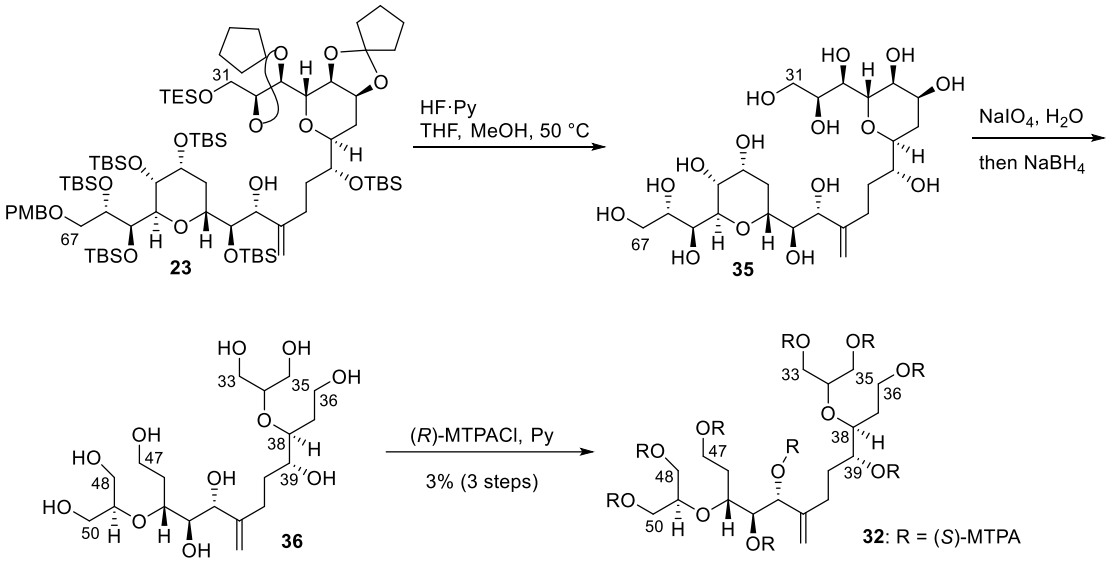


Figure 2-4-1. Strategy for the confirmation of the absolute configuration at C38–C39 using degradation products from natural product and synthetic samples.

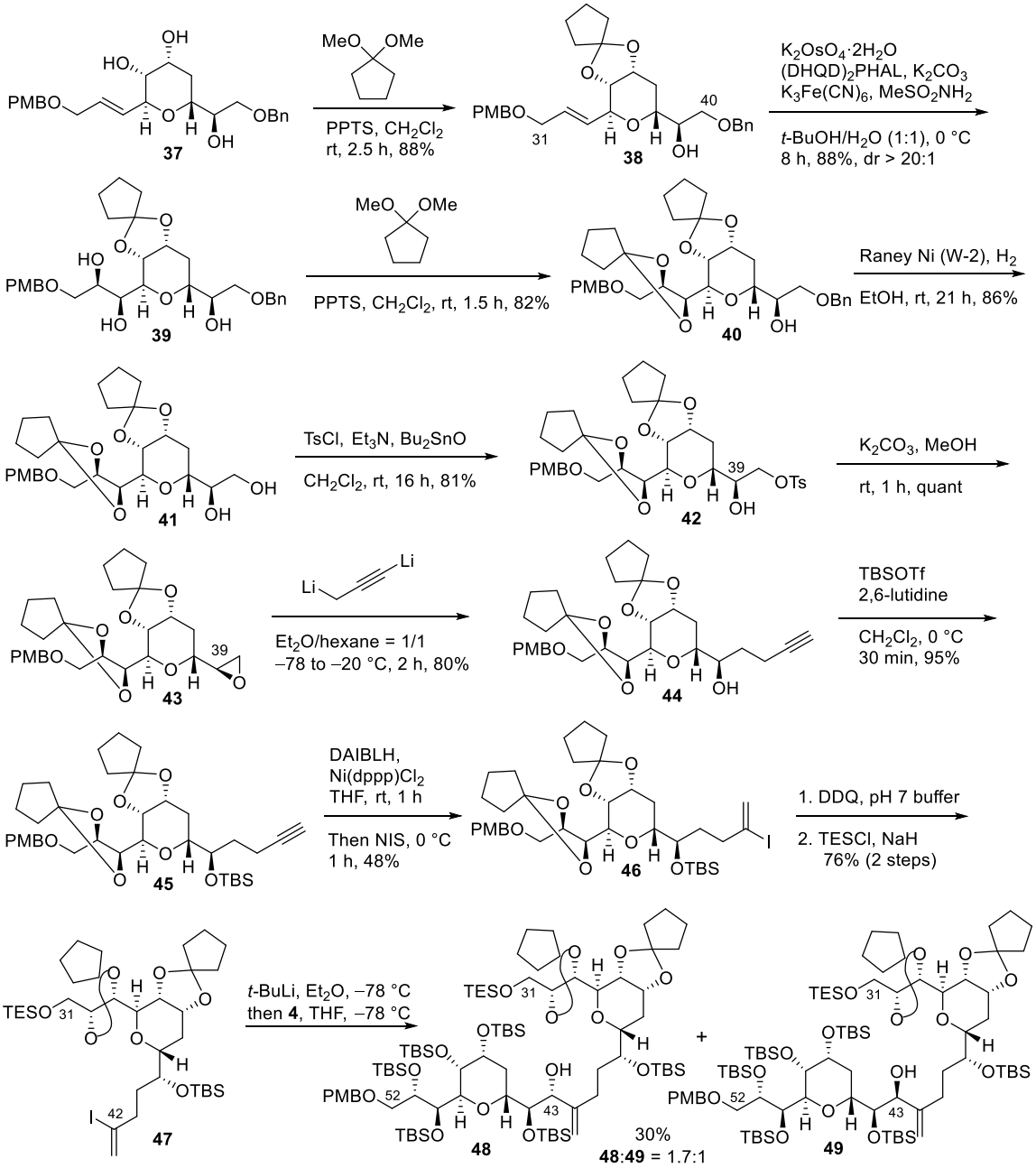
Preparation of the MTPA ester **32** corresponding to the diastereomer at C38 was carried out (Scheme 2-4-1). Removal of all protecting groups in compound **23** with HF·Py in THF/MeOH afforded compound **35**. Oxidative cleavage with $NaIO_4$ followed by the reduction with $NaBH_4$ of compound **35** furnished compound **36**. Polyol **36** was transformed to per-(*S*)-MTPA ester **32** in 3% yield for the three steps after purification by using HPLC.



Scheme 2-4-1. Preparation of (*S*)-MTPA ester **32** corresponding to the C32–C38 diastereomer.

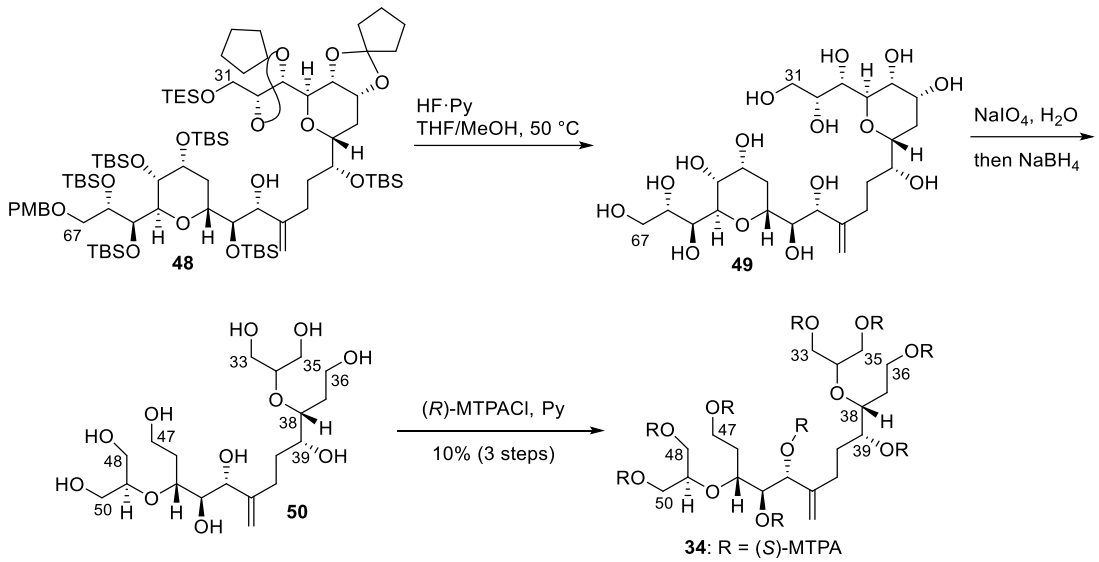
Synthesis of the MTPA ester **34** corresponding to the proposed structure commenced with tetrahydropyran **37**, an enantiomer of **9** (Scheme 2-4-2). 1,2-diol moiety of compound **37** was protected as cyclopentylidene acetal to afford **38** in 88% yield.[5] Sharpless asymmetric dihydroxylation[6] proceeded successfully to produce 1,2-diol **39** in 88% yield with 20:1 diastereoselectivity. 1,2-diol moiety was protected as cyclopentylidene acetal to afford secondary alcohol **40** in 82% yield. Selective removal of the benzyl group of **40** was achieved by treating with Raney Ni (W-2)[8] to afford diol **41**. Diol **41** was subjected tin acetal mediated regioselective tosylation[18] to afford tosylate **42** in 81% yield. Treatment of tosylate **42** with K_2CO_3 resulted in intramolecular S_N2 reaction to afford epoxide **43** quantitatively. Propargylation of epoxide **44** using dilithium reagent[2] proceeded successfully to furnish terminal alkyne **44** in 80% yield. Resulting secondary alcohol **44** was protected as TBS ether to afford terminal alkyne **45** in 95% yield. Terminal alkyne **45** was subjected to Ni-catalyzed regioselective hydroalumination[3] followed by iodination to afford iodoolefin **46** in 48% yield. Removal of the PMB group of compound **46** following by TES protection furnished the C31–C42 part **47** in 76% yield for the two steps. Alkenyllithium–aldehyde coupling reaction of the C43–C52 part **4** and C31–C42 part **47** was carried out to afford **48** along with the

corresponding diastereomer **49** in the ratio of 1.7:1 in 30% combined yield.



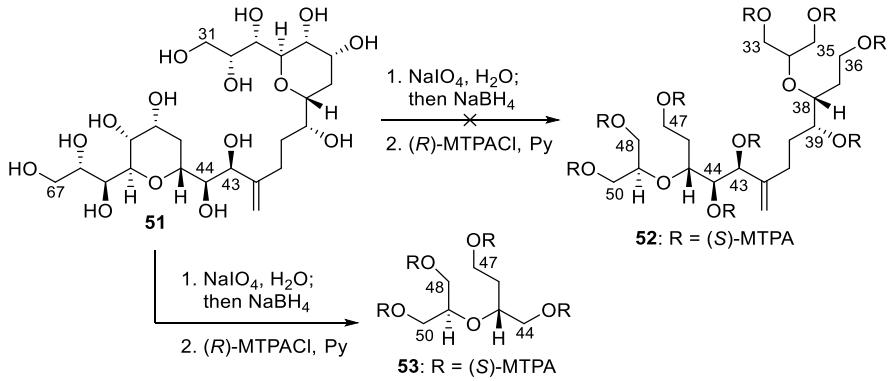
Scheme 2-4-2. Synthesis of the C31–C52 part corresponding to the proposed structure.

Removal of all protecting groups from **48** with using HF·Py afforded compound **49**. Compound **49** was subjected to oxidative cleavage with $NaIO_4$ and reduction with $NaBH_4$ to produce compound **50**. Finally, (*S*)-MTPA ester **34** was prepared by the treatment with (*R*)-MTPACl in pyridine in 10% yield for the three steps after purification by using HPLC (Scheme 2-4-4).



Scheme 2-4-3. Preparation of (*S*)-MTPA ester **34** corresponding to the proposed structure.

Because there was only a little amount of natural product, it was necessary to figure out an optimal condition of degradation experiment of AM3 with using model compound. Thus model experiment using compound **51**, undesired diastereomer at C43, was attempted. Surprisingly, undesired compound **53** was generated instead of objective MTPA ester **52**. This is probably because that the 1,2-diol at C43–C44 was cleaved due to its *syn* configuration which has high reactivity for degradation reaction.



Scheme 2-4-4. Attempt of model experiments using undesired compound **51**

Therefore, model experiments using compound **35**, desired C43 diastereomer, were carried out as shown in table 2-4-1. In this reaction, it was a serious problem that a large amount of byproducts having a molecular weight smaller by two protons than the objective compound **36** was generated. Although the equivalent of reagents did not affect the ratio of

byproduct (entry 1 vs 2 vs 3), it was found that in higher the concentration of substrate, the lower formation of byproduct (entry 1 vs 4 vs 5).

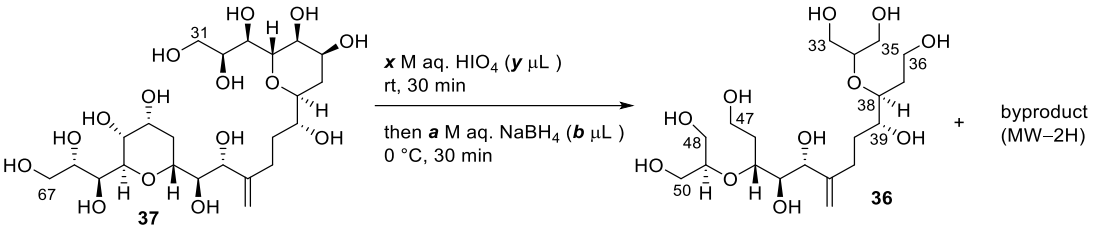
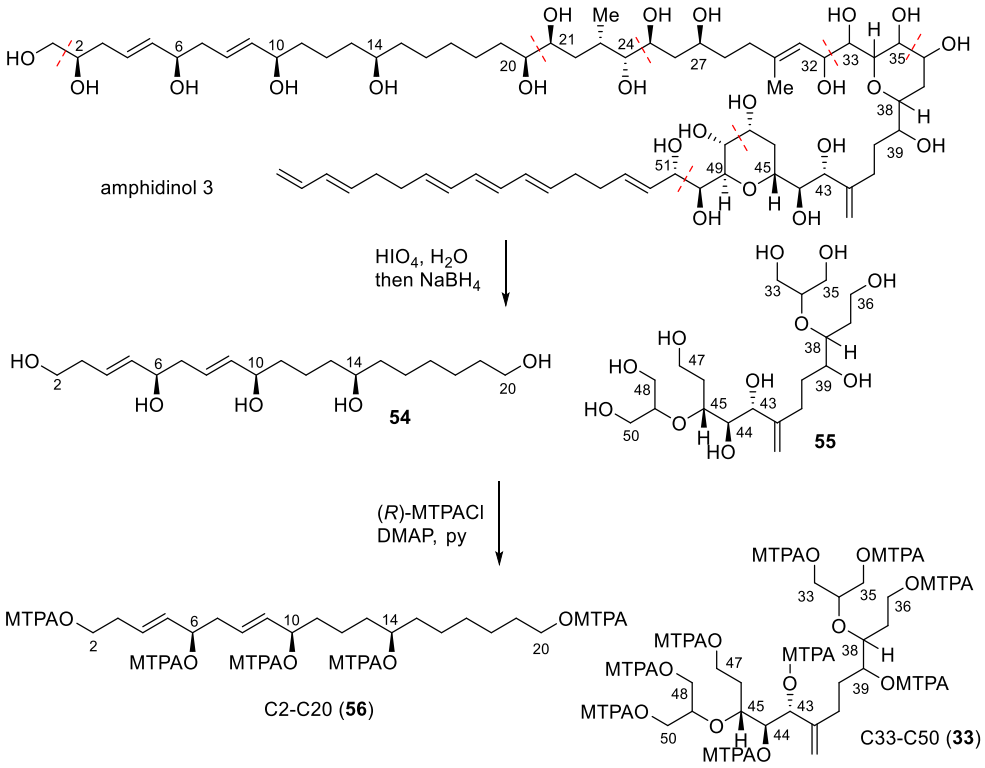


Table 2-4-1. Model experiments using compound **35** for optimizing the condition of the degradation reaction.

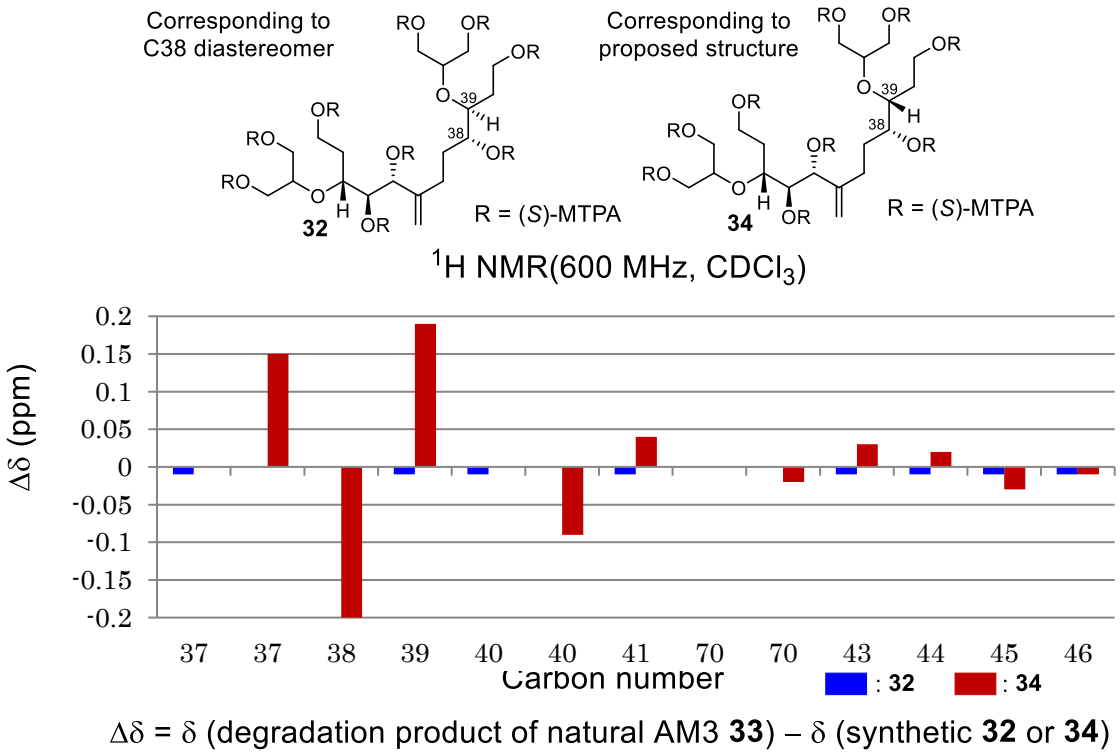
	HIO_4			$NaBH_4$			**36** :
entry	***x***(M)	***y*** (μL)	eq.	***a*** (M)	***b*** (μL)	eq.	byproduct (MW−2H)
1	0.1	41	32	1.0	16	128	1.0 : 0.72
2	0.05	41	16	0.5	16	64	1.0 : 0.90
3	0.2	41	64	2.0	16	256	1.0 : 0.85
4	0.1	82	64	1.0	32	256	1.0 : 1.4
5	0.1	20	16	1.0	8	64	1.0 : 0.45

The degradation experiment of natural product was performed (Scheme 2-4-5). A small amount of amphidinol 3 (0.3 mg, 0.23 μmol) was subjected to oxidative cleavage with $NaIO_4$ followed by the reduction with $NaBH_4$ to afford a mixture of compounds **54** and **55**, which was converted to a mixture of MTPA esters **56** and **33**. MTPA ester **33** was isolated by using HPLC. Because of the small scale, the yields are not calculated yet.



Scheme 2-4-5. Preparation of the (*S*)-MTPA ester **33** from amphidinol 3.

^{1}H NMR data (600 MHz, $CDCl_3$) of synthetic MTPA esters **32** and **34** were compared with those of MTPA ester **33** derived from the natural product. The horizontal axis of the graph represents carbon number, and the vertical axis indicates the deviations of the data with the **33**. The deviation in the chemical shifts at C36–C47 for **33** and either **32** or **34** are shown in Figure 2-4-2. It is obvious that deviations between **33** and **34** are large (red bars), but chemical shits of **32** are identical to those of **33b** (blue bars).



Δδ = δ (degradation product of natural AM3 **33**) – δ (synthetic **32** or **34**)

Figure 2-4-2. Comparison of the ^{1}H NMR data of **32** and **34** with those of degradation product derived from natural AM3.

Therefore, the correct absolute configurations at C32–C36 and C38 are opposite to those in the originally proposed structure. Therefore, the proposed structure of AM3 has been revised to be 32*S*, 33*R*, 34*S*, 35*S*, 36*S* and 38*S* as shown in figure 2-5-2. Based on these results, it was revealed that AM3 is a unique natural product having both antipodal THP counterparts on a single carbon chain (C33–C38 and C45–C50 fragments).

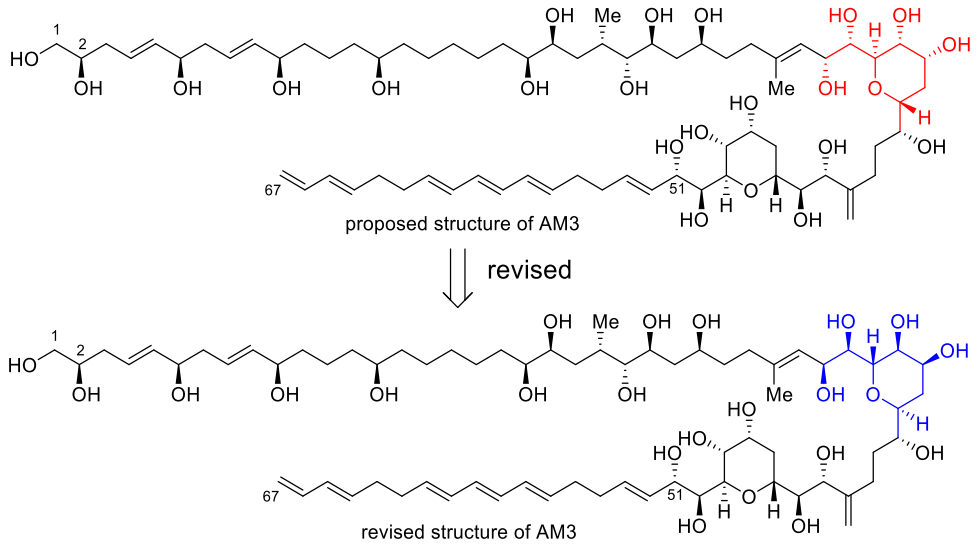


Figure 2-5-2. Structure revision at C32–C38 of AM3

Although biosynthetic pathways of the amphidinols are not fully elucidated, a ^{13}C-labeling pattern of metabolite was reported by feeding experiment suing ^{13}C-enriched acetate (Figure 2-5-3a).[19] The labeling patterns are not symmetrical between the A and B ring moieties, and arrangement of the A and B rings is anti-parallel, head-to-tail to tail-to head (Figure 2-5-3b). Therefore, it is plausible that the two antipodal THP moieties were constructed coincidentally in the biosynthetic pathway, and it is no considered to be an unnatural phenomenon. It has been reported that enantiomeric natural products can arise from a single ore different species, and that both diastereomer possessing enantiomeric partial structure can arise from a single species.[20,21] It is interesting to note that both enantiomers of the partial structures exist in a single molecule in the nonactines[22] and oxasqualenoids.[23] However, to the best of our knowledge, this is the first example of two antipodal THP rings existing on a single carbon chain in the family of amphidinols and related compounds. It is also noteworthy that stereochemical revision of AM3 would afford significant contribution to elucidate the three-dimensional structure and mode of action of AM3.

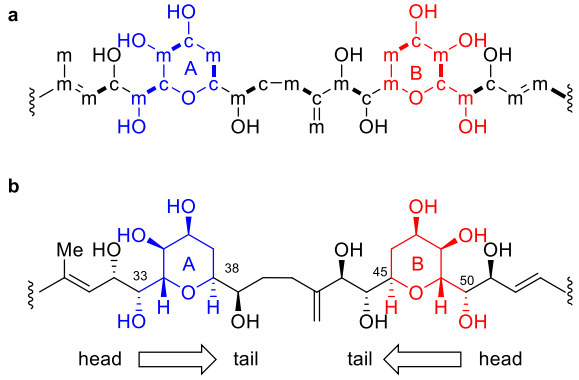


Figure 2-5-3. a) ^{13}C-labeling pattern of themetabolite of AM3. c = carbonyl carbon atom of acetate, m = methyl carbon atom of acetate. b) Arrangement of the A and B rings of AM3.

The absolute configuration at C39 was determined by modified Mosher's method against degradation product of AM3 **33**. However, because **33** has a lot of MTPA esters, there is a possibility that modified Mosher's method cannot be applied. Thus, synthesis of C33–C50 MTPA ester corresponding to C39-diasteromer (**57**) and comparison of NMR data with those of degradation product of natural AM3 was carried out to confirm the absolute configuration at C39 (Figure 2-5-4).

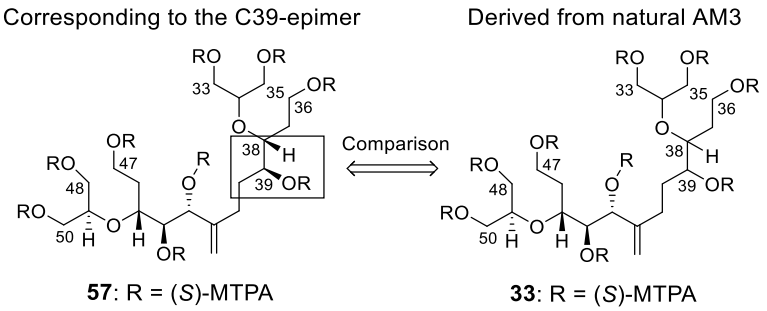
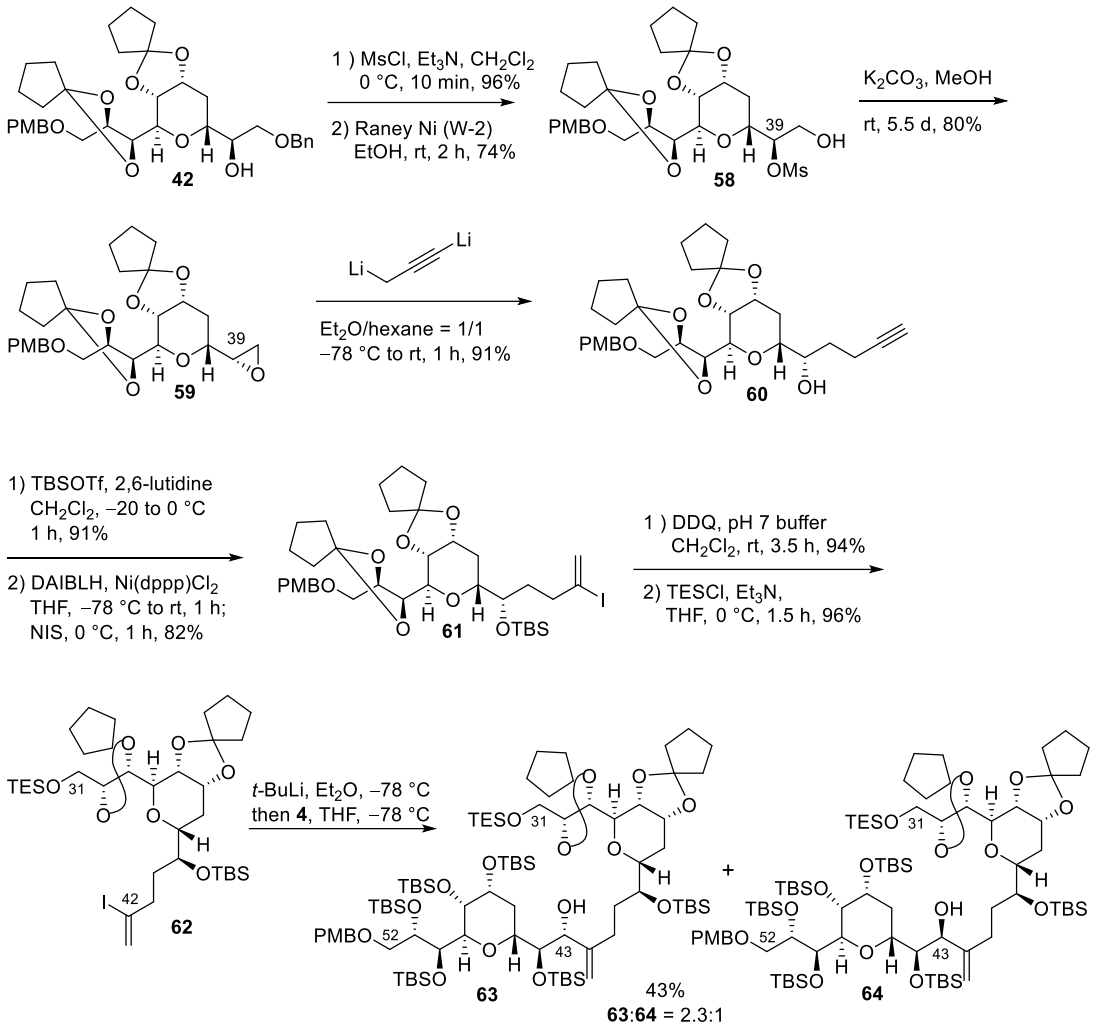


Figure 2-5-4. Strategy for the confirmation of the absolute configuration at C39 of AM3

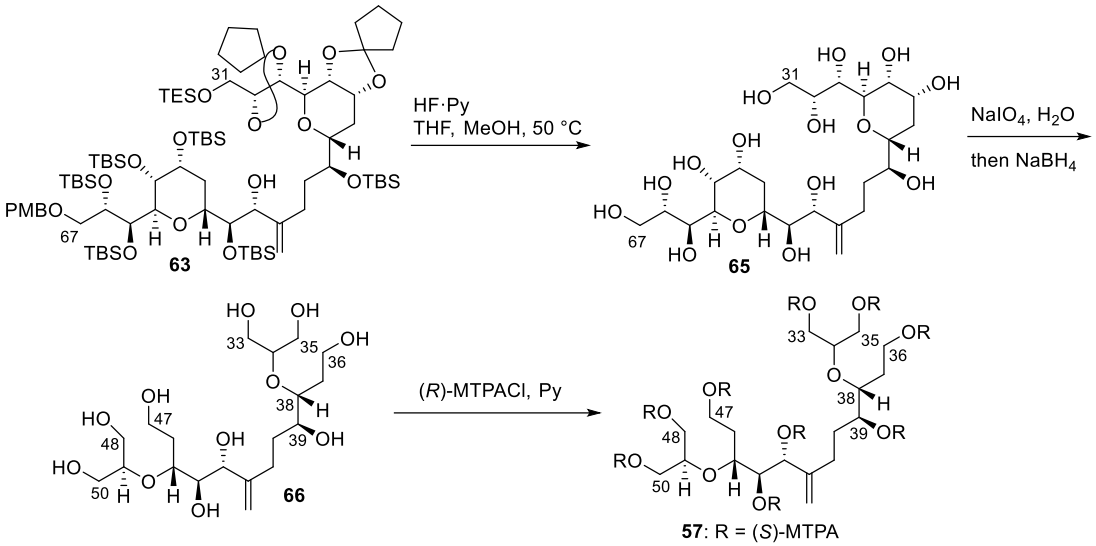
Synthesis of the MTPA ester **57** corresponding to the C39-epimer commenced with compound **42** shown in Scheme 2-5-1. Mesylation of secondary alcohol **42** proceeded in 96% yield. Selective removal of benzyl group was achieved by treating with Raney Ni (W-2)[8] to afford primary alcohol **58** in 74% yield. Treatment of primary alcohol **58** with K_2CO_3 resulted in intramolecular Sn2 reaction to afford epoxide **59** in 83% yield with inversion at C39. Propargylation of epoxide **59** using dilithium reagent[2] proceeded successfully to furnish terminal alkyne **60** in 91% yield. Resulting secondary alcohol was protected as TBS ether in 91% yield. Ni-catalyzed regioselective hydroalumination[3] followed by iodination was

performed to give iodoolefin **61** in 82% yield. Removal of the PMB group of compound **61** following by TES protection furnished the C31–C42 part **62**. Alkenyllithium–aldehyde coupling reaction of the C43–C52 part **4** and C31–C42 part **62** was carried out to afford **63** along with the corresponding diastereomer **64** in the ratio of 2.3:1 in 43% combined yield.



Scheme 2-5-1. Synthesis of the C31–C52 part corresponding to C39-diasteromer.

Removal of all protecting groups from **63** with using HF·Py afforded compound **65**. Compound **65** was subjected to oxidative cleavage with $NaIO_4$ and reduction with $NaBH_4$ to produce compound **66.** Finally, (*S*)-MTPA ester **57** was prepared by the treatment with (*R*)-MTPACl in pyridine. However, purification using HPLC was not successful.



Scheme 2-5-2. Preparation of the (*S*)-MTPA ester **54** corresponding to C39-diastereomer.

Although MTPA ester **57** corresponding to C39-epimer could not be purified, comparison of ^{1}H NMR with those of degradation product of natural AM3 **33** was carried out (Figure 2-5-5). As the result, chemical shifts of **57** and those of **33** were clearly different. Therefore, it was confirmed that the absolute configuration at C39 of the proposed structure is correct.

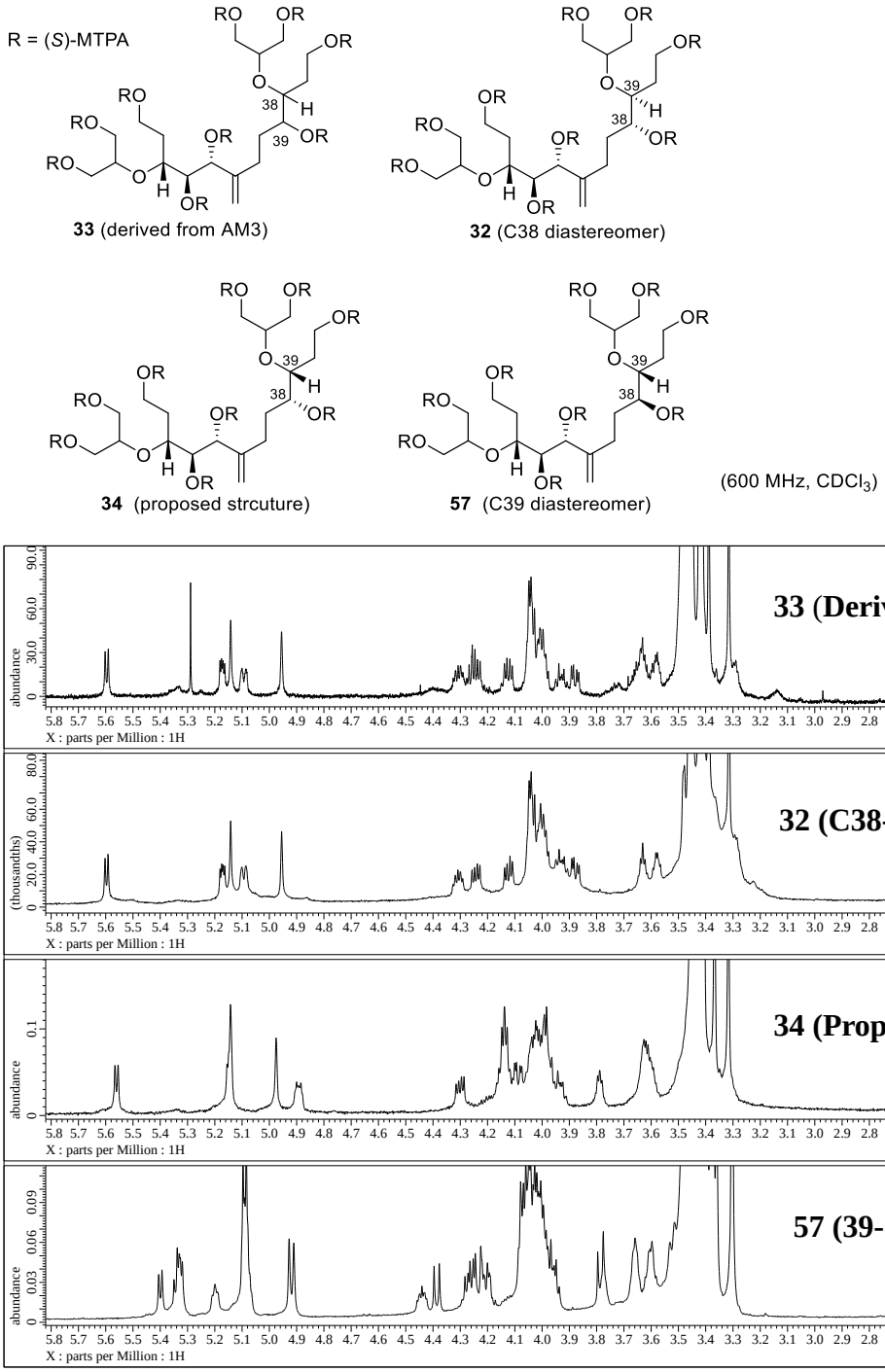


Figure 2-5-5. Comparison of the ^{1}H NMR spectrum (600 MHz, $CDCl_3$, 5.8–1.7 ppm) between **33**, **32**, **34** and **54**.

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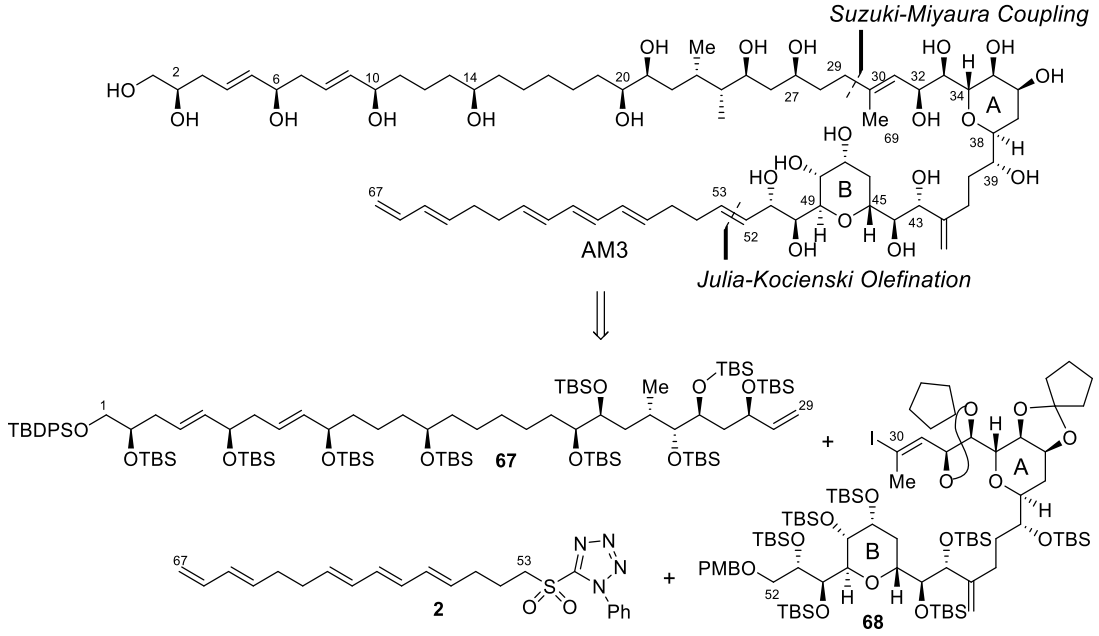
Chapter 3. Total Synthesis of AM3

3-1. Synthesis plan

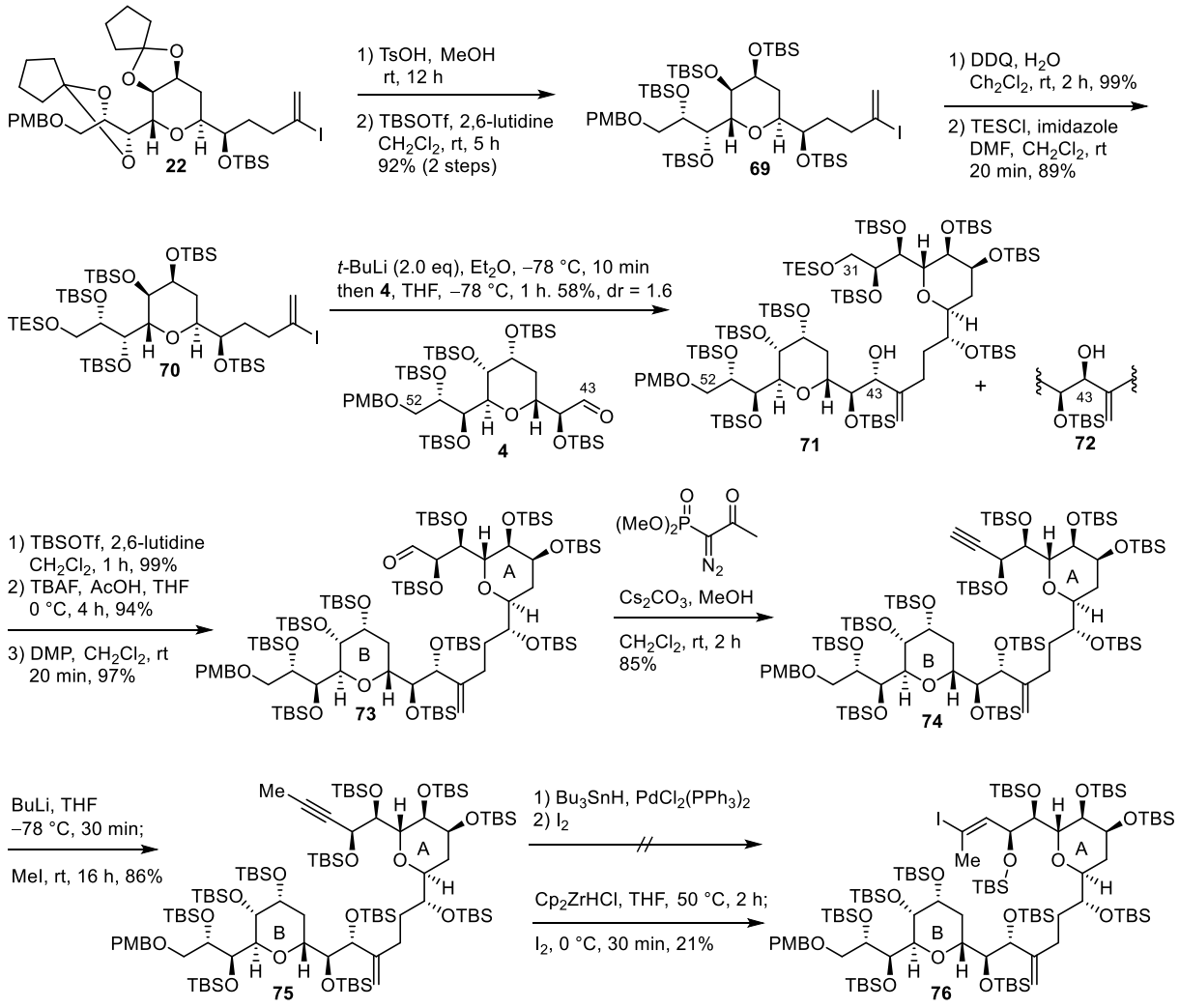
Since the structure revision of AM3 was achieved as described in chapter 2, attempt for total synthesis based on the revised structure was performed. Synthesis of plan of AM3 is shown in Scheme 3-1-1. AM3 would be synthesized via Suzuki–Miyaura coupling[1] between polyol fragment **67**[2] and AB ring fragment **68** followed by Julia–Kocienski olefination with polyene fragment **2**.[3] As synthesis of polyol **67** had been already reported, this section mainly focuses on the synthesis of AB ring **68** and development of the coupling method of huge fragments. Challenges in this strategy are connection of the large segments **67** (MW 1844) and **68** (MW 1747) and elaboration to complete the synthesis of **1** (MW 1328) including global deprotection. A successful precedent to apply the Suzuki–Miyaura coupling in the total synthesis of palytoxin (MW 2680) was reported by Kishi.[4]



Scheme 3-1-1. Convergent synthesis of the AM3 via Suzuki–Miyaura coupling and Julia–Kocienski olefination.

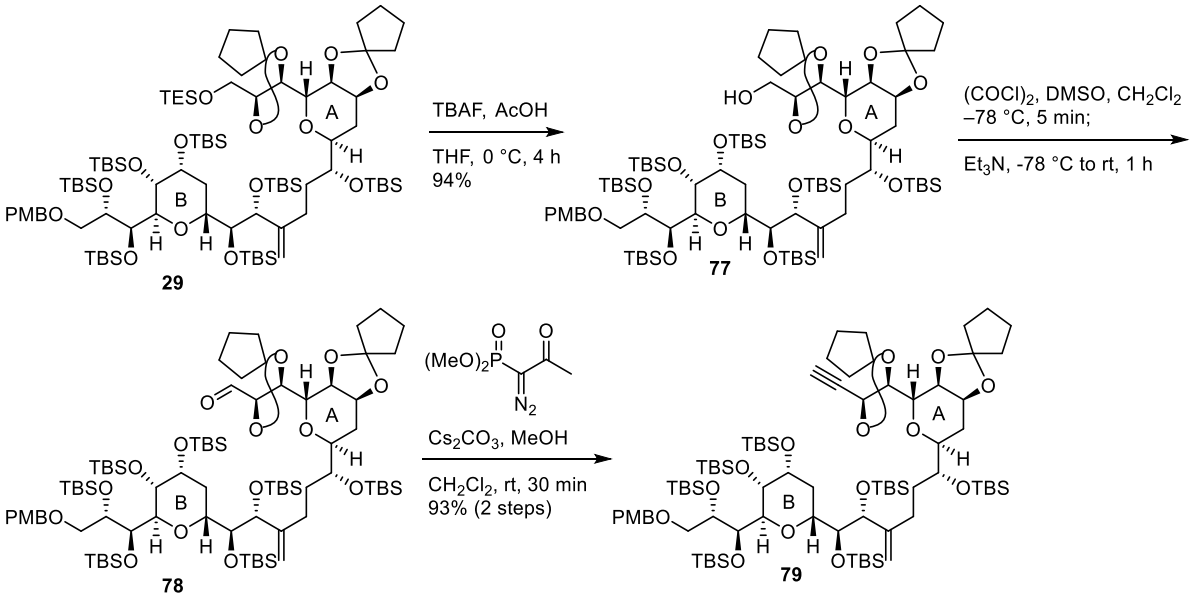
3-2. Synthesis of the C30–C52 section

Synthesis of TBS protected bis-THP fragments was attempted from compound **22** as shown is scheme 3-2-1. Removal of acetal groups, TBS protection, removal of PMB group followed by TES protection gave iodoolefin **69**. Coupling reaction with aldehyde **4** proceeded in 58% yield and 1.6:1 diastereoselectivity to afford compound **71**. The obtained compound was converted to aldehyde **73** via TBS protection, removal of TES group and Dess–Martin oxidation. To the aldehyde **73**, Ohira–Bestman alkyne synthesis was performed to give terminal alkyne **74**. Methylation of compound **74** afforded alkyne **75**. Transformation to iodoolefin **75** was very difficult maybe due to the steric hindrance of TBS groups. The hydrostannylation did not proceeded at all and starting material was recovered almost completely. Hydrozirconization followed by iodination was also attempted. However, the yield was too low as 21%, and compound **76** was obtained as an inseparable mixture of protonated byproduct. Thus, the synthesis of TBS protected bis-THP fragment was suspended.



Scheme 3-2-1. Synthesis of TBS protected AB ring fragment.

Synthesis of the bis-THP fragment commenced with using compound **29** having cyclopentylidene acetals at C32–C33 and C35–C36 as a starting material. Removal of the TES group was performed to give terminal alcohol **77**. Swern oxidation[5] of alcohol **77** afforded aldehyde **78**. The obtained aldehyde was converted to terminal alkyne **79** via Ohira–Bestman alkyne synthesis.[6]



Scheme 3-2-2. Synthesis of bis-THP fragment.

Methylation of terminal alkyne **79** was examined as shown in Table 3-2-1. When 12 equivalents of *n*-BuLi was used as a base and the time of deprotonation was 30 minutes, compound **80** was obtained as an inseparable mixture of recovered **79** in 1:2 ratio (entry 1). The ratio of **80** was increased to 3:1 with decreasing the time of deprotonation from 30 to 5 minutes (entry 2). When the time of deprotonation was further decreased from 5 to 1 minute, alkyne **79** was obtained as a single compound (entry 3). The ratio of **79** was decreased to 9:1 with reducing the equivalent of base (entry 4) and alkyne **79** was obtained quantitatively with using LHMDS as a base (entry 5).

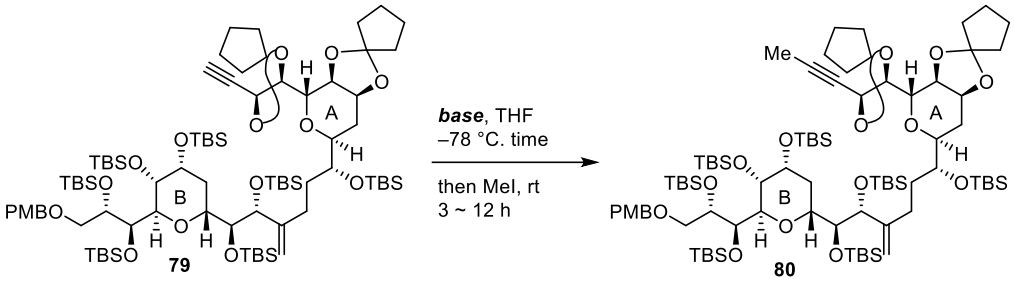


Table 3-2-1. Methylation of terminal alkyne **79**.

entry	base (eq)	time/min	ratio (**80**:RSM)	yield/%
1	*n*-BuLi (12)	30	1:2	97
2	*n*-BuLi (11)	5	3:1	95
3	*n*-BuLi (13)	1	1:0	93
4	*n*-BuLi (5)	1	9:1	94
5	LHMDS (10)	1	1:0	quant

Regioselective hydrostannylation followed by iodination of alkyne **80** was examined as shown in Table 3-2-2. When $PdCl_2(PPh_3)_2$ was used as a catalyst (entry 1),[7] compound **81** was obtained as a mixture of regioisomer **81** in 4:1 ratio. Iodination of the obtained mixture was performed without purification by silica gel column to give an inseparable mixture of **68** and **83** in 82% yield. When $Pd(OAc)_2$ was used in the presence of PCy_3 (entry 2),[8] regioselectivity was decreased to 1.7:1. After separating the **81** and **82**, iodination was performed to afford compound **68** as a single isomer. Although using $Pd_2(dba)_3{\cdot}CHCl_3$ gave compound **68** in 75% yield (entry 3),[9] 300 equivalents of Bu_3SnH was necessary for completely consumption of the starting material. When using $PdCl_2(P\text{-}o\text{-}tol_3)_2$, the **68** was obtained in 76% yield with 40 equivalents of Bu_3SnH (entry 4).[10]

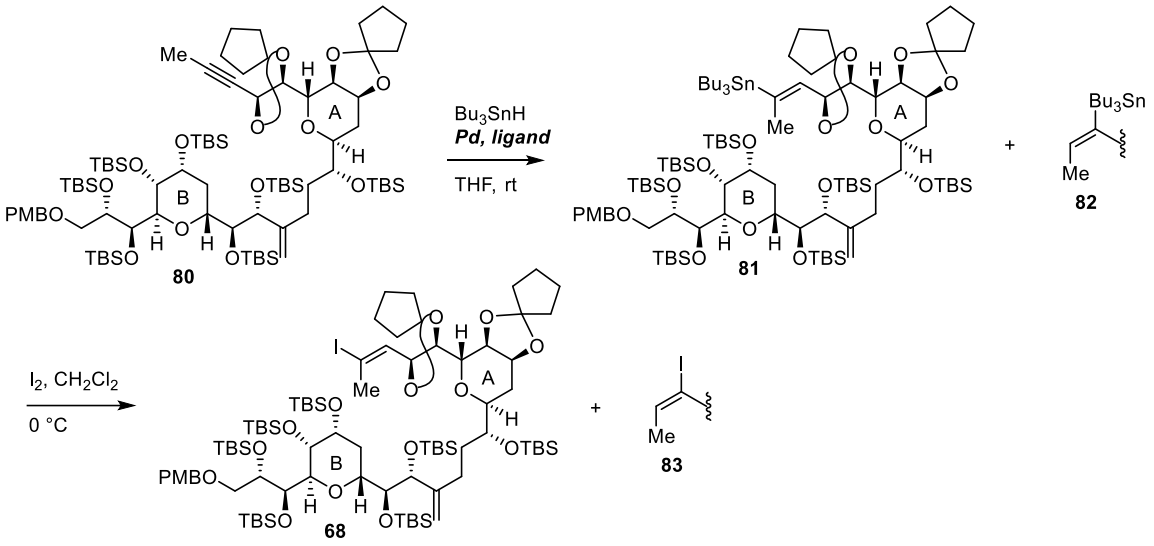


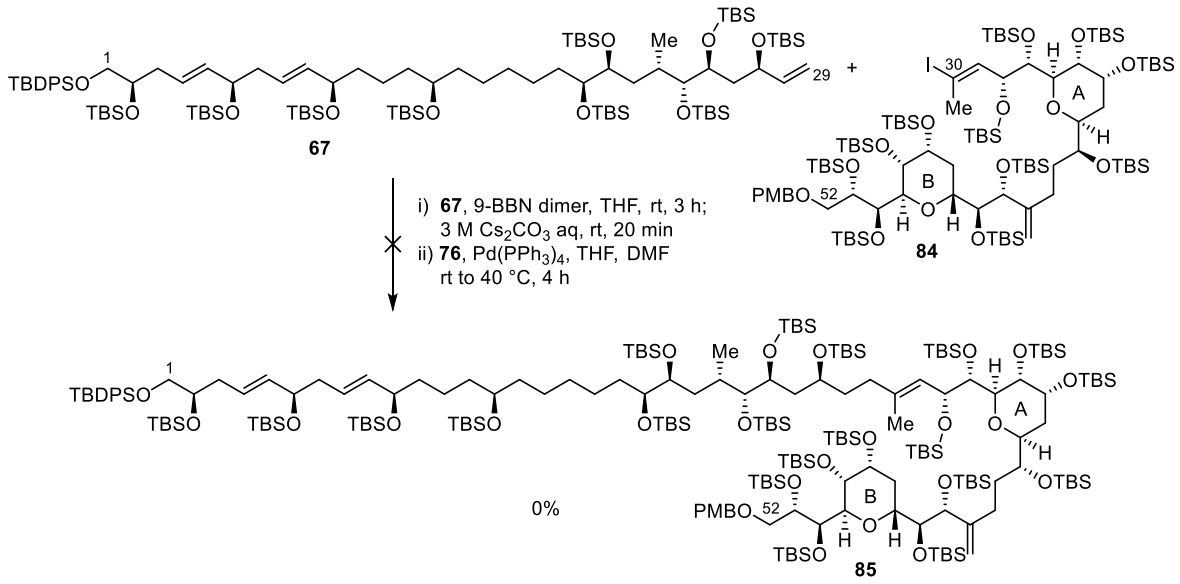
Table 3-2-2. Regioselective hydrostannylation followed by iodination of alkyne **80**.

				Stanyation/%		
entry	***Pd cat***	***ligand***	Bu_3SnH/eq	**81**	**82**	iodination/%[a]
1	$PdCl_2(PPh_3)_2$	-	42	-	-	82[b]
2	$Pd(OAc)_2$	PCy_3	14	58	34	53
3	$Pd_2(dba)_3{\cdot}CHCl_3$	-	300	76	13	75
4	$PdCl_2(P\text{-}o\text{-}tol_3)_2$	-	40	77	14	76

[a] Yiled for two steps, [b] A mixture of **68** and **83** (4:1)

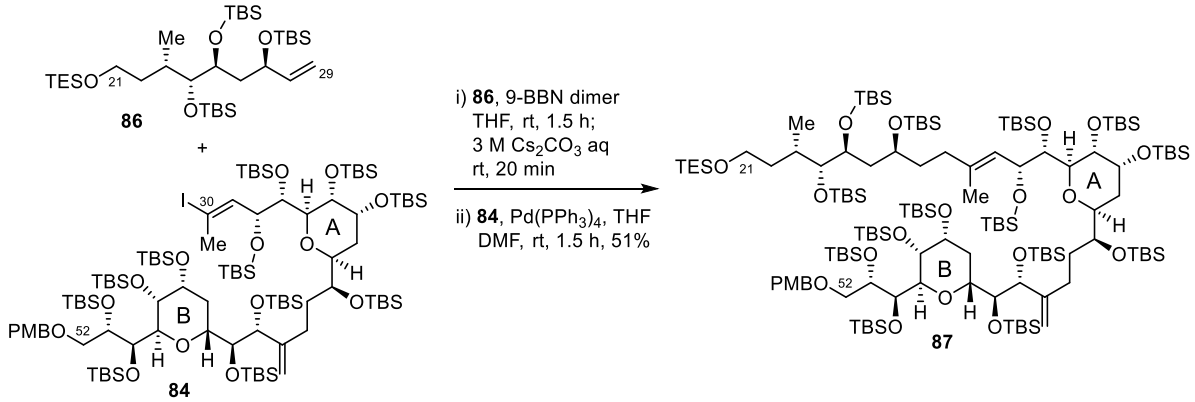
3-3. Total stnthesis

Next, investigation of Suzuki–Miyaura coupling between polyol fragment and bis-THP ring fragment was performed. Previously, the coupling was attempted with using polyol fragment **67** and AB ring fragment **84**[11] which corresponds to proposed structure.[12] However objective compound **85** was not obtained at all.



Scheme 3-3-1. Previous result of Suzuki–Miyaura coupling between C1–C29 fragment and bis-THP fragment (proposed structure).

On the other hand, the coupling reaction between shorter polyol fragment **86**[13] and AB ring fragment **84** was successful to give compound **87** in 51% yield.[12] From these results, it was indicated that the low reactivity of the coupling of compound **67** and **84** is caused by the long linear structure with high hydrophobicity of compound **67**.



Scheme 3-3-2. Previous result of Suzuki–Miyaura coupling between C21–C29 fragment and bis-THP fragment (proposed structure).

Compound **88**[13] having long linear structure and high hydrophobicity was designed as a model compound of polyol fragment. The coupling between compound **88** and iodoolefin **89**[14] did not proceed at all as expected. Thus, further optimization was performed with using

compound **88** and **89**. As a result, it was revealed that the reactivity was dramatically improved by changing the concentration of the base aqueous from 3 M to 1 M and compound **90** was obtained in 60% yield (entry 1 vs 2). As a supplemental experiment, the coupling was also performed with *n*-Bu_4NOH (entry 3). However objective compound was not obtained.

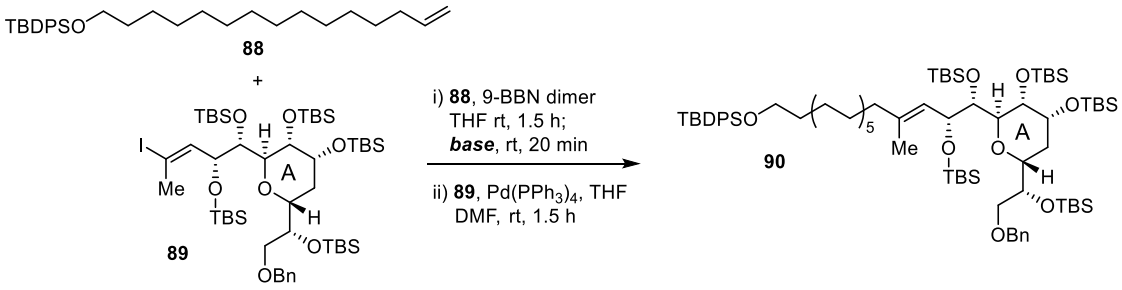
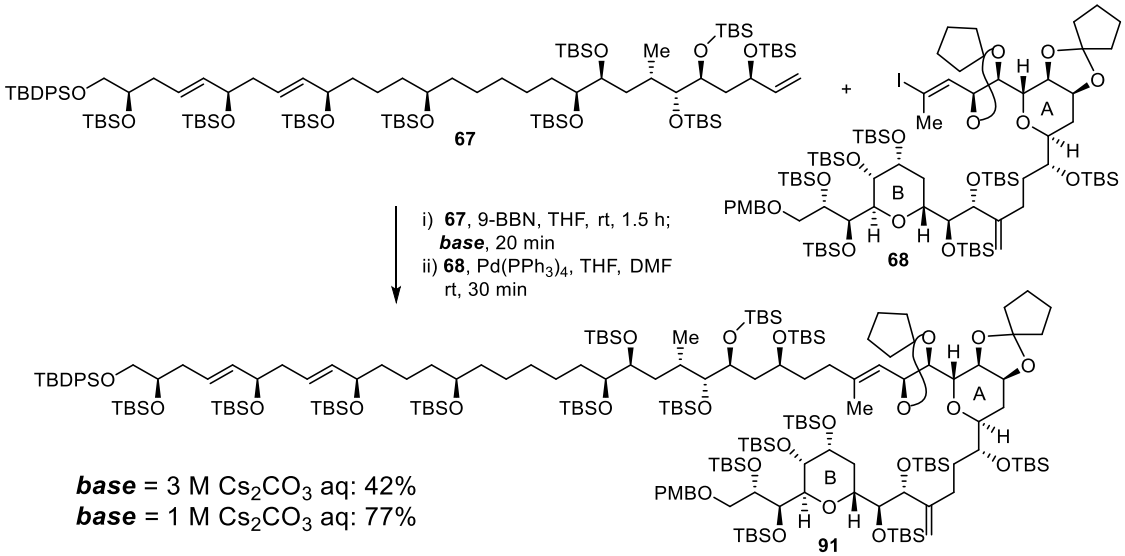


Table 3-3-1. Model experiments of Suzuki–Miyaura coupling using **80** and **81**.

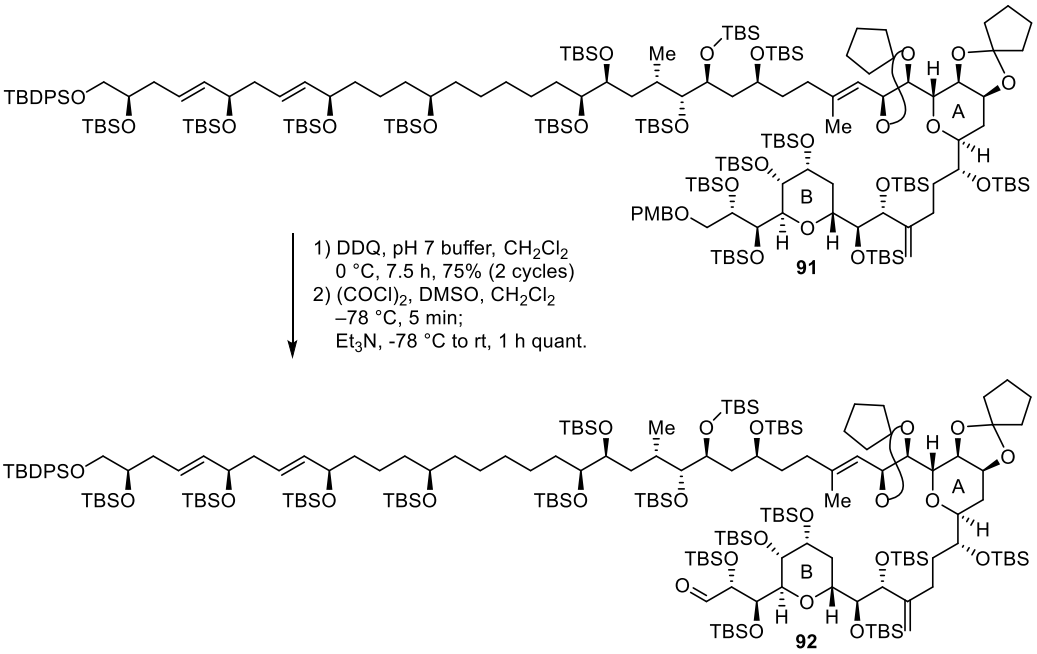
entry	***base***	Yield/%
1	3 M Cs_2CO_3 aq	0
2	1 M Cs_2CO_3 aq	60
3	1 M *n*-Bu_4NOH aq	0

Based on the above result, the coupling reaction of compound **67** and **68** was attempted with using 1 M cesium carbonate. As a result, the coupling proceeded successfully and compound **91** was obtained in 77% yield. Unexpectedly, compound **91** was also obtained in medium yield with using 3 M base. Thus, it was indicated that steric repulsion of adjacent protecting group of iodoolefin is also important for the coupling reaction.



Scheme 3-3-3. Effect of the base concentration for Suzuki–Miyaura coupling between C1–29 and bis-THP fragment.

Compound **91** was converted to aldehyde **92** via removal of PMB group followed by Swern oxidation.



Scheme 3-3-4. Synthesis of aldehyde **92**.

Investigation of Julia–Kocienski olefination of **92** and polyene **2** was performed. When the reaction was attempted in a mixed solvent of THF and toluene, compound **93** was obtained in 67% yield, but *E/Z* selectivity was too low as 2:1 (entry 1). The *E/Z* selectivity was slightly enhanced in the case using only THF as a solvent (entry 2). When a mixed solvent of THF and HMPA was used as a more polar solvent, compound **93** was obtained in 75% yield and 10:1 *E*/Z selectivity (entry 3).

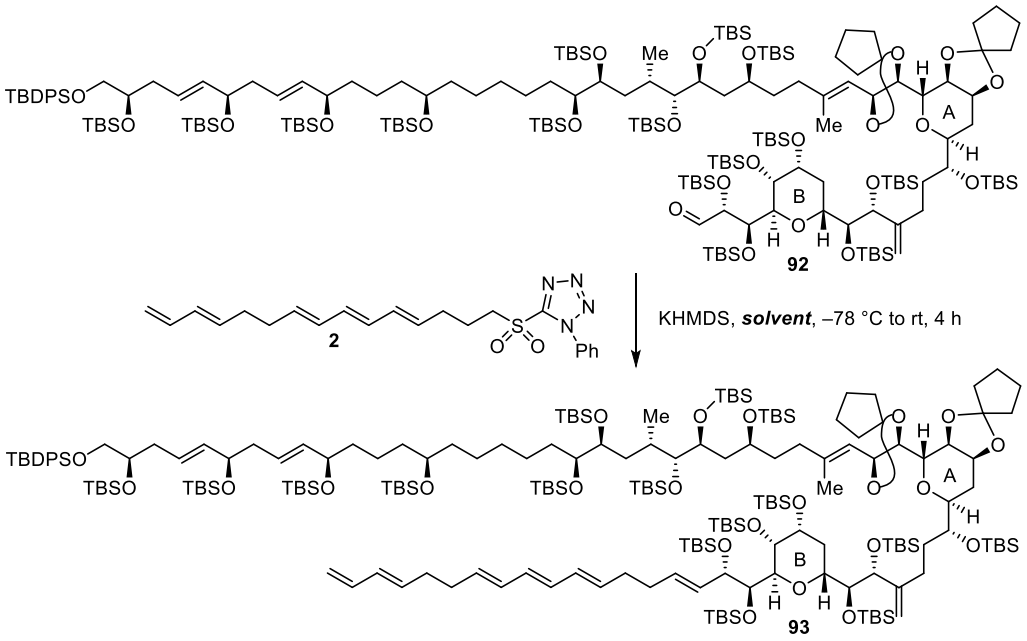
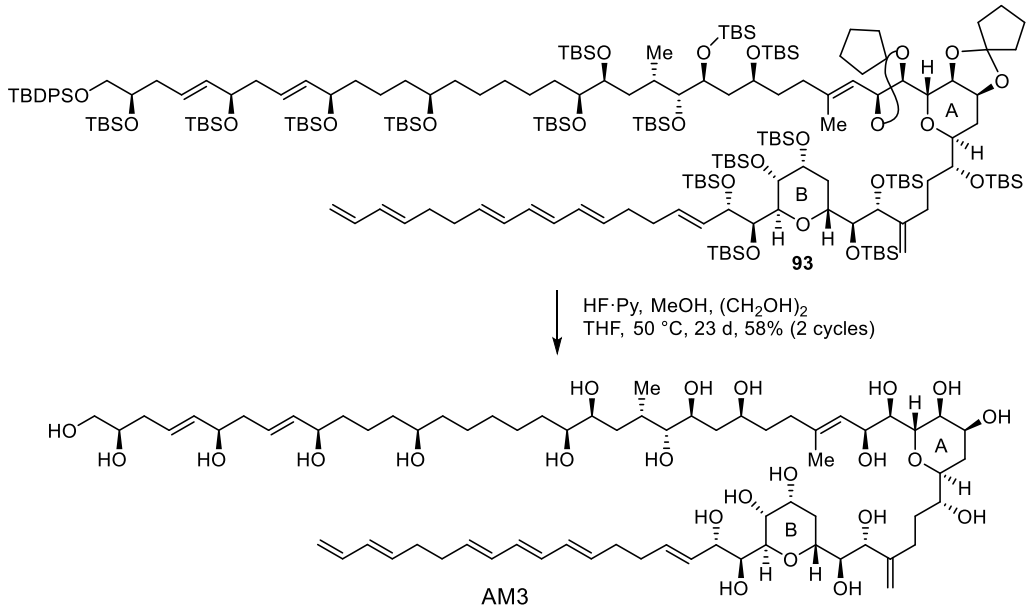


Table 3-3-2. Julia–Kocienski olefination between **92** and **2**.

entry	***solvent***	yield/%	*E/Z* ratio
1	THF/toluene = 7.5:1	67	2:1
2	THF	79	4:1
3	THF/HMPA = 4:1	75	10:1

The careful global deprotection of silyl groups and cyclopentyliden acetals was achieved by treatment with HF·Py in THF followed by addition of ethylene glycol and methanol to afford AM3 in 58% yiled (two cycles) after purification by HPLC.



Scheme 3-3-5. Total synthesis of AM3.

The spectral data for the synthetic specimen were in agreement with those for natural product (Figure 3-3-1, 3-3-2, 3-3-3, 3-3-4, Table 3-3-3) including the sign and magnitude of the specific rotation (natural product: $[\alpha]_D^{27}$ = –11.3, synthetic specimen: $[\alpha]_D^{26}$ = –11.4), confirming the structure of AM3 revised in chapter 2. Thus, the first total synthesis of AM3 has been achieved, revealing its true structure after more than twenty years since its first discovery. The antifungal activity of the synthetic specimen was evaluated by the disk diffusion method against fungus *Aspergillus niger* (NBRC No. 31012), and compared with that of natural product. The MIC balue of the synthetic specimen was identical to that of natural product (8 μg/disk). The

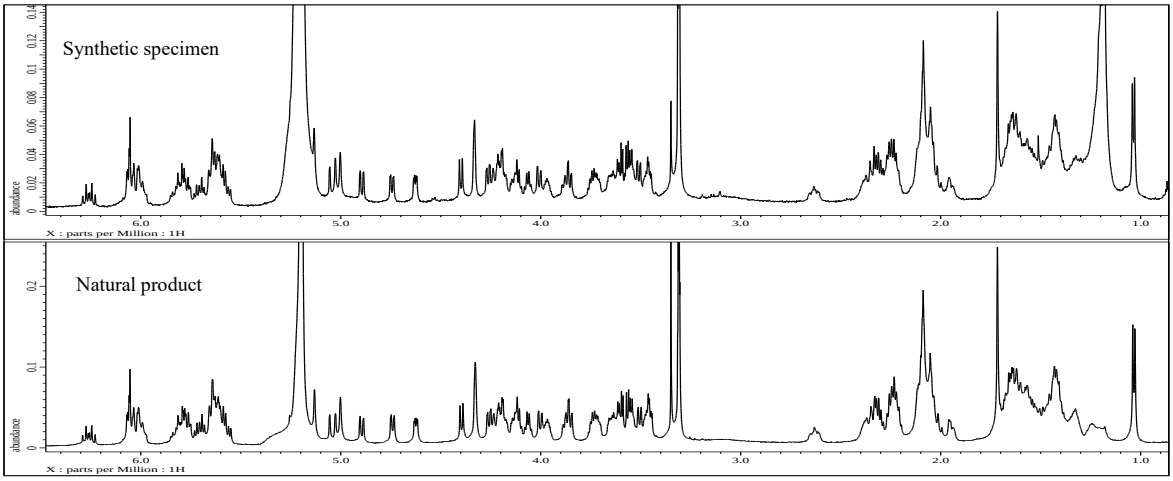


Figure 3-3-1. Comparison of ^{1}H NMR data of synthetic product and natural product (600 MHz, C_5D_5N/CD_3OD = 2:1).

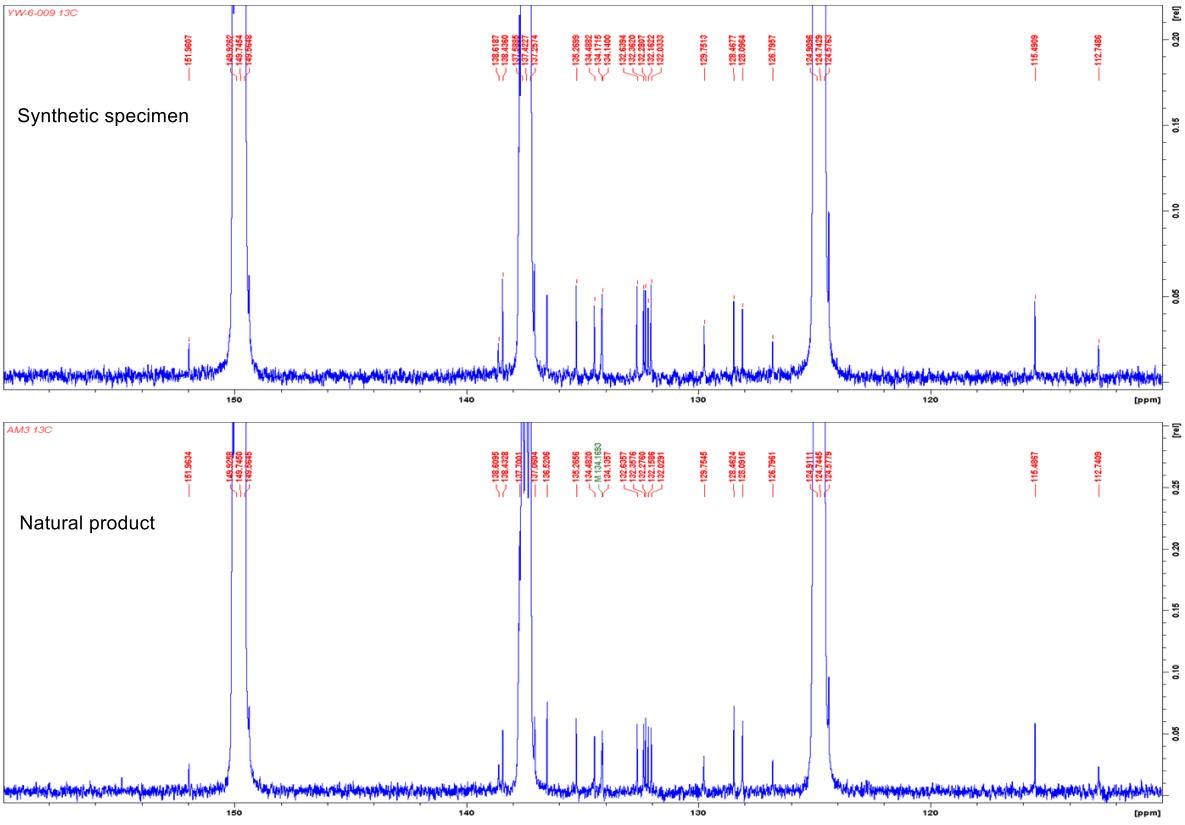


Figure 3-3-2. Comparison of ^{13}C NMR spectrum of synthetic product and natural product (150 MHz, C_5D_5N/CD_3OD = 2:1, 160.0–110.0 ppm).

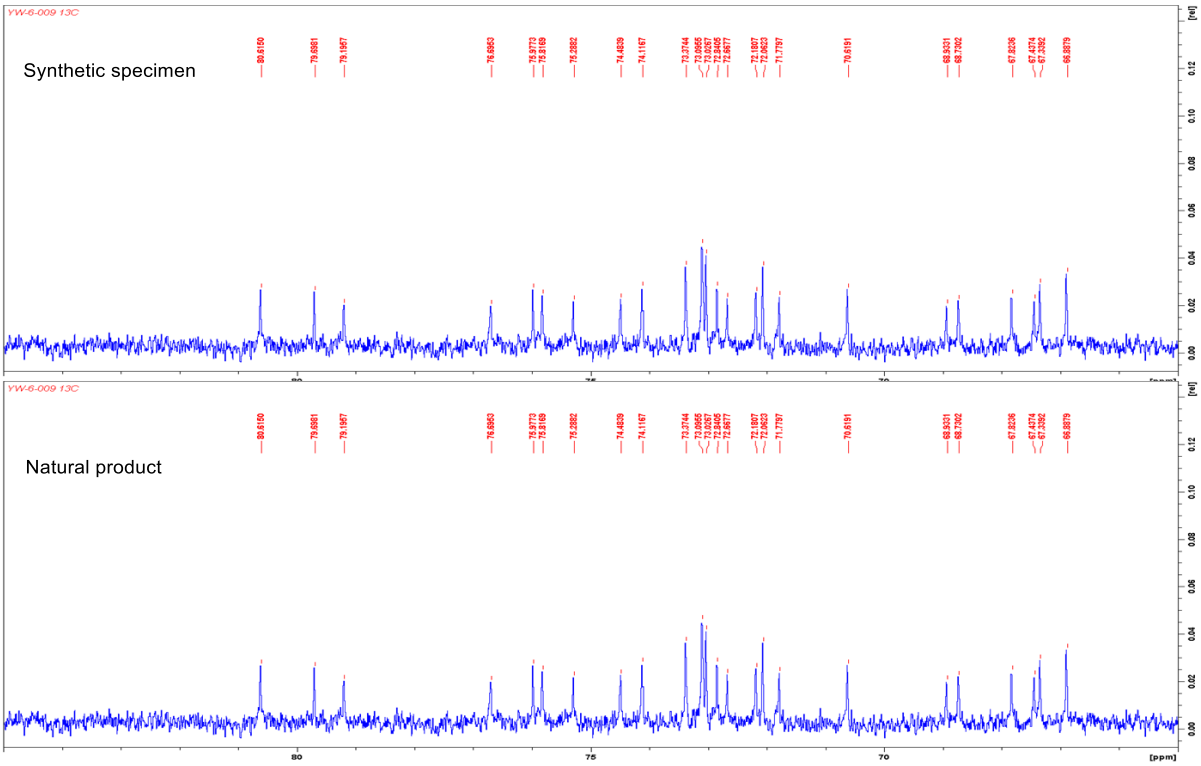


Figure 3-3-3. Comparison of ^{13}C NMR spectrum of synthetic product and natural product (150 MHz, C_5D_5N/CD_3OD = 2:1, 85.0–65.0 ppm).

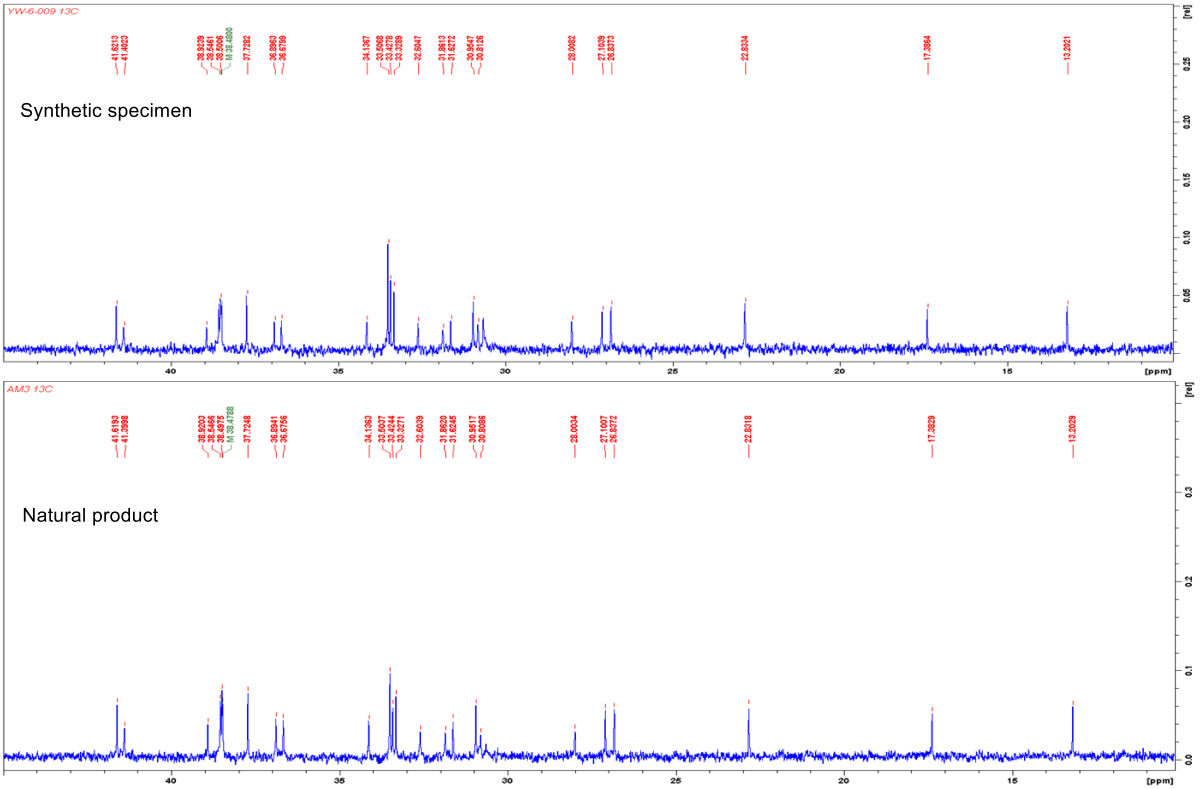


Figure 3-3-4. Comparison of ^{13}C NMR spectrum of synthetic product and natural product (150 MHz, C_5D_5N/CD_3OD = 2:1, 45.0–10.0 ppm).

Table 3-3-3. Comparison of NMR data of synthetic sample and natural product. ^{1}H NMR (600 MHz, C_5D_5N/CD_3OD = 2:1). ^{13}C NMR (150 MHz, C_5D_5N/CD_3OD = 2:1)

^{1}H					^{13}C			
carbon No.	natural	synthetic	Δppm		carbon No.	natural	synthetic	Δppm
1H	3.53	3.56	−0.03		1	66.9	66.9	0.0
1L	3.58	3.58	0.00		2	73.0	73	0.0
2	3.74	3.73	0.01		3	37.7	37.7	0.0
3H	2.22	2.23	−0.01		4	128.5	128.5	0.0
3L	2.31	2.31	0.00		5	136.5	136.5	0.0
4	5.76	5.76	0.00		6	73.1	73.1	0.0
5	5.61	5.61	0.00		7	41.6	41.6	0.0
6	4.11	4.1	0.01		8	128.1	128.1	0.0
7H	2.25	2.24	0.01		9	137.2	137.1	0.1
7L	2.29	2.29	0.00		10	73.4	73.4	0.0
8	5.69	5.7	−0.01		11	38.5	38.5	0.0
9	5.56	5.56	0.00		12	22.8	22.8	0.0
10	4.06	4.06	0.00		13	38.5	38.5	0.0
11H	1.52	1.51	0.01		14	72.1	72.1	0.0
11L	1.57	1.54	0.03		15	38.5	38.5	0.0
12H	1.43	1.42	0.01		16	26.8	26.8	0.0
12L	1.6	1.6	0.00		17	31.0	31	0.0
13	1.43	1.42	0.01		18	27.1	27.1	0.0
14	3.54	3.53	0.01		19	34.1	34.1	0.0
15	1.43	1.42	0.01		20	76.0	76	0.0
16H	1.34	1.32	0.02		21	73.1	73.1	0.0
16L	1.45	1.45	0.00		22	38.9	38.9	0.0
17H	1.25	1.25	0.00		23	31.6	31.6	0.0
17L	1.33	1.32	0.01		68	13.2	13.2	0.0
18H	1.38	1.37	0.01		24	79.7	79.7	0.0
18L	1.56	1.56	0.00		25	72.8	72.8	0.0
19H	1.48	1.49	−0.01		26	41.4	41.4	0.0
19L	1.56	1.56	0.00		27	71.8	71.8	0.0
20	3.46	3.46	0.00		28	36.9	36.9	0.0
21H	3.63	3.64	−0.01		29	36.7	36.7	0.0
21L	3.63	3.64	−0.01		30	138.6	138.6	0.0
22H	1.58	1.59	−0.01		69	17.4	17.4	0.0
22L	1.63	1.65	−0.02		31	126.8	126.8	0.0

23	2.32	2.36	−0.04
68	1.01	1.02	−0.01
24	3.45	3.45	0.00
25	3.86	3.86	0.00
26H	1.63	1.65	−0.02
26L	2.08	2.11	−0.03
27	3.95	3.96	−0.01
28H	1.65	1.65	0.00
28L	1.65	1.65	0.00
29H	2.10	2.09	0.01
29L	2.21	2.22	−0.01
69	1.71	1.71	0.00
31	5.63	5.64	−0.01
32	4.72	4.73	−0.01
33	3.83	3.84	−0.01
34	4.22	4.25	−0.03
35	4.29	4.32	−0.03
36	4.12	4.12	0.00
37H	1.92	1.94	−0.02
37L	2.01	2.01	0.00
38	3.60	3.61	−0.01
39	3.71	3.71	0.00
40H	1.68	1.68	0.00
40L	2.05	2.08	−0.03
41H	2.23	2.23	0.00
41L	2.59	2.6	−0.01
70H	5.00	5	0.00
70L	5.13	5.12	0.01
43	4.38	4.39	−0.01
44	3.50	3.5	0.00
45	4.21	4.21	0.00
46H	1.64	1.63	0.01
46L	2.30	2.32	−0.02
47	4.17	4.17	0.00
48	4.30	4.32	−0.02
49	3.98	4	−0.02
50	4.18	4.18	0.00

32	67.8	67.8	0.0
33	72.6	72.7	-0.1
34	79.2	79.2	0.0
35	68.9	68.9	0.0
36	67.4	67.4	0.0
37	30.6	30.7	-0.1
38	75.8	75.8	0.0
39	74.5	74.5	0.0
40	32.6	32.6	0.0
41	28.0	28	0.0
42	151.9	152	-0.1
70	112.8	112.7	0.1
43	76.7	76.7	0.0
44	75.3	75.3	0.0
45	70.6	70.6	0.0
46	31.8	31.9	-0.1
47	67.3	67.3	0.0
48	68.7	68.7	0.0
49	80.6	80.6	0.0
50	72.1	72.2	-0.1
51	74.1	74.1	0.0
52	129.7	129.8	-0.1
53	134.2	134.2	0.0
54	33.5	33.5	0.0
55	33.5	33.5	0.0
56	134.1	134.1	0.0
57	132.4	132.4	0.0
58	132.3	132.3	0.0
59	132.2	132.2	0.0
60	132.0	132	0.0
61	134.5	134.5	0.0
62	33.4	33.4	0.0
63	33.3	33.3	0.0
64	135.3	135.3	0.0
65	132.6	132.6	0.0
66	138.4	138.4	0.0
67	115.5	115.5	0.0

51	4.59	4.62	−0.03
52	5.75	5.78	−0.03
53	5.80	5.8	0.00
54	2.05	2.04	0.01
55	2.09	2.08	0.01
56	5.59	5.59	0.00
57	6.05	6.04	0.01
58	5.97	5.98	−0.01
59	5.98	5.99	−0.01
60	5.99	5.99	0.0
61	5.62	5.6	0.02
62	2.06	2.05	0.01
63	2.08	2.07	0.01
64	5.62	5.61	0.01
65	6.01	6	0.01
66	6.25	6.25	0.00
67H	4.89	4.88	0.01
67L	5.05	5.03	0.02

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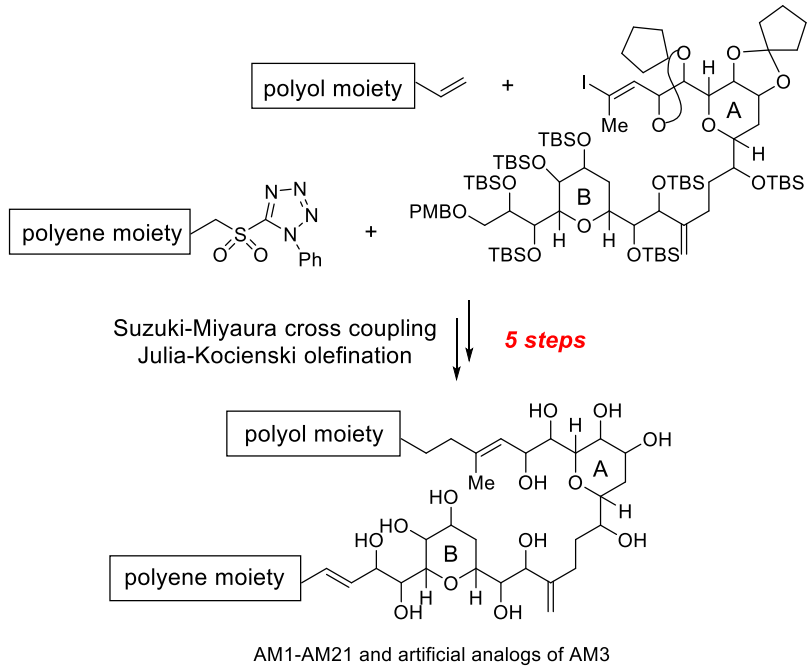
Chapter 4. Structure–Activity Relationship Study

4-1. Design of artificial analogs

The established method for the total synthesis of AM3 could serve as a general strategy for synthesizing not only other naturally occurring congeners but also various designed analogs by changing the coupling partners corresponding to the polyol and polyene segments via Suzuki–Miyaura coupling and Julia–Kocienski olefination (Scheme 4-1-1). Recently, design and syntheses of simplified analogs of natural products have been a trend in drug discovery.[1] For instance, eribulin, a cancer treatment drug,[2] was developed by the Kishi and Eisai groups as a designed analog of a natural product, halichondrin B. The molecular weight (MW) was reduced by 34% [eribulin (MW 730) vs. halichondrin B (MW 1111)].



Scheme 4-1-1. General strategy for synthesizing amphidinol analogs.

Based on the concept of minimum structure requirement, we expected that it would be possible to develop a simplified analog of AM3 while retaining the antifungal activity. Focusing on the common core structure among amphidinol congeners, truncated analogs **94** (MW 955) and **95** (MW 983) corresponding to the C21–C67 and C20−C67 section of AM3 were designed. If these compounds elicited antifungal activity, the MW could be reduced by 28% or 26%.

Furthermore, the bis-THP moiety of AM3 is completely conserved among AM analogs, it is assumed that bis-THP ring has a critical role for its antifungal activity. To investigate the role of bis-THP moiety, proposed structure type C21–C67 analog **96** and C43*epi*-C21–C67 analog **97** were also designed as artificial molecules. Because both of the bis-THP fragments corresponding to proposed structure and C43-*epimer* had been already synthesized in chapter 2, **96** and **97** is easy to be synthesized.

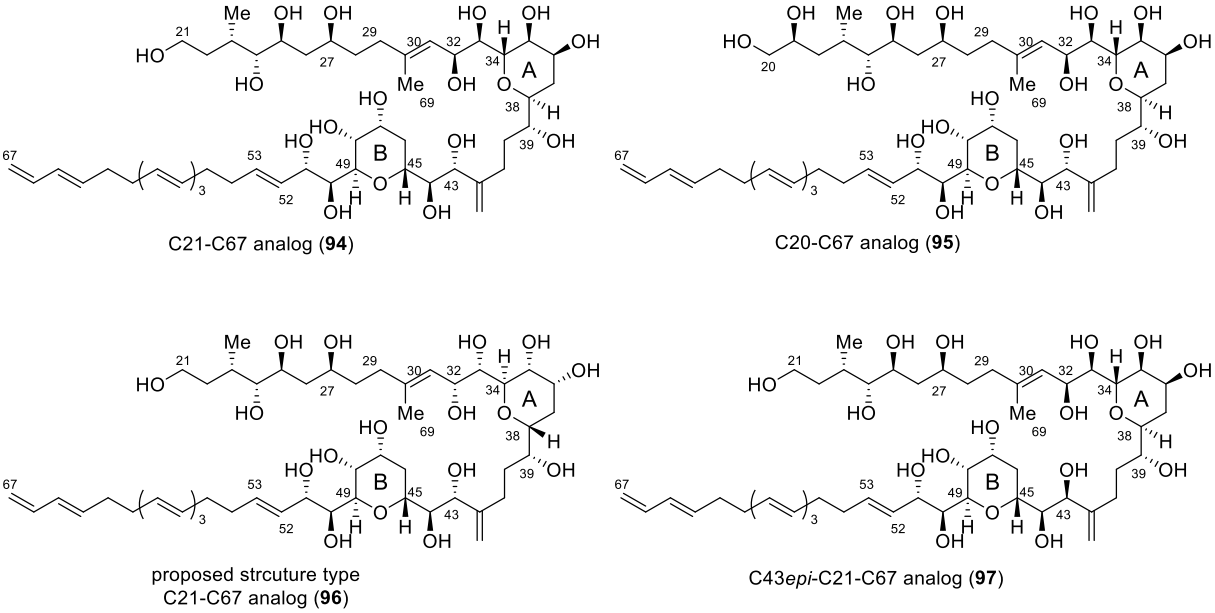
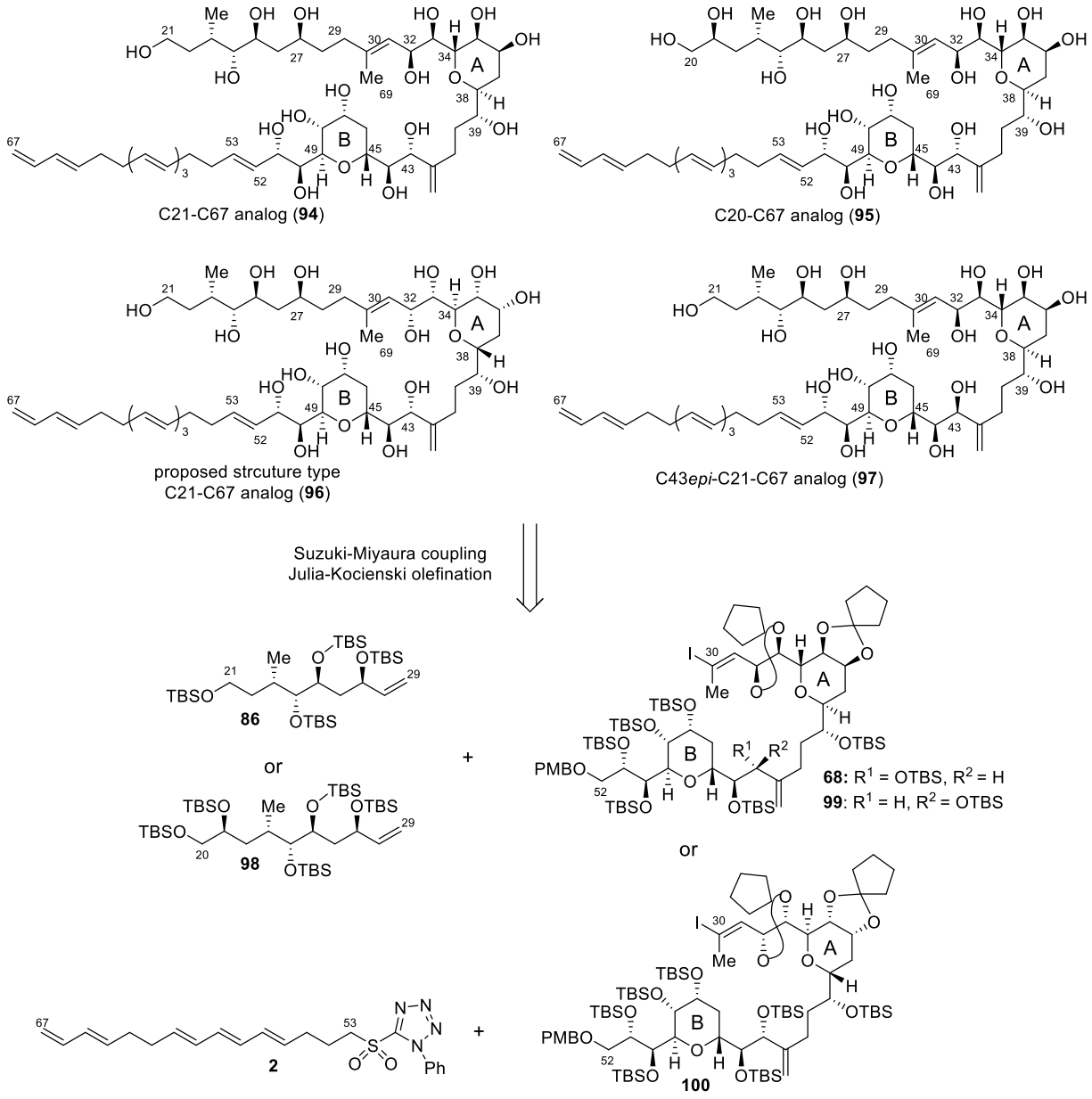


Figure 4-1-1. Design of artificial analogs.

4-2. Synthesis plan

Synthesis plan of artificial analogs **94**–**97** is shown in Scheme 4-2-1. The analogs would be synthesized via Suzuki–Miyaura coupling between polyol fragment **86** or **98** and bis-THP fragment **68** or **99** or **100** followed by Julia–Kocienski olefination with polyene fragment **2**.



Scheme 4-2-1. Synthesis plan of artificial analogs of AM3.

4-3. Synthesis of artificial analogs

4-3-1. The C21–C67 analog

Suzuki–Miyaura coupling of polyol fragment **86** and AB ring fragment **68** was examined. Unexpectedly, when the reaction was carried out with 1 M cesium carbonate, the yield was medium as 45% (entry 1). Although the condition using 3 M base was also attempted, the yield was decreased (entry 2). But surprisingly, compound **101** was obtained in excellent yield with an unusual condition which adding water to the mixture under conditions of entry 1 to dilute 3 M Cs_2CO_3 aq to 1 M (entry 3).

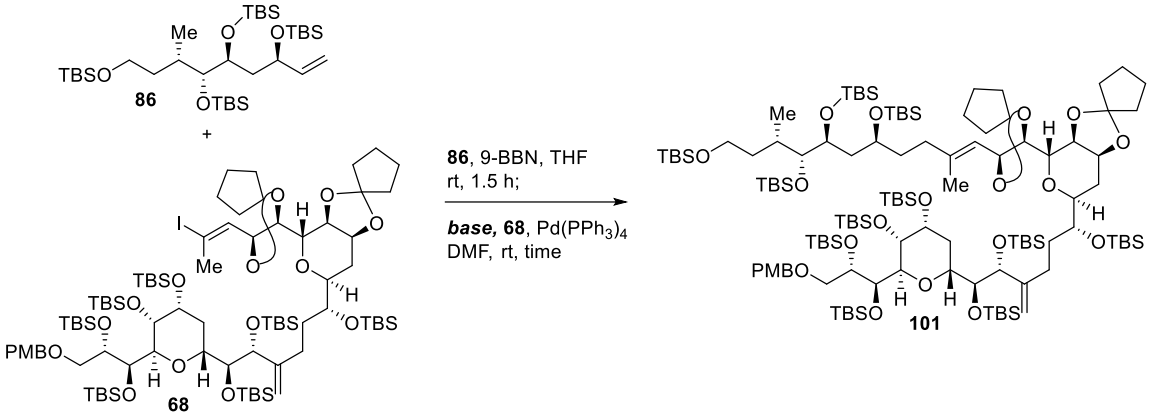


Table 4-3-1. Effect of base concentration for Suzuki–Miyaura coupling of **86** and **68**.

entry	***base***	$Pd(PPh_3)_4$/eq	time	yield/%
1	1 M Cs_2CO_3 aq	0.25 (+ 0.25)	1 h	45
2	3 M Cs_2CO_3 aq	0.25 (+ 0.25)	1.5 h	29
3	3 M→1 M Cs_2CO_3 aq (adding water)	0.25	15 /15 min	80

Although the reaction mechanism of Suzuki–Miyaura coupling is still controversial, the present results can be explained as shown in Figure 4-2-1. Hydroboration of **67** or **86** with 9-BBN gives alkylborane A. Oxidative addition of iodoolefin **68** with Pd(0) catalyst furnishes Pd(II) complex **D** (k_1, 10^4 faster than k_2),[3] which reacts with alkylborane A via coordination of the oxygen atom to the borane (intermediate **E**), to afford the coupling product **91** or **101**, respectively. Formation of the hydroxo Pd(II) complex **D** might occur in the surface of the organic and aqueous phases (or aqueous phase). Therefore, under conditions ***a*** (3 M Cs_2CO_3 aq), formation of **D** might be retarded due to the low accessibility (or low solubility) of Pd(II) iodide complex **C** in the organic phase. This salting out effect due to the large hydrophobic property of **C** results in the low yield of the coupling products **91** (42%) and **101** (29%).

Under condition ***b*** (1 M Cs_2CO_3 aq), formation of hydroxo Pd(II) complex **D** would be accelerated by reducing the concentration of Cs_2CO_3 aq to react with alkylborane A giving **91** in 77% yield. However, in the case of alkylborane **A** from **86**, formation of borate **B** would be accelerated under condition ***b*** to inhibit the reaction with **D**, giving **101** in 45% yield. Under conditions ***c***, dilution of Cs_2CO_3 aq by adding water was carried out at the final steps, therefore, the alkylborane could react with hydroxo Pd(II) complex **D** immediately prior to the formation of borate **B** ($k_3 > k_4$) to form coupling product in good yield (80%). Alternatively, it is reported that borate **B** is more reactive than alkylborane **A** to react with Pd(II) iodide complex **C** to form intermediate **F** via elimination of I^-.[4] However, the present results suggest that the reaction proceed via hydroxo Pd(II) complex **D**, which reacts with alkylborane A directly. If the borate **B** is more reactive than alkylborane **A**, coupling with olefin **86** would be give better yield than **67** under both conditions ***a*** and ***b***, because formation of borate **B** from **A** is more favorable for **86**, which possesses a shorter carbon chain than **67**, due to its higher accessibility (or higher solubility) to the aqueous phase.

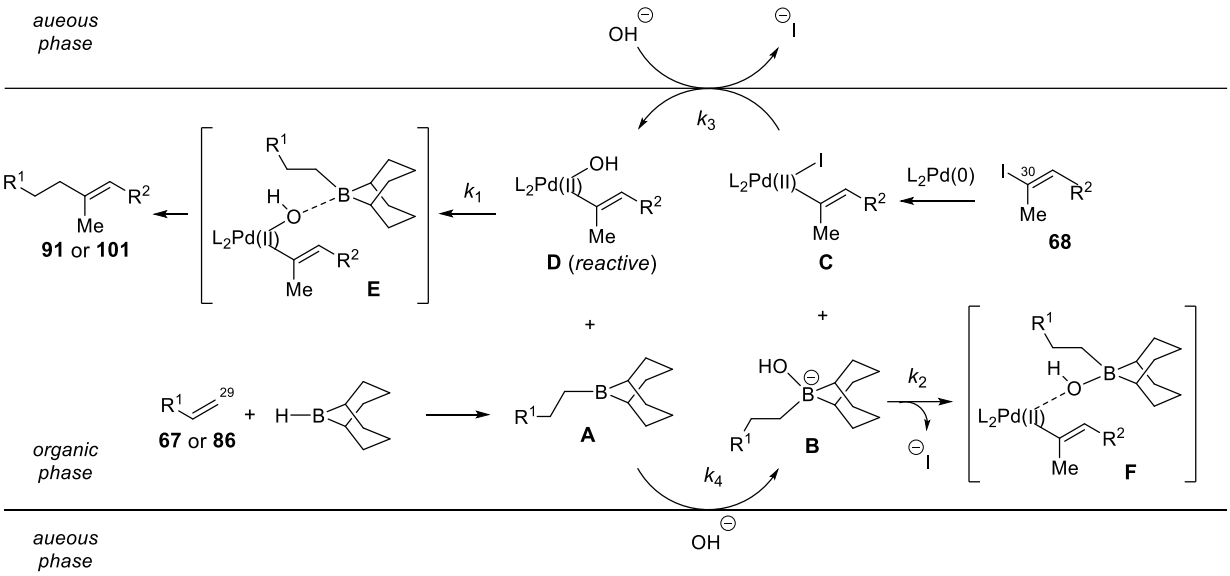
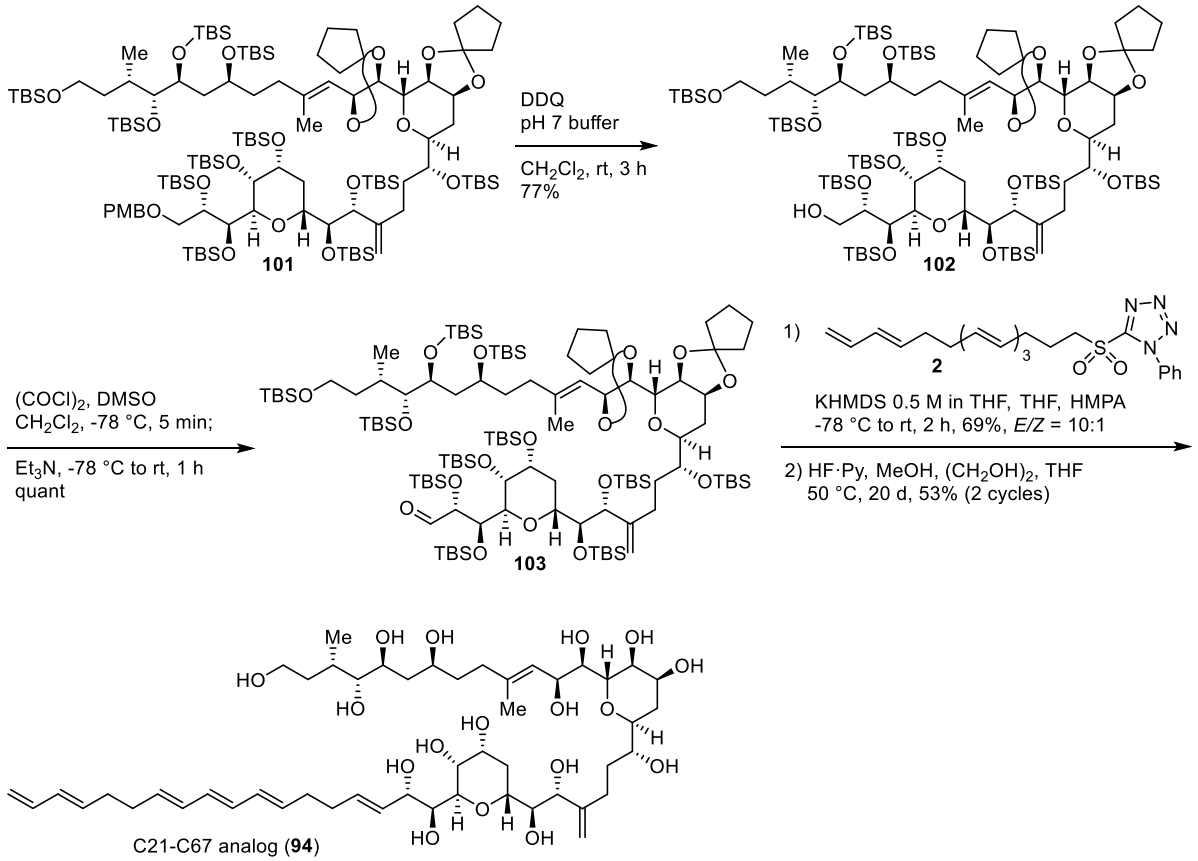


Figure 4-3-1. Plausible mechanism of Suzuki–Miyaura coupling.

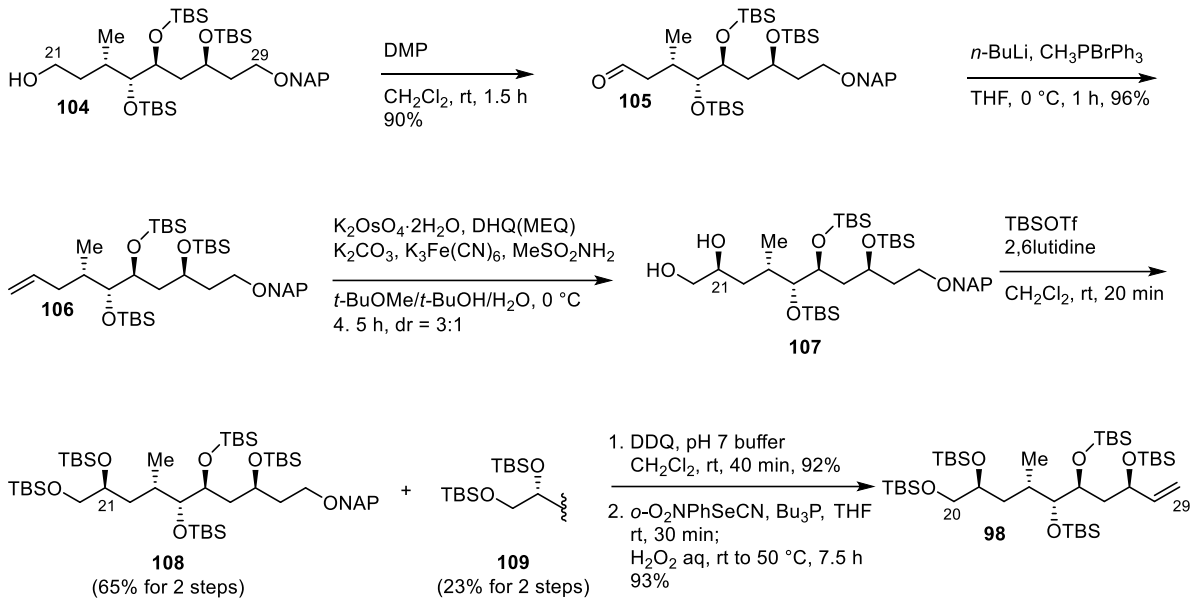
The obtained compound **101** was converted to aldehyde **103** via removal of PMB group followed by Swern oxidation. Julia–Kocienski olefination with polyene sulfone **2** proceeded successfully in 69% yield and 10:1 *E/Z* selectivity. Finally, C21–C67 analog (**94**) was synthesized via removal of all protecting groups.



Scheme 4-3-1. Synthesis of the C21–C67 analog.

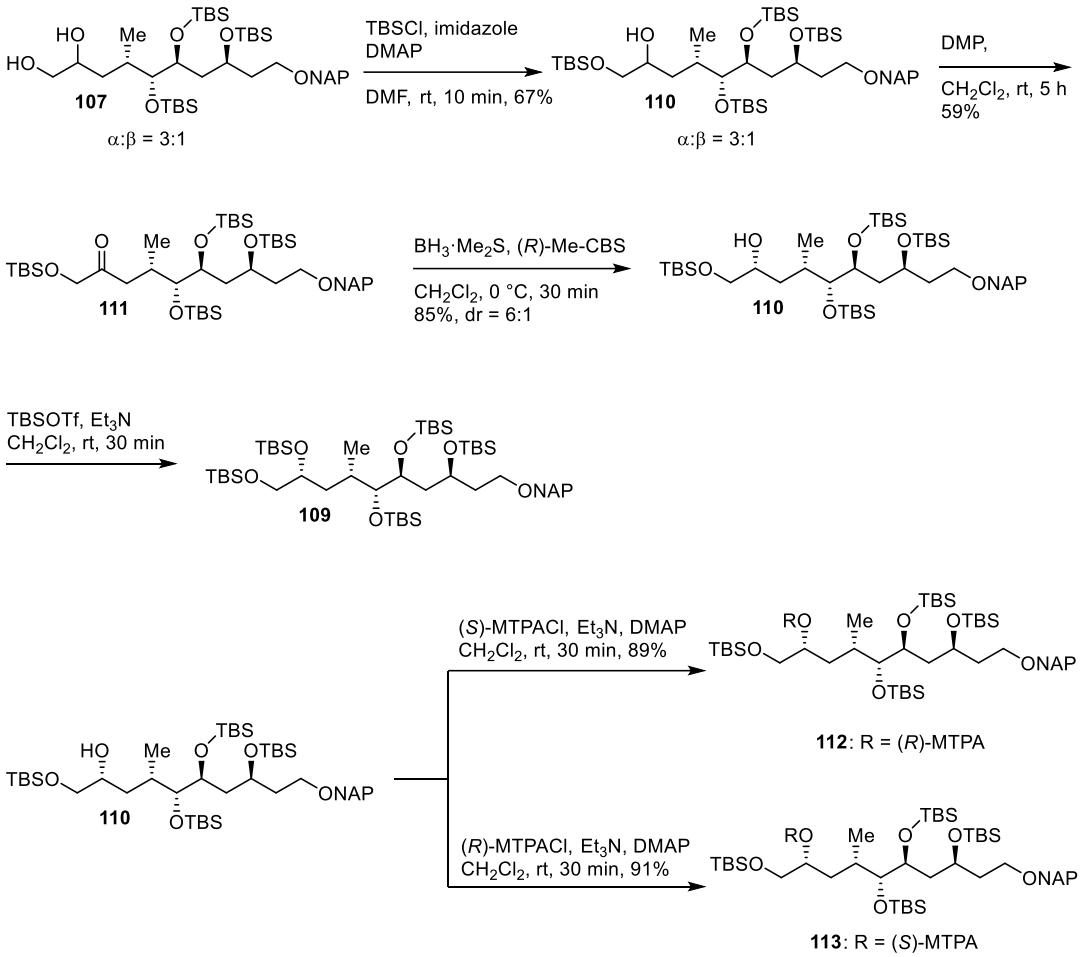
4-3-2. The C20–C67 analog

Synthesis of the C20–C29 fragment was carried out as shown in Scheme 4-3-2. Using known compound **104** as a starting material, Dess–Martin oxidation followed by Wttig reaction afforded terminal olefin **102**. To the obtained olefin **106** Sharpless asymmetric dihydroxylation followed by TBS protection was performed to give compound **108** in 65% yield for 2 steps. C20–C29 fragment **98** was synthesized via removal of NAP group of **108** followed by Nishizawa–Grieco olefination.[5]

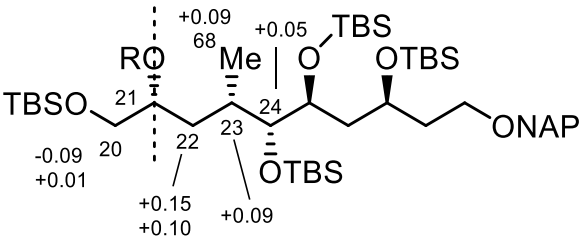


Scheme 4-3-2. Synthesis of the C20–C29 fragment.

To determine the absolute configuration at C21 of compound **107** by modified Mosher method, 3:1 diasteromixture of compound **107** was converted to ketone **111** via primary alcohol selective TBS protection followed by Dess–Martin oxidation. To the obtained ketone **111**, CBS asymmetric reduction was performed to give 6:1 diastereomixture of the secondary alcohol **110**. TBS protection of **110** afforded compound **109** which is consist with the minor product of the reaction from **106** to **108**. (*R*)- or (*S*)-MTPA esterification of compound **110** were performed to give (*R*)-MTPA ester **112** and (*S*)-MTPA ester **113** (Scheme 4-3-3). Applying the modified Mosher method, it was revealed that the absolute configuration at C21 position of compound **94** corresponding to the minor product of asymmetric dihydroxylation is *(R)*, that is, the major product of dihydroxylation is (*S*)-isomer (Figure 4-3-2).



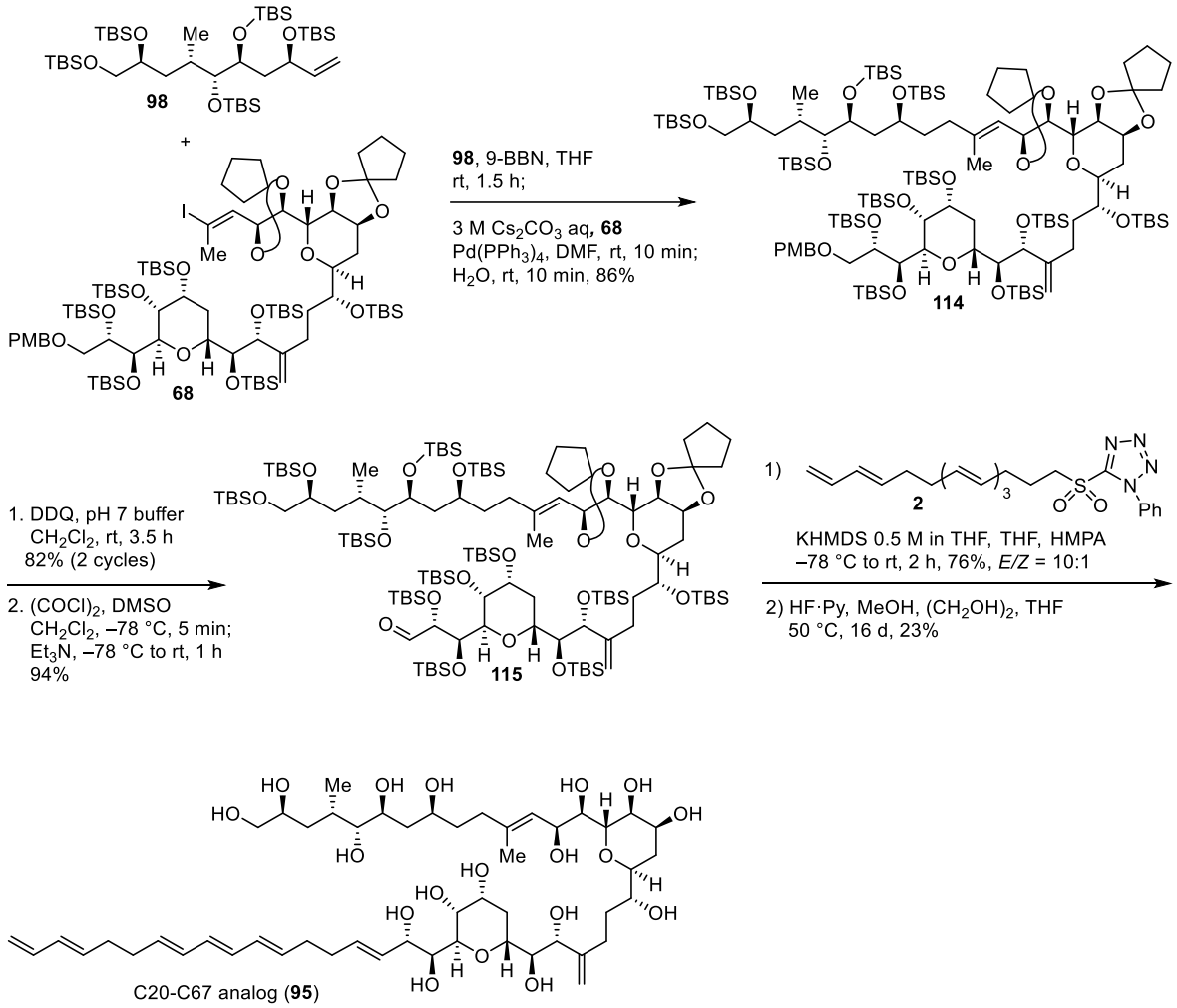
Scheme 4-3-3. Synthesis of the (*R*)- and (*S*)-MTPA ester of **110**.



proton	ppm (S)	ppm R	Δppm
20a	3.65	3.74	–0.09
20b	3.65	3.64	+0.01
21	5.1	5.13	-0.03
22a	1.78	1.63	+0.15
22b	1.46	1.36	+0.10
23	1.58	1.49	+0.09
68	0.94	0.85	+0.09
24	3.52	3.47	+0.05

Figure 4-3-2. Determination of the absolute configuration of compound **106** by modified Mosher method

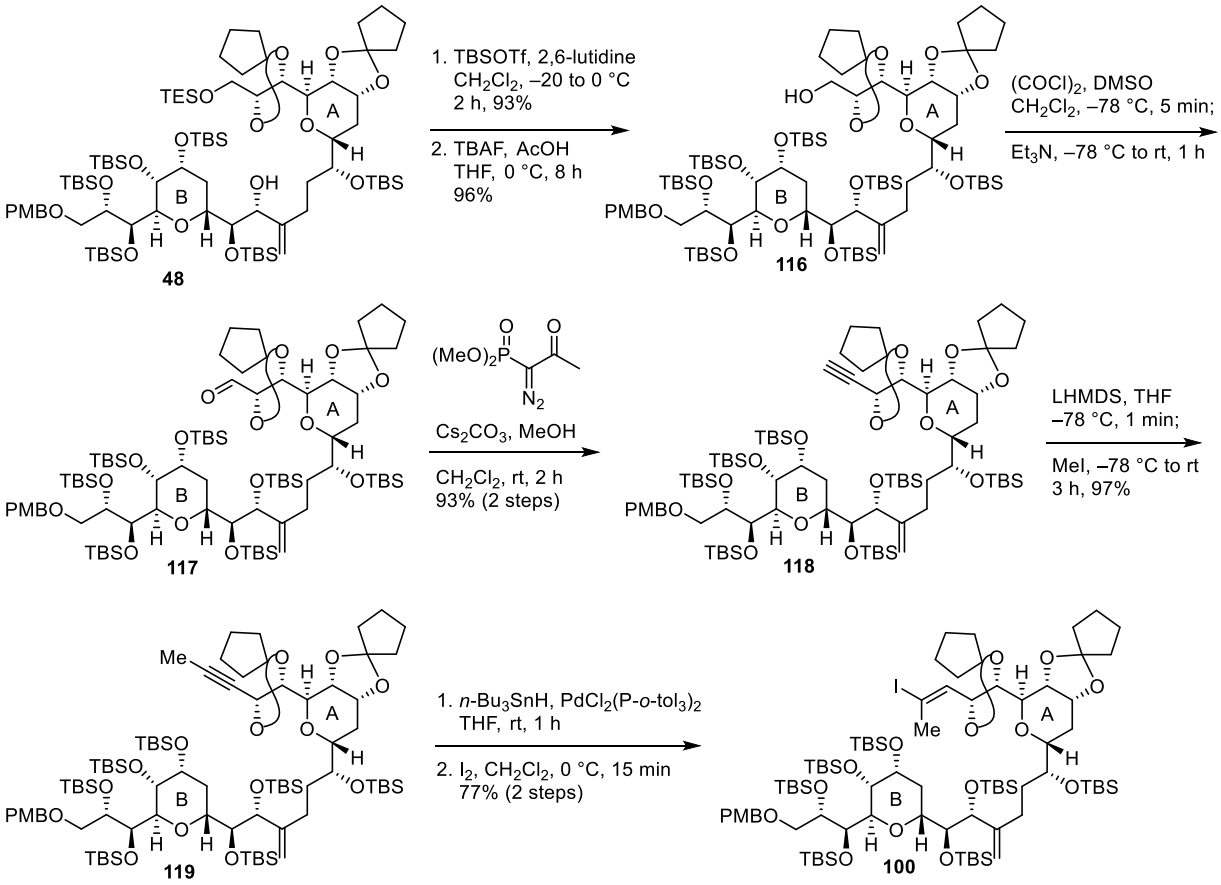
The Suzuki–Miyaura coupling between C20–C67 fragment **98** and iodoolefin **68** was attempted in the conditions ***c*** (dilution of Cs_2CO_3 aq by adding water). As a result, coupling product **114** was obtained in 86% yield. Compound **114** was converted to aldehyde **115** via removal of PMB group followed by Swern oxidation. To the obtained aldehyde **115**, Julia–Kocienski olefination with sulfone **2** was performed to give coupling product in 76% yield and 10:1 *E/Z* selectivity. C20–C67 analog (**95**) was synthesized via removal of all protecting groups.



Scheme 4-3-3. Synthesis of the C20–C67 analog.

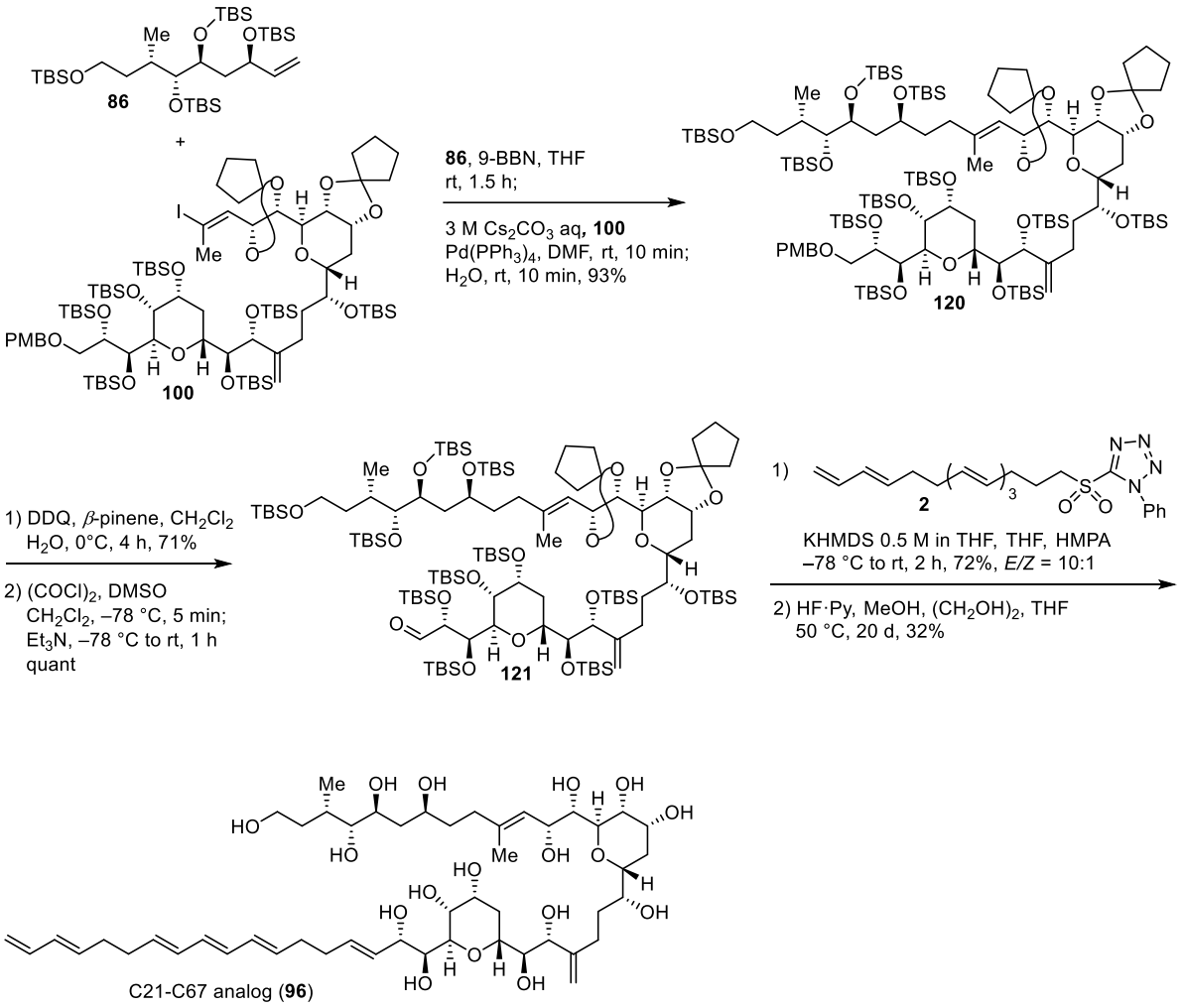
4-3-3. The C21–C67 analog corresponding to the proposed structure.

Synthesis of the AB ring fragment commenced with using compound **48** as the starting material. TBS protection, removal of the TES group, Swern oxidation followed by Ohira–Bestamn alkyne synthesis was performed to give terminal alkyne **118**. To the obtained alkyne **118**, methylation, hydrostannylation followed by iodination was performed to furnish proposed structure type AB ring fragment **100**.



Scheme 4-3-4. Synthesis of the bis THP fragment (proposed structure).

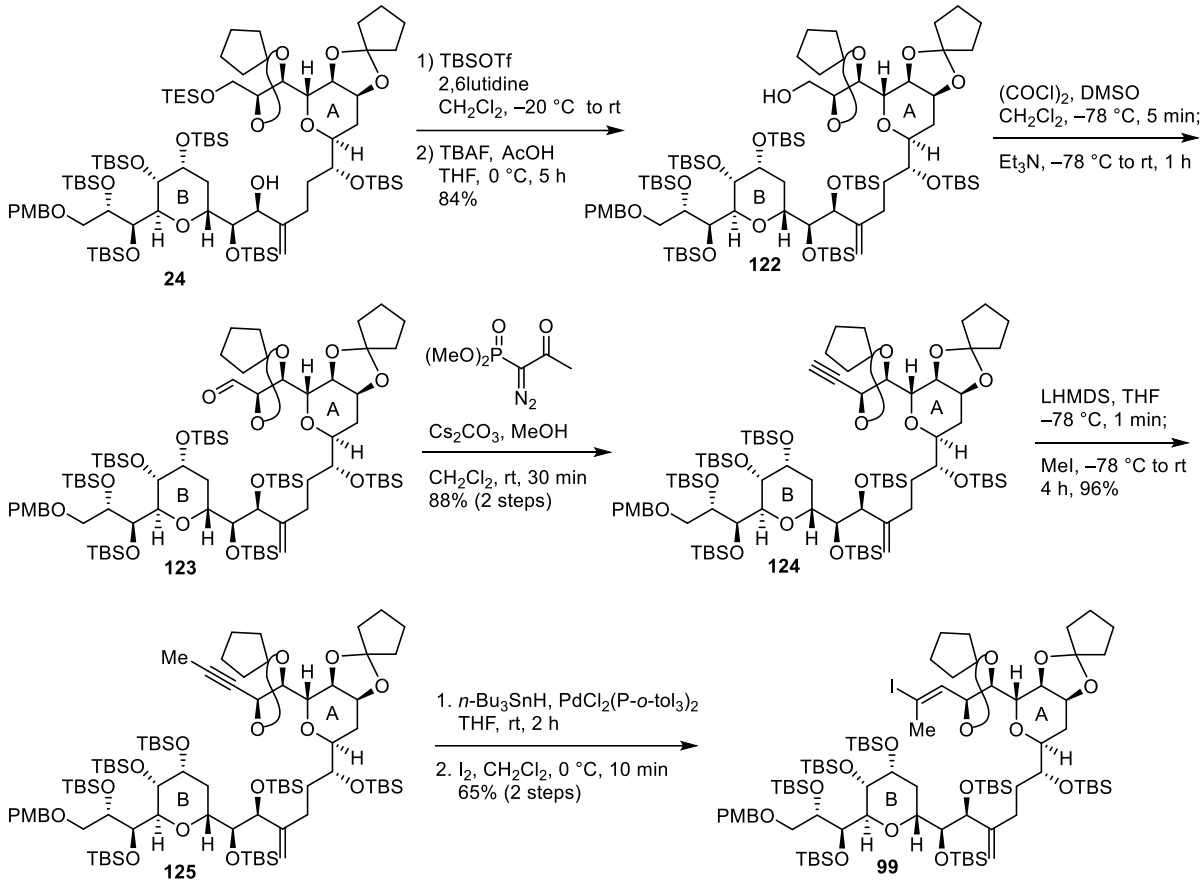
The Suzuki–Miyaura coupling between C21–C67 fragment **86** and iodoolefin **100** was attempted in the conditions ***c*** (dilution of Cs_2CO_3 aq by adding water). As a result, coupling product **120** was obtained in 93% yield. Compound **120** was converted to aldehyde **121** via removal of PMB group followed by Swern oxidation. To the obtained aldehyde **121**, Julia–Kocienski olefination with sulfone **2** was performed to give coupling product in 76% yield and 10:1 *E/Z* selectivity. Proposed structure type C21–C67 analog (**96**) was synthesized via removal of all protecting groups.



Scheme 4-3-5. Synthesis of the C21–C67 analog corresponding to the proposed structure.

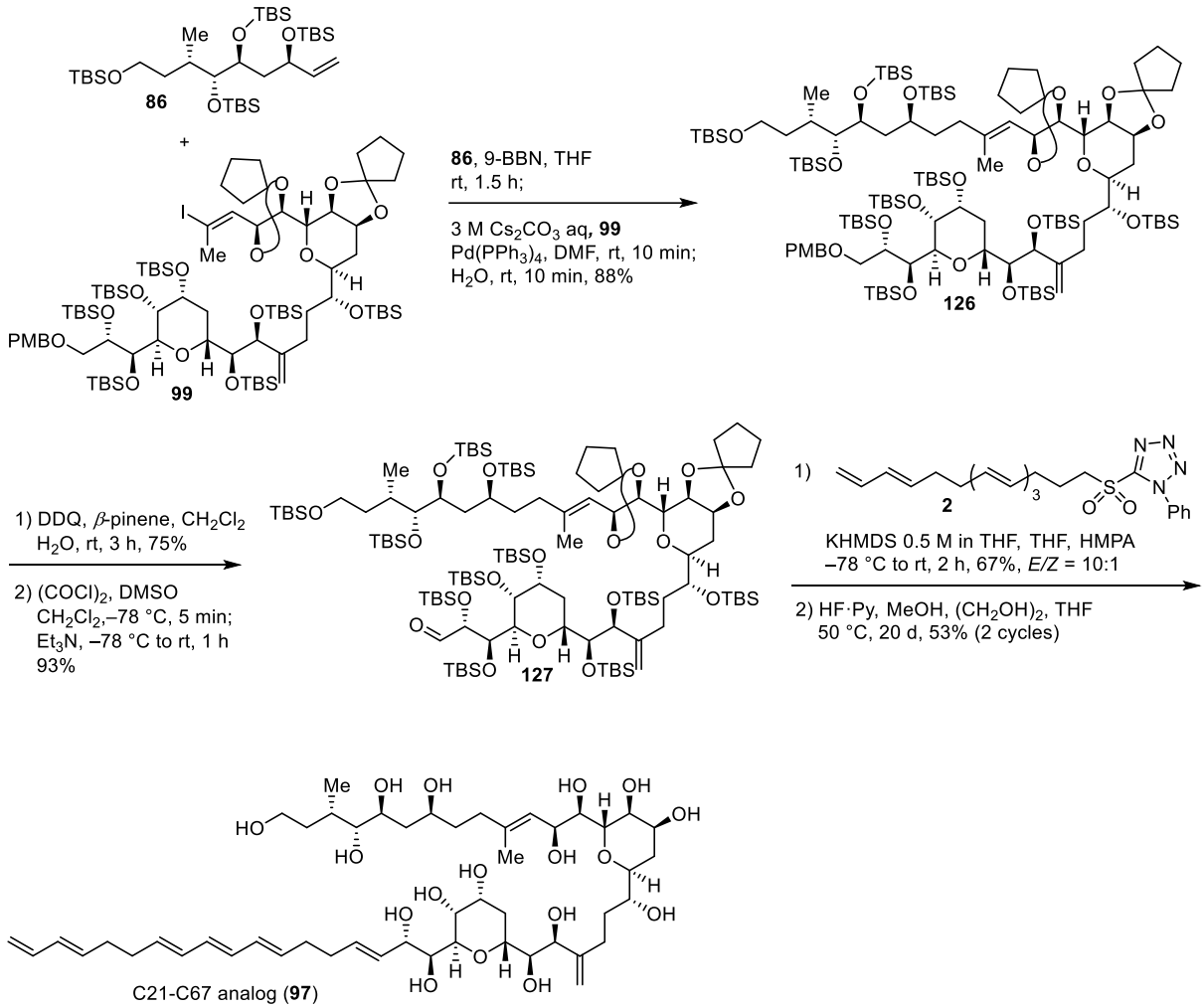
4-3-4. The C21–C67 analog corresponding to the C43 diastereomer

Synthesis of the AB ring fragment commenced with using compound **24** as the starting material. TBS protection, removal of the TES group, Swern oxidation followed by Ohira–Bestamn alkyne synthesis was performed to give terminal alkyne **124**. To the obtained alkyne **124**, methylation, hydrostannylation followed by iodination was performed to furnish proposed structure type AB ring fragment **99**.



Scheme 4-3-6. Synthesis of the bis-THP fragment (C43*epi*).

The Suzuki–Miyaura coupling between C21–C67 fragment **86** and iodoolefin **99** was attempted in the conditions ***c*** (dilution of Cs_2CO_3 aq by adding water). As a result, coupling product **126** was obtained in 88% yield. Compound **126** was converted to aldehyde **127** via removal of PMB group followed by Swern oxidation. To the obtained aldehyde **127**, Julia–Kocienski olefination with sulfone **2** was performed to give coupling product in 76% yield and 10:1 *E/Z* selectivity. C43 diastereomer type C21–C67 analog (**97**) was synthesized via removal of all protecting groups.



Scheme 4-3-7. Synthesis of the C21–C67 analog corresponding to the C43 diastereomer.

4-3-5. Comparison of NMR data of artificial analogs.

Comparison of ^{13}C NMR data between C21−C67 analog and natural product was carried out as shown in Figure 4-3-3. As a result, the ^{13}C NMR data of C21−C67 analog was almost identical to those of natural product. As a noteworthy point, there were not any deviation at C38−C41 position where the critical differences were observed between C31−C67 and natural product. This result suggested that the deviation at C38−C41 was induced by the lack of the magnetic anisotropic effect of C30−C31 olefin.

Comparison of ^{13}C NMR data of C43*epi*-C21–C67 analog with natural product was also performed as shown in Figure 4-3-4. As a result, large differences of the chemical shift were observed around C40–C45 section. Thus, it was suggested that notable alternation of the conformation is happened by the stereo inversion at C43 position. The conformational change may be induced by the formation of the intramolecular hydrogen bonding among C43-OH and C44-OH corresponding to the syn 1,2-diol. The analysis for the C21–C67 analog corresponding to the proposed structure is now progress.

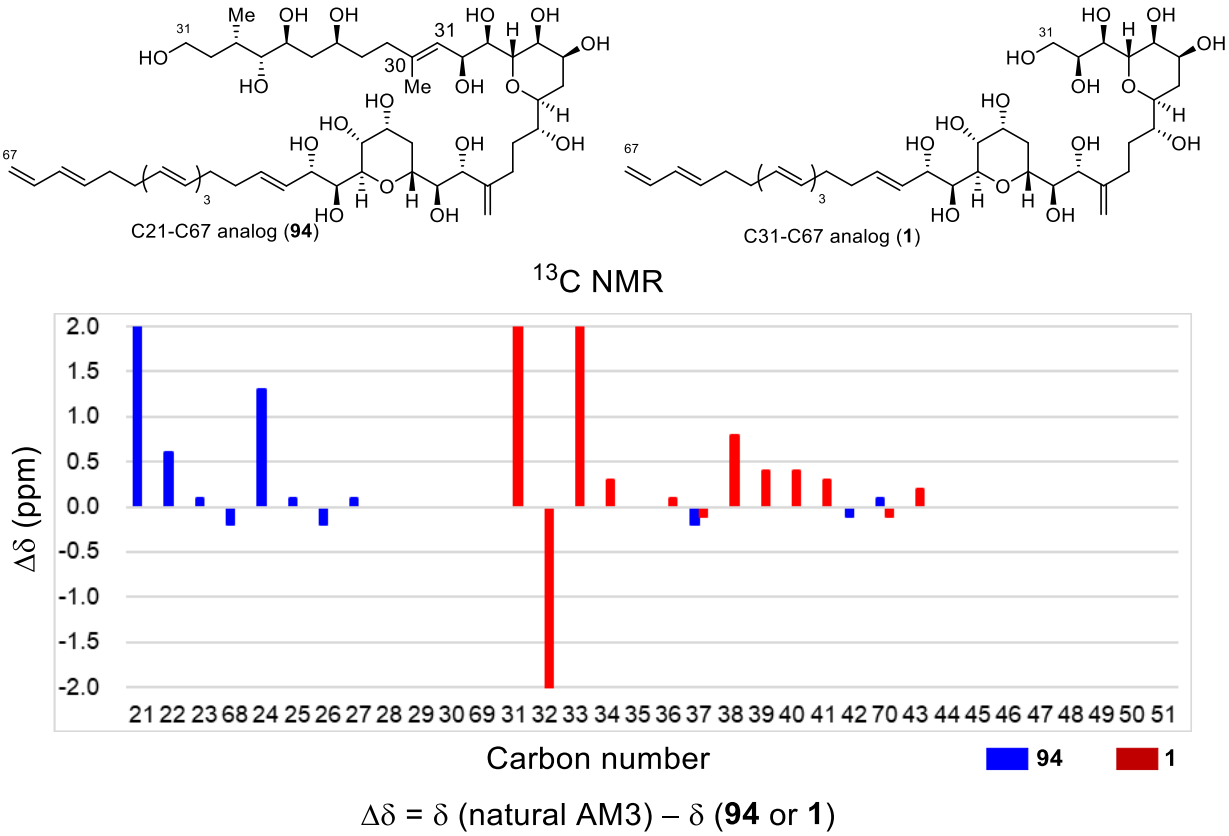


Figure 4-3-3. Comparison of ^{13}C NMR data between the natural product and C21–C67 analog or C31–C67 analog.

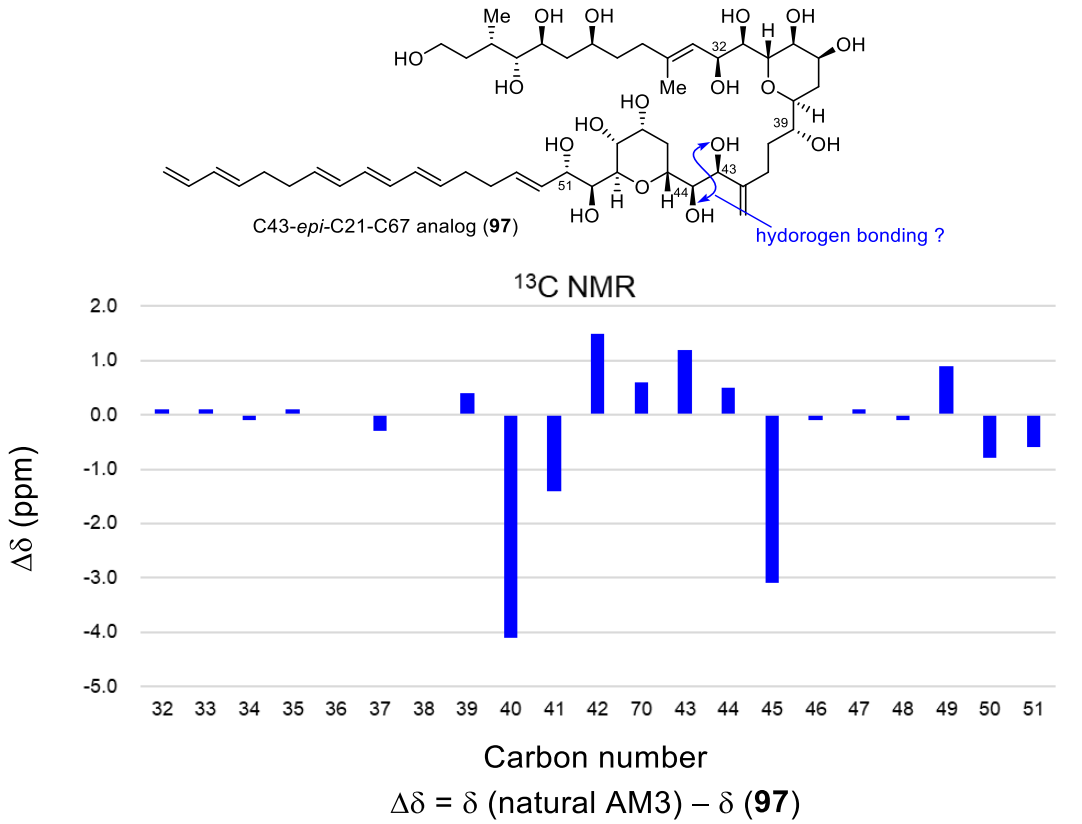


Figure 4-3-4. Comparison of the ^{13}C NMR data between the natural product and the C21–C67 analog corresponding to the C43 diastereomer.

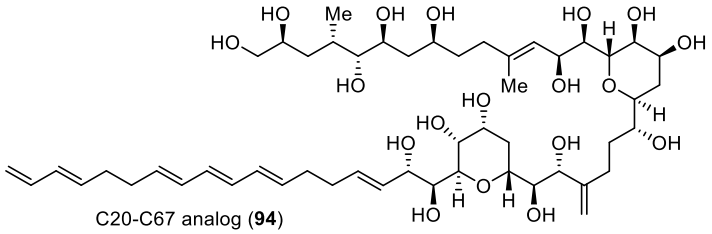
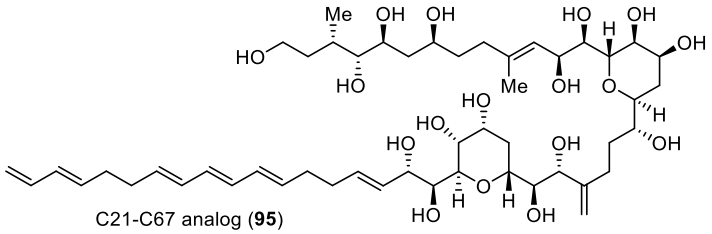
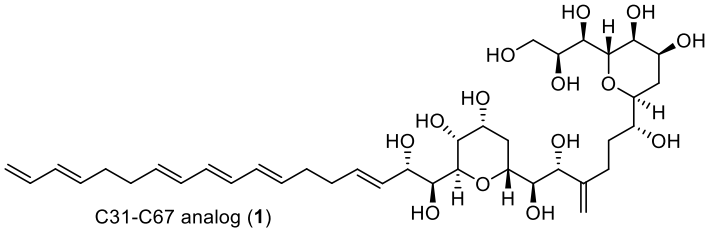
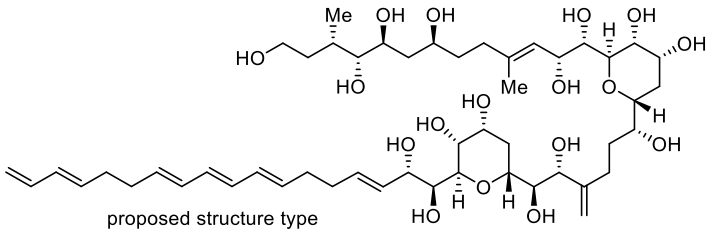
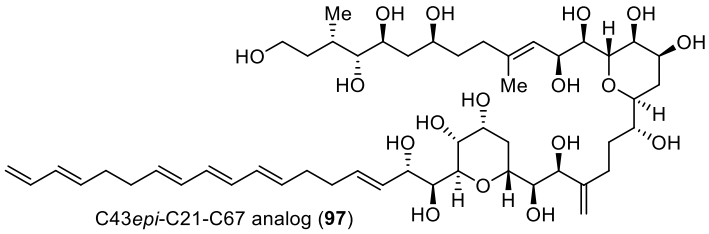
4-4. Antifungal Assay

The antifungal activity of artificial analogs was evaluated by the disk diffusion method against fungus *Aspergillus niger* (NBRC No. 31012). The results are summarized in Figure 4-4-1 and. The MIC value of C21–C67 analog (**94**) was estimated to be 20 μg/disk, which is comparable to that for AM3 (MIC = 8 μg/disk). This is the first example of a biologically active artificial analog of AM3 possessing a shorter polyol moiety. Unexpectedly, the MIC value of C20–C67 analog (**95**) was 52 μg/disk which is larger than that of C21–C67 analog. This result might be due to the primary 1,2-dilol structure at C20–C21. Because the primary 1,2-diol can easily form the intramolecular hydrogen bonding, it is assumed that the role of hydroxy group at C20 and C21 position was inhibited. Moreover, it is interesting to note that the further truncated analog **1** corresponding to the C31–C67 part of AM3 elicited no antifungal activity (>300 μg/disk). Based on these results and a comparison of the molecular structures of AM3, the C21–C67 analog (**94**), and the C31–C67 analog (**1**) as shown in Figure 4-4-2, the polyol chain from C1 to C20 is not necessary for eliciting biological activity, but the C21 to C30 section, which is a highly conserved region of amphidinol congeners (colored in red), must be important for eliciting biological activity. Although the mode-of-action of AM3 is not fully elucidated, it is considered that the hydrophobic polyene tail of AM3 is inserted into the lipid bilayer membrane, and molecular assemblage of AM3 molecules results in the formation of a pore that increases membrane permeability in a sterol dependent manner.[6] It has also been reported that a hairpin conformation in the lipid bilayer membrane is important for eliciting biological activity.[7,8] There are two hypothetical models: (i) the barrel stave model in which AM3 molecules are inserted across the lipid bilayer membrane to form a pore, and (ii) the toroidal model in which the polyene part is inserted into the lipids and the polyol part interacts with the surface of the cell membrane to form a pore (Figure 4-4-4).[9] As shown in Figure 4-4-3, the CPK model of the hairpin conformation of AM3 is compared with that of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC), a component of the lipid bimolecular membrane, showing that the molecular length of AM3 matches the thickness of the lipid bilayer membrane. On the other hand, the molecular length of truncated analog **94** does not match the thickness of the lipid bilayer membrane, but it elicits antifungal activity comparable to that of AM3. Judging from the molecular models, it would be difficult for truncated analog **94** to form a pore across the cell membrane, suggesting that the mode-of-action of **94** is not the barrel stave model but the toroidal model.

Surprisingly, both of the MIC values of proposed structure type C21–C67 analog (**96**) and C43*epi* type C21–C67 analog (**97**) were > 100 μg/disk. It is reported that the antifungal activity of almost all AM analogs require the sterols in lipid membrane and AMs recognizes the 3*β*-sterols stereospecifically.[10] Because the bis-THP ring is completely conserved partial structure, it can be related to this common feature recognizing sterols. Therefore, these results

of antifungal assay suggested that the A ring and C43 hydroxyl group have important roles relating to the recognition of the sterols.

Table 4-4-1. Results of antifungal assay of artificial analogs.

analogs	antifungal activity (MIC: μg/disk)
 C20-C67 analog (**94**)	52
 C21-C67 analog (**95**)	20
 C31-C67 analog (**1**)	>300
 proposed structure type C21-C67 analog (**96**)	>100
 C43*epi*-C21-C67 analog (**97**)	>100

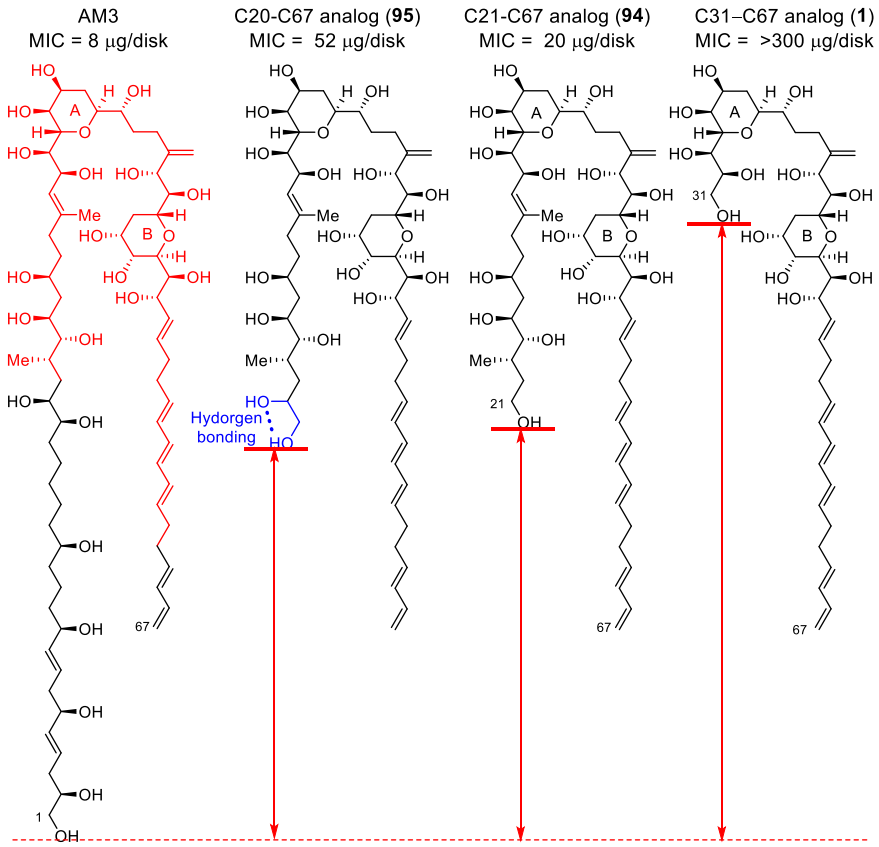


Figure 4-4-2. Comparison of the structures of AM3, the C20–C67 analog (**95**), the C21–C67 analog (**94**) and the C31–C67 analog (**1**).

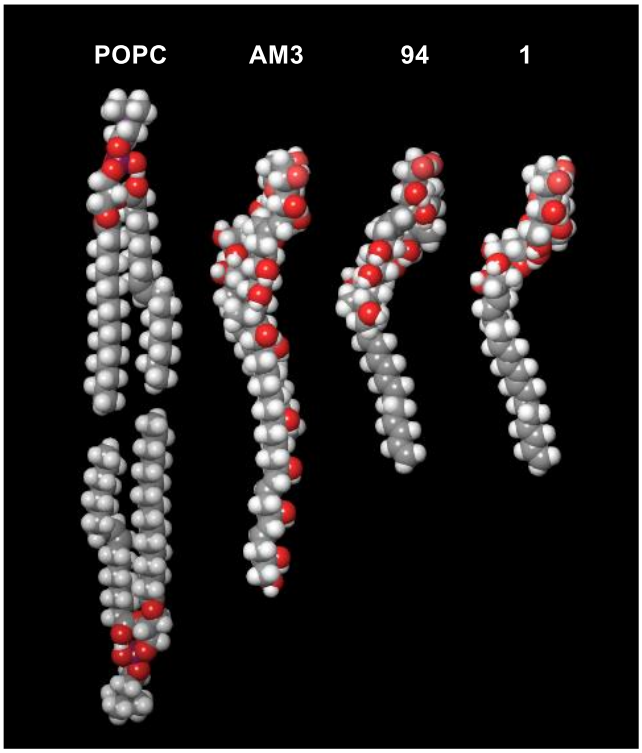


Figure 4-4-3. Comparison of the CPK models of POPC, AM3, **94** and **1**.

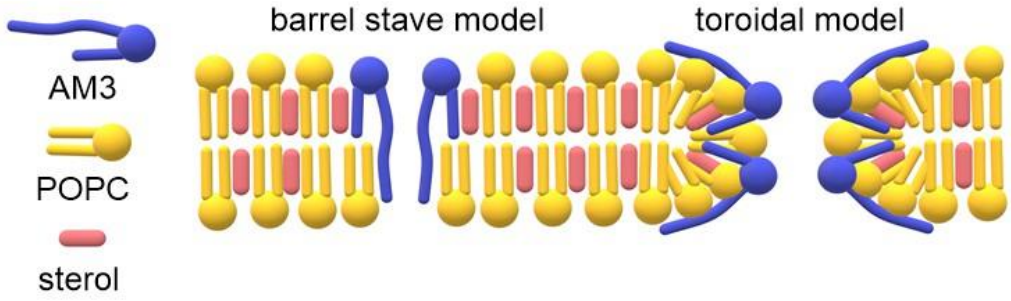


Figure 4-4-4. Hypothetical mode-of – action of AM3: barrel stave model and toroidal model.

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10. Houdai, T.; Matsumori, N.; Murata, M.; *Org. Lett.* **2008**, *10*, 4191.

Chapter 5. Conclusion

In conclusion, synthesis of the C31–C67 part of amphidinol 3 (AM3) and the diastereomer at C32–C36 and C38 were achieved to confirm the absolute configuration of the natural product. By comparison of the NMR data of synthetic partial structures with those of AM3 in combination with the degradation of the natural product, the absolute configuration of AM3 was revised to be 32*S*, 33*R*, 34*S*, 35*S*, 36*S* and 38*S*. The first total synthesis of AM3 was achieved via highly convergent three-component coupling in five steps by Suzuki–Miyaura coupling of the large segments corresponding to the C1–C29 and the C30–C52 sections, followed by introduction of the C53–C67 section by Julia–Kociensky olefination. The longest linear sequence and total steps of the present synthesis are 40 and 112 steps, respectively. The spectral data of the synthetic specimen are in accord with those of the natural product, thus, the complete structural confirmation of AM3 has been achieved after more than twenty years since its first discovery. A simplified analog of AM3 corresponding to the C21–C67 section was designed and synthesized based on the concept of minimum structure requirement, and it elicited antifungal activity comparable to that of AM3. This is the first example of a biologically active artificial analog of AM3 possessing a shorter polyol moiety than the natural product, suggesting that the mode-of-action of the artificial analog is best explained by a toroidal model. Other C21–C67 section corresponding to the proposed structure and C43 diastereomer were also synthesized. However they elicited no antifungal activity suggested that the absolute configuration at C32–C38 and C43 are crucial for antifungal activity.

Supporting Information

Synthetic Studies of Amphidinol 3

Table of contents

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. THF was distilled from sodium/benzophenone prior to use. The dehydrated solvents, CH_2Cl_2, toluene, DMF were purchased from local venders and were used without further dehydrations. $(COCl)_2$, Et_3N and Bu_3SnH were distilled before use. Ohira–Bestman reagent[1] was prepared according to the literature. All other chemicals were obtained from local venders, and used as supplied unless otherwise stated. TLC of E. Merck silica gel 60 F_{254} pre-coated plates (0.25-mm thickness) was used for the reaction analyses. For column chromatograohy, Kanto silica gel 60N (spherical, neutral, 100–210 μm) was used. For flash chromatography, Kanto silica gel 60N (spherical, neutral, 40–50 μm) was used. For reverse-phase column chromatography, waters SepPak vac (C18, 1 g/6cc) cartridge was used.

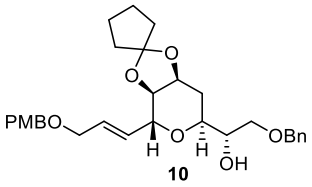
Instrumentations:

Optical roatations were recorded on a JASCO P-1010 polarimeter. IR spectra were recorded on a JASCO FT/IR-4000. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA 600, JEOL-ECS400 or Bruker AVANCE III 600 MHz (cryoprobe) spectrometer. Chemical shifts are reported in ppm drom tetramethysilane (TMS) with reference to internal residual solvent [^1H NMR: C_6HD_5 (7.16), CD_2HOD (3.31; ^{13}C NMR: C_6D_6 (128.06), CD_3OD (49.0)]. The following abbreviation are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were recorded on Bruker microTOFfocus conditions.

Biological Assay

Dried specimens of *Aspergillus niger* (NBRC 31012) obtained from the NITE Biological Resource Center (Chiba, Japan) were cultured at 25℃ in a glucose/peptone agar medium (2% glucose, 0.2% yeast extract, 0.5% peptone, 0.05% $MgSO_4$, KH_2PO_4 and 1.5% agar) for 1 weeks. An aliquot of the broth was spread onto an agar plate made of the same medium. The samples were dissolved in MeOH, spotted on to 8 mm paper disk, and placed on the plate containing *A. niger* mycelia. After incubating at 25℃ for 2 days, the zone of inhibition for each paper disk was measured.

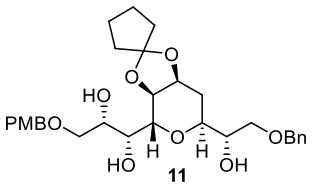
Synthetic procedures for C31–C67 analog



10

Acetal 10. To a solution of tetrahydropyran derivative **9** (530 mg, 1.13 mmol) in CH_2Cl_2 (11.3 mL) at 0 °C was added 1,1-dimethoxycyclopentane (1.2 mL, 9.0 mmol) and PPTS (56.5 mg, 0.225 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with Et_3N and diluted with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (toluene/EtOAc = 10/1 → 5/1) afforded acetal **10** (560 mg, 1.10 mmol, 97%) as a colorless syrup.

R_f = 0.50 (Hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.90 (ddd, *J* = 15.6, 5.4, 1.2 Hz, 1H), 5.80 (ddd, *J* = 15.6, 5.4, 1.2 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H) 4.53 (d, *J* = 12.0 Hz, 2H), 4.46 (s, 2H), 4.41 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.24 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.01 (d, *J* = 5.4 Hz, 2H), 3.87 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.80 (s, 3H), 3.80–3.76 (m, 2H), 3.59 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.54 (dd, *J* = 9.6, 4.8 Hz, 1H) 2.63 (d, *J* = 4.2 Hz, 1H), 1.92–1.81 (m, 4H), 1.72–1.65 (m, 6H).

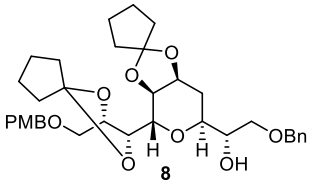


11

Triol 11. A mixture of $K_2OsO_4{\cdot}2H_2O$ (25.8 mg, 0.070 mmol), (DHQ)MEQ (164 mg, 0.350 mmol), $K_3Fe(CN)_6$ (2.77 g, 8.41 mmol), K_2CO_3 (1.16 g, 8.41 mmol) and $MeSO_2NH_2$ (0.799 g, 8.41 mmol) in *t*-BuOH (7 mL) and H_2O (15 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. To the resultant suspension was added a solution of olefin **10** (1.43 g, 2.80 mmol) in *t*-BuOH (4 mL + 2 × 2 mL rinse) via cannula. After being stirred at 0 °C for 4.5 h, the resultant mixture was quenched with solid $Na_2S_2O_3{\cdot}5H_2O$ (8.00 g, 32.2 mmol), and allowed to warm to room temperature over 1 h. Layers were separated and the aqueous layer was extracted with EtOAc. Combined organic layers were washed with saturated aqueous

NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/acetone = 4/1 → 2/1) afforded triol **11** (1.47 g, 2.70 mmol, 96%) as a colorless syrup as a mixture with inseparable diastereomer (dr = 10:1).

R_f = 0.20 (Hexane/EtOAc = 1/2); $[\alpha]^{26}_D$ +22.9 (*c* 1.1, $CHCl_3$); IR (neat) 3437, 2934, 2871, 2359, 2341, 1612, 1512, 1454, 1335, 1302, 1036, 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33–7.22 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.27 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 4.09 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.01 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.84–3.75 (m, 4H), 3.78 (s, 3H), 3.64–3.58 (m, 2H), 3.55–3.49 (m, 2H), 3.18–3.01 (brs, 2H), 2.93–2.88 (brs, 1H), 2.03–1.96 (m, 2H), 1.87 (t, *J* = 7.2 Hz, 2H), 1.72–1.61 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 138.1, 130.0, 129.6 (2C), 128.5 (2C), 127.9 (3C), 119.3, 114.0 (2C), 73.9, 73.6 (2C), 73.4, 71.9, 71.7 (2C), 71.5, 71,1, 70.9, 69.3, 55.4, 36.9, 36.7, 28.2, 24.0, 23.3; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{30}H_{40}O_9Na$ 567.2565, found 567.2575.

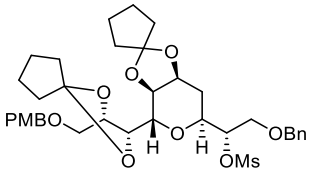


8

Acetal 8. To a solution of triol **11** (508 mg, 0.932 mmol) in CH_2Cl_2 (4.7 mL) were added 1,1-dimethoxycyclopentane (2.57 mL, 18.7 mmol) and PPTS (47.0 mg, 0.187 mmol) at 0 °C. After being stirred at room temperature for 2 h, the resultant mixture was quenched with Et_3N and diluted with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (toluene/EtOAc = 10/1 → 5/1) afforded acetal **8** (469 mg, 0.767 mmol, 82%) as a colorless syrup.

R_f = 0.61 (Hexane/EtOAc = 1/1); $[\alpha]^{22}_D$ +1.9 (*c* 0.83, $CHCl_3$); IR (neat) 3466, 2957, 2871, 2369, 2359, 2338, 1514, 1248, 1105, 1038, 753, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 9.2, 6.0, 6.0 Hz, 1H), 4.18 (ddd, *J* = 7.2, 5.2, 5.2 Hz, 1H), 4.06 (dd, *J* = 5.2, 5.2 Hz, 1H), 3.99–3.96 (m, 2H), 3.85–3.75 (m, 2H), 3.77 (s, 3H), 3.62–3.49 (m, 4H), 2.75 (d, *J* = 3.6 Hz, 1H), 1.95–1.62 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 138.1, 130.0, 129.6 (2C), 128.5 (2C), 127.8 (3C),

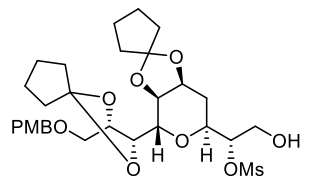
120.0, 118.6, 113.9 (2C), 79.7, 76.6, 73.6, 73.2, 72.9, 72.2, 71.4 (2C), 71.0, 70.8, 70.4, 55.4, 37.5, 37.4, 37.32, 37.28, 29.0, 23.8, 23.7, 23.6, 23.4; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{35}H_{46}O_9Na$ 633.3034, found 633.3031.



12

Mesylate 12. To a solution of acetal **8** (448 mg, 0.734 mmol) in CH_2Cl_2 (7.3 mL) were added Et_3N (0.19 mL, 1.8 mmol) and MsCl (68 μL, 0.88 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 7/1 → 1/1) afforded mesylate **12** (484 mg, 0.703 mmol, 96%) as a colorless syrup.

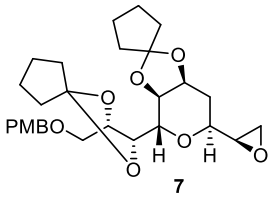
R_f = 0.74 (Hexane/EtOAc = 1/1); $[\alpha]^{20}_D$ −0.66 (*c* 0.86, $CHCl_3$); IR (neat) 3014, 2957, 2872, 2363, 2341, 1514, 1355, 1335, 1248, 1219, 1173, 1106, 1036, 921, 771 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.31–7.29 (m, 3H), 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.91–4.88 (m, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 10.2 Hz, 2H), 4.24 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.21 (ddd, *J* = 7.8, 5.4, 5.4 Hz, 1H), 4.12 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.02 (ddd, *J* = 9.0, 6.6, 4.2 Hz, 1H), 3.98–3.95 (m, 2H), 3.79 (s, 3H), 3.76–3.74 (m, 2H), 3.59 (d, *J* = 4.8 Hz, 2H), 3.01 (s, 3H), 1.99 (ddd, *J* = 12.6, 4.8, 4.8 Hz, 1H), 1.90–1.62 (m, 17H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 137.5, 130.2, 129.5 (2C), 128.6 (2C), 128.1, 127.9 (2C), 120.1, 118.8, 113.9 (2C), 81.8, 79.5, 76.7, 73.6, 73.2, 72.6, 71.1, 71.0, 70.3, 69.9, 69.5, 55.4, 38.8, 37.5, 37.4, 37.32, 37.29, 28.5, 23.8, 23.7, 23.6, 23.4; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{36}H_{48}O_{11}SNa$ 711.2810, found 711.2817.



13

Alcohol 13. To a solution of mesylate **12** (31.6 mg, 45.9 μmol) in EtOH (0.46 mL) was added Raney Ni (excess), and placed under H_2 atmosphere. After being stirred at room temperature for 7.5 h, the insoluble materials were removed by filtration through a Celite pad and rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 2/1 → 0/1) afforded alcohol **13** (22.0 mg, 36.7 μmol, 88%) as a colorless oil.

R_f = 0.21 (Hexane/EtOAc = 1/1); $[\alpha]^{21}_D$ +8.7 (*c* 0.94, $CHCl_3$); IR (neat) 3482, 2956, 2873, 2360, 2334, 1612, 1514, 1334, 1247, 1173, 1102, 1035, 973, 913, 819 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.78 (ddd, *J* = 5.4, 5.4, 3.6 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.26 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.20 (dd, *J* = 6.6, 5.4, 5.4 Hz, 1H), 4.12 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.03–3.96 (m, 3H), 3.94–3.89 (m, 1H), 3.83–3.78 (m, 1H), 3.80 (s, 3H), 3.61 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.58 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.06 (s, 3H), 2.35–2.29 (brs, 1H), 2.01 (ddd, *J* = 13.8, 5.4, 5.4 Hz, 1H), 1.90–1.63 (m, 17H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 130.0, 129.6 (2C), 120.1, 118.9, 113.9 (2C), 83.2, 79.3, 76.6, 73.3, 72.6, 70.91, 70.86, 70.2, 69.9, 62.3, 55.4, 38.8, 37.6, 37.4, 37.35, 37.31, 28.6, 23.8, 23.7, 23.6, 23.4; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{29}H_{42}O_{11}SNa$ 621.2340, found 621.2355.

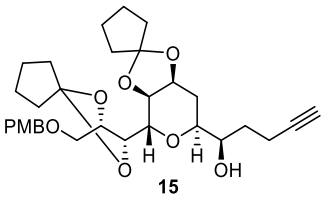


7

Epoxide 7. To a solution of alcohol **13** (22.0 mg, 36.7 μmol) in MeOH (1.2 mL) was added K_2CO_3 (2.54 mg, 18.4 μmol) at 0 °C and stirred at room temperature for 48 h. To the reaction mixture was added K_2CO_3 (2.54 mg, 18.4 μmol) and stirred at room temperature for 12 h. Additional K_2CO_3 (2.54 mg, 18.4 μmol) was added and stirred at room temperature for 12 h. The resultant mixture was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 5/1 → 1/0) afforded epoxide **7** (15.3 mg, 30.4 μmol, 83%) as a colorless syrup.

R_f = 0.21 (Hexane/EtOAc = 1/1); $[\alpha]^{20}_D$ +3.3 (*c* 1.02, $CHCl_3$); IR (neat) 3016, 2958, 2873, 2359, 2342, 1612, 1514, 1334, 1248, 1215, 1106, 1037, 751, 668 cm^{-1}; ^1H NMR (600 MHz,

$CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.26 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.18 (ddd, *J* = 7.2, 5.4, 5.4 Hz, 1H), 4.09 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.00 (dd, *J* = 7.2, 4.2 Hz, 1H), 3.96–3.94 (m, 1H), 3.80 (s, 3H), 3.61–3.54 (m, 3H), 3.05 (ddd, *J* = 4.2, 4.2, 3.0 Hz, 1H), 2.73 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.63 (dd, *J* = 5.4, 3.6 Hz, 1H), 1.99 (ddd, *J* = 13.2, 5.4, 4.2 Hz, 1H), 1.91–1.61 (m, 17H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 130.1, 129.5 (2C), 120.0, 118.5, 113.9 (2C), 79.2, 76.7, 73.3, 73.2, 71.2, 71.0, 70.7, 70.3, 55.4, 53.2, 45.2, 37.5, 37.4, 37.3 (2C), 29.3, 23.8, 23.61, 23.56, 23.4; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{28}H_{38}O_8Na$ 525.2459, found 525.2451.

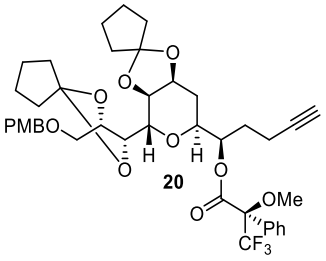


15

Alkyne 15. Two-necked flask is equipped with Liebig condenser and the exit from the condenser is connected to a trap cooled in dry ice-MeOH bath. A mixture of Zn powder (7.0 g, 0.11 mol, 2 eq), EtOH (9.3 mL) and water (1.9 mL) was placed in the reaction flask. The reaction mixture was heated under reflux, and the 1,2-dichloropropene (5.0 mL, 54.2 mmol) was added dropwise in such a rate that reflux is maintained without external heating. After the addition was complete, the reaction mixture was stirred under reflux for 1 h. The residual allene is purged from the reaction flask with a very slow stream of Ar. The crude allene was distilled at −30 °C.

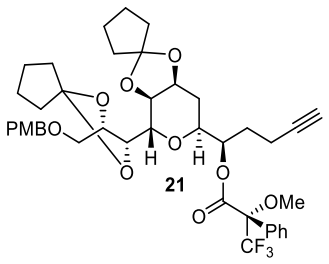
To a mixture of Et_2O (3.28 mL) and hexane (1.23 mL) at −78 °C were added allene (0.11 mL, 1.8 mmol) followed by a solution of *n*-BuLi (1.6 M in hexane, 2.05 mL, 3.28 mmol). The reaction mixture was allowed to warm to −15 °C where a white precipitate was formed and stirred at this temperature for 15 min. After this time, the reaction mixture was cooled to −78 °C and the solution of epoxide **7** (31.8 mg, 63.3 μmol) in Et_2O/hexane (1:1, v/v, 0.2 mL + 2 × 0.1 mL rinse) was added to the reaction mixture. When the addition was completed, the reaction mixture was allowed to warm to room temperature over 2 h. The resultant mixture was quenched with pH 7.0 phosphate buffer at −78 °C and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 3/1) afforded alkyne **15** (28.0 mg, 51.6 μmol, 82%) as an yellow syrup.

R_f = 0.34 (Hexane/EtOAc = 2/1); $[\alpha]^{20}_D$ +7.0 (*c* 0.92, $CHCl_3$); IR (neat) 3486, 3291, 2957, 2873, 2360, 2336, 2116, 1612, 1514, 1334, 1248, 1107, 1038, 975, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.27 (ddd, *J* = 8.8, 6.0, 6.0 Hz, 1H), 4.17 (ddd, *J* = 6.8, 4.8, 4.8 Hz, 1H), 4.05 (dd, *J* = 5.6, 4.0 Hz, 1H), 4.00–3.97 (m, 2H), 3.88–3.82 (m, 1H), 3.80 (s, 3H), 3.61–3.52 (m, 3H), 2.37–2.30 (m, 2H), 2.30–2.25 (brs, 1H), 1.93 (t, *J* = 2.8 Hz, 1H), 1.91–1.50 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.0, 129.5 (2C), 120.0, 118.4, 113.9 (2C), 84.1, 79.3, 77.0, 73.5, 73.2, 73.0, 71.7, 71.3 (2C), 70.3, 68.9, 55.4, 37.52, 37.47, 37.4, 37.3, 31.1, 27.0, 23.8, 23.63, 23.56, 23.4, 12.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{31}H_{42}O_8Na$ 565.2772, found 565.2778.



(*R*)-MTPA Ester 21. Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*R*)-MTPA (24 mg, 0.10 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered through a cotton plug and concentrated under reduced pressure to afford (*S*)-MTPACl. The residue was diluted with CH_2Cl_2 (0.6 mL) and added to the flask containing secondary alcohol **15** (3.0 mg, 5.5 μmol). To the reaction mixture were added Et_3N (14 μL, 0.10 mmol) and DMAP (12.2 mg, 0.100 mmol). After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1 → 2/1) afforded (*R*)-MTPA ester **20** (2.6 mg, 3.4 μmol, 62%).

R_f = 0.67 (Hexane/EtOAc = 2/1); ^1H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.6 Hz, 2H), 7.42–7.38 (m, 3H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.38 (ddd, *J* = 9.0, 4.2, 4.2 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 9.6, 6.0, 6.0 Hz, 1H), 4.10 (ddd, *J* = 7.2, 4.8, 4.8 Hz, 1H), 4.07 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.02–3.98 (m, 2H), 3.89 (ddd, *J* = 10.8, 3.6, 3.6 Hz, 1H), 3.79 (s, 3H), 3.60 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.57 (s, 3H), 3.55 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.20–2.14 (m, 1H), 2.02 (dddd, *J* = 16.2, 8.4, 8.4, 3.0 Hz, 1H), 1.95 (dd, *J* = 3.0, 3.0 Hz, 1H), 1.90–1.74 (m, 9H), 1.71–1.69 (m, 11H).



(*S*)-MTPA Ester 21. Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*S*)-MTPA (24 mg, 0.10 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered through a cotton plug and concentrated under reduced pressure to afford (*R*)-MTPACl. The residue was diluted with CH_2Cl_2 (0.6 mL) and added to a flask containing secondary alcohol **15** (2.7 mg, 5.0 μmol). To the reaction mixture were added Et_3N (14 μL, 0.1 mmol) and DMAP (12.2 mg, 0.100 mmol). After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1 → 2/1) afforded (*S*)-MTPA ester **21** (2.9 mg, 3.8 μmol, 78%).

R_f = 0.67 (Hexane/EtOAc = 2/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2H), 7.41–7.38 (m, 3H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 7.8, Hz, 2H), 5.37 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.17 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.13 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 4.00 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.95–3.90 (m, 2H), 3.82 (ddd, *J* = 9.6, 5.4, 4.2 Hz, 1H), 3.78 (s, 3H), 3.61–3.51 (m, 2H), 3.53 (s, 3H), 2.27 (dddd, *J* = 16.8, 7.2, 7.2, 1.8 Hz, 1H), 2.16 (dddd, *J* = 16.8, 8.4, 8.4, 1.8 Hz, 1H), 1.94–1.53 (m, 21H).

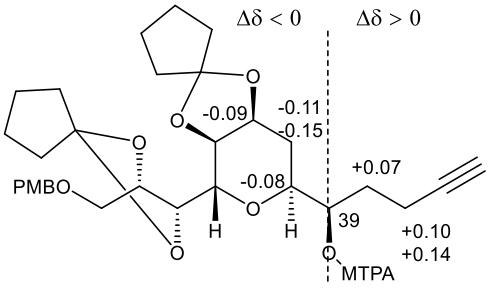
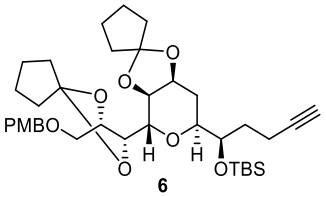


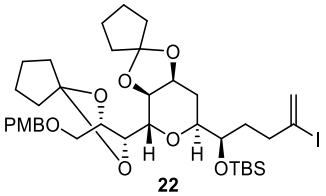
Figure S1. Determination of the absolute configuration at C39 of compound **15** by the modified Mosher method.



6

TBS Ether 6. To a solution of alkyne **15** (18.4 mg, 33.9 μmol) in CH_2Cl_2 (1.13 mL) were added 2,6-lutidine (58.9 μL, 0.509 mmol) and TBSOTf (47 μL, 0.20 mmol) at −20 °C and stirred at 0 °C for 45 min. The resultant mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 20/1 → 5/1) afforded TBS ether **6** (22.2 mg, 33.8 μmol, 99%) as a yellow syrup.

R_f = 0.80 (Hexane/EtOAc = 2/1); $[\alpha]^{20}_D$ +1.08 (*c* 1.1, $CHCl_3$); IR (neat) 3309, 2954, 2931, 2856, 2361, 2340, 2117, 1613, 1514, 1334, 1249, 1219, 1108, 1040, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.23 (ddd, *J* = 9.2, 6.0, 6.0 Hz, 1H), 4.17 (ddd, *J* = 7.6, 5.2, 5.2 Hz, 1H), 4.03 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.97 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.90 (dd, *J* = 4.0, 4.0 Hz, 1H), 3.88–3.84 (m, 1H), 3.80 (s, 3H), 3.60–3.54 (m, 2H), 3.53–3.47 (m, 1H), 2.24 (ddd, *J* = 8.0, 8.0, 2.4 Hz, 2H), 1.91 (t, *J* = 2.4 Hz, 1H), 1.91–1.59 (m, 20H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.1, 129.5 (2C), 120.0, 118.3, 113.9 (2C), 84.6, 79.6, 76.9, 73.2, 73.1, 72.9, 72.3, 71.7, 71.3, 70.5, 68.6, 55.4, 37.53, 37.49, 37.4, 37.3, 32.6, 28.1, 26.1 (3C), 23.8, 23.7, 23.6, 23.4, 18.3, 14.1, −4.0, −4.4; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{37}H_{56}O_8SiNa$ 679.3637, found 679.3653.

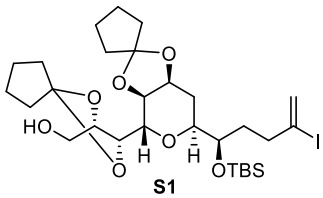


22

Iodoolefin 22. To a mixture of Ni(dppp)Cl_2 (7.5 mg, 0.014 mmol) and DIBALH (1M in toluene, 0.60 mL, 0.60 mmol) was added a solution of alkyne **6** (304 mg, 0.462 mmol) in THF (0.25 mL + 2 × 0.1 mL rinse) at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 1 h. To the resultant mixture was added

a solution of NIS (208 mg, 0.924 mmol, 2 eq) in THF (1.5 mL) via cannula at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was diluted with Et_2O and saturated aqueous Na^+/K^+ tartrate. The mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and 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 = 20/1 → 5/1) to afford iodoolefin **22** (224 mg, 0.286 mmol, 62%) as a colorless oil.

R_f = 0.40 (Hexane/EtOAc = 5/1); $[\alpha]^{22}_D$ −6.2 (*c* 1.00, $CHCl_3$); IR (neat) 2953, 2929, 2856, 2360, 2342, 2117, 1614, 1514, 1333, 1249, 1219, 1103, 1039, 835, 778 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.00 (s, 1H), 5.66 (s, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.24 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4,17 (ddd, *J* = 7.2, 5.4, 5.4 Hz, 1H), 4.03 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.00 (dd, *J* = 7.2, 3.0 Hz, 1H), 3,91 (dd, *J* = 4.2, 3.6 Hz, 1H), 3.80 (s, 3H), 3.81–3.77 (m, 1H), 3.60 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.55 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.51 (ddd, *J* = 10.2, 6.0, 3.6 Hz, 1H), 2.50–2.40 (m, 2H), 1.95 (ddd, *J* = 13.8, 6.0, 3.0 Hz, 1H), 1.91–1.76 (m, 7H), 1.73–1.60 (m, 12H), 0.89 (s, 9H), 0.070 (s, 3H), 0.068 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 130.1, 129.5 (2C), 125.4, 120.0, 118.3, 113.9 (2C), 112.5, 80.2, 76.7, 73.3, 73.0, 72.5, 72.4, 71.8, 71.3, 70.7, 55.4, 40.4, 37.6, 37.5, 37.4, 37.3, 33.6, 28.5, 26.1 (3C), 23.80, 23.76, 23.6, 23.4, 18.3, −4.1, −4.2; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{37}H_{57}IO_8SiNa$ 807.2760, found 807.2801.

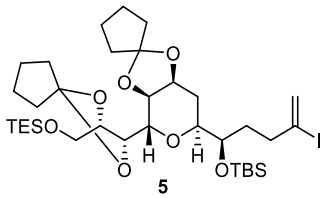


S1

Primary Alcohol S1. To a solution of PMB ether **22** (339 mg, 0.495 mmol) in CH_2Cl_2/pH 7 buffer (v/v = 10/1, 5.5 mL) at 0 °C was added DDQ (135 mg, 0.594 mmol). After being stirred for 3.5 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ethyl acetate, and the organic layer was 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 = 20/1 → 8/1) to afford primary alcohol **S1** (326 mg, 0.491 mmol, 99%) as a colorless oil.

R_f = 0.41 (Hexane/EtOAc = 3/1); $[\alpha]^{23}_D$ −8.8 (*c* 0.72, $CHCl_3$); IR (neat) 3479, 2953, 2929,

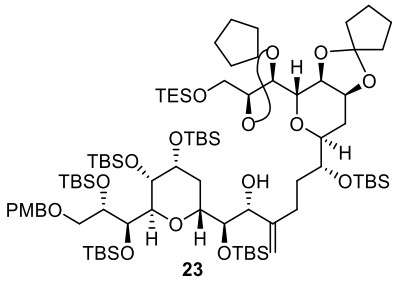
2875, 2856, 2360, 2341, 1617, 1333, 1252, 1201, 1042, 1103, 976, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.68 (s, 1H), 4.26 (ddd, *J* = 9.6, 6.0, 6.0 Hz, 1H), 4.11–4.08 (m, 1H), 4.07–4.02 (m, 2H), 3.87 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.85–3.80 (m, 2H), 3.69–3.65 (m, 1H), 3.53 (ddd, *J* = 10.2, 6.0, 3.6 Hz, 1H), 2.51–2.41 (m, 2H), 1.96 (ddd, *J* = 13.8, 6.0, 3.6 Hz, 1H), 1.97–1.64 (m, 19H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 125.6, 119.9, 118.5, 112.3, 78.6, 78.1, 73.3, 72.7, 72.5, 71.81, 71.75, 62.7, 40.5, 37.55, 37.48, 37.45, 37.3, 33.6, 28.2, 26.1 (3C), 23.8, 23.6, 23.5, 23.4, 18.3, −4.0, −4.2; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{29}H_{49}IO_7SiNa$ 687.2184, found 687.2194.



5

TES Ether 5. To a solution of primary alcohol **S1** (66.7 mg, 0.100 mmol) in THF (9.9 mL) at −78 °C were added NaH (60% in oil, 80.5 mg, 2.01 mmol) and TESCl (0.29 mL, 1.7 mmol). The reaction mixture was allowed to warm to −20 °C over 2 h. After being stirred at −20 °C for 1 h, the resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 1/0 → 30/1) to afford TES ether **5** (72.8 mg, 93.5 μmol, 93%) as a colorless oil.

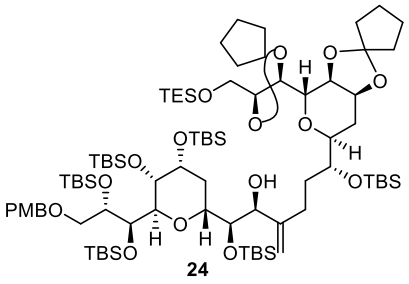
R_f = 0.50 (Hexane/EtOAc = 10/1); $[\alpha]^{23}_D$ −7.4 (*c* 0.89, $CHCl_3$); IR (neat) 2954, 2934, 2875, 1333, 1251, 1200, 1106, 1044, 1006, 975, 835, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.67 (s, 1H), 4.26 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.09–4.01 (m, 3H), 3.97 (dd, *J* = 4.2, 3.0 Hz, 1H), 3.81–3.77 (m, 1H), 3.78 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.71 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.56 (ddd, *J* = 10.2, 6.6, 3.0 Hz, 1H), 2.53–2.42 (m, 2H), 1.97 (ddd, *J* = 13.8, 6.6, 3.0 Hz, 1H), 1.94–1.62 (m, 19H), 0.96 (t, *J* = 8.4 Hz, 9H), 0.90 (s, 9H), 0.61 (q, *J* = 7.8 Hz, 6H), 0.084 (s, 3H), 0.081 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 125.3, 119.9, 118.2, 112.5, 80.6, 77.8, 73.3, 72.6, 72.5, 71.9, 71.2, 63.8, 40.5, 37.7, 37.5, 37.4, 37.3, 33.7, 28.9, 26.1 (3C), 23.81, 23.77, 23.5, 23.4, 18.3, 6.9 (3C), 4.5 (3C), −4.1, −4.2; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{35}H_{63}IO_7SiNa$ 801.3049, found 801.3054.



23

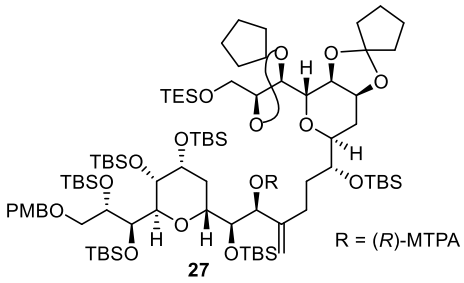
Secondary Alcohol 23. To a solution of iodoolefin **5** (76.9 mg, 98.7 μmol) in dist. Et_2O (2.5 mL) at −78 °C was added *t*-BuLi (1.72 M in pentane, 116 μL, 197 μmol). After being stirred at −78 °C for 15 min, a solution of aldehyde **4** (102 mg, 106 μmol) in THF (1.9 mL + 0.6 mL rinse) was added and the reaction mixture was stirred at −78 °C for 1 h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with *n*-hexane. The organic layer was 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/ethyl acetate = 1/0 → 30/1) to afford secondary alcohol **23** (72.8 mg, 70.4 μmol, 71%) as a mixture of diastereomers (dr = 1.7:1).

R_f = 0.37 (Hexane/EtOAc = 10/1); $[\alpha]^{25}_D$ +8.4 (*c* 0.69, C_6H_6); IR (neat) 3501, 2953, 2929, 2857, 2359, 2341, 1250, 1106, 834, 781 cm^{-1}; ^1H NMR of major compound (600 MHz, C_6D_6) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 5.40 (s, 1H), 5.08 (s, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.48 (dd, *J* = 6.0, 4.8 Hz, 1H), 4.43 (s, 2H), 4.40 (brs, 1H), 4.38 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.34 (dd, *J* = 7.8, 3.6 Hz, 1H), 4.32–4.28 (m, 2H), 4.27 (brs, 1H), 4.24–4.20 (m, 2H), 4.16–4.09 (m, 2H), 4.06–3.90 (m, 2H), 3.88 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.81 (d, *J* = 4.8 Hz, 2H), 3.72 (ddd, *J* = 10.8, 3.6, 3.6 Hz, 1H), 3.63 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.36 (s, 3H), 2.72 (ddd, *J* = 15.6, 12.0, 4.2 Hz, 1H), 2.50 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.20–1.85 (m, 12H), 1.83–1.75 (m, 3H), 1.65–1.54 (m, 7H), 1.12 (s, 9H), 1.11 (s, 9H), 1.09 (s, 9H), 1.05 (s, 9H), 1.05 (t, *J* = 8.4 Hz, 9H), 1.04 (s, 9H), 1.03 (s, 9H), 0.65 (q, *J* = 7.8 Hz, 6H), 0.33 (s, 6H), 0.323 (s, 3H), 0.317 (s, 3H), 0.30 (s, 3H), 0.29 (s, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.23 (s, 6H), 0.22 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 149.6, 130.6, 129.5 (2C), 119.8, 118.3, 114.2 (2C), 112.4, 81.2 (2C), 80.1, 79.2, 77.2, 74.8, 74.2, 73.9, 73.5, 73.4, 73.2, 72.6, 72.2, 71.0 (2C), 69.5, 68.8, 64.0, 54.8, 38.02, 37.97, 37.8, 37.6, 32.7, 29.6, 29.0, 28.4, 26.6 (3C), 26.5 (6C), 26.34 (3C), 26.28 (3C), 26.26 (3C), 24.0, 23.9, 23.74, 23.69, 18.7, 18.62, 18.60, 18.5 (2C), 18.4, 7.1 (3C), 4.9 (3C), −2.8, −3.6 (2C), −3.7, −3.8, −3.9 (2C), −4.03, −4.06, −4.24, −4.26, −5.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{83}H_{160}O_{16}Si_7Na$ 1631.9983, found 1632.0044.



24

Secondary Alcohol 24. R_f = 0.37 (Hexane/EtOAc = 10/1); $[\alpha]^{21}_D$ −3.0 (*c* 1.14, $CHCl_3$); IR (neat) 3544, 2953, 2929, 2883, 2856, 1513, 1471, 1462, 1249, 1219, 1102, 1041, 1005, 834, 7774, 673 cm^{-1}; ^1H NMR of minor compound (600 MHz, C_6D_6) δ 7.31 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 5.12 (s, 1H), 4.54 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.41–4.39 (m, 2H), 4.37–4.30 (m, 5H), 4.24–4.20 (m, 1H), 4.19–4.14 (m, 2H), 4.05 (ddd, *J* = 7.8, 4.2, 4.2 Hz, 1H), 4.01–3.96 (m, 2H), 3.85 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.82 (d, *J* = 4.2 Hz, 2H), 3.68 (ddd, *J* = 10.8, 3.6, 3.6 Hz, 1H), 3.64 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.35 (s, 3H), 3.14 (d, *J* = 9.0 Hz, 1H), 2.42–2.34 (m, 2H), 2.32–2.25 (m, 1H), 2.16–2.02 (m, 3H), 1.97–1.69 (m, 10H), 1.66–1.55 (m, 8H), 1.130 (s, 9H), 1.126 (s, 9H), 1.10 (s, 9H), 1.057 (s, 18H), 1.053 (s, 9H), 1.048 (t, *J* = 8.4 Hz, 9H), 0.65 (q, *J* = 8.4 Hz, 6H), 0.36 (s, 6H), 0.34 (s, 3H), 0.331 (s, 3H), 0.325 (s, 6H), 0.29 (s, 3H), 0.28 (s, 6H), 0.233 (s, 3H), 0.225 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 150.1, 130.8, 129.7 (2C), 119.9, 118.3, 114.0 (2C), 110.8, 80.7, 79.7, 79.1, 75.9, 74.7 (2C), 74.4, 73.6, 73.4 (2C), 73.2, 72.5, 72.2, 72.1, 71.1, 69.2, 68.5, 64.0, 54.8, 38.1, 38.0, 37.8, 37.6, 32.8, 32.2, 29,4, 28.1, 26.62 (3C), 26.60 (3C), 26.49 (3C), 26.47 (3C), 26.3 (6C), 24.0, 23.9, 23.8, 23.7, 18.80, 18.76, 18.65 (2C), 18.61, 18.4, 7.1 (3C), 4.82 (3C), −3.2, −3.46, −3.51, −3.7, −3.8, −3.96, −3.98, −4.03, −4.1, −4.4, −5.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{83}H_{160}O_{16}Si_7Na$ 1631.9983, found 1632.0055.

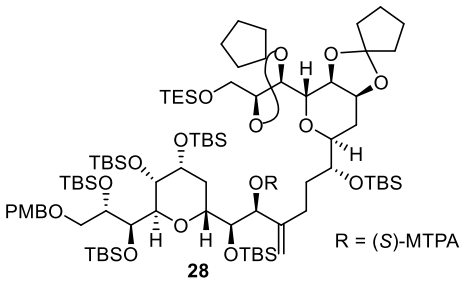


27

(*R*)-MTPA Ester 27. Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*R*)-MTPA (100 mg, 0.426 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered through a cotton plug and concentrated under reduced pressure to give (*S*)-MTPACl. The residue was diluted with CH_2Cl_2 (0.6 mL) and

added to a flask containing secondary alcohol **22** (30.6 mg, 19.0 μmol), Et_3N (118 μL, 0.852 mmol) and DMAP (12.2 mg, 0.100 mmol). After being stirred at 40 °C for 64 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1 → 2/1) afforded (*R*)-MTPA ester **27** (4.5 mg, 2.5 μmol, 12%).

R_f = 0.39 (Hexane/EtOAc = 10/1); ^1H NMR (600 MHz, C_6D_6) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.24 (t, *J* = 8.4 Hz, 1H), 7.20–7.12 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.90–5.88 (m, 1H), 5.37 (s, 1H), 5.19 (s, 1H), 4.45–4.37 (m, 5H), 4.33 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.29 (dd, *J* = 6.0, 4.2 Hz, 1H), 4.20 (ddd, *J* = 7.8, 4.8, 4.8 Hz, 1H), 4.19–4.15 (m, 2H), 4.10–4.05 (m, 2H), 3.98 (d, *J* = 7.8 Hz, 1H), 3.86–3.77 (m, 4H), 3.65 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.57 (s, 3H), 3.36–3.32 (m, 1H), 3.35 (s, 3H), 3.27–3.25 (m, 1H), 2.68–2.62 (m, 1H), 2.44 (ddd, *J* = 15.0, 7.8, 7.8 Hz, 1H), 2.17–1.75 (m, 15H), 1.66–1.55 (m, 7H), 1.13 (s, 9H), 1.12 (s, 9H), 1.11 (s, 9H), 1.093 (s, 9H), 1.06 (s, 9H), 1.048 (s, 9H), 1.041 (t, *J* = 8.4 Hz, 9H), 0.64 (q, *J* = 8.4 Hz, 6H), 0.38 (s, 3H), 0.34 (s, 6H), 0.314 (s, 3H), 0.309 (s, 3H), 0.306 (s, 3H), 0.29 (s, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.22 (s, 3H).



28

(*S*)-MTPA Ester 28. Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*S*)-MTPA (100 mg, 0.426 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered through a cotton plug and concentrated under reduced pressure to afford (*R*)-MTPACl. The residue was diluted with CH_2Cl_2 (0.6 mL) and added to a flask containing secondary alcohol **22** (28.8 mg, 17.9 μmol). To the mixture was added Et_3N (118 μL, 0.852 mmol) and DMAP (12.2 mg, 0.10 mmol). After being stirred at 40℃ for 14 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1 → 2/1) afforded (*S*)-MTPA ester **28** (7.1 mg, 3.9 μmol, 22%).

R_f = 0.39 (Hexane/EtOAc = 10/1); ^{1}H NMR (600 MHz, C_6D_6) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.19–7.13 (m, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.91–5.89 (m, 1H), 5.02 (s, 1H), 4.93 (s, 1H), 4.49–4.40 (m, 6H), 4.38 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.30 (dd, *J* = 10.8, 10.2 Hz, 1H), 4.24 (d, *J* = 10.2 Hz, 1H), 4.21–4.17 (m, 1H), 4.19 (ddd, *J* = 7.8, 4.8, 4.8 Hz, 1H), 4.13–4.09 (m, 1H), 4.07 (ddd, *J* = 9.0, 3.0, 3.0 Hz, 1H), 4.04 (d, *J* = 7.8 Hz, 1H), 3.91–3.78 (m, 5H), 3.70 (s, 3H), 3.67 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.53 (s, 3H), 2.65–2.58 (m, 1H), 2.39 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 1H), 2.18–2.09 (m, 4H), 2.02 (ddd, *J* = 13.8, 7.2, 2.4 Hz, 1H), 1.99–1.89 (m, 5H), 1.87–1.76 (m, 3H), 1.67–1.55 (m, 9H), 1.14 (s, 9H), 1.13 (s, 9H), 1.11 (s, 9H), 1.07 (s, 9H), 1.06 (s, 9H), 1.05 (s, 9H), 1.03 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.40 (s, 3H), 0.36 (s, 3H), 0.34 (s, 3H), 0.333 (s, 6H), 0.326 (s, 3H), 0.31 (s, 3H), 0.291 (s, 3H), 0.28 (s, 3H), 0.23 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H).

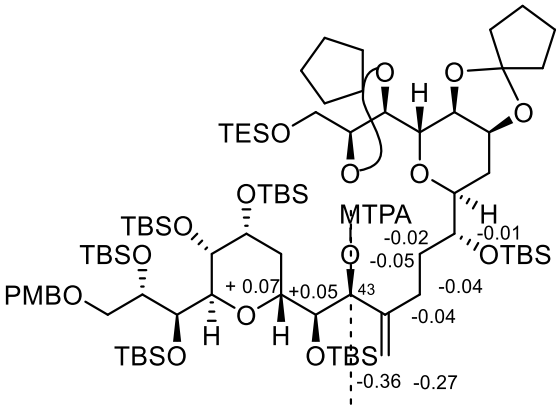
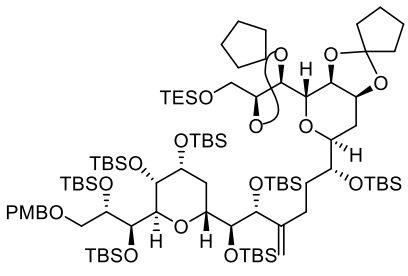


Figure S2. Determination of the absolute configuration at C39 of compound **24** by the modified Mosher method.

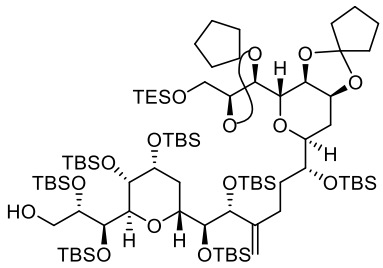


29

TBS Ether 29. To a solution of secondary alcohol **23** (154 mg, 95.7 μmol) in CH_2Cl_2 (1.9 mL) at −20 °C were added 2,6-lutidine (55 μL, 0.48 mmol) and TBSOTf (44 μL, 0.19 mmol). After being stirred at 0 °C for 30 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with *n*-hexane. The organic layer was 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 = 1/0 → 50/1) to afford TBS ether **29** (154 mg, 89.4 μmol, 93%) as a colorless oil.

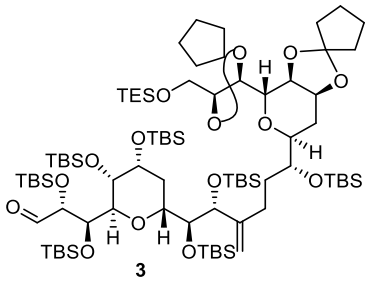
R_f = 0.70 (Hexane/EtOAc = 10/1); $[\alpha]^{22}_D$ −6.3 (*c* 1.10, C_6H_6); IR (neat) 2953, 2929, 2884, 2856, 2360, 2341, 1471, 1462, 1250, 1109, 1041, 776 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.31 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.41 (s, 1H), 5.15 (s, 1H), 4.74 (brs, 1H), 4.51–4.35 (m, 8H), 4.28–4.23 (m, 2H), 4.22–4.14 (m, 3H), 4.11–4.06 (m, 1H), 3.91 (ddd, *J* = 12.0, 3.6, 3.6 Hz, 1H), 3.87 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.90–3.84 (m, 1H), 3.83 (d, *J* = 4.8 Hz, 2H), 3.67 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.33 (s, 3H), 2.77–2.69 (m, 1H), 2.51–2.44 (m, 1H), 2.38–2.29 (m, 1H), 2.21 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.16–2.07 (m, 3H), 1.99–1.91 (m, 7H), 1.85–1.77 (m, 2H), 1.67–1.57 (m, 8H), 1.15 (s, 9H), 1.14 (s, 9H), 1.12 (s, 9H), 1.11 (s, 9H), 1.09 (s, 9H), 1.07 (s, 9H), 1.06 (t, *J* = 7.8 Hz, 9H), 1.05 (s, 9H), 0.66 (q, *J* = 7.8 Hz, 6H), 0.40 (s, 3H), 0.38 (s, 3H), 0.35 (s, 3H), 0.34 (s, 3H), 0.33 (s, 6H), 0.32 (s, 3H), 0.30 (s, 3H), 0.28 (s, 6H), 0.26 (s, 6H), 0.24 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.1, 130.9, 129.6 (2C), 119.9, 118.4, 114.1 (2C), 81.3, 80.5, 80.3, 78.7, 78.0, 75.3, 74.1 (3C), 73.8, 73.3, 73.1, 72.6, 72.2, 71.4, 69.4, 69.1, 64.1, 54.8, 38.0, 37.8, 37.6 (2C), 33.0, 30.7, 27.7 (2C), 26.7 (3C), 26.6 (6C), 26.55 (3C), 26.51 (3C), 26.4 (3C), 26.3 (3C), 24.0, 23.9, 23.7, 23.6, 18.9 (2C), 18.74, 18.67, 18.65, 18.62, 18.5, 7.2 (3C), 4.9 (3C), −2.7, −3.5, −3.6, −3.7 (2C), −3.76, −3.81 (3C), −3.97, −4.01, −4.2, −4.3, −5.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{88}H_{174}O_{16}Si_8Na$ 1746.0848, found 1746.0810.



30

Primary Alcohol 30. To a solution of PMB ether **29** (61.6 mg, 35.7 μmol) in CH_2Cl_2/pH 7 buffer (v/v = 2/1, 5.4 mL) at 0 °C was added DDQ (40.5 mg, 0.179 mmol). After being stirred for 1.5 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ at 0 °C. The mixture was extracted with hexane, and the organic layer was 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/acetone = 100/1 → 30/1) to afford primary alcohol **30** (52.1 mg, 32.5 μmol, 91%) as a colorless oil.

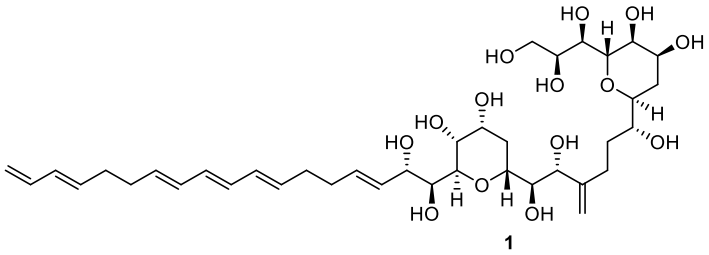
R_f = 0.47 (Hexane/Acetone = 30/1); $[\alpha]^{19}_D$ +2.6 (*c* 1.08, C_6H_6); IR (neat) 2953, 2928, 2884, 2856, 2360, 2341, 1251, 1107, 1056 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 5.41 (s, 1H), 5.14 (s, 1H), 4.62 (brs, 1H), 4.44 (ddd, *J* = 9.6, 6.0, 6.0 Hz, 1H), 4.41–4.34 (m, 4H), 4.32–4.20 (m, 3H), 4.25 (ddd, *J* = 7.8, 4.8, 4.8 Hz, 1H), 4.14–4.10 (m, 2H), 4.06 (ddd, *J* = 12.0, 4.2, 2.4 Hz, 1H), 3.97–3.89 (m, 2H), 3.86 (ddd, *J* = 10.8, 3.6, 3.6 Hz, 1H), 3.82 (d, *J* = 10.8 Hz, 2H), 3.82–3.78 (m, 1H), 2.68 (t, *J* = 12.0 Hz, 1H), 2.36 (t, *J* = 12.0 Hz, 1H), 2.25–2.05 (m, 5H), 2.01–1.75 (m, 9H), 1.68–1.56 (m, 9H), 1.14 (s, 9H), 1.130 (s, 9H), 1.126 (s, 9H), 1.10 (s, 9H), 1.08 (s, 9H), 1.06 (s, 9H), 1.05 (t, *J* = 7.8 Hz, 9H), 1.03 (s, 9H), 0.65 (q, *J* = 7.8 Hz, 6H), 0.39 (s, 3H), 0.37 (s, 3H), 0.35 (s, 3H), 0.31 (s, 3H), 0.30 (s, 6H), 0.286 (s, 6H), 0.283 (s, 3H), 0.278 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 150.8, 119.9, 118.4, 112.2, 81.0, 79.8, 79.6, 78.7 (2C), 76.0, 75.0, 74.1, 73.7, 72.5, 72.1 (3C), 69.4, 69.0, 64.1, 63.6, 38.0, 37.9, 37.7, 37.6, 32.9, 32.0, 28.2, 28.0, 26.8 (3C), 26.61 (3C), 26.58 (3C), 26.51 (3C), 26.45 (3C), 26.41 (3C), 26.37 (3C), 24.0, 23.9, 23.7, 23.6, 19.1, 18.9, 18.73, 18.66, 18.64, 18.51, 18.48, 7.2 (3C), 4.9 (3C), −2.7, −3.47, −3.51, −3.56, −3.7, −3.77 (2C), −3.84, −3.89, −4.0 (2C), −4.2, −4.4, −4.8; HRMS (ESI-TOF) *m/z* [M + Na] calcd for $C_{81}H_{166}O_{15}Si_8Na^+$ 1626.0274, found 1626.0288.



Aldehyde 3. To a solution of primary alcohol **30** (9.1 mg, 5.7 μmol) in CH_2Cl_2 (0.57 mL) was added MS4A powder (50 mg). After being stirred for 20 min, to the resultant mixture at 0 °C were added NMO (1.0 mg, 6.5 μmol) and TPAP (0.3 mg, 0.9 μmol). The reaction mixture was stirred for 1 h at room temperature. The insoluble materials were removed by filtration through a short silica and rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 50/1 → 30/1) afforded aldehyde **3** (8.9 mg, 5.5 μmol, 97%) as a colorless oil.

R_f = 0.64 (Hexane/EtOAc = 10/1), ^1H NMR (600 MHz, C_6D_6) δ 9.81 (s, 1H), 5.47 (s, 1H), 5.12 (s, 1H), 4.73–4.70 (m, 1H), 4.52–4.47 (m, 2H), 4.44–4.42 (m, 1H), 4.39–4.19 (m, 6H), 4.18–4.15 (m, 1H), 4.03–4.01 (m, 1H), 3.98–3.95 (m, 1H), 3.92–3.88 (m, 1H), 3.83–3.81 (m, 2H), 3.59–3.54 (m, 1H), 2.73–2.67 (m, 1H), 2.60–2.51 (m, 1H), 2.48–2.41 (m, 1H), 2.25–2.18 (m, 1H), 2.17–2.07 (m, 3H), 1.99–1.91 (m, 6H), 1.88–1.79 (m, 2H), 1.69–1.57 (m,

9H), 1.15 (s, 9H), 1.14 (s, 9H), 1.12 (s, 9H), 1.11 (s, 9H), 1.07 (s, 9H), 1.06 (s, 9H), 1.06 (t, *J* = 7.8 Hz, 9H), 0.97 (s, 9H), 0.65 (q, *J* = 7.8 Hz, 6H), 0.47–0.08 (m, 42H).



1

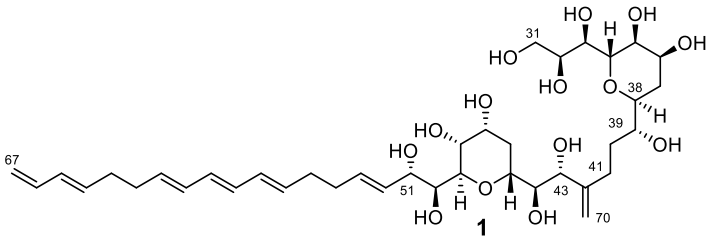
C31-C67 part of AM3 (1). To a mixture of sulfone **2** (18.3 mg, 44.6 μmol) and aldehyde **3** (17.0 mg, 10.6 μmol) in THF (0.82 mL) at −78 °C was added KHMDS (0.5 M in toluene, 64 μL, 32.0 μmol) dropwise. After being stirred at −78 °C for 1.5 h, the reaction mixture was allowed to warm to room temperature and then stirred for 2.5 h at the temperature. The resultant mixture was quenched with saturated aqueous NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was 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 = 100/1 → 5/1) to afford a mixture of byproduct and desired coupled product (13.2 mg). The mixture was used in next reaction without further purification.

To a solution of crude coupling product in THF (2.2 mL) at 0 °C was added 18% HF·Py (440 μL, 1.3 mmol) and stirred at 50 °C for 12 h. 18% HF·Py was added two times every 12 h (880 uL, 2.7 mmol). After further 24 h, 70% HF·Py (110 μL, 1.3 mmol) and MeOH (0.1 mL) was added and stirred for 12 h. 70% HF·Py was added two times (220 μL, 2.7 mmol each) and three times (440 μL, 5.3 mmol each) every 12 h. After 12 h from final addition, the reaction mixture was quenched with Et_3N. The resultant mixture was concentrated by blowing argon stream. Purification by reversed phase silica gel column chromatography (H_2O/MeOH = 1/1 → 1/10) afforded a crude mixture (3.5 mg), which consists of the C31-C67 part of AM3 (3.5 mg) and its acetal.

The crude mixture obtained above was once again dissolved in MeOH (1.2 mL) and warmed at 50℃. 44% HF·Py (1.0 mL, 7.6 mmol) was added to the flask and stirred at 50 °C for 1 h. 70% HF·Py (250 μL, 3.0 mmol) was then added to the flask and stirred for 14 h. The reaction was quenched with Et_3N and concentrated by blowing argon stream. Purification by reversed-phase silica gel column chromatography (H_2O/MeOH = 2/1 → 1/2) afforded the C31-C67 part of AM3 with some impurities. Further purification by reversed phase HPLC

(C18-MS-II waters 10 × 250 mm, MeOH/H_2O = 62/38, 64/36, 70/30 5mL/min) afforded C31-C67 part of AM3 (**1**) (2.2 mg, 3.0 μmol, 28%)

R_f = 0.27 (MeOH/H_2O = 3/1); ^{1}H NMR (600 MHz, CD_3OD/C_5D_5N = 2:1, Shigemi micro cell MMS-005J) δ 6.26 (ddd, *J* = 18.0, 12.0, 12.0, 1H), 6.08–5.96 (m, 5H), 5.85–5.75 (m, 2H), 5.66–5.57 (m, 3H), 5.12 (s, 1H), 5.04 (d, *J* = 16.2 Hz, 1H), 5.00 (s, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 4.62 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.39 (d, *J* = 8.4 Hz, xH), 4.38–4.36 (m, 1H), 4.35–4.32 (m, 1H), 4.25 (dd, *J* = 10.8, 10.8 Hz, 1H), 4.23–4.13 (m, 4H), 4.12 (ddd, *J* = 10.8, 4.8, 3.0 Hz, 1H), 4.09 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.01 (d, *J* = 10.8 Hz, 1H), 3.81 (d, *J* = 12.0 Hz, 2H), 3.74 (ddd, *J* = 8.4, 5.4, 3.0 Hz, 1H), 3.61 (ddd, *J* = 10.8, 5.4, 2.4 Hz, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 2.57 (ddd, *J* = 15.0, 10.8, 4.8 Hz, 1H), 2.34 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.25 (ddd, *J* = 15.6, 9.6, 6.0 Hz, 1H), 2.11–1.89 (m, 7H), 1.74 (dddd, *J* = 13.8, 9.6, 9.0, 4.8 Hz, 1H), 1.67–1.62 (m, 1H); HRMS (ESI-TOF) *m/z* [M + Na] calcd for $C_{38}H_{60}O_{14}Na^+$ 763.3875, found 763.3888.

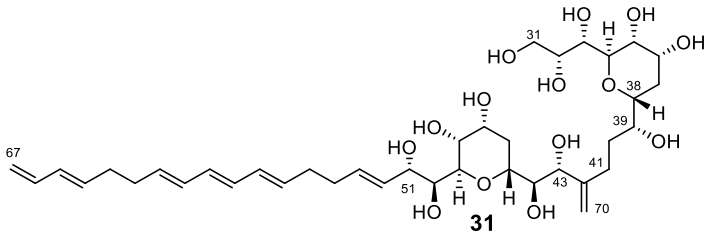


1

^{1}H NMR				^{13}C NMR			
carbon	natural	compound **1**	Δppm	carbon	natural	compound **1**	Δppm
51	4.59	4.58	0.01	51	74.1	74.1	0.0
50	4.18	4.18	0.00	50	72.1	72.1	0.0
49	3.98	4.00	−0.02	49	80.6	80.6	0.0
48	4.30	4.31	−0.01	48	68.7	68.7	0.0
47	4.17	4.18	−0.01	47	67.3	67.3	0.0
46	2.30	2.32	−0.02	46	31.8	31.8	0.0
46	1.64	1.62	0.02	45	70.6	70.6	0.0
45	4.21	4.21	0.00	44	75.3	75.3	0.0
44	3.50	3.50	0.00	43	76.7	76.5	0.2
43	4.38	4.37	0.01	70	112.8	112.9	−0.1
70	5.13	5.11	0.02	42	151.9	151.9	0.0
70	5.00	4.99	−0.01	41	28.0	27.7	0.3
41	2.23	2.23	0.00	40	32.6	32.2	0.4
41	2.59	2.55	0.04	39	74.5	74.1	0.4
40	2.05	1.95	0.10	38	75.8	75.0	0.8
40	1.68	1.71	−0.03	37	30.6	30.5	0.1
39	3.71	3.73	−0.02	36	67.4	67.3	0.1
38	3.60	3.60	0.00	35	68.9	68.9	0.0
37	2.01	2.01	0.00	34	79.2	78.9	0.3
37	1.92	1.90	0.02	33	72.6	67.8	4.8
36	4.12	4.10	0.02	32	67.8	70.9	−3.1
35	4.29	4.34	−0.05	31	126.8	64.3	62.5
34	4.22	4.21	0.01				
33	3.83	4.13	−0.30				
32	4.72	4.05	0.67				
31	5.63	3.78	1.85				

Figure S3. ^{1}H and ^{13}C chemical shift of AM3 and compound **1** in CD_3OD-C_5D_5N (2:1) and Δppm of them.

※$^{3}J_{(H\text{-}38,\ H\text{-}39)}$ of compound **1** was 5.4 Hz. It could be regarded equivalent to the value of natural AM3 (5.1 Hz). $^{3}J_{(c,\ H)}$ of compound **1** could not be analyzed.



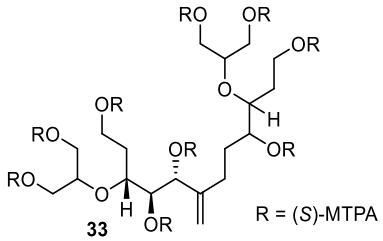
31

^{1}H NMR				^{13}C NMR			
carbon	natural	compound **32**	Δppm	carbon	natural	compound **32**	Δppm
51	4.59	4.59	0.00	51	74.1	74.1	0.0
50	4.18	4.18	0.00	50	72.1	72.1	0.0
49	3.98	3.97	0.01	49	80.6	80.6	0.0
48	4.30	4.30	0.00	48	68.7	68.7	0.0
47	4.17	4.16	0.01	47	67.3	67.3	0.0
46	2.30	2.28	0.02	46	31.8	31.8	0.0
46	1.64	1.60	0.04	45	70.6	70.6	0.0
45	4.21	4.20	0.01	44	75.3	75.3	0.0
44	3.50	3.48	0.02	43	76.7	76.5	0.2
43	4.38	4.36	0.02	70	112.8	112.8	0.0
70	5.13	5.12	0.01	42	151.9	152.0	−0.1
70	5.00	4.97	0.03	41	28.0	27.8	0.2
41	2.23	2.22	0.01	40	32.6	32.2	0.4
41	2.59	2.51	0.08	39	74.5	74.2	0.3
40	2.05	1.90	0.15	38	75.8	74.8	1.0
40	1.68	1.72	−0.04	37	30.6	31.7	−1.1
39	3.71	3.63	0.08	36	67.4	67.3	0.1
38	3.60	3.60	0.00	35	68.9	69.1	−0.2
37	2.01	2.03	−0.02	34	79.2	78.3	0.9
37	1.92	1.69	0.23	33	72.6	68.3	4.3
36	4.12	4.09	0.03	32	67.8	71.1	−3.3
35	4.29	4.28	0.01	31	126.8	64.2	62.6
34	4.22	4.21	0.01				
33	3.83	4.10	−0.27				
32	4.72	4.04	0.68				
31	5.63	3.78	1.85				

Figure S4. ^{1}H and ^{13} Chemical shift of AM3 and compound **32** in CD_3OD-C_5D_5N (2:1) and Δppm of them.

※$^{3}J_{(H\text{-}38,\ H\text{-}39)}$ of compound **31** was 4.6 Hz. It could be regarded equivalent to the value of natural AM3 (5.1 Hz). $^{3}J_{(c,\ H)}$ of compound **31** could not be analyzed.

Synthetic procedures for degradation products

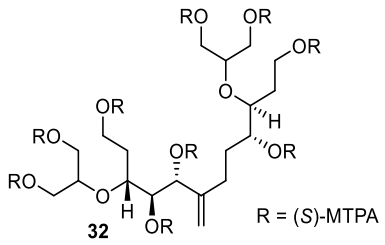


33

(*S*)-MTPA Ester 33. To a flask containing amphidinol 3 (0.3 mg, 0.2 μmol) was added 0.2 M aq. HIO_4 (18 μL, 3.6 μmol) and stirred at room temperature for 30 min. To the reaction mixture at 0℃ was added 2 M aq. $NaBH_4$ (7.2 μL, 15 μmol). After being stirred at 0 °C for 30 min, the reaction mixture was quenched with AcOH. The resultant mixture was concentrated under reduced pressure. Purification by reversed phase silica gel column chromatography (H_2O/MeOH = 1/0 → 0/1) afforded a crude mixture of alcohols. The mixture was used in the next reaction without further purification.

Oxalyl chloride (36 μL, 0.43 mmol) was added to a solution of (*S*)-MTPA (33 mg, 0.14 mmol) and DMF (2 μL, 0.03 mmol) in hexane (1.7 mL) at room temperature. After 2 h the mixture was filtered and concentrated under reduced pressure. The residue was diluted with Py (117 μL) and added to a flask containing above crude alcohols. To the reaction mixture was added DMAP (0.13 M in Py, 10 μL, 1.3 μmol). After being stirred at room temperature for 14.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reversed phase HPLC (C18-MS-II Waters 4 × 250 mm, 4% H_2O in methanol, 1 mL/min) afforded (*S*)-MTPA ester **33**. The amount and yield of ester **33** was not determined here.

R_f = 0.49 (Hexane/EtOAc = 2/1); ^{1}H NMR (Bruker 600 MHz cryoprobe, $CDCl_3$, shigemi tube CMS-005TJ) δ 7.50–7.17 (m, 45H), 5.62 (d, *J* = 7.2 Hz, 1H), 5.18 (dd, *J* = 7.2, 3.6 Hz, 1H), 5.15 (s, 1H), 5.12–5.09 (m, 1H), 4.97 (s, 1H), 4.32 (ddd, *J* = 10.8, 5.4, 5.4 Hz, 1H), 4.25 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.13 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.07–3.96 (m, 9H), 3.94 (ddd, *J* = 10.8, 7.2, 7.2 Hz, 1H), 3.89 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.64 (ddd, *J* = 9.6, 5.4 Hz, 1H), 3.59 (ddd, *J* = 6.0, 6.0, 3.6 Hz, 1H), 3.48–3.45 (m, 12H), 3.44 (s, 3H), 3.43–3.42 (m, 6H), 3.40 (s, 3H), 3.32 (s, 3H), 2.12–1.95 (m, 2H), 1.73–1.42 (m, 6H); HRMS (ESI-TOF) *m/z* [M + Na] calcd for $C_{109}H_{101}F_{27}O_{29}Na^+$ 2409.5890, found 2409.5862.



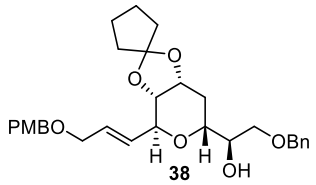
32

(*S*)-MTPA Ester 32. To a solution of compound **23** in THF (0.6 mL) at 50 °C was added 70% HF·Py (35 μL, 1.7 mmol). After 44 h, to the reaction mixture was added 70% HF·Py (35 μL, 1.7 mmol) and MeOH (0.05 mL). After being stirred 4 d, the reaction mixture was quenched with Et_3N and concentrated under reduced pressure. Purification by flash silica gel column chromatography ($MeOH/CH_3Cl$ = 1/5 → 1/2) afforded a mixture of alcohols. The mixture was used in the next reaction without further purification.

To the crude alcohols, HIO_4 (0.1 M in H_2O, 760 μL, 76.0 μmol) was added. After being stirred at room temperature for 30 min, the reaction mixture was cooled to 0 °C and treated with $NaBH_4$ (1 M in H_2O, 300 μL, 300 μmol). After being stirred at 0℃ for 30 min, the reaction mixture was quenched with AcOH and concentrated under reduced pressure. Purification by reversed phase silica gel column chromatography ($MeOH/H_2O$ = 0/1 → 1/0) afforded a mixture of alcohols. The mixture was used in the next reaction without further purification.

Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*S*)-MTPA (100 mg, 0.426 mmol) and DMF (7.7 μL, 0.10 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered and concentrated under reduced pressure. The residue was diluted with Py (200 μL) and added to the crude mixture of alcohols. After being stirred at room temperature for 17 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by HPLC (C18-MS-II waters 10 × 250 mm, 9% H_2O in methanol, 1.0 mL/min) afforded (*S*)-MTPA ester **32** (0.4 mg, 0.2 μmol, 3% for the three steps).

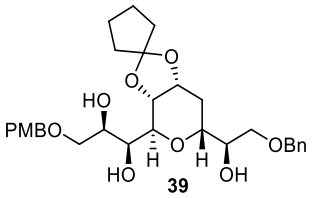
R_f = 0.49 (Hexane/EtOAc = 2/1); ^1H NMR (600 MHz, $CDCl_3$, shigemi tube CMS-005TJ) δ 7.50–7.17 (m, 45H), 5.62 (d, *J* = 7.2 Hz, 1H), 5.18 (dd, *J* = 7.2, 3.6 Hz, 1H), 5.15 (s, 1H), 5.12–5.09 (m, 1H), 4.97 (s, 1H), 4.32 (ddd, *J* = 10.8, 5.4, 5.4 Hz, 1H), 4.25 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.13 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.07–3.96 (m, 9H), 3.94 (ddd, *J* = 10.8, 7.2, 7.2 Hz, 1H), 3.89 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.64 (ddd, *J* = 9.6, 5.4 Hz, 1H), 3.59 (ddd, *J* = 6.0, 6.0, 3.6 Hz, 1H), 3.48–3.45 (m, 12H), 3.44 (s, 3H), 3.43–3.42 (m, 6H), 3.40 (s, 3H), 3.32 (s, 3H), 2.12–1.95 (m, 2H), 1.73–1.42 (m, 6H); HRMS (ESI-TOF) *m/z* [M + Na] calcd for $C_{109}H_{101}F_{27}O_{29}Na^+$ 2409.5890, found 2409.5907.



38

Acetal 38. To a solution of triol **37** (0.91 g, 2.0 mmol) in CH_2Cl_2 (20.4 mL) was added 1,1-dimethoxycyclopentane (2.2 mL, 16 mmol) and PPTS (102 mg, 0.408 mmol) at 0 °C. After being stirred at room temperature for 30 min, the resultant mixture was quenched with Et_3N and diluted with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (toluene/EtOAc = 10/1 → 5/1) afforded acetal **38** (1.01 g, 1.98 mmol, 98%) as a colorless syrup.

R_f = 0.50 (Hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.90 (ddd, *J* = 15.6, 5.4, 1.2 Hz, 1H), 5.80 (ddd, *J* = 15.6, 5.4, 1.2 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H) 4.53 (d, *J* = 12.0 Hz, 2H), 4.46 (s, 2H) 4.41 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.24 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.01 (d, *J* = 5.4 Hz, 2H), 3.87 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.54 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.61–3.53 (m, 2H), 2.64 (d, *J* = 3.6 Hz, 1H), 1.92–1.81 (m, 4H), 1.72–1.65 (m, 6H).

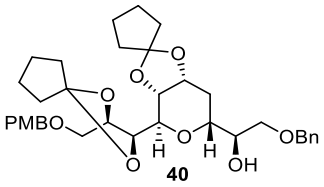


39

Triol 39. A mixture of $K_2OsO_4{\cdot}2H_2O$ (0.86 mg, 2.3 μmol), $(DHQD)_2PHAL$ (9.1 mg, 12 μmol), $K_3Fe(CN)_6$ (116 mg, 0.352 mmol), K_2CO_3 (48.5 mg, 0.351 mmol) and $MeSO_2NH_2$ (33.4 mg, 0.351 mmol) in *t*-BuOH (0.5 mL) and H_2O (1.2 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. To the resultant suspension was added a solution of olefin **38** (59.6 mg, 0.117 mmol) in *t*-BuOH (0.4 mL + 0.2, 0.2 mL rinse) via cannula. After being stirred at 0 °C for 5.5 h, the resultant mixture was quenched with solid $Na_2S_2O_3{\cdot}5H_2O$ (1.00 g, 4.0 mmol), and allowed to warm to room temperature over 1 h. Layers were separated and the aqueous layer was extracted with EtOAc. Combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/acetone = 4/1 → 2/1) afforded triol **39** (55.8 mg, 0.101 mmol, 87%) as a colorless syrup as a mixture with inseparable diastereomer (dr = 20:1).

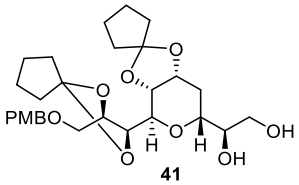
R_f = 0.20 (Hexane/EtOAc = 1/2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.22 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.27 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 4.09 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.01 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.84–3.75 (m, 4H), 3.78 (s, 3H), 3.64–3.58 (m, 2H), 3.55–3.49 (m, 2H), 3.18–3.01 (brs, 2H), 2.93–2.88 (brs, 1H), 2.03–1.96 (m, 2H), 1.87 (t, *J* = 7.2 Hz, 2H), 1.72–1.61 (m, 6H).



40

Acetal 40. To a solution of triol **39** (67.6 mg, 0.124 mmol) in CH_2Cl_2 (0.6 mL) was added 1,1-dimethoxycyclopentane (170 μL, 1.24 mmol) and PPTS (6.2 mg, 25 μmol) at 0 °C. After being stirred at room temperature for 1.5 h, the resultant mixture was quenched with Et_3N and diluted with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1) afforded acetal **40** (62.1 mg, 0.102 mmol, 82%) as a colorless syrup.

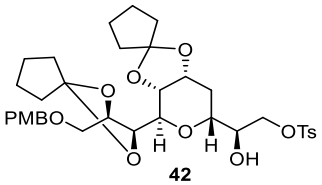
R_f = 0.61 (Hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.23 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 9.2, 6.0, 6.0 Hz, 1H), 4.18 (ddd, *J* = 7.2, 5.2, 5.2 Hz, 1H), 4.06 (dd, *J* = 5.2, 5.2 Hz, 1H), 3.99–3.96 (m, 2H), 3.82 (ddd, *J* = 10.8, 4.8, 4.2 Hz, 1H) 3.79–3.76 (m, 1H), 3.79 (s, 3H), 3.60 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.57 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.54 (dd, *J* = 9.6, 5.4 H, 1H), 3,52 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.75 (d, *J* = 3.6 Hz, 1H), 1.95–1.62 (m, 18H).



41

Diol 41. To a solution of benzyl ether **40** (12.3 mg, 20.1 μmol) in EtOH (0.20 mL) was added Raney Ni (excess), and placed under H_2 atmosphere. After being stirred at room temperature for 16 h, the insoluble materials were removed by filtration through a Celite® pad and rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 2/1 → 0/1) afforded diol **41** (10.5 mg, 20.1 μmol, 100%) as a colorless oil.

R_f = 0.34 (Hexane/EtOAc = 1/2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.26 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.19 (ddd, *J* = 7.2, 6.0, 6.0 Hz, 1H), 4.06 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.00 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.97 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.80 (s, 3H), 3.78 (ddd, *J* = 9.6, 5.4, 4.2 Hz, 1H), 3.70 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.64–3.58 (m, 3H), 3.53 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.98–2.91 (br, 1H), 2.37–2.28 (br, 1H), 1.95 (ddd, *J* = 13.2, 7.2, 3.6 Hz, 1H), 1.90–1.64 (m, 17H).

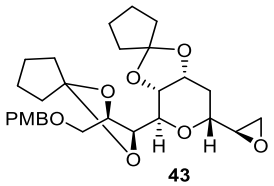


42

Tosylate 42. To a solution of diol **41** (267 mg, 513 μmol) in CH_2Cl_2 (5.1 mL) at 0 °C was added Et_3N (143 μL. 1.03 mmol), Bu_2SnO (12.7 mg, 51.3 μmol) and TsCl (108 mg, 564 μmol). After stirring at room temperature for 14 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 5/1 → 0/1) afforded tosylate **42** (280 mg, 415 μmol, 81%) as a colorless syrup.

Rf = 0.48 (Hexane/EtOAc = 1/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.13–4.08 (m, 2H), 4.05–4.01 (m, 2H), 3.98–3.94 (m, 2H), 3.81–3.78 (m, 1H), 3.80 (s, 3H), 3.76–3.73 (m, 1H),

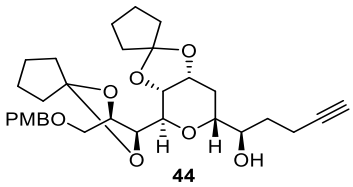
3.60 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.51 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.86–2.82 (br, 1H), 2.43 (s, 3H), 1.90 (ddd, *J* = 13.8, 5.4, 4.2 Hz, 1H), 1.86–1.63 (m, 17H).



43

Epoxide 43. To a solution of tosylate **42** (35.4 mg, 52.5 μmol) in CH_2Cl_2/MeOH (10:1 v/v, 1.8 mL) at 0 °C was added K_2CO_3 (7.3 mg, 53 μmol). After being stirred at room temperature for 1 h, the reaction mixture was quenched with pH 7 phosphate buffer. The resultant mixture was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1) afforded epoxide **43** (24.8 mg, 49.4 μmol, 94%) as a colorless syrup.

Rf = 0.55 (Hexane/EtOAc = 1/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0, 1H), 4.26 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 4.2 (ddd, *J* = 6.6, 5.4, 5.4 Hz, 1H), 4.12 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.01 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.98 (dd, *J* = 5.4, 3.6 Hz, 1H), 3.80 (s, 3H), 3.63–3.56 (m, 2H), 3.53 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 1H), 3.12 (ddd, *J* = 9.6, 3.0, 3.0 Hz, 1H), 2.77 (dd, *J* = 4.8 4.8 Hz, 1H), 2.66 (dd, *J* = 4.8, 3.0 Hz, 1H), 1.99 (ddd, *J* = 13.8, 4.8, 4.8 Hz, 1H), 1.91–1.64 (m, 17H).

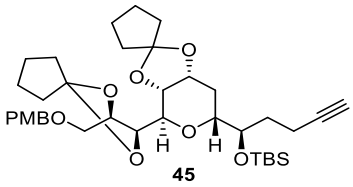


44

Alkyne 44. Two-necked flask is equipped with Liebig condenser and the exit from the condenser is connected to a trap cooled in dry ice-MeOH bath. A mixture of Zn powder (3.0 g, 46 mmol), EtOH (5.4 mL) and water (1.3 mL) was placed in the reaction flask. The reaction mixture was heated under reflux, and the 1,2-dichloropropene (3.0 mL, 33 mmol) was added dropwise such a rate that reflux is maintained without external heating. After the addition was complete, the reaction mixture was stirred under reflux for 1 h. The residual allene is purged from the reaction flask with a very slow stream of Ar. The crude allene was distilled at −30 °C.

To the mixture of Et_2O (11.1 mL) and hexane (3.8 mL) was added allene (355 μL, 5.73 mmol), and a solution of *n*-BuLi (1.51 M in hexane, 7.35 mL, 11.1 mmol) at −78 °C. The reaction mixture was allowed to warm to −15 °C where a white precipitate was formed and stirred at this temperature for 15 min. After this time, the reaction mixture was cooled to −78 °C, epoxide **43** (192 mg, 382 μmol) in Et_2O/hexane (v/v = 1:1, 4.9 mL + 2 × 1.6 mL rinse) was added, and the reaction mixture was allowed to warm to room temperature over 2 h. The resultant mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was separated and the aqueous layer was extracted with E_2tO. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 0/1) afforded alkyne **44** (167 mg, 307 μmol, 80%) as an yellow syrup.

Rf = 0.20 (Hexane/Acetone = 3/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.18 (ddd, *J* = 6.6, 5.4, 5.4 Hz, 1H), 4.06 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.99 (dd, *J* = 7.8, 3,6 Hz, 1H), 3.97 (dd, *J* = 5.4, 3.6 Hz, 1H), 3.80 (s, 3H), 3.70–3.66 (m, 1H), 3.62 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.58–3.53 (m, 2H), 2.70 (brd, *J* = 3.6 Hz, 1H), 2.42–2.31 (m, 2H), 1.96 (ddd, *J* = 10.8, 6.6, 4.2 Hz, 1H), 19.4 (t, *J* = 3.0 Hz, 1H), 1.90–1.62 (m, 17H).

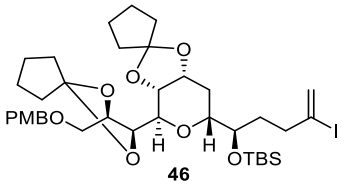


45

TBS Ether 45. To a solution of alkyne **44** (167 mg, 308 μmol) in CH_2Cl_2 (6.2 mL) were added 2,6-lutidine (106 μL, 1.08 mmol) and TBSOTf (108 μL, 0.462 mmol) at −20 °C and stirred at 0 °C for 1.5 h. The resultant mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 20/1 → 0/1) afforded TBS ether **45** (191 mg, 0.292 μmol, 95%) as a yellow syrup.

Rf = 0.60 (Hexane/EtOAc = 3/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 10.8, 6.0, 6.0 Hz, 1H), 4,16 (ddd, *J* = 6.6, 6.0, 6.0 Hz, 1H), 4.07 (dd, *J* = 5.4, 5.4 Hz, 1H),

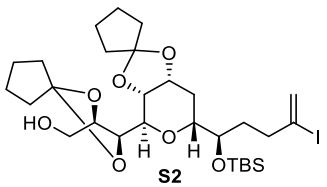
3.99–3.96 (m, 2H), 3.81 (s, 3H), 3.77 (ddd, *J* = 8.4, 4.2, 4.2 Hz, 1H), 3.70 (ddd, *J* = 12.0, 4.2, 4.2 Hz, 1H), 3.59–3.53 (m, 2H), 2.29–2.17 (m, 2H), 1.93 (t, *J* = 3.0 Hz, 1H), 1.91–1.59 (m, 18H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).



46

Iodoolefin 46. To a mixture of Ni(dppp)Cl_2 (4.6 mg, 8.6 μmol) and DIBALH (1M in toluene, 0.37 mL, 0.37 mmol) was added a solution of alkyne **45** (187 mg, 0.285 mmol) in THF (0.15 mL + 0.1 mL rinse) at 0 °C. After stirring at room temperature for 1 h, to the resultant mixture was added a solution of NIS (138 mg, 0.609 mmol) in THF (0.9 mL) via cannula at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was diluted with Et_2O and saturated aqueous Na^+/K^+ tartrate. The mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and 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 = 30/1 → 5/1) to afford iodoolefin **46** (105 mg, 0.133 mmol, 48%) as a colorless oil.

Rf = 0.47 (Hexane/EtOAc = 7/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.00 (s, 1H), 5.67 (s, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.25 (ddd, *J* = 10.2, 6.0, 6.0 Hz, 1H), 4.19–4.15 (m, 1H), 4.08 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.01–3.97 (m, 2H), 3.80 (s, 3H), 3.68 (ddd, *J* = 12.0, 3.0, 3.0 Hz, 1H), 3.62 (ddd, *J* = 6.6, 4.8, 4.8 Hz, 1H), 3.59–3.54 (m, 2H), 2.48 (ddd, *J* = 15.0, 10.2, 6.0 Hz, 1H), 2.39 (ddd, *J* = 15.0, 10.2, 6.0 Hz, 1H), 1.91–1.57 (m, 20H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

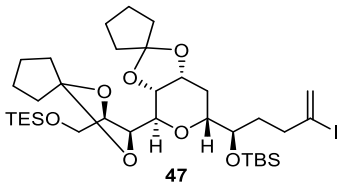


S2

Primary Alcohol S2. To a solution of PMB ether **46** (72.7 mg, 92.5 μmol) in CH_2Cl_2/pH 7 buffer (v/v = 10/1, 1.0 mL) at 0 °C was added DDQ (25.2 mg, 112 μmol). After being stirred at room temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ethyl acetate, and

the organic layer was 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 = 15/1 → 5/1) to afford primary alcohol **S2** (52.4 mg, 79.8 μmol, 99%) as a colorless oil.

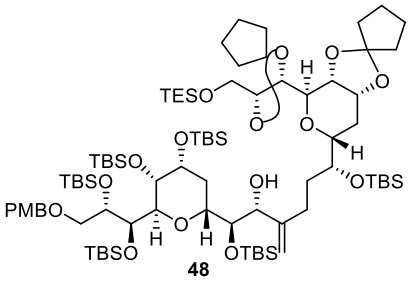
Rf = 0.33 (Hexane/EtOAc = 3/1), ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.69 (s, 1H), 4.27 (ddd, *J* = 10.4, 6.4, 6.4 Hz, 1H), 4.14–4.10 (m, 2H), 4.05 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.96 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.81 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.71–3.62 (m, 3H,), 2.48 (ddd, *J* = 1.52, 9.0, 6.0 Hz, 1H), 2.41 (ddd, *J* = 1.52, 9.0, 6.0 Hz, 1H), 1.92–1.60 (m, 20H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).



47

TES Ether 47. To a solution of primary alcohol **S2** (49.1 mg, 73.9 μmol) in THF (2.5 mL) at −20 °C was added NaH (60% in oli, 11.8 mg, 296 μmol) and TESCl (24.8 μL, 148 μmol). The reaction mixture was allowed to warm to 0 °C over 2 h. After being stirred at 0 °C for 1 h, the resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 100/1 → 30/1) to afford TES ether **47** (56.2 mg, 72.1 μmol, 98%) as a colorless oil.

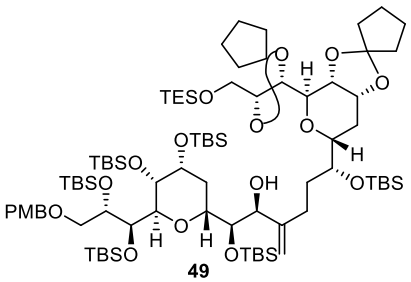
Rf = 0.80 (Hexane/EtOAc = 3/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.69 (s, 1H), 4.26 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 4.11 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.07 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.04–4.00 (m, 2H), 3.77–3.69 (m, 3H), 3.66 (ddd, *J* = 6.6, 4.8, 4.8 Hz, 1H), 2.50 (ddd, *J* = 15.0, 10.2, 5.4 Hz, 1H), 2.42 (ddd, *J* = 15.0, 10.2, 5.4 Hz, 1H), 1.91–1.60 (m, 20H), 0.96 (t, *J* = 8.4 Hz, 9H), 0.89 (s, 9H), 0.61 (q, *J* = 8.4 Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H).



48

Secondary Alcohol 48. To a solution of iodoolefin **47** (53.1 mg, 68.2 μmol) in dist Et_2O (1.7 mL) at −78 °C was added *t*-BuLi (1.92 M in pentane, 71 μL, 136 μmol). After being stirred at −78 °C for 10 min, a solution of aldehyde **4** (70.0 mg, 73.1 μmol) in THF (1.3 mL + 0.4 mL rinse) was added and the reaction mixture was stirred at −78 °C for 1 h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with *n*-hexane. The organic layer was 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/ethyl acetate = 1/0 → 30/1) to afford secondary alcohol **48** (32.5 mg, 20.3 μmol, 30%) as a mixture of diastereomers (dr = 1.7:1).

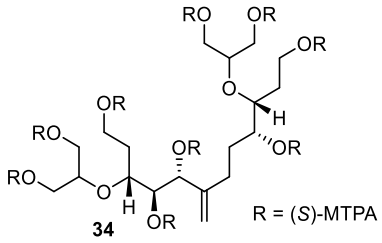
Rf = 0.48 (Hexane/EtOAc = 10/1), ^{1}H NMR of major compound (600 MHz, C_6D_6) δ 7.29 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 2H), 5.36 (s, 1H), 5.09 (s, 1H), 4.61 (d, *J* = 8.4 Hz, 1H), 4.48 (dd, *J* = 6.0, 4.8 Hz, 1H), 4.44 (s, 2H), 4.41–4.39 (br, 1H). 4.38–4.22 (m, 6H), 4.19–4.10 (m, 2H), 4.05 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.00–3.98 (br, 1H), 3.01–3.82 (m, 4H), 3.80 (ddd, *J* = 7.2, 4,2, 4.2 Hz, 1H), 3.62 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.37 (s, 3H), 2.67–2.59 (m, 2H), 2.50 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.19–1.88 (m, 12H), 1.81–1.75 (m, 2H), 1.65–1.55 (m, 8H), 1.11 (s, 9H), 1.09 (s, 9H), 1.06–1.03 (m, 36H), 0.66 (q, *J* = 7.8 Hz, 6H), 0.33 (s, 6H), 0.32 (s, 3H), 0.30 (s, 3H), 0.27 (s, 6H), 0.25 (s, 3H), 0.234 (s, 3H), 0.229 (s, 3H), 0.22 (s, 3H), 0.19 (s, 3H).



49

Secondary Alcohol 49. Rf = 0.48 (Hexane/EtOAc = 10/1), ^{1}H NMR of minor compound (600 MHz, C_6D_6) δ 7.30 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.47 (s, 1H), 5.15 (s,

1H), 4.53 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.46–4.30 (m, 9H), 4.29–4.25 (m, 1H), 4.18–4.14 (m, 2H), 4.01–3.96 (m, 2H), 3.88–3.80 (m, 5H), 3.65 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.34 (s, 3H), 3.08 (d, *J* = 9.0 Hz, 1H), 2.40 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.32–2.27 (m, 2H), 2.10–1.75 (m, 13H), 1.65–1.56 (m, 8H), 1.13 (s, 9H), 1.10 (s, 9H), 1.08 (s, 9H), 1.054 (s, 9H), 1.050 (s, 9H), 1.048 (s, 9H), 1.048 (t, *J* = 8.4 Hz, 9H), 0.66 (q, *J* = 8.4 Hz, 6H), 0.363 (s, 3H), 0.357 (s, 3H), 0.33 (s, 3H), 0.32 (s, 6H), 0.29 (s, 3H), 0.28 (s, 3H), 0.23 (s, 6H), 0.22 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H).



34

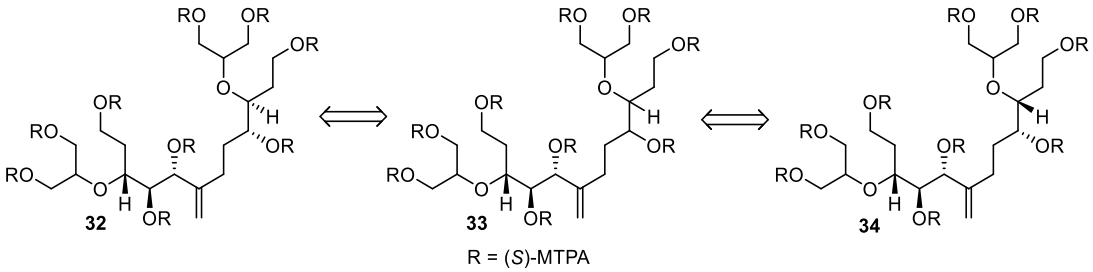
(*S*)-MTPA Ester 34. To a solution of compound **48** (5.2 mg, 3.3 μmol) in THF (0.3 mL) at 50 °C was added 70% HF·Py (19 μL, 0.92 mmol). After being stirred at 50℃ for 3 d, to the reaction mixture was added 70% HF·Py (38 μL, 1.8 mmol) and MeOH (0.15 mL). After stirring 3 d, the reaction mixture was quenched with Py and concentrated under reduced pressure. Purification by flash silica gel column chromatography ($MeOH/CH_3Cl$ = 1/5 → 1/2) afforded mixture of alcohol. The mixture was used in next reaction without further purification.

To the crude of alcohol was added HIO_4 (0.1 M in H_2O, 420 μL, 42.0 μmol). After being stirred at room temperature for 30 min, to the reaction mixture at 0 °C was added $NaBH_4$ (1 M in H_2O, 170 μL, 170 μmol). After stirring 30 min at 0 °C, the reaction mixture was quenched with AcOH and concentrated under reduced pressure. Purification by reversed phase silica gel colum chromatography ($MeOH/H_2O$ = 0/1 → 1/0) afforded mixture of alcohol. The mixture was used in next reaction without further purification.

Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*S*)-MTPA (100 mg, 0.426 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered and concentrated under reduced pressure. The residue was diluted with py (200 μL) and added to the crude of alcohol. After stirring 17 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by reversed phase HPLC (C18-MS-II waters 10 × 250 mm, 9% H_2O in methanol, 1.0 mL/min) afforded (*S*)-MTPA ester **34** (0.8 mg, 0.3 μmol, 10% for three steps).

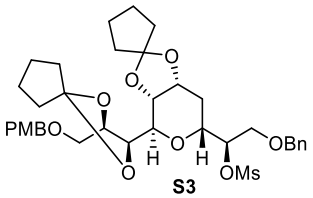
R_f = 0.49 (Hexane/EtOAc = 2/1); ^1H NMR (600 MHz, $CDCl_3$, shigemi tube CMS-005TJ) δ

7.48–7.28 (m, 45H), 5.17–5.14 (m, 1H), 5.15 (s, 1H), 4.99 (s, 1H), 4.90 (ddd, *J* = 9.6, 3.0, 3.0 Hz, 1H), 4.31 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.17–3.92 (m, 11H), 3.80 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.65–3.59 (m, 3H), 3.47 (s, 3H), 3.45 (s, 6H), 3.44 (s, 6H), 3.41 (s, 3H), 3.42 (s, 3H), 3.33 (s, 3H), 2.08–1.98 (m, 2H), 1.87–1.50 (m, 6H); HRMS (ESI-TOF) *m/z* [M + Na] calcd for $C_{109}H_{101}F_{27}O_{29}Na^+$ 2409.5890, found 2409.5869.



Carbon	δ (**33**)	δ (**32**)	Δδ [ppm]	δ (**34**)	Δδ [ppm]
36	4.31	4.31	0.00	●	●
36	4.00	4.01	−0.01	●	●
37	1.68	1.69	−0.01	1.53	0.15
37	1.53	1.53	0.00	1.53	0.00
38	3.42	3.42	0.00	3.62	−0.20
39	5.09	5.10	−0.01	4.90	0.19
40	1.72	1.73	−0.01	1.81	−0.09
40	1.58	1.58	0.00	1.58	0.00
41	2.08	2.09	−0.01	2.04	0.04
43	5.59	5.60	−0.01	5.56	0.03
44	5.17	5.18	−0.01	5.15	0.02
45	3.57	3.58	−0.01	3.60	−0.03
46	1.52	1.53	−0.01	1.53	−0.01
47	4.04	4.04	0.00	●	●
47	3.93	3.94	−0.01	●	●
70	5.14	5.14	0.00	5.14	0.00
70	4.96	4.96	0.00	4.98	−0.02

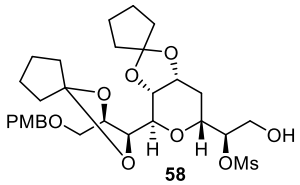
Figure S5. ^{1}H chemical shifts of **32**, **33**, **34** (600 MHz, $CDCl_3$), ●: not analyzed .



Mesylate S3. To a solution of acetal **42** (127 mg, 0.208 mmol) in CH_2Cl_2 (7.3 mL) were added Et_3N (91 μL, 0.83 mmol) and MsCl (32 μL, 0.42 mmol) at 0 °C. After being stirred at 0 °C for 10 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 7/1 → 1/1) afforded mesylate **S3** (138 mg, 0.200 mmol, 96%) as a colorless syrup.

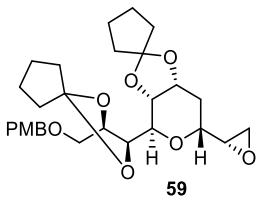
R_f = 0.74 (Hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.31–7.29 (m, 3H), 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.89 (ddd, *J* = 5.4, 4.8, 4.8 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 10.2 Hz, 2H), 4.24 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.20 (ddd, *J* = 7.8, 5.4, 5.4 Hz, 1H), 4.12 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.02 (ddd, *J* = 9.0, 6.6, 4.2 Hz, 1H), 3.98–3.95 (m, 2H), 3.79 (s, 3H), 3.76–3.74 (m, 2H), 3.59 (d, *J* = 4.8 Hz, 2H), 3.01 (s, 3H), 1.99 (ddd, *J* = 12.6, 4.8, 4.8 Hz, 1H), 1.90–1.73 (m, 7H), 1.72–1.62 (m, 10H).



58

Alcohol 58. To a solution of mesylate **S3** (347 mg, 0.503 mmol) in EtOH (5.0 mL) was added Raney Ni (excess), and placed under H_2 atmosphere. After being stirred at room temperature for 7.5 h, the insoluble materials were removed by filtration through a Celite pad and rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 2/1 → 0/1) afforded alcohol **58** (223 mg, 0.370 mol, 74%) as a colorless oil.

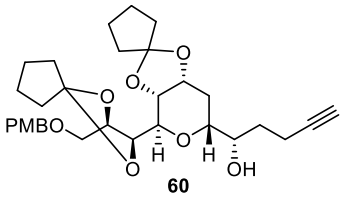
R_f = 0.21 (Hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.79 (ddd, *J* = 5.4, 5.4, 3.6 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.26 (dd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.20 (ddd, *J* = 6.6, 5.4, 5.4 Hz, 1H), 4.12 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.01 (ddd, *J* = 9.6, 6.0, 4.2 Hz, 1H), 3.99–3.97 (m, 2H), 3.93 (dd, *J* = 12.0, 3.0 Hz 1H), 3.83–3.79 (m, 1H), 3.81 (s, 3H), 3.61 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.58 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.06 (s, 3H), 2.01 (ddd, *J* = 13.8, 5.4, 5.4 Hz, 1H), 1.91–1.76 (m, 7H), 1.72–1.64 (m, 10H).



59

Epoxide 59. To a solution of alcohol **58** (241.3 mg, 0.403 mmol) in MeOH (13.4 mL) was added K_2CO_3 (27.9 mg, 0.202 mmol) at 0 °C and stirred at room temperature for 24 h. To the reaction mixture was added K_2CO_3 (27.9 mg, 0.202 mmol) five times every 24 h. After 12 h from final addition, the mixture was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 5/1 → 1/0) afforded epoxide **59** (162 mg, 0.323 mmol, 80%) as a colorless syrup.

R_f = 0.21 (Hexane/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.26 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.18 (ddd, *J* = 7.2, 5.4, 5.4 Hz, 1H), 4.09 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.00 (dd, *J* = 7.2, 4.2 Hz, 1H), 3.95 (dd, *J* = 4.2, 4.2 Hz, 1H), 3.80 (s, 3H), 3.61–3.54 (m, 3H), 3.05 (ddd, *J* = 4.2, 4.2, 3.0 Hz, 1H), 2.72 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.63 (dd, *J* = 5.4, 3.6 Hz, 1H), 1.99 (ddd, *J* = 13.2, 5.4, 4.2 Hz, 1H), 1.91–1.63 (m, 17H).



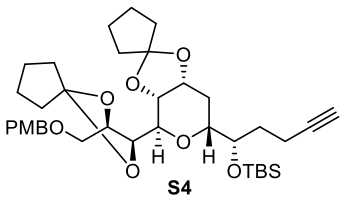
60

Alkyne 60. Two-necked flask is equipped with Liebig condenser and the exit from the condenser is connected to a trap cooled in dry ice-MeOH bath. A mixture of Zn powder (7.0 g, 0.11 mol), EtOH (9.3 mL) and water (1.9 mL) was placed in the reaction flask. The reaction mixture was heated under reflux, and the 1,2-dichloropropene (5.0 mL, 54 mmol) was added dropwise in such a rate that reflux is maintained without external heating. After the addition was complete, the reaction mixture was stirred under reflux for 1 h. The residual allene is purged from the reaction flask with a very slow stream of Ar. The crude allene was distilled at −30 °C.

To a mixture of Et_2O (15.1 mL) and hexane (5.6 mL) at −78 °C were added allene (0.48 mL, 7.7 mmol) followed by a solution of *n*-BuLi (1.6 M in hexane, 9.46 mL, 15.1 mmol). The reaction mixture was allowed to warm to −15 °C where a white precipitate was formed and stirred at this temperature for 15 min. After this time, the reaction mixture was cooled to −78 °C and the solution of epoxide **59** (155 mg, 0.309 mmol) in Et_2O/hexane (1:1, v/v, 4.0 mL + 2 × 1.3 mL rinse) was added to the reaction mixture. When the addition was completed,

the reaction mixture was allowed to warm to room temperature over 2 h. The resultant mixture was quenched with pH 7.0 phosphate buffer at −78 °C and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 7/1 → 3/1) afforded alkyne **60** (152 mg, 0.280 mmol, 91%) as an yellow syrup.

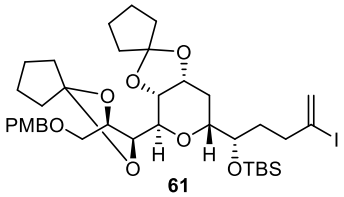
R_f = 0.34 (Hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.27 (ddd, *J* = 8.8, 6.0, 6.0 Hz, 1H), 4.17 (ddd, *J* = 6.8, 4.8, 4.8 Hz, 1H), 4.05 (dd, *J* = 5.6, 4.0 Hz, 1H), 4.01–3.96 (m, 2H), 3.85 (ddd, *J* = 9.6, 4.8, 3.2 Hz 1H), 3.81 (s, 3H), 3.61–3.53 (m, 3H), 2.37–2.30 (m, 2H), 1.93 (t, *J* = 2.8 Hz, 1H), 1.91–1.50 (m, 20H).



S4

TBS Ether S4. To a solution of alkyne **60** (146 mg, 0.270 mmol) in CH_2Cl_2 (5.4 mL) were added 2,6-lutidine (110 μL, 0.950 mmol) and TBSOTf (93 μL, 0.41 mmol) at −20 °C and stirred at 0 °C for 45 min. The resultant mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 20/1 → 5/1) afforded TBS ether **S4** (161 mg, 0.244 mmol, 91%) as a yellow syrup.

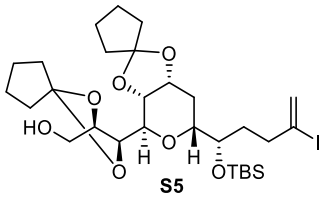
R_f = 0.80 (Hexane/EtOAc = 2/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.24 (ddd, *J* = 9.2, 6.0, 6.0 Hz, 1H), 4.18 (ddd, *J* = 7.6, 5.2, 5.2 Hz, 1H), 4.04 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.97 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.90 (dd, *J* = 4.0, 4.0 Hz, 1H), 3.88–3.85 (m, 1H), 3.81 (s, 3H), 3.60–3.54 (m, 2H), 3.50 (ddd, *J* = 10.2, 5.4, 3.6 Hz, 1H), 2.26–2.22 (m, 2H), 1.91 (t, *J* = 2.4 Hz, 1H), 1.91–1.59 (m, 20H), 0.88 (s, 9H), 0.08 (s, 6H).



61

Iodoolefin 61. To a mixture of Ni(dppp)Cl_2 (3.7 mg, 6.0 μmol) and DIBALH (1M in toluene, 292 μL, 0.292 mmol) was added a solution of alkyne **S4** (144 mg, 0.219 mmol) in THF (0.15 mL + 0.075 mL rinse) at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 1 h. To the resultant mixture was added a solution of NIS (101 mg, 0.450 mmol, 2 eq) in THF (0.75 mL) via cannula at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was diluted with Et_2O and saturated aqueous Na^+/K^+ tartrate. The mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and 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 = 20/1 → 5/1) to afford iodoolefin **61** (141 mg, 0.179 mmol, 82%) as a colorless oil.

R_f = 0.40 (Hexane/EtOAc = 5/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.00 (s, 1H), 5.66 (s, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.24 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4,17 (ddd, *J* = 7.2, 5.4, 5.4 Hz, 1H), 4.02 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.00 (dd, *J* = 7.2, 3.0 Hz, 1H), 3,91 (dd, *J* = 4.2, 3.6 Hz, 1H), 3.80 (s, 3H), 3.81–3.76 (m, 1H), 3.60 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.55 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.51 (ddd, *J* = 10.2, 6.0, 3.6 Hz, 1H), 2.50–2.39 (m, 2H), 1.95 (ddd, *J* = 13.8, 6.0, 3.0 Hz, 1H), 1.91–1.74 (m, 7H), 1.73–1.60 (m, 12H), 0.88 (s, 9H), 0.070 (s, 6H).

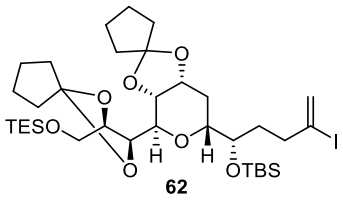


S5

Primary Alcohol S5. To a solution of PMB ether **61** (135 mg, 0.172 mmol) in CH_2Cl_2/pH 7 buffer (v/v = 10/1, 1.9 mL) at 0 °C was added DDQ (46.5 mg, 0.205 mmol). After being stirred for 3.5 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ethyl acetate, and the organic layer was 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 = 20/1 → 8/1) to afford primary alcohol **S5** (106 mg, 0.159 mmol, 94%) as a colorless oil.

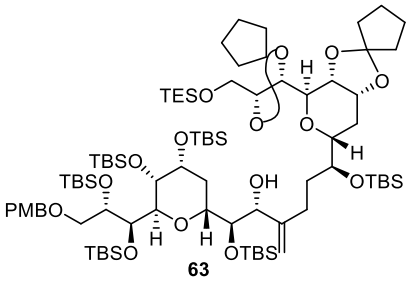
R_f = 0.41 (Hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (d, *J* = 1.6 Hz, 1H), 5.68 (d, *J* = 1.6, 1H), 4.27 (ddd, *J* = 9.6, 6.0, 6.0 Hz, 1H), 4.12–4.02 (m, 3H), 3.87 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.86–3.80 (m, 2H), 3.67 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.53 (ddd, *J* = 10.0, 6.0, 3.6 Hz, 1H), 2.46 (ddd, *J* = 10.0, 6.0, 6.0, 2H), 1.96 (ddd, *J* = 13.2, 6.0, 3.6 Hz, 1H), 1.93–1.64 (m, 19H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).



62

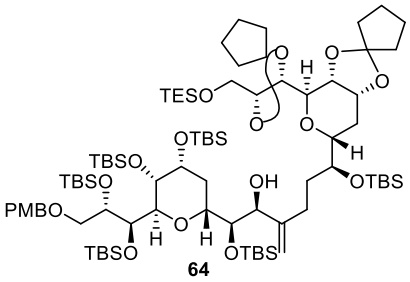
TES Ether 62. To a solution of primary alcohol **S5** (69.8 mg, 0.105 mmol) in THF (3.5 mL) at 0 °C were added NaH (60% in oil, 17.0 mg, 0.425 mmol) and TESCl (35 μL, 0.21 mmol). After being stirred at 0 °C for 30 min, additional NaH (60% in oil, 34.0 mg, 0.853 mmol) and TESCl (70 μL, 0.42 mmol) were added at 0 °C. After being stirred at 0 °C for 1 h, the resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 1/0 → 0/1) to afford TES ether **62** (80.9 mg, 0.104 mmol, 99%) as a colorless oil.

R_f = 0.50 (Hexane/EtOAc = 10/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.01 (d, *J* = 1.2 Hz, 1H), 5.67 (d, *J* = 1.2 Hz, 1H), 4.26 (ddd, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.09–4.01 (m, 3H), 3.97 (dd, *J* = 4.2, 3.0 Hz, 1H), 3.81–3.78 (m, 1H), 3.78 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.71 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.56 (ddd, *J* = 10.2, 6.6, 3.0 Hz, 1H), 2.53–2.42 (m, 2H), 1.97 (ddd, *J* = 13.8, 6.6, 3.0 Hz, 1H), 1.94–1.62 (m, 19H), 0.96 (t, *J* = 8.4 Hz, 9H), 0.90 (s, 9H), 0.61 (q, *J* = 7.8 Hz, 6H), 0.083 (s, 3H), 0.081 (s, 3H).

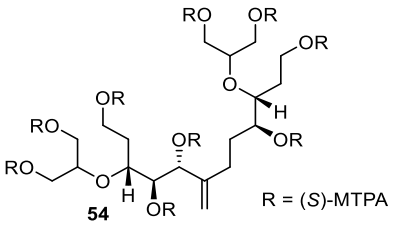


Secondary Alcohol 63. To a solution of iodoolefin **62** (29.4 mg, 37.7 μmol) in dist. Et_2O (0.94 mL) at −78 °C was added *t*-BuLi (1.64 M in pentane, 46 μL, 75 μmol). After being stirred at −78 °C for 10 min, a solution of aldehyde **4** (38.7 mg, 40.4 μmol) in THF (0.70 mL + 0.24 mL rinse) was added and the reaction mixture was stirred at −78 °C for 1 h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with *n*-hexane. The organic layer was 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/ethyl acetate = 1/0 → 30/1) to afford secondary alcohol **63** (26.5 mg, 16.4 μmol, 43%) as a mixture of diastereomers (dr = 2.3:1).

R_f = 0.37 (Hexane/EtOAc = 10/1); ^{1}H NMR of major compound (600 MHz, C_6D_6), δ 7.31 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.33 (s, 1H), 5.05 (s, 1H), 4.66 (dd, *J* = 7.2 Hz, 1H), 4.48 (dd, *J* = 6.0, 4.2 Hz, 1H), 4.44 (s, 2H), 4.42–4.41 (m, 1H), 4.40 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.36 (dd, *J* = 7.8, 4.2 Hz, 1H), 4.34–4.31 (m, 2H), 4.29 (d, *J* = 10.8 Hz, 1H), 4.24 (d, *J* = 10.8 Hz, 1H), 4.21 (ddd, *J* = 7.8, 4.8, 4.8 Hz, 1H), 4.18–4.12 (m, 2H), 4.12–4.10 (m, 1H), 4.06 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.00 (ddd, *J* = 8.4, 3.6, 3.6 Hz, 1H), 3.88 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.84–3.78 (m, 2H), 3.69 (ddd, *J* = 12.0, 3.6, 3.6 Hz, 1H), 3.63 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.35 (s, 3H), 2.54 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.53–2.41 (m, 2H), 2.17–2.03 (m, 4H), 1.97–1.86 (m, 6H), 1.85–1.75 (m, 3H), 1.65–1.54 (m, 8H), 1.15 (s, 9H), 1.12 (s, 9H), 1.09 (s, 9H), 1.05 (t, *J* = 8.4 Hz, 9H), 1.05 (s, 9H), 1.03 (s, 18H), 0.65 (q, *J* = 8.4 Hz, 6H), 0.342 (s, 3H), 0.340 (s, 3H), 0.33 (s, 3H), 0.31 (s, 6H), 0.27 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.23 (s, 6H).



Secondary Alcohol 64. R_f = 0.37 (Hexane/EtOAc = 10/1); ^{1}H NMR of minor compound (600 MHz, C_6D_6) δ 7.32 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 5.53 (s, 1H), 5.13 (s, 1H), 4.54 (dd, *J* = 6.6, 3.6 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.42–4.31 (m, 8H), 4.21 (ddd, *J* = 7.8, 4.8, 4.8 Hz, 1H), 4.20–4.15 (m, 2H), 4.03–3.97 (m, 3H), 3.85 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.81 (d, *J* = 4.8 Hz, 2H), 3.74 (ddd, *J* = 10.2, 3.6, 3.6 Hz, 1H), 3.65 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.33 (s, 3H), 3.17 (d, *J* = 9.6 Hz, 1H), 2.57–2.50 (m, 1H), 2.38 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.17–1.72 (m, 14H), 1.66–1.54 (m, 8H), 1.14 (s, 9H),, 1.13 (s, 9H), 1.01 (s, 9H), 1.058 (s, 9H), 1.054 (s, 18H), 1.04 (t, *J* = 8.4 Hz, 9H), 0.64 (q, *J* = 8.4 Hz, 6H), 0.37 (s, 6H), 0.34 (s, 3H), 0.33 (s, 9H), 0.293 (s, 3H), 0.289 (s, 3H), 0.28 (s, 3H), 0.23 (s, 3H), 0.213 (s, 3H), 0.211 (s, 3H).



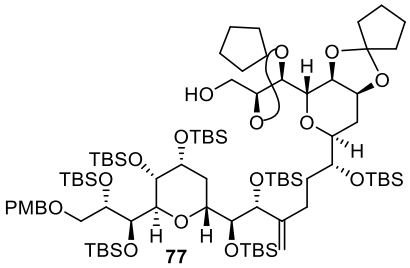
MTPA Ester 54. To a solution of compound **63** (9.4 mg, 5.8 μmol) in THF (0.6 mL) at 50 °C was added 70% HF·Py (35 μL, 1.7 mmol). After 36 h, to the reaction mixture was added 70% HF·Py (35 μL, 1.7 mmol) and MeOH (0.05 mL). After being stirred 5 d, the reaction mixture was quenched with Py and concentrated under reduced pressure. Purification by flash silica gel column chromatography (MeOH/CH_3Cl = 1/5, 2/1, 1/2) afforded a mixture of alcohols. The mixture was used in the next reaction without further purification.

To the crude alcohols, HIO_4 (0.2 M in H_2O, 448 μL, 89.6 μmol) was added. After being stirred at room temperature for 30 min, the reaction mixture was cooled to 0 °C and treated with $NaBH_4$ (2 M in H_2O, 179 μL, 358 μmol). After being stirred at 0 °C for 30 min, the reaction mixture was quenched with AcOH and concentrated under reduced pressure. Purification by reversed phase silica gel column chromatography (MeOH/H_2O = 0/1 → 1/0)

afforded a mixture of alcohols. The mixture was used in the next reaction without further purification.

Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*S*)-MTPA (100 mg, 0.426 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h the mixture was filtered and concentrated under reduced pressure. The residue was diluted with Py (350 μL) and added to the crude mixture of alcohols. After being stirred at room temperature for 1 h, Py (700 μL) and Et_3N (118 μL, 0.852 mmol) were added. After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by HPLC (C18-MS-II waters 10 × 250 mm, 9% H_2O in methanol, 1.0 mL/min) afforded mixture of (*S*)-MTPA ester **54**.

Synthetic Procedures for Amphidinol 3

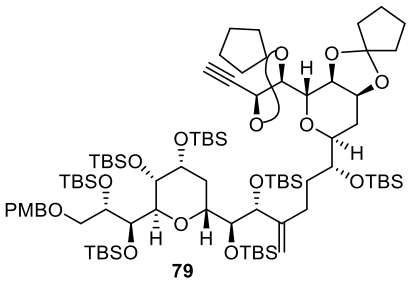


77

Alcohol 77. To a solution of TES ether **29** (210 mg, 0.121 mmol) in THF (6.1 mL) was added TBAF-AcOH (0.2 M in THF, 1.2 mL, 0.24 mmol) at 0 °C. After being stirred at 0 °C for 4 h, the resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/CH_2Cl_2 = 20/1 → 5/1) to afforded alcohol **77** (183 mg, 0.114 mmol, 94%) as a colorless oil.

R_f = 0.33 (hexane/EtOAc = 5/1); $[\alpha]_D^{26}$ −8.9 (*c* 0.34, $CHCl_3$); IR (film) ν 3493, 2953, 2928, 2885, 2856, 2360, 2342, 1514, 1472, 1388, 1361, 1334, 1251, 1111, 1040, 1005, 938, 834, 777, 669 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ7.31 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.38 (s, 1H), 5.12 (s, 1H), 4.72 (s, 1H), 4.51–4.46 (m, 1H), 4.43 (s, 2H), 4.40 (s, 1H), 4.36–4.32 (m, 2H), 4.30 (dd, *J* = 5.4, 3.6 Hz, 1H), 4.26 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.24 (d, *J* =

10.8 Hz, 1H), 4.20–4.13 (m, 3H), 4.12–4.05 (m, 2H), 3.89–3.82 (m, 2H), 3.78–3.73 (m, 2H), 3.68–3.61 (m, 2H), 3.34 (s, 3H), 2.71 (ddd, *J* = 16.2, 12.0, 4.2 Hz, 1H), 2.47 (ddd, *J* = 16.2, 10.8, 4.8 Hz, 1H), 2.35–2.25 (m, 1H), 2.22–2.14 (m, 1H), 2.14–2.06 (m, 2H), 2.05–1.99 (m, 1H), 1.96–1.74 (m, 8H), 1.66–1.52 (m, 9H), 1.14 (s, 9H), 1.12 (s, 9H), 1.11 (s, 9H), 1.10 (s, 9H), 1.08 (s, 9H), 1.06 (s, 9H), 1.05 (s, 9H), 0.40 (s, 3H), 0.356 (s, 3H), 0.350 (s, 3H), 0.346 (s, 3H), 0.331 (s, 3H), 0.328 (s, 3H), 0.304 (s, 3H), 0.297 (s, 3H), 0.279 (s, 3H), 0.273 (s, 3H), 0.266 (s, 3H), 0.259 (s, 3H), 0.234 (s, 3H), 0.230 (s, 3H) ; ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 130.9, 129.6 (2C), 119.7, 118.6, 114.1 (2C), 112.8, 80.4, 80.3, 80.0, 78.0, 77.9, 75.3, 74.8, 74.1 (2C), 73.8, 73.3, 73.0, 72.8, 72.1, 71.4, 69.4, 68.9, 62.8, 54.8, 37.9, 37.8, 37.7, 37.6, 32.9, 30.8, 28.0, 27.4, 26.7 (3C), 26.60 (3C), 26.55 (6C), 26.51 (3C), 26.4 (3C), 26.3 (3C), 24.0, 23.9, 23.71, 23.66, 18.9 (2C), 18.73, 18.67, 18.65, 18.63, 18.5, −2.7, −3.5, −3.6 (3C), −3.77, −3.83 (2C), −3.9, −4.01, −4.02, −4.2, −4.3, −5.1; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{83}H_{160}O_{16}Si_7Na$ 1631.9983, found 1632.0041.



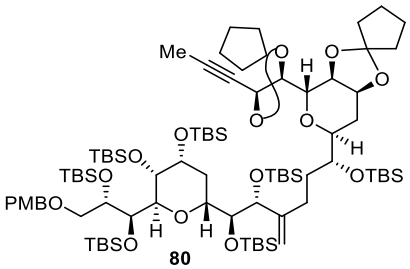
79

Terminal alkyne 79. To a solution of $(COCl)_2$ (32 μL, 0.37 mmol) in CH_2Cl_2 (1.8 mL) was added DMSO (52 μL, 0.74 mmol) at −78 ℃. After being stirred at −78 °C for 15 min, a solution of alcohol **77** (119 mg, 73.6 μmol) in CH_2Cl_2 (1.2 mL + 0.6 mL rinse) was added to the mixture at −78 °C. After being stirred at −78 ℃ for 5 min, Et_3N (0.21 mL, 1.47 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was warmed to room temperature over 1h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. Organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford mixture of aldehyde **78** (122 mg). The mixture was used in the next reaction without further purification.

To a solution of Ohira–Bestman reagent (32.3 mg, 0.168 mmol) in MeOH (0.30 mL) was added Cs_2CO_3 (54.0 mg, 0.168 mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of aldehyde **S3** in CH_2Cl_2 (0.97 mL + 0.5 mL rinse) was added. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. Organic layer was washed with saturated aqueous

NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1 → 5/1) to afforded terminal alkyne **79** (110 mg, 68.2 μmol, 93% for two steps) as a colorless oil.

R_f = 0.70 (hexane/EtOAc = 5/1); $[\alpha]_D^{26}$ −9.5 (*c* 0.39, $CHCl_3$); IR (film) ν 3312, 2953, 2928, 2895, 2886, 2856, 1515, 1472, 1389, 1361, 1335, 1251, 1108, 1042, 1005, 938, 834, 777, 669 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.39 (s, 1H), 5.14 (s, 1H), 4.99 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.72 (brs, 1H), 4.58 (dd, *J* = 7.2, 4.2 Hz, 1H), 5.50–4.46 (m, 1H), 4.43–4.38 (m, 3H), 4.38–4.30 (m, 3H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.20–4.16 (m, 2H), 4.14 (brd, *J* = 6.0 Hz, 1H), 4.07 (brd, *J* = 10.8 Hz, 1H), 3.88–3.81 (m, 3H), 3.65 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.34 (s, 3H), 2.70 (ddd, *J* = 16.2, 6.0, 4.2 Hz, 1H), 2.44 (ddd, *J* = 16.2, 12.0, 4.8 Hz, 1H), 2.35–2.20 (m, 2H), 2.23 (d, *J* = 1.8 Hz, 1H), 2.16–2.03 (m, 4H), 1.98–1.85 (m, 6H), 1.77–1.72 (m, 2H), 1.62–1.50 (m, 8H), 1.117 (s, 9H), 1.113 (s, 9H), 1.105 (s, 9H), 1.10 (s, 9H), 1.08 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 0.38 (s, 3H), 0.35 (s, 3H), 0.334 (s, 6H), 0.326 (s, 3H), 0.324 (s, 3H), 0.31 (s, 3H), 0.29 (s, 3H), 0.28 (s, 3H), 0.267 (s, 3H), 0.262 (s, 3H), 0.255 (s, 3H), 0.230 (s, 3H), 0.225 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 130.8, 129.6 (2C), 121.1, 118.8, 114.1 (2C), 112.6, 82.38, 82.30, 80.5, 80.2, 78.0, 74.8, 74.7, 74.1 (2C), 73.6, 73.40, 73.35, 73.0, 72.5, 72.3, 71.4, 69.4, 69.0, 67.4, 54.8, 37.6, 37.3, 37.11, 37.06, 32.8, 30.6, 27.6, 27.2, 26.7 (3C), 26.59 (3C), 26.54 (6C), 26.50 (3C), 26.40 (3C), 26.36 (3C), 24.1 (2C), 23.6, 23.5, 18.9 (2C), 18.7 (4C), 18.5, −2.7, −3.6 (3C), −3.7, −3.79, −3.82 (2C), −3.85, −3.95, −3.40, −4.2, −4.3, −5.0; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{84}H_{158}O_{15}Si_7Na$ 1625.9878, found 1625.9843.

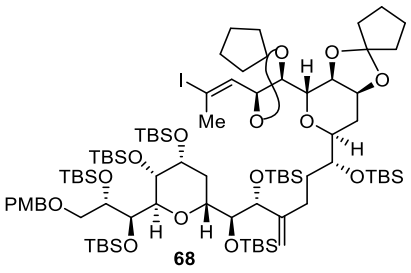


80

Alkyne 80. To a solution of terminal alkyne **79** (108 mg, 67.4 μmol) in THF (6.7 mL) was added LHMDS (1.3 M in THF, 0.52 mL, 0.67 mmol) at −78 °C. After being stirred at −78 °C for 1 min, MeI (50 μL, 0.80 mml) was added. The reaction mixture was warmed to room temperature and stirred for 4 h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. Organic layer was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1 →

5/1) to afforded alkyne **80** (109 mg, 67.4 μmol, quant) as a colorless oil.

R_f = 0.70 (hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ −12.9 (*c* 0.31, C_6H_6); IR (film) ν 2953, 2928, 2898, 2856, 2358, 2343, 2331, 1516, 1472, 1463, 1362, 1335, 1251, 1110, 1099, 1042, 835, 775, 674 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.31 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 1H), 5.15 (s, 1H), 5.04 (brd, *J* = 7.2 Hz, 1H), 4.72 (brs, 1H), 4.59 (dd, *J* = 7.2, 3.6 Hz, 1H), 4,50–4,46 (m, 1H), 4.45–4.35 (m, 6H), 4,24 (d, *J* = 10.2 Hz, 1H), 4.21–4.12 (m, 3H), 4.07 (brd, *J* = 10.2 Hz, 1H), 3.92–3.83 (m, 3H), 3.66 (dd, *J* = 8.4, 7.8 Hz, 1H), 3.33 (s, 3H), 2.74–2.66 (m, 1H), 2.47–2.39 (m, 1H), 2.36–2.25 (m, 1H), 2.26 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.21–2.10 (m, 2H), 2.09–1.89 (m, 8H), 1.79–1.74 (m, 2H), 1.65–1.52 (m, 8H), 1.51 (s, 3H), 1.11 (s, 18H), 1.10 (s, 18H), 1.08 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 0.38 (s, 3H), 0.34 (s, 9H), 0.33 (s, 6H), 0.31 (s, 3H), 0.29 (s, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.263 (s, 3H), 0.259 (s, 3H), 0.233 (s, 3H), 0.229 (s, 3H) ; ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.1, 130.9, 129.6 (2C), 120.5, 118.8, 114.1 (2C), 112.7, 83.2, 82.7, 80.5, 80.2, 77.7, 77.2, 75.1, 74.13, 74.06, 73.7, 73.3, 73.1 (2C), 72.5, 72.3, 71.4, 69.4, 69.1, 67.9, 54.8, 37.6, 37.4, 37.3 (2C), 32.9, 30.2, 27.6, 27.3, 26.64 (3C), 26.58 (3C), 26.53 (6C), 26.51 (3C), 26.4 (3C), 26.3 (3C), 24.1, 24.0, 23.6 (2C), 18.9 (2C), 18.6 (4C), 18.5, 3.5, −2.7, −3.6, −3.70 (3C), −3.76, −3.82 (3C), −3.9, −4.0, −4.2, −4.3, −5.0; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{85}H_{160}O_{15}Si_7Na$ 1640.0034, found 1640.0053.



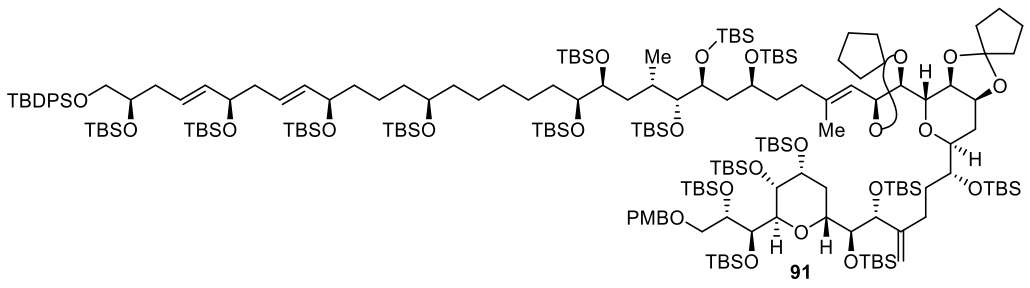
68

Iodoolefin 68. To a mixture of alkyne **80** (72.7 mg, 0.449 mmol) and $PdCl_2(P\text{-}o\text{-}tol_3)_2$ (3.5 mg, 4.5 μmol) in THF (0.45 mL) was added Bu_3SnH (0.6 mL, 2.25 mmol) dropwise over 2 h at room temperature. After being stirred for further 10 min, the resultant mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 200/1 → 50/1) to afforded vinyl stannane **81** (62.6 mg) as a colorless oil. Obtained compound was immediately used for the next reaction because of its instability.

To a solution of vinyl stannane **81** (62.6 mg) in CH_2Cl_2 (0.82 mL) at 0 °C was added a solution of I_2 (2 grain) in CH_2Cl_2 (800 μL) until the color of I_2 ceased to disappear. After being stirred at 0 °C for 10 min, the resultant mixture was quenched with satd. aq. $Na_2S_2O_3$.

The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 50/1) to afforded iodoolefin **68** (57.6 mg, 0.330 mmol, 73% for two steps) as a colorless oil.

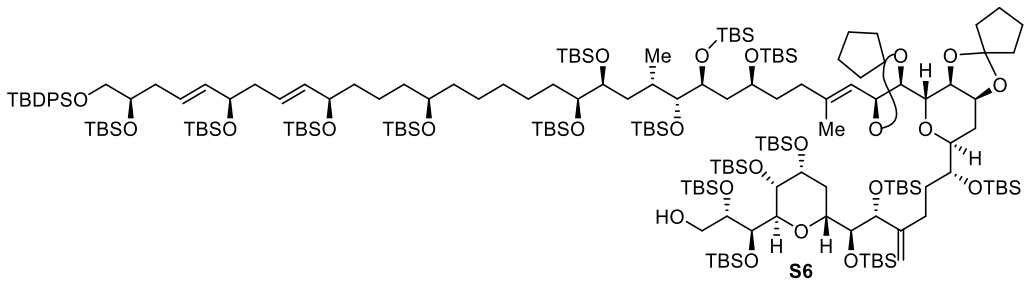
R_f = 0.54 (hexane/EtOAc = 10/1); $[\alpha]_D^{19}$ −22.8 (*c* 1.14, C_6H_6); IR (film) ν 2952, 2929, 2885, 2856, 1750, 1614, 1513, 1471, 1387, 1361, 1333, 1249, 1104, 1093, 1040, 1005, 938, 834, 775, 669 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.46 (dd, *J* = 9.0, 1.2 Hz, 1H), 5.40 (s, 1H), 5.14 (s, 1H), 4.92 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.71 (brs, 1H), 4.51–4.46 (m, 2H), 4.43–4.36 (m, 4H), 4.23 (d, *J* = 10.2 Hz, 1H), 4.20–4.12 (m, 5H), 4.07 (brd, *J* = 10.2 Hz, 1H), 3.89–3.81 (m, 3H), 3.65 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.33 (s, 3H), 2.65 (ddd, *J* = 10.2, 8.4, 7.8 H, 1H), 2.44–2.36 (m, 1H), 2.39 (d, *J* = 1.2 Hz, 3H), 2.35–2.26 (m, 1H), 2.28 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.1 (ddd, *J* = 12.0, 6.0, 3.6 Hz, 1H), 2.01 (ddd, *J* = 13.8, 7.8, 6.0 Hz, 1H), 1.96–1.85 (m, 8H), 1.80–1.70 (m, 2H), 1.62–1.50 (m, 8H), 1.11 (s, 18H), 1.10 (a, 18H), 1.07 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 0.36 (s, 3H), 0.34 (s, 3H), 0.33 (s, 6H), 0.32 (s, 3H), 0.30 (s, 3H), 0.29 (s, 3H), 0.27 (s, 3H), 0.26 (s, 12H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 150.9, 139.1, 130.8, 129.6 (2C), 119.7, 118.8, 114.1 (2C), 112.8, 101.5, 81.3, 80.5, 80.2, 77.9, 75.4, 74.8, 74.1 (2C), 73.8, 73.3, 73.0, 72.9, 72.7, 72.1, 71.4, 69.4, 69.0, 54.8, 37.8, 37.6, 37.1, 36.8, 33.1, 30.2, 28.7, 27.5, 26.62 (3C), 26.57 (3C), 26.53 (3C), 26.49 (3C), 26.4 (6C), 26.3 (3C), 26.22, 24.1, 23.77, 23.74, 23.4, 18.9 (2C), 18.7, 18.64, 18.62, 18.55, 18.5, −2.7, −3.65, −3.69 (2C), −3.78, −3.80 (2C), −3.82 (2C), −3.97, −4.01, −4.25, −4.29, −5.1; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{85}H_{161}O_{15}Si_7INa$ 1767.9157, found 1767.9105.



Coupling compound 91. To the mixture of polyol **67** (19.5 mg, 10.6 μmol) and 9-BBN dimer (12.9 mg, 52.8 μmol) at 0℃ was added THF (108 μL). After being stirred at room temperature for 1.5 h, 1 M Cs_2CO_3 aqueous (113 μL, 113 μmol) was added to the reaction mixture and then stirred at room temperature for 20 min. To the resultant mixture were added DMF (352 μL), a solution of iodoolefin **68** (12.3 mg, 7.04 μmol) in THF (174 μL + 70 μL

rinse) and $Pd(PPh_3)_4$ (1.2 mg, 1.1 μmol). The reaction mixture was stirred at room temperature for 30 min. The resultant mixture was diluted with Et_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 5/1) afforded coupling compound **91** (17.6 mg, 5.42 μmol, 77%) as a colorless oil.

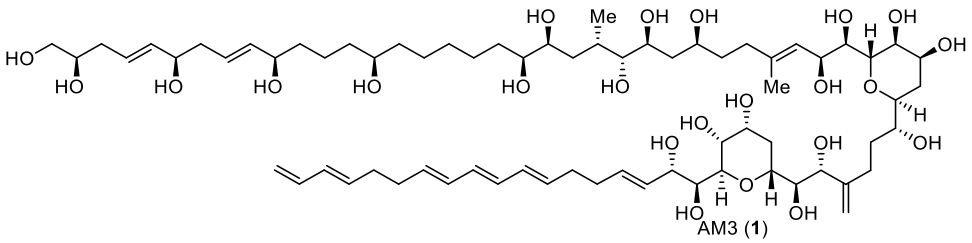
R_f = 0.67 (hexane/EtOAc = 10/1); $[\alpha]_D^{20}$ −23.0 (*c* 0.94, $CHCl_3$); IR (film) ν 2954, 2930, 2894, 2856, 2365, 2342, 2331, 1472, 1362, 1253, 1110, 1090, 1005, 836, 815, 775, 737, 709, 678, 668 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.84–7.79 (m, 4H), 7.32–7.24 (m, 8H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.84–5.77 (m, 2H), 5.71–5.61 (m, 3H), 5.39 (s, 1H), 5.14 (s, 1H), 5.12 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.73 (brs, 1H), 4.58 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.52–4.46 (m, 2H), 4.42 (s, 2H), 4.40 (brs, 1H), 4.30 (d, *J* = 6.6 Hz, 1H), 4.27–4.09 (m, 8H), 4.07 (brd, *J* = 10.8 Hz, 1H), 4.0 (brd, *J* = 12.0 Hz, 1H), 3.96 (d, *J* = 10.8 Hz, 1H), 3.94–3.71 (m, 9H), 3.65 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.36 (s, 3H), 2.71–2.57 (m, 2H), 2.54 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1H), 2.49–2.27 (m, 6H), 2.23 (ddd, *J* = 13.2, 13.2, 3.6 Hz, 1H), 2.18–1.98 (m, 10H), 1.97–1.78 (m, 8H), 1.95 (s, 3H), 1.77–1.36 (m, 25H), 1.21 (s, 9H), 1.13 (s, 9H), 1.12 (s, 18H), 1.11 (s, 9H), 1.10 (s, 9H), 1.083 (s, 18H), 1.080 (s, 9H), 1.075–1.057 (m, 45H), 1.04 (s, 18H), 1.00–0.96 (m, 12H), 0.376–0.052 (m, 96H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 142.7, 136.7, 136.3, 136.1 (2C), 134.1, 134.0, 130.8, 130.1, 129.6 (2C), 128.6, 128.4 (4C), 128.2 (2C), 126.6, 126.5, 123.2, 119.2, 118.6, 114.1 (2C), 112.9, 83.7, 83.5, 80.5, 80.3, 77.8, 75.8, 75.6, 75.5, 74.4, 74.3 (2C), 74.0 (2C), 73.8, 73.3, 73.2, 73.1 (2C), 72.9, 72.7, 72.6, 72.1, 71.4, 70.4, 69.4, 69.1, 67.5, 54.8, 42.1 (2C), 41.9, 39.5, 38.0, 37.9, 37.8 (2C), 37.6 (2C), 37.2, 37.0, 36.8, 36.7, 35.0, 34.1, 33.0, 30.71, 30.66, 27.7, 27.6, 27.2 (3C), 26.61 (3C), 26.59 (3C), 26.54 (3C), 26.50 (6C), 26.48 (3C), 26.41 (3C), 26.34 (3C), 26.32 (9C), 26.29 (6C), 26.26 (3C), 26.22 (3C), 26.19 (3C), 26.0, 24.2, 23.9, 23.8, 23.5, 21.8, 19.5, 18.9 (2C), 18.8, 18.67, 18.65 (2C), 18.62, 18.58, 18.55, 18.53, 18.51, 18.46, 18.44, 18.42, 18.38, 18.3, 17.3, 13.5, −2.8, −2.87, −2.95, −3.60, −3.61, −3.62, −3.65 (2C), −3.70, −3.77 (2C), −3.81, −3.83 (3C), −3.87, −4.0 (3C), −4.05, −4.08, −4.09, −4.23 (2C), −4.25, −4.26, −4.29, −4.35 (2C), −4.39, −4.5, −5.1; HRMS (ESI-TOF) *m/z* $[M + 2Na]^{2+}$ calcd for $C_{185}H_{362}O_{25}Si_{17}Na_2$ 1753.1459, found 1753.1610.



S6

Alcohol S6. To a solution of compound **91** (26.5 mg, 7.65 μmol) in CH_2Cl_2/pH 7 buffer (3/1, v/v, 1.0 mL) at 0 °C was added DDQ (3.5 mg, 15 μmol). After being stirred for 7.5 h at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with hexane, and the organic layer was 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 = 100/1 → 30/1) to afford primary alcohol **S6** (19.1 mg, 5.73 μmol, 75% for 2 cycles) as a colorless oil.

R_f = 0.44 (hexane/EtOAc = 20/1 ×2); $[\alpha]_D^{22}$ −20.1 (*c* 0.73, $CHCl_3$); IR (film) ν 2954, 2929, 2893, 2857, 1471, 1254, 1111, 1989, 1079, 834, 806, 775, 740 cm^{-1}; NMR (600 MHz, C_6D_6) δ 7.85–7.80 (m, 4H), 7.32–7.25 (m, 6H), 5.85–5.78 (m, 2H), 5.72–5.62 (m, 3H), 5.39 (s, 1H), 5.14–5.11 (m, 1H), 5.13 (s, 1H), 4.63 (s, 1H), 4.56 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.47 (ddd, *J* = 9.6, 6.6, 6.6 Hz, 1H), 4.38 (s, 1H), 4.32–4.19 (m, 7H), 4.18–4.10 (m, 3H), 4.07 (brd, *J* = 12.0 Hz, 1H), 3.98–3.85 (m, 6H), 3.84–3.71 (m, 6H), 2.67–2.58 (m, 2H), 2.55 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 2.49–2.33 (m, 4H), 2.32–2.20 (m, 3H), 2.18–1.80 (m, 19H), 1.95 (s, 3H), 1.78–1.38 (m, 24H), 1.21 (s, 9H), 1.14 (s, 9H), 1.13 (s, 18H), 1.12 (s, 9H), 1.10 (s, 9H), 1.090 (s, 9H), 1.088 (s, 9H), 1.085 (s, 9H), 1.079 (s, 9H), 1.077 (s, 9H), 1.071 (s, 27H), 1.05 (s, 9H), 1.03 (s, 9H), 1.01–0.97 (m, 12H) , 0.41–0.05 (m, 96H), ; ^{13}C NMR (150 MHz, C_6D_6) δ 150.8, 142.8, 136.7, 136.3, 136.1 (2C), 134.1, 133.9, 130.1, 128.6, 128.4 (4C), 128.2 (2C), 126.6, 126.5, 123.1, 119.3, 118.6, 112.3, 83.7, 83.5, 79.9 (2C), 78.3, 75.7 (2C), 75.4, 75.3, 74.4, 74.3, 74.0, 73.7, 73.2, 72.9, 72.8, 72.7 (2C), 72.5, 72.3, 72.0, 70.4, 69.4, 68.9, 67.5, 63.5, 42.1, 41.9, 39.5, 38.0, 37.85, 37.76 (2C), 37.6, 37.2, 37.0, 36.8, 36.6, 35.0, 34.0, 32.9, 31.4, 30.7, 30.6, 27.8, 27.7, 27.2 (3C), 27.0, 26.7 (3C), 26.6 (6C), 26.49 (3C), 26.47 (6C), 26.43 (3C), 26.40 (3C), 26.35 (3C), 26.32 (6C), 26.29 (6C), 26.26 (3C), 26.21 (3C), 26.19 (3C), 26.0, 24.2, 24.0, 23.8, 23.5, 21.8, 19.5, 19.1, 18.9, 18.8, 18.66, 18.63, 18.57 (2C), 18.52 (2C), 18.49, 18.46, 18.44, 18.41, 18.38 (2C), 18.32, 17.3, 13.5, −2.7, −2.87, −2.94, −3.59 (3C), −3.61 (2C), −3.65 (2C), −3.68, −3.8 (3C), −3.9 (3C), −4.0 (4C), −4.1, −4.21, −4.23 (3C), −4.34, −4.36 (2C), −4.39, −4.5, −4.9; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{177}H_{354}O_{24}Si_{17}Na$ 3363.2450, found 3363.2602.



Amphidinol 3. To a solution of $(COCl)_2$ (10 μL, 115 μmol) in CH_2Cl_2 (536 μL) at −78 °C was added DMSO (17 μL, 239 μmol). After being stirred at −78 °C for 15 min, a solution of primary alcohol **S6** (17.9 mg, 5.36 μmol) in CH_2Cl_2 (350 μL + 186 μL rinse) was added and then stirred at −78 °C for 5 min. To the reaction mixture was added Et_3N (64 μL, 459 μmol). The resultant mixture was warmed to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 200/1 to 100/1) to afford aldehyde **92** (17.9 mg) as a colorless oil, which was used in the next reaction immediately.

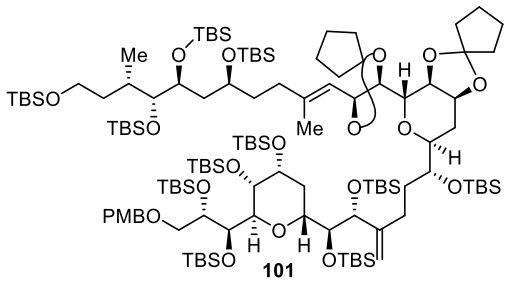
To a solution of sulfone **2** (11.0 mg, 26.8 μmol) and aldehyde **92** (17.9 mg) in THF/HMPA (4/1, v/v, 0.5 mL) at −78 °C was added KHMDS (0.5 M in THF, 43 μL, 21 μmol) dropwise. The resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was warmed to room temperature over 1 h and then stirred at room temperature for 3 h. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc, and the organic layer was 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 = 100/1 to 5/1) to provide coupling compound **93** (9.3 mg, *E*/*Z* = 10:1). The *E*/*Z* mixture of **93** was used in next reaction without further purification.

To a solution of the *E*/*Z* mixture of coupled product **93** (9.3 mg) in THF (1.5 mL) at 0 °C was added 18% HF·pyridine (120 μL, 0.39 mmol), and the mixture was stirred at 50 °C for 17 days, while 18% HF·pyridine was added six times (120 μL, 0.39 mmol at 10, 34, 94, 129, 177, 225 h). MeOH (0.3 mL) and $(CH_2OH)_2$ (0.3 mL) was also added at 141 h to facilitate the removal of the acetal group. The reaction was quenched with Et_3N and concentrated by blowing argon stream. Purification by reversed phase ODS column chromatography (MeOH/H_2O = 1/2 → 2/1) gave *E*/*Z* mixture of AM3 (2.0 mg) as a colorless oil. Further purification by reversed-phase HPLC (column: C18-MS-II waters 10 × 250 mm, eluent: MeOH/H_2O = 62/38, flow rate: 4 mL/min, detection: UV 250 nm) afforded AM3 (1.5 mg, 1.1 μmol) and intermediates remaining an acetal group (0.5 mg). The obtained intermediates were dissolved in MeOH (0.4 mL). To the solution of intermediates was added $(CH_2OH)_2$

(0.1 mL) and 18% HF·pyridine (40 μL, 0.13 mmol), and the mixture was stirred at 50 °C for 8 days, while 18% HF·pyridine was added 3 times (40 μL, 0.13 mmol at 24, 48, 96 h). After being quenched with Et_3N, the same manner of purification afforded desired AM3 (**1**) (0.4 mg, 0.30 μmol). In totally, 1.9 mg of AM3 (**1**) (1.4 μmol, 28% for 3 steps) was obtained.

R_f = 0.35 (MeOH/H_2O = 3/1), $[\alpha]_D^{26}$ −11.4 (*c* 0.09, CH_3OH); IR (film) ν 3360, 2927, 2853, 2360, 2341, 1651, 1418, 1077, 1038, 1027, 996, 973 cm^{-1}; NMR (600 MHz, CD_3OD/C_5D_5N = 2:1) δ 6.24 (ddd, *J* = 16.8, 10.8, 10.8 Hz, 1H), 6.08–5.97 (m, 5H), 5.86–5.74 (m, 3H), 5.71 (ddd, *J* = 16.2, 7.2, 7.2 Hz, 1H), 5.67–5.54 (m, 6H), 5.13 (s, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 5.00 (s, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.74 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.62 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.33 (s, 2H), 4.26 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.24–4.16 (m, 3H), 4.15–4.09 (m, 2H), 4.07 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.01 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.00–3.94 (m, 1H), 3.90–3.83 (m, 2H), 3.77–3.70 (m, 2H), 3.67–3.59 (m, 3H), 3.58–3.53 (m, 2H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.49–3.44 (m, 2H), 2.65–2.59 (m, 1H), 2.40–2.19 (m, 8H), 2.13–1.99 (m, 12H), 1.97–1.92 (m, 1H), 1.72 (s, 3H), 1.71–1.17 (m, 23H), 1.03 (d, *J* = 6.6 Hz, 3H) ; ^{13}C NMR (150 MHz, C_6D_6) δ 152.0, 138.6, 138.4, 137.1, 136.5, 135.3, 134.5, 134.2, 134.1, 132.6, 132.4, 132.3, 132.2, 132.0, 129.8, 128.5, 128.1, 126.8, 115.5, 112.7, 80.6, 79.7, 79.2, 76.7, 76.0, 75.8, 75.3, 74.5, 74.1, 73.4, 73.1 (2C), 73.0, 72.8, 72.7, 72.2, 72.1, 71.8, 70.6, 68.9, 68.7, 67.8, 67.4, 67.3, 66.9, 41.6, 41.4, 38.9, 38.54, 38.50, 38.48, 37.7, 36.9, 36.7, 34.1, 33.5 (2C), 33.4, 33.3, 32.6, 31.9, 31.6, 31.0, 30.8, 28.0, 27.1, 26.8, 22.8, 17.4, 13.2; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{70}H_{118}O_{23}Na$1349.7956, found 1349.7979.

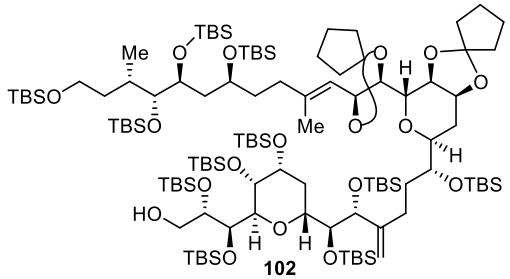
Synthesis procedure for C21–C67 analog



Coupling compound 101. To the mixture of polyol **86** (4.4 mg, 6.7 μmol) and 9-BBN dimer (8.2 mg, 34 μmol) at 0 °C was added THF (64 μL). After being stirred at room temperature for 1.5 h, 3 M Cs_2CO_3 aqueous (24 μL, 72 μmol) was added to the reaction mixture and then stirred at room temperature for 20 min. To the resultant mixture were added DMF (224 μL), a solution of iodoolefin **68** (7.8 mg, 4.5 μmol) in THF (110 μL + 50 μL rinse) and $Pd(PPh_3)_4$ (1.3 mg, 1.1 μmol). After being stirred at room temperature for 15 min, H_2O (48 μL) was

added and the reaction mixture was stirred for further 15 min at room temperature. The resultant mixture was diluted with Et_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 5/1) afforded coupling compound **101** (8.2 mg, 3.6 μmol, 80%) as a colorless oil.

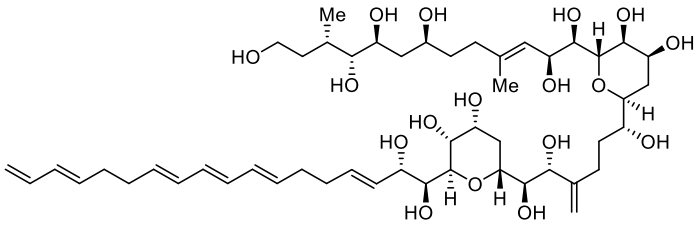
R_f = 0.50 (hexane/EtOAc = 10/1), $[\alpha]_D^{20}$ −22.9 (*c* 0.76, $CHCl_3$); IR (neat) ν 2953, 2929, 2894, 2857, 1513, 1472, 1388, 1361, 1334, 1252, 1099, 1041, 1005, 939, 834, 775 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.29 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.63 (d, *J* = 9.0 Hz, 1H), 5.38 (s, 1H), 5.13 (s, 1H), 5.10 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.72 (s, 1H), 4.55 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.50–4.45 (m, 2H), 4.42 (s, 2H), 4.39 (s, 1H), 4.29 (d, *J* = 8.4 Hz, 1H), 4.24 (d, *J* = 6.6 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.20–4.12 (m, 3H), 4.10–4.04 (m, 2H), 3.99 (ddd, *J* = 12.0, 9.0, 9.0 Hz, 1H), 3.89–3.81 (m, 3H), 3.70–3.60 (m, 4H), 3.34 (s, 3H), 2.70–2.63 (m, 1H), 2.58 (ddd, *J* = 12.0, 12.0, 3.6 Hz, 1H), 2.43 (ddd, *J* = 16.2, 8.4, 8.4 Hz, 1H), 2.37–2.25 (m, 2H), 2.21 (ddd, *J* = 12.0, 12.0, 3.6 Hz. 1H), 2.16–1.77 (18 H), 1.91 (s, 3H), 1.69–1.58 (m, 9H), 1.11 (s, 18H), 1.103 (s, 9H), 1.096 (s, 9H), 1.075 (s, 9H), 1.073 (s, 9H), 1.065 (s, 9H), 1.062 (s, 9H), 1.05 (s, 9H), 1.03 (s, 9H), 1.02–1.00 (m, 12H), 0.37 (s, 3H), 0.33 (s, 3H), 0.32 (s, 15 H), 0.29 (s, 3H), 0.28 (s, 3H), 0.270 (s, 3H), 0.267 (s, 3H), 0.257 (s, 6H), 0.253 (s, 3H), 0.23 (s, 3H), 0.22 (s, 6H), 0.18 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H) ; ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 142.8, 130.8, 129.6 (2C), 123.1, 119.3, 118.6, 114.1 (2C), 112.9, 83.6, 82.1, 80.5, 80.3, 77.8, 75.6, 74.4, 74.1, 74.0, 73.81, 73.76, 73.3, 73,1 (2C), 72.6, 72.0, 71.4, 70.4, 69.4, 69.1, 61.4, 54.8, 41.7, 38.02, 37.99, 37.9, 37.2, 37.0, 36.7, 35.1, 34.4, 33.0, 30.2, 27.5, 26.7, 26.62 (3C), 26.59 (3C), 26.55 (3C), 26.49 (9C), 26.44 (3C), 26.41 (3C), 26.34 (3C), 26.27 (6C), 24.2, 23.9, 23.8, 23.48, 18.9 (2C), 18.8, 18.67, 18.65, 18.63, 18.59 (2C), 18.51, 18.44, 18.41, 17.3, 15.4, −2.8, −2.9, −3.0, −3.62, −3.65 (2C), −3.70, −3.77, −3.80 (2C), −3.82 (2C), −4.01, −4.05, −4.09, −4.19, −4.25, −4.28, −4.4, −4.99, −5.05 (2C) ; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{119}H_{238}O_{19}Si_{11}Na$ 2302.5011, found 2302.5039.



102

Alcohol 102. To a solution of compound **101** (12.9 mg, 5.65 μmol) in CH_2Cl_2/pH 7 buffer (3/1, v/v, 760 μL) at 0 °C was added DDQ (2.6 mg, 11 μmol). After being stirred for 3 h at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with hexane, and the organic layer was 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 = 100/1 → 30/1) to afford primary alcohol **102** (9.4 mg, 4.4 μmol, 77% for 2 cycles) as a colorless oil.

R_f = 0.45 (hexane/EtOAc = 10/1), $[\alpha]_D^{26}$ −19.5 (*c* 0.83, $CHCl_3$); IR (neat) ν 2953, 2928, 2885, 2857, 2359, 2332, 1472, 1388, 1362, 1334, 1253, 1099, 1006, 835, 813, 774 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 5.65 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 1H), 5.13 (s, 1H), 5.11 (dd, *J* = 7.8 ,7.8 Hz, 1H), 4.63 (s, 1H), 4.54 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.46 (ddd, *J* = 10.2, 6.6, 6.6 Hz, 1H), 4.38 (s, 1H), 4.31–4.26 (m, 2H), 4.25–4.21 (m, 3H), 4.15 (ddd, *J* = 6.0, 6.0, 3.6 Hz, 1H), 4.13–4.04 (m, 3H), 3.98–3.85 (m, 4H), 3.79 (ddd, *J* = 10.8, 6.0, 4.2 Hz, 1H), 3.71–3.61 (m, 3H), 2.67–2.55 (m, 2H), 2.41–2.33 (m, 1H), 2.30–2.19 (m, 3H), 2.17–1.78 (m, 18H), 1.92 (s, 3H), 1.71–1.58 (m, 9H), 1.13 (s, 9H), 1.12 (s, 9H), 1.11 (s, 9H), 1.09 (s, 9H), 1.08 (s, 18H), 1.074 (s, 9H), 1.066 (s, 9H), 1.06 (s, 9H), 1.04–1.02 (m, 21H), 0.37 (s, 3H), 0.334 (s, 3H), 0.325 (s, 3H). 0.32 (s, 3H), 0.31 (s, 3H), 0.30 (s, 9H), 0.281 (s, 6H), 0.275 (s, 6H), 0.26 (s, 3H), 0.244 (s, 3H), 0.236 (s, 3H), 0.23 (s, 3H), 0.22 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H) ; ^{13}C NMR (150 MHz, C_6D_6) δ 150.8, 143.0, 123.0, 119.3, 118.6, 112.2, 83.5, 82.1, 79.9 (2C), 78.3, 75.9, 75.3, 74.4, 73.8, 73.7, 73.0, 72.6 (2C), 72.3, 72.0, 70.3, 69.4, 68.9, 63.5, 61.5, 41.7, 38.04, 38.01, 37.8, 37.3, 37.0, 36.7, 35.1, 34.4, 32.9, 30.2, 27.8, 27.1, 26.7 (3C), 26.6 (3C), 26.5 (15C), 26.41 (3C), 26.36 (3C), 26.3 (6C), 24.2, 23.9, 23.8, 23.5, 19.0, 18.9, 18.8, 18.66, 18.64, 18.6 (2C), 18.53, 18.49, 18.45, 18.41, 17.3, 15.4, −2.7, −2.9, −3.0, −3.6, −3.7 (4C), −3.77 (2C), −3.83 (2C), −3.99, −4.02, −4.1, −4.2 (2C), −4.3, −4.4, −4.8, −4.98, −5.04; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{111}H_{230}O_{18}Si_{11}Na$ 2182.4436, found 2182.4434.



C21-C67 analog (**94**)

C21–C67 analog (**94**). To a solution of $(COCl)_2$ (10 μL, 115 μmol) in CH_2Cl_2 (504 μL) at

−78 °C was added DMSO (17 μL, 239 μmol). After being stirred at −78 °C for 15 min, a solution of primary alcohol **102** (10.8 mg, 5.00 μmol) in CH_2Cl_2 (350 μL + 154 μL rinse) was added and then stirred at −78 °C for 5 min. To the reaction mixture was added Et_3N (64 μL, 459 μmol). The resultant mixture was warmed to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 200/1 → 100/1) to afford aldehyde **103** (10.3 mg) as a colorless oil, which was used in the next reaction immediately.

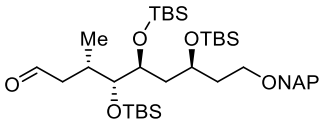
To a solution of sulfone **2** (15.7 mg, 38.2 μmol) and aldehyde **103** (10.3 mg) in THF/HMPA (4/1, v/v, 434 μL) at −78 °C was added KHMDS (0.5 M in THF, 57 μL, 29 μmol) dropwise. The reaction mixture was warmed to room temperature over 1 h and stirred at room temperature for further 1 h. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc, and the organic layer was 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 = 100/1 → 5/1) to provide coupling compound (7.9 mg, *E*/*Z* = 10:1). The *E/Z* mixture was used in next reaction without further purification.

To a solution of the *E/Z* mixture of couplling product (7.9 mg) in THF (1.5 mL) at 0 °C was added 18% HF·pyridine (120 μL, 0.39 mmol), and the mixture was stirred at 50 °C for 15 days, while HF·pyridine was added two times (18% in pyridine, 120 μL, 0.39 mmol at 14, 66 h). MeOH (0.3 mL) and $(CH_2OH)_2$ (0.3 mL) was also added at 123 h to facilitate the removal of the acetal group. The reaction was quenched with Et_3N and concentrated by blowing argon stream. Purification by reversed phase ODS column chromatography (MeOH/H_2O = 1/2 → 2/1) gave *E/Z* mixture of **94** (3.5 mg) as a colorless oil. Further purification by reversed-phase HPLC (column: C18-MS-II waters 10 × 250 mm, eluent: MeOH/H_2O = 62/38, flow rate: 4 mL/min, detection: UV 250 nm) afforded C21–C67 analog **11** (1.3 mg, 1.8 μmol) and intermediates remaining an acetal group (1.1 mg). The obtained intermediates were dissolved in MeOH (0.48 mL). To the solution of intermediates was added $(CH_2OH)_2$ (0.1 mL) and 18% HF·pyridine (40 μL, 0.13 mmol), and the mixture was stirred at 50 °C for 17 days, while 18% HF·pyridine was added 3 times (40 μL, 0.13 mmol at 24, 48, 78 h). After being quenched with Et_3N, the same manner of purification afforded desired C21–C67 analog **94** (0.4 mg, 0.42 μmol). In total, 1.7 mg of C21–C67 analog **94** (1.8 μmol, 36% for 3 steps) was obtained.

R_f = 0.35 (MeOH/H_2O = 3/1), $[\alpha]_D^{26}$ −9.3 (*c* 0.19, CH_3OH); IR (neat) ν 3354, 3012, 2924, 2852, 2360, 2342, 1652, 1418, 1067, 997, 898 cm^{-1}; NMR (600 MHz, CD_3OD/C_5D_5N = 2:1) δ 6.26 (ddd, *J* = 16.8, 10.8, 10.8 Hz, 1H), 6.08–5.96 (m, 5H), 5.86–5.80 (m, 1H), 5.77 (dd, *J*

= 9.6, 7.2 Hz, 1H), 5.67–5.57 (m, 4H), 5.13 (s, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 5.00 (s, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.74 (dd, *J* = 8.4, 1.8 Hz, 1H), 4,62 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.33 (s, 2H), 4.26 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.25–4.16 (m, 3H), 4.13 (ddd, *J* = 10.8, 3.6, 3.6 Hz, 1H), 4.01 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.96 (dddd, *J* = 10.8, 6.6, 3.6, 3.6 Hz, 1H), 3.87–3.80 (m, 2H), 3.74–3.59 (m, 4H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.43 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.67–2.59 (m, 1H), 2.34 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.28–2.17 (m, 3H), 2.13–1.99 (m, 12H), 1.97–1.92 (m, 1H), 1.80–1.56 (m, 7H), 1.72 (s, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 152.0, 138.6, 138.4, 135.3, 134.5, 134.2, 134.1, 132.6, 132.4, 132.3, 132.2, 132.0, 129.7, 126.8, 115.5, 112.7, 80.6, 79,2, 78.4, 76.7, 75.8, 75.3, 74.5, 74.1, 72.7, 72.6, 72.1, 71.7, 70.6, 68.9, 68.7, 67.8, 67.4, 67.3, 60.8, 41.6, 38.3, 36.9, 36.7, 33.5 (2C), 33.4, 33.3, 32.6, 31.8, 31.6, 30.8, 28.0, 17.4, 13.4; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{50}H_{82}O_{17}Na$ 977.5444, found 977.5467.

Synthesis procedure for C20–C67 analog

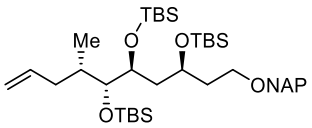


105

Aldehyde 105. To a solution of primary alcohol **104** (101 mg, 0.144 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was added DMP (122 mg, 0.287 mmol). After being stirred at room temperature for 1.5 h, the resultant mixture was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with hexane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 50/1 → 30/1) afforded aldehyde **105** (90.8 mg, 0.129 mmol, 90%) as a colorless oil.

R_f = 0.58 (hexane/EtOAc = 5/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.83–7.77 (m, 4H), 7.49–7.43 (m, 3H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.99 (dddd, *J* = 10.2, 9.0, 3.0, 3.0 Hz, 1H), 3.67–3.57 (m, 4H), 2.57–2.51 (m, 1H), 2.22–2.14 (m, 2H), 1.93 (dddd, *J* = 13.8, 7.2, 7.2, 3.0 Hz, 1H), 1.81 (ddd, *J* = 13.8, 10.2, 3.0 Hz, 1H), 1.64–1.51 (m,

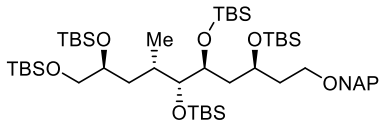
2H), 0.91–0.89 (m, 12H), 0.86 (s, 9H), 0.85 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.052 (s, 3H), 0.049 (s, 3H), 0.01 (s, 6H).



106

Terminal olefin 106. To a solution of CH_3PPh_3Br (128 mg, 0.359 mmol) in THF (0.80 mL) was added *n*-BuLi (1.6 M in hexane, 224 μL, 0.359 mmol) at 0℃. After being stirred for 30 min at 0 °C, a solution of aldehyde **105** (116 mg, 0.165 mmol) in THF (0.75 mL + 0.25 mL rinse) was added. The reaction mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 50/1) afforded terminal olefin **106** (111 mg, 0.158 mmol, 96%) as a colorless oil.

R_f = 0.73 (hexane/EtOAc = 10/1), $[\alpha]_D^{21}$ −26.7 (*c* 0.76, $CHCl_3$); IR (neat) ν 3058, 2954, 2928, 2885, 2856, 1472, 1462, 1361, 1252, 1094, 1065, 1047, 1025, 1004, 940, 835, 810, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84–7.77 (m, 4H), 7.49–7.44 (m, 3H), 5.75–5.67 (m, 1H), 5.02–4.98 (m, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.02–3.96 (m, 1H), 3.69–3.59 (m, 3H), 3.52 (d, *J* = 4.8 Hz, 1H), 2.20 (ddd, *J* = 13.2, 6.0, 6.0 Hz, 1H), 1.95 (dddd, *J* = 13.2, 7.8, 7.8, 2.4 Hz, 1H), 1.86–1.76 (m, 2H), 1.64–1.54 (m, 3H), 0.91 (s, 9H), 0.88–0.85 (m, 21H), 0.13 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6, 136.3, 133.5, 133.1, 128.1, 128.0, 127.8, 126.5, 126.1, 126.0, 125.8, 116.1, 81.1, 73.3, 73.1, 67.5, 67.2, 41.6, 38.8, 37.8, 36.5, 26.3 (6C), 26.0 (3C), 18.6, 18.21, 18.18, 15.5, –3.1, –3.2, –4.0, –4.3, –4.62, –4.64; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{40}H_{72}O_4Si_3Na$ 723.4631, found 723.4660.



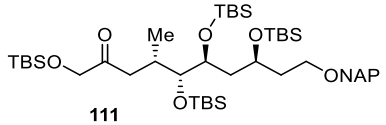
108

TBS ether x. A mixture of $K_2OsO_4 \cdot 2H_2O$ (4.0 mg, 0.011 mmol), (DHQ)MEQ (40.4 mg,

0.086 mmol), $K_3Fe(CN)_6$ (107 mg, 0.324 mmol), K_2CO_3 (44.8 mg, 0.324 mmol) and $MeSO_2NH_2$ (0.799 g, 8.41 mmol) in *t*-BuOH (0.9 mL) and H_2O (1.8 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. To the resultant suspension was added a solution of olefin **x** (74.4 mg, 0.106 mmol) in *t*-BuOMe (1.2 mL + 0.6 mL rinse) via cannula. After being stirred at 0 °C for 4.5 h, the resultant mixture was quenched with solid $Na_2S_2O_3 \cdot 5H_2O$, and stirred room temperature for 1 h. Layers were separated and the aqueous layer was extracted with EtOAc. Combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 1/1) afforded diol **107** (75.3 mg) as a mixture with inseparable diastereomer (dr = 3:1).

To a solution of the diastereomixture diol **107** (75.3 mg) in CH_2Cl_2 (1.1 mL) at 0 °C were added 2,6-lutidine (98 μL, 0.85 mmol) and TBSOTf (97 μL, 0.42 mmol). After being stirred at room temperature for 20 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with *n*-hexane. The organic layer was 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/CH_2Cl_2 = 3/1) to afford TBS ether **108** (66.2 mg, 68.9 μmol, 65% for 2 steps) as a colorless oil.

R_f = 0.61 (Hexane/CH_2Cl_2 = 2/1); $[\alpha]_D^{16}$ – 38.4 (*c* 1.13, $CHCl_3$); IR (neat) ν 3056, 2953, 2928, 2886, 2856, 1472, 1463, 1387, 1361, 1254, 1099, 1042, 1005, 960, 939, 809, 773, 750, 665 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84–7.76 (m, 4H), 7.48–7.43 (m, 3H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.98 (brdd, *J* = 9.6, 9.6 Hz, 1H), 3.69–3.64 (m, 2H), 3.61 (dd, *J* = 7.2, 6.6 Hz, 1H), 3.53 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.51 (d, *J* = 4.8 Hz, 1H), 3.31 (dd, *J* = 9.6, 6.6 Hz, 1H), 1.96 (dddd, *J* = 12.0, 7.8, 7.8, 2.4 Hz, 1H), 1.84–1.76 (m, 2H), 1.59–1.52 (m, 2H), 1.40 (ddd, *J* = 12.0, 12.0, 2.4 Hz, 1H), 1.34 (ddd, *J* = 12.0, 10.8, 2.4 Hz, 1H), 0.90–0.84 (m, 48H), 0.12 (s, 3H), 0.057 (s, 3H), 0.053 (s, 3H), 0.050 (s, 3H), 0.046 (s, 3H), 0.038 (s, 3H), 0.031 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 133.5, 133.1, 128.1, 128.0, 127.8, 126.4, 126.1, 126.0, 125.8, 82.8, 73.7, 73.3, 70.9, 68.3, 67.6, 67.2, 41.9, 39.8, 36.6, 33.8, 26.3 (3C), 26.2 (3C), 26.13 (3C), 26.10 (3C), 26.0 (3C), 18.54, 18.48, 18.3, 18.17, 18.15, 14.3, –3.1, –3.2, –3.9, –4.0, –4.44, –4.46, –4.6 (2C), –5.18, –5.20; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{52}H_{102}O_6Si_5Na$ 985.6415, found 985.6465.

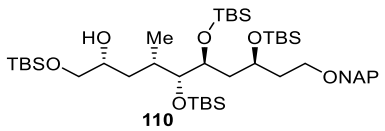


111

Ketone 111. To a solution of the diastereomixture of **107** (20.1 mg, 27.3 μmol) in CH_2Cl_2 (0.14 mL) at 0 °C were added imidazole (4.1 mg, 60.1 μmol), TBSCl (8.2 mg, 54.6 μmol) and DMAP (0.3 mg, 2.7 μmol). After being stirred at room temperature for 10 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The organic layer was 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 = 50/1 → 30/1) to afford TBS ether **110** (16.0 mg) as a 3:1 diastereomixutre.

To a solution of secondary alcohol **110** (16.0 mg) in CH_2Cl_2 (0.15 mL) at 0 °C was added DMP (12.5 mg, 29.4 μmol). After being stirred at room temperature for 5 h, the resultant mixture was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with EtOAc. The organic layer was 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 = 100/1 → 50/1) to afford ketone **111** (7.3 mg, 8.6 μmol, 32% for 2 steps).

R_f = 0.64 (hexane/EtOAc = 5/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.77 (m, 4H), 7.49–7.43 (m, 3H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.12 (d, *J* = 18.0 Hz, 1H), 4.08 (d, *J* = 18.0 Hz, 1H), 3.98 (dddd, *J* = 9.6, 9.6, 2.4, 2.4 Hz, 1H), 3.67–3.57 (m, 4H), 2.60 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.33 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.22–2.14 (m, 1H), 1.94 (dddd, *J* = 13.8, 7.2, 7.2, 2.4 Hz, 1H), 1.82 (ddd, *J* = 13.8, 10.8, 3.6 Hz, 1H), 1.63–1.51 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88–0.84 (m, 12H), 0.85 (s, 9H), 0.12 (s, 3H), 0.08 (s, 9H), 0.052 (s, 3H), 0.049 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).

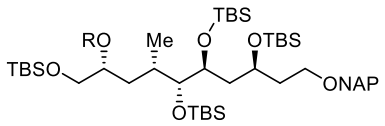


110

Secondary alcohol 110. To a solution of ketone **111** (7.3 mg,8.6 μmol) in CH_2Cl_2 (0.43 mL) at 0 °C were added (*S*)-Me-CBS (95 mg, 44 μmol) and BH_3·Me_2S (25 μL, 258 μmol). After being stirred at 0 °C for 30 min, the resultant mixture was quenched with MeOH. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dired over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by slash silica gel column chromatography (hexane/EtOAc = 50/1 → 30/1) to afford secondary alcohol **111** (6.2 mg, 7.3 μmol, 85%, dr = 6:1) as a colorless oil.

R_f = 0.64 (hexane/EtOAc = 5/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.76 (m, 4H),

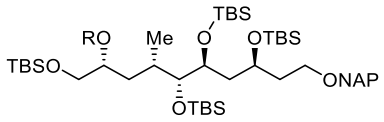
7.48–7.43 (m, 3H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.98 (dddd, *J* = 9.6, 9.6, 3.0, 3.0 Hz, 1H), 3.69–3.56 (m, 6H), 3.31 (dd, *J* = 9.6, 7.8 Hz, 1H), 2.46 (d, *J* = 3.0 Hz, 1H), 1.95 (dddd, *J* = 13.2, 7.8, 7.8, 1.8 Hz, 1H), 1.81 (ddd, *J* = 13.8, 10.8, 3.0 Hz, 1H), 1.73–1.53 (m, 3H), 1,46 (ddd, *J* = 13.2, 6.0, 6.0 Hz, 1H), 1.21 (ddd, *J* = 13.8, 7.8, 7.8 Hz, 1H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 18H), 0.86 (s, 9H), 0.85 (s, 9H), 0.13 (s, 3H), 0.07 (s, 6H), 0.052 (s, 3H), 0.046 (s, 3H), 0,01 (s, 6H).



112: R = (*R*)-MTPA

(*R*)-MTPA ester 112. Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*R*)-MTPA (100 mg, 0.426 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h, the mixture was filtered through a cotton plug and concentrated under reduced pressure to afford (*S*)-MTPACl. The residue was diluted with CH_2Cl_2 and added to a flask containing secondary alcohol **110** (2.7 mg, 3.2 μmol), Et_3N (28 μL, 0.2 mmol) and DMAP (12.2 mg, 0.1 mmol). After being stirred at room temperature for 30 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with hexane. The organic layer was 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 = 50/1) to afford (*R*)-MTPA ester **112** (3.0 mg, 2.8 μmol. 89%) as a colorless oil.

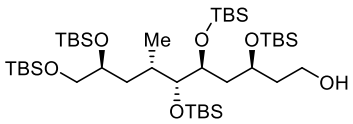
R_f = 0.76 (hexane/EtOAC = 5/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.76 (m, 4H), 7.60–7.57 (m, 2H), 7.48–7.44 (m, 3H), 7.39–7.35 (m, 3H), 5.16–5.10 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.97 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.74 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.67–3.55 (m, 4H), 3.59 (s, 3H), .349–3.45 (m, 1H), 1.92 (ddd, *J* = 13.8, 7.2, 7.2 Hz, 1H), 1.78 (ddd, *J* = 13.8, 10.2, 3.6 Hz, 1H), 1.63 (ddd, *J* = 13.2, 8.4, 3.6 Hz, 1H), 1,57–1.41 (m, 3H), 1.36 (ddd, *J* = 13.2, 10.2, 5.4 Hz, 1H), 0.90–0.88 (m, 12H), 0.87 (s, 9H), 0.850 (s, 9H), 0.846 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H), 0.03 (s, 6H), 0.01 (s, 3H), −0.01 (s, 3H).



113: R = (*S*)-MTPA

(*S*)-MTPA ester 113. Oxalyl chloride (86 μL, 1.0 mmol) was added to a solution of (*S*)-MTPA (100 mg, 0.426 mmol) and DMF (8 μL, 0.1 mmol) in hexane (5.0 mL) at room temperature. After 2 h, the mixture was filtered through a cotton plug and concentrated under reduced pressure to afford (*R*)-MTPACl. The residue was diluted with CH_2Cl_2 and added to a flask containing secondary alcohol **110** (2.9 mg, 3.4 μmol), Et_3N (28 μL, 0.2 mmol) and DMAP (12.2 mg, 0.1 mmol). After being stirred at room temperature for 30 min, the resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with hexane. The organic layer was 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 = 50/1) to afford (*S*)-MTPA ester **113** (3.3 mg, 3.1 μmol. 91%) as a colorless oil.

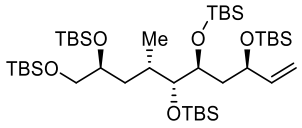
R_f = 0.76 (hexane/EtOAC = 5/1), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83–7.76 (m, 4H), 7.57–7.54 (m, 2H), 7.48–7.43 (m, 3H), 7.39–7.35 (m, 3H), 5.10 (dddd, *J* = 9.0, 6.0, 6.0, 3.6 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.98 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.68–3.58 (m, 6H), 3.53 (s, 3H), 1.93 (dddd, *J* = 13.2, 7.8, 7.8, 1.8 Hz, 1H), 1.82–1.75 (m, 2H), 1.61–1.51 (m, 3H), 1.46 (ddd, *J* = 13.2, 9.6, 5.4 Hz, 1H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.854 (s, 9H), 0.849 (s, 9H), 0.83 (s, 9H), 0.13 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 6H), −0.035 (s, 3H), –0.044 (s, 3H).



S7

Terminal alcohol S7. To a solution of NAP ether **108** (64.8 mg, 67.2 μmol) in CH_2Cl_2/pH 7 buffer (3:1, v/v, 1.7 mL) was added DDQ (30.5 mg, 0.135 mmol) at 0 °C. After being stirred for 40 min at 0 °C, the resultant mixture was quenched with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The mixture was extracted with EtOAc. The combined organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 50/1 → 30/1) afforded terminal alcohol **S7** (50.8 mg, 61.7 μmol, 92%) as a colorless oil.

R_f = 0.61 (Hexane/EtOAC= 5/1); $[\alpha]_D^{21}$ – 39.9 (*c* 1.06, $CHCl_3$); IR (neat) ν 3481, 2954, 2928, 2885, 2857, 1472, 1462, 1387, 1361, 1252, 1107, 1063, 1028, 1004, 959, 938, 833, 808, 771, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.10 (ddd, *J* = 6.6, 6.6, 4.8 Hz, 1H), 3.85–3.79 (m, 1H), 3.73 (ddd, *J* = 4.8, 4.8, 4.8 Hz, 1H), 3.71–3.66 (m, 1H), 3.61 (d, *J* = 9.6 Hz, 1H), 3.55 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.51(d, *J* = 4.8 Hz, 1H), 2.64 (t, *J* = 5.4 Hz, 1H), 1.92–1.82 (m, 2H), 1.81–1.75 (m, 1H), 1.66 (dd, *J* = 14.4, 10.8 Hz, 1H), 1.61–1.55 (m, 1H), 1.41 (ddd, *J* = 10.8, 10.8, 2.4 Hz, 1H), 1.35 (ddd, *J* = 10.8, 10.8, 2.4 Hz, 1H), 0.91 (s, 18H), 0.89–0.86 (m, 30H), 0.13 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 82.8, 73.8, 70.8, 70.4, 68.2, 60.8, 40.4, 39.8, 37.0, 33.8, 26.3 (3C), 26.2 (3C), 26.12 (3C), 26.07 (3C), 25.95 (3C), 18.6, 18.5, 18.3 (2C), 18.0, 14.4, –3.11, –3.13, –3.9, –4.0, –4.5 (2C), –4.6, –4.7, –5.2 (2C); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{41}H_{94}O_6Si_5Na$ 845.5789. found 845.5778.

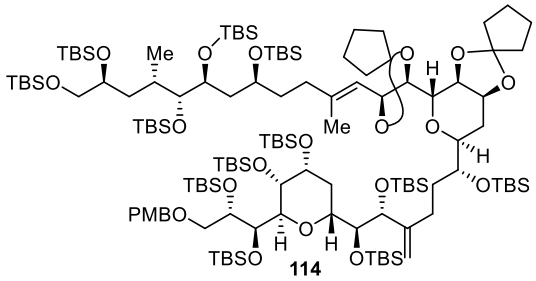


98

Terminal olefin 98. To a solution of terminal alcohol **S7** (47.6 mg, 57.8 μmol) in THF (1.16 mL) were added *o*-O_2NPhSeCN (39.3 mg, 0.173 mmol) and *n*-Bu_3P (71.3 μL, 0.289 mmol) at room temperature. After being stirred for 30 min at room temperature, 30% H_2O_2 (197 μL, 1.73 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and then warmed up to 50 °C. After being stirred at 50 °C for 1.5 h, the resultant mixture was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ at 0 °C. The mixture was extracted with Et_2O. The organic layer was 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 = 100/1 → 50/1) to afford terminal olefin **98** (43.4 mg, 53.9 μmol, 93%) as a colorless oil.

R_f = 0.60 (Hexane/EtOAc = 30/1); $[\alpha]_D^{20}$ – 32.6 (*c* 0.935, $CHCl_3$); IR (neat) ν 2955, 2929, 2886, 2857, 1472, 1462, 1388, 1361, 1252, 1108, 1071, 1034, 1004, 939, 921, 834, 808, 773, 675 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.4, 10.8, 7.2 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 4.24 (ddd, *J* = 10.8, 7.2, 3.6 Hz, 1H), 3.69–3.63 (m, 2H), 3.55–3.51 (m, 2H), 3.31 (dd, *J* = 9.6, 6.6 Hz, 1H), 1.84 (ddd, *J* = 14.4, 9.6, 4.2 Hz, 1H), 1.83–1.76 (m, 1H), 1.65 (ddd, *J* = 14.4, 10.2, 1.8 Hz, 1H), 1.41 (ddd, *J* = 14.4, 12.6, 1.8 Hz, 1H), 1,31 (ddd, *J* = 12.6, 10.2, 2.4 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.887 (s, 9H), 0.885 (s,

9H), 0.87 (s, 9H), 0.84 (d, J = 6.6 Hz, 3H), 0.12 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.043 (s, 9H), 0.036 (s, 6H), 0.028 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.2, 114.9, 82.6, 73.7, 71.8, 70.9, 68.3, 42.3, 40.0, 33.4, 26.3 (3C), 26.2 (3C), 26.14 (3C), 26.09 (3C), 26.04 (3C), 18.6, 18.49, 18.46, 18.2 (2C), 14.1, –3.0, –3.2, –3.9, –4.30, –4.34, –4.53, –4.58, –4.63, –5.19, –5.21; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{41}H_{92}O_5Si_5Na$ 827.5683. found 827.5702.

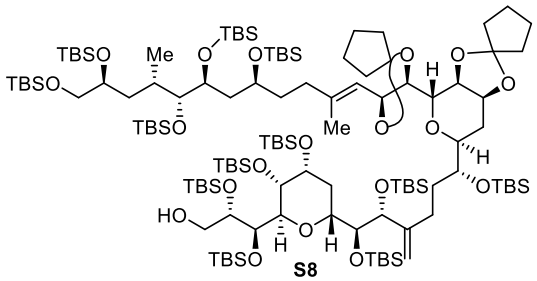


114

Coupling compound 114. To the mixture of polyol **98** (8.6 mg, 10.7 μmol) and 9-BBN dimer (13.0 mg, 53.3 μmol) at °C was added THF (120 μL). After being stirred at room temperature for 1.5 h, 3 M Cs_2CO_3 aqueous (38 μL, 114 μmol) was added to the reaction mixture and then stirred at room temperature for 20 min. To the resultant mixture were added DMF (355 μL), a solution of iodoolefin **68** (12.4 mg, 7.1 μmol) in THF (175 μL + 60 μL rinse) and $Pd(PPh_3)_4$ (1.2 mg, 1.1 μmol). After being stirred at room temperature for 10 min, H_2O (76 μL) was added and the reaction mixture was stirred for further 10 min at room temperature. The resultant mixture was diluted with Et_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 5/1) afforded coupling compound **114** (14.8 mg, 6.1 μmol, 86%) as a colorless oil.

R_f = 0.58 (hexane/EtOAc = 10/1), $[\alpha]_D^{20}$ −28.2 (*c* 0.90, $CHCl_3$); IR (neat) ν 2953, 2928, 2886, 2856, 2359, 2335, 1513, 1471, 1462, 1387, 1360, 1332, 1250, 1104, 1038, 1004, 832, 810, 774, 675 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.31 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.66 (d, J = 8.4 Hz, 1H), 5.40 (s, 1H), 5.15 (s, 1H), 5.12 (dd, J = 8.4, 8.4 Hz, 1H), 4.73 (s, 1H), 4.58 (dd, J = 7.2, 7.2 Hz, 1H), 4.52–4.47 (m, 2H), 4.44–4.39 (m, 3H), 4.31 (d, J = 9.0 Hz, 1H), 4.26 (d, J = 6.6 Hz, 1H), 4.24 (d, J = 10.8 Hz, 1H), 4.22–4.05 (m, 5H), 4.01 (ddd, J = 12.0, 3.0, 3.0 Hz, 1H), 3.97 (d, J = 10.8 Hz, 1H), 3.92–3.82 (m, 3H), 3.78 (d, J = 4.2 Hz, 1H), 3.72 (dd, J = 8.4, 6.0 Hz, 1H), 3.66 (dd, J = 8.4, 7.8 Hz, 1H), 3.53 (dd, J = 8.4, 6.0 Hz, 1H), 3.33 (s, 3H), 2.71–2.58 (m, 2H), 2.48–2.41 (m, 1H), 2.39–2.27 (m, 1H), 2.31 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 2.24 (ddd, J = 12.0, 12.0, 3.6 Hz, 1H), 2.19–1.98 (m, 10H),

1.96–1.87 (m, 4H), 1.95 (s, 3H), 1.86–1.79 (m, 2H), 1.76–1.58 (m, 11H), 1.13–1.07 (m, 84H), 1.05 (s, 9H), 1.04 (s, 9H), 1.01 (s, 9H), 0.38 (s, 3H), 0.36 (s, 3H), 0.35–0.32 (m, 15H), 0.31 (s, 3H), 0.294 (s, 3H), 0.291 (s, 3H), 0.28 (s, 3H), 0.27 (s, 6H), 0.26 (s, 3H), 0.234 (s, 3H), 0.239 (s, 3H), 0.233 (s, 3H), 0.230 (s, 3H), 0.226 (s, 3H), 0.218 (s, 3H), 0.171 (s, 3H), 0.167 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 142.7, 130.8, 129.6 (2C), 123.2, 119.2, 118.6, 114.1 (2C), 112.9, 83.6, 83.3, 80.5, 80.3, 77.8, 75.6, 74.5, 74.4, 74.1, 74.0, 73.8, 73.3, 73,1 (2C), 72.6, 72.1, 71.4, 71.3, 70.5, 69.4, 69.1, 68.6, 61.4, 54.8, 41.6, 40.6, 38.03, 37.87, 37.2, 37.0, 36.8, 35.1, 33.9, 33.0, 30.2, 27.5, 26.7, 26.62 (3C), 26.58 (3C), 26.53 (6C), 26.49 (6C), 26.45 (3C), 26.40 (3C), 26.34 (3C), 26.28 (6C), 26.24 (3C), 24.2, 23.9, 23.8, 23.5, 18.9 (2C), 18.8, 18.66, 18.64, 18.62, 18.59 (2C), 18.50, 18.46 (2C), 18.41, 17.3, 14.6, −2.75, −2.86, −2.93, −3.61, −3.65 (2C), −3.70, −3.79 (2C), −3.80 (2C), −3.83 (2C), −4.01, −4.05, −4.09, −4.25 (2C), −4.28, −4.4 (2C), −5.06, −5.13 (2C); HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{126}H_{254}O_{20}Si_{12}Na$ 2446.5982, found 2446.5933.

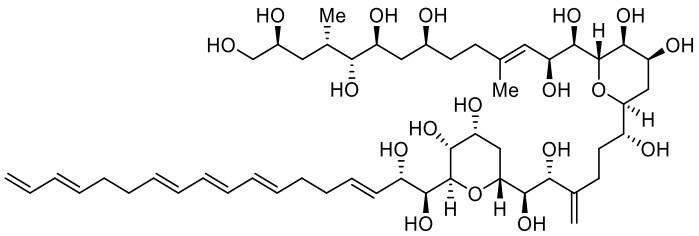


S8

Alcohol S8. To a solution of compound **114** (26.8 mg, 11.1 μmol) in CH_2Cl_2/pH 7 buffer (3/1, v/v, 1.1 mL) at 0 °C was added DDQ (5.0 mg, 22.1 μmol). After being stirred for 3 h at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with hexane, and the organic layer was 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 = 100/1 → 30/1) to afford primary alcohol **S8** (20.8 mg, 9.0 μmol, 82% for 2 cycles) as a colorless oil.

R_f = 0.45 (hexane/EtOAc = 10/1), $[\alpha]_D^{24}$ −23 (*c* 0.92, $CHCl_3$); IR (neat) ν 3502, 2953, 2929, 2885, 2857, 1472, 1462, 1387, 1360, 1333, 1252, 1107, 1038, 1004, 835, 810, 774, 669 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 5.65 (d, *J* = 9.0 Hz, 1H), 5.38 (s, 1H), 5.12 (s, 1H), 5.11 (dd, *J* = 9.0 ,9.0 Hz, 1H), 4.62 (s, 1H), 4.54 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.46 (ddd, *J* = 10.2, 6.6, 6.6 Hz, 1H), 4.37 (s, 1H), 4.30–4.26 (m, 2H), 4.25–4.21 (m, 3H), 4.17–4.09 (m, 3H), 4.06 (brd, *J* = 10.2 Hz, 1H), 3.98–3.85 (m, 5H), 3.81–3.78 (m, 1H), 3.78 (d, *J* = 9.6 Hz, 1H), 3.72 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.53 (dd, *J* = 9.6, 4.8 Hz, 1H) 2.67–2.57 (m, 2H), 2.40–2.32 (m, 1H),

2.30–2.20 (m, 3H), 2.18–1.78 (m, 17H), 1.95 (s, 3H), 1.76–1.59 (m, 10H), 1.13–1.09 (m, 48H), 1.080 (s, 9H), 1.077 (s, 9H), 1.072 (s, 9H), 10.67 (s, 9H), 1.05 (s, 9H), 1.03 (s, 9H), 1.01 (s, 9H), 0.363 (s, 3H), 0.359 (s, 3H), 0.33 (s, 3H). 0.313 (s, 3H), 0.307 (s, 3H), 0.393 (s, 6H), 0.290 (s, 6H), 0.28 (s, 3H), 0.27 (s, 6H), 0.26 (s, 3H), 0.242 (s, 3H), 0.238 (s, 3H), 0.234 (s, 6H), 0.225 (s, 3H), 0.214 (s, 6H), 0.172 (s, 3H), 0.168 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 150.8, 142.8, 123.1, 119.3, 118.6, 112.3, 83.5, 83.3, 80.0, 79.9, 78.3, 75.8, 75.4, 74.5, 74.4, 73.7, 73.0, 72.6 (2C), 72.3, 72.0, 71.3, 70.4, 69.4, 68.9, 68.6, 63.5, 41.6, 40.6, 38.04, 37.86, 37.3, 37.0, 36.8, 35.1, 33.9, 32.9, 30.2, 27.8, 27.1, 26.7 (3C), 26.6 (3C), 26.5 (3C), 26.48 (6C), 26.45 (6C), 26.40 (3C), 26.34 (3C), 26.28 (6C), 26.24 (3C), 24.2, 23.9, 23.8, 23.5, 19.1, 18.9, 18.8, 18.66, 18.63, 18.60, 18.58, 18.52, 18.49, 18.46 (2C), 18.41, 17.3, 14.6, −2.7, −2.86, −2.90, −3.58, −3.64 (3C), −3.67, −3.78 (4C), −3.84 (2C), −4.00, −4.03, −4.1, −4.20, −4.24, −4.34 (2C), −4.9, −5.1 (2C); HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{118}H_{246}O_{19}Si_{12}Na$ 2326.5407, found 2326.5437.



C20-C67 analog (**95**)

C20–C67 analog 95. To a solution of $(COCl)_2$ (10 μL, 115 μmol) in CH_2Cl_2 (200 μL) at −78 °C was added DMSO (20 μL, 282 μmol). After being stirred at −78 °C for 15 min, a solution of primary alcohol **S8** (4.7 mg, 2.0 μmol) in CH_2Cl_2 (150 μL + 50 μL rinse) was added and then stirred at −78 °C for 5 min. To the reaction mixture was added Et_3N (62 μL, 443 μmol). The resultant mixture was warmed to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 200/1 → 100/1) to afford aldehyde **115** (4.4 mg) as a colorless oil, which was used in the next reaction immediately.

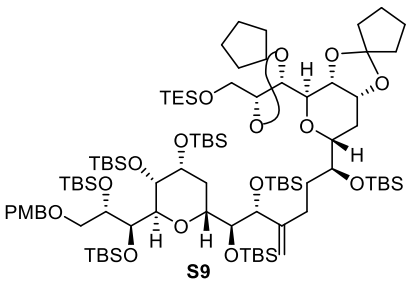
To a solution of sulfone **115** (8.8 mg, 21.4 μmol) and aldehyde **x** (4.4 mg) in THF/HMPA (4/1, v/v, 200 μL) at −78 °C was added KHMDS (0.5 M in THF, 31 μL, 15.5 μmol) dropwise. The reaction mixture was warmed to room temperature over 1 h and stirred at room temperature for further 1 h. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc, and the organic layer was 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 = 100/1 → 5/1) to provide coupling compound (2.9 mg, *E*/*Z* = 10:1). The *E/Z* mixture was used in next reaction without further purification.

To a solution of the *E/Z* mixture of coupled product (2.9 mg) in THF (0.5 mL) at 0 °C was added 18% HF·pyridine (80 μL, 0.16 mmol), and the mixture was stirred at 50 °C for 139 h, while HF·pyridine was added three times (18% in pyridine, 80 μL, 0.26 mmol at 19, 43 h, 70% in pyridine 40 μL, 0.52 mmol at 67 h). $(CH_2OH)_2$ (0.25 mL), MeOH (0.1 mL) and additional $(CH_2OH)_2$ (0.15 mL) were also added at 67, 91, 139 h to facilitate the removal of the acetal group. The reaction was quenched with Et_3N and concentrated by blowing argon stream. Purification by reversed phase ODS column chromatography ($MeOH/H_2O$ = 1/2 → 2/1) gave *E/Z* mixture of **95** as a colorless oil. Further purification by reversed-phase HPLC (column: C18-MS-II waters 10 × 250 mm, eluent: $MeOH/H_2O$ = 62/38, flow rate: 4 mL/min, detection: UV 250 nm) afforded C20–C67 analog **95** (0.51 mg, 0.52 μmol 25% for three steps) as a colorless oil.

R_f = 0.35 ($MeOH/H_2O$ = 3/1), $[\alpha]_D^{27}$ −12.2 (*c* 0.16, CH_3OH); IR (neat) ν 3364, 2927, 2851, 1649, 1416, 1308, 1245, 1077, 1038, 1026, 996, 897 cm^{-1}; NMR (600 MHz, CD_3OD/C_5D_5N = 2:1) δ 6.26 (ddd, *J* = 16.8, 10.2, 10.2 Hz, 1H), 6.08–5.96 (m, 5H), 5.86–5.80 (m, 1H), 5.77 (dd, *J* = 9.6, 7.2 Hz, 1H), 5.67–5.57 (m, 4H), 5.13 (s, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 5.00 (s, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 4.74 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.62 (dd, *J* = 6.6, 3.0 Hz, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.35–4.32 (m, 2H), 4.28–4.17 (m, 4H), 4.13 (ddd, *J* = 10.8, 4.2, 3.0 Hz, 1H), 4.01 (d, *J* = 10.2 Hz, 1H), 3.96 (dddd, *J* = 12.0, 7.2, 3.6, 3.6 Hz, 1H), 3.88–3.83 (m, 3H), 3.74–3.70 (m, 1H), 3.65–3.55 (m, 3H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.44 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.63 (ddd, *J* = 15.6, 12.0, 4.2 Hz. 1H), 2.39–2.31 (m, 2H), 2.28–2.19 (m, 2H), 2.13–1.99 (m, 12H), 1.97–1.92 (m, 1H), 1.75–1.53 (m, 7H), 1.72 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 152.0, 138.6, 138.4, 135.3, 134.5, 134.17, 134.14, 132.6, 132.4, 132.3, 132.2, 132.0, 129.7, 126.8, 115.5, 112.8, 80.6, 79.4, 79,2, 76.7, 75.8, 75.3, 74.5, 74.1, 72.8, 72.6, 72.2, 71.8, 71.1, 70.6, 68.9, 68.7, 68.3, 67.8, 67.4, 67.3, 41.3, 39.2, 36.9, 36.7, 33.5 (2C), 33.4, 33.3, 32.6, 31.9, 31.4, 30.8, 28.0, 17.4, 13.3; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{51}H_{84}O_{18}Na$ 1007.5550, found 1007.5558.

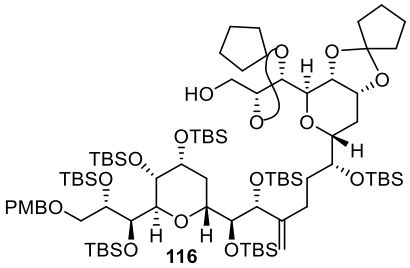
Synthetic Procedures for proposed structure type C21–C67 analog



S9

TBS ether S9. To a solution of secondary alcohol **48** (118 mg, 73.1 μmol) in CH_2Cl_2 (3.7 mL) were added 2,6-lutidine (85 μL, 0.731 mmol) and TBSOTf (67 μL, 0.292 mmol) at −20 °C. After being stirred at 0 °C for 2 h, the resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with hexane. The combined organic layer was 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 = 50/1) to afford TBS ether **S9** (118 mg, 68.1 μmol, 93%) as a colorless oil.

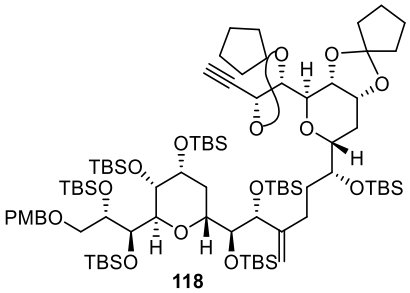
R_f = 0.53 (Hexane/EtOAc = 10/1); $[\alpha]_D^{28}$ +1.9 (*c* 0.99, $CHCl_3$); IR (neat) ν 2953, 2929, 2929, 2884, 2856, 1514, 1472, 1361, 1333, 1250, 1111, 1084, 1041, 1004, 938, 834, 776, 672 cm^{-1}; ^1H NMR (600 MHz, C_6D_6), δ 7.31 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.34 (s, 1H), 5.18 (s, 1H), 4.69 (s, 1H), 4.50 (brs, 1H), 4.46–4.39 (m, 5H), 4.37–4.33 (m, 2H), 4.27 (ddd, *J* = 7.8, 4.2, 4.2 Hz, 1H), 4.20–4.08 (m, 3H), 3.98–3.92 (m, 2H), 3.89 (ddd, *J* = 6.6, 4.2, 4.2 Hz, 1H), 3.87–3.80 (m, 3H), 3.66 (dd, *J* = 9.0, 7.8 Hz, 1H), 3.33 (s, 3H), 2.69 (ddd, *J* = 16.8, 12.0, 4.2 Hz, 1H), 2.49 (ddd, *J* = 15.6, 12.0, 4.2 Hz, 1H), 2.29–2.21 (m, 2H), 2.12–2.08 (m, 3H), 2.04 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.99–1.91 (m, 5H), 1.86–1.75 (m, 3H), 1.66–1.56 (m, 8H), 1.15 (s, 9H), 1.12 (s, 18H), 1.10–1.07 (m, 27H), 1.06 (s, 9H), 1.05 (s, 9H), 0.70 (q, *J* = 8.4 Hz, 6H), 0.40 (s, 3H), 0.36 (s, 3H), 0.35 (s, 3H), 0.34 (s, 6H), 0.32 (s, 3H), 0.282 (s, 3H), 0.278 (s, 3H), 0.271 (s, 3H), 0.268 (s, 3H), 0.258 (s, 3H), 0.24 (s, 3H), 0.233 (s, 3H), 0.225 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 130.9, 129.6 (2C), 120.0, 118.6, 114.0 (2C), 112.4, 80.7, 80.3, 79.9, 79.7, 78.1, 75.5, 75.3, 74.4, 73.9, 73.4, 73.2, 72.9, 72.7 (2C), 71.4, 69.3, 68.7, 64.1, 54.7, 37.91, 37.86, 37.7, 37.5, 31.6, 31.2, 29.4, 28.1, 26.8 (3C), 26.63 (3C), 26.61 (3C), 26.5 (3C), 26.41 (3C), 26.38 (3C), 26.32 (3C), 24.1, 23.84, 23.81, 23.6, 19.0, 18.9, 18.66, 18.64 (2C), 18.52, 18.48, 7.2 (3C), 5.0 (3C), −2.7, −3.7 (2C), −3.8 (2C), −3.9, −3.96 (3C), −3.98, −4.01, −4.2, −4.3, −5.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{89}H_{174}O_{16}Si_8Na$ 1746.0848, found 1746.0829.



116

Primary alcohol 116. To a solution of TES ether **S9** (118 mg, 68.1 μmol) in THF (3.4 mL) was added TBAF-AcOH (0.2 M in THF, 0.68 mL, 0.14 mmol) at 0 °C. After being stirred at 0 °C for 8 h, the resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. The organic layer was 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 = 20/1 → 5/1) to afforded primary alcohol **116** (105 mg, 65.3 μmol, 96%) as a colorless oil.

R_f = 0.12 (hexane/EtOAc = 10/1); $[\alpha]_D^{26}$ −3.2 (*c* 1.04, $CHCl_3$); IR (neat) ν 3489, 2953, 2929, 2884, 2856, 1613, 1513, 1471, 1388, 1360, 1333, 1250, 1111, 1085, 1041, 1004, 939, 835, 776, 673 cm^{-1}; ^{1} H NMR (600 MHz, C_6D_6) δ7.30 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.33 (s, 1H), 5.17 (s, 1H), 4.69 (s, 1H), 4.51–4.47 (m, 1H), 4.41 (s, 2H), 4.39 (s, 1H), 4.39–4.36 (m, 1H), 4.36 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.33 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.28–4.21 (m, 3H), 4.18–4.07 (m, 3H), 3.92–3.79 (m, 5H), 3.77–3.72 (m, 1H), 3.66 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.33 (s, 3H), 2.65 (ddd, *J* = 16.2, 12.0, 4.2 Hz, 1H), 2.47 (ddd, *J* = 16.8, 11.4, 4.2 Hz, 1H), 2.49 (ddd, *J* = 16.8, 11.4, 4.2, 1H), 2.29–2.23 (m, 2H), 2.10–2.04 (m, 4H), 1.96–1.89 (m, 4H), 1.85–1.75 (m, 4H), 1.73–1.68 (br, 1H), 1.63–1.53 (m, 8H), 1.13 (s, 9H), 1.12 (s, 18H), 1.07 (s, 9H), 1.061 (s, 9H), 1.056 (s, 9H), 1.04 (s, 9H), 0.38 (s, 3H), 0.35 (s, 6H), 0.34 (s, 6H), 0.31 (s, 3H), 0.28 (s, 3H), 0.262 (s, 3H), 0.258 (s, 3H), 0.252 (s, 3H), 0.246 (s, 3H), 0.22 (s, 3H), 0.214 (s, 3H), 0.207 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 130.9, 129.6 (2C), 119.9, 118.8, 114.0 (2C), 112.4, 80.7, 80.42, 80.36, 78.3, 77.9, 75.8, 75.5, 74.3, 74.1, 73.8, 73.4, 72.7, 72.5, 71.4, 69.3, 68.7, 63.0, 54.8, 38.0, 37.8, 37.7, 37.5, 31.6, 31.0, 29.2, 28.0, 26.7 (3C), 26.6 (6C), 26.5 (3C), 26.4 (3C), 26.34 (3C), 26.31 (3C) 24.1, 23.9, 23.7, 23.6, 18.9 (2C), 18.7, 18.6 (2C), 18.48, 18.46, −2.7, −3.68, −3.71, −3.81, −3.84, −3.86 (2C), −4.0 (3C), −4.1, −4.2, −4.3 −5.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{83}H_{160}O_{16}Si_7Na$ 1631.9983, found 1631.9952.



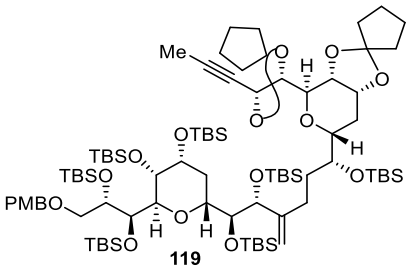
118

Terminal alkyne 118. To a solution of $(COCl)_2$ (30 μL, 0.34 mmol) in CH_2Cl_2 (3.3 mL) was added DMSO (60 μL, 0.85 mmol) at −78 °C. After being stirred at −78 °C for 15 min, a solution of alcohol **116** (105 mg, 65.3 μmol) in CH_2Cl_2 (2.3 mL + 1.0 mL rinse) was added to the mixture at −78 °C. After being stirred at −78 °C for 5 min, Et_3N (0.18 mL, 1.29 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was warmed to room temperature over 1h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. Organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford mixture of aldehyde **117** (115 mg). The mixture was used in the next reaction without further purification.

To a solution of Ohira–Bestman reagent (28.9 mg, 0.150 mmol) in MeOH (0.26 mL) was added Cs_2CO_3 (48.9 mg, 0.150 mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of aldehyde **117** (115 mg) in CH_2Cl_2 (0.9 mL + 0.5 mL rinse) was added. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. Organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1) to afforded terminal alkyne **118** (97.2 mg, 60.6 μmol, 93% for two steps) as a colorless oil.

R_f = 0.55 (hexane/EtOAc = 10/1); $[\alpha]_D^{27}$ −4.0 (*c* 0.98, $CHCl_3$); IR (neat) ν 3314, 2953, 2929, 2885, 2857, 1513, 1472, 1388, 1360, 1334, 1250, 1111, 1085, 1042, 1004, 938, 834, 778, 672 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.31 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.34 (s, 1H), 5.17 (s, 1H), 5.03 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.69 (brs, 1H), 4.55 (dd, *J* = 6.0, 4.8 Hz, 1H), 4.51–4.47 (m, 1H), 4.42 (s, 2H), 4.40 (s, 1H), 4.38 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.36–4.29 (m, 2H), 4.23 (d, *J* = 11.4 Hz, 1H), 4.20–4.11 (m, 2H), 4.09 (brd, *J* = 11.4 Hz, 1H), 3.91 (ddd, *J* = 11.4, 3.6, 3.6 Hz, 1H), 3.89–3.80 (m, 3H), 3.66 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.32 (s, 3H), 2.64 (ddd, *J* = 15.6, 11.4, 4.2 Hz, 1H), 2.44 (ddd, *J* = 15.6, 11.4, 4.2 Hz, 1H), 2.35–2.22 (m, 2H), 2.18 (d, *J* = 2.4 Hz, 1H), 2.16–2.08 (m, 2H), 2.07–2.03 (m, 3H), 2.02–1.91 (m, 4H), 1.85–1.70 (m, 3H), 1.62–1.51 (m, 8H), 1.13 (s, 9H), 1.120 (s, 9H), 1.117 (s, 9H), 1.072 (s,

9H), 1.069 (s, 9H), 1.06 (s, 9H), 1.05 (s, 9H), 0.38 (s, 3H), 0.35 (s, 6H), 0.34 (s, 6H), 0.31 (s, 3H), 0.28 (s, 3H), 0.263 (s, 3H), 0.260 (s, 3H), 0.253 (s, 3H), 0.247 (s, 3H), 0.23 (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 130.9, 129.6 (2C), 121.3, 119.0, 114.1 (2C), 112.4, 84.5, 83.3, 82.5, 80.6, 80.4, 77.9, 75.4, 74.5, 74.22, 73.97, 73.38, 73.35, 72.8, 72.69, 72.65, 71.4, 69.3, 68.8, 67.8, 54.8, 37.7, 37.23, 37.19 (2C), 31.7, 30.9, 29.1, 27.9, 26.7 (3C), 26.6 (3C), 26.5 (3C), 26.38 (3C), 26.35 (3C), 26.32 (3C), 24.13, 24.06, 23.6, 23.5, 18.9 (2C), 18.7, 18.6 (2C), 18.49, 18.45, −2.7, −3.65 −3.72, −3.79, −3.82, −3.86 (2C), −3.89, −4.0 (2C), −4.1, −4.2, −4.3 −5.1; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{84}H_{158}O_{15}Si_7Na$ 1625.9878, found 1625.9868.

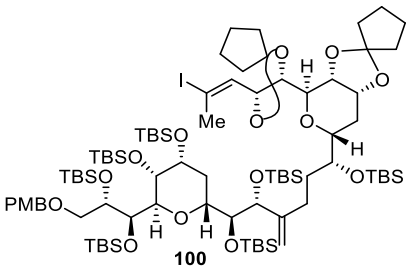


119

Alkyne 119. To a solution of terminal alkyne **118** (97.2 mg, 58.7 μmol) in THF (6.1 mL) was added LHMDS (1.3 M in THF, 0.47 mL, 0.61 mmol) at −78 °C. After being stirred at −78 °C for 1 min, MeI (76 μL, 1.21 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. Organic layer was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1) to afforded alkyne **119** (95.0 mg, 58.7 μmol, 97%) as a colorless oil.

R_f = 0.55 (hexane/EtOAc = 10/1); $[\alpha]_D^{26}$ −0.3 (*c* 0.98, $CHCl_3$); IR (neat) ν 2953, 2928, 2885, 2856, 1614, 1513, 1471, 1462, 1360, 1333, 1249, 1108, 1084, 1041, 1004, 939, 873, 833, 777, 672 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.32 (s, 1H), 5.16 (s, 1H), 5.02 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.68 (s, 1H), 4.54 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.51–4.46 (m, 1H), 4.44–4.34 (m, 6H), 4.22 (d, *J* = 11.4 Hz, 1H), 4.16 (brd, *J* = 9.6 Hz, 1H), 4.12 (d, *J* = 6.6 Hz, 1H), 4.09 (brd, *J* = 11.4 Hz, 1H), 3.94 (ddd, *J* = 10.2, 4.2, 4.2 Hz, 1H), 3.89 (ddd, *J* = 5.4, 5.4, 4.2 Hz, 1H), 3.85 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.84–3.79 (m, 1H), 3.66 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.33 (s, 3H), 2.65 (ddd, *J* = 16.2, 12.0, 4.2 Hz, 1H), 2.49

(ddd, *J* = 16.2, 12.0, 4.2 Hz, 1H), 2.34–2.20 (m, 2H), 2.16 (ddd, *J* = 12.0, 7.2 Hz, 1H), 2.10–2.04 (m, 4H), 2.03–1.92 (m, 4H), 1.84–1.71 (m, 3H), 1.65–1.53 (m, 8H), 1.54 (d, *J* = 1.8 Hz, 3H), 1.13 (s, 9H), 1.119 (s, 9H), 1.115 (s, 9H), 1.08 (s, 9H), 1.07 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 0.38 (s, 3H), 0.350 (s, 3H), 0.348 (s, 3H), 0.34 (s, 6H), 0.31 (s, 3H), 0.27 (s, 3H), 0.26 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H), 0.21 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.0, 130.9, 129.6 (2C), 120.7, 118.8, 114.0 (2C), 112.3, 83.7, 82.4, 80.6, 80.3, 77.9 (2C), 75.4, 74.3, 73.9, 73.8, 73.4, 73.0, 72.8, 72.7 (2C), 71.4, 69.3, 68.7, 68.3, 54.7, 37.8, 37.4, 37.3 (2C), 31.6, 31.2, 29.1, 28.0, 26.7 (3C), 26.6 (6C), 26.5 (3C), 26.37 (3C), 26.35 (3C), 26.31 (3C), 24.1, 24.0, 23.6, 23.5, 18.9 (2C), 18.6 (3C), 18.5 (2C), 3.5, −2.7, −3.4, 3.68, −3.72, −3.81 (2C), −3.85, −3.95, −3.99, −4.02, −4.1, −4.2, −4.3, −5.1; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{85}H_{160}O_{15}Si_7Na$ 1640.0034, found 1640.0002.

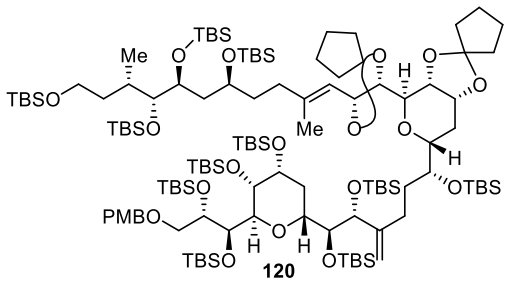


100

Iodoolefin 100. To a mixture of alkyne **119** (71.1 mg, 44.3 μmol) and $PdCl_2$(P-*o*-tol_3)$_2$ (3.5 mg, 4.4 μmol) in THF (0.44 mL) was added Bu_3SnH (0.6 mL, 2.22 mmol) dropwise over 1 h at room temperature. After being stirred for further 10 min, the resultant mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 200/1 → 50/1) to afforded vinyl stannane (625.8 mg) as a colorless oil. Obtained compound was immediately used for the next reaction because of its instability.

To a solution of vinyl stannane (65.8 mg) in CH_2Cl_2 (1.73 mL) at 0 °C was added a solution of I_2 (2 grain) in CH_2Cl_2 (0.9 mL) until the color of I_2 ceased to disappear. After being stirred at 0 °C for 10 min, the resultant mixture was quenched with satd. aq. $Na_2S_2O_3$. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 50/1) to afforded iodoolefin **100** (59.2 mg, 33.9 μmol, 77% for two steps) as a colorless oil.

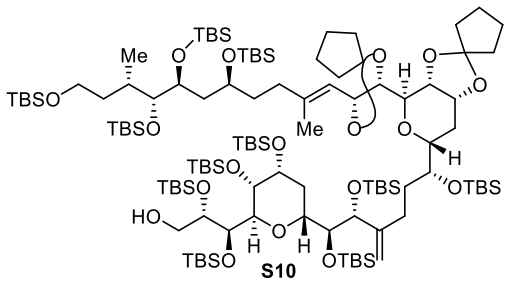
R_f = 0.55 (hexane/EtOAc = 10/1); $[\alpha]_D^{26}$ +2.0 (*c* 1.14, $CHCl_3$); IR (neat) ν 2953, 2929, 2885, 2855, 1513, 1471, 1387, 1360, 1333, 1250, 1111, 1041, 1004, 939, 834, 779, 675 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.45 (dd, *J* = 9.0, 1.2 Hz, 1H), 5.33 (s, 1H), 5.16 (s, 1H), 4.89 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.67 (brs, 1H), 4.51–4.46 (m, 1H), 4.43–4.38 (m, 4H), 4.35 (ddd, *J* = 10.8, 6.0, 6.0 Hz, 1H), 4.25–4.06 (m, 6H), 3.91 (ddd, *J* = 12.0, 3.6, 3.6 Hz, 1H), 3.88–3.78 (m, 3H), 3.66 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.33 (s, 3H), 2.67–2.59 (m, 1H), 2.51–2.40 (m, 1H), 2.42 (d, *J* = 1.2 Hz, 3H), 2.33–2.21 (m, 2H), 2.11 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.05–1.99 (m, 2H), 1.967–1.90 (m, 4H), 1.90–1.68 (m, 5H), 1.64–1.51 (m, 8H), 1.13 (s, 9H), 1.120 (s, 9H), 1.117 (s, 9H), 1.09 (s, 9H), 1.07 (s, 9H), 1.06 (s, 9H), 1.04 (s.9H), 0.37 (s, 3H), 0.35 (s, 6H), 0.34 (s, 6H), 0.31 (s, 3H), 0.27 (s, 3H), 0.263 (s, 3H), 0.257 (s, 3H), 0.252 (s, 3H), 0.245 (s, 3H), 0.23 (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 150.9, 139.2, 130.9, 129.6 (2C), 119.9 118.9, 114.0 (2C), 112.4, 101.3, 82.0, 80.6, 80.3, 78.0, 75.5, 75.1, 74.2, 73.9, 73.45, 73.37, 72.9, 72.7, 72.6, 71.4, 69.3, 68.7, 54.8, 37.9, 37.7, 37.4, 37.0, 31.8, 31.1, 29.1, 28.7, 27.9, 26.7 (3C), 26.6 (6C), 26.5 (3C), 26.4 (6C), 26.3 (3C), 24.1, 23.80, 23.75, 23.4, 18.94, 18.91, 18.7, 18.6 (2C), 18.51, 18.49, −2.7, −3.7 (2C), −3.8 (4C), −4.0, −4.1, −4.2 (2C), −4.3, −5.1; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{85}H_{161}O_{15}Si_7INa$ 1767.9157, found 1767.9096.



120

Coupling compound 120. To the mixture of polyol **86** (12.9 mg, 19.6 μmol) and 9-BBN dimer (24 mg, 98 μmol) at 0 °C was added THF (186 μL). After being stirred at room temperature for 1.5 h, 3 M Cs_2CO_3 aqueous (70 μL, 210 μmol) was added to the reaction mixture and then stirred at room temperature for 20 min. To the resultant mixture were added DMF (653 μL), a solution of iodoolefin **100** (22.8 mg, 13.1 μmol) in THF (300 μL + 167 μL rinse) and $Pd(PPh_3)_4$ (2.3 mg, 2.0 μmol). After being stirred at room temperature for 10 min, H_2O (140 μL) was added and the reaction mixture was stirred for further 10 min at room temperature. The resultant mixture was diluted with Et_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 5/1) afforded coupling compound **120** (27.7 mg, 12.1 μmol, 93%) as a colorless oil.

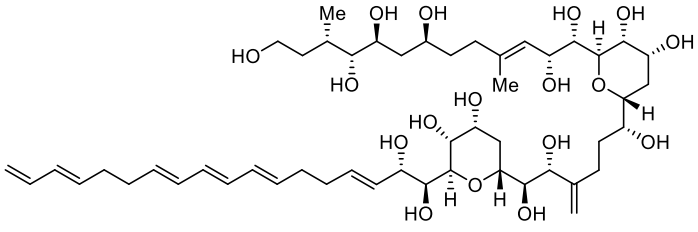
R_f = 0.67 (hexane/EtOAc = 10/1), $[\alpha]_D^{24}$ −7.5 (*c* 1.37, $CHCl_3$); IR (neat) ν 2953, 2928, 2885, 2856, 1614, 1513, 1471, 1462, 1387, 1360, 1332, 1250, 1085, 1041, 1004, 938, 833, 774, 676 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.31 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.62 (d, *J* = 9.0 Hz, 1H), 5.34 (s, 1H), 5.14 (s, 1H), 5.03 (ddd, *J* = 8.4, 8.4, 1.8 Hz, 1H), 4.68 (s, 1H), 4.52–4.38 (m, 6H), 4.33–4.31 (m, 1H), 4.25 (ddd, *J* = 8.4, 1.8, 1.8 Hz, 1H), 4.23 (d, *J* = 11.4 Hz, 1H), 4.21–4.06 (m, 4H), 4.02–3.96 (m, 1H), 3.89–3.80 (m, 4H), 3.71–3.59 (m, 4H), 3.34 (s, 3H), 2.64 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.54–2.45 (m, 2H), 2.37–2.22 (m, 3H), 2.16–1.71 (m, 18H), 1.90 (s, 3H), 1.68–1.57 (m, 8H), 1.42–1.34 (m, 1H), 1.14 (s, 9H), 1.12 (s, 18H), 1.11 (s, 9H), 1.09 (s, 9H), 1.08 (s, 18H), 1.07 (s, 9H), 1.06 (s, 9H), 1.05 (s, 9H), 1.02 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.39 (s, 3H), 0.36 (s, 3H), 0.35 (s, 9H), 0.33 (s, 3H), 0.31 (s, 3H), 0.29 (s, 3H), 0.28 (s, 6H), 0.26 (s, 12 H), 0.242 (s, 3H), 0.238 (s, 3H), 0.22 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 151.1, 142.9, 130.9, 129.6 (2C), 123.3, 119.3, 118.6, 114.0 (2C), 112.4, 83.5, 82.1, 80.5, 80.3, 78.1, 75.5, 74.7, 74.2, 74.0, 73.8, 73.4, 73.2, 73.0, 72.9, 72.84, 72.81, 72.3, 71.4, 70.2, 69.3, 68.7, 61.4, 54.8, 41.9, 38.1, 38.0, 37.9, 37.6, 37.3, 37.0, 35.5, 34.5, 31.9, 30.9, 29.4, 27.8, 26.8 (3C), 26.6 (6C), 26.50 (3C), 26.47 (3C), 26.44 (3C), 26.42 (3C), 26.40 (3C), 26.32 (3C), 26.30 (3C), 26.3 (3C), 24.1, 23.9, 23.8, 23.5, 19.0, 18.9, 18.8, 18.7, 18.64 (2C), 18.56 (2C), 18.5, 18.4 (2C), 17.1, 15.4, −2.7, −2.9, −3.1, −3.5, −3.7 (2C), −3.80 (3C), −3.9, −3.98, −4.00, −4.03, −4.07, −4.2 (3C), −4.3, −4.4, −5.0, −5.1 (2C); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{119}H_{238}O_{19}Si_{11}Na$ 2302.5011, found 2302.5020.



S10

Alcohol S10. To a solution of compound **120** (27.4 mg, 12.0 μmol) in CH_2Cl_2/H_2O (3/1, v/v, 1.6 mL) at 0 °C was added DDQ (8.2 mg, 32 μmol). After being stirred for 4 h at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with hexane, and the organic layer was 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 = 100/1 → 30/1) to afford primary alcohol **S10** (18.3 mg, 8.5 μmol, 71%) as a colorless oil.

R_f = 0.60 (hexane/EtOAc = 10/1), $[\alpha]_D^{22}$ −0.6 (*c* 0.91, $CHCl_3$); IR (neat) ν 3519, 2954, 2929 2886, 2857, 1472, 1462, 1387, 1360, 1333, 1253, 1190, 1108, 1086, 1004, 938, 835, 774, 672 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 5.61 (d, *J* = 8.4 Hz, 1H), 5.3 (s, 1H), 5.1 (s, 1H), 5.06 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.56 (s, 1H), 4.53 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.50 (ddd, *J* = 10.8, 6.0, 6.0 Hz, 1H), 4.38 (s, 1H), 4.34–4.28 (m, 3H), 4.26 (d, *J* = 9.0 Hz, 1H), 4.23 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.12–4.05 (m, 3H), 4.03 (ddd, *J* = 12.0, 3.6, 3.6 Hz, 1H), 4.01–3.96 (m, 1H), 3.89–3.78 (m, 4H), 3.70–3.60 (m, 3H), 2.56–2.48 (m, 3H), 2.37–2.25 (m, 2H), 2.19–1.59 (m, 27H), 1.91 (s, 3H), 1.42–1.35 (m, 1H), 1.15 (s, 9H), 1.13 (s, 9H), 1.11 (s, 9H), 1.091 (s, 9H), 1.088 (s, 9H), 1.079 (s, 9H), 1.069 (s, 27H), 1.04 (s, 9H), 1.02 (s, 9H), 1.00 (d, *J* 7.2 Hz, 3H), 0.38 (s, 3H), 0.37 (s, 3H), 0.33 (s, 3H), 0.313 (s, 3H), 0.306 (s, 6H), 0.301 (s, 6H), 0.29 (s, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 025 (s, 3H), 0.24 (s, 3H), 0.234 (s, 3H), 0.230 (s, 3H), 0.19 (s, 6H), 0.18 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.120 (s, 3H), 0.117 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 150.9, 143.2, 123.1, 119.4, 118.7, 111.7, 83.3, 82.1, 80.1, 79.4, 78.5, 76.7, 75.7, 74.6, 73.3, 73.0, 72.6, 72.2, 71.6 (2C), 70.2, 69.3, 68.6, 63.5, 61.4, 42.0, 38.03, 38.01, 37.8, 37.4, 37.12, 37.10, 35.6, 34.5, 32.5, 31.6, 29.3, 28.1, 26.9 (3C), 26.6 (3C5.1), 26.53 (3C), 26.51 (3C), 26.47 (3C), 26.44 (3C), 26.39 (3C), 26.34 (6C), 26.31 (3C), 26.25 (3C), 24.2, 23.9, 23.7, 23.5, 19.1, 18.9, 18.8, 18.69, 18,64, 18.58, 18.47 (3C), 18.42 (2C), 17.0, 15.4, −2.6, −2.9, −3.1, −3.5, −3.57, −3.59, −3,82 (2C), 3.84 (2C), −3.92, −3.94, −4.02, −4.08, −4.13, −4.23, −4.24, −4.4 (2C), −4.8, −5.0, −5.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{111}H_{230}O_{18}Si_{11}Na$ 2182.4436, found 2182.4395.



proposed structure type
C21-C67 analog (**96**)

Proposed structure type C21–C67 analog (**96**). To a solution of $(COCl)_2$ (20 μL, 230 μmol) in CH_2Cl_2 (416 μL) at −78 °C was added DMSO (34 μL, 479 μmol). After being stirred at −78 °C for 15 min, a solution of primary alcohol **S10** (9.0 mg, 4.2 μmol) in CH_2Cl_2 (300 μL + 116 μL rinse) was added and then stirred at −78 °C for 5 min. To the reaction mixture was added Et_3N (145 μL, 1.04 mmol). The resultant mixture was warmed to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash

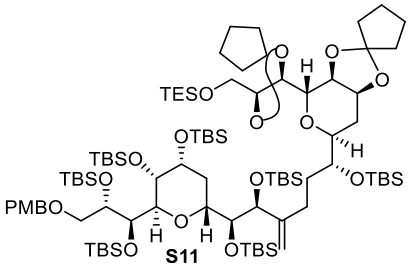
silica gel column chromatography (hexane/EtOAc = 200/1 → 100/1) to afford aldehyde **121** (9.0 mg) as a colorless oil, which was used in the next reaction immediately.

To a solution of sulfone **2** (20.9 mg, 50.9 μmol) and aldehyde **121** (9.0 mg) in THF/HMPA (4/1, v/v, 417 μL) at −78 °C was added KHMDS (0.5 M in THF, 67 μL, 33 μmol) dropwise. After being stirred at −78 °C for 30 min, the reaction mixture was warmed to room temperature over 1 h and stirred at room temperature for further 30 min. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc, and the organic layer was 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 = 100/1 → 5/1) to provide coupling compound (7.0 mg, *E*/*Z* = 10:1). The *E*/*Z* mixture was used in next reaction without further purification.

To a solution of the *E*/*Z* mixture of coupled product (7.0 mg) in THF (1.0 mL) at 0 °C was added 18% HF·pyridine (160 μL, 0.52 mmol), and the mixture was stirred at 50 °C for 7 days, and then cooled to room temperature and stirred for further 12 days while HF·pyridine was added four times (18% in pyridine, 160 μL, 0.52 mmol at 10, 82 h, 70% in pyridine, 50 μL, 0.65 mmol at 106, 346 h). MeOH (0.2 mL) and $(CH_2OH)_2$ (0.6 mL) was also added at 106 h to facilitate the removal of the acetal group. The reaction was quenched with Et_3N and concentrated by blowing argon stream. Purification by reversed phase ODS column chromatography (MeOH/H_2O = 1/2 → 2/1) gave *E*/*Z* mixture of **96** (4.0 mg) as a colorless oil. Further purification by reversed-phase HPLC (column: C18-MS-II waters 10 × 250 mm, eluent: MeOH/H_2O = 62/38, flow rate: 4 mL/min, detection: UV 250 nm) afforded proposed structural C21–C67 analog **96** (0.9 mg, 0.9 μmol, 23% for 3 steps).

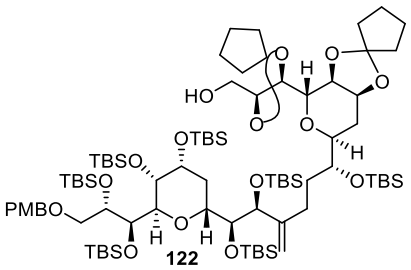
R_f = 0.32 (MeOH/H_2O = 3/1), NMR (600 MHz, CD_3OD/C_5D_5N = 2:1) δ 6.26 (ddd, *J* = 16.8, 10.2, 10.2 Hz, 1H), 6.08–5.97 (m, 5H), 5.83 (ddd, *J* = 15.6, 6.0, 6.0 Hz, 1H), 5.78 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.68–5.57 (m, 4H), 5.14 (s, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 4.99 (s, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 4.76 (dd, *J* = 9.9, 1.8 Hz, 1H), 4.63 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.39 (d, *J* = 9.0 Hz. 1H), 4.33 (s, 1H), 4.28–4.16 (m, 6H), 4.11 (ddd, *J* = 10.8, 4.2, 3.0 Hz, 1H), 4.0 (d, *J* = 10.8 Hz, 1H), 3.95 (ddd, *J* = 12.0, 7.2, 3.6 Hz, 1H), 3.86 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.82 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 3.75–3.60 (m, 4H), 3.51 (d, *J* = 8.4 Hz, 1H), 3.43 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.61 (ddd, *J* = 15.0, 10.2, 4.8 Hz, 1H), 2.38–2.17 (m, 4H), 2.13–1.99 (m, 11H), 1.91–1.83 (m, 1H), 1.82–1.55 (m, 8H), 1.72 (s, 3H), 0.97 (s, 4.8 Hz, 3H).

Synthetic procedure for C43-*epi*mer type C21–C67 analog



TBS ether S11. To a solution of secondary alcohol **24** (108 mg, 67.0 μmol) in CH_2Cl_2 (3.4 mL) were added 2,6-lutidine (78 μL, 0.67 mmol) and TBSOTf (62 μL, 0.27 mmol) at −20 °C. After being stirred at 0 °C for 2 h, the reaction mixture was warmed to room temperature and stirred for further 1 h. The resultant mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with hexane. The combined organic layer was 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 = 50/1) to afford TBS ether **S11** (109 mg, 63.4 μmol, 95%) as a colorless oil.

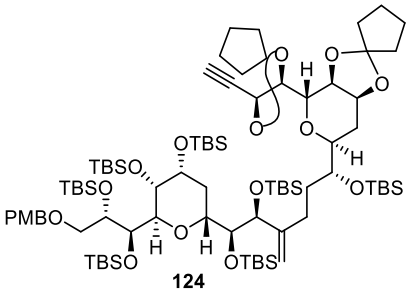
R_f = 0.52 (Hexane/EtOAc = 10/1); $[\alpha]_D^{20}$ −14.9 (*c* 1.05, $CHCl_3$); IR (neat) ν 2953, 2929, 2884, 2856, 1513, 1471, 1387, 1360, 1331, 1249, 1094, 1041, 1005, 939, 876, 834, 776, 746, 673 cm^{-1}; ^1H NMR (600 MHz, C_6D_6), δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.50 (s, 1H), 5.24 (s, 1H), 4.56–4.52 (m, 2H), 4.49 (ddd, *J* = 10.2, 6.0, 6.0 Hz, 1H), 4.46 (dd, *J* = 3.6, 2.4 Hz, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.37–4.33 (m, 3H), 4.28 (dd, *J* = 5.4, 3.6 Hz, 1H), 4.24 (d, *J* = 10.8 Hz, 1H), 4.15 (ddd, *J* = 8.4, 4.8, 4.8 Hz, 1H), 4.13–4.08 (m, 2H), 4.02 (brd, *J* = 10.2 Hz, 1H), 3.98 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.85 (ddd, *J* = 12.0, 3.0, 3.0 Hz, 1H), 3.81–3.77 (m, 3H), 3.71–3.64 (m, 2H), 3.32 (s, 3H), 2.80–2.72 (m, 1H), 2.60 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 1H), 2.19–2.09 (m, 5H), 2.05 (ddd, *J* = 12.6, 6.6, 2.4 Hz, 1H), 2.02–1.76 (m, 8H), 1.69–1.55 (m, 8H), 1.15 (s, 27H), 1.13 (s, 9H), 1.11 (s, 9H), 1.08 (s, 9H), 1.07 (s, 9H), 1.04 (t, *J* = 8.4 Hz, 9H), 0.63 (q, *J* = 8.4 Hz, 6H), 0.40 (s, 6H), 0.39 (s, 3H), 0.37 (s, 6H), 0.35 (s, 3H), 0.34 (s, 3H), 0.31 (s, 3H), 0.30 (s, 3H), 0.29 (s, 3H), 0.28 (s, 6H), 0.242 (s, 3H), 0.239 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.4, 149.3, 130.6, 129.4 (2C), 119.7, 117.9, 113.6 (2C), 111.4, 81.6, 80.1 (2C), 78.3, 76.6, 75.3, 74.1, 73.81, 73.78, 73.2, 72.6, 72.1, 71.6, 70.7, 69.0, 67.6, 63.7, 54.4, 37.7, 37.6, 37.4, 37.2, 32.6, 31.6, 30.4, 27.9, 26.5 (3C), 26.3 (6C), 26.2 (3C), 26.1 (3C), 26.0 (3C), 25.9 (3C), 23.7, 23.6, 23.3 (2C), 18.8, 18.5, 18.39, 18.36, 18.33, 18.28, 18.1, 6.8 (3C), 4.5 (3C), −2.8 −3.4, −3.5, −3.8, −3.96, −4.05, −4.2 (2C), −4.3, −4.4, −4.5, −4.8, −5.1, −5.3; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{89}H_{174}O_{16}Si_8Na$ 1746.0848, found 1746.0848.



122

Primary alcohol 122. To a solution of TES ether **S11** (109 mg, 63.4 μmol) in THF (3.2 mL) was added TBAF-AcOH (0.2 M in THF, 0.634 mL, 0.127 mmol) at 0 °C. After being stirred at 0 °C for 6 h, the resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/CH_2Cl_2 = 20/1 → 5/1) to afforded alcohol **122** (101 mg, 62.8 μmol, 99%) as a colorless oil.

R_f = 0.23 (hexane/EtOAc = 7/1); $[\alpha]_D^{23}$ −13.9 (*c* 1.12, $CHCl_3$); IR (neat) ν 3490, 2953, 2928, 2884, 2856, 1513, 1472, 1462, 1387, 1360, 1333, 1249, 1095, 1077, 1040, 1005, 876, 834, 776, 676 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.31 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.49 (s, 1H), 5.20 (s, 1H), 4.55–4.50 (m, 2H), 4.42 (d, *J* = 10.8 Hz, 1H), 4.38–4.26 (m, 5H), 4.25–4.22 (m, 2H), 4.12–4.08 (m, 1H), 4.08–4.01 (m, 3H), 3.97 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.80 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.73 (d, *J* = 12.0 Hz, 1H), 3.71–3.64 (m, 3H), 3.56 (ddd, *J* = 12.0, 7.8, 4.2 Hz, 1H), 3.33 (s, 3H), 2.74–2.67 (m, 1H), 2.55 (ddd, *J* = 13.8, 7.8, 7.8 Hz, 1H), 2.17–2.06 (m, 5H), 2.02–1.94 (m, 2H), 1.93–1.87 (m, 1H), 1.86–1.71 (m, 6H), 1.65–1.50 (m, 9H), 1.14 (s, 18H), 1.13 (s, 9H), 1.10 (s, 9H), 1.09 (s, 9H), 1.08 (s, 9H), 1.06 (s, 9H), 0.394 (s, 3H), 0.387 (s, 3H), 0.362 (s, 3H), 0.357 (s, 3H), 0.348 (s, 3H), 0.346 (s, 3H), 0.339 (s, 3H), 0.30 (s, 3H), 0.29 (s, 3H), 0.28 (s, 6H), 0.27 (s, 3H), 0.24 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 150.0, 131.0, 129.7 (2C), 119.8, 118.5, 114.0 (2C), 111.5, 80.5 (2C), 79.9, 78.4, 77.0, 75.6, 74.8, 74.2, 73.8, 73.5, 73.1, 73.0, 72.6, 72.0, 71.1, 69.3, 68.0, 62.7, 54.8, 37.9, 37.8, 37.7 (2C), 33.1, 31.8, 30.6, 27.8, 26.9 (3C), 26.60 (3C), 26.56 (6C), 26.4 (3C), 26.34 (3C), 26.25 (3C), 24.0, 23.8, 23.71, 23.66, 19.1, 18.8, 18.69, 18.65 (2C), 18.60, 18.4, −2.5, −3.1, −3.2, −3.5, −3.6, −3.7, −3.86, −3.90, −4.0, −4.11, −4.14, −4.5, −4.7, −5.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{83}H_{160}O_{16}Si_7Na$ 1631.9983, found 1631.9980.



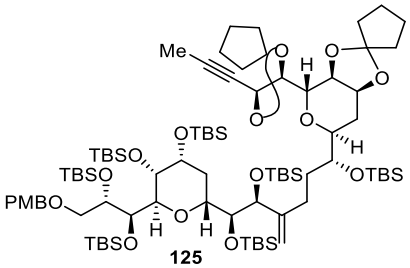
124

Terminal alkyne 124. To a solution of $(COCl)_2$ (30 μL, 0.34 mmol) in CH_2Cl_2 (3.14 mL) was added DMSO (60 μL, 0.85 mmol) at −78 °C. After being stirred at −78 °C for 15 min, a solution of alcohol **122** (101 mg, 62.8 μmol) in CH_2Cl_2 (2.1 mL + 1.0 mL rinse) was added to the mixture at −78 °C. After being stirred at −78 °C for 5 min, Et_3N (0.18 mL, 1.29 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was warmed to room temperature over 1h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. Organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford mixture of aldehyde **123** (113 mg). The mixture was used in the next reaction without further purification.

To a solution of Ohira–Bestman reagent (27.7 mg, 0.144 mmol) in MeOH (0.25 mL) was added Cs_2CO_3 (47.0 mg, 0.144 mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of aldehyde **123** in CH_2Cl_2 (0.90 mL + 0.37 mL rinse) was added. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. Organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1 → 5/1) to afforded terminal alkyne **124** (86.7 mg, 54.0 μmol, 86% for two steps) as a colorless oil.

R_f = 0.69 (hexane/EtOAc = 7/1); $[\alpha]_D^{22}$ −13.1 (*c* 1.12, $CHCl_3$); IR (neat) ν 3312, 2953, 2929, 2885, 2856, 1472, 1387, 1360, 1334, 1250, 1096, 1041, 1005, 939, 877, 834, 776, 670 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.48 (s, 1H), 5.20 (s, 1H), 4.92 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.55 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.54–4.50 (m, 2H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.36–4.32 (m, 3H), 4.31–4.27 (m, 2H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.12–4.08 (m, 2H), 4.03 (brd, *J* = 9.0 Hz, 1H), 3.96 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.81–3.74 (m, 2H), 3.71–3.63 (m, 2H), 3.33 (s, 3H), 2.70–2.62 (m, 1H), 2.57–2.49 (m, 1H), 2.17–1.89 (m, 12H), 2.16 (d, *J* = 1.8 Hz, 1H), 1.79–1,71 (m, 3H), 1.61–1.49 (m, 8H), 1.14 (s, 18H), 1.13 (s, 9H), 1.09 (s, 9H), 1.08 (s, 18H), 1.06 (s, 9H), 0.40 (s, 3H), 0.391 (s, 3H), 0.385 (s, 3H), 0.35 (s, 3H), 0.342 (s, 3H), 0.336 (s, 3H), 0.328 (s, 3H), 0.30 (s, 3H), 0.29 (s, 3H), 0.284 (s, 3H),

0.278 (s, 3H), 0.271 (s, 3H), 0.26 (s, 3H), 0.24 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 149.8, 130.9, 129.7 (2C), 121.2, 118.8, 114.0 (2C), 111.4, 82.8, 82.2, 80.5 (2C), 77.1, 75.5, 74.1, 73.8, 73.5, 73.4, 73.1, 73.0, 72.3, 72.2, 71.1, 69.3, 68.0, 67.3, 54.8, 37.6, 37.4, 37.1, 37.0, 33.4, 31.8, 30.4, 27.6, 26.9 (3C), 26.59 (3C), 26.56 (3C), 26.53 (3C), 26.4 (3C), 26.3 (3C), 26.2 (3C), 24.1, 24.0, 23.6, 23.5, 19.1, 18.7 (2C), 18.64 (2C), 18.60. 18.4, −2.5, −3.1, −3.4, −3.5, −3.6, −3.7, −3.86, −3.90. −4.0 (2C), −4.1, −4.5, −4.7, −5.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{84}H_{158}O_{15}Si_7Na$ 1625.9878, found 1625.9848.

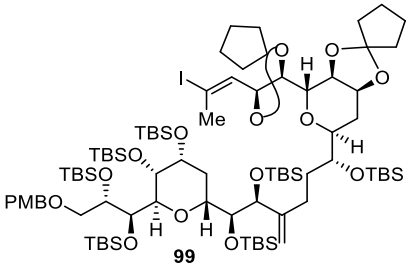


125

Alkyne 125. To a solution of terminal alkyne **124** (86.7 mg, 54.0 μmol) in THF (5.4 mL) was added LHMDS (1.3 M in THF, 0.42 mL, 0.54 mmol) at −78 °C. After being stirred at −78 °C for 1 min, MeI (67 μL, 1.08 mml) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. The resultant mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane. Organic layer was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1 → 30/1) to afforded alkyne **125** (85.2 mg, 52.6 μmol, 97%) as a colorless oil.

R_f = 0.69 (hexane/EtOAc = 7/1); $[\alpha]_D^{17}$ −17.6 (*c* 0.31, C_6H_6); IR (neat) ν 2952, 2928, 2884, 2856, 1513, 1471, 1462, 1387, 1369, 1333, 1249, 1094, 1077, 1032, 1004, 939, 877, 834, 785, 671 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.48 (s, 1H), 5.22 (s, 1H), 4.96 (dd, *J* = 7.8, 2.4 Hz, 1H), 4.56 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.55–4.51 (m, 2H), 4.42–4.32 (m, 6H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.12–4.08 (m, 2H), 4.03 (brd, *J* = 7.2 Hz, 1H), 3.96 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.84–3.77 (m, 2H), 3.70–3.64 (m, 2H), 3.32 (s, 3H), 2.73–2.65 (m, 1H), 2.58–2.50 (m, 1H), 2.20–1.97 (m, 9H), 1.93 (dd, *J* = 7.8, 7.8 Hz, 2H), 1.82–1.72 (m, 3H), 1.67–1.52 (m, 8H), 1.48 (d, *J* = 1.8 Hz, 3H), 1.15 (s, 9H), 1.142 (s, 9H), 1.138 (s, 9H), 1.09 (s, 9H), 1.08 (s, 18H), 1.06 (s, 9H), 0.40 (s, 3H), 0.39 (s, 3H), 0.36 (s, 3H), 0.35 (s, 6H), 0.34 (s, 6H), 0.30 (s, 3H), 0.29 (s, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 0.24 (s, 3H), 0.21 (s, 3H).; ^{13}C NMR (150 MHz, C_6D_6) δ 160.3, 150.3, 131.5, 130.2 (2C), 121.2, 119.2, 114.5 (2C), 112.1, 84.1, 83.4, 81.0 (2C), 78.1, 77.6, 76.0, 74.8, 74.4, 74.0, 73.8, 73.6, 73.5, 72.8, 72.7, 71.5, 69.8, 68.5 (2C), 55.3, 38.2, 37.91, 37.85, 37.76, 33.9,

32.4, 30.9, 28.4, 27.4 (3C), 27.13 (3C), 27.09 (3C), 27.06 (3C), 26.91 (3C), 26.86 (3C), 26.78 (3C), 24.6 (2C), 24.13, 24.08, 19.6, 19.24, 19.21, 19.19 (2C), 19.13, 19.0, 4.0, −1.9, −2.6, −2.88, −2.93, −3.1, −3.2, −3.3, −3.4, −3.5 (2C), −3.6, −4.0, −4.2, −4.5; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{85}H_{160}O_{15}Si_7Na$ 1640.0034, found 1640.0068.



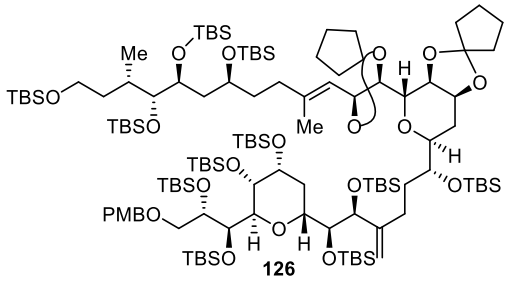
99

Iodoolefin 99. To a mixture of alkyne **125** (85.2 mg, 52.6 μmol) and $PdCl_2$(P-*o*-tol_3)$_2$ (4.1 mg, 5.3 μmol) in THF (0.53 mL) was added Bu_3SnH (0.57 mL, 2.10 mmol) dropwise over 1 h at room temperature. After being stirred for further 10 min, the resulting mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 200/1 → 50/1) to afforded vinyl stannane (69.0 mg) as a colorless oil. Obtained compound was immediately used for the next reaction because of its instability.

To a solution of vinyl stannane (69.0 mg) in CH_2Cl_2 (1.8 mL) at 0 °C was added a solution of I_2 (2 grain) in CH_2Cl_2 (1.0 mL) until the color of I_2 ceased to disappear. After being stirred at 0 °C for 10 min, the resultant mixture was quenched with satd. aq. $Na_2S_2O_3$. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 50/1) to afforded iodoolefin **99** (62.5 mg, 35.8 μmol, 68% for two steps) as a colorless oil.

R_f = 0.54 (hexane/EtOAc = 10/1); $[\alpha]_D^{22}$ −28.6 (*c* 1.36, C_6H_6); IR (neat) ν 2953, 2928, 2884, 2856, 1513, 1471, 1462, 1387, 1360, 1333, 1249, 1095, 1078, 1031, 1005, 939, 877, 834, 777, 670 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.44 (dd, *J* = 9.0, 1.2 Hz, 1H), 5.47 (s, 1H), 5.18 (s, 1H), 4.86 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.53–4.49 (m, 2H), 4.43−4.39 (m, 2H), 4.37−4.33 (m, 3H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.17 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.14 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.12−4.06 (m, 2H), 4.03 (brd, *J* = 9.6 Hz. 1H), 3.95 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.82−3.76 (m, 2H), 3.69−3.63 (m, 2H), 3.33 (s, 3H), 2.66−2.59 (m, 1H), 2.52−2.45 (m, 1H), 2.36 (d, *J* = 1.2 Hz, 3H), 2.20 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 2.15−2.10 (m, 2H), 2.09−1.83, 1.82−1.70 (m, 3H), 1.62−1.52 (m, 8H), 1.141 (s,

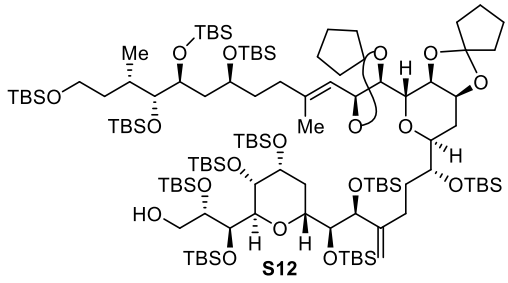
9H), 1.137 (s, 9H), 1.128 (s, 9H), 1.09 (s, 9H), 1.080 (s, 9H), 1.075 (s, 9H), 1.06 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.35 (s, 3H), 0.341 (s, 3H), 0.336 (s, 6H), 0.30 (s, 6H), 0.29 (s, 3H), 0.28 (s, 3H), 0.250 (s, 6H), 0.245 (s, 6H), 0.2 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 149.8, 139.0, 130.9, 129.7 (2C), 119.8, 118.7, 114.0 (2C), 111.6, 101.6, 81.5, 80.4 (2C), 77.1, 75.4, 74.9, 74.6, 73.9, 73.5, 73.0 (2C), 72.9, 72.5, 72.0, 71.0, 69.3, 68.0, 54.8, 37.8, 37.6, 37.2, 37.0, 33.8, 31.8, 30.3, 28.6, 26.9 (4C), 26.59 (3C), 26.55 (3C), 26.40 (3C), 26.38 (3C), 26.34 (3C), 26.2 (3C), 24.1, 23.8, 23.7, 23.4, 19.1, 18.69, 18.65 (2C), 18.59 (2C), 18.4, −2.5, −3.1, −3.4, −3.5, −3.6, −3.7, −3.9 (2C), −3.97, −4.01, −4.1, −4.5, −4.7, −5.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{85}H_{161}O_{15}Si_7INa$ 1767.9157, found 1767.9207.



Coupling compound 126. To the mixture of polyol **86** (8.4 mg, 12.6 μmol) and 9-BBN dimer (15 mg, 63 μmol) at 0 °C was added THF (64 μL). After being stirred at room temperature for 1.5 h, 3 M Cs_2CO_3 aqueous (45 μL, 135 μmol) was added to the reaction mixture and then stirred at room temperature for 20 min. To the resultant mixture were added DMF (421 μL), a solution of iodoolefin **99** (14.7 mg, 8.4 μmol) in THF (200 μL + 100 μL rinse) and $Pd(PPh_3)_4$ (1.5 mg, 1.3 μmol). After being stirred at room temperature for 10 min, H_2O (90 μL) was added and the reaction mixture was stirred for further 10 min at room temperature. The resultant mixture was diluted with Et_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 100/1 → 5/1) afforded coupling compound **126** (17.0 mg, 7.5 μmol, 88%) as a colorless oil.

R_f = 0.55 (hexane/EtOAc = 10/1), $[\alpha]_D^{20}$ −21.7 (*c* 0.58, $CHCl_3$); IR (neat) ν 2953, 2928, 2885, 2856, 1513, 1471, 1462, 1387, 1360, 1250, 1091, 1029, 1004, 939, 876, 832, 807, 773, 758, 670 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.63 (d, *J* = 9.0 Hz, 1H), 5.48 (s, 1H), 5.20 (s, 1H), 5.03 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.56–4.45 (m, 4H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.37–4.33 (m, 2H), 4.29 (d, *J* = 4.8 Hz, 1H), 4.26 (d, *J* = 10.8 Hz, 1H), 4.24 (d, *J* = 12.0 Hz. 1H), 4.14–4.06 (m, 3H), 4.02 (brd, *J* = 9.6 Hz, 1H), 3.97 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.91 (ddd, *J* = 12.0, 3.0, 3.0 Hz, 1H), 3.87 (d, *J* = 10.8 Hz, 1H),

3.79 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.71–3.61 (m, 5H), 3.34 (s, 3H), 2.72–2.65 (m, 1H), 2.60–2.49 (m, 2H), 2.25–2.18 (m, 2H), 2.17–2.07 (m, 6H), 2.05–1.72 (m, 12H), 1.87 (s, 3H), 1.70–1.59 (m, 9H), 1.43–1.35 (m, 1H), 1.144 (s, 18H), 1.142 (s, 9H), 1.11 (s, 9H), 1.09 (s, 9H), 1.08 (s, 18H), 1.07 (s, 9H), 1.06 (s, 18H), 1.02 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.40 (s, 3H), 0.38 (s, 3H), 0.36 (s, 3H), 0.353 (s, 3H), 0.348 (s, 3H), 0.344 (s, 3H), 0.33 (s, 3H), 0.32 (s, 3H), 0.30 (s, 3H), 0.285 (s, 6H), 0.282 (s, 3H), 0.277 (s, 3H), 0.27 (s, 3H), 0.24 (s, 3H), 0.23 (s, 6H), 0.19 (s, 3H), 0.174 (s, 3H), 0.165 (s, 3H), 0.123 (s, 3H), 0.118 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 149.6, 143.2, 130.9, 129.7 (2C), 122.8, 119.4, 118.5, 114.0 (2C), 111.6, 84.0, 82.1, 80.4 (2C), 77.1, 75.6, 74.54, 74.45, 74.0, 73.8, 73.5, 72.9 (2C), 72.81, 72.77, 72.0, 71.0, 70.3, 69.3, 67.9, 61.4, 54.7, 41.6, 38.0 (2C), 37.8, 37.4, 37.2, 36.7, 35.1, 34.4, 33.4, 31.8, 30.4, 27.3, 26.9 (3C), 26.6 (3C), 26.55 (3C), 26.52 (3C), 26.46 (3C), 26.42 (3C), 26.34 (3C), 26.25 (9C), 24.2, 23.9, 23.7, 23.5, 19.1, 18.8, 18.70, 18.66 (4C), 18.59, 18.43 (2C), 18.40, 17.2, 15.4, −2.5, −2.9, −3.0, −3.1, −3.3, −3.5, −3.65 (3C), −3.70, −3.8 (2C), −4.01, −4.04, −4.1 (2C), −4.2, −4.4, −4.5, −5.00, −5.03, −5.07; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{119}H_{238}O_{19}Si_{11}INa$ 2302.5011, found 2302.5049.

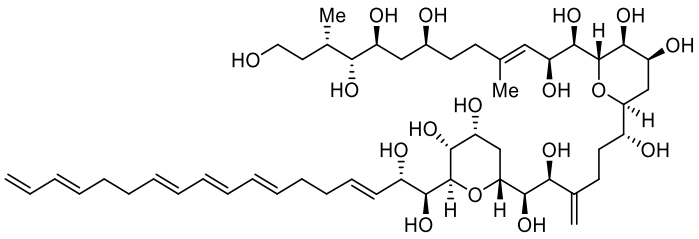


S12

Alcohol S12. To a solution of compound **126** (17.0 mg, 7.5 μmol) in CH_2Cl_2/H_2O (3/1, v/v, 1.0 mL) at 0 °C were added *β*-pinene (7 μL, 44 μmol) and DDQ (5.1 mg, 22.4 μmol). After being stirred for 3 h at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted with hexane, and the organic layer was 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 = 100/1 → 30/1) to afford primary alcohol **S12** (12.1 mg, 5.6 μmol, 75%) as a colorless oil.

R_f = 0.50 (hexane/EtOAc = 10/1), ^{1}H NMR (600 MHz, C_6D_6) δ 5.63 (d, *J* = 7.8 Hz, 1H), 5.48 (s, 1H), 5.19 (s, 1H), 5.04 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.52–4.45 (m, 3H), 4.34–4.30 (m, 2H), 4.28–4.23 (m, 3H), 4.12–4.04 (m, 4H), 3.96–3.81 (m, 5H), 3.71–3.61 (m, 4H), 2.64–2.54 (m, 1H), 2.57 (ddd, *J* = 13.2, 13.2, 4.2 Hz, 1H), 2.53–2.45 (m, 1H), 2.25–2.17 (m, 2H), 2.14–2.08 (m, 6H), 2.06–1.72 (m, 12H), 1.88 (s, 3H), 1.70–1.59 (m, 9H), 1.43–1.35 (m, 1H), 1.14 (s,

9H), 1.13 (s, 9H), 1.11 (s, 18H), 1.09 (s, 9H), 1.08 (s, 18H), 1.07 (s, 9H), 1.06 (s, 9H), 1.04 (s, 9H), 1.03–1.01 (m, 12H), 0.36 (s, 3H), 0.341 (s, 3H), 0.336 (s, 3H), 0.332 (s, 3H), 0.326 (s, 3H), 0.323 (s, 3H), 0.31 (s, 6H), 0.29 (s, 3H), 0.281 (s, 3H), 0.277 (s, 3H), 0.271 (s, 3H), 0.267 (s, 3H), 0.260 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.121 (s, 3H), 0.118 (s, 3H).



C43-*epimer* type
C21-C67 analog (**97**)

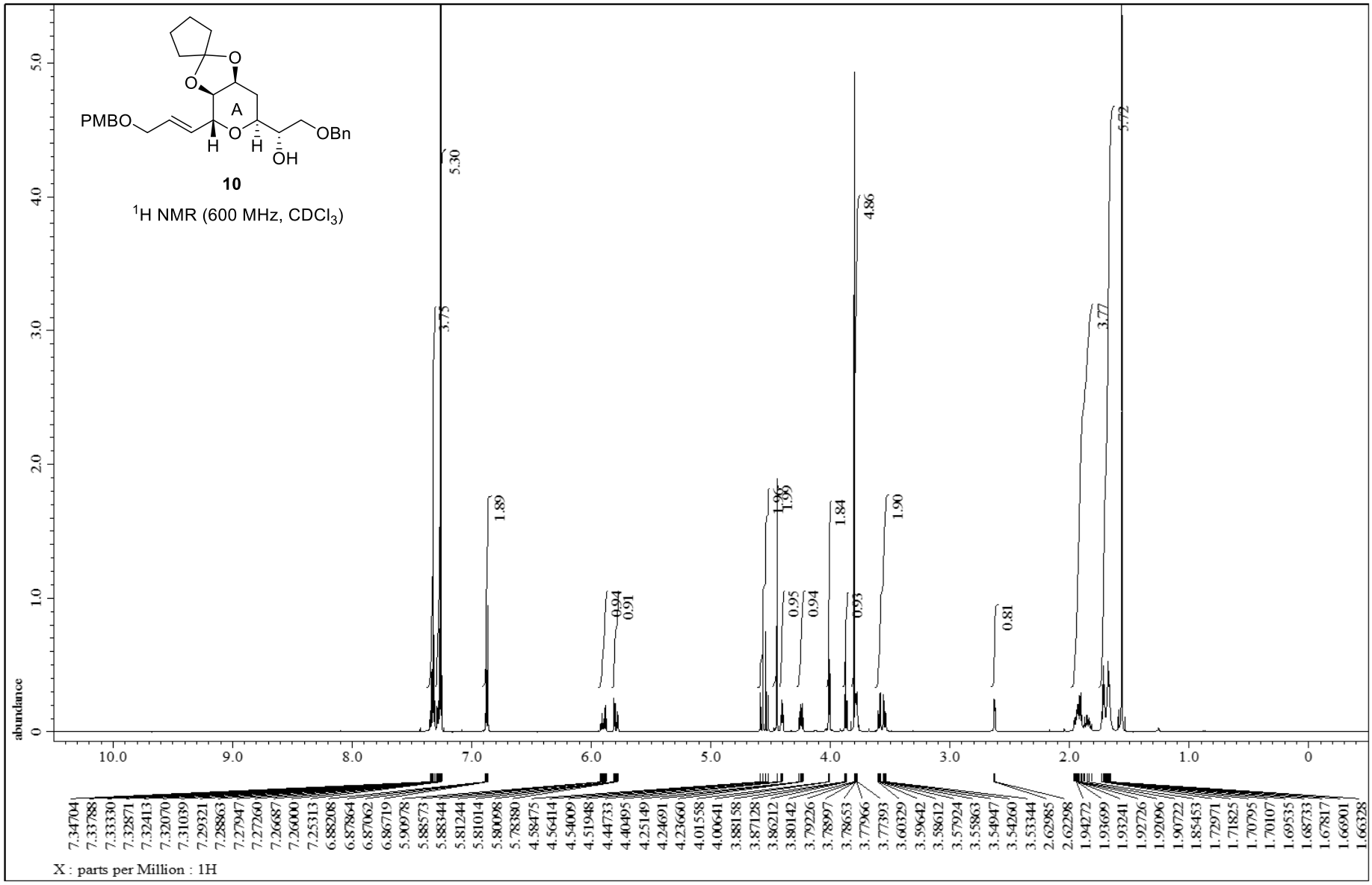
C43-*epimer* type C21–C67 analog (97). To a solution of $(COCl)_2$ (20 μL, 230 μmol) in CH_2Cl_2 (560 μL) at −78 °C was added DMSO (34 μL, 479 μmol). After being stirred at −78 °C for 15 min, a solution of primary alcohol **S12** (12.1 mg, 5.6 μmol) in CH_2Cl_2 (400 μL + 160 μL rinse) was added and then stirred at −78 °C for 5 min. To the reaction mixture was added Et_3N (145 μL, 1.04 mmol). The resultant mixture was warmed to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic layer was 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 = 200/1 → 100/1) to afford aldehyde **127** (11.2 mg) as a colorless oil, which was used in the next reaction immediately.

To a solution of sulfone **2** (27.8 mg, 67.7 μmol) and aldehyde **127** (11.2 mg) in THF/HMPA (4/1, v/v, 520 μL) at −78 °C was added KHMDS (0.5 M in THF, 83 μL, 42 μmol) dropwise. After being stirred at −78 °C for 30 min, the reaction mixture was warmed to room temperature over 1 h and stirred at room temperature for further 30 min. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc, and the organic layer was 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 = 100/1 → 5/1) to provide coupling compound (8.2 mg, *E*/*Z* = 10:1). The *E*/*Z* mixture was used in next reaction without further purification.

To a solution of the *E*/*Z* mixture of coupled product (8.2 mg) in THF (1.0 mL) at 0 °C was added 18% HF·pyridine (160 μL, 0.52 mmol), and the mixture was stirred at 50 °C for 11 days, and then cooled to room temperature and stirred for further 13 days while HF·pyridine

was added seven times (18% in pyridine, 160 μL, 0.52 mmol at 46, 62 h, 70% in pyridine, 50 μL, 0.65 mmol at 134, 254, 326, 395 h, 70% in pyridine, 25 μL, 0.33 mmol at 450 h). MeOH (0.2 mL) and $(CH_2OH)_2$ (0.6 mL) was also added at 134 h to facilitate the removal of the acetal group. The reaction was quenched with Et_3N and concentrated by blowing argon stream. Purification by reversed phase ODS column chromatography ($MeOH/H_2O$ = 1/2 → 2/1) gave *E/Z* mixture of **97** (4.1 mg) as a colorless oil. Further purification by reversed-phase HPLC (column: C18-MS-II waters 10 × 250 mm, eluent: $MeCN/H_2O$ = 35/65, flow rate: 4.5 mL/min, detection: UV 250 nm) afforded C43*epi*-C21–C67 analog **97** (1.4 mg, 1.5 μmol, 26% for 3 steps).

R_f = 0.35 ($MeOH/H_2O$ = 3/1), $[\alpha]_D^{22}$ −14.1 (*c* 0.14, CH_3OH); IR (neat) ν 3362, 3010, 2923, 2861, 2845, 1418, 1258, 1056, 1032, 1002, 897, 835, 780 cm^{-1}; NMR (600 MHz, CD_3OD/C_5D_5N = 2:1) δ 6.26 (ddd, *J* = 16.8, 10.2, 10.2 Hz, 1H), 6.08–5.96 (m, 5H), 5.83–5.74 (m, 2H), 5.67–5.57 (m, 4H), 5.28 (s, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.03 (s, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 4.73 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.44 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.36–4.32 (m, 2H), 4.29 (dd, *J* = 2.4, 2.4 Hz, 1H), 4.26 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.17–4.08 (m, 3H), 4.06 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.01–3.93 (m, 2H), 3.86–3.80 (m, 2H), 3.77 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.74–3.63 (m, 3H), 3.58 (ddd, *J* = 10.2, 6.0, 3.0 Hz, 1H), 3.42 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.39 (ddd, *J* = 13.8, 10.2, 4.2 Hz, 1H), 2.32–1.93 (m, 17H), 1.83 (ddd, *J* = 12.1, 3.0, 3.0 Hz, 1H), 1.80–1.56 (m, 6H), 1.72 (s, 3H), 0.97 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD/C_5D_5N = 2:1) δ 150.5, 138.6, 138.4, 135.3, 134.5, 134.1, 134.0, 132.6, 132.4, 132.3, 132.1, 132.0, 130.2, 126.8, 115.5, 112.1, 79.7, 79.3, 78.1, 75.8, 75.5, 74.8, 74.7, 74.1, 73.7, 72.9, 72.6, 72.5, 71.7, 68.8 (2C), 67.7, 67.4, 67.2, 60.8, 41.6, 38.3, 36.8, 36.7, 33.5 (2C), 33.4, 33.3, 32.6, 31.9, 31.5, 31.1, 29.4, 17.4, 13.3; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{50}H_{82}O_{17}Na$ 977.5444, found 977.5471.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O
H
10
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abundance
X : parts per Million : 13C
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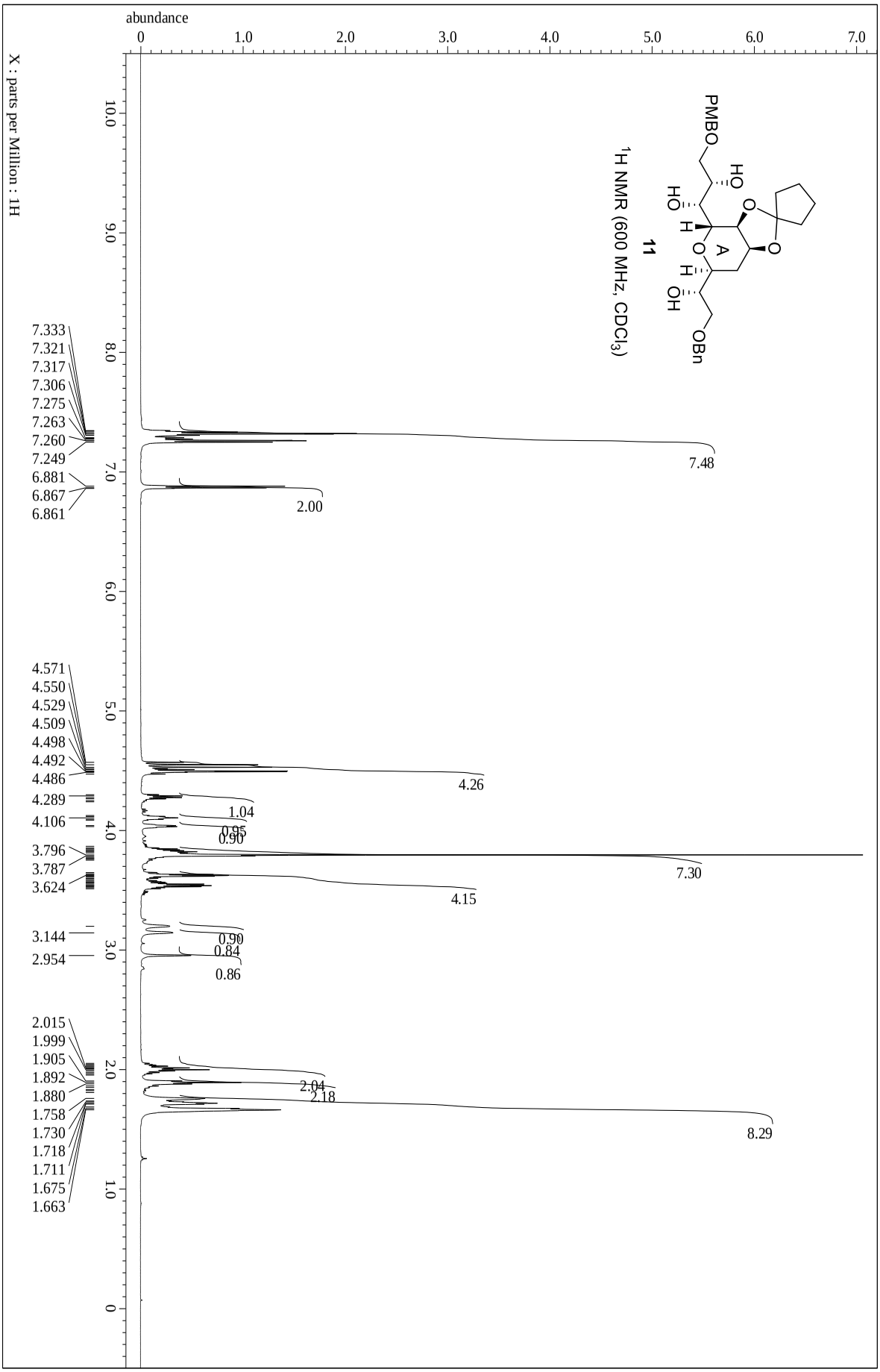
abundance
X : parts per Million : 1H
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O
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4.15
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0.86
2.04
2.18
8.29

HO
PMBO
A
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H
H
HO
OH
OBn
11
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73.378
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71.702
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X : parts per Million : 13C

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OBn
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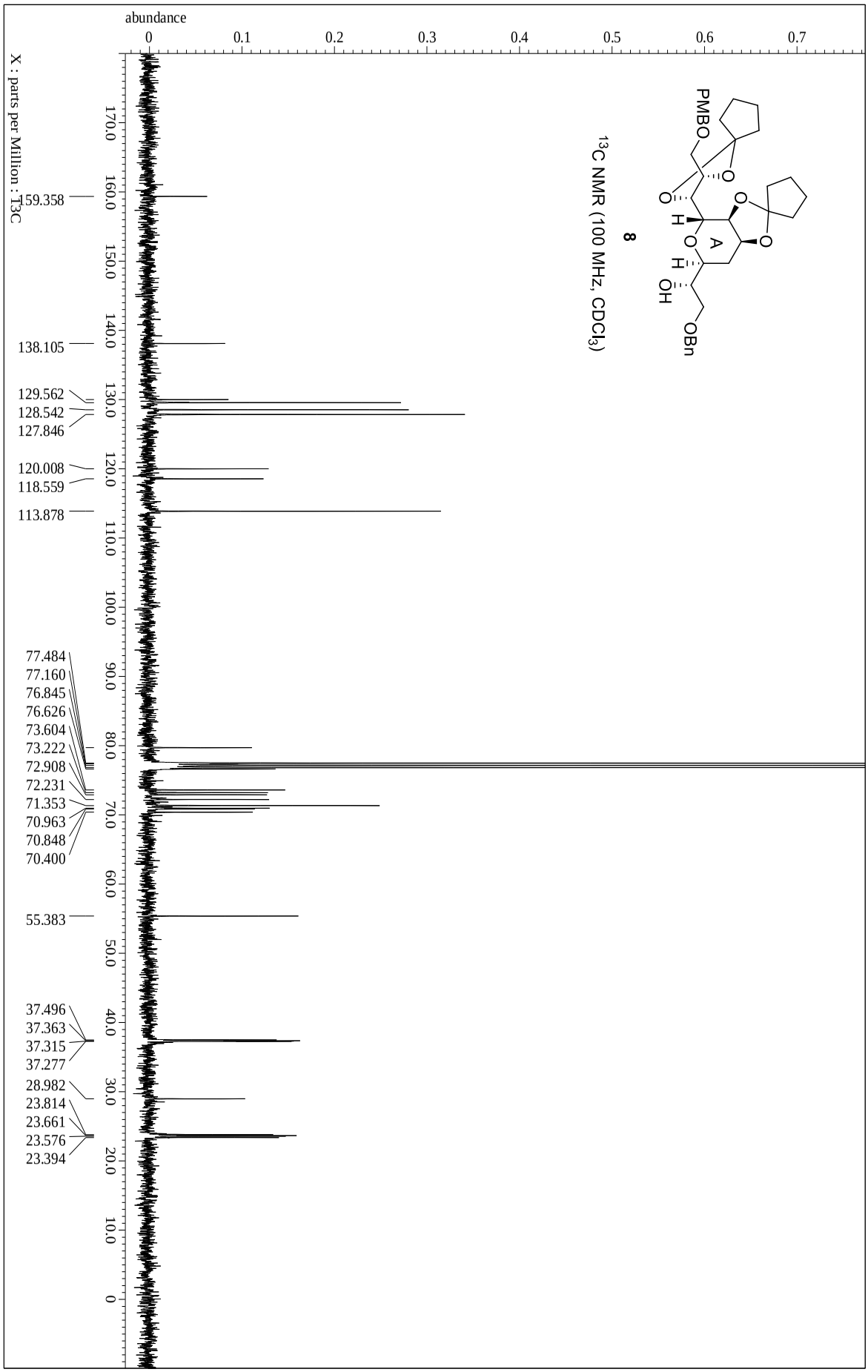
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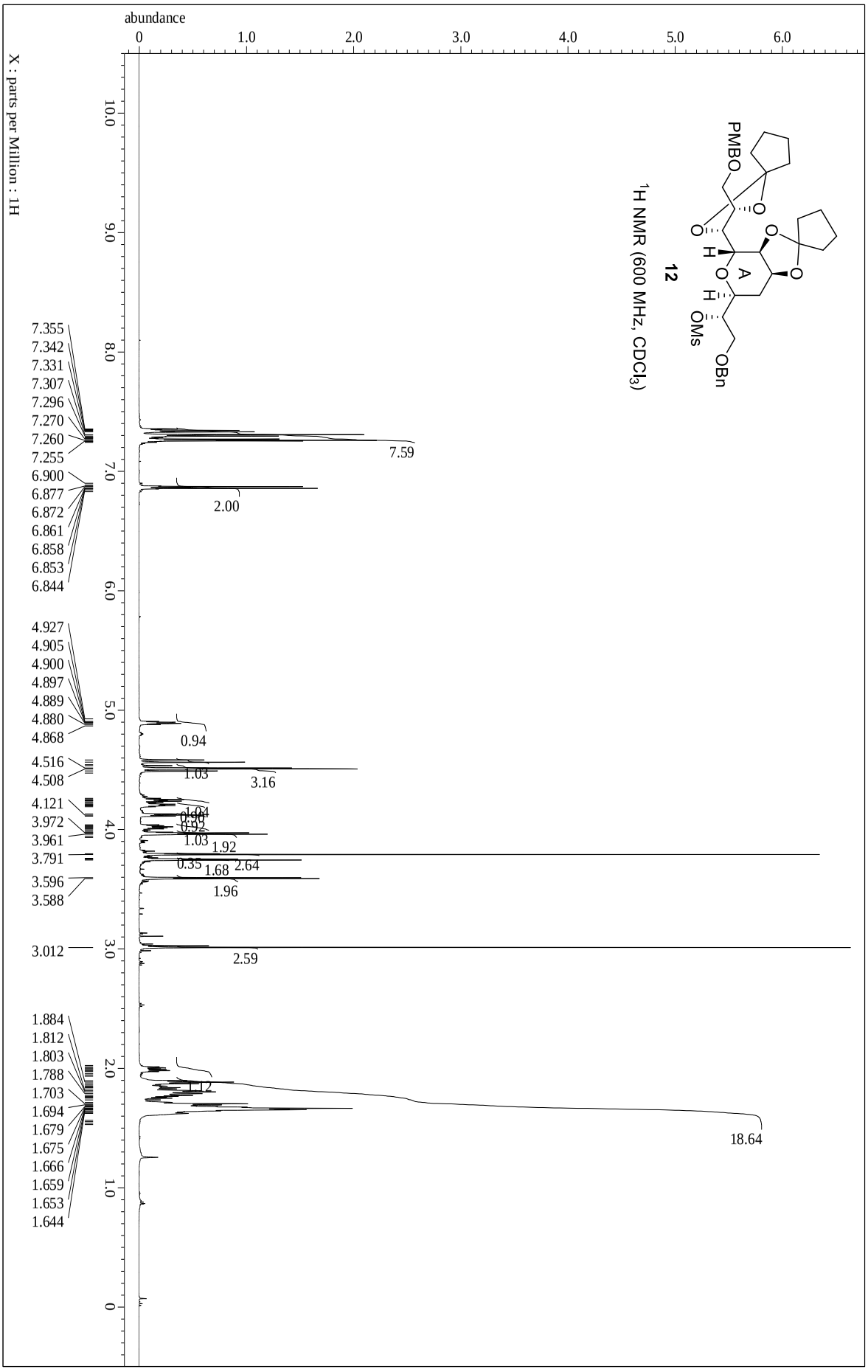
13C NMR (100 MHz, CDCl3)


abundance
X : parts per Million : 1H
^{1}H NMR (600 MHz, CDCl$_3$)
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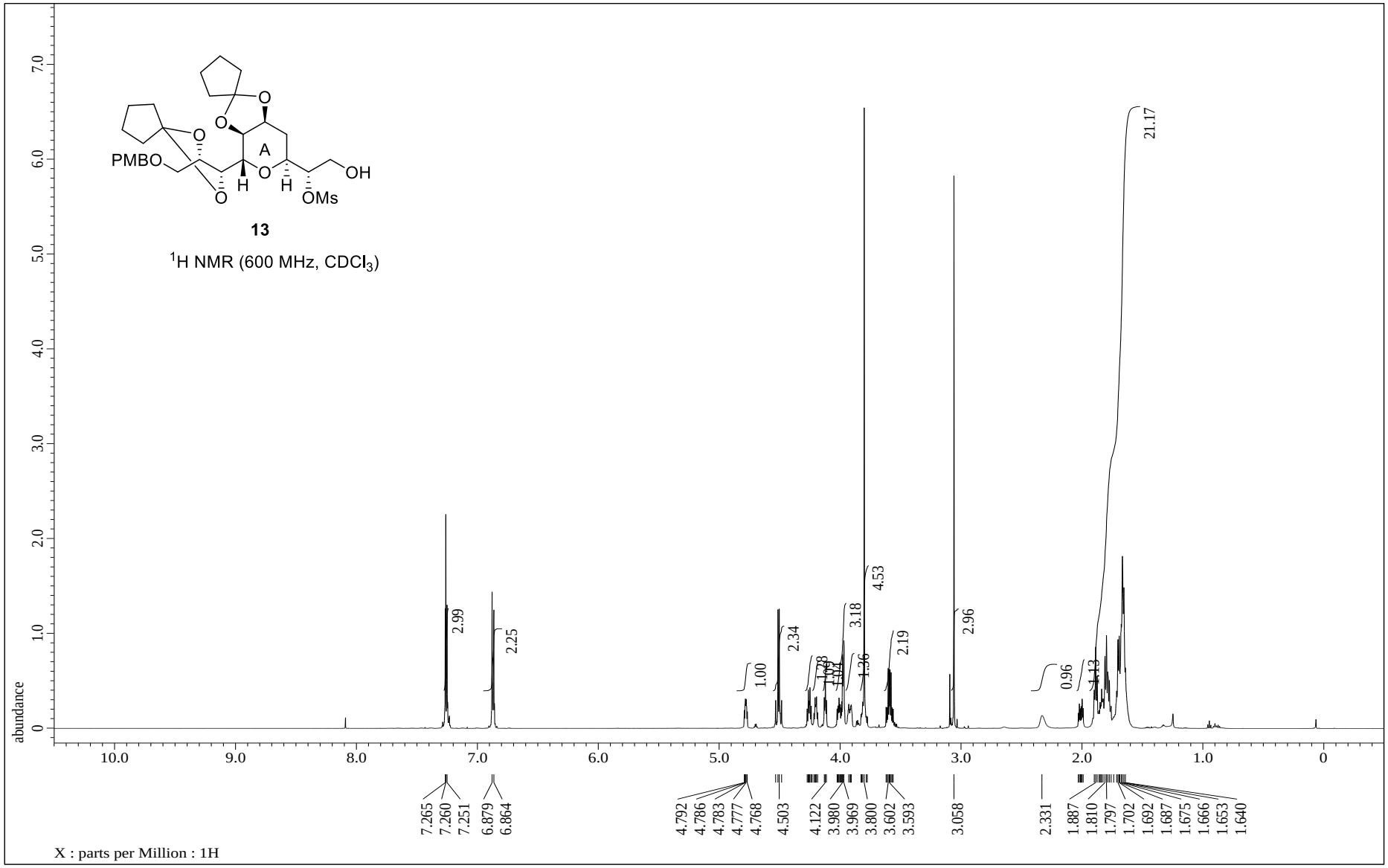
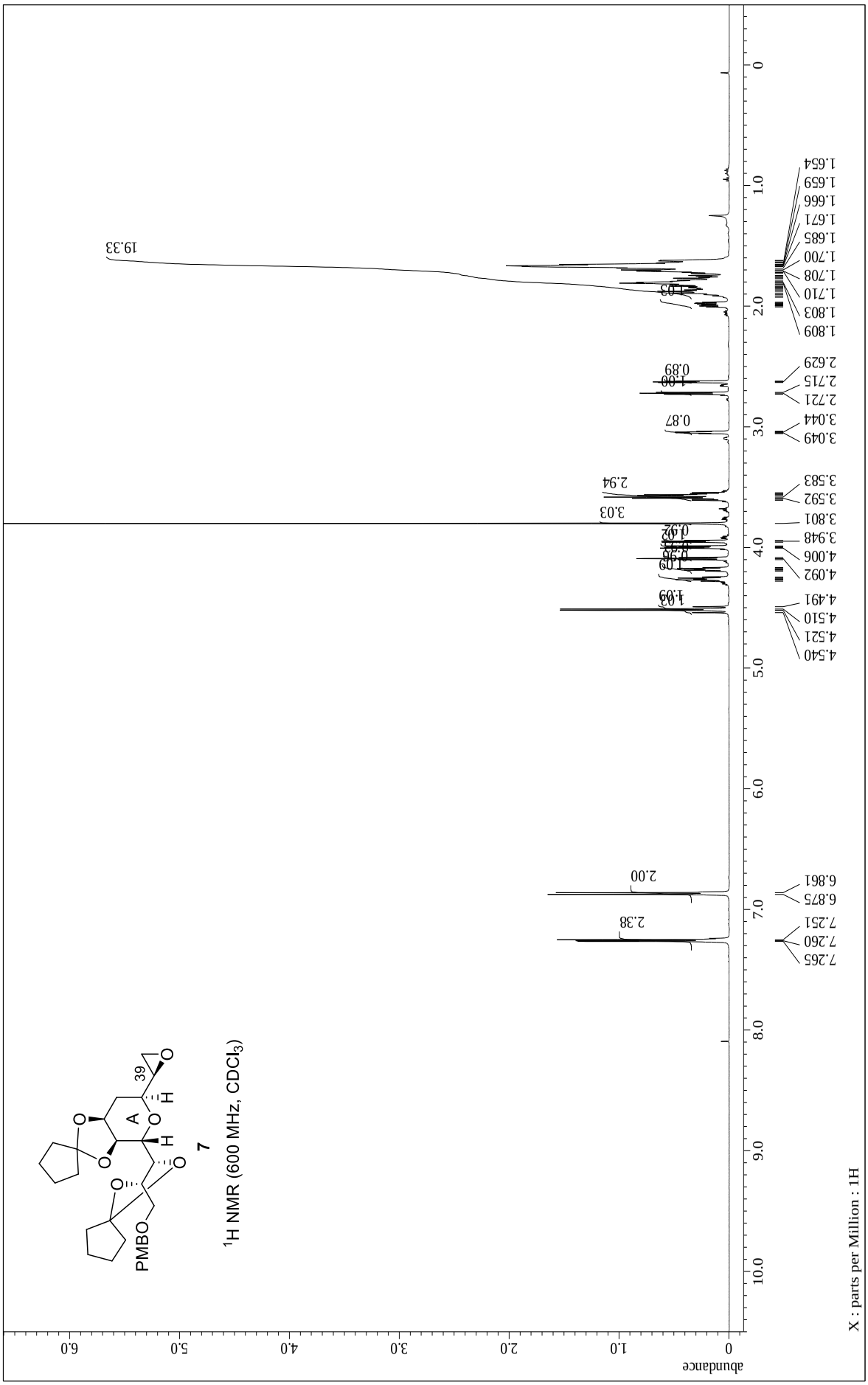
OBn
OMs
7.355
7.342
7.331
7.307
7.296
7.270
7.260
7.255
6.900
6.877
6.872
6.861
6.858
6.853
6.844
4.927
4.905
4.900
4.897
4.889
4.880
4.868
4.516
4.508
4.121
3.972
3.961
3.791
3.596
3.588
3.012
1.884
1.812
1.803
1.788
1.703
1.694
1.679
1.675
1.666
1.659
1.653
1.644
7.59
2.00
0.94
1.03
3.16
1.04
0.96
0.92
1.03
1.92
0.35
1.68
2.64
1.96
2.59
1.12
18.64

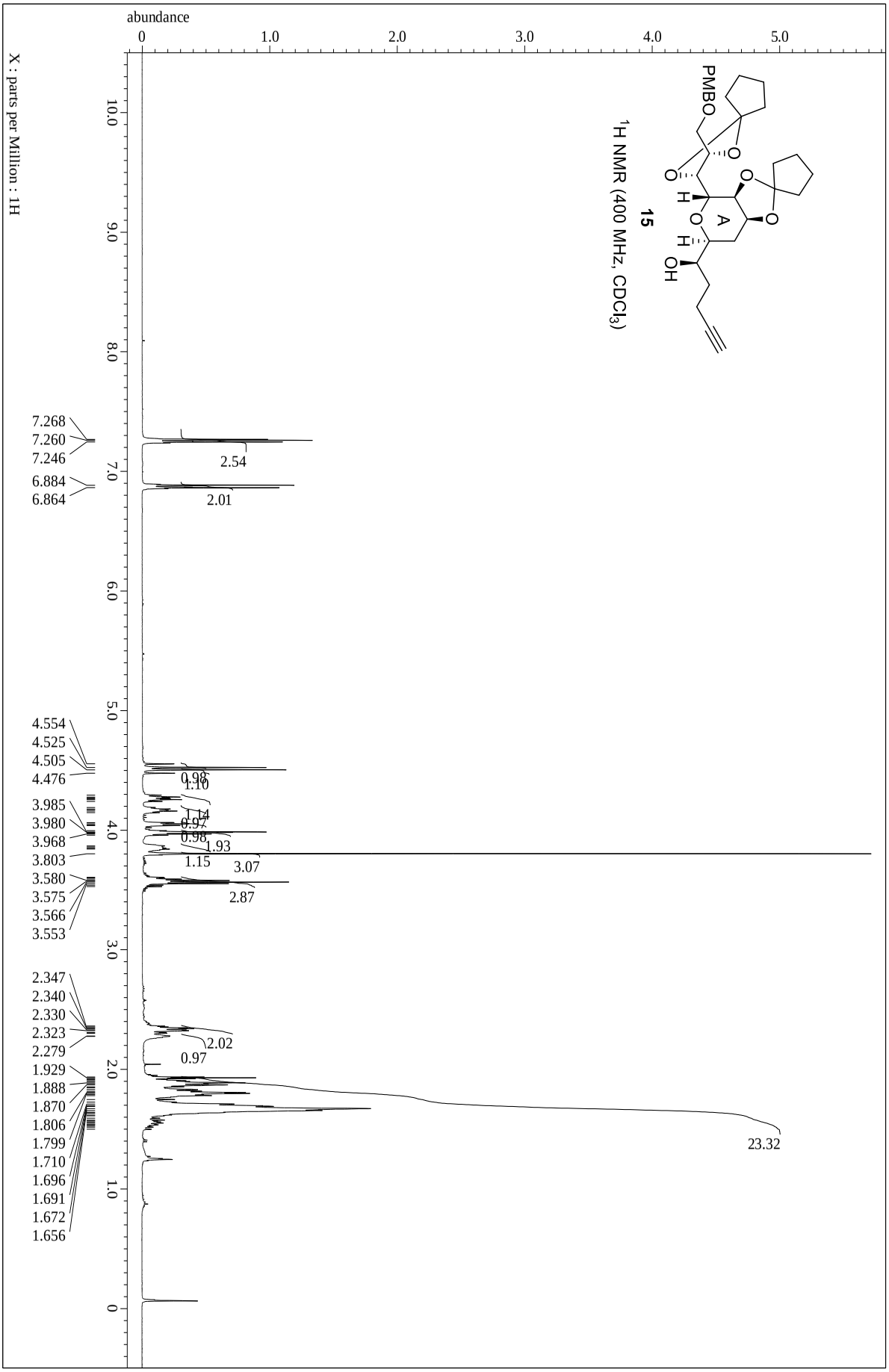
PMBO
A
OBn
OMs
12
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
159.350
137.510
129.544
128.634
127.858
120.103
118.829
113.879
81.794
79.458
77.371
77.160
76.949
76.700
73.627
73.234
71.128
70.956
70.295
69.883
69.529
55.387
38.842
37.511
37.434
37.319
37.291
28.482
23.876
23.752
23.675
23.618
23.446


PMBO
O
O
A
O
H
H
O
OMs
OH
13
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
2.99
2.25
1.00
2.34
3.18
4.53
1.36
2.19
2.96
0.96
21.17
7.265
7.260
7.251
6.879
6.864
4.792
4.786
4.783
4.777
4.768
4.503
4.122
3.980
3.969
3.800
3.602
3.593
3.058
2.331
1.887
1.810
1.797
1.702
1.692
1.687
1.675
1.666
1.653
1.640

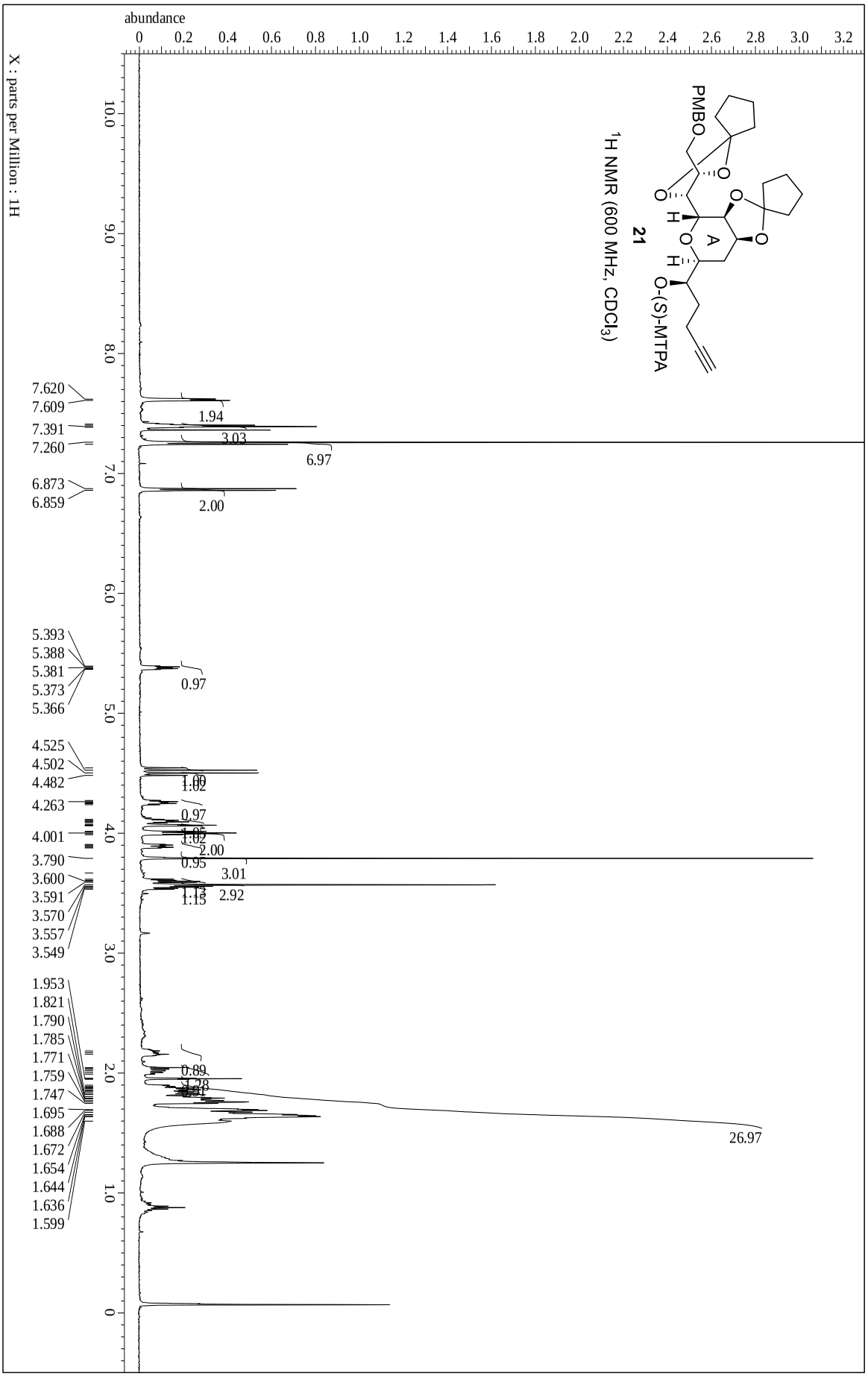
PMBO
O
O
O
A
O
H
H
OH
OMs
13
13C NMR (150 MHz, CDCl3)
abundance
159.407
130.032
129.611
120.132
118.877
113.918
83.230
79.343
77.380
77.160
76.949
76.557
73.301
72.583
70.908
70.860
70.228
69.883
62.348
55.416
38.765
37.616
37.434
37.348
37.310
28.578
23.781
23.694
23.599
23.446
X : parts per Million : 13C

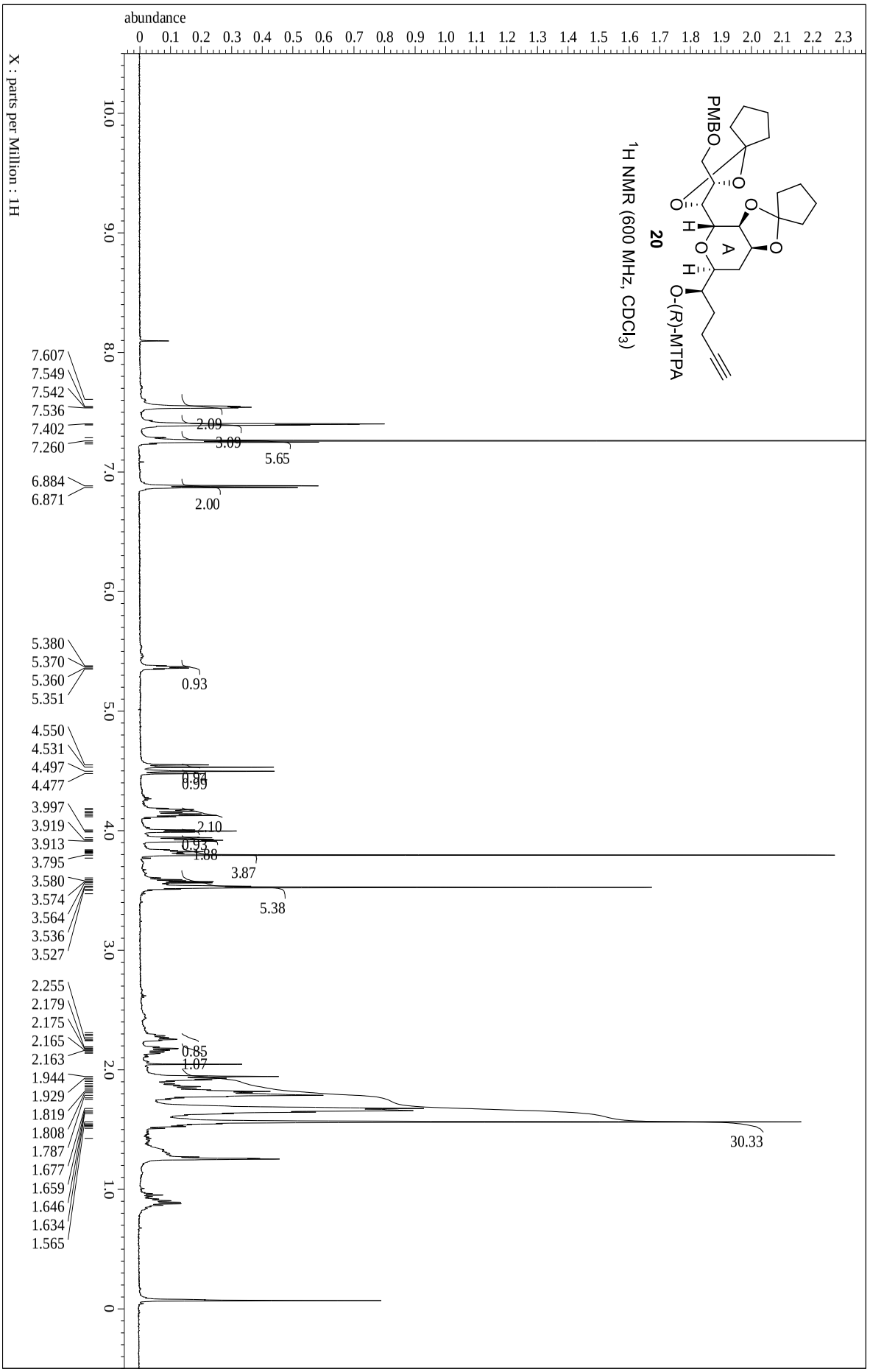

PMBO
7
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H

PMBO
A
39
H
H
7
13C NMR (150 MHz, CDCl3)
abundance
159.398
130.128
129.524
120.074
118.600
113.908
79.276
77.371
77.160
76.949
76.787
73.359
73.263
71.281
71.099
70.707
70.314
55.416
53.242
45.228
37.568
37.425
37.310
29.363
23.857
23.666
23.608
23.426
X : parts per Million : 13C


abundance
X : parts per Million : 1H
^{1}H NMR (400 MHz, CDCl$_3$)
15
PMBO
OH
A
7.268
7.260
7.246
6.884
6.864
4.554
4.525
4.505
4.476
3.985
3.980
3.968
3.803
3.580
3.575
3.566
3.553
2.347
2.340
2.330
2.323
2.279
1.929
1.888
1.870
1.806
1.799
1.710
1.696
1.691
1.672
1.656
2.54
2.01
0.98
1.10
0.97
0.96
1.93
1.15
3.07
2.87
2.02
0.97
23.32

PMBO
O
O
A
O
H
H
O
OH
15
13C NMR (100 MHz, CDCl3)
abundance
X : parts per Million : 13C
159.353
129.958
129.500
120.023
118.411
113.873
84.125
79.281
77.441
77.127
76.964
76.802
73.484
73.208
72.979
71.682
71.320
70.281
68.917
55.369
37.520
37.472
37.367
37.329
31.055
23.771
23.628
23.561
23.390
15.123


abundance
X : parts per Million : 1H
^{1}H NMR (600 MHz, CDCl$_3$)
21
PMBO
O-(S)-MTPA
7.620
7.609
7.391
7.260
6.873
6.859
5.393
5.388
5.381
5.373
5.366
4.525
4.502
4.482
4.263
4.001
3.790
3.600
3.591
3.570
3.557
3.549
1.953
1.821
1.790
1.785
1.771
1.759
1.747
1.695
1.688
1.672
1.654
1.644
1.636
1.599
1.94
3.03
6.97
2.00
0.97
1.00
1.02
0.97
1.02
2.00
0.95
3.01
1.13
2.92
0.89
26.97


abundance
X : parts per Million : 1H
^{1}H NMR (600 MHz, CDCl$_3$)
20
PMBO
O-(R)-MTPA
7.607
7.549
7.542
7.536
7.402
7.260
6.884
6.871
5.380
5.370
5.360
5.351
4.550
4.531
4.497
4.477
3.997
3.919
3.913
3.795
3.580
3.574
3.564
3.536
3.527
2.255
2.179
2.175
2.165
2.163
1.944
1.929
1.819
1.808
1.787
1.677
1.659
1.646
1.634
1.565
2.09
3.09
5.65
2.00
0.93
2.10
3.87
5.38
0.85
1.07
30.33

PMBO
O
O
O
A
O
H
H
OTBS
6
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.279
7.273
7.260
7.251
7.244
6.889
6.881
6.876
6.865
6.860
6.852
4.560
4.530
4.505
4.475
4.032
3.974
3.899
3.801
3.575
3.569
3.561
3.558
3.498
2.255
2.240
2.235
2.223
2.219
1.907
1.689
1.684
1.664
1.653
0.876
0.075
2.39
2.00
0.95
1.09
3.07
2.01
0.97
2.06
22.69
9.75
6.13

PMBO
O
O
O
O
A
O
H
H
OTBS
6
13C NMR (100 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0.5
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
159.319
130.096
129.467
120.027
118.254
113.878
79.620
77.475
77.160
76.893
76.836
73.241
73.060
72.869
72.345
71.735
71.277
70.476
68.636
55.383
37.534
37.487
37.401
37.334
32.567
28.114
26.093
23.795
23.700
23.595
23.414
18.293
14.070
-4.036
-4.418
X : parts per Million : 13C

PMBO
O
O
A
O
H
H
O
OTBS
I
22
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
2.48
2.02
1.00
0.96
2.06
1.01
0.98
1.89
0.99
4.12
3.15
1.90
0.86
7.29
14.11
9.86
5.92
7.263
7.260
7.250
6.875
6.860
6.038
5.999
5.997
5.961
5.659
4.544
4.524
4.505
4.485
4.166
4.029
3.803
3.593
3.584
3.563
3.555
2.471
2.452
2.443
2.434
2.426
1.703
1.694
1.679
1.669
1.656
1.642
0.886
0.070
0.068

PMBO
O
O
O
A
O
H
H
O
OTBS
I
22
^{13}C NMR (150 MHz, CDCl$_3$)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
159.379
130.128
129.496
125.388
120.026
118.293
113.927
112.529
80.186
77.371
77.160
76.949
76.681
73.349
72.976
72.449
71.846
71.281
70.659
55.406
40.412
37.626
37.530
37.406
37.339
33.624
28.501
26.107
23.800
23.762
23.560
23.426
18.275
-4.111
-4.206
X : parts per Million : 13C

S1
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.260
6.025
6.023
5.681
4.272
4.266
4.262
4.256
4.246
4.055
3.819
3.680
3.671
3.543
3.531
2.482
2.464
2.453
2.443
2.435
1.726
1.691
1.677
1.672
1.668
1.663
0.895
0.087
0.082
1.00
0.96
1.07
0.99
2.05
0.93
2.01
1.02
0.96
1.89
21.87
8.85
6.19

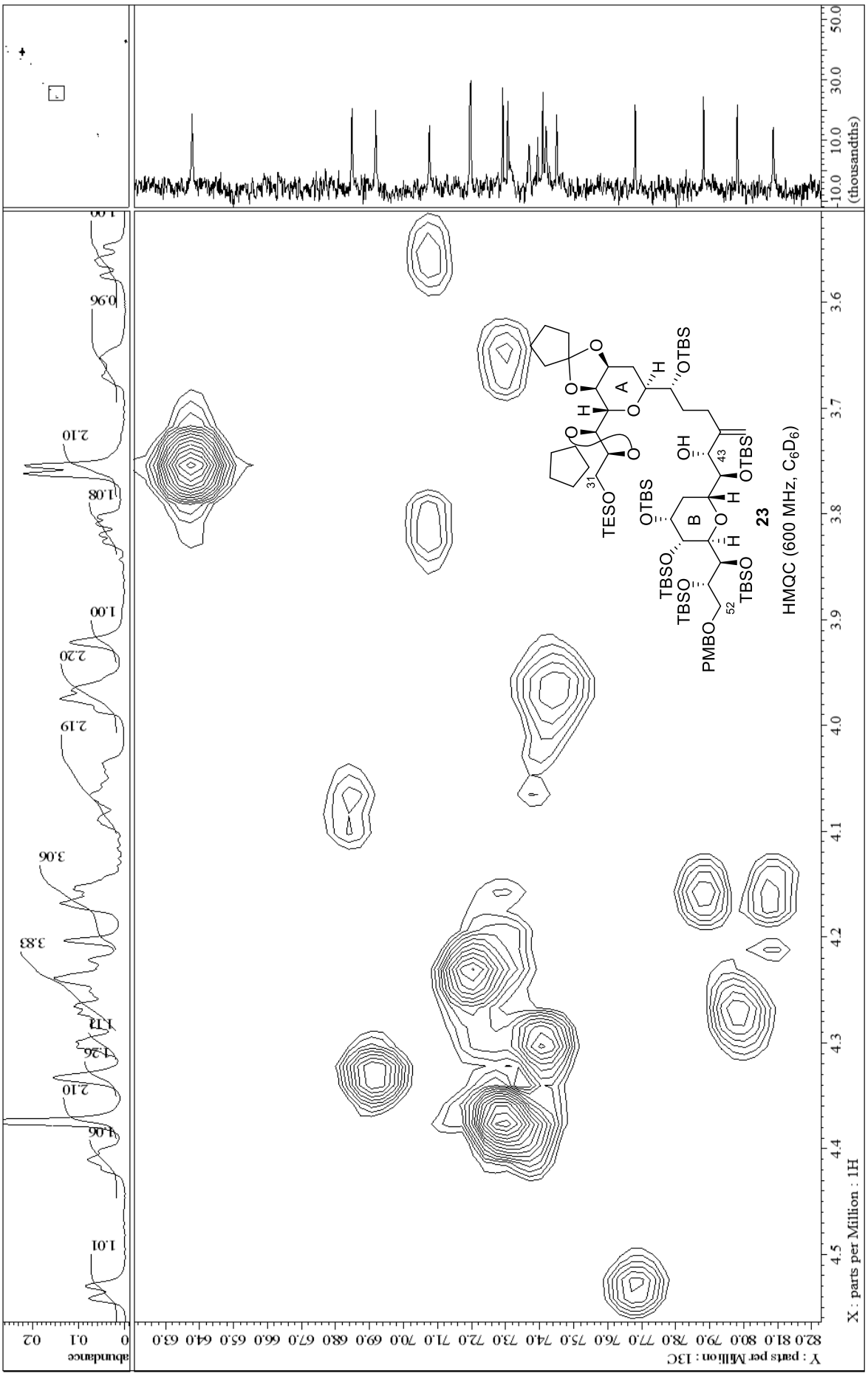
S1
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
125.560
119.892
118.485
112.290
78.615
78.127
77.371
77.160
76.949
73.253
72.689
72.545
71.808
71.750
62.702
40.537
37.549
37.482
37.453
37.310
33.624
28.204
26.107
23.848
23.637
23.541
23.426
18.304
-4.063
-4.187

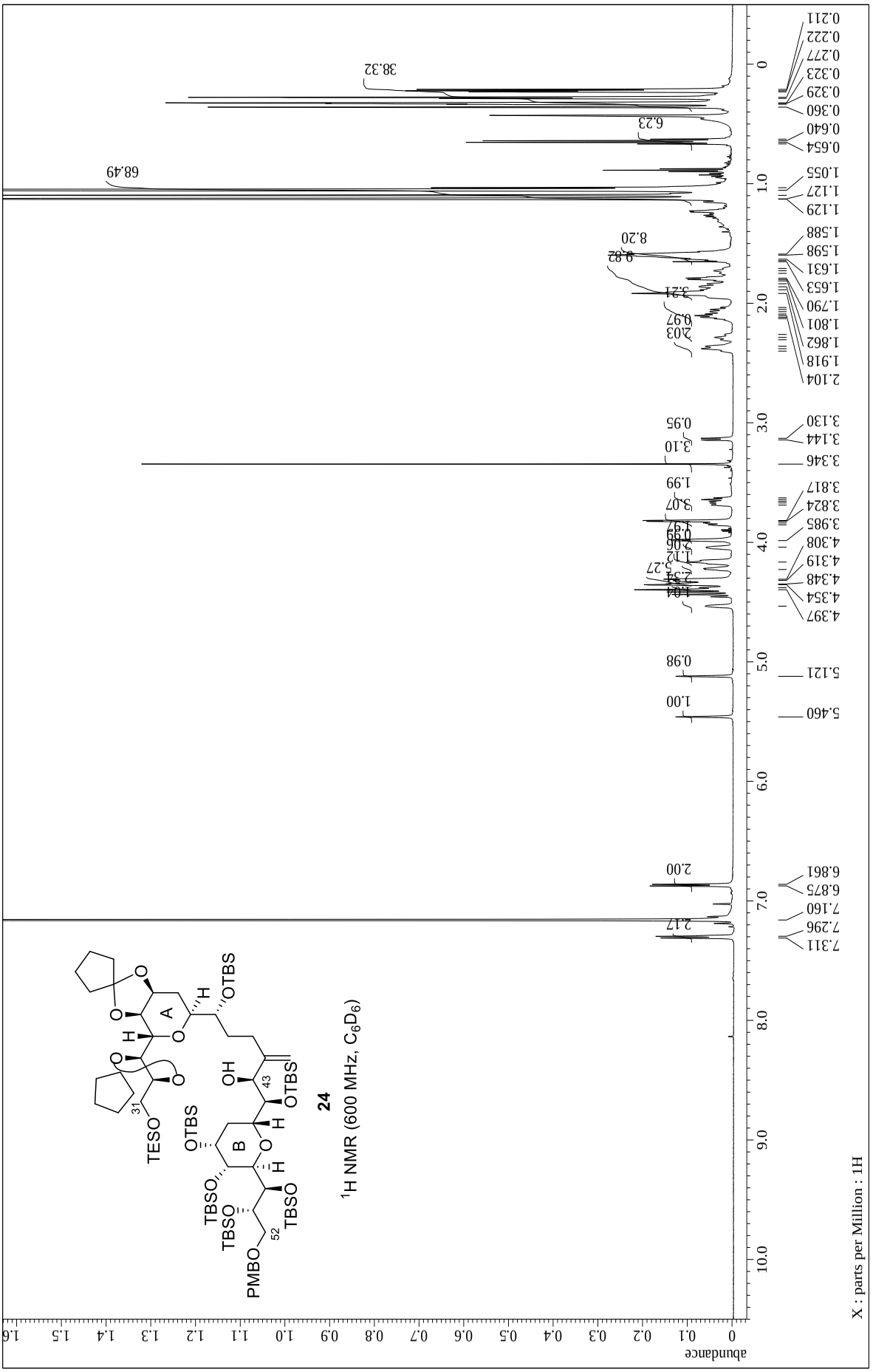
TESO
O
O
A
O
H
H
OTBS
I
O
O
5
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
20.30
10.18
9.49
6.42
6.50
3.22
2.18
1.97
1.05
1.00
1.12
1.11
1.05
1.03
0.91
7.260
6.009
5.668
5.666
4.263
4.257
4.254
4.248
4.238
4.072
3.779
3.570
3.559
3.547
2.500
2.482
2.474
2.463
2.455
1.686
1.683
1.674
1.661
1.650
0.960
0.946
0.895
0.622
0.609
0.084
0.081

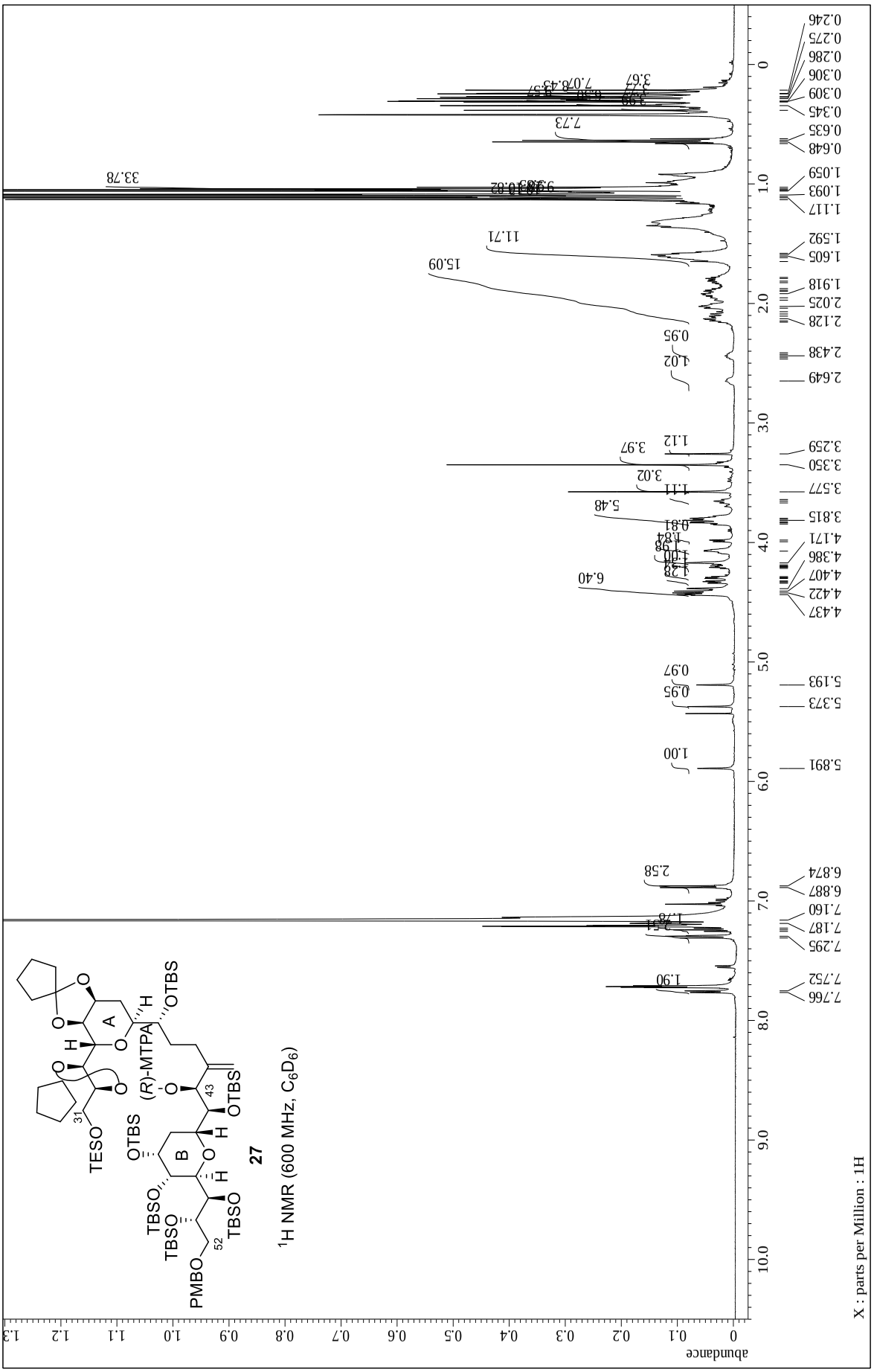
SETO
O
O
A
O
O
H
H
OTBS
I
5
13C NMR (150 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
125.273
119.873
118.226
112.491
80.607
77.802
77.371
77.160
76.949
73.282
72.641
72.459
71.932
71.214
63.803
40.450
37.683
37.530
37.434
37.272
33.681
28.874
26.117
23.809
23.771
23.484
23.417
18.294
6.939
4.516
-4.120
-4.206
X : parts per Million : 13C

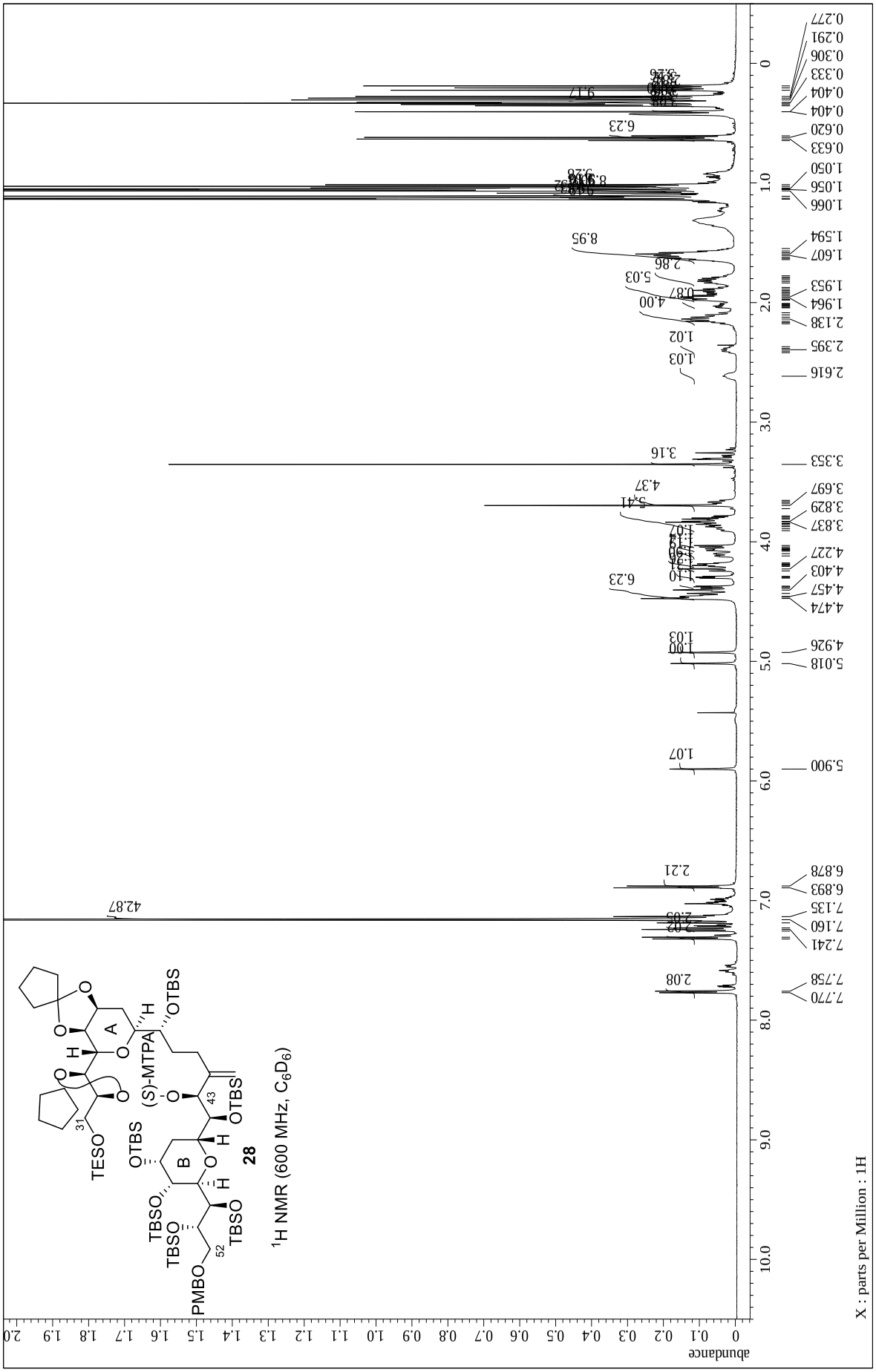
TESO
31
OTBS
TBSO
TBSO
PMBO
52
TBSO
B
H
O
H
OH
43
H
OTBS
O
H
O
O
O
A
O
H
OTBS
23
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H
7.301
7.288
7.160
6.891
6.877
5.395
5.084
4.605
4.594
4.438
4.397
4.302
4.232
3.825
3.817
3.372
2.707
2.689
2.500
2.481
1.931
1.919
1.798
1.594
1.586
1.047
1.033
0.657
0.644
0.326
0.315
0.262
0.246
0.230
0.222
2.28
2.05
1.00
1.03
1.06
1.09
15.81
9.52
70.08
6.89
41.46

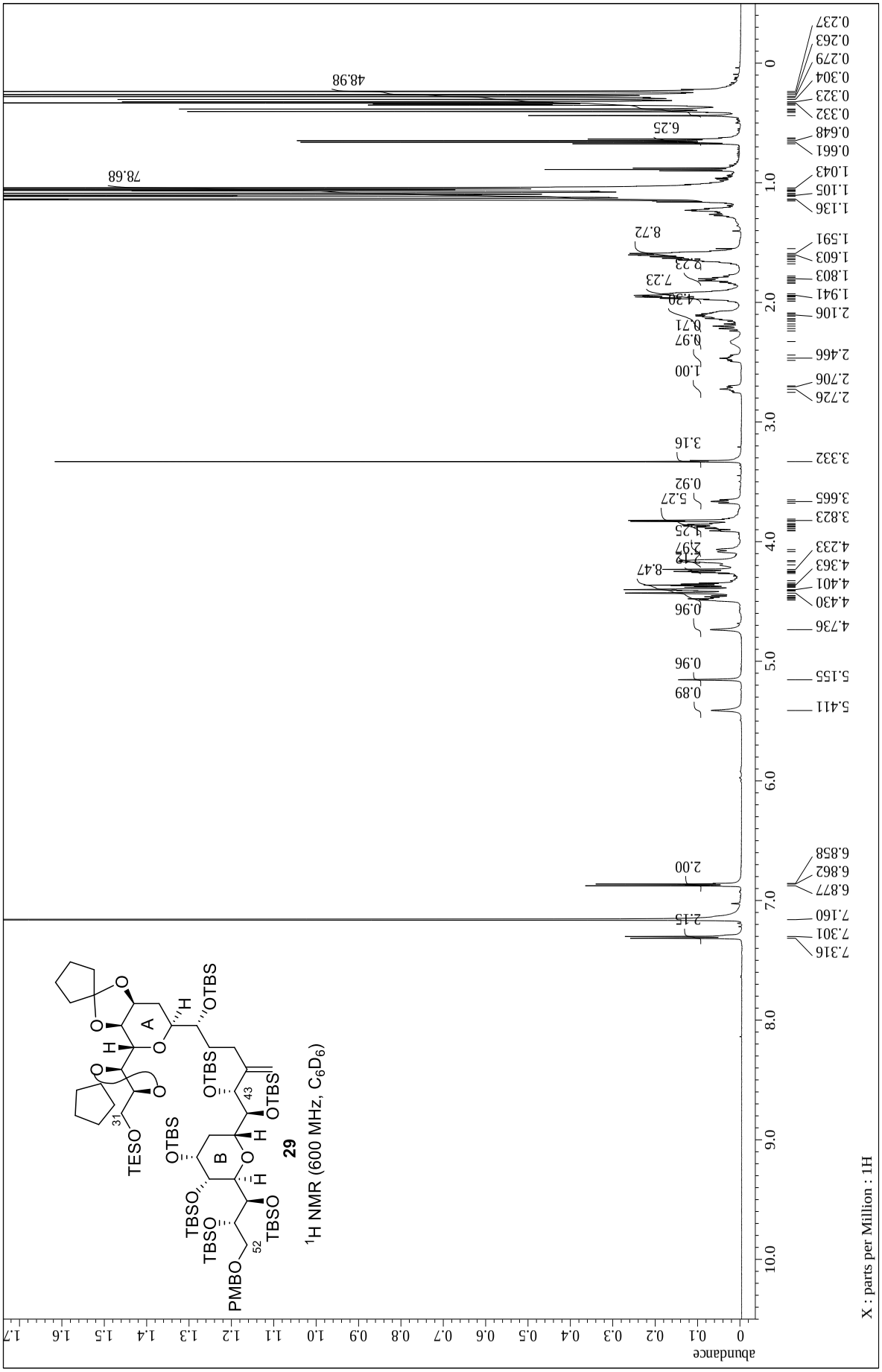
TESO
31
O
H
O
A
O
O
O
OTBS
TBSO
H
TBSO
B
OH
OTBS
PMBO
O
H
H
43
52
TBSO
OTBS
23
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C


HMQC (600 MHz, C6D6)
23
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OH
OTBS
Y : parts per Million : 13C
X : parts per Million : 1H
abundance
(thousandths)

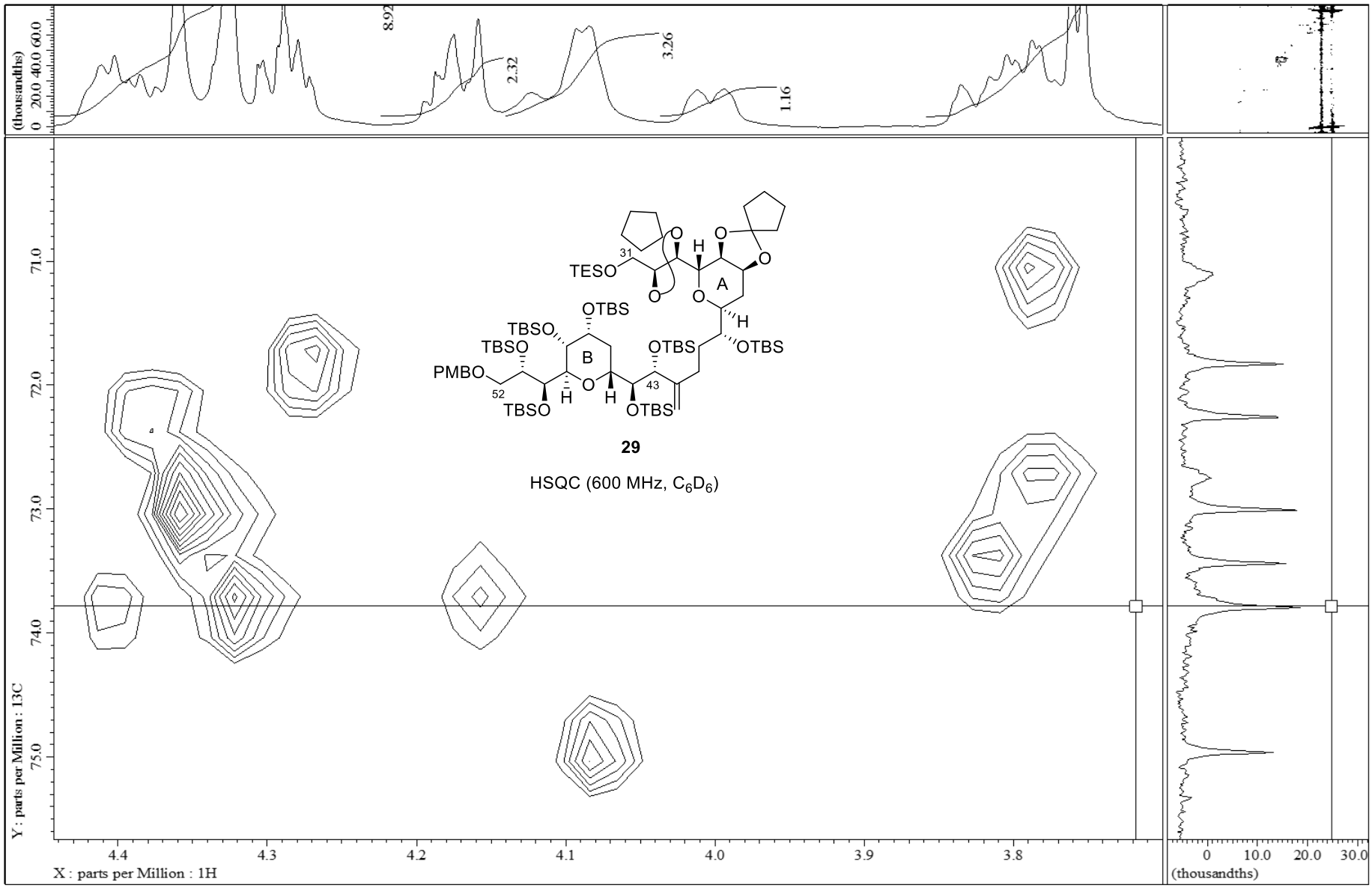

24
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OH
OTBS
OTBS
A
B
31
43
52

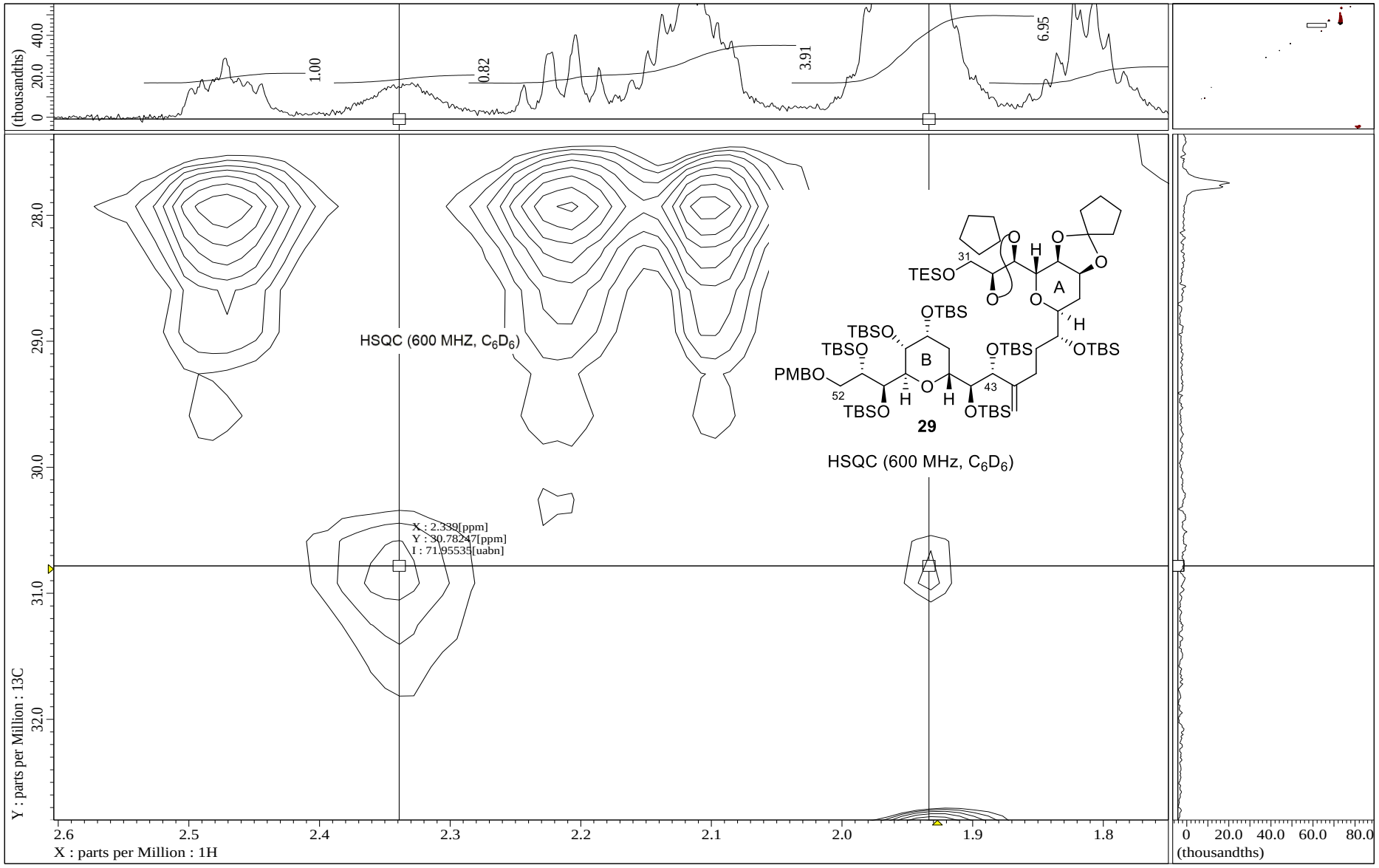

27
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance

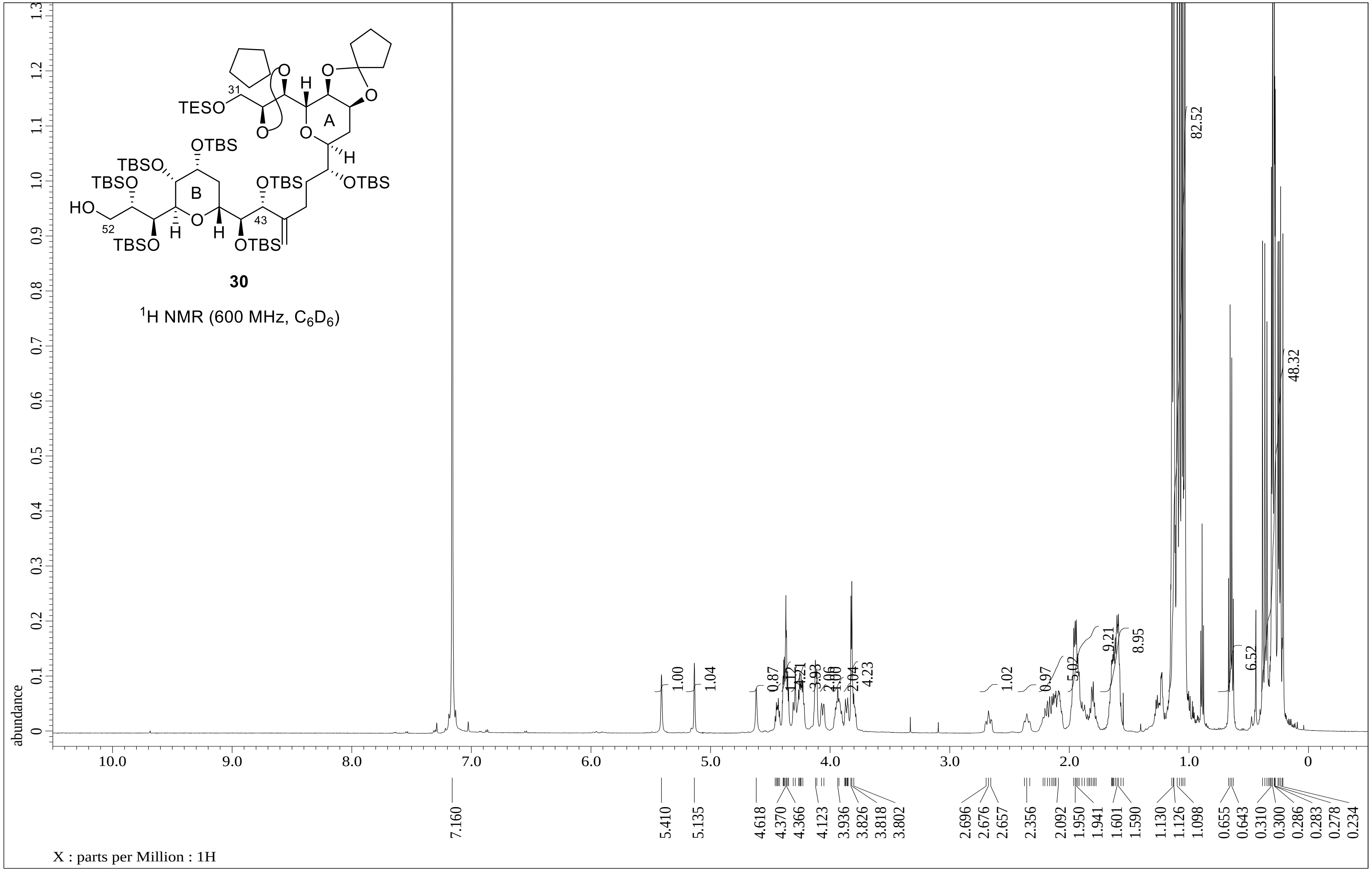

28
(S)-MTPA
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
A
B
31
43
52
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance


29
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance

TESO
31
OTBS
TBSO
TBSO
PMBO
52
TBSO
B
A
OTBS
OTBS
43
OTBS
29
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C

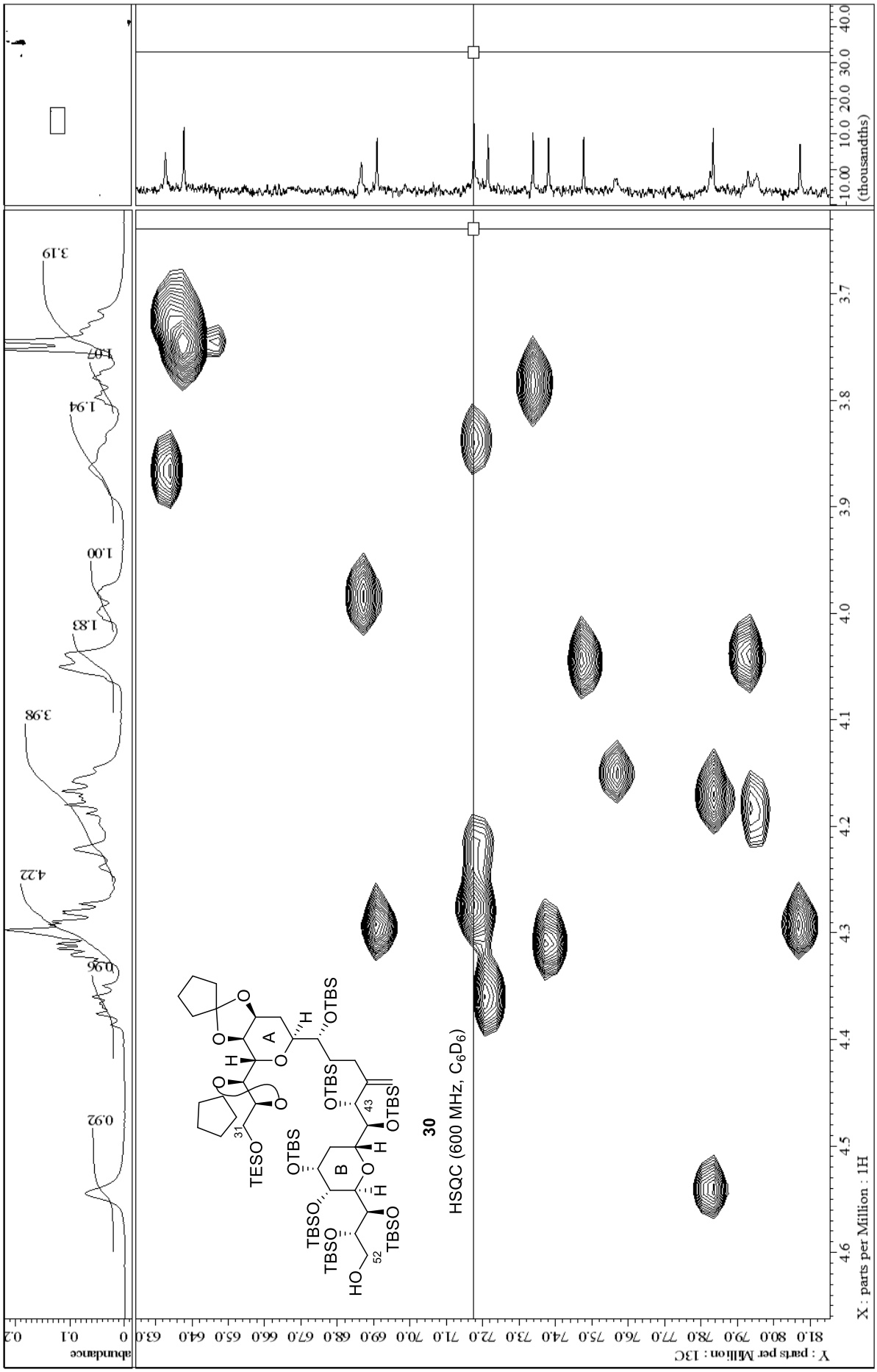

(thousandths)
0 20.0 40.0 60.0
8.92
2.32
3.26
1.16
TESO
31
O
H
O
O
A
O
O
H
OTBS
TBSO
TBSO
B
OTBS
OTBS
PMBO
52
O
H
H
43
TBSO
OTBS
29
HSQC (600 MHz, C6D6)
Y : parts per Million : 13C
71.0
72.0
73.0
74.0
75.0
4.4
4.3
4.2
4.1
4.0
3.9
3.8
X : parts per Million : 1H
0 10.0 20.0 30.0
(thousandths)

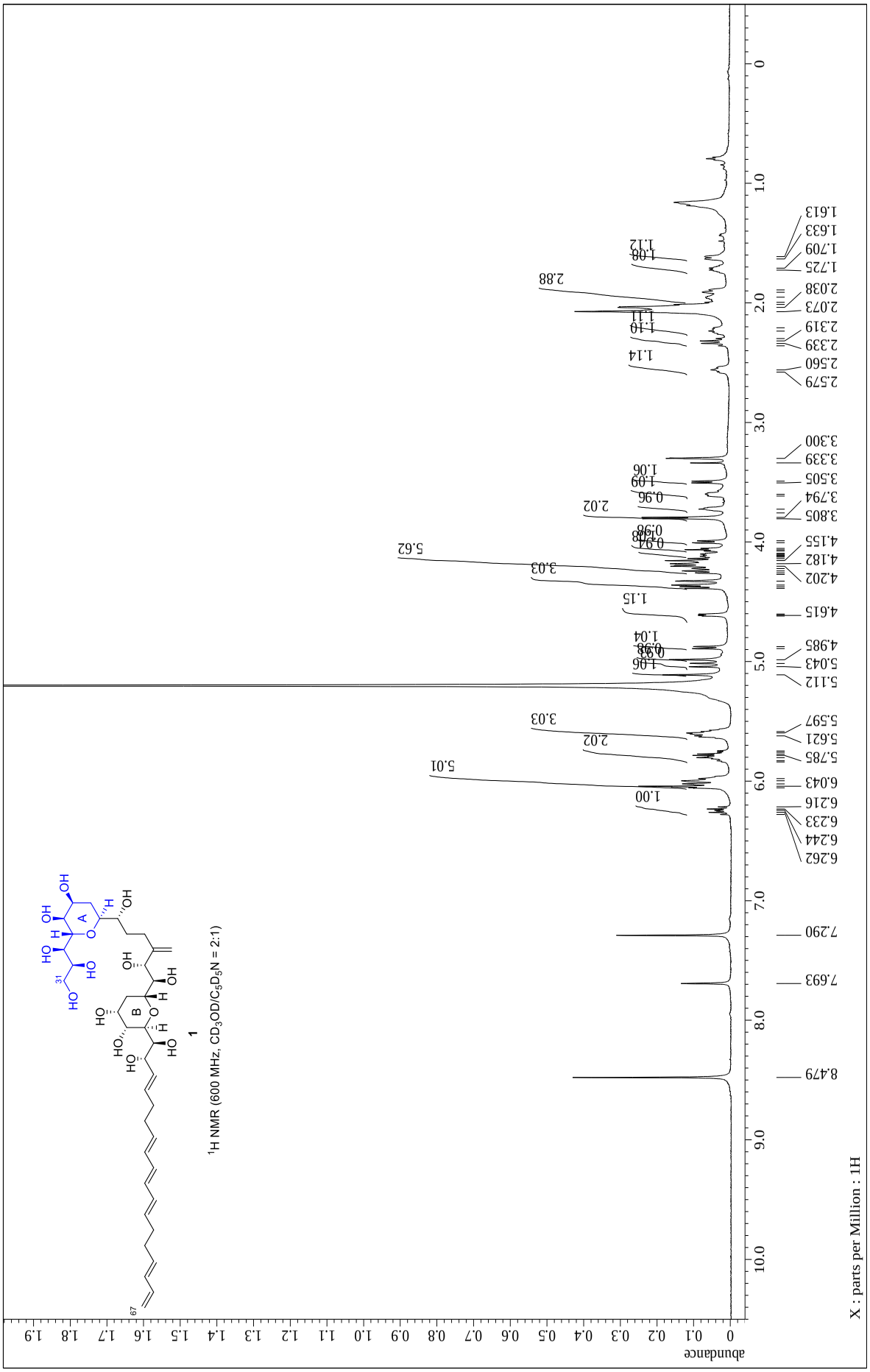

(thousandths)
1.00
0.82
3.91
6.95
HSQC (600 MHZ, C6D6)
TESO
PMBO
TBSO
OTBS
29
HSQC (600 MHz, C6D6)
X : 2.339[ppm]
Y : 30.78247[ppm]
I : 71.95535[uabn]
Y : parts per Million : 13C
X : parts per Million : 1H
(thousandths)



TESO
31
O
O
H
O
O
A
O
H
OTBS
TBSO
TBSO
B
OTBS
OTBS
HO
52
TBSO
H
O
H
43
OTBS
30
^{1}H NMR (600 MHz, C_6D_6)
abundance
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
X : parts per Million : 1H
1.00
1.04
0.87
1.12
1.21
3.93
2.06
1.00
2.04
4.23
1.02
0.97
5.02
9.21
8.95
82.52
6.52
48.32
7.160
5.410
5.135
4.618
4.370
4.366
4.123
3.936
3.826
3.818
3.802
2.696
2.676
2.657
2.356
2.092
1.950
1.941
1.601
1.590
1.130
1.126
1.098
0.655
0.643
0.310
0.300
0.286
0.283
0.278
0.234

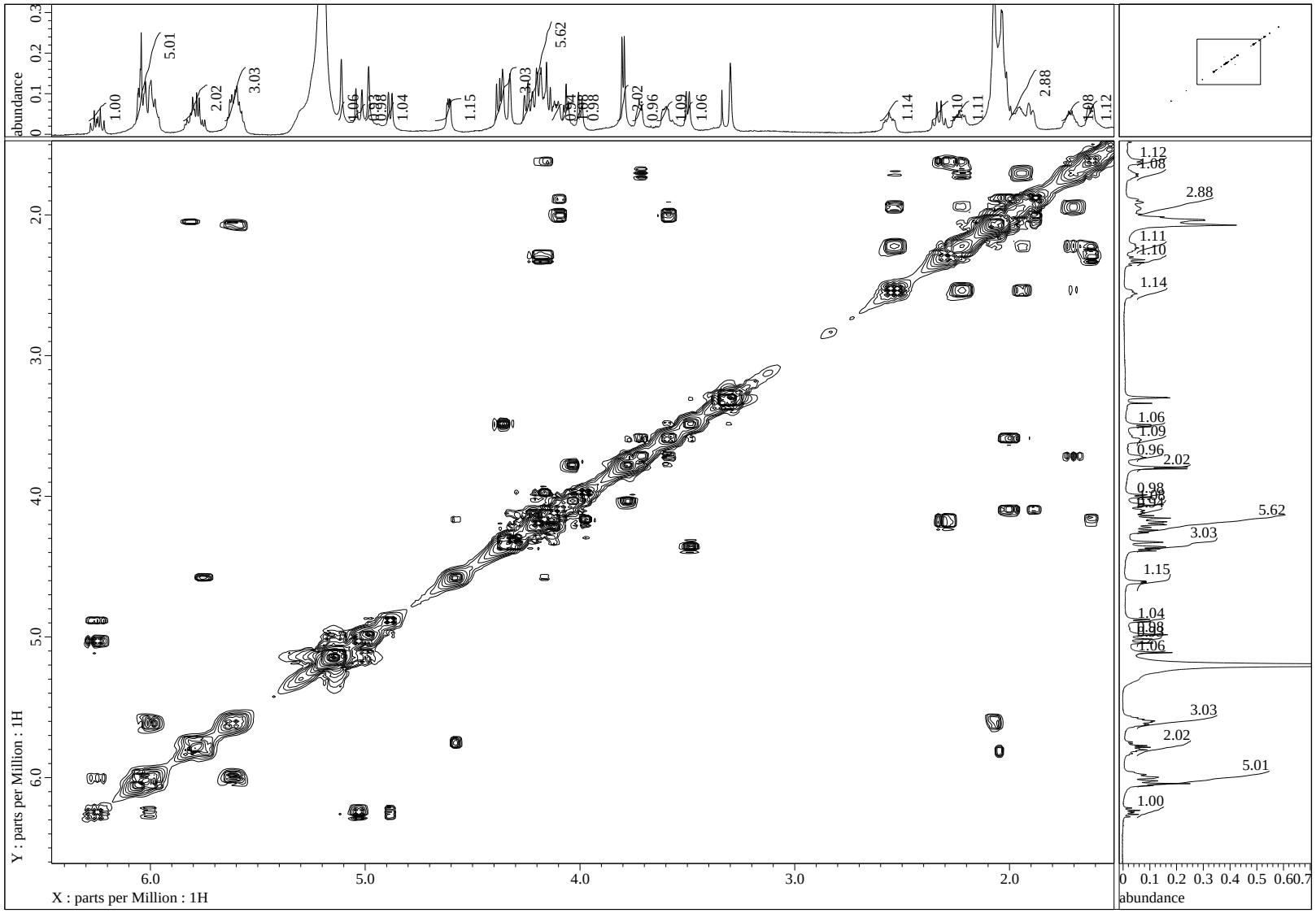
TESO
31
OTBS
TBSO
TBSO
HO
52
TBSO
B
A
OTBS
OTBS
OTBS
43
H
O
H
H
O
O
O
O
O
H
H
30
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
150.781
128.223
128.060
127.897
119.931
118.399
112.185
81.038
79.813
79.564
78.645
75.945
75.064
74.125
73.694
72.440
72.048
69.395
68.965
64.072
63.583
38.019
37.885
37.655
37.588
32.877
30.225
28.176
27.975
26.797
26.606
26.577
26.500
26.453
26.405
26.366
24.021
23.915
23.733
23.638
19.128
18.879
18.726
18.668
18.640
18.505
18.477
7.159
4.852
-2.664
-3.469
-3.507
-3.555
-3.679
-3.765
-3.852
-3.899
-3.986
-4.187
-4.359
-4.838


HSQC (600 MHz, C_6D_6)
30
TESO
OTBS
TBSO
TBSO
HO
TBSO
OTBS
OTBS
OTBS
OTBS
A
B
31
43
52
X : parts per Million : 1H
Y : parts per Million : 13C
abundance
(thousandths)

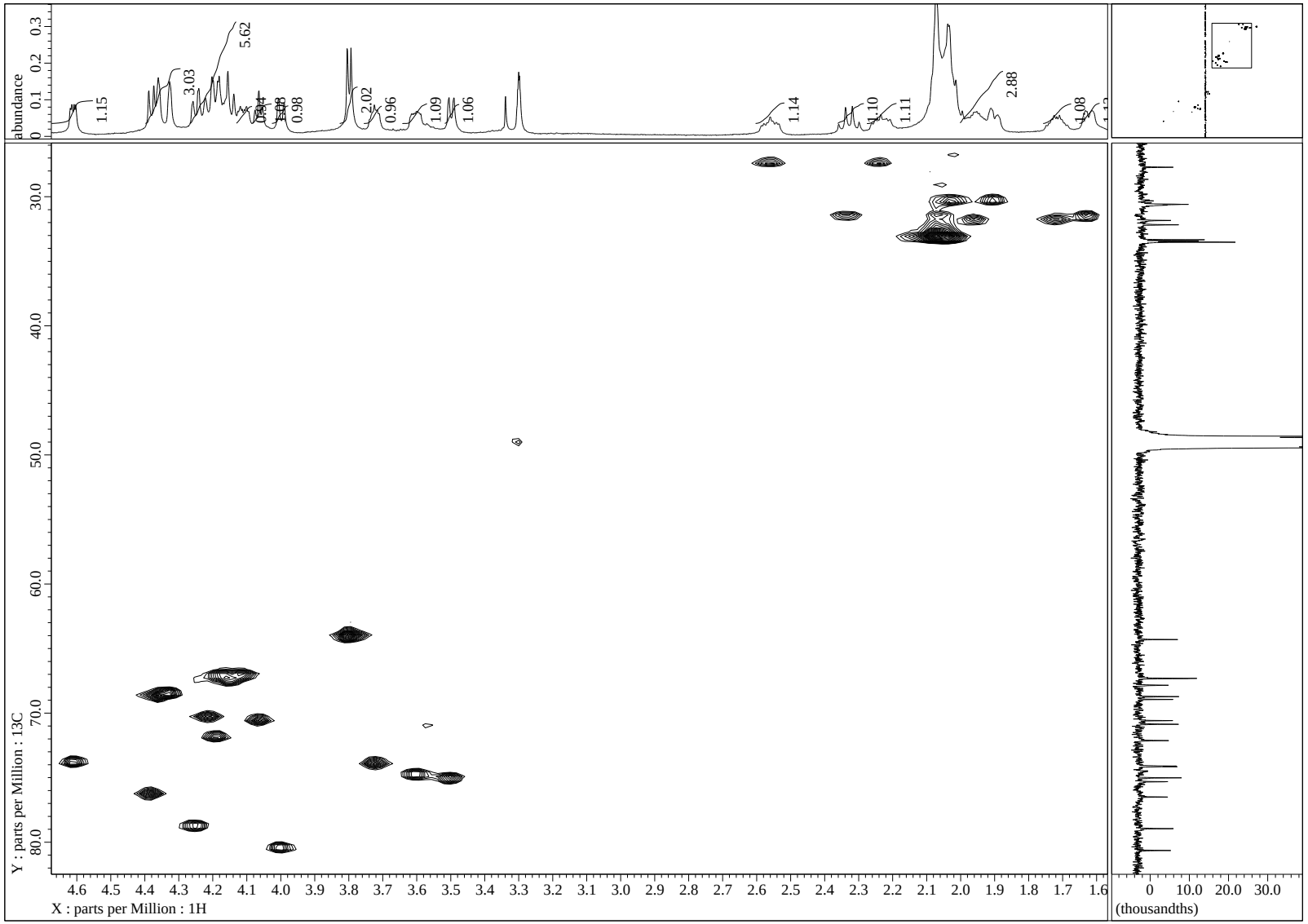

1
^{1}H NMR (600 MHz, CD_3OD/C_5D_5N = 2:1)
X : parts per Million : 1H
abundance

1
^{13}C NMR (150 MHz, CD$_3$OD/C$_5$D$_5$N = 2:1)
(thousandths)
X : parts per Million : 13C
151.871
150.071
149.928
149.746
149.564
149.143
137.595
137.433
137.270
137.078
132.368
132.281
124.756
124.583
115.506
112.873
80.645
78.950
76.508
75.311
75.015
74.153
72.133
70.869
70.582
68.944
68.724
67.843
67.307
64.300
49.287
49.144
49.000
48.866
48.722
33.518
33.431
33.336
32.168
31.842
30.655
30.588
27.715

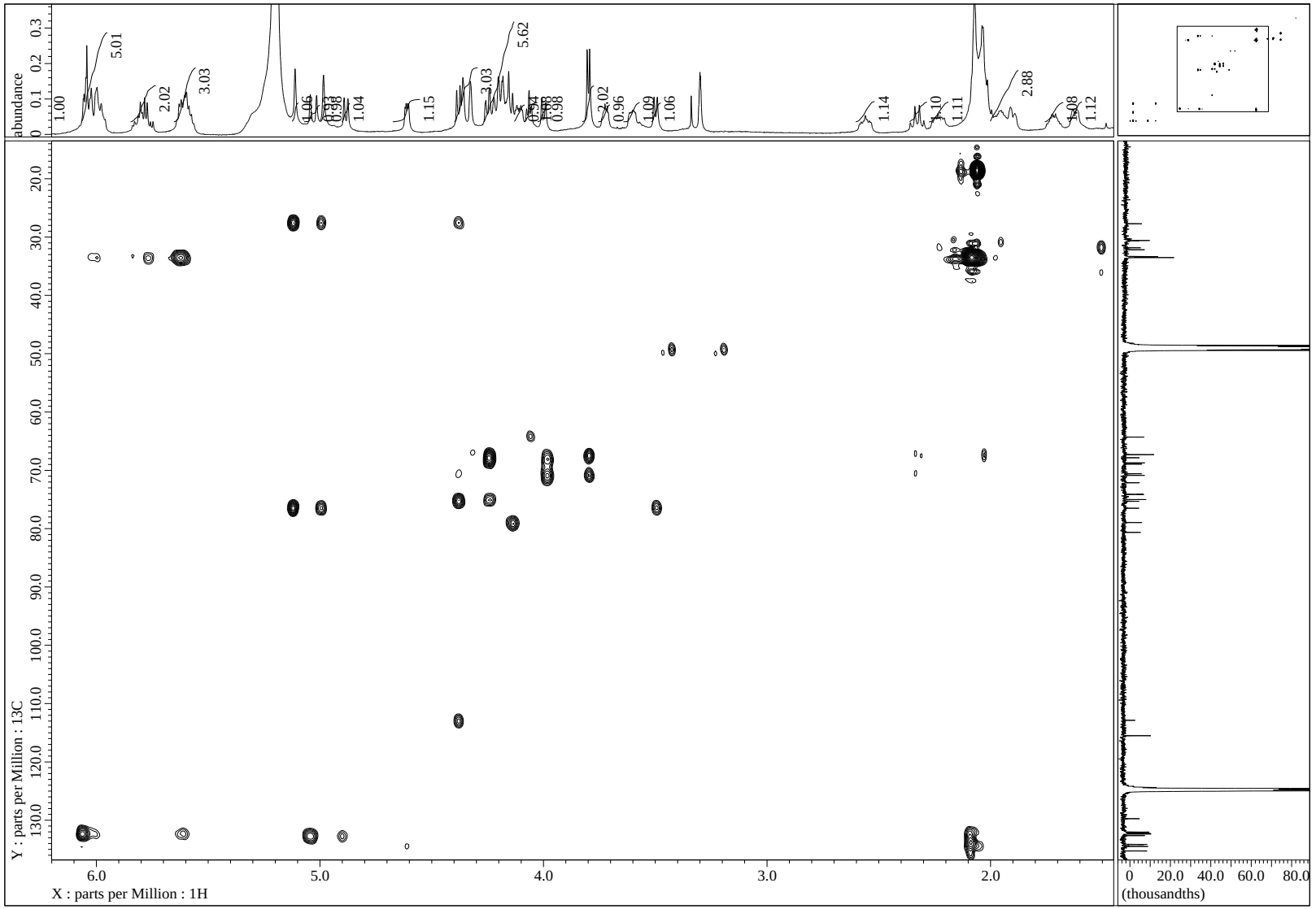
COSY spectrum of compound **1** (600 MHz, CD_3OD/C_5D_5N = 2:1)



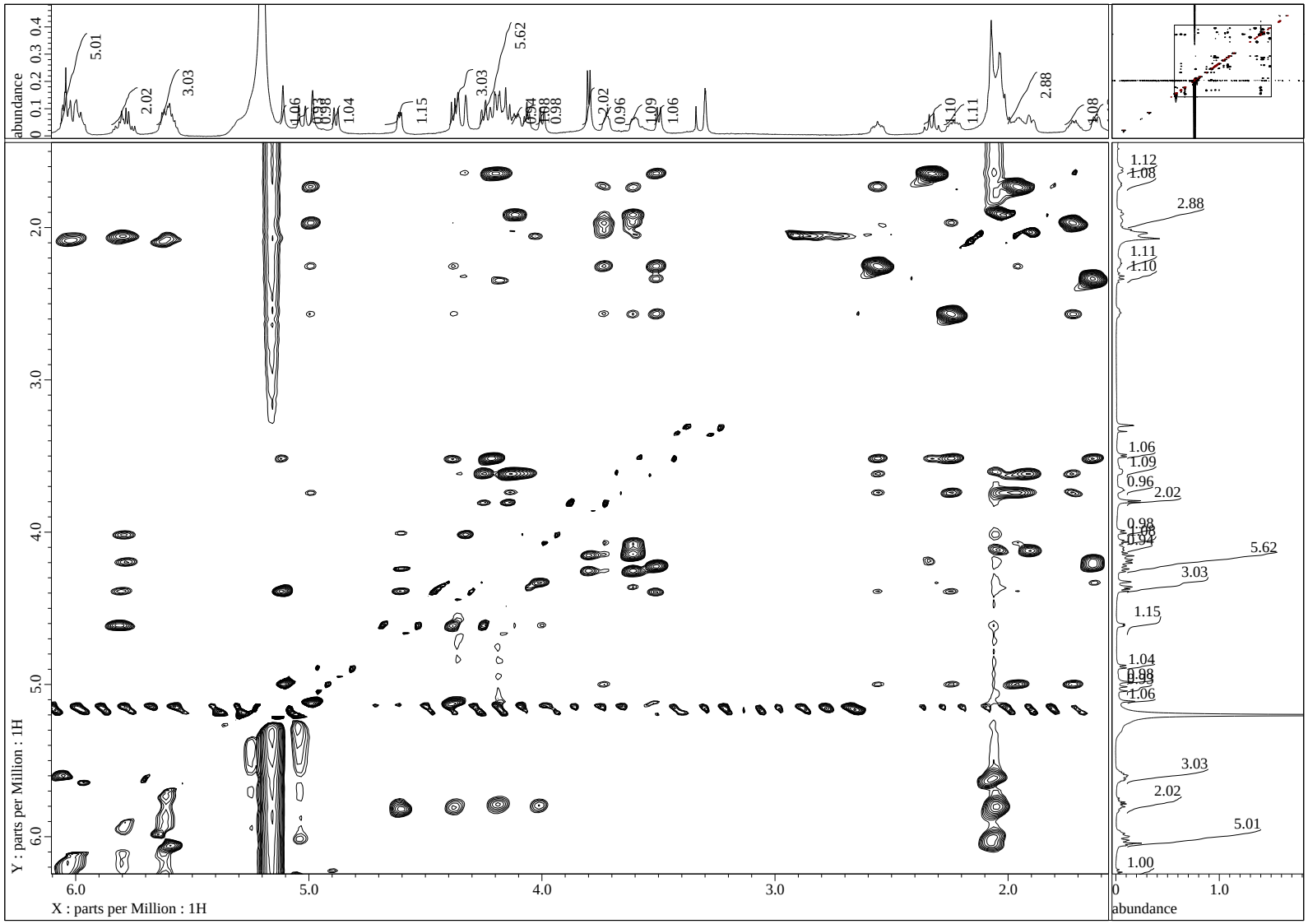
HSQC spectrum of compound **1** (600 MHz, CD_3OD/C_5D_5N = 2:1)

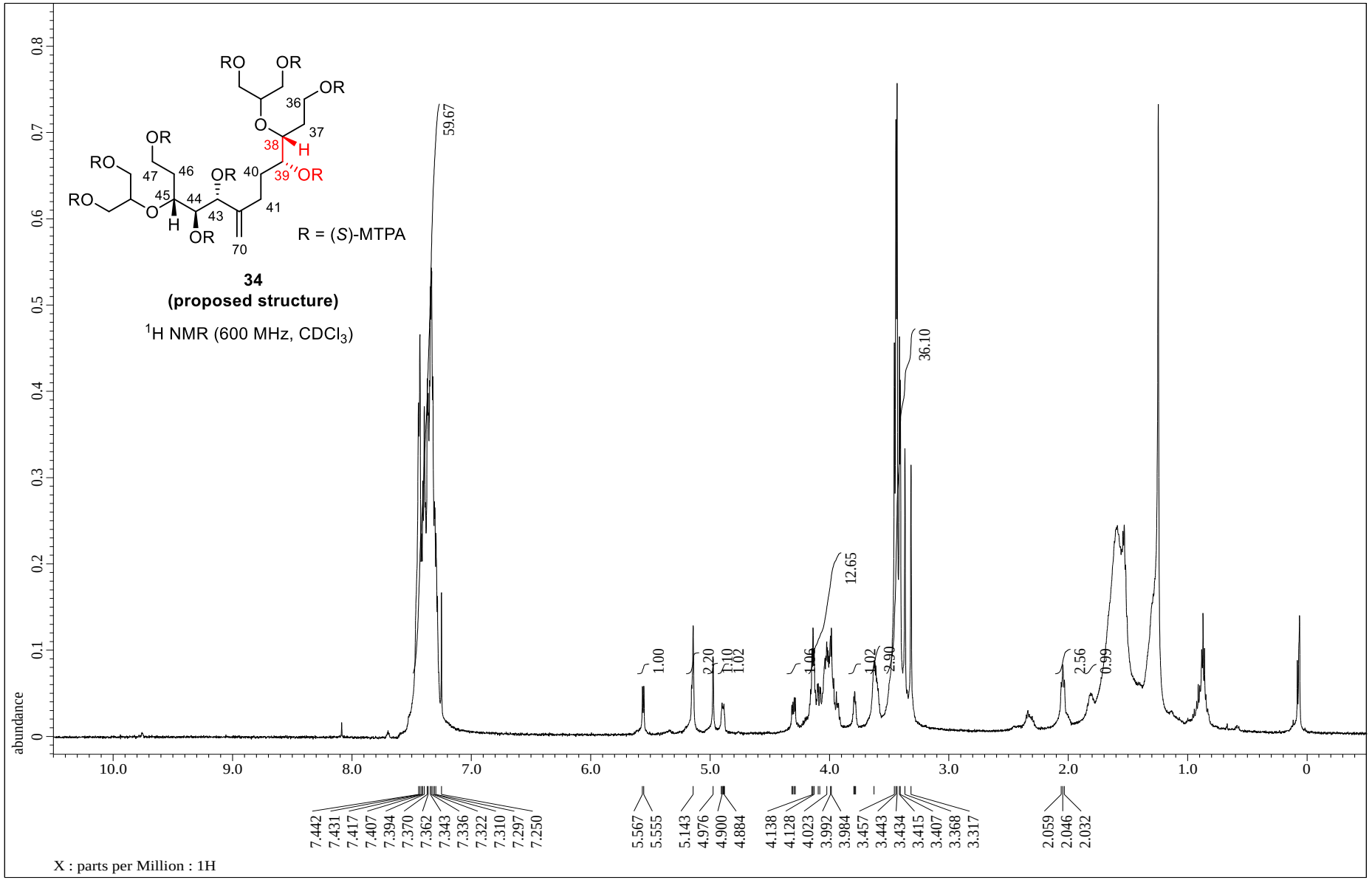


HMBC spectrum of compound **1** (600 MHz, CD_3OD/C_5D_5N = 2:1)

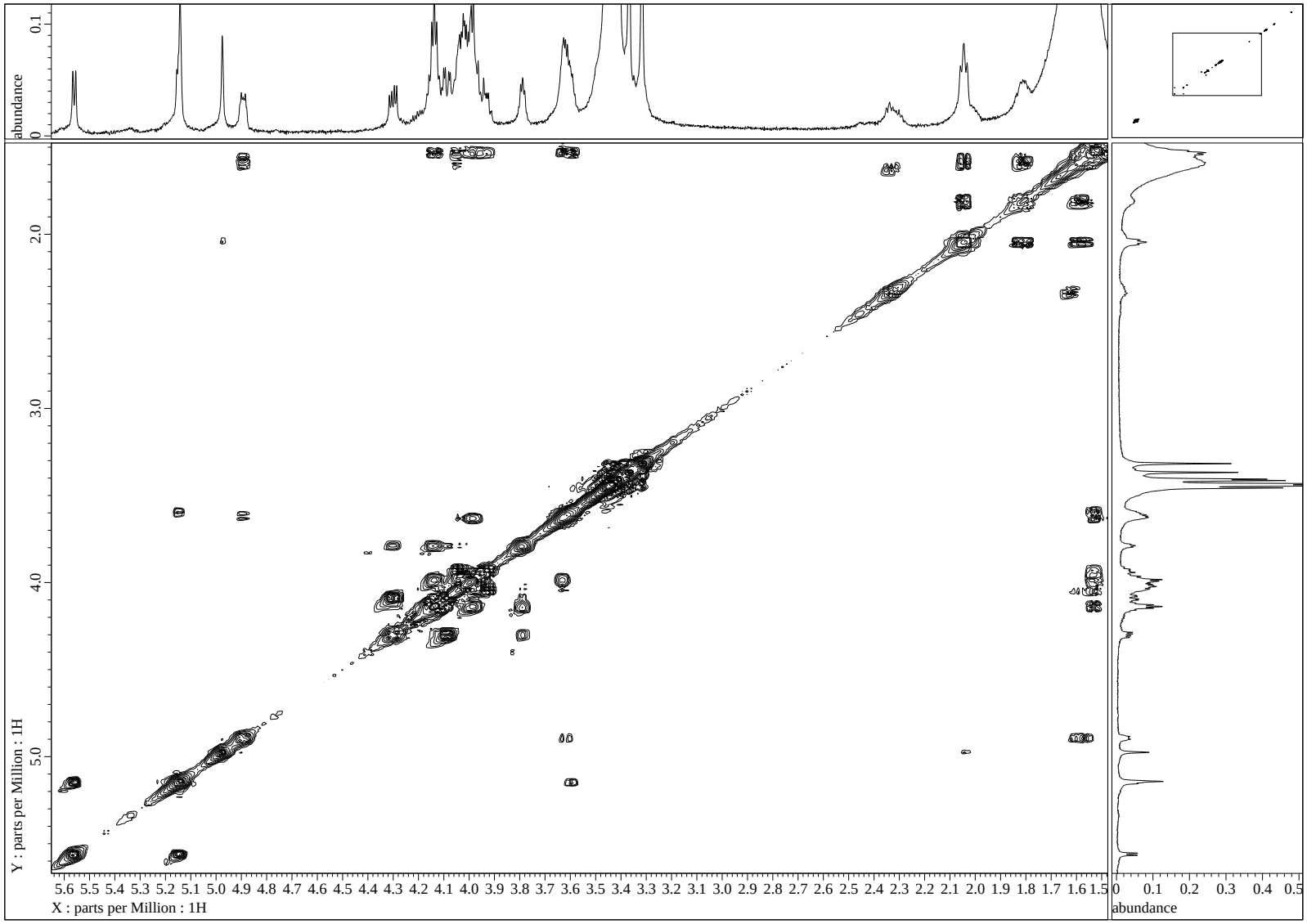


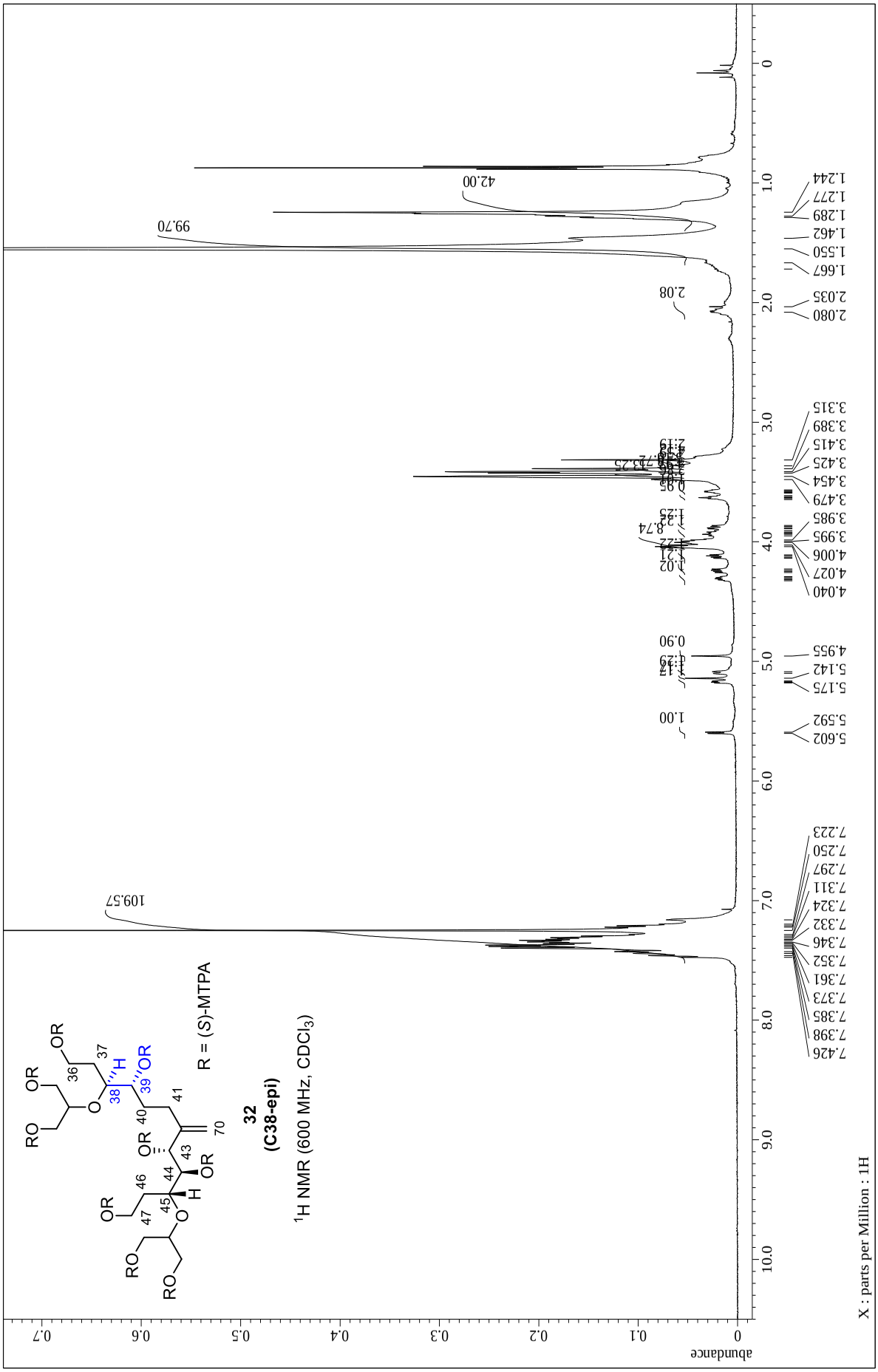
ROESY spectrum of compound **1** (600 MHz, CD_3OD/C_5D_5N = 2:1)



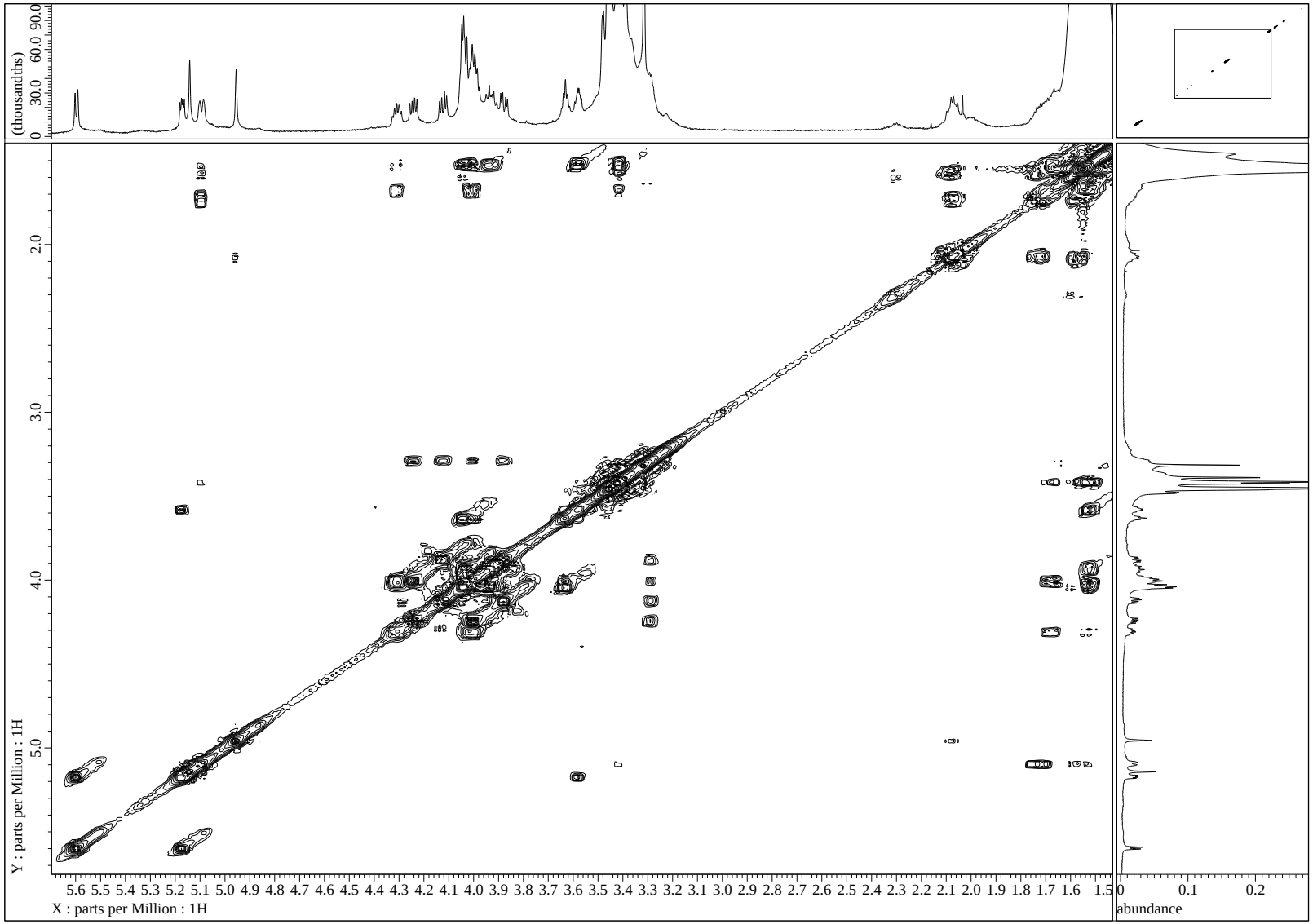

RO
OR
OR
36
37
O
38
H
OR
RO
47
46
OR
40
39
OR
RO
45
44
43
41
O
H
OR
70
R = (S)-MTPA
34
(proposed structure)
1H NMR (600 MHz, CDCl3)
abundance
59.67
36.10
12.65
1.00
2.20
1.10
1.02
1.06
1.02
2.90
2.56
0.99
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.442
7.431
7.417
7.407
7.394
7.370
7.362
7.343
7.336
7.322
7.310
7.297
7.250
5.567
5.555
5.143
4.976
4.900
4.884
4.138
4.128
4.023
3.992
3.984
3.457
3.443
3.434
3.415
3.407
3.368
3.317
2.059
2.046
2.032
X : parts per Million : 1H

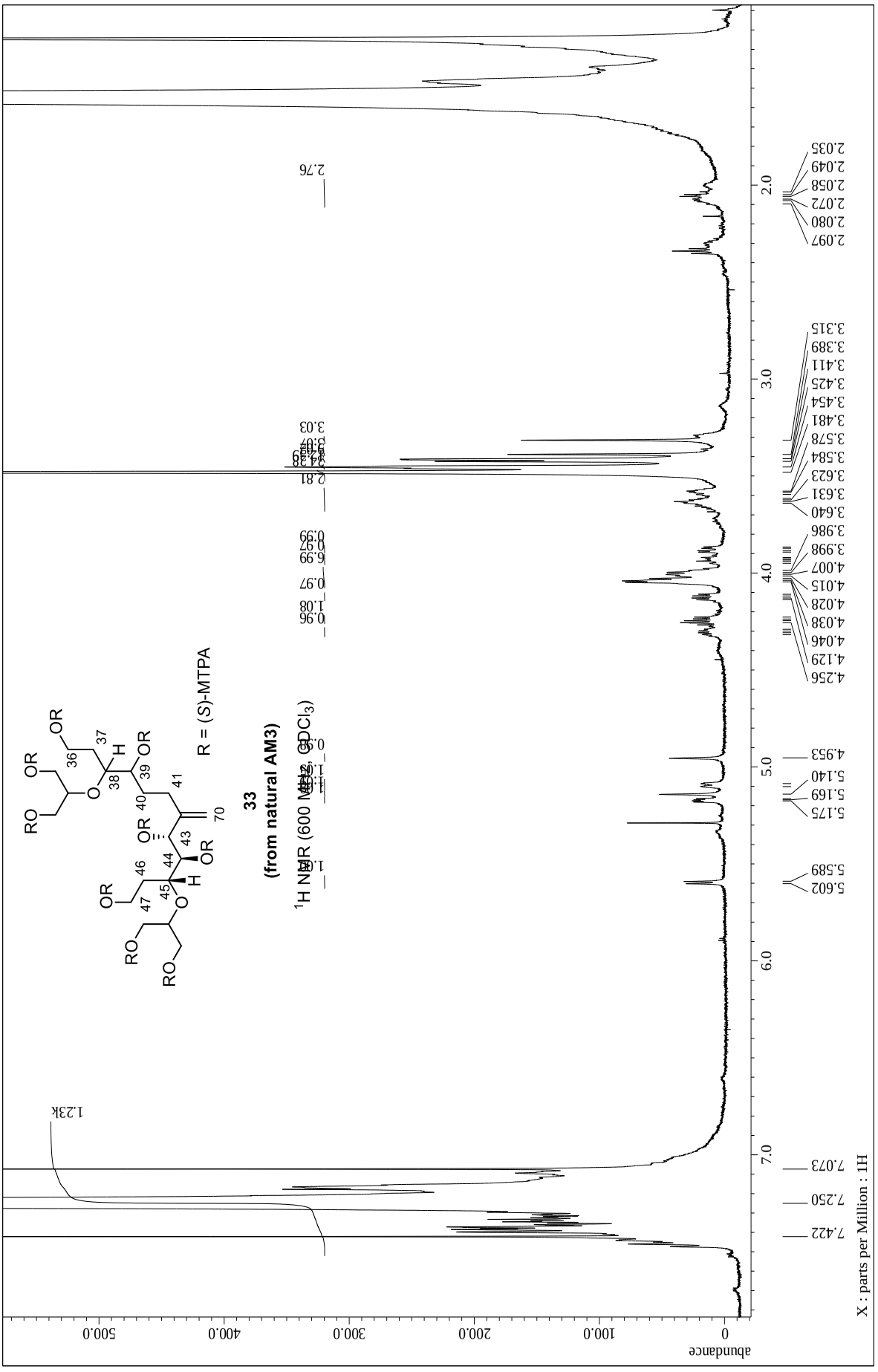
COSY spectrum of compound **34** (600 MHz, $CDCl_3$)



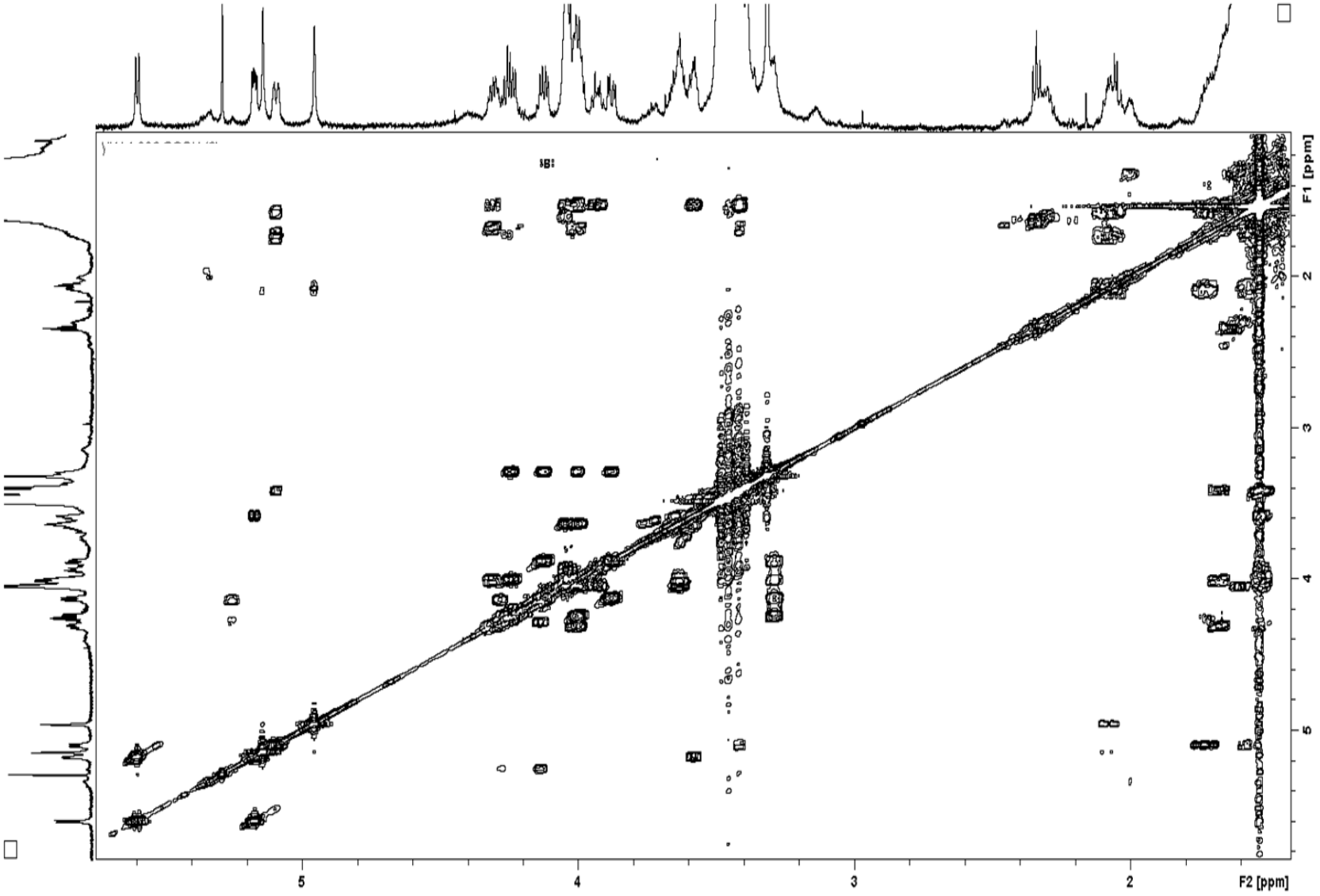

32
(C38-epi)
R = (S)-MTPA
1H NMR (600 MHz, CDCl3)
X : parts per Million : 1H
abundance

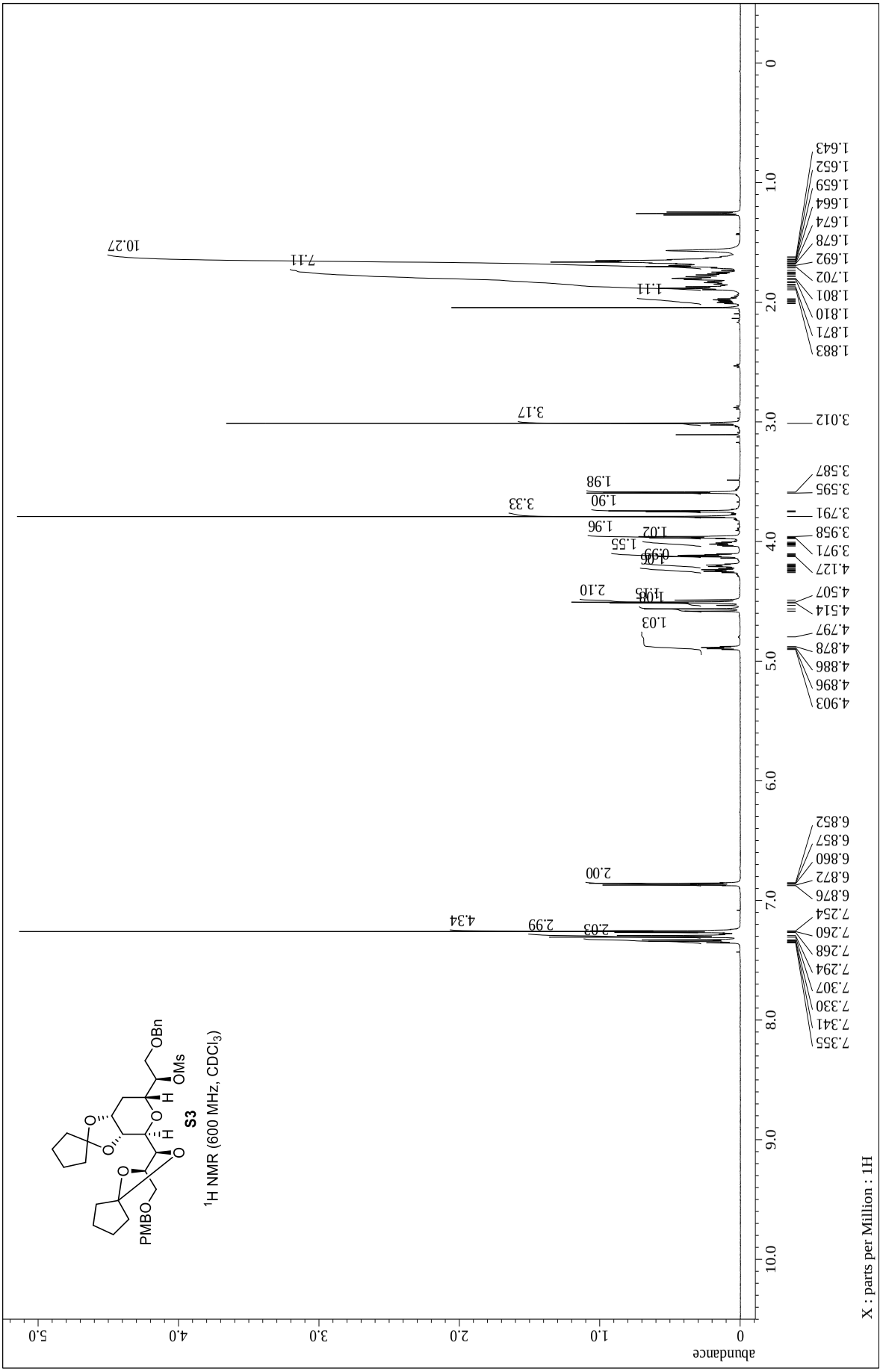
COSY Spectrum of Compound **32** (600 MHz, $CDCl_3$)

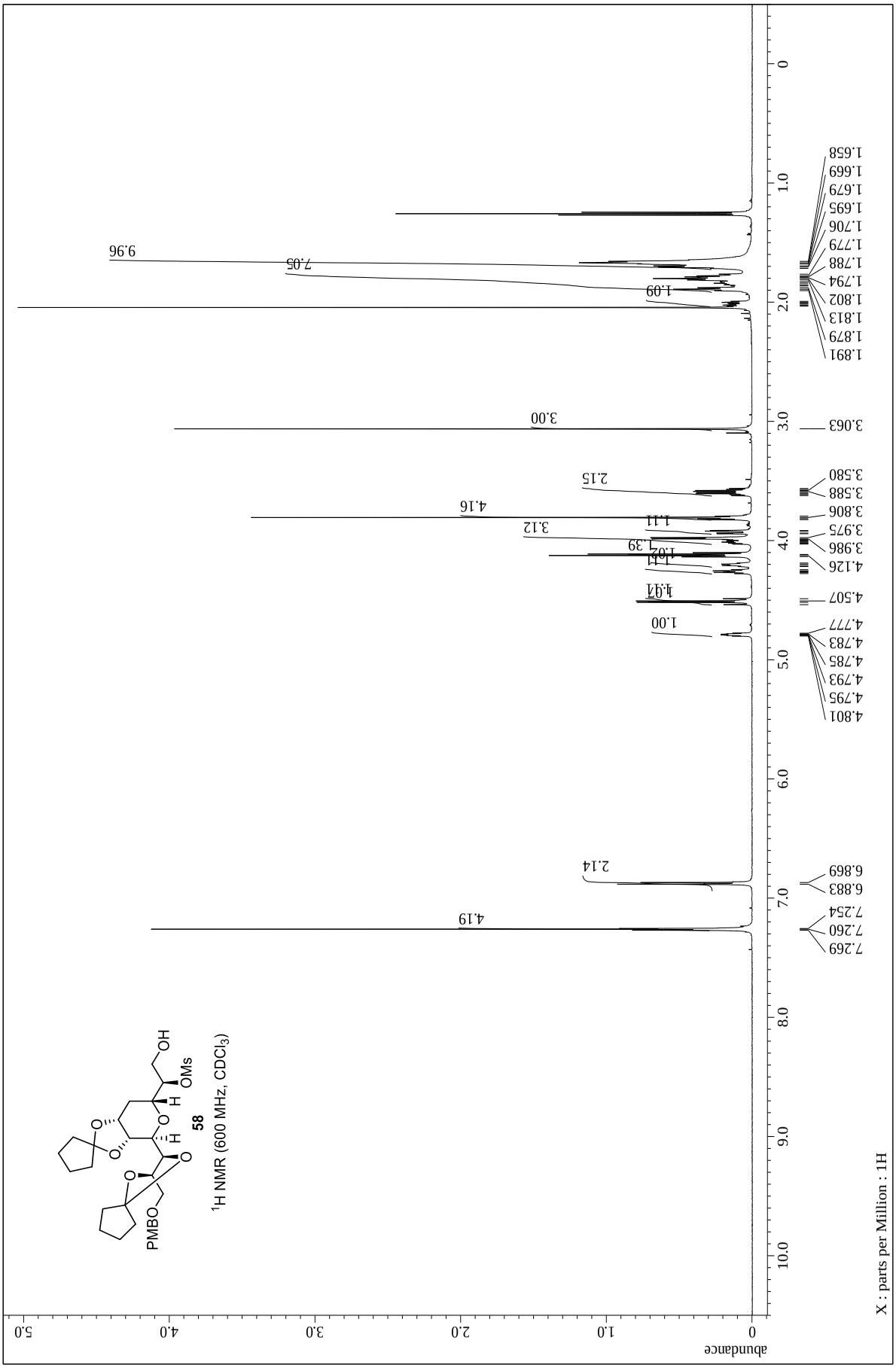


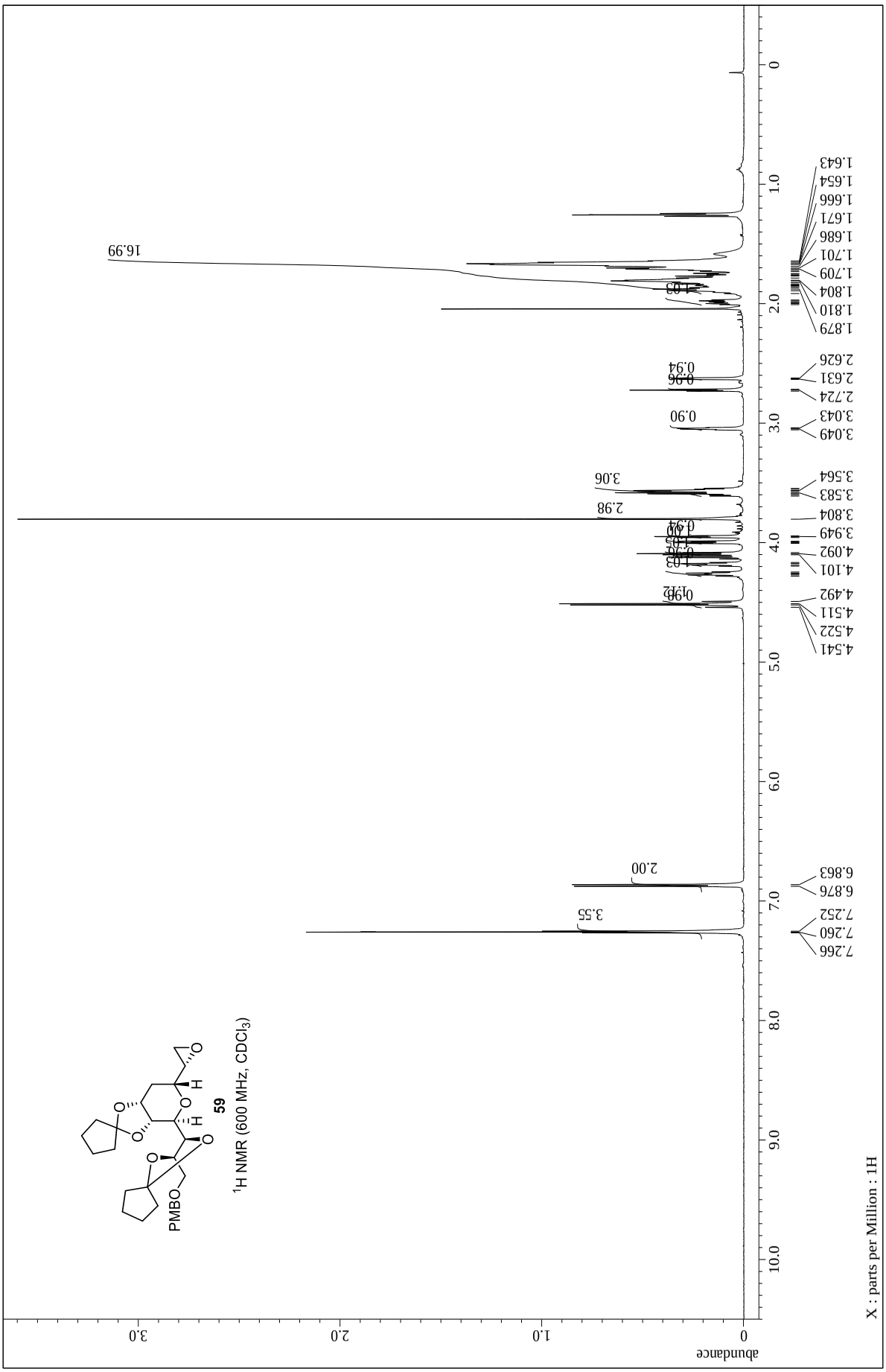

33
(from natural AM3)
^{1}H NMR (600 MHz, CDCl$_3$)
R = (S)-MTPA
X : parts per Million : 1H
abundance

COSY spectrum of compound **33** (600 MHz cryoprobe, $CDCl_3$)




S3
^{1}H NMR (600 MHz, CDCl$_3$)
PMBO
OMs
OBn
abundance
X : parts per Million : 1H


PMBO
OMs
OH
58
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
4.19
2.14
1.00
1.71
1.02
1.39
3.12
1.11
4.16
2.15
3.00
1.09
7.05
9.96
7.269
7.260
7.254
6.883
6.869
4.801
4.795
4.793
4.785
4.783
4.777
4.507
4.126
3.986
3.975
3.806
3.588
3.580
3.063
1.891
1.879
1.813
1.802
1.794
1.788
1.779
1.706
1.695
1.679
1.669
1.658


PMBO
59
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
16.99
3.55
2.98
3.06
2.00
0.90
0.94
0.96
1.03
1.05
0.98
1.12
7.266
7.260
7.252
6.876
6.863
4.541
4.522
4.511
4.492
4.101
4.092
3.949
3.804
3.583
3.564
3.049
3.043
2.724
2.631
2.626
1.879
1.810
1.804
1.709
1.701
1.686
1.671
1.666
1.654
1.643

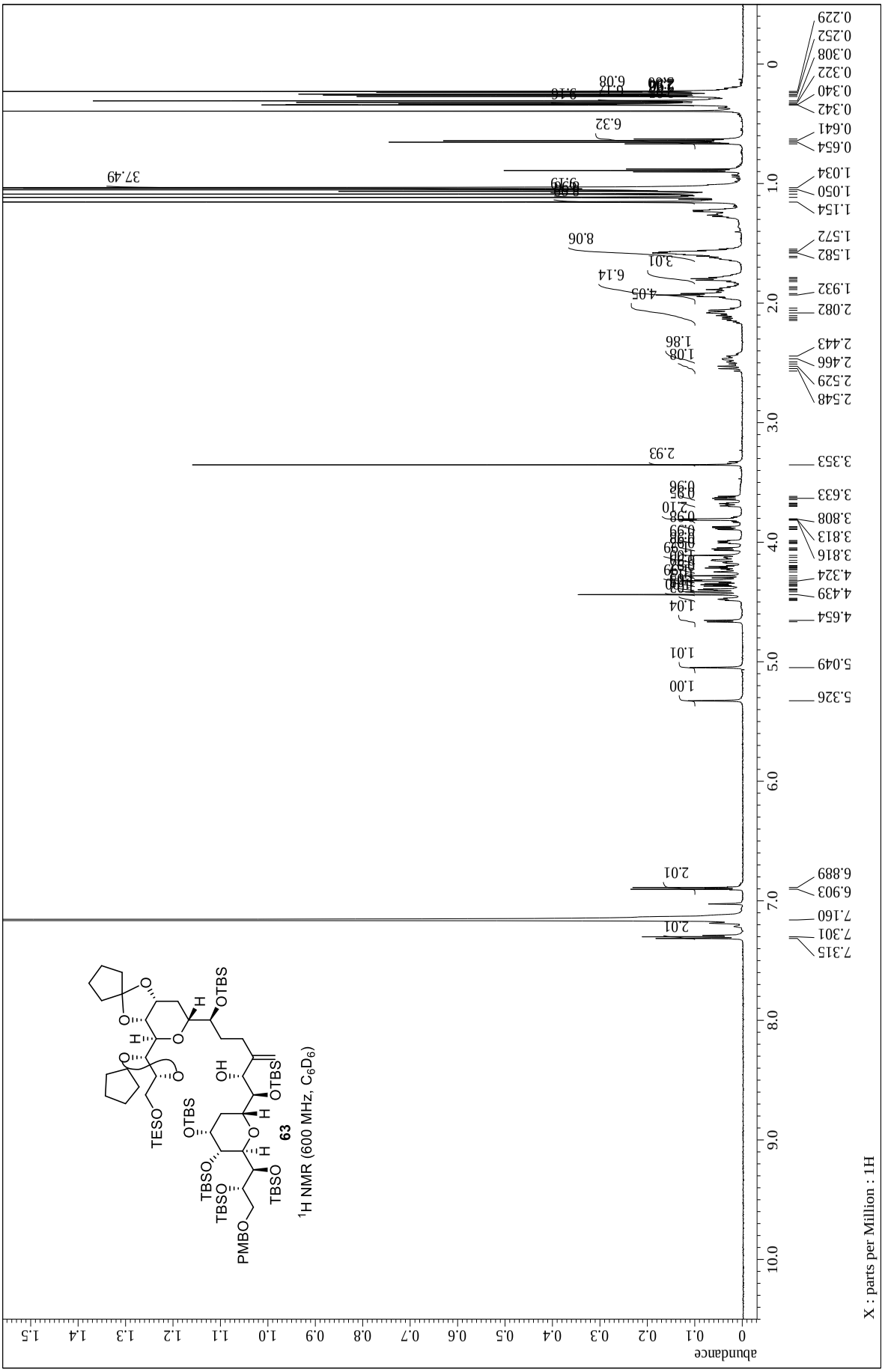
PMBO
O
O
O
H
O
H
OH
60
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.269
7.260
7.248
6.887
6.882
6.871
6.865
4.556
4.526
4.509
4.479
3.991
3.985
3.972
3.807
3.595
3.583
3.568
3.556
2.359
2.351
2.344
2.327
2.313
1.931
1.891
1.881
1.872
1.801
1.782
1.714
1.694
1.675
1.660
3.86
2.00
0.96
1.01
0.95
0.96
2.00
1.04
3.02
3.00
1.99
20.16

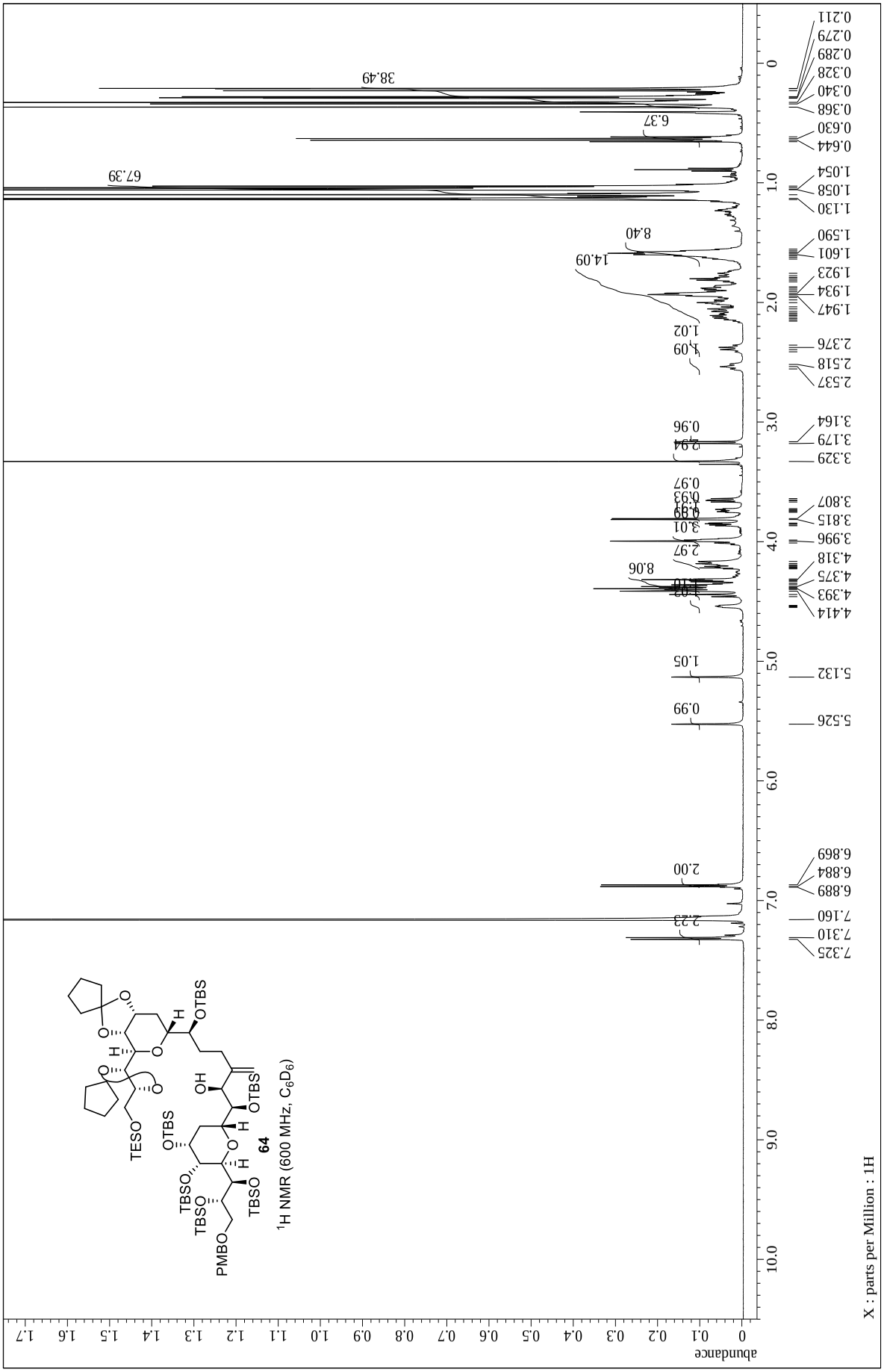
PMBO
O
O
O
O
H
O
H
OTBS
S4
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
5.03
2.00
3.07
2.14
1.06
1.96
21.37
9.35
5.85
7.271
7.260
7.258
6.881
6.871
6.867
4.556
4.537
4.507
4.486
4.035
3.975
3.904
3.805
3.577
3.569
3.561
3.505
3.489
2.255
2.244
2.230
1.696
1.680
1.669
1.663
1.656
0.880
0.079

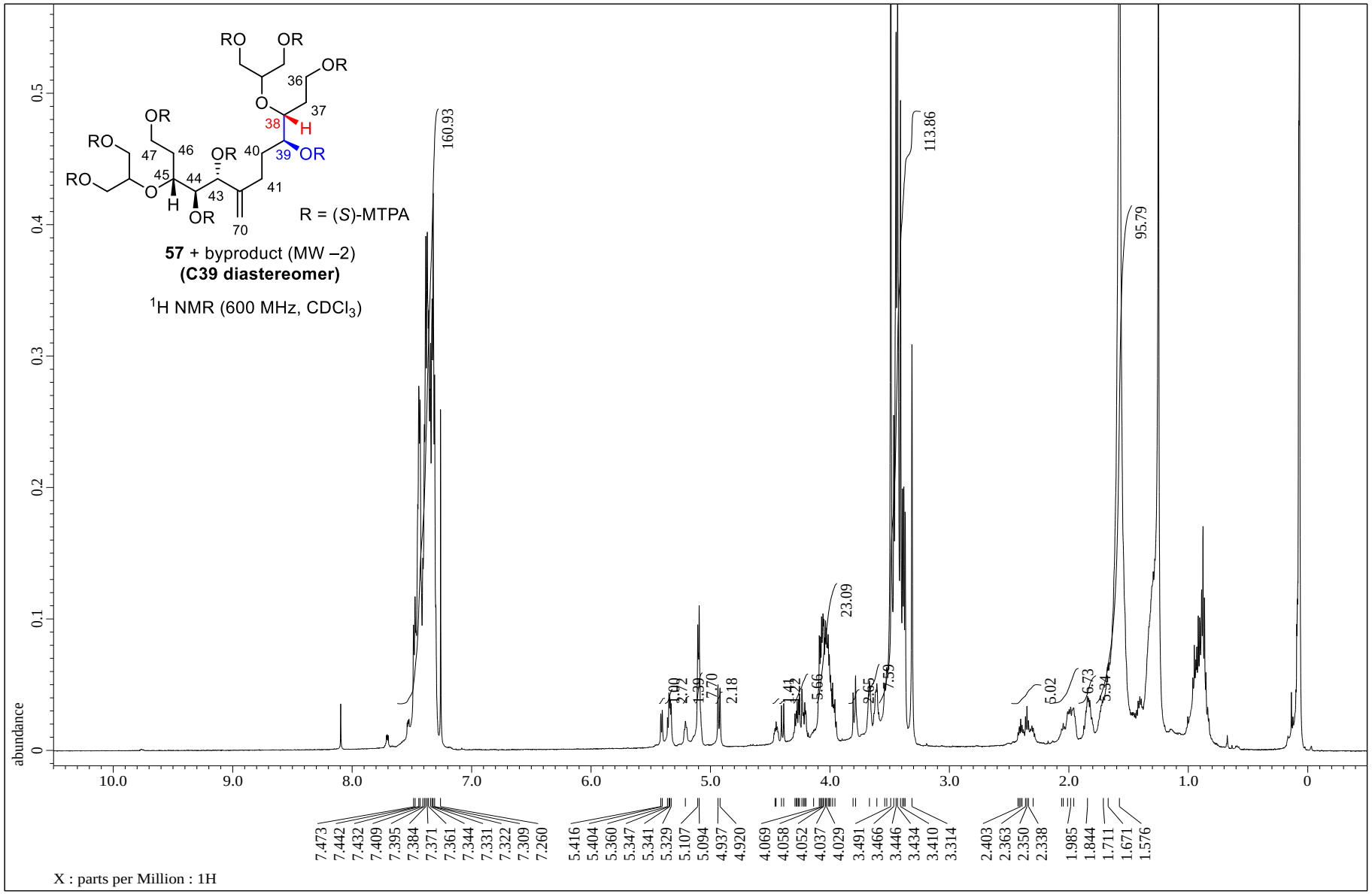
PMBO
O
O
O
H
O
H
I
OTBS
61
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H
5.83
2.00
0.95
0.94
1.02
1.04
2.00
3.94
3.06
1.94
12.32
6.73
8.95
6.14
7.269
7.260
7.247
6.880
6.858
5.998
5.661
4.553
4.523
4.506
4.478
4.030
4.014
4.006
3.804
3.794
3.592
3.577
3.567
3.554
2.473
2.459
2.447
2.434
2.420
1.860
1.844
1.825
1.801
1.693
1.669
0.884
0.069

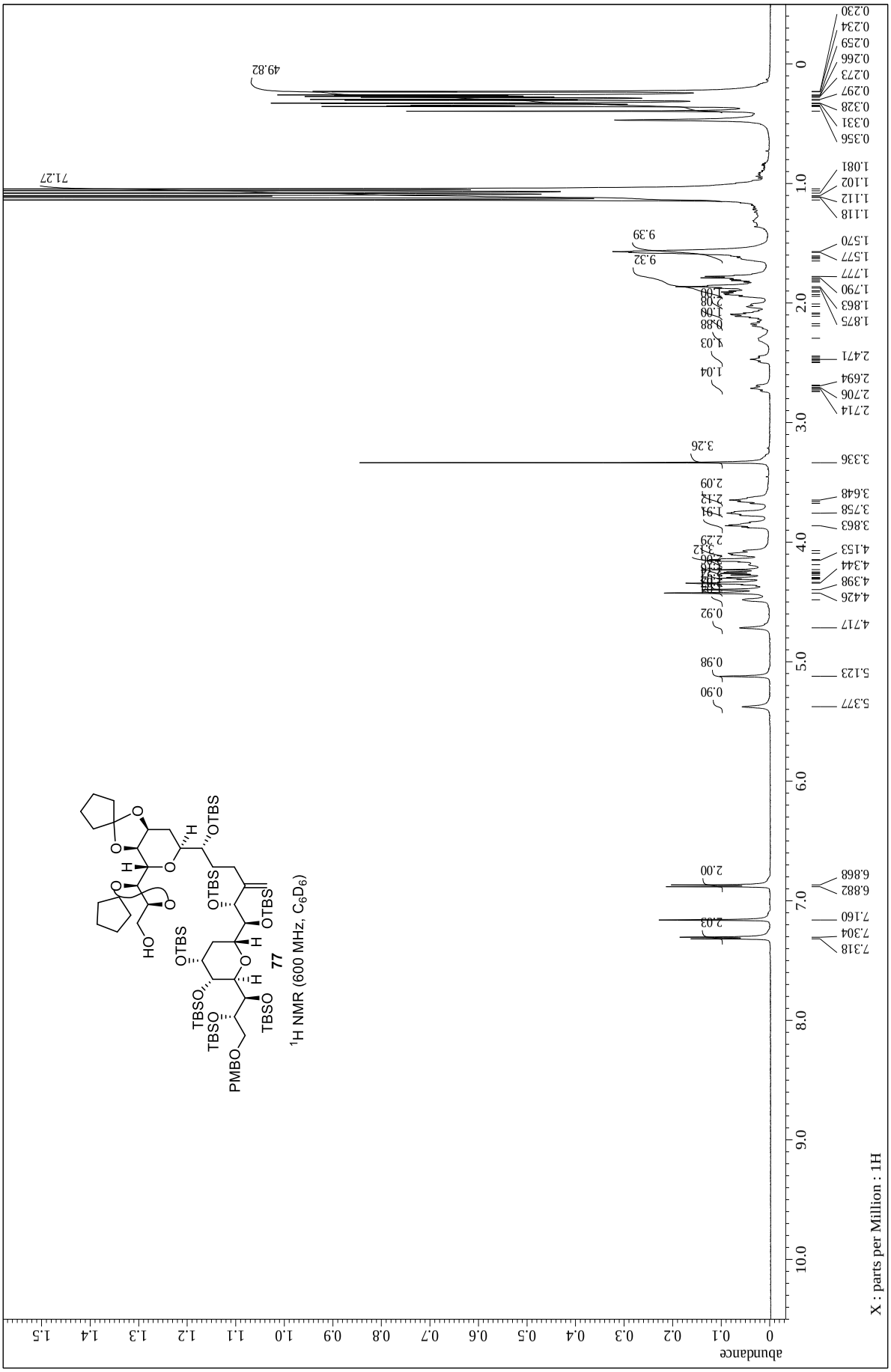
S5
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.260
6.029
6.025
5.684
5.680
4.110
4.092
4.071
4.058
4.048
4.043
3.870
3.825
3.817
3.810
3.691
3.679
2.471
2.462
2.456
2.446
2.432
1.896
1.822
1.724
1.714
1.680
1.669
0.895
0.088
0.082
1.00
0.97
1.01
3.03
3.01
0.98
1.05
1.97
19.07
9.67
6.13

TESO
O
O
O
H
O
H
OTBS
I
62
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.260
6.013
6.011
5.669
5.667
4.265
4.260
4.255
4.249
4.240
4.073
3.797
3.790
3.780
3.772
3.719
2.498
2.481
2.472
2.462
2.453
1.828
1.684
1.674
1.662
1.651
0.959
0.946
0.895
0.621
0.607
0.083
0.081
0.075
1.00
1.05
1.03
3.04
0.99
2.01
0.99
1.01
2.05
0.99
19.05
9.46
6.86
6.23

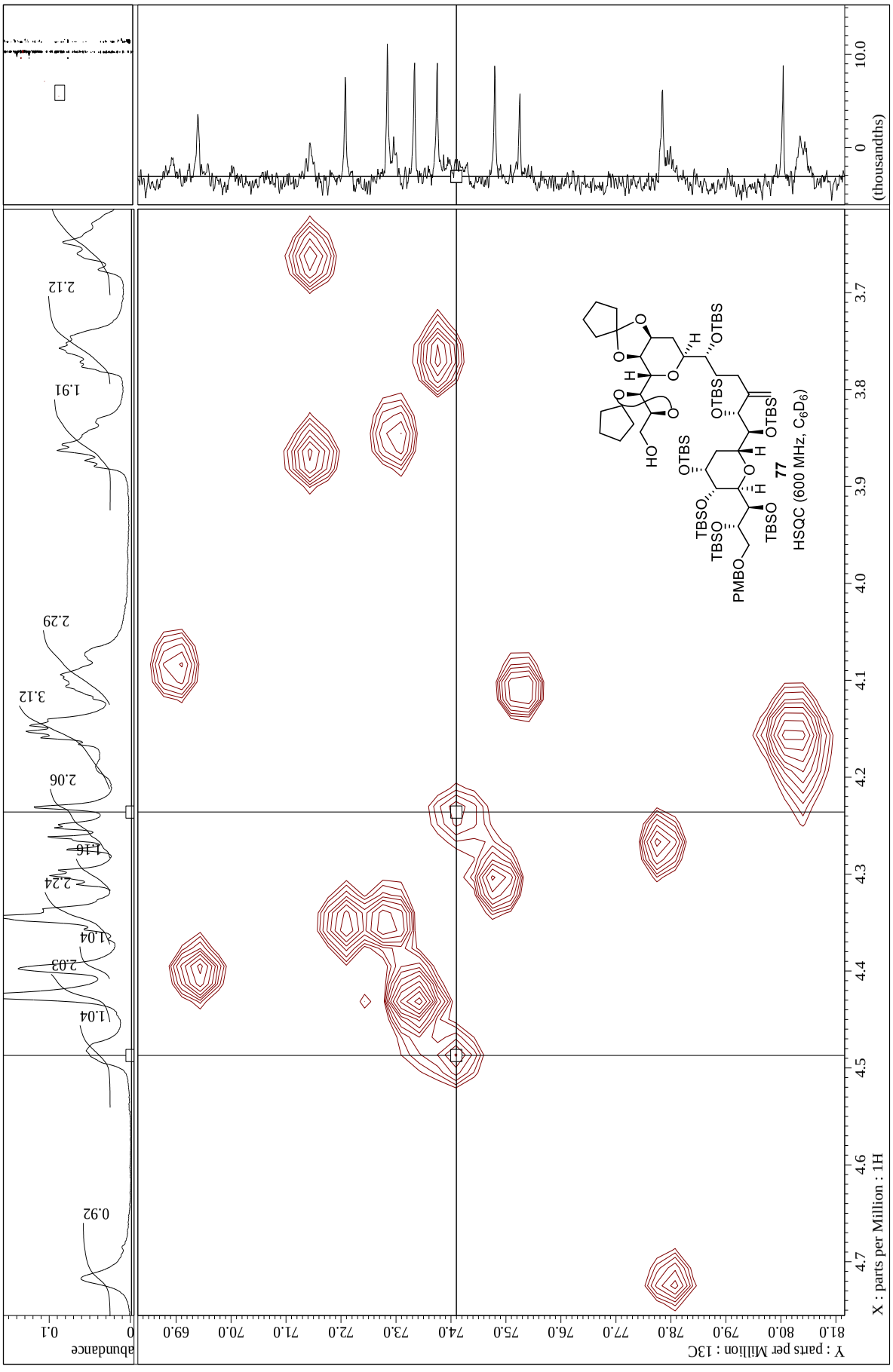

63
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance

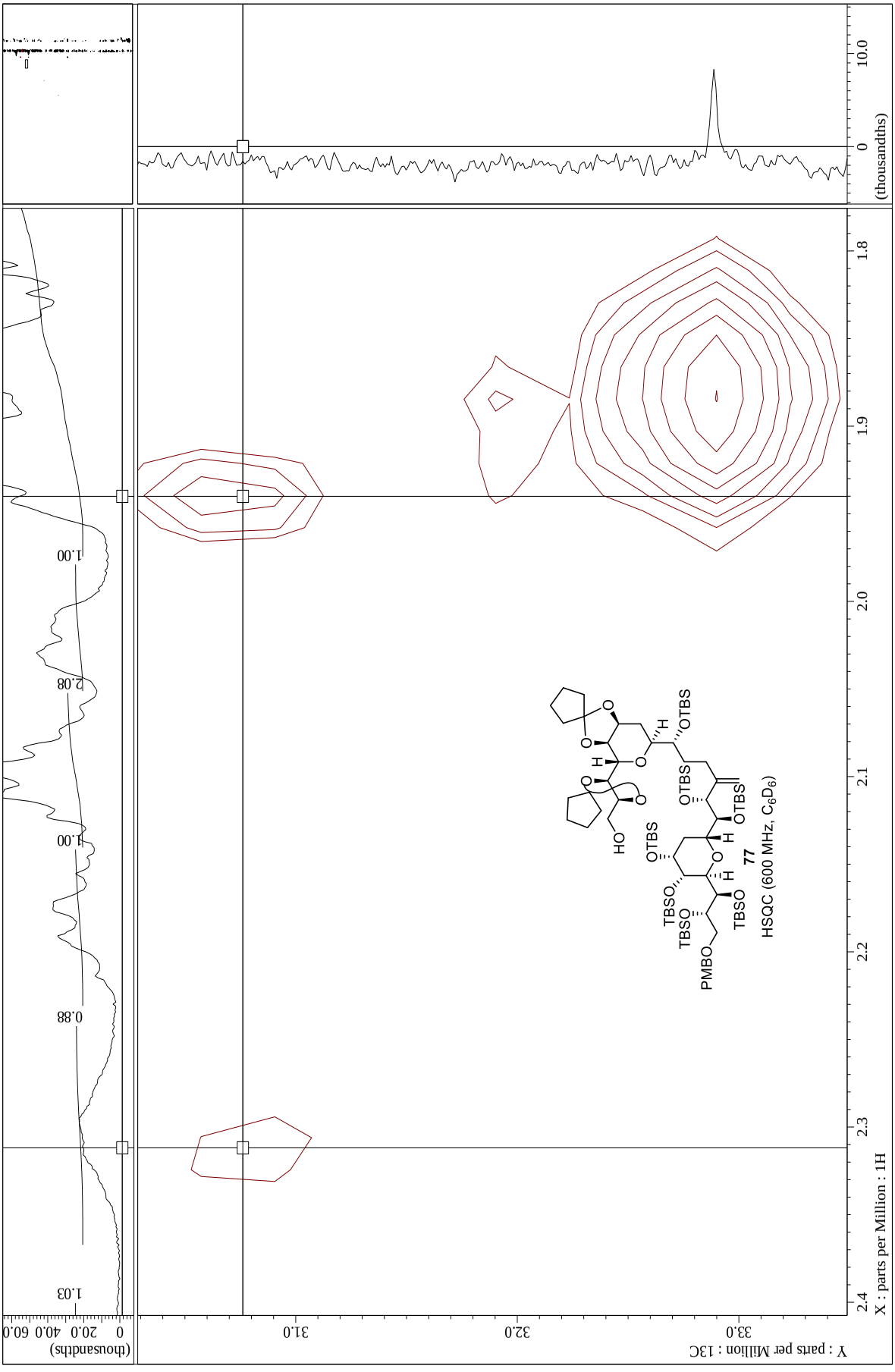

64
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance


RO
OR
OR
36
37
38
H
39
OR
OR
RO
47
46
OR
40
RO
45
44
43
41
O
H
OR
70
R = (S)-MTPA
57 + byproduct (MW –2)
(C39 diastereomer)
1H NMR (600 MHz, CDCl3)
160.93
113.86
95.79
23.09
abundance
X : parts per Million : 1H


77
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance

77
13C NMR (150 MHz, C6D6)
X : parts per Million : 13C
159.791
151.001
130.865
129.582
128.223
128.060
127.897
119.692
118.552
114.081
80.043
77.850
75.255
74.796
73.752
73.340
72.957
72.842
72.076
69.395
62.798
54.775
37.866
37.789
37.684
32.887
26.596
26.548
26.510
18.908
18.726
18.649
18.486
-2.731
-3.507
-3.641
-3.765
-3.832
-4.024
-4.225
-4.321
-5.039

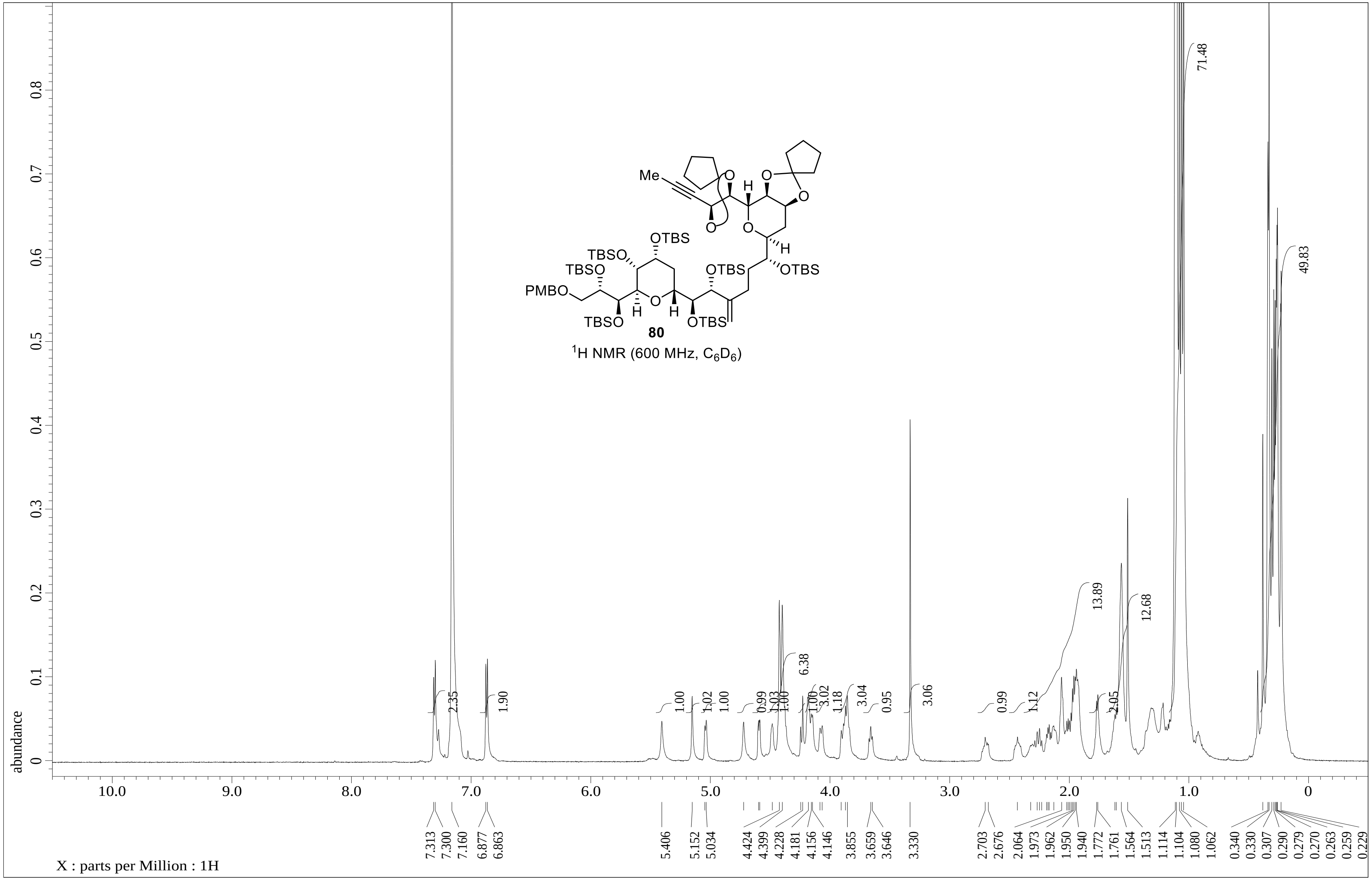

X : parts per Million : 1H
Y : parts per Million : 13C
abundance
(thousandths)
HSQC (600 MHz, C6D6)
77
PMBO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
OTBS
HO
0.92
1.04
2.03
1.04
2.24
1.16
2.06
3.12
2.29
1.91
2.12


HSQC (600 MHz, C_6D_6)
77
X : parts per Million : 1H
Y : parts per Million : 13C
(thousandths)
(thousandths)
1.03
0.88
1.00
2.08
1.00

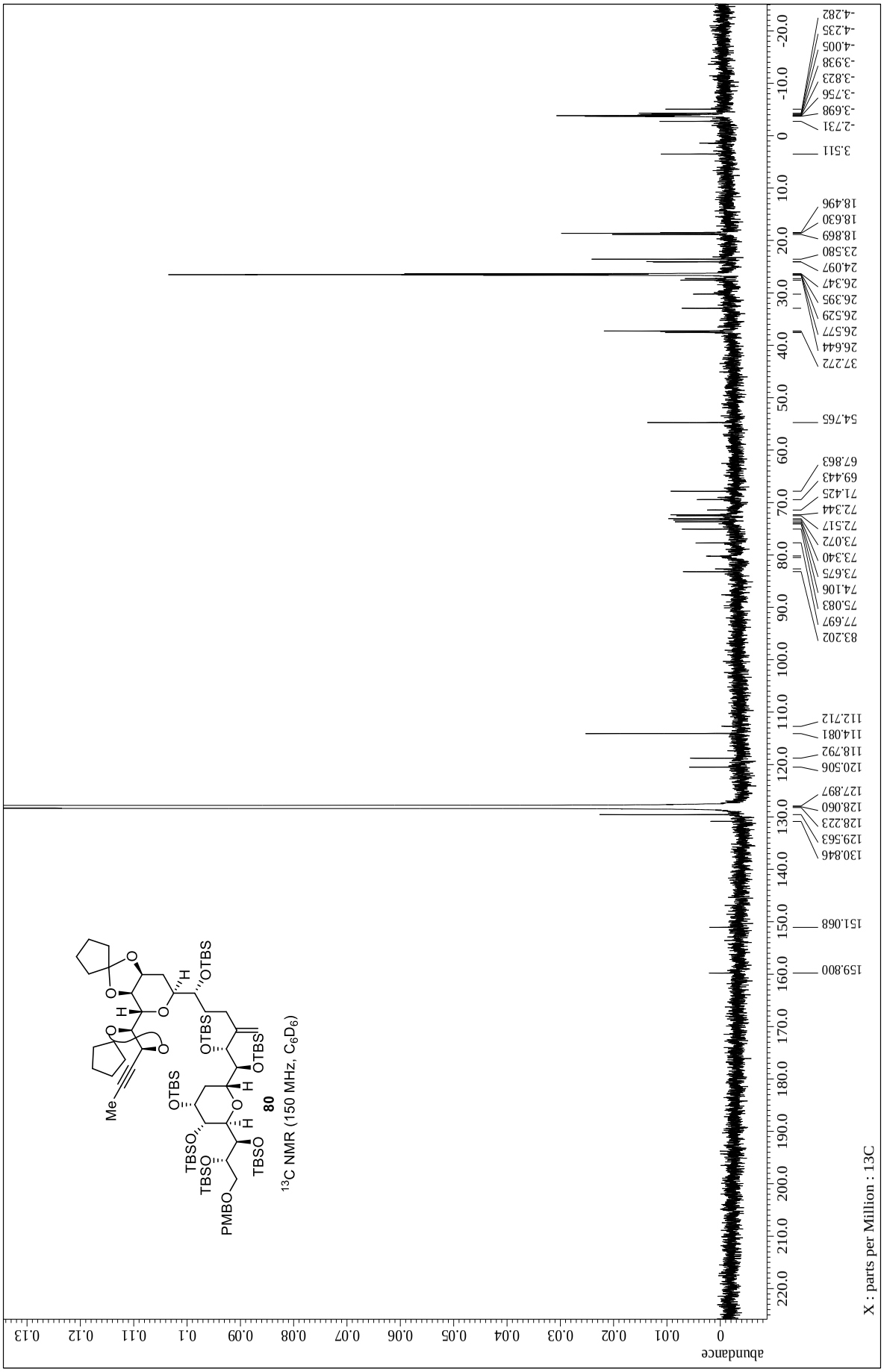
79
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

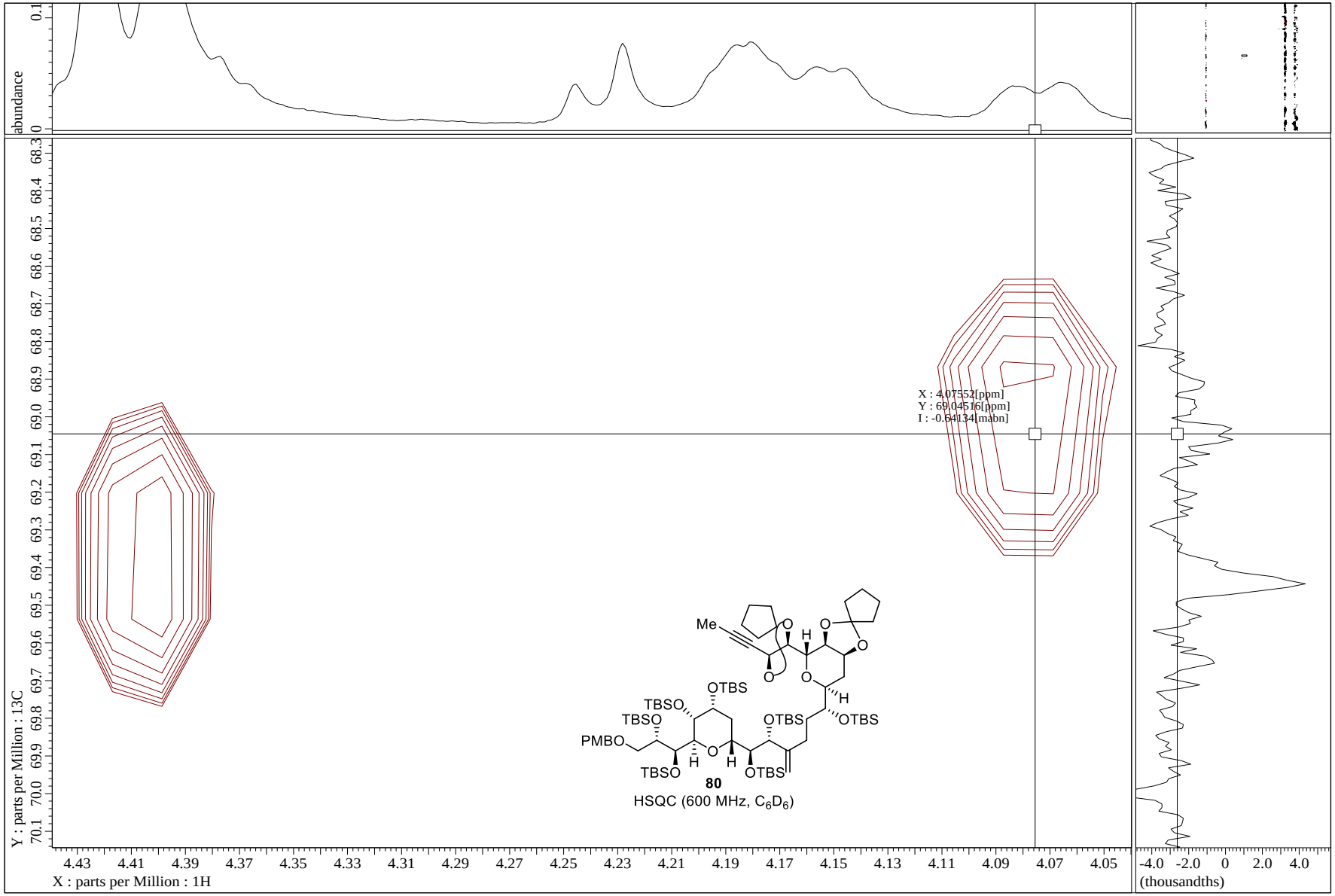
79
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.800
151.039
130.837
129.582
128.223
128.060
127.897
121.080
118.878
114.081
112.578
82.379
82.302
74.834
74.738
73.589
73.398
73.350
72.469
72.268
69.424
67.404
54.775
37.645
37.329
37.109
37.061
32.810
26.587
26.539
18.888
18.668
18.496
-2.731
-3.641
-3.746
-3.823
-3.947
-3.995
-4.225
-4.282
-5.048

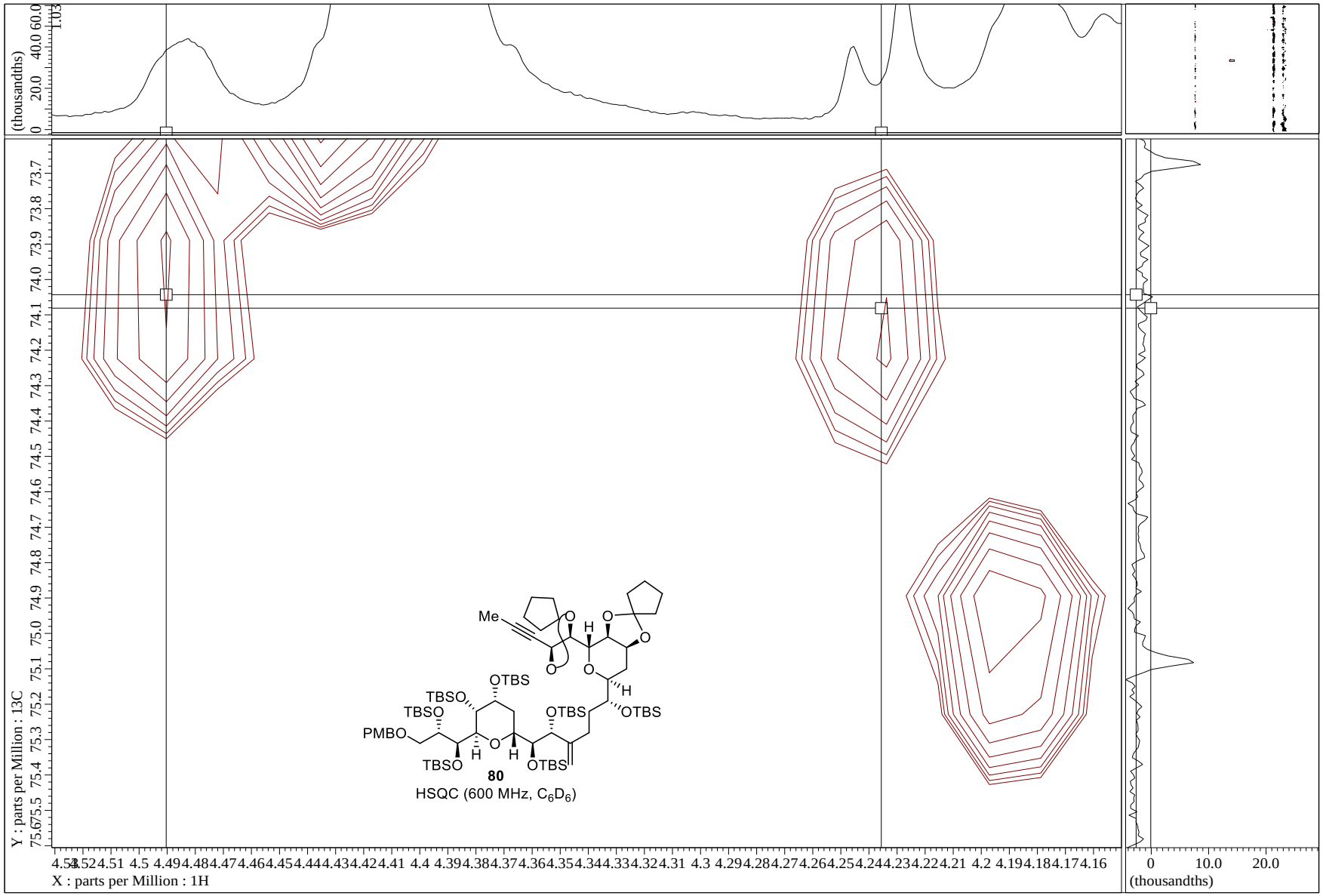
abundance
0.97
0.91
0.90
3.03
3.09
1.01
1.93
1.12
1.01
3.25
Y : parts per Million : 13C
X : parts per Million : 1H
(thousandths)
PMBO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
OTBS
H
H
H
O
O
O
O
O
O
O
79
HSQC (600 MHz, C6D6)

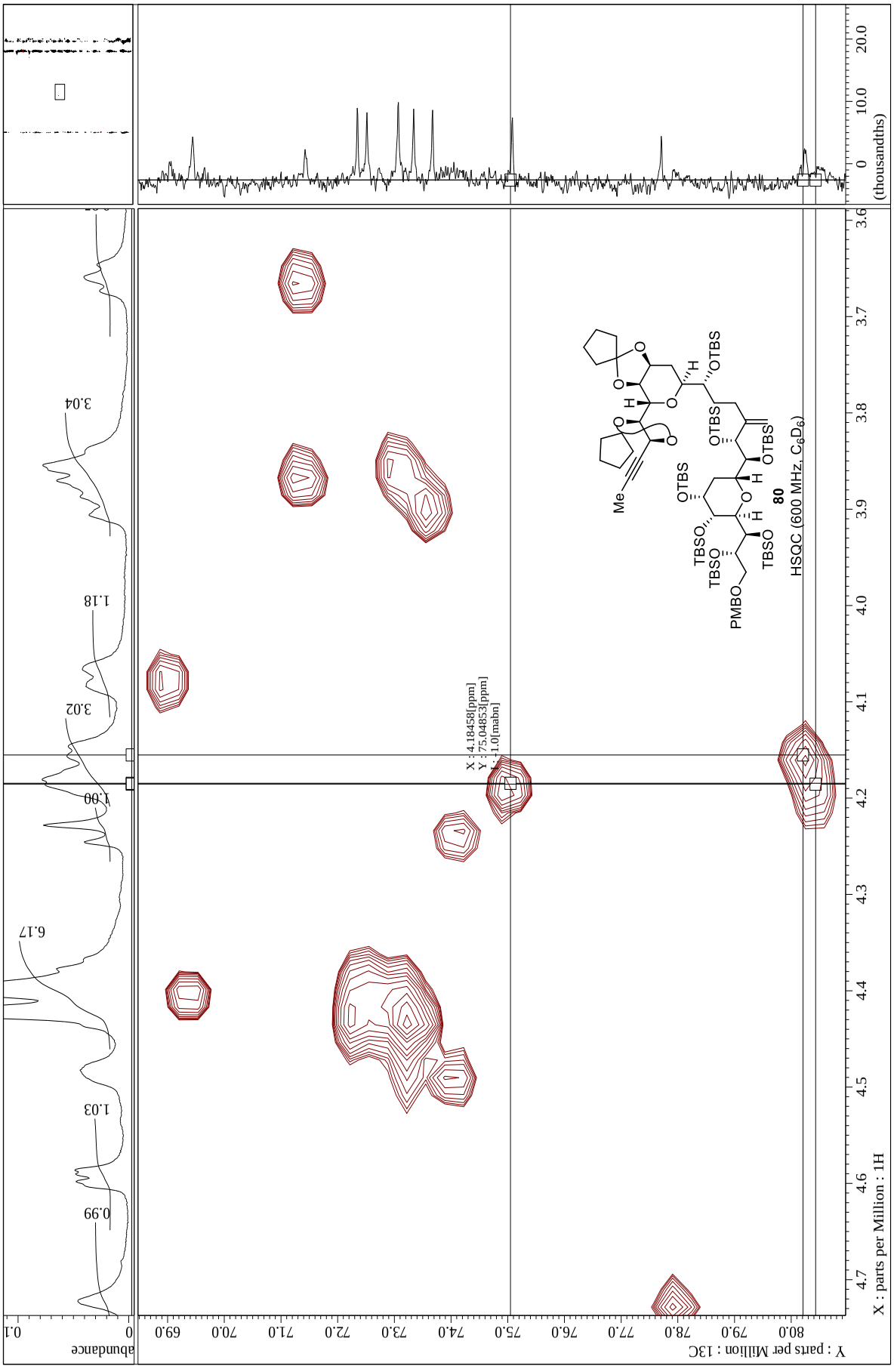


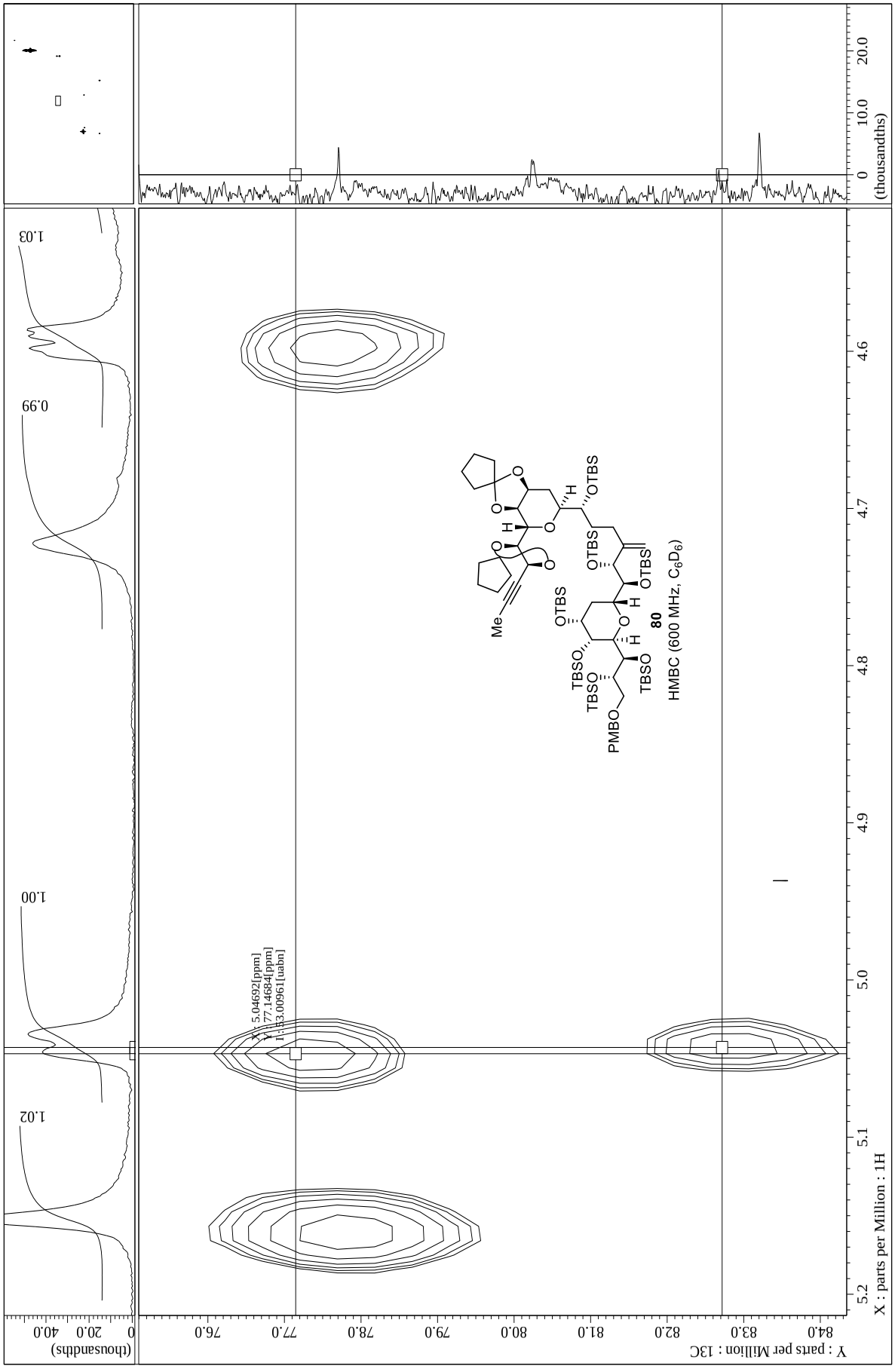
Me
OTBS
TBSO
TBSO
PMBO
OTBS
OTBS
TBSO
OTBS
80
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H


80
^{13}C NMR (150 MHz, C_6D_6)
abundance
X : parts per Million : 13C
159.800
151.068
130.846
129.563
128.223
128.060
127.897
120.506
118.792
114.081
112.712
83.202
77.697
75.083
74.106
73.675
73.340
73.072
72.517
72.344
71.425
69.443
67.863
54.765
37.272
26.644
26.577
26.529
26.395
26.347
24.097
23.580
18.869
18.630
18.496
3.511
-2.731
-3.698
-3.756
-3.823
-3.938
-4.005
-4.235
-4.282


abundance
0.1
0
X : 4.07552[ppm]
Y : 69.04516[ppm]
I : -0.64134[mabn]
Me
O
H
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
80
HSQC (600 MHz, C6D6)
Y : parts per Million : 13C
68.3
68.4
68.5
68.6
68.7
68.8
68.9
69.0
69.1
69.2
69.3
69.4
69.5
69.6
69.7
69.8
69.9
70.0
70.1
4.43
4.41
4.39
4.37
4.35
4.33
4.31
4.29
4.27
4.25
4.23
4.21
4.19
4.17
4.15
4.13
4.11
4.09
4.07
4.05
X : parts per Million : 1H
-4.0
-2.0
0
2.0
4.0
(thousandths)

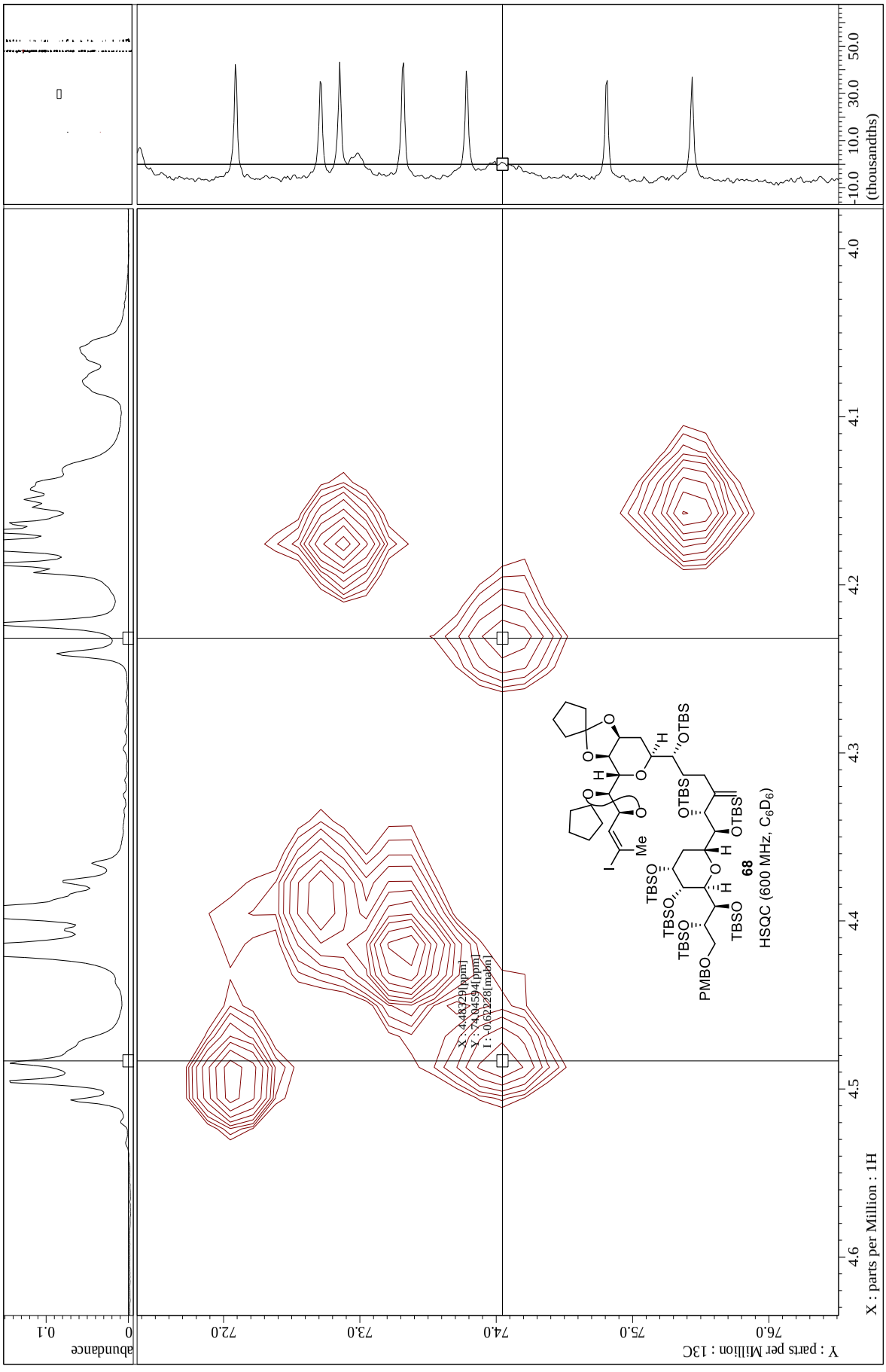

(thousandths)
Y : parts per Million : 13C
X : parts per Million : 1H
(thousandths)
Me
PMBO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
OTBS
H
H
H
O
80
HSQC (600 MHz, C6D6)


HSQC (600 MHz, C6D6)
80
X : parts per Million : 1H
Y : parts per Million : 13C
abundance
(thousandths)
X : 4.18458[ppm]
Y : 75.04853[ppm]
Z : 1.0[mabn]
6.17
1.00
1.03
0.99
3.02
1.18
3.04
Me
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
H
O


X : parts per Million : 1H
Y : parts per Million : 13C
(thousandths)
(thousandths)
X: 5.04692[ppm]
Y: 77.14684[ppm]
I: 53.00961[uabs]
1.02
1.00
0.99
1.03
HMBC (600 MHz, C6D6)
80
Me
OTBS
TBSO
PMBO
H
O

68
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

68
^{13}C NMR (150 MHz, C_6D_6)
abundance
X : parts per Million : 13C
159.781
150.944
139.128
128.213
128.060
127.897
119.720
118.753
114.062
112.788
101.538
81.326
75.437
74.815
73.781
73.321
72.852
72.718
72.086
69.395
54.756
37.626
37.138
36.841
26.567
26.529
26.491
26.395
18.869
18.659
18.640
18.620
-2.751
-3.651
-3.689
-3.775
-3.804
-3.823
-3.976
-4.014
-4.254
-4.292


X : parts per Million : 1H
Y : parts per Million : 13C
abundance
(thousandths)
HSQC (600 MHz, C6D6)
68
X: 4.48329[ppm]
Y: 74.0459[ppm]
I : 0.062228[magn]

abundance
0.1
0
26.0
27.0
28.0
29.0
Y : parts per Million : 13C
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
X : parts per Million : 1H
0
10.0
20.0
(thousandths)
I
Me
O
O
O
O
O
O
H
H
H
H
TBSO
TBSO
TBSO
TBSO
PMBO
OTBS
OTBS
OTBS
68
HSQC (600 MHz, C6D6)

91
1H NMR (600 MHz, C6D6)
TBDPSO
TBSO
Me
TBS
OTBS
PMBO
H
O
abundance
X : parts per Million : 1H
7.830
7.818
7.279
7.267
7.160
6.875
6.861
5.816
5.802
5.790
5.691
5.654
5.641
5.390
5.136
5.120
4.725
4.421
4.397
4.225
3.919
3.854
3.824
3.770
3.336
2.668
2.083
2.058
2.019
1.947
1.917
1.822
1.637
1.499
1.117
1.083
1.070
1.066
1.040
0.329
0.324
0.265
0.259
0.243
0.236
0.200
0.194
4.30
8.35
2.07
1.94
3.12
1.00
2.05
1.04
0.94
3.03
3.01
1.06
8.16
9.10
0.97
3.14
3.01
6.00
1.08
21.31
25.59
186.40
115.17

91
13C NMR (150 MHz, C6D6)
(thousandths)
X : parts per Million : 13C
159.785
151.026
142.700
136.073
128.060
127.900
123.167
118.567
114.074
83.714
83.542
73.973
73.315
67.532
54.763
42.119
41.889
37.771
37.578
26.314
26.291
18.643
13.543
-3.618
-3.652
-3.767
-3.806
-3.834
-4.022
-4.230
-4.258
-4.354

abundance
0
0.1
Y : parts per Million : 13C
67.0
68.0
69.0
70.0
71.0
72.0
73.0
74.0
75.0
76.0
77.0
78.0
79.0
80.0
81.0
82.0
83.0
84.0
85.0
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
X : parts per Million : 1H
-1.0
0
1.0
2.0
3.0
4.0
5.0
(thousandths)
TBDPSO
TBSO
Me
TBS
OTBS
PMBO
H
O
91
13C NMR (150 MHz, C6D6)

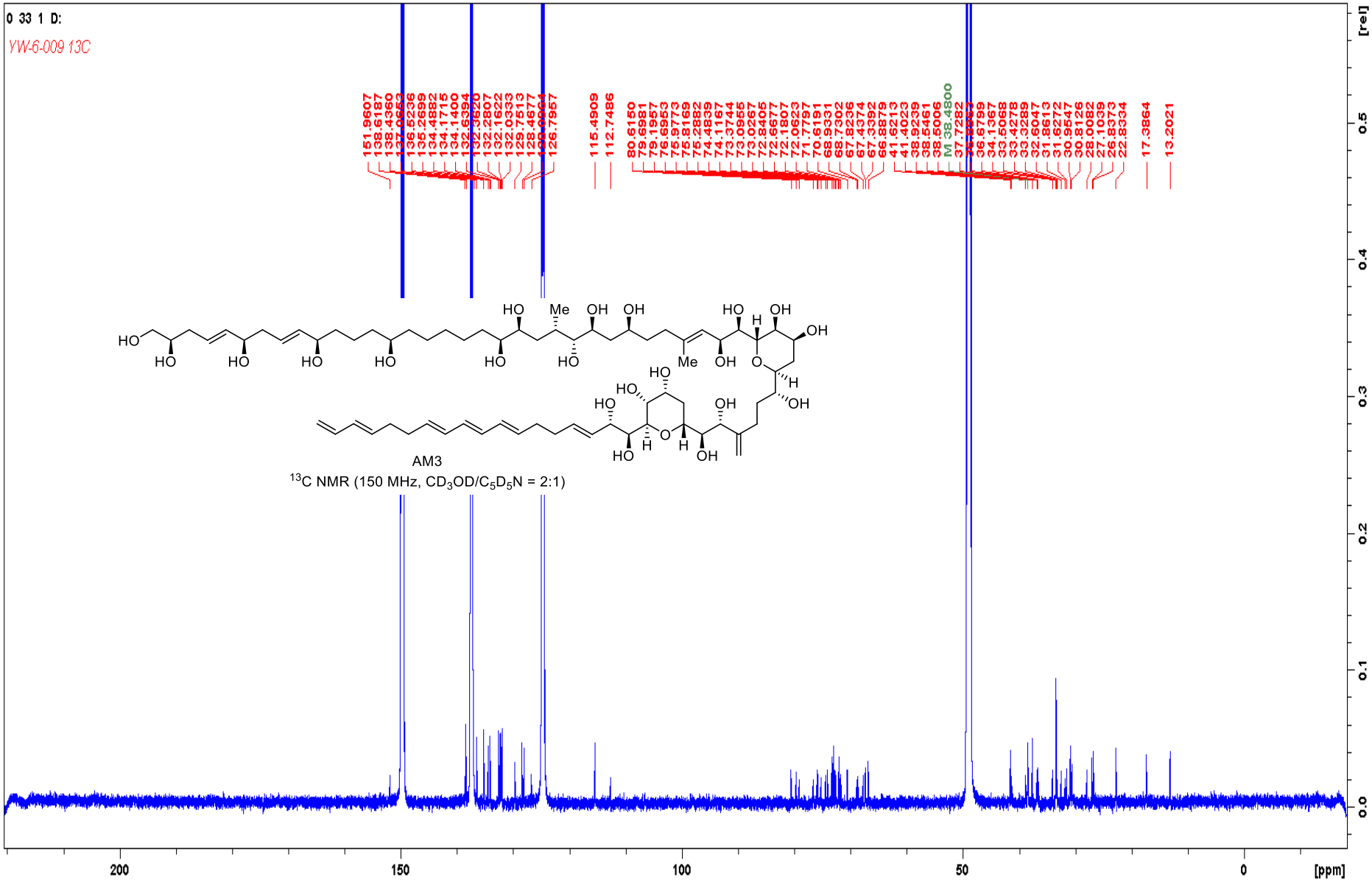
S6
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H
7.838
7.825
7.281
7.270
7.160
5.810
5.708
5.698
5.667
5.651
5.624
5.387
5.126
4.377
4.297
4.256
4.244
4.235
4.225
4.121
4.108
3.955
3.924
3.829
3.777
2.635
2.611
2.096
2.069
2.018
1.948
1.918
1.627
1.506
1.128
1.088
1.085
1.077
1.071
0.299
0.294
0.281
0.276
0.245
0.238
0.207
0.199
0.195
4.44
6.60
2.10
3.29
1.00
2.14
6.12
2.03
1.03
4.02
3.93
24.40
24.12
198.71
122.24

S6
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
151.120
143.173
136.662
136.423
128.572
128.256
123.411
119.619
112.611
84.039
83.857
80.286
74.608
74.321
67.858
63.846
42.466
42.217
38.195
38.109
37.918
26.840
26.821
26.667
26.639
13.895
-2.517
-3.244
-3.426
-3.512
-3.675
-3.742
-3.876
-4.010
-4.039

(thousandths)
0
20.0
40.0
60.0
TBDPSO
TBSO
TBSO
TBSO
TBSO
TBSO
TBSO
TBSO
Me
O
TBS
OTBS
Me
O
O
H
O
O
H
TBSO
TBSO
TBSO
OTBS
OTBS
HO
O
H
H
OTBS
TBSO
S6
HSQC (600 MHz, C6D6)
Y : parts per Million : 13C
63.0
64.0
65.0
66.0
67.0
68.0
69.0
70.0
71.0
72.0
73.0
74.0
75.0
76.0
77.0
78.0
79.0
80.0
81.0
82.0
83.0
84.0
85.0
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
X : parts per Million : 1H
-10.0
0
10.0
20.0
30.0
(thousandths)

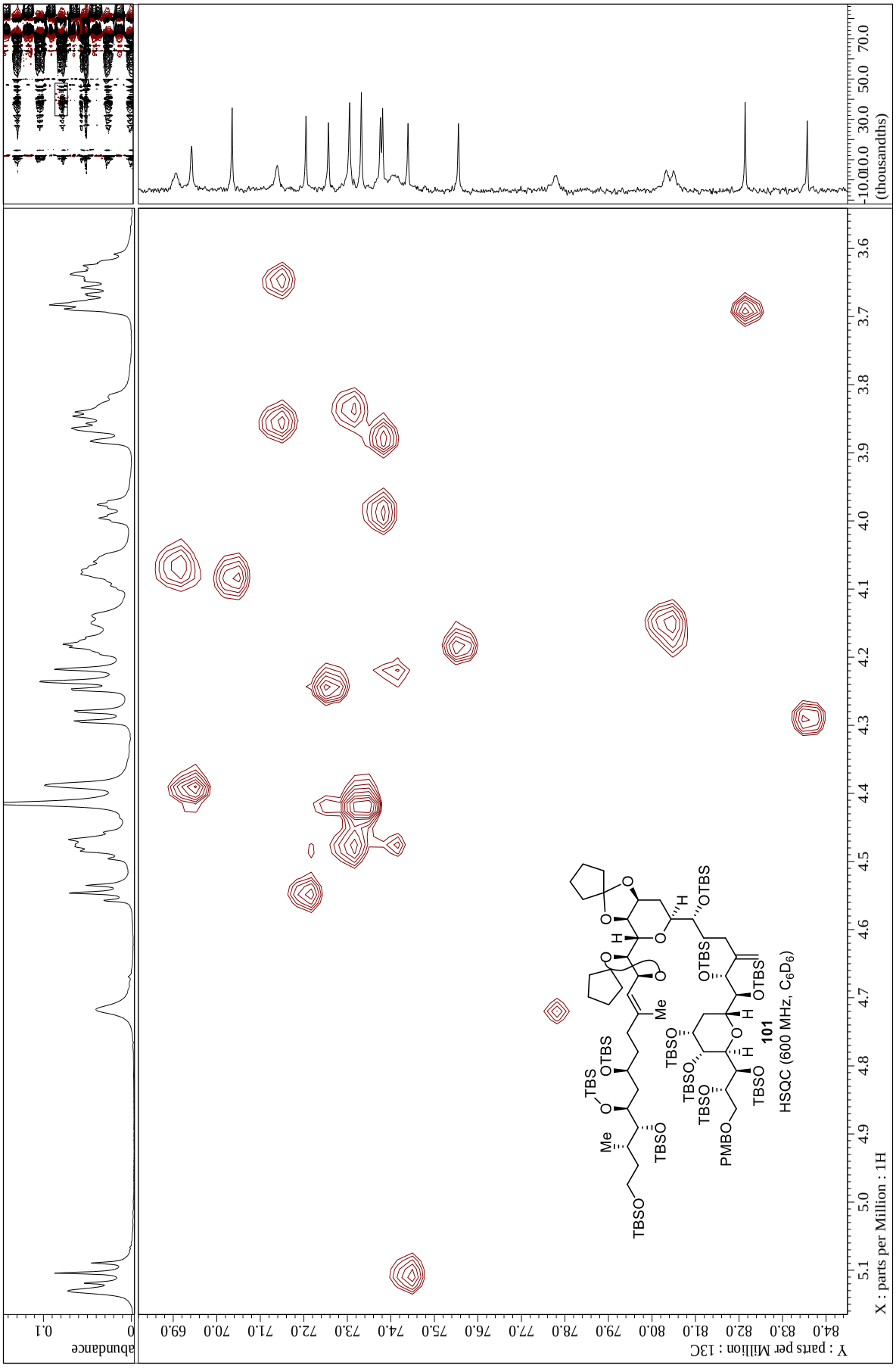
(thousandths)
10.0 30.0 50.0 70.0
Y : parts per Million : 13C
31.0
32.0
33.0
34.0
2.3
2.2
2.1
2.0
1.9
1.8
1.7
X : parts per Million : 1H
-10.0 0 10.0 20.0 30.0
(thousandths)
TBDPSO
TBSO
Me
TBS
OTBS
HO
H
O
S6
HSQC (600 MHz, C6D6)

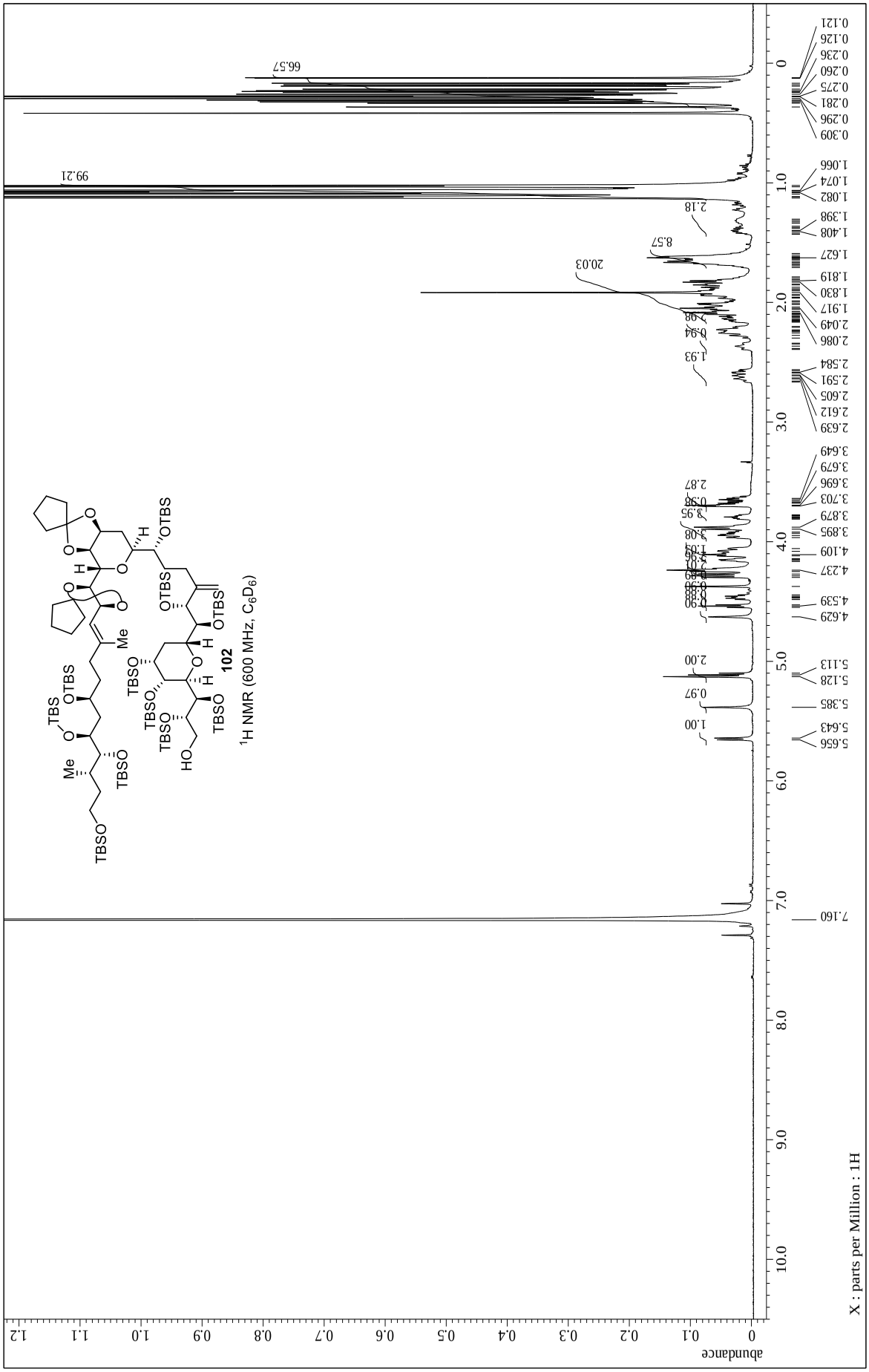
AM3
^{1}H NMR (600 MHz, CD_3OD/C_5D_5N = 2:1)
abundance
X : parts per Million : 1H


0 33 1 D:
YW-6-009 13C
AM3
^{13}C NMR (150 MHz, CD_3OD/C_5D_5N = 2:1)
[rel]
[ppm]

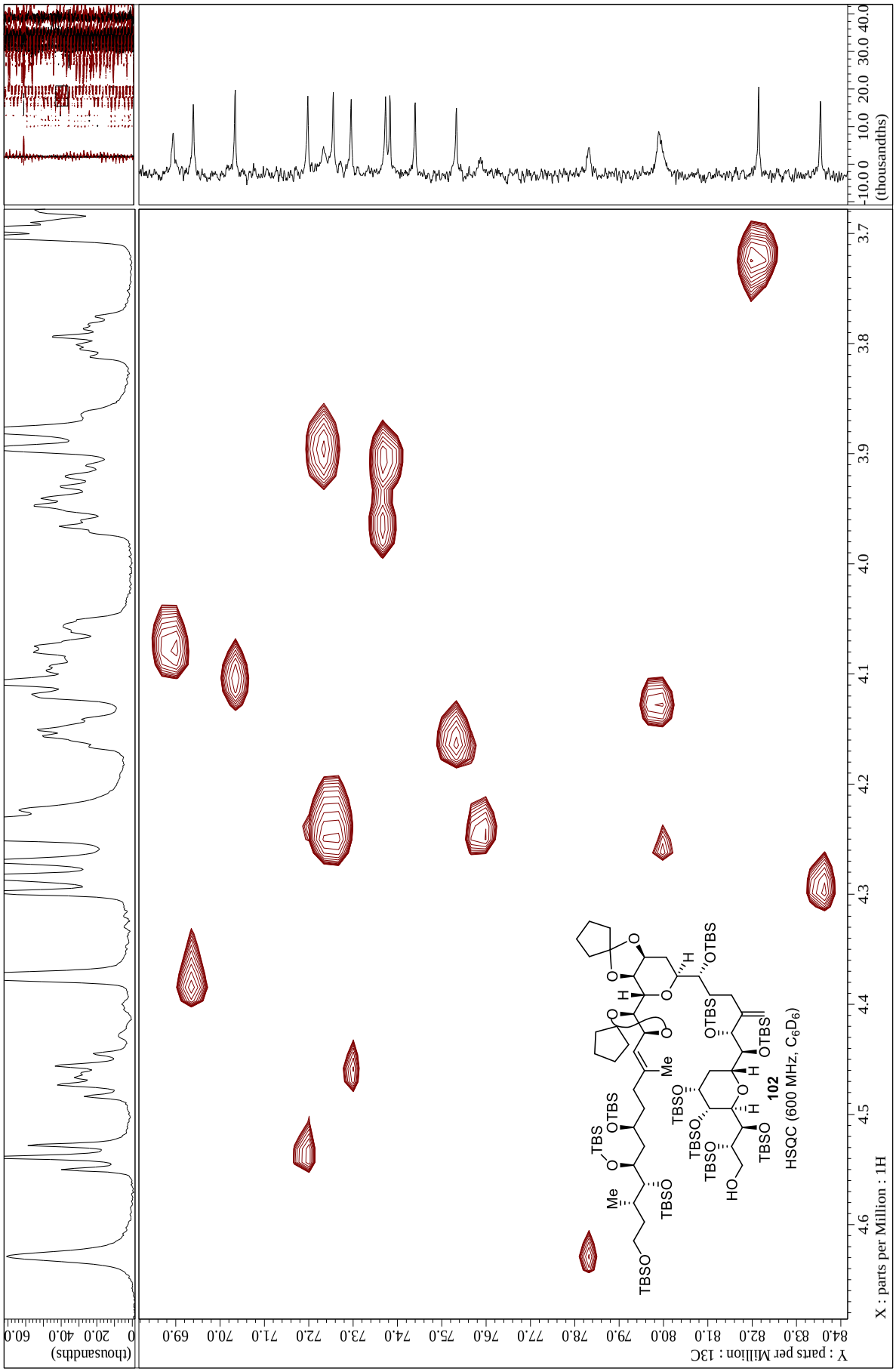
101
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

101
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.791
151.049
142.834
128.223
128.060
127.907
123.091
118.571
114.081
112.903
83.566
82.139
75.552
74.393
73.809
73.761
73.321
73.053
72.048
70.353
61.448
54.775
41.667
26.587
26.548
26.491
26.443
26.405
26.271
18.668
18.649
18.630
18.592
-3.028
-3.641
-3.698
-3.765
-3.804
-3.823
-4.091
-4.254
-4.282
-5.048


HSQC (600 MHz, C6D6)
101
X : parts per Million : 1H
Y : parts per Million : 13C
abundance
(thousandths)


102
^{1}H NMR (600 MHz, C_6D_6)
X : parts per Million : 1H
abundance
7.160
99.21
66.57
20.03
8.57
2.18
1.93
2.87
1.00
0.97
2.00
4.629
4.539
4.237
4.109
3.895
3.879
3.703
3.696
3.679
3.649
2.639
2.612
2.605
2.591
2.584
2.086
2.049
1.917
1.830
1.819
1.627
1.408
1.398
1.082
1.074
1.066
0.309
0.296
0.281
0.275
0.260
0.236
0.126
0.121
5.656
5.643
5.385
5.128
5.113

TBSO
Me
O
TBS
OTBS
TBSO
Me
O
O
O
H
O
O
TBSO
TBSO
TBSO
OTBS
OTBS
H
HO
O
H
H
TBSO
OTBS
102
13C NMR (150 MHz, C6D6)
abundance
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.1
0.11
0.12
0.13
0.14
0.15
0.16
0.17
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
150.819
142.949
128.223
128.060
127.907
123.033
118.581
112.290
83.547
82.149
74.403
73.828
73.733
72.957
72.555
71.981
70.343
69.395
63.526
61.467
41.657
26.740
26.596
26.491
26.405
26.357
26.280
18.640
18.582
18.525
18.448
-2.865
-3.584
-3.651
-3.765
-3.832
-3.986
-4.024
-4.187
-4.321
-5.039
X : parts per Million : 13C


(thousandths)
0 20.0 40.0 60.0
-10.0 0 10.0 20.0 30.0 40.0
(thousandths)
Y : parts per Million : 13C
84.0 83.0 82.0 81.0 80.0 79.0 78.0 77.0 76.0 75.0 74.0 73.0 72.0 71.0 70.0 69.0
X : parts per Million : 1H
4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7
HSQC (600 MHz, C6D6)
102
TBSO
OTBS
TBS
Me
HO
H
O

C21-C67 analog (94)
1H NMR (600 MHz, CD3OD/C5D5N = 2:1)
abundance
X : parts per Million : 1H

C21-C67 analog (94)
13C NMR (150 MHz, CD3OD/C5D5N = 2:1)
abundance
X : parts per Million : 13C
158.818
149.914
149.732
149.550
137.601
137.438
137.275
132.028
124.924
124.751
124.589
115.502
112.745
78.419
75.805
72.674
72.607
71.726
70.577
68.911
68.710
67.791
67.331
60.763
49.139
49.005
48.862
38.291
36.864
36.682
33.513
33.437
33.331
31.550
17.380
13.358

TBS
Me
O
OTBS
O
ONAP
OTBS
105
1 H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
9.670
7.829
7.817
7.803
7.774
7.463
7.451
7.260
4.674
4.655
4.633
4.613
3.987
3.985
3.970
3.664
3.647
3.604
3.584
3.578
2.567
2.553
2.533
2.518
2.184
2.179
1.921
1.808
1.559
1.548
1.538
0.910
0.896
0.860
0.849
0.121
0.069
0.052
0.049
0.012
1.00
4.24
3.15
1.00
1.15
1.10
4.42
1.08
2.14
1.08
1.07
1.17
5.70
13.30
20.24
19.96

TBS
Me
O
OTBS
ONAP
OTBS
106
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

TBS
Me
O
OTBS
ONAP
OTBS
106
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
137.625
136.294
133.469
133.105
128.146
127.992
127.811
126.499
126.106
126.039
125.838
116.139
81.134
77.380
77.160
76.949
73.349
73.129
67.537
67.241
41.638
38.842
37.846
36.515
26.251
26.002
18.582
18.208
18.179
15.451
-3.115
-3.201
-4.034
-4.312
-4.618
-4.637

TBS
TBSO
Me
O
OTBS
TBSO
ONAP
OTBS
108
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
4.01
2.97
2.11
1.05
1.94
1.00
2.02
4.66
50.33
31.19
7.827
7.810
7.797
7.774
7.463
7.457
7.260
4.666
4.645
4.628
4.609
3.995
3.978
3.962
3.614
3.519
3.328
3.317
3.312
3.301
1.964
1.955
1.945
1.816
1.810
1.798
1.793
1.565
1.543
1.401
1.337
0.878
0.868
0.855
0.846
0.057
0.053
0.050
0.046
0.038
0.031
0.008

TBS
TBSO
Me
O
OTBS
TBSO
ONAP
OTBS
108
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
136.380
133.469
133.077
128.088
127.983
127.801
126.403
126.068
126.020
125.790
82.838
77.371
77.160
76.949
73.713
73.253
70.869
68.294
67.604
67.183
41.896
39.771
36.563
33.796
26.126
26.098
18.543
18.256
18.170
18.151
14.254
-3.134
-3.220
-3.919
-4.005
-4.436
-4.455
-4.647
-5.183
-5.202

TBS
O
Me
O
OTBS
TBSO
ONAP
OTBS
111
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.828
7.813
7.801
7.774
7.464
7.459
7.260
4.672
4.652
4.633
4.613
4.104
4.100
3.982
3.966
3.664
3.647
3.618
3.610
3.604
2.618
2.612
2.589
2.582
2.353
2.338
2.308
1.932
1.819
1.558
1.546
1.542
0.914
0.891
0.872
0.858
0.847
0.117
0.077
0.052
0.049
0.010
0.000
3.96
2.95
1.01
1.06
2.00
1.04
4.13
0.95
1.14
0.97
1.01
1.03
4.00
41.45
25.04

TBS
HO
Me
O
OTBS
TBSO
ONAP
OTBS
110
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

TBS
RO
Me
O
OTBS
TBSO
ONAP
OTBS
R = (R)-MTPA
112
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

TBS
RO
Me
O
OTBS
TBSO
ONAP
OTBS
R = (S)-MTPA
113
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

TBS
TBSO
Me
O
OTBS
TBSO
OH
OTBS
S7
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.260
4.112
4.106
4.099
4.093
4.088
4.081
3.615
3.598
3.519
3.511
3.340
3.328
3.323
2.652
2.642
2.634
1.877
1.872
1.853
1.660
1.603
1.406
1.349
0.906
0.886
0.879
0.873
0.128
0.089
0.070
0.063
0.051
0.039
0.031
1.06
1.00
0.99
2.05
2.02
1.05
1.71
2.02
48.79
30.79

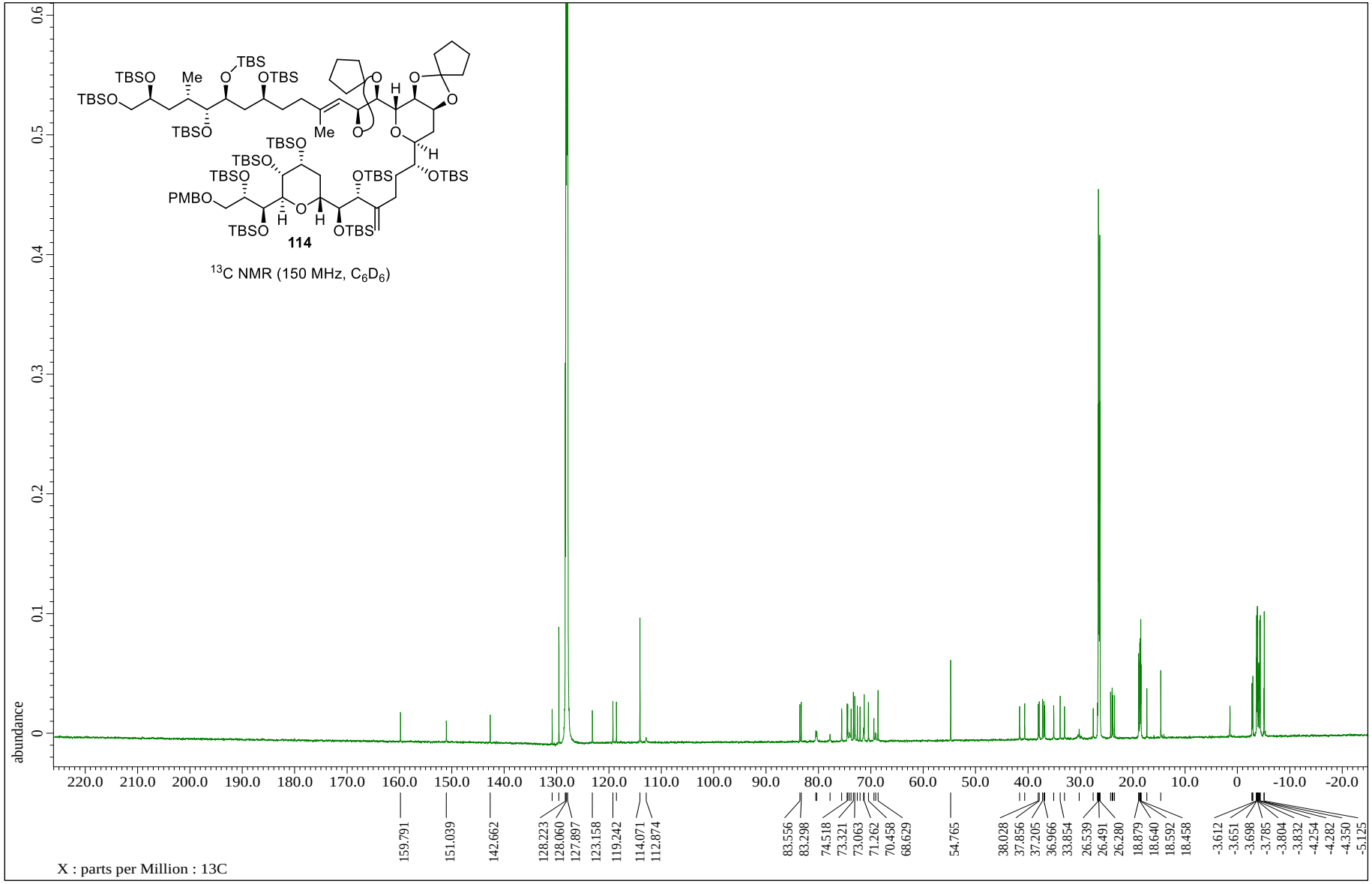
S7

^{13}C NMR (150 MHz, $CDCl_3$)

TBS
TBSO
Me
O
OTBS
TBSO
OTBS
98
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.260
5.838
5.826
5.820
5.809
5.798
5.792
5.780
5.197
5.169
5.084
5.066
4.256
4.251
4.245
4.239
4.234
3.650
3.527
3.523
3.517
3.325
3.315
3.309
3.298
1.836
1.829
1.820
1.814
1.667
1.650
1.646
1.408
1.388
1.313
0.910
0.887
0.885
0.867
0.116
0.073
0.057
0.043
0.036
0.028
1.00
1.01
0.97
1.01
1.98
1.90
0.98
1.98
0.97
0.99
1.04
45.31
3.47
30.57

TBS
TBSO
Me
O
OTBS
TBSO
OTBS
98
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
141.158
114.865
82.579
77.371
77.160
76.949
73.665
71.817
70.908
68.332
42.337
39.981
33.422
26.280
26.241
26.136
26.088
26.040
18.572
18.486
18.457
18.246
14.148
-2.981
-3.249
-3.919
-4.302
-4.340
-4.532
-4.580
-4.637
-5.193
-5.212

TBSO
Me
TBS
O
OTBS
TBSO
TBSO
Me
O
O
H
O
O
TBSO
TBSO
TBSO
H
OTBS
OTBS
PMBO
O
H
TBSO
H
OTBS
114
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H


TBSO
Me
TBS
O
OTBS
TBSO
TBSO
Me
O
O
H
O
O
O
TBSO
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
114
13C NMR (150 MHz, C6D6)
abundance
0.6
0.5
0.4
0.3
0.2
0.1
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
159.791
151.039
142.662
128.223
128.060
127.897
123.158
119.242
114.071
112.874
83.556
83.298
74.518
73.321
73.063
71.262
70.458
68.629
54.765
38.028
37.856
37.205
36.966
33.854
26.539
26.491
26.280
18.879
18.640
18.592
18.458
-3.612
-3.651
-3.698
-3.785
-3.804
-3.832
-4.254
-4.282
-4.350
-5.125
X : parts per Million : 13C

abundance
0.1
0.92
0.95
2.07
3.10
0.88
2.00
5.02
0.92
1.01
3.08
0.97
1.10
72.0
73.0
74.0
75.0
76.0
Y : parts per Million : 13C
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
X : parts per Million : 1H
0
10.0
20.0
(thousandths)
TBSO
Me
O
TBS
OTBS
H
PMBO
114
HSQC (600 MHz, C6D6)

S8
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

S8
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
150.819
142.805
128.223
128.060
127.897
123.081
119.280
112.271
83.537
83.298
72.565
71.981
71.282
70.449
68.639
63.526
26.730
26.587
26.539
26.453
26.395
26.347
26.280
26.242
23.944
23.494
18.659
18.630
18.515
18.486
18.458
-2.856
-3.584
-3.641
-3.775
-3.842
-3.995
-4.091
-4.196
-4.340
-5.125

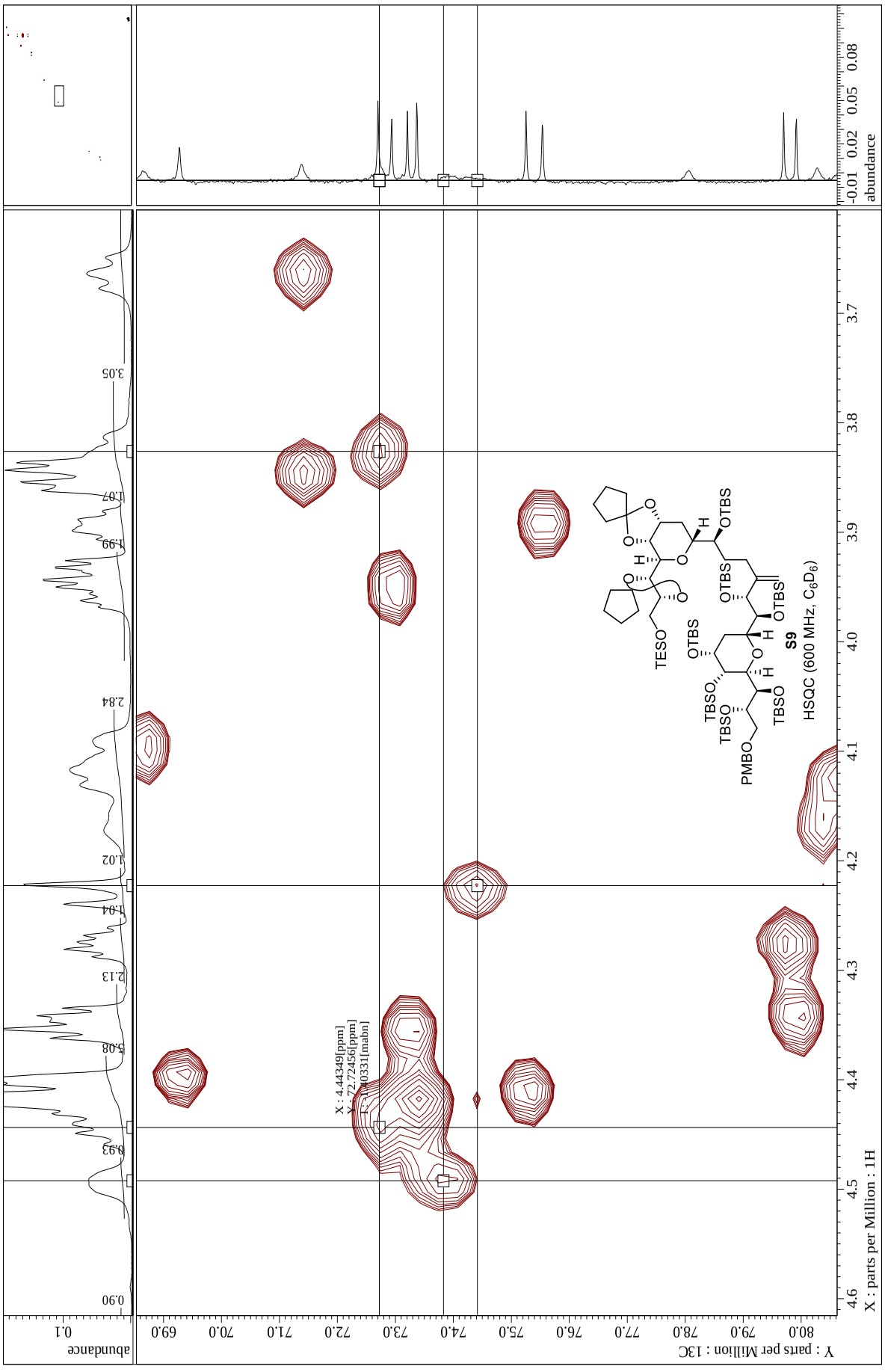
HSQC (600 MHz, C_6D_6)

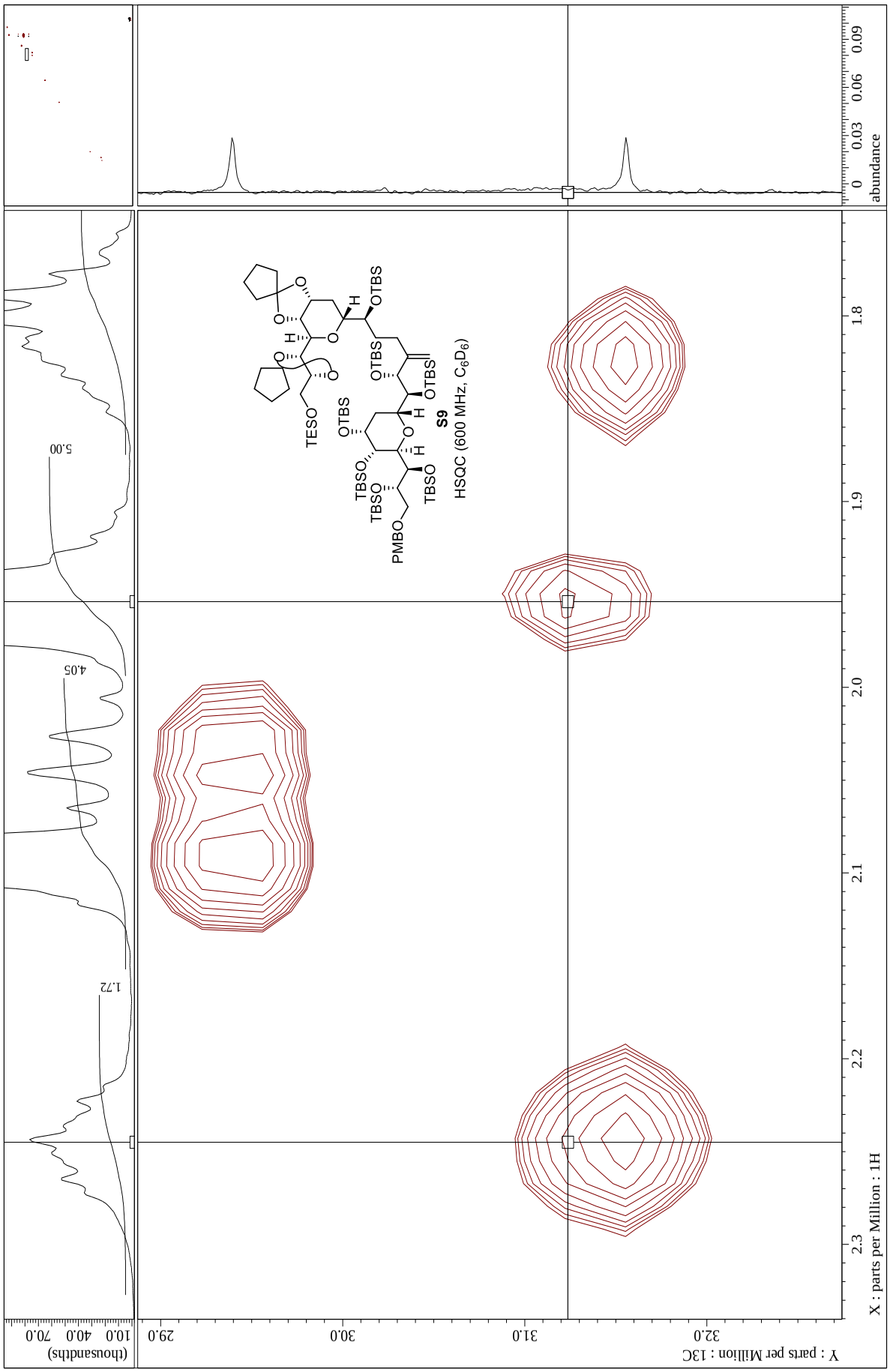
C20-C67 analog (95)
1H NMR (600 MHz, CD3OD/C5D5N = 2:1)
abundance
X : parts per Million : 1H

C20-C67 analog (95)
13C NMR (150 MHz, CD3OD/C5D5N = 2:1)
abundance
X : parts per Million : 13C
151.938
149.909
149.727
149.545
138.428
137.595
137.423
137.260
124.909
124.746
124.583
115.497
112.758
79.438
75.800
74.105
72.784
71.750
71.070
70.591
68.714
68.264
67.814
67.422
67.326
49.144
49.000
48.856
48.713
39.234
36.850
36.668
33.498
33.422
33.317
31.449
17.375
13.344

TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
S9
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H
7.313
7.300
7.160
6.874
6.859
5.338
5.176
4.686
4.419
4.413
4.399
4.354
3.843
3.837
3.664
3.332
2.707
2.687
2.666
2.492
2.244
2.094
1.964
1.952
1.618
1.616
1.122
1.079
1.064
0.702
0.688
0.344
0.282
0.278
0.271
0.268
0.244
0.233

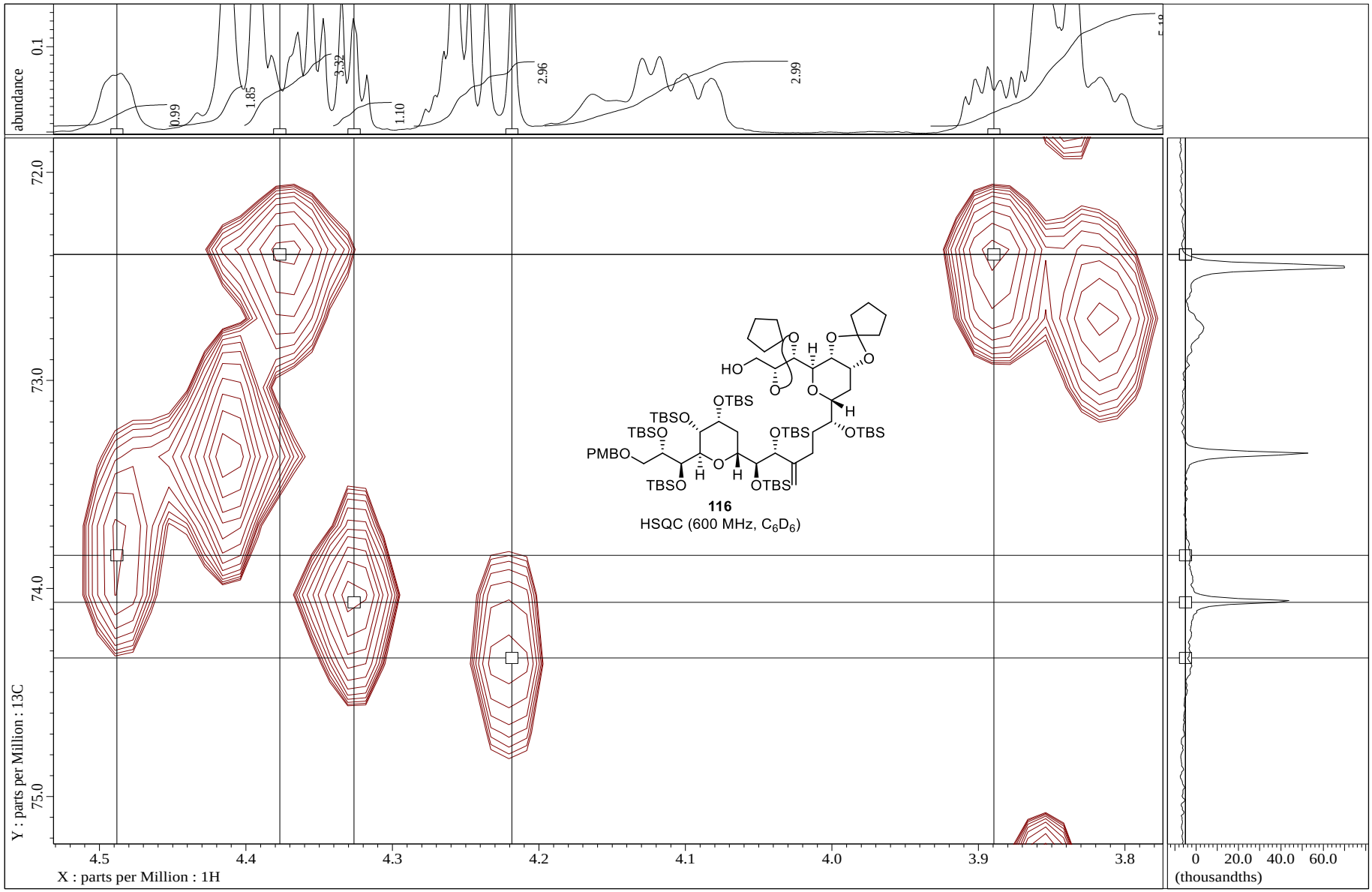
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
S9
13C NMR (150 MHz, C6D6)
abundance
0
0.1
0.2
0.3
0.4
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
159.752
151.049
128.347
128.213
128.060
127.974
127.897
119.950
118.581
114.043
112.357
79.918
79.698
75.542
75.255
73.369
73.206
72.938
72.699
69.280
64.053
54.746
37.914
37.856
37.693
26.625
26.606
26.405
26.376
18.659
18.640
7.179
4.957
-2.712
-3.660
-3.813
-3.852
-3.957
-3.976
-4.206
-4.311
X : parts per Million : 13C


X : parts per Million : 1H
Y : parts per Million : 13C
abundance
HSQC (600 MHz, C6D6)
S9
PMBO
TBSO
TBSO
TBSO
OTBS
TESO
OTBS
OTBS
OTBS
OTBS
X : 4.44349[ppm]
Y : 72.72456[ppm]
Z : 1.40331[mabn]


HSQC (600 MHz, C6D6)
S9
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
OTBS
Y : parts per Million : 13C
X : parts per Million : 1H
abundance
(thousandths)
5.00
4.05
1.72

116
1H NMR (600 MHZ, C6D6)
abundance
X : parts per Million : 1H

116
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.752
150.934
129.563
128.347
128.213
128.060
127.897
119.864
118.772
114.043
112.377
80.416
80.358
78.329
75.782
75.495
74.058
73.350
72.450
71.377
69.290
63.038
54.756
37.952
37.779
37.483
26.596
26.500
26.338
26.309
18.659
18.630
18.477
18.458
-2.722
-3.679
-3.708
-3.813
-3.842
-3.861
-4.014
-4.139
-4.215
-4.330



116

HSQC (600 MHz, C_6D_6)

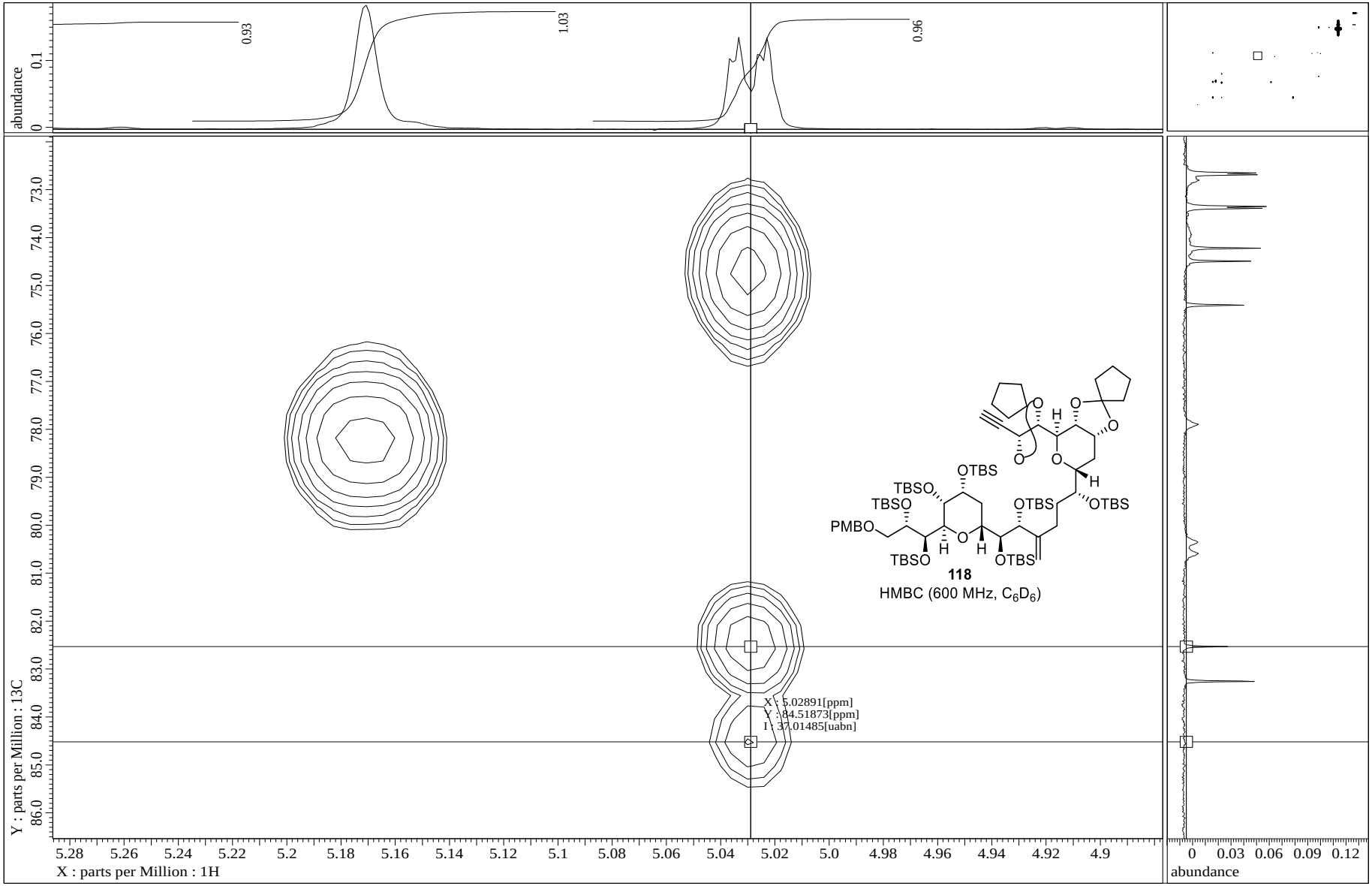
116

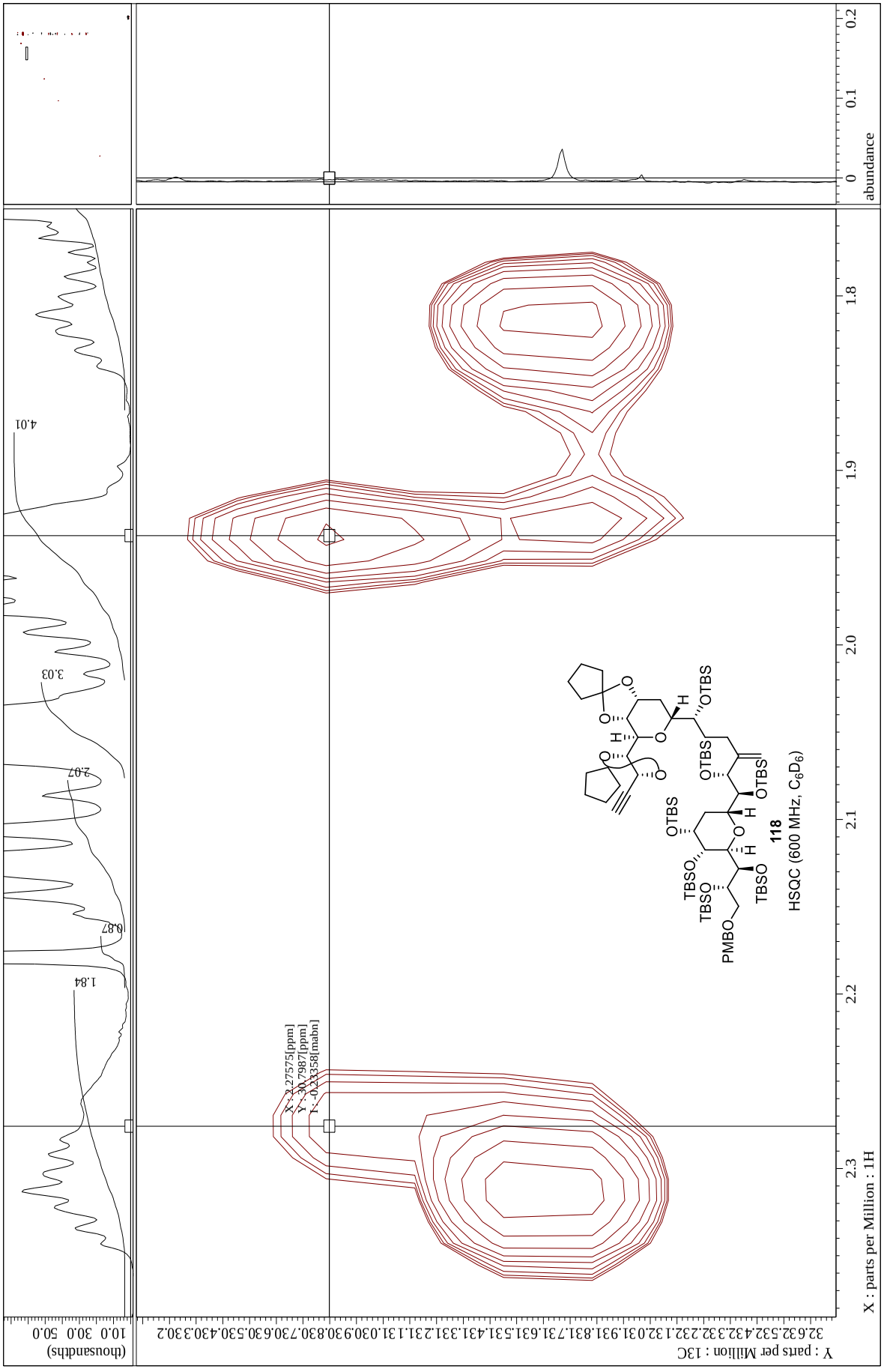
HSQC (600 MHz, C_6D_6)

118
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H

118
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.762
150.982
129.563
128.347
128.213
128.060
127.897
121.300
118.993
114.052
112.415
83.260
82.532
75.408
74.489
74.221
73.388
73.350
72.689
72.651
69.309
67.777
54.756
37.712
37.234
37.186
26.596
26.500
26.376
26.347
18.898
18.659
18.640
18.486
-3.651
-3.718
-3.794
-3.823
-3.861
-3.890
-4.005
-4.129
-4.225
-4.321

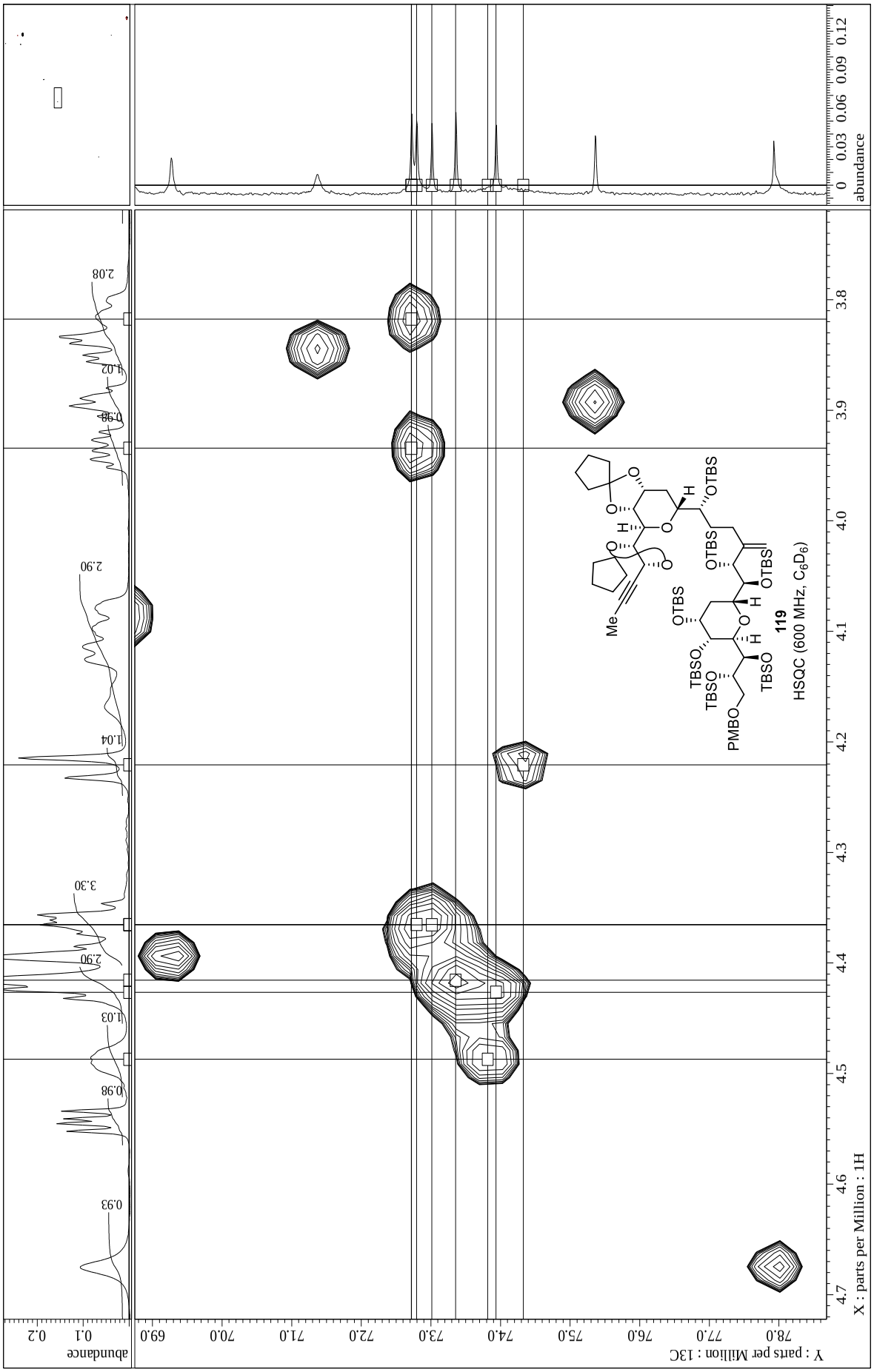
abundance
0.1
0.2
0.3
1.00
1.02
6.15
1.14
2.86
0.97
3.01
70.0
71.0
72.0
73.0
74.0
75.0
76.0
Y : parts per Million : 13C
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
X : parts per Million : 1H
0
20.0
40.0
(thousandths)
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
118
HSQC (600 MHz, C6D6)

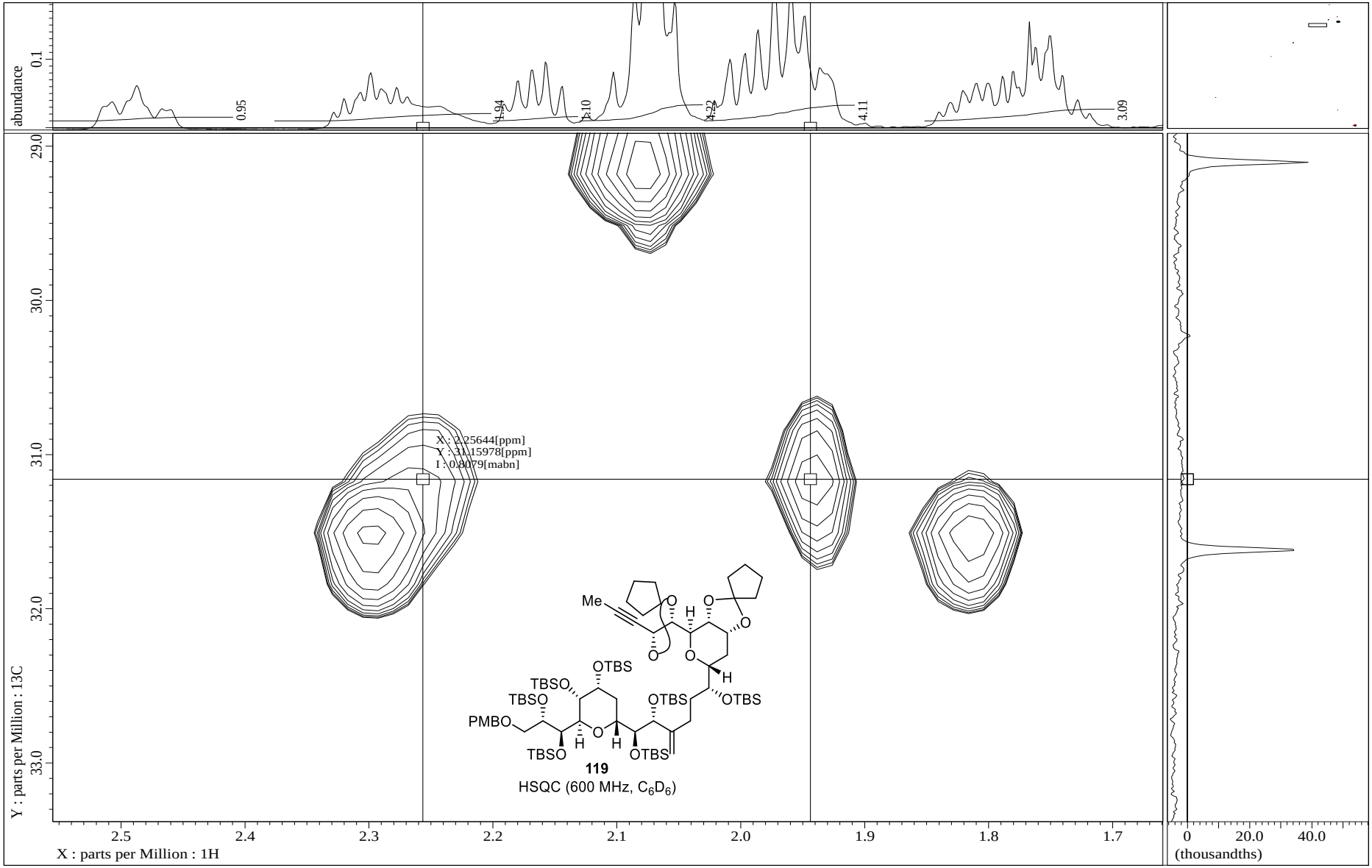

abundance
0.93
1.03
0.96
Y : parts per Million : 13C
X : parts per Million : 1H
X : 5.02891[ppm]
Y : 84.51873[ppm]
I : 37.01485[uabn]
118
HMBC (600 MHz, C6D6)
abundance

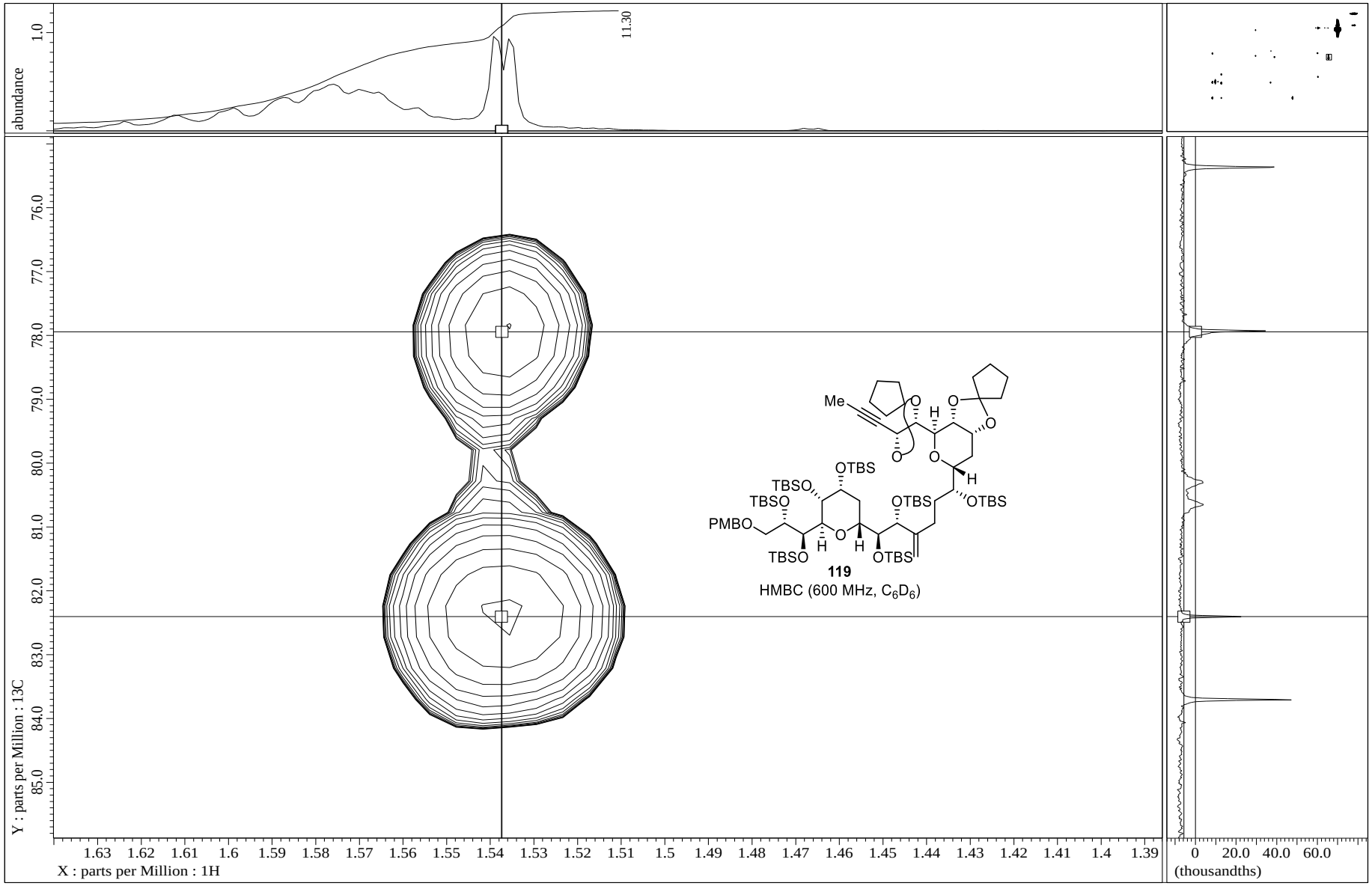

X : parts per Million : 1H
Y : parts per Million : 13C
(thousandths)
abundance
HSQC (600 MHz, C6D6)
118
PMBO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
OTBS
X: 2.27575[ppm]
Y: 30.7987[ppm]
I: -0.233358[mabn]
4.01
3.03
2.07
0.87
1.84

Me
O
H
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
119
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H

Me
O
H
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
119
13C NMR (150 MHz, C6D6)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
159.752
151.039
129.563
128.347
128.213
128.060
127.897
120.726
118.839
114.043
112.348
83.710
82.407
77.926
75.360
73.943
73.359
73.015
72.794
72.727
69.271
68.285
54.746
37.751
37.406
37.329
26.606
26.366
26.347
26.309
18.917
18.630
18.467
3.531
-2.722
-3.679
-3.718
-3.813
-3.852
-3.947
-3.986
-4.148
X : parts per Million : 13C

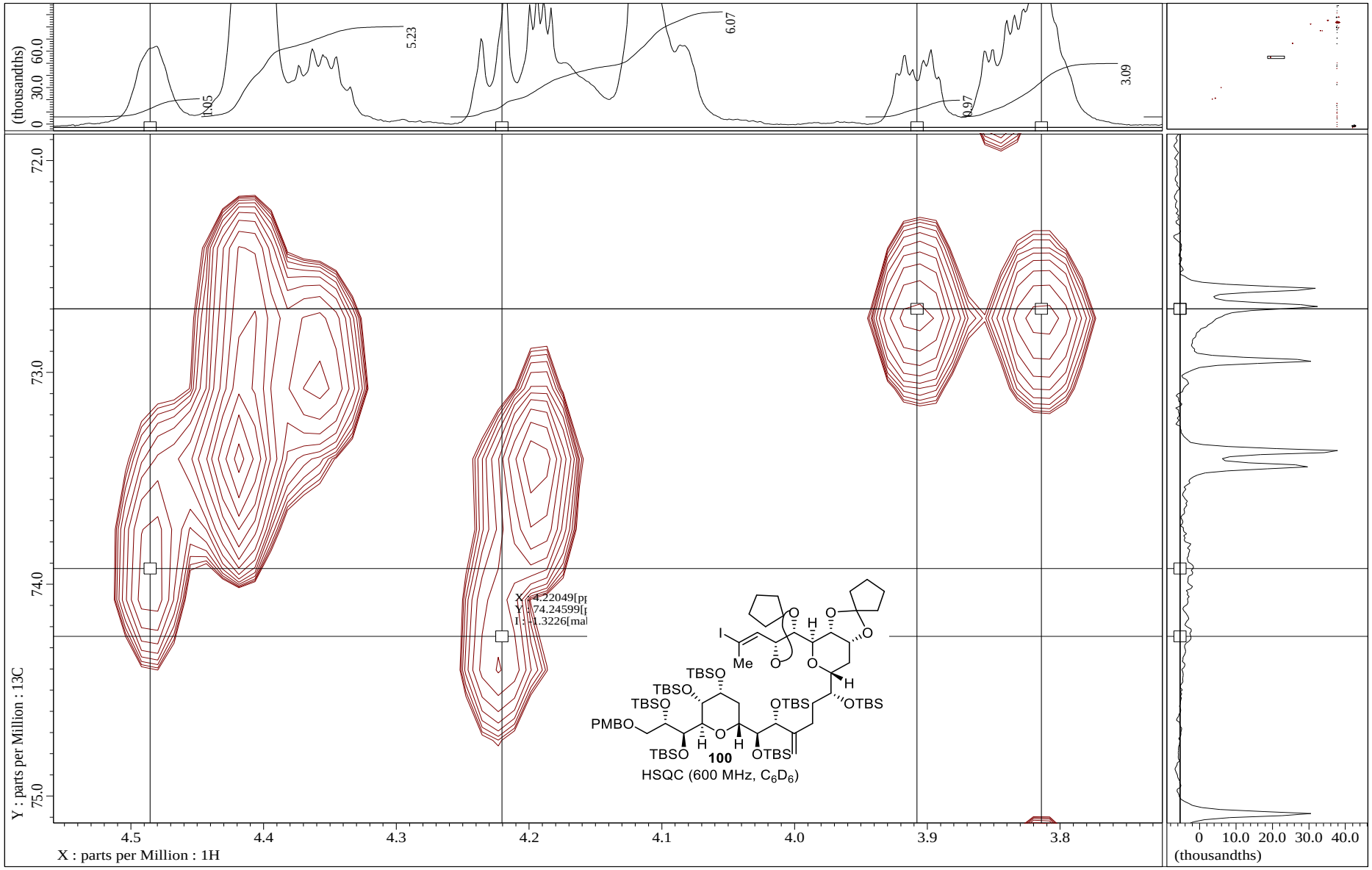

HSQC (600 MHz, C6D6)
119
X : parts per Million : 1H
Y : parts per Million : 13C
abundance

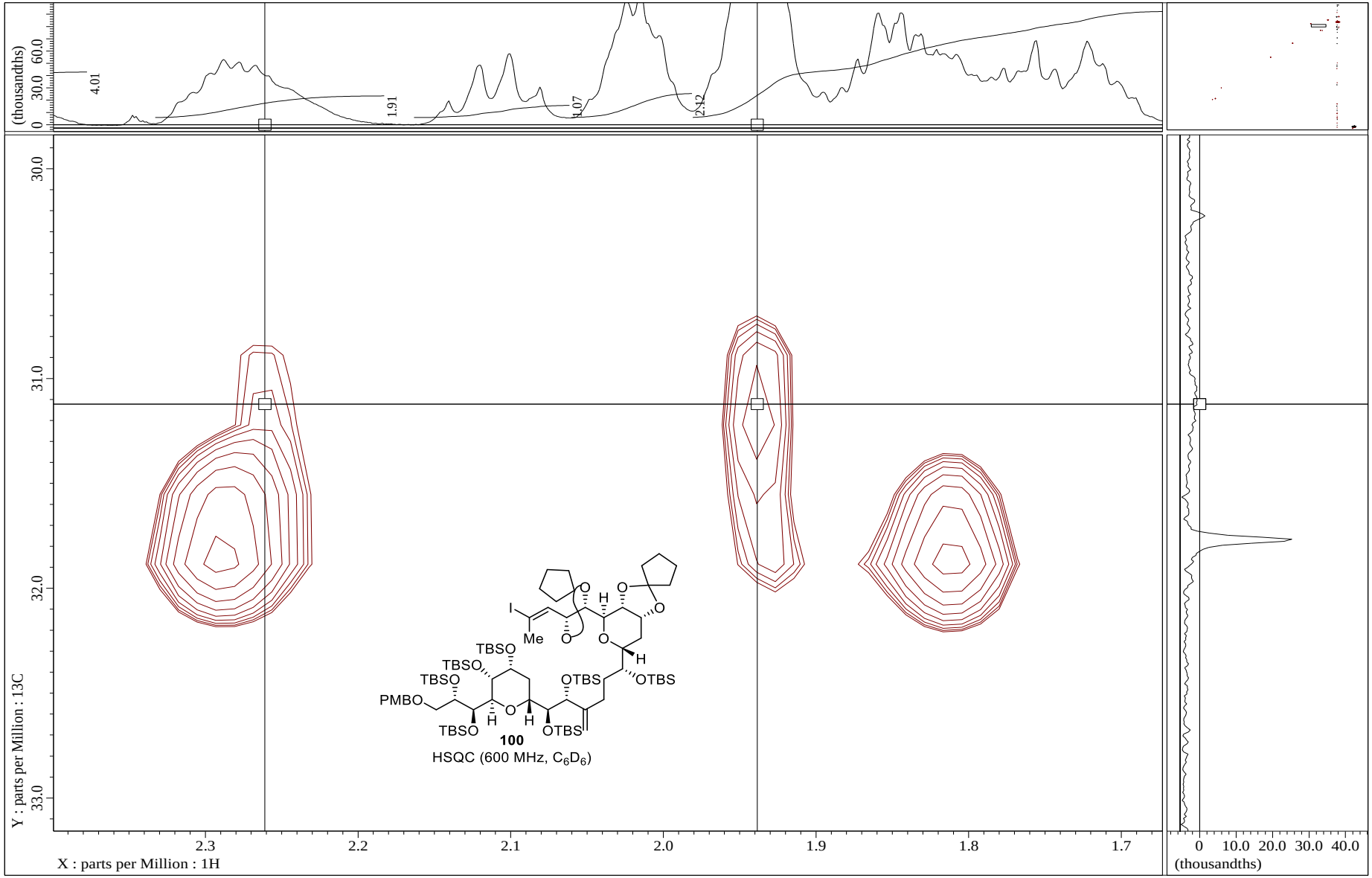

abundance
0.1
0.95
1.94
3.10
4.22
4.11
3.09
29.0
30.0
31.0
32.0
33.0
Y : parts per Million : 13C
X : 2.25644[ppm]
Y : 31.15978[ppm]
I : 0.8079[mabn]
Me
O
H
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
119
HSQC (600 MHz, C6D6)
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
X : parts per Million : 1H
0
20.0
40.0
(thousandths)


abundance
1.0
11.30
76.0
77.0
78.0
79.0
80.0
81.0
82.0
83.0
84.0
85.0
Y : parts per Million : 13C
1.63 1.62 1.61 1.6 1.59 1.58 1.57 1.56 1.55 1.54 1.53 1.52 1.51 1.5 1.49 1.48 1.47 1.46 1.45 1.44 1.43 1.42 1.41 1.4 1.39
X : parts per Million : 1H
0 20.0 40.0 60.0
(thousandths)
Me
O
H
O
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
119
HMBC (600 MHz, C6D6)

100
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

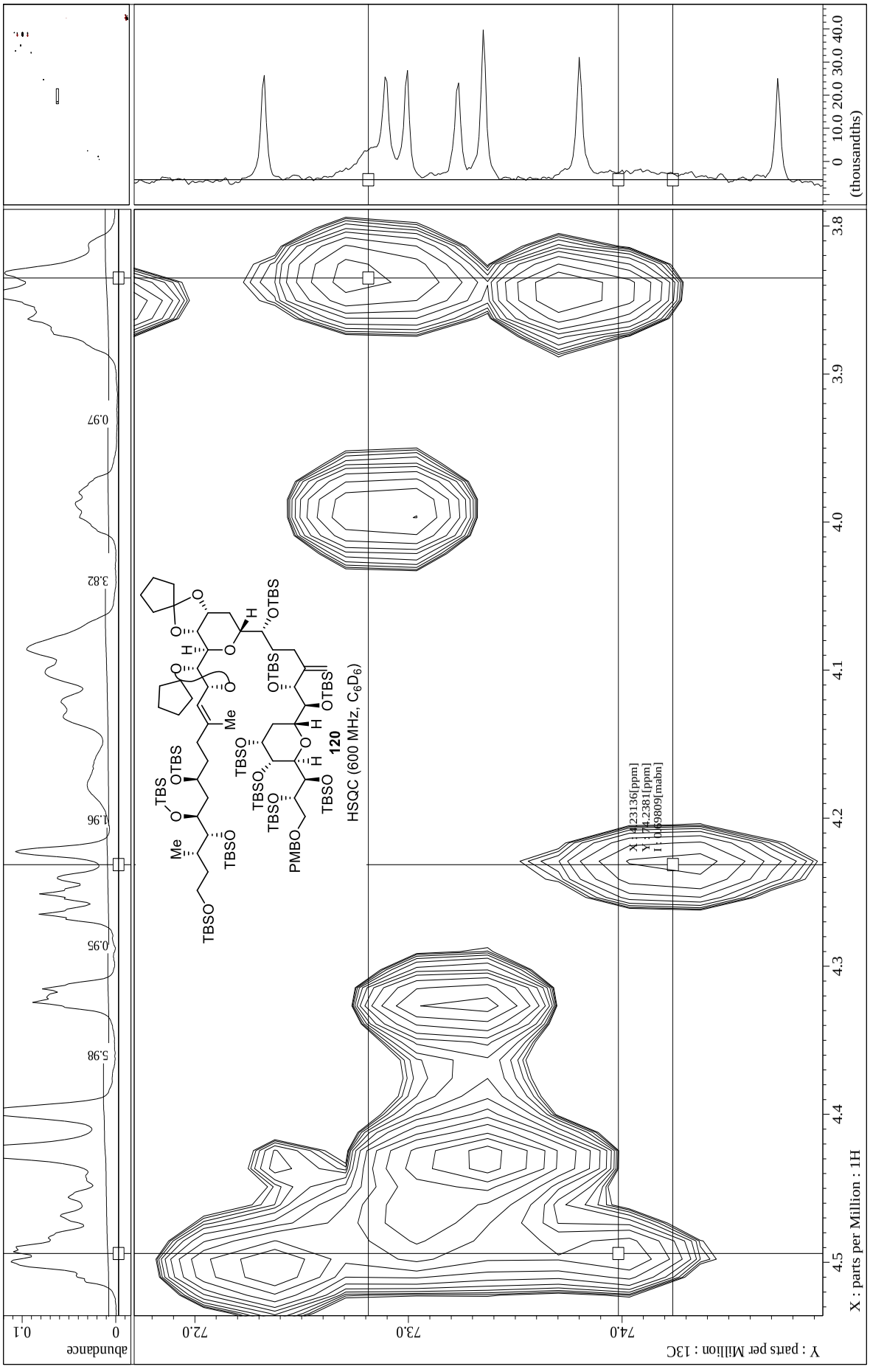
100
^{13}C NMR (150 MHz, C_6D_6)
abundance
X : parts per Million : 13C
159.762
150.934
139.157
128.223
128.060
127.897
119.883
118.859
114.043
112.415
101.289
81.957
75.504
75.083
73.446
73.369
72.948
72.689
72.603
69.271
54.756
37.856
37.674
37.425
26.596
26.500
26.366
26.318
18.668
18.630
18.505
18.486
-2.712
-3.430
-3.689
-3.804
-3.986
-4.053
-4.206
-4.302
-5.077

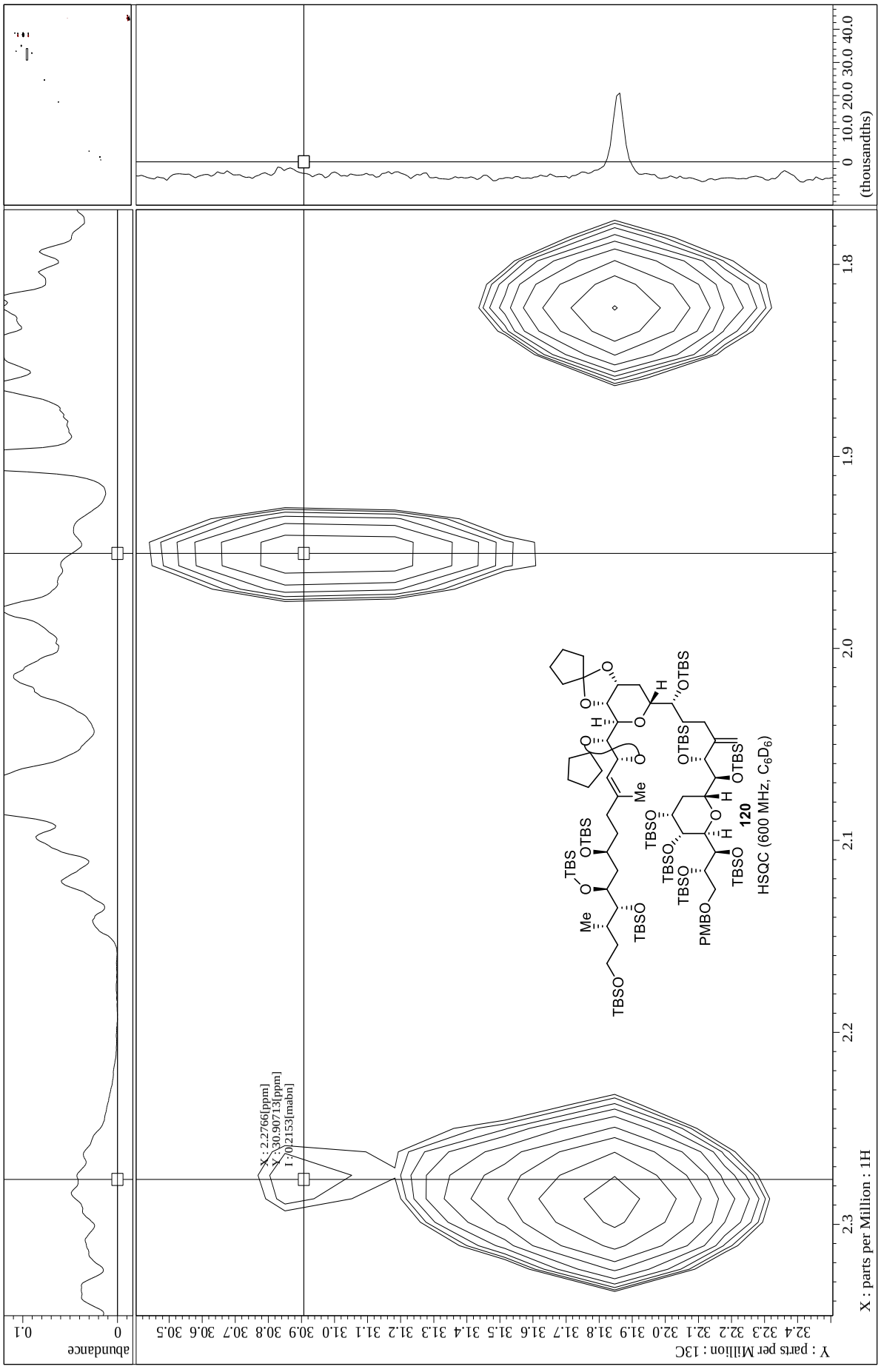

(thousandths)
0
30.0
60.0
5.23
6.07
0.97
3.09
72.0
73.0
74.0
75.0
Y : parts per Million : 13C
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
X : parts per Million : 1H
0
10.0
20.0
30.0
40.0
(thousandths)
TBSO
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
Me
I
100
HSQC (600 MHz, C6D6)

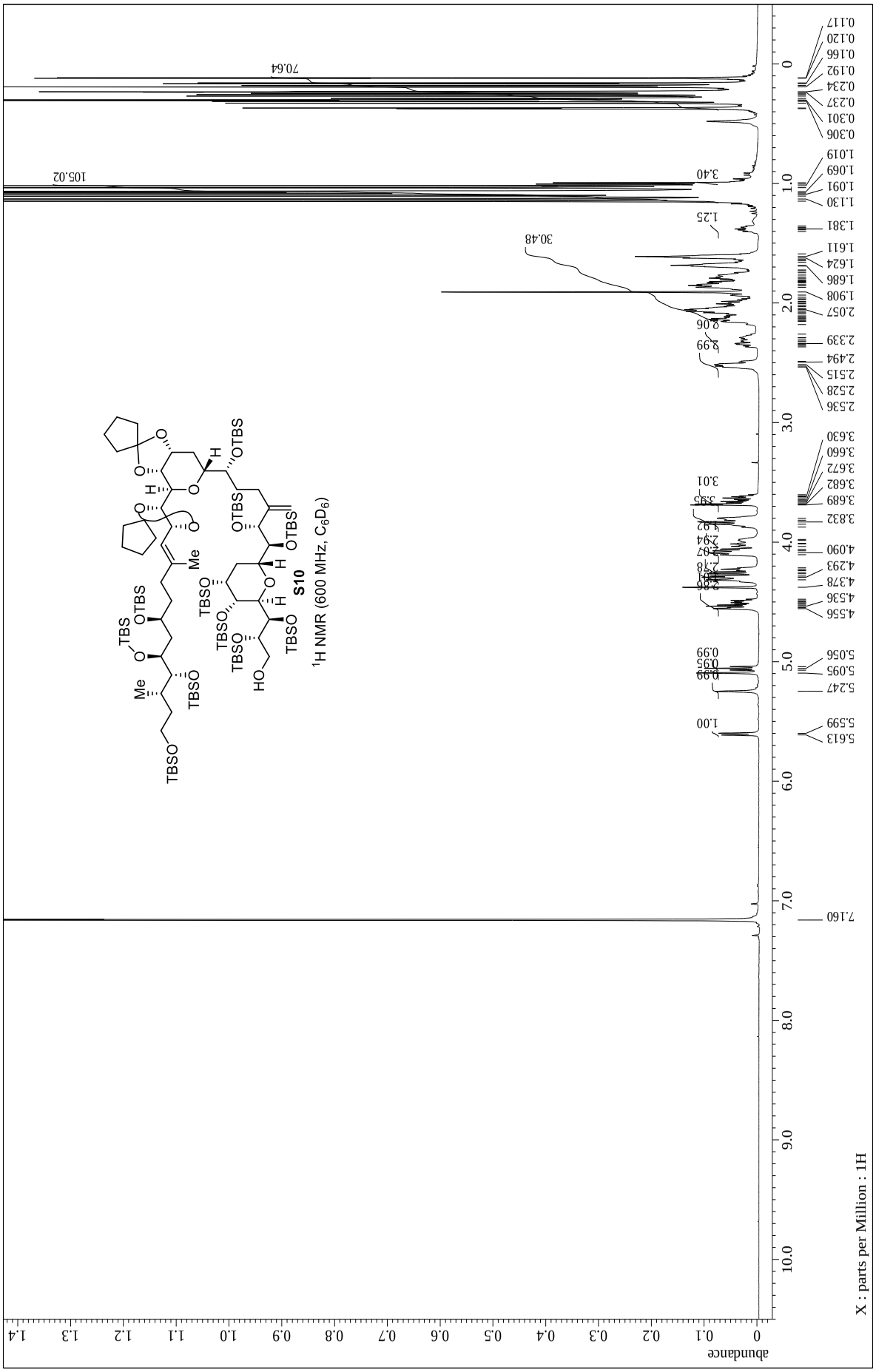

(thousandths)
0 30.0 60.0
4.01
1.91
3.07
2.32
30.0
31.0
32.0
33.0
Y : parts per Million : 13C
2.3
2.2
2.1
2.0
1.9
1.8
1.7
X : parts per Million : 1H
0 10.0 20.0 30.0 40.0
(thousandths)
I
Me
O
H
TBSO
PMBO
OTBS
100
HSQC (600 MHz, C6D6)

TBS
Me
O
OTBS
TBSO
TBSO
Me
O
O
O
H
O
O
TBSO
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
120
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H
7.317
7.302
7.160
6.873
6.861
5.630
5.615
5.336
5.143
5.024
4.681
4.500
4.493
4.425
4.399
3.847
3.687
3.679
3.335
2.665
2.644
2.624
2.509
2.283
1.902
1.641
1.633
1.621
1.610
1.377
1.122
1.075
1.064
1.018
0.346
0.278
0.266
0.262
0.238
0.166
0.158
0.117

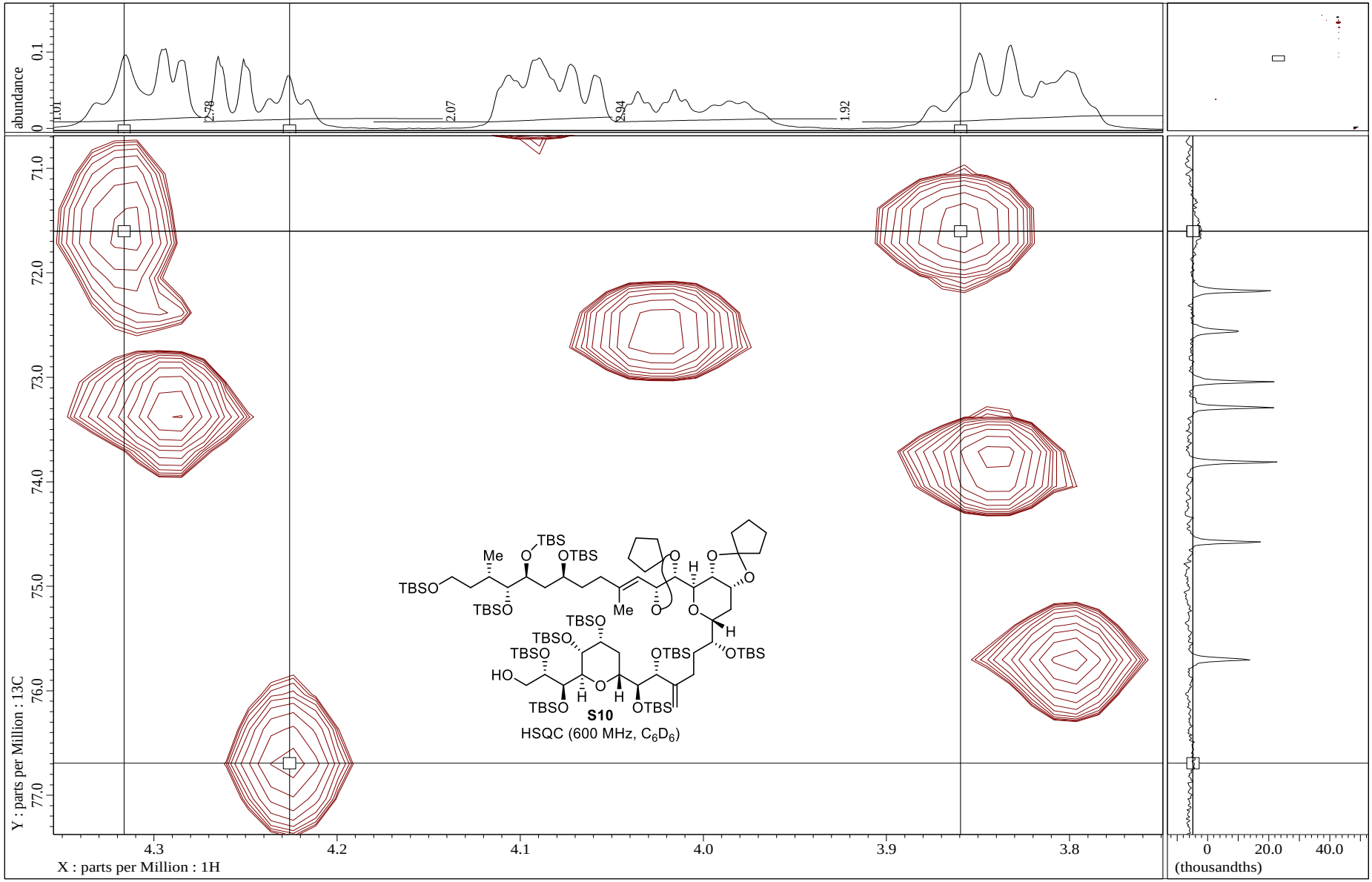
TBS
Me
O
OTBS
TBSO
TBSO
Me
O
O
H
O
O
TBSO
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
OTBS
120
13C NMR (150 MHz, C6D6)
abundance
0
0.1
0.2
0.3
0.4
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
159.752
151.068
142.863
128.213
128.060
127.897
123.330
119.337
114.043
112.424
83.518
82.139
74.729
73.800
73.350
73.235
72.995
72.900
72.325
70.238
61.429
54.756
41.935
26.615
26.472
26.443
26.424
26.318
26.299
18.783
18.668
18.640
18.419
-2.865
-3.086
-3.526
-3.670
-3.804
-3.852
-4.034
-4.215
-4.991
-5.058
X : parts per Million : 13C

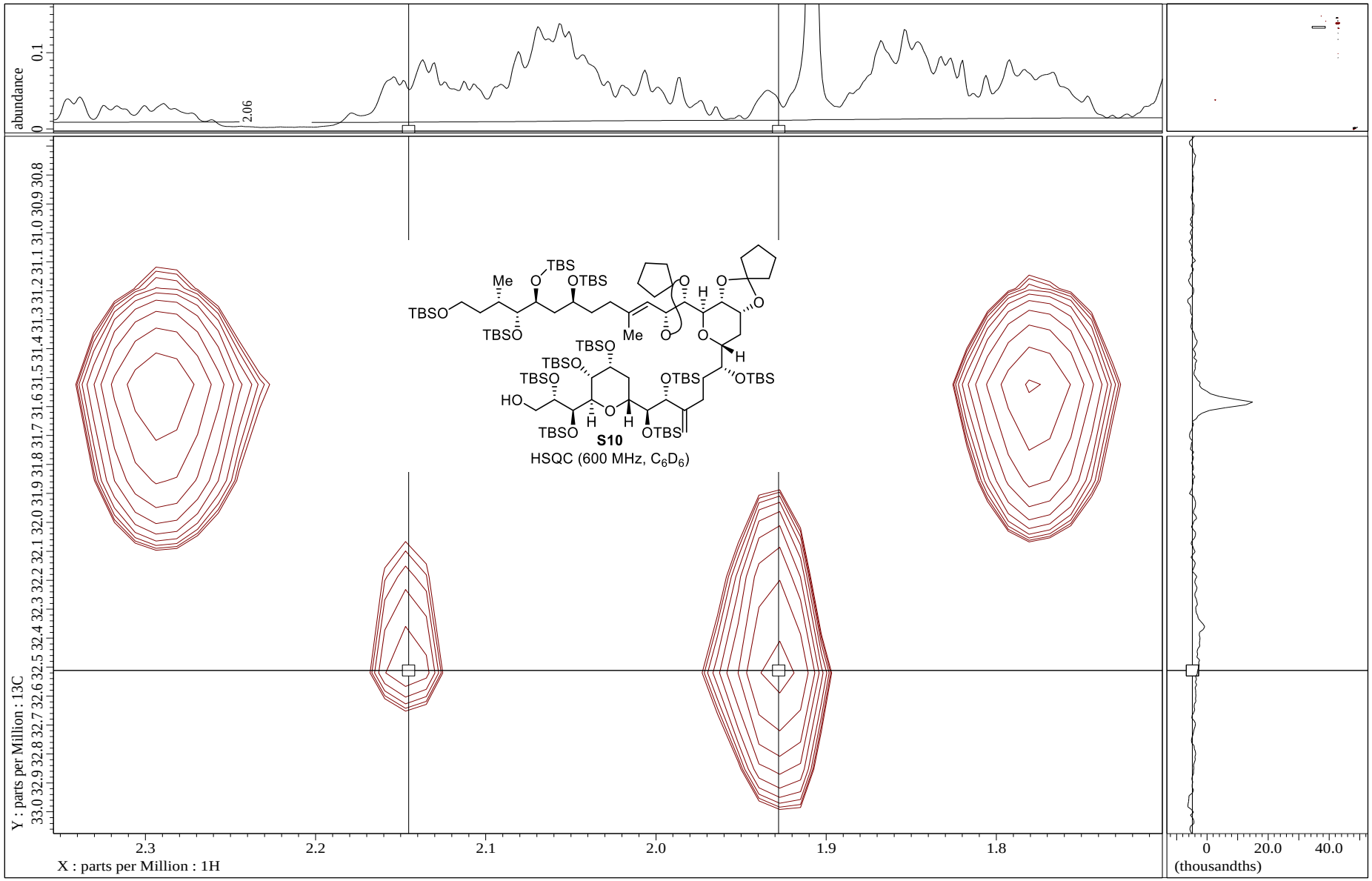

HSQC (600 MHz, C6D6)
120
X : parts per Million : 1H
Y : parts per Million : 13C
abundance
(thousandths)
X 1 4.23136[ppm]
Y 1 74.2381[ppm]
I 1 0.69809[mabn]


X : parts per Million : 1H
Y : parts per Million : 13C
abundance
X : 2.2766[ppm]
Y : 30.90713[ppm]
I : 70.21531[mabn]
HSQC (600 MHz, C6D6)
120
(thousandths)


S10
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

S10
^{13}C NMR (150 MHz, C_6D_6)
abundance
X : parts per Million : 13C
150.858
143.159
128.223
128.060
127.897
123.052
118.725
111.697
83.317
82.139
75.705
74.575
73.809
73.292
73.043
72.172
70.248
69.300
63.526
61.429
41.954
26.529
26.510
26.472
26.443
26.338
26.309
18.687
18.640
18.467
18.419
-2.865
-3.086
-3.517
-3.823
-3.919
-4.024
-4.225
-4.436
-4.991
-5.058

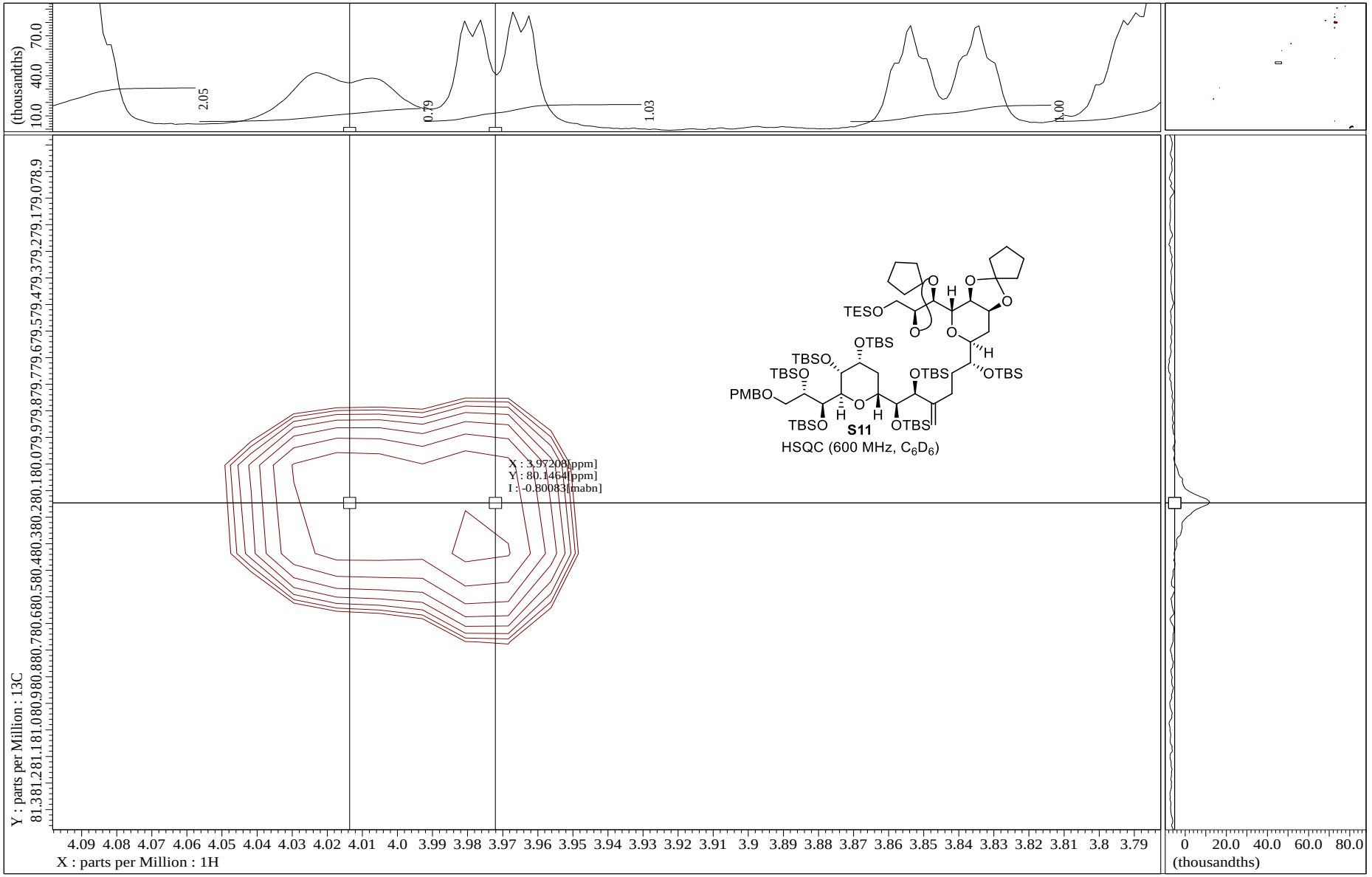

abundance
0
0.1
1.01
2.78
2.07
2.94
1.92
71.0
72.0
73.0
74.0
75.0
76.0
77.0
Y : parts per Million : 13C
4.3
4.2
4.1
4.0
3.9
3.8
X : parts per Million : 1H
0
20.0
40.0
(thousandths)
TBS
Me
O
OTBS
TBSO
TBSO
Me
O
O
H
O
O
O
H
TBSO
TBSO
TBSO
OTBS
OTBS
HO
H
O
H
TBSO
OTBS
S10
HSQC (600 MHz, C6D6)

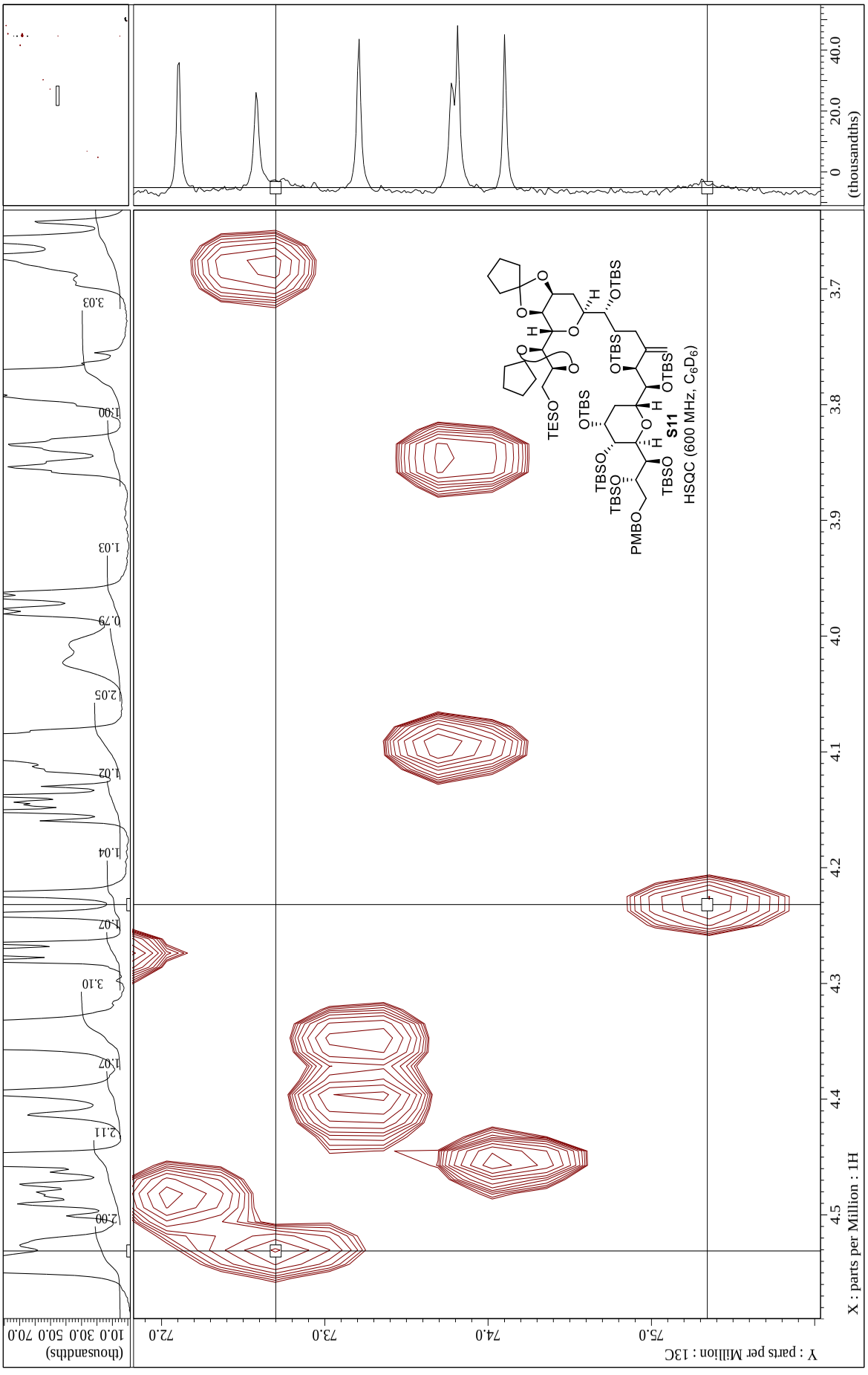

abundance
0.1
0
2.06
Y : parts per Million : 13C
33.0 32.9 32.8 32.7 32.6 32.5 32.4 32.3 32.2 32.1 32.0 31.9 31.8 31.7 31.6 31.5 31.4 31.3 31.2 31.1 31.0 30.9 30.8
2.3
2.2
2.1
2.0
1.9
1.8
X : parts per Million : 1H
0
20.0
40.0
(thousandths)
TBS
Me
O
OTBS
TBSO
TBSO
Me
O
O
H
O
O
O
TBSO
TBSO
TBSO
OTBS
OTBS
HO
O
H
H
TBSO
OTBS
S10
HSQC (600 MHz, C6D6)

proposed C21-C67 analog (96)
1H NMR (600 MHz, CD3OD/C5D5N = 2:1)
abundance
X : parts per Million : 1H

TESO
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
OTBS
OTBS
H
H
H
O
S11
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H
7.304
7.289
7.160
6.870
6.857
5.493
5.235
4.543
4.452
4.352
4.342
4.338
4.241
4.222
3.783
3.658
3.321
2.754
2.610
2.598
2.122
2.102
1.929
1.918
1.594
1.584
1.141
1.138
1.075
0.633
0.620
0.396
0.356
0.333
0.285
0.275
0.237
0.234
1.97
2.00
1.01
1.00
2.96
0.91
0.93
6.16
8.14
8.23
65.81
9.83
5.95
42.55

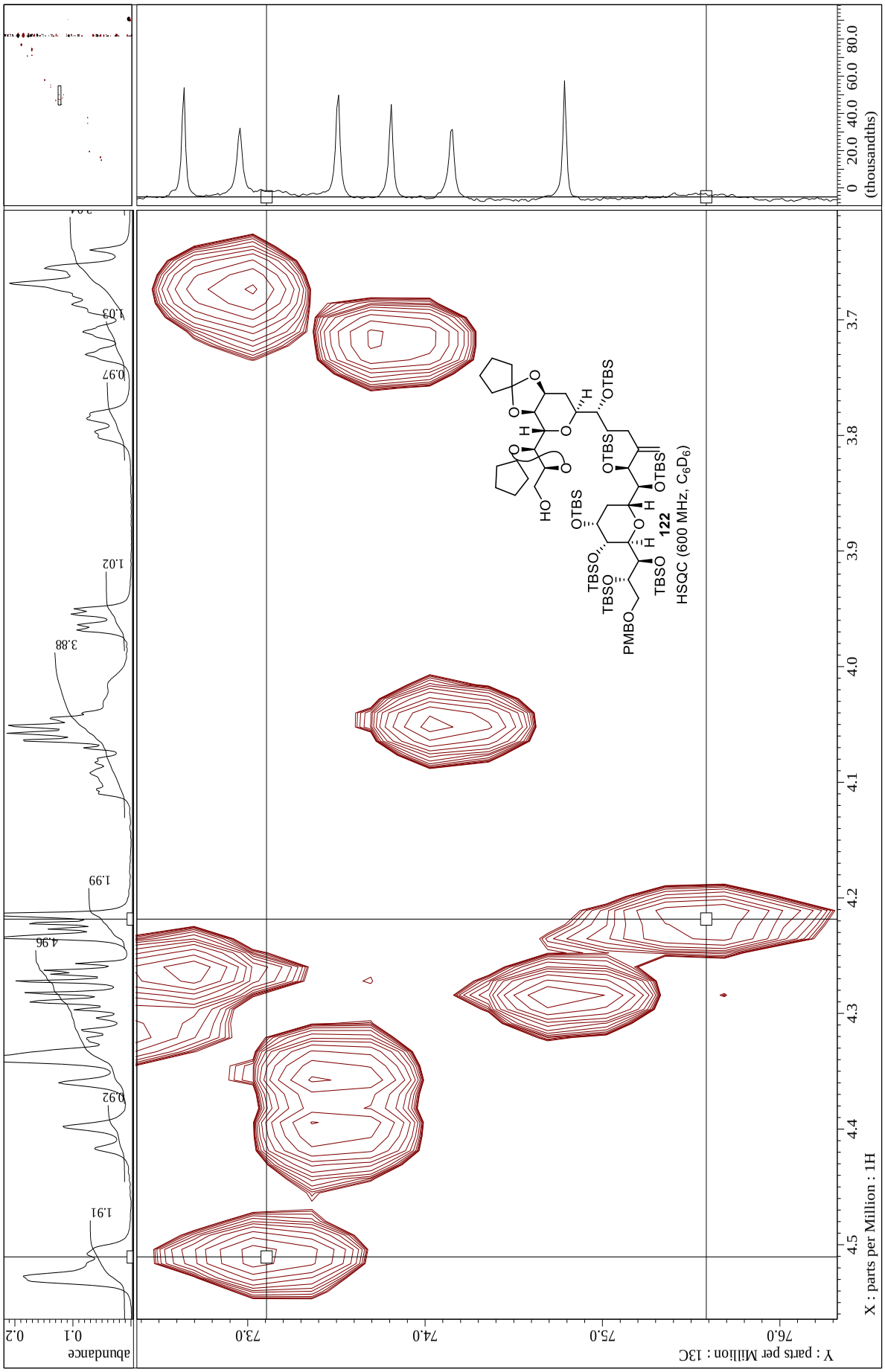
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
OTBS
S11
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.411
149.253
128.025
127.901
127.738
127.662
127.575
119.743
117.943
113.644
111.356
81.588
78.256
74.100
73.813
73.775
73.210
72.578
72.109
71.649
68.987
63.683
54.424
37.611
37.438
37.190
26.313
26.236
26.054
25.920
18.385
18.356
6.809
4.492
-2.814
-3.417
-3.963
-4.193
-4.317
-4.432
-4.470
-4.786


(thousandths)
10.0 40.0 70.0
2.05
0.79
1.03
1.00
Y : parts per Million : 13C
81.381.281.181.081.980.880.780.680.580.480.380.280.180.079.979.879.779.679.579.479.379.279.179.078.9
X : 3.97208[ppm]
Y : 80.1464[ppm]
I : -0.80083[mabn]
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
S11
HSQC (600 MHz, C6D6)
4.09 4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01 4.0 3.99 3.98 3.97 3.96 3.95 3.94 3.93 3.92 3.91 3.9 3.89 3.88 3.87 3.86 3.85 3.84 3.83 3.82 3.81 3.8 3.79
X : parts per Million : 1H
0 20.0 40.0 60.0 80.0
(thousandths)


Y : parts per Million : 13C
X : parts per Million : 1H
(thousandths)
(thousandths)
HSQC (600 MHz, C6D6)
S11
TESO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
OTBS
2.00
2.11
1.07
3.10
1.07
1.04
1.02
2.05
0.79
1.03
1.00
3.03

HO
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
TBSO
OTBS
122
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H

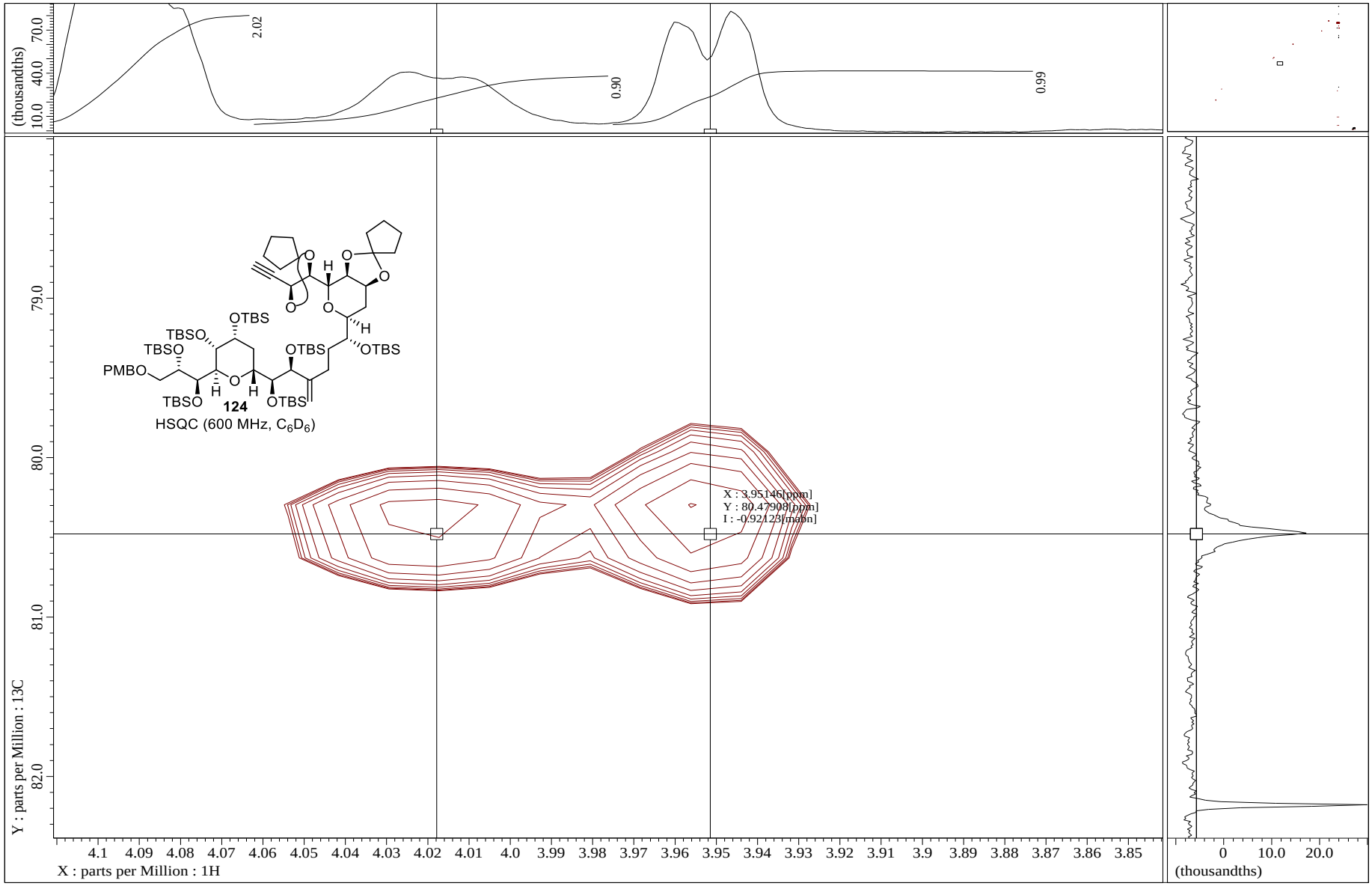
HO
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
122
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.743
149.651
130.952
129.688
128.213
128.060
127.897
119.787
118.466
113.976
111.505
79.861
78.396
74.786
74.154
73.809
73.513
72.957
72.641
71.981
69.338
62.712
54.765
37.904
37.799
37.655
26.596
26.558
26.376
26.338
18.754
18.687
18.649
18.429
-2.502
-3.248
-3.641
-3.718
-3.861
-3.899
-4.005
-4.110
-4.139
-4.512

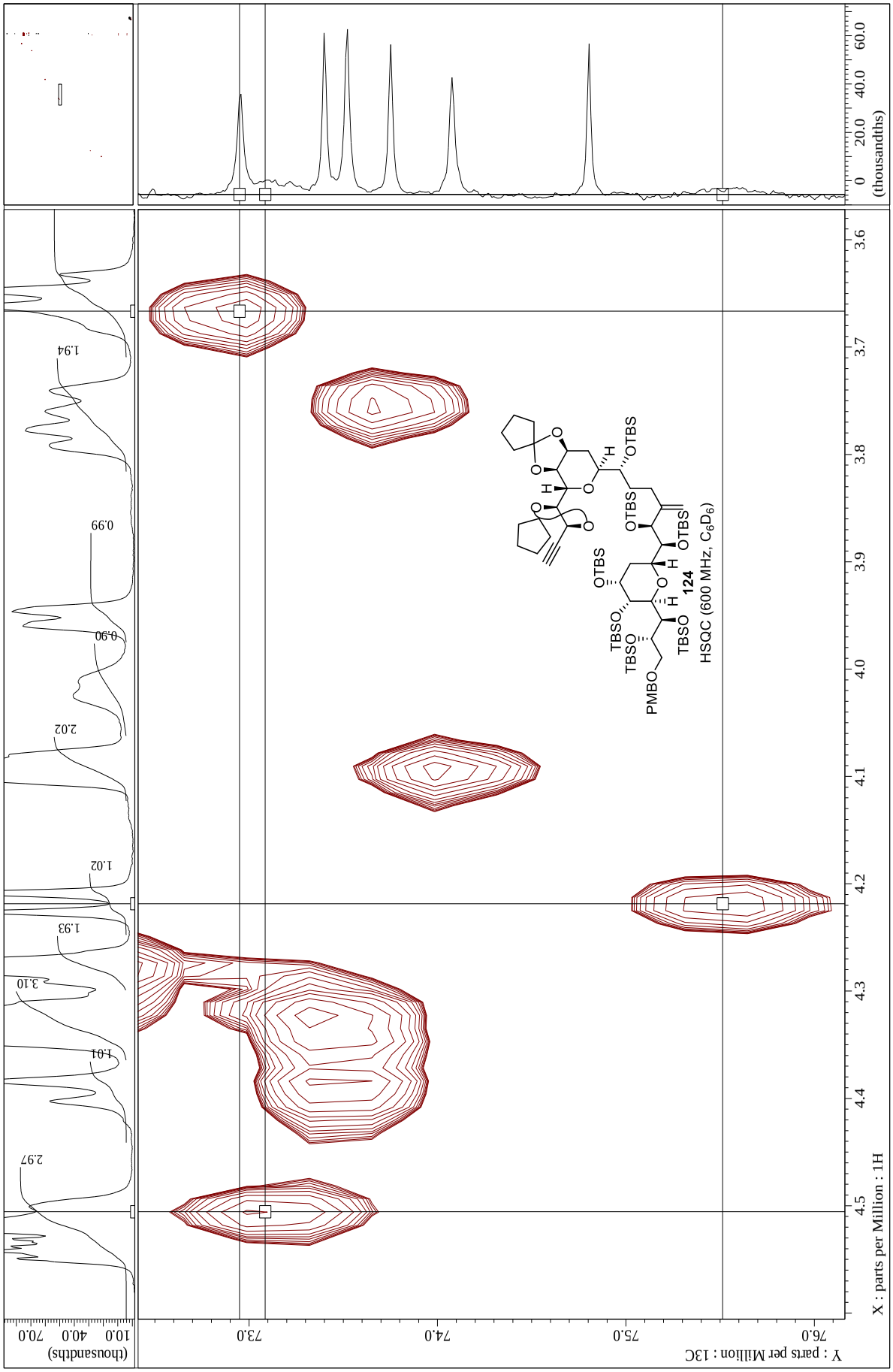

Y : parts per Million : 13C
X : parts per Million : 1H
abundance
(thousandths)
HSQC (600 MHz, C6D6)
122
PMBO
TBSO
TBSO
OTBS
HO
OTBS
OTBS
OTBS
OTBS
1.91
0.92
4.96
1.99
3.88
1.02
0.97
1.03

abundance
0.2
0.1
4.96
1.99
3.88
1.02
78.0
79.0
80.0
81.0
Y : parts per Million : 13C
4.26 4.24 4.22 4.2 4.18 4.16 4.14 4.12 4.1 4.08 4.06 4.04 4.02 4.0 3.98 3.96 3.94 3.92 3.9 3.88 3.86
X : parts per Million : 1H
0 20.0 40.0 60.0 80.0
(thousandths)
HO
O
H
O
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
H
O
H
TBSO
122
OTBS
HSQC (600 MHz, C6D6)

124
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

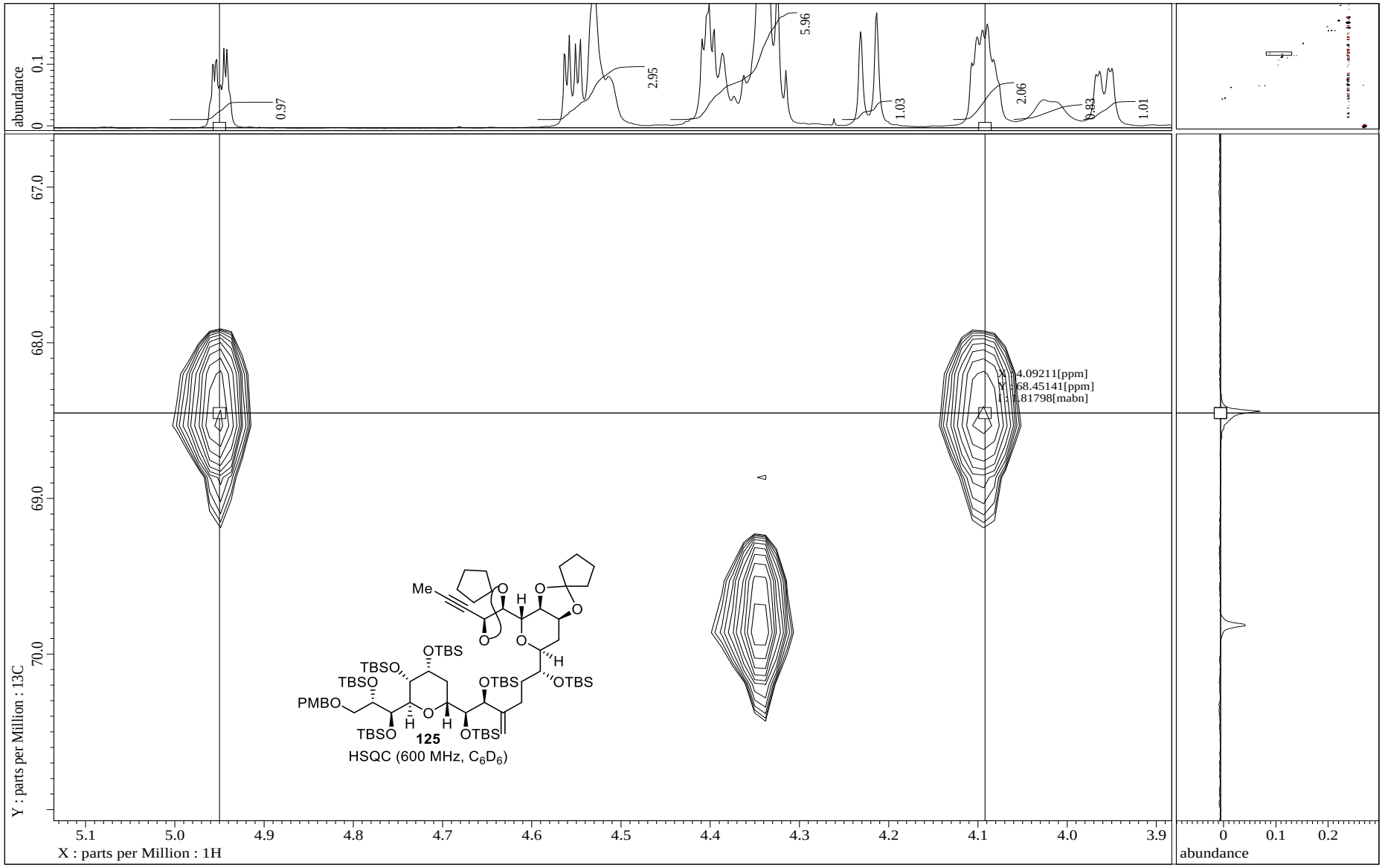
124
13C NMR (150 MHz, C6D6)
abundance
X : parts per Million : 13C
159.743
149.814
130.913
129.678
128.213
128.060
127.897
121.166
118.811
113.985
111.438
82.752
74.805
74.077
73.752
73.522
73.398
72.957
72.287
72.162
69.319
67.346
54.765
26.874
26.587
26.558
26.529
26.376
26.338
26.242
24.078
18.687
18.640
18.601
18.429
-2.502
-3.421
-3.469
-3.603
-3.861
-3.899
-4.014
-4.110
-4.493
-5.010

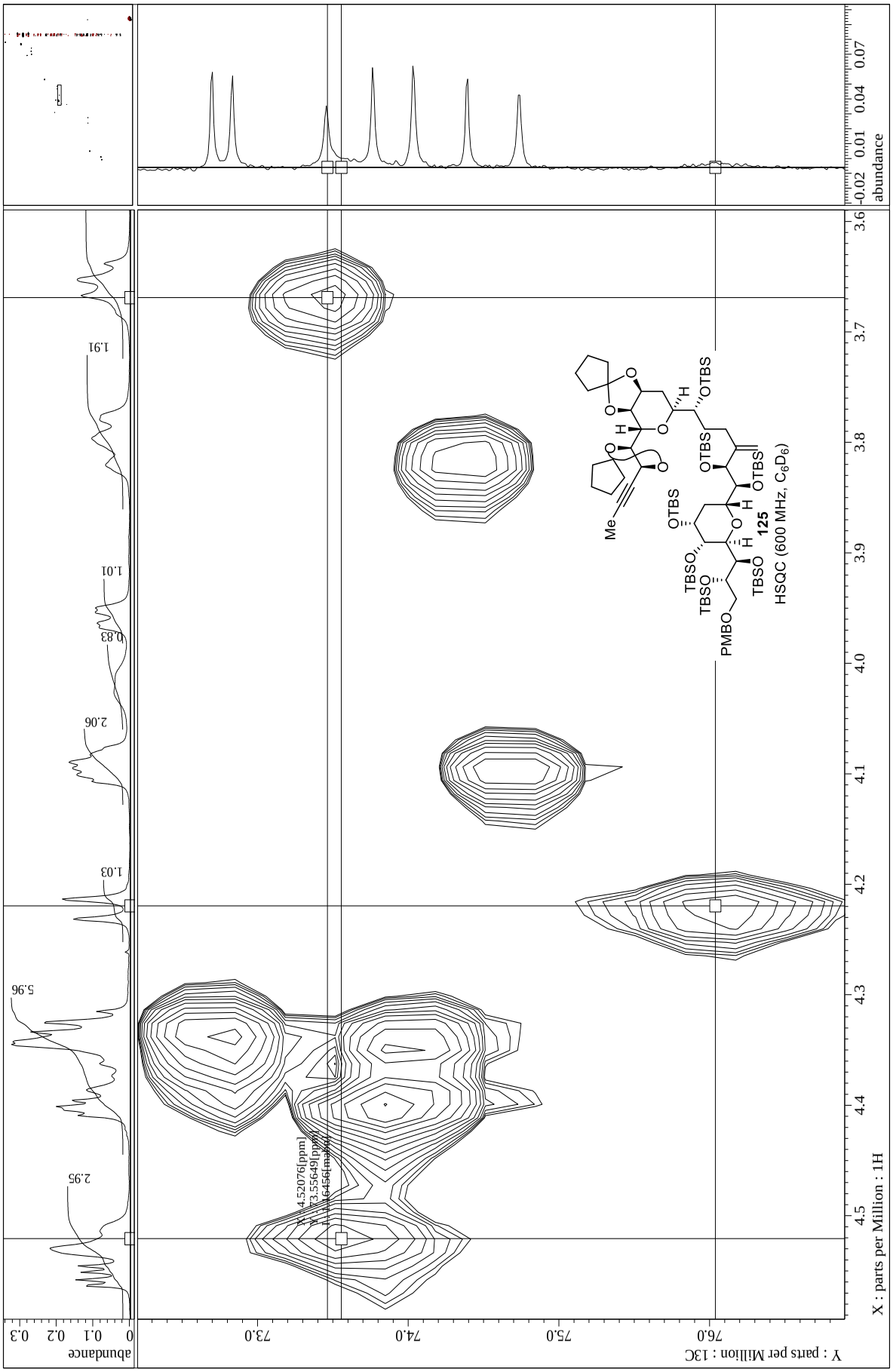

(thousandths)
70.0
40.0
10.0
2.02
0.90
0.99
79.0
80.0
81.0
82.0
Y : parts per Million : 13C
4.1 4.09 4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01 4.0 3.99 3.98 3.97 3.96 3.95 3.94 3.93 3.92 3.91 3.9 3.89 3.88 3.87 3.86 3.85
X : parts per Million : 1H
0 10.0 20.0
(thousandths)
OTBS
TBSO
TBSO
PMBO
TBSO
OTBS
OTBS
OTBS
124
HSQC (600 MHz, C6D6)
X : 3.95146[ppm]
Y : 80.47908[ppm]
I : -0.92123[main]

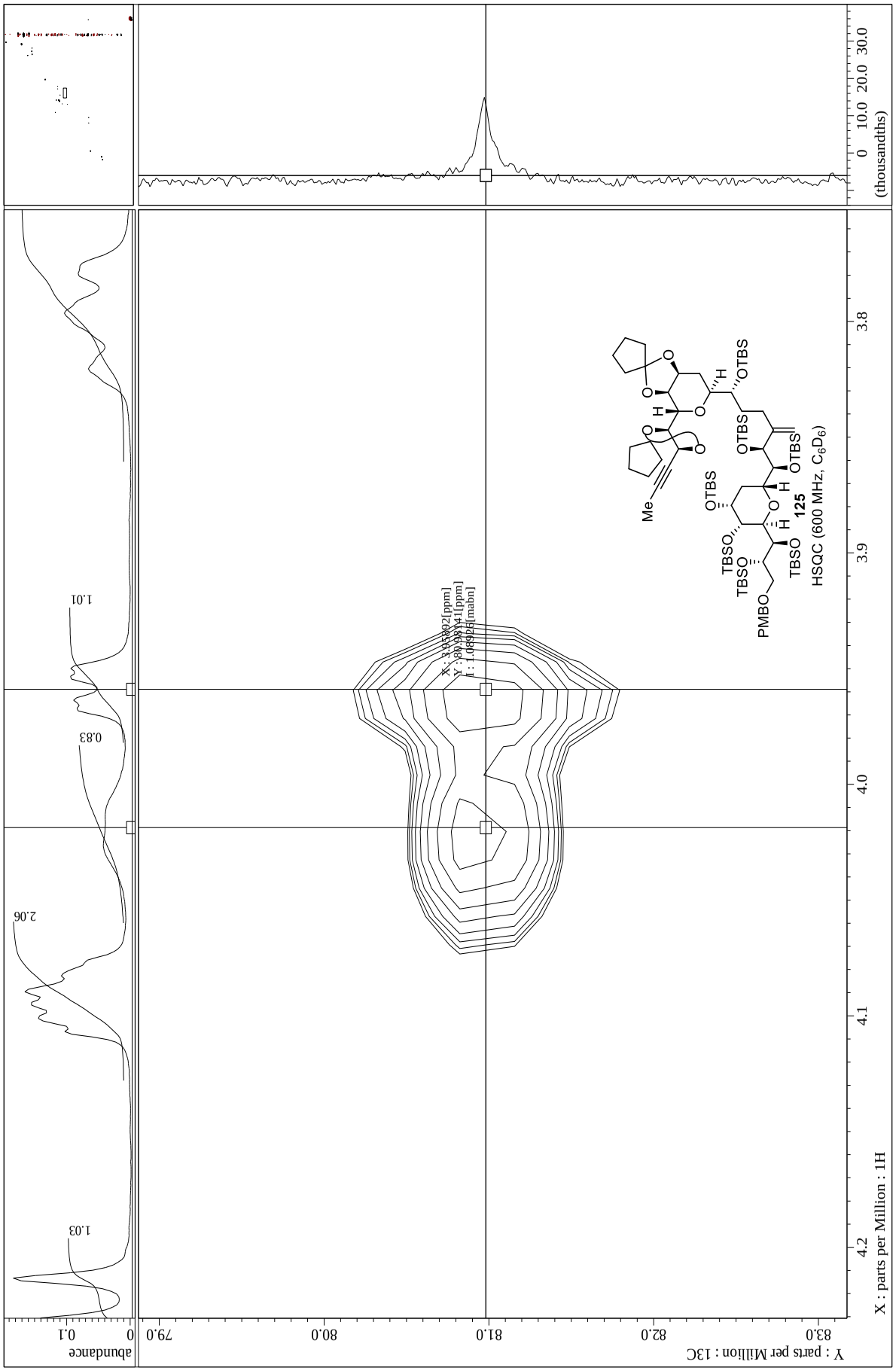

HSQC (600 MHz, C_6D_6)
124
PMBO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
OTBS
H
H
H
O
O
O
O
O
O
O
X : parts per Million : 1H
Y : parts per Million : 13C
(thousandths)
(thousandths)
2.97
1.01
3.10
1.93
1.02
2.02
0.90
0.99
1.94

Me
O
H
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
O
TBSO
OTBS
125
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H
65.83
44.09
9.37
8.28
5.96
2.96
2.86
2.04
2.00
1.03
1.01
0.97
2.95
1.03
2.06
2.03
2.01
1.94
1.97
2.89
0.93
2.01
3.06
7.302
7.287
7.160
6.873
6.858
5.477
5.209
4.945
4.942
4.558
4.529
4.345
4.343
4.094
4.090
3.796
3.653
3.320
2.684
2.534
2.076
2.069
1.922
1.569
1.556
1.475
1.472
1.138
1.133
1.083
1.073
0.344
0.331
0.292
0.284
0.273
0.262
0.257
0.235
0.206

Me
O
H
O
O
O
O
OTBS
TBSO
TBSO
PMBO
O
H
H
TBSO
OTBS
OTBS
OTBS
H
125
13C NMR (150 MHz, C6D6)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
160.254
150.306
131.453
130.199
128.600
128.514
128.437
121.160
119.217
114.496
112.055
84.077
78.103
74.751
74.407
74.043
73.775
73.468
72.846
72.712
69.830
68.451
55.286
37.908
37.850
37.755
27.127
27.088
27.059
26.906
19.208
19.189
18.959
4.003
-1.962
-2.881
-2.929
-3.111
-3.331
-3.474
-3.580
-3.953
X : parts per Million : 13C

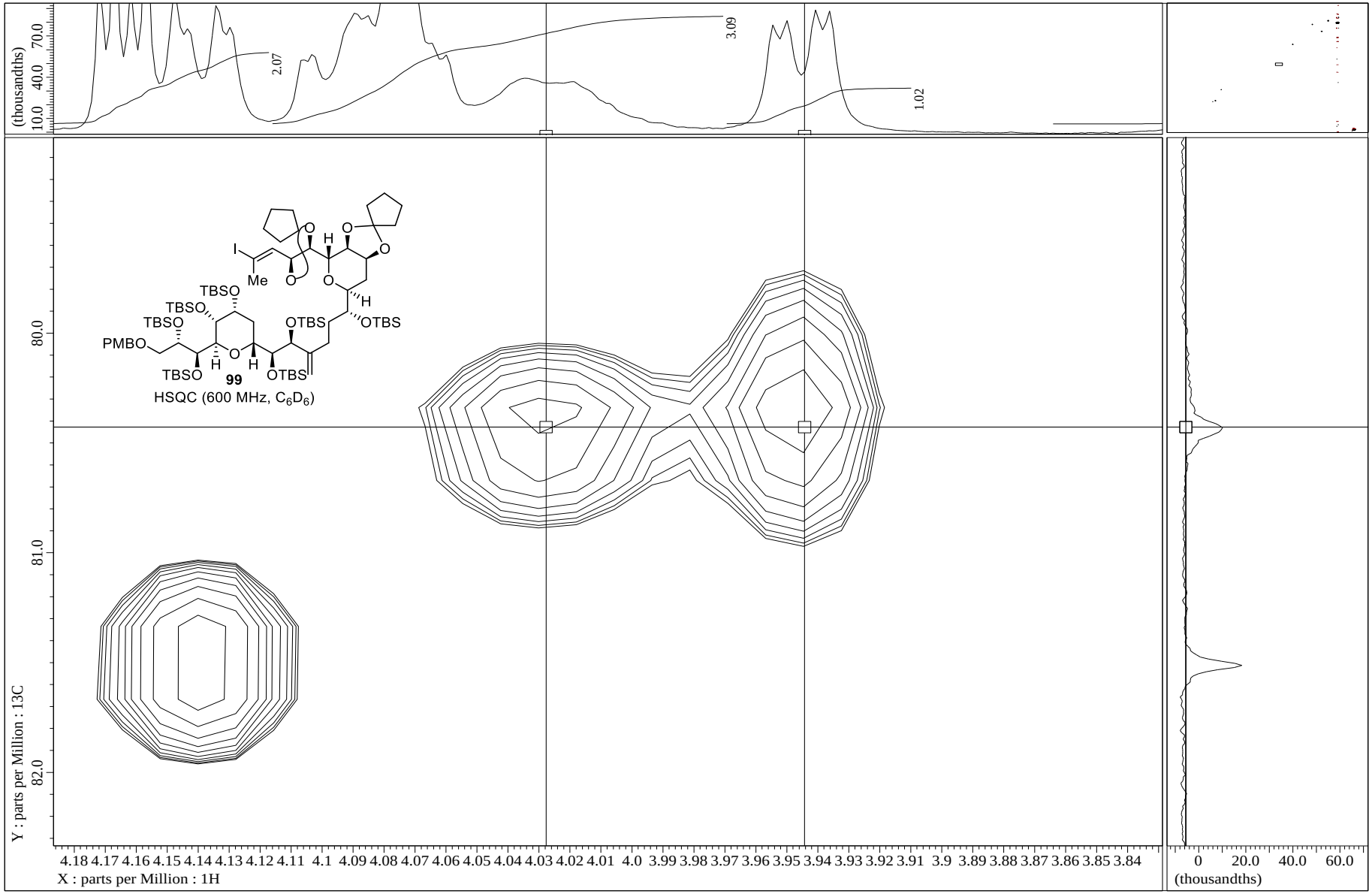

abundance
0.1
0
0.97
2.95
5.96
1.03
2.06
0.83
1.01
67.0
68.0
69.0
70.0
Y : parts per Million : 13C
X = 4.09211[ppm]
Y = 68.45141[ppm]
I = 1.81798[mabn]
Me
O
H
O
O
O
O
H
OTBS
TBSO
TBSO
OTBS
OTBS
PMBO
O
H
H
TBSO
125
OTBS
HSQC (600 MHz, C6D6)
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
X : parts per Million : 1H
0
0.1
0.2
abundance

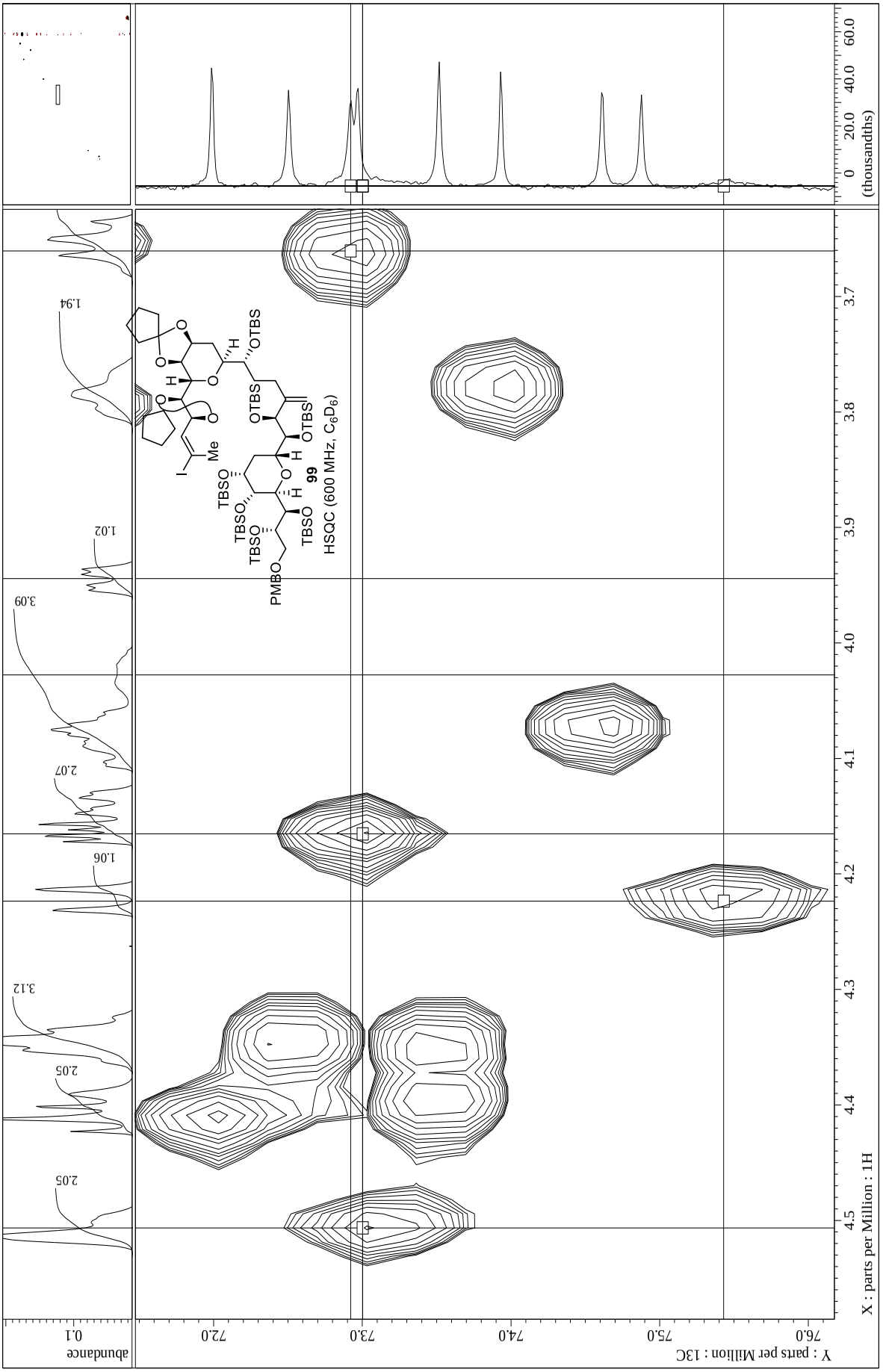

Y : parts per Million : 13C
X : parts per Million : 1H
abundance
HSQC (600 MHz, C6D6)
125
PMBO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
OTBS
Me
2.95
5.96
1.03
2.06
0.83
1.01
1.91

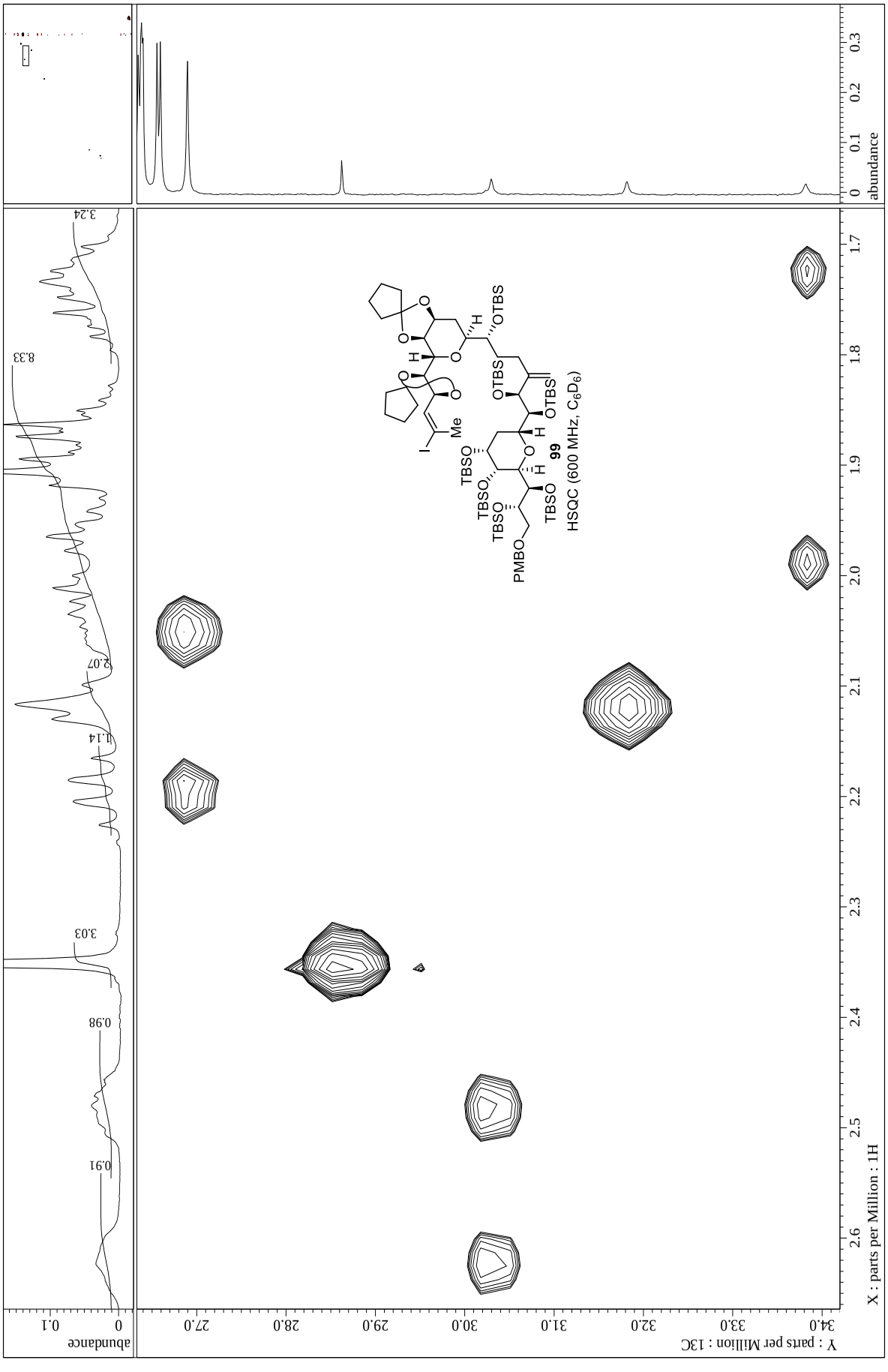

X : parts per Million : 1H
Y : parts per Million : 13C
abundance
1.03
2.06
0.83
1.01
X : 3.95892[ppm]
Y : 80.9891[ppm]
I : 1.08926[mabn]
HSQC (600 MHz, C6D6)
125
(thousandths)

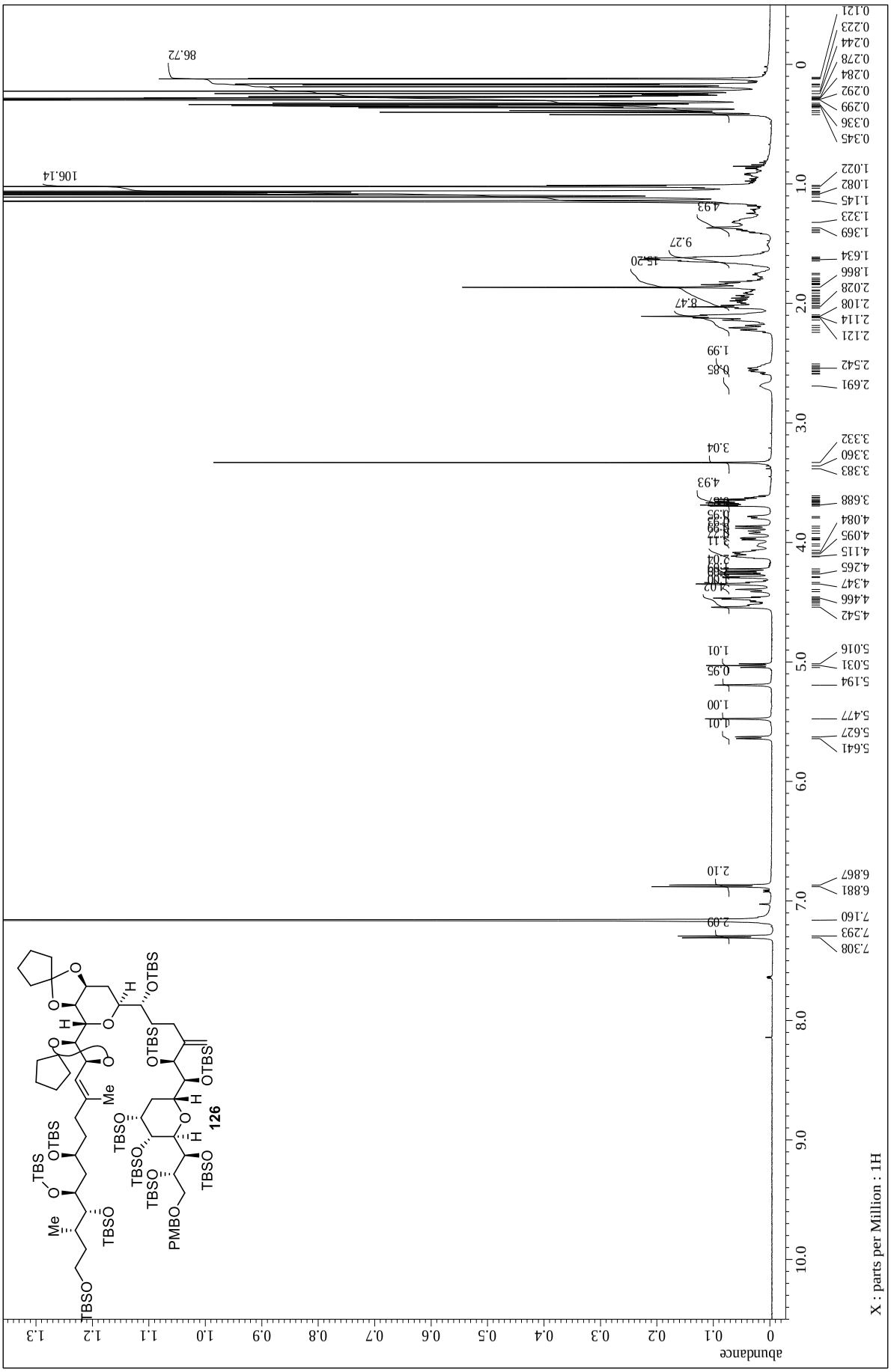
99
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

99
^{13}C NMR (150 MHz, C_6D_6)
abundance
X : parts per Million : 13C
159.729
149.781
138.952
128.219
128.056
127.903
119.812
118.711
113.981
111.568
101.649
74.878
74.619
73.930
73.518
72.972
72.924
72.503
71.986
69.286
54.761
26.898
26.592
26.554
26.401
26.381
26.343
26.247
23.777
18.693
18.645
18.588
18.425
-2.496
-3.434
-3.540
-3.588
-3.683
-3.856
-3.971
-4.009
-4.086
-4.478

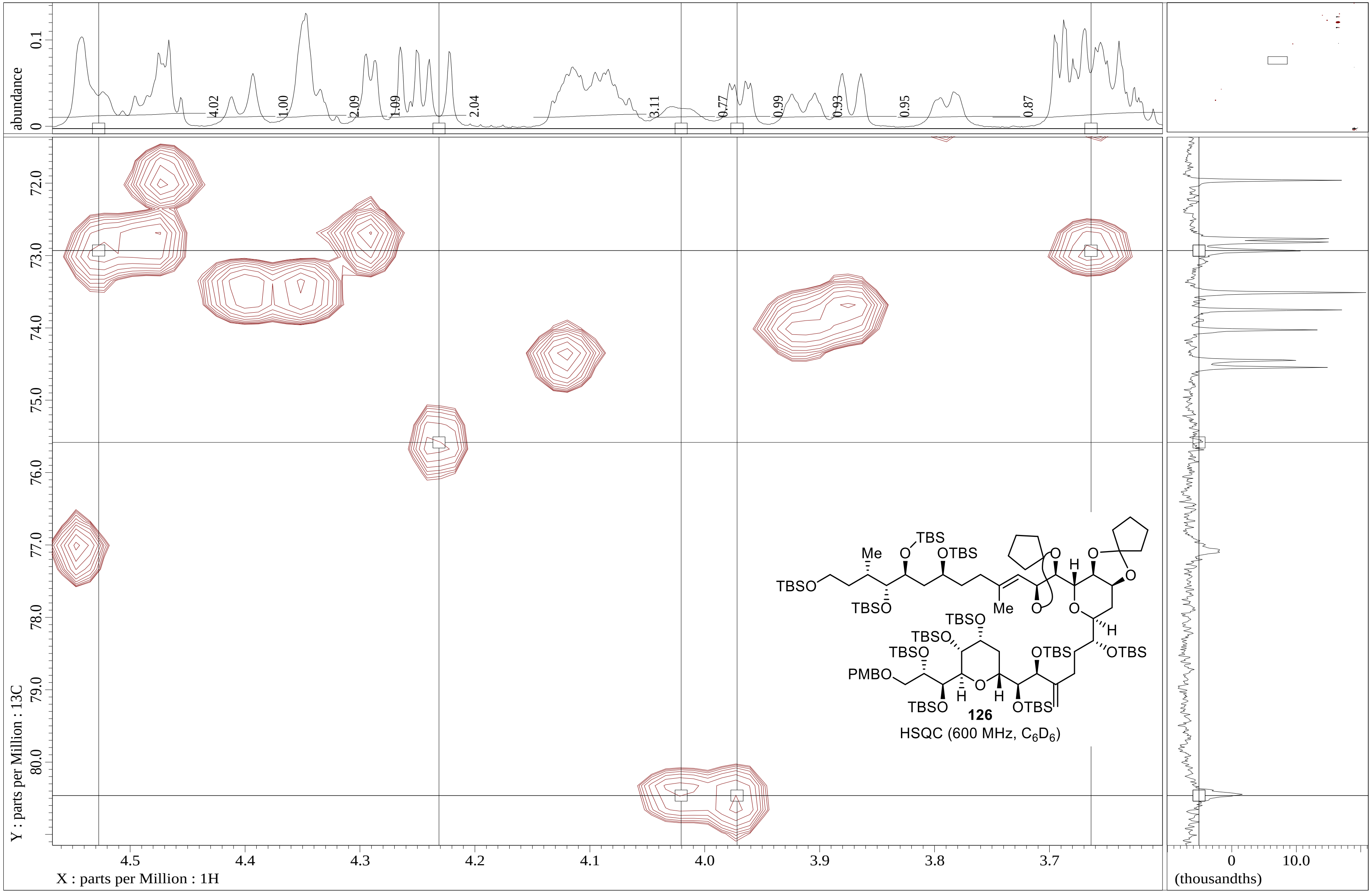

(thousandths)
10.0
40.0
70.0
2.07
3.09
1.02
80.0
81.0
82.0
Y : parts per Million : 13C
4.18 4.17 4.16 4.15 4.14 4.13 4.12 4.11 4.1 4.09 4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01 4.0 3.99 3.98 3.97 3.96 3.95 3.94 3.93 3.92 3.91 3.9 3.89 3.88 3.87 3.86 3.85 3.84
X : parts per Million : 1H
0 20.0 40.0 60.0
(thousandths)
I
Me
O
H
TBSO
PMBO
OTBS
99
HSQC (600 MHz, C6D6)


HSQC (600 MHz, C6D6)
99
PMBO
TBSO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
Me
H
O
Y : parts per Million : 13C
X : parts per Million : 1H
abundance
(thousandths)
1.94
1.02
3.09
2.07
1.06
3.12
2.05
2.05

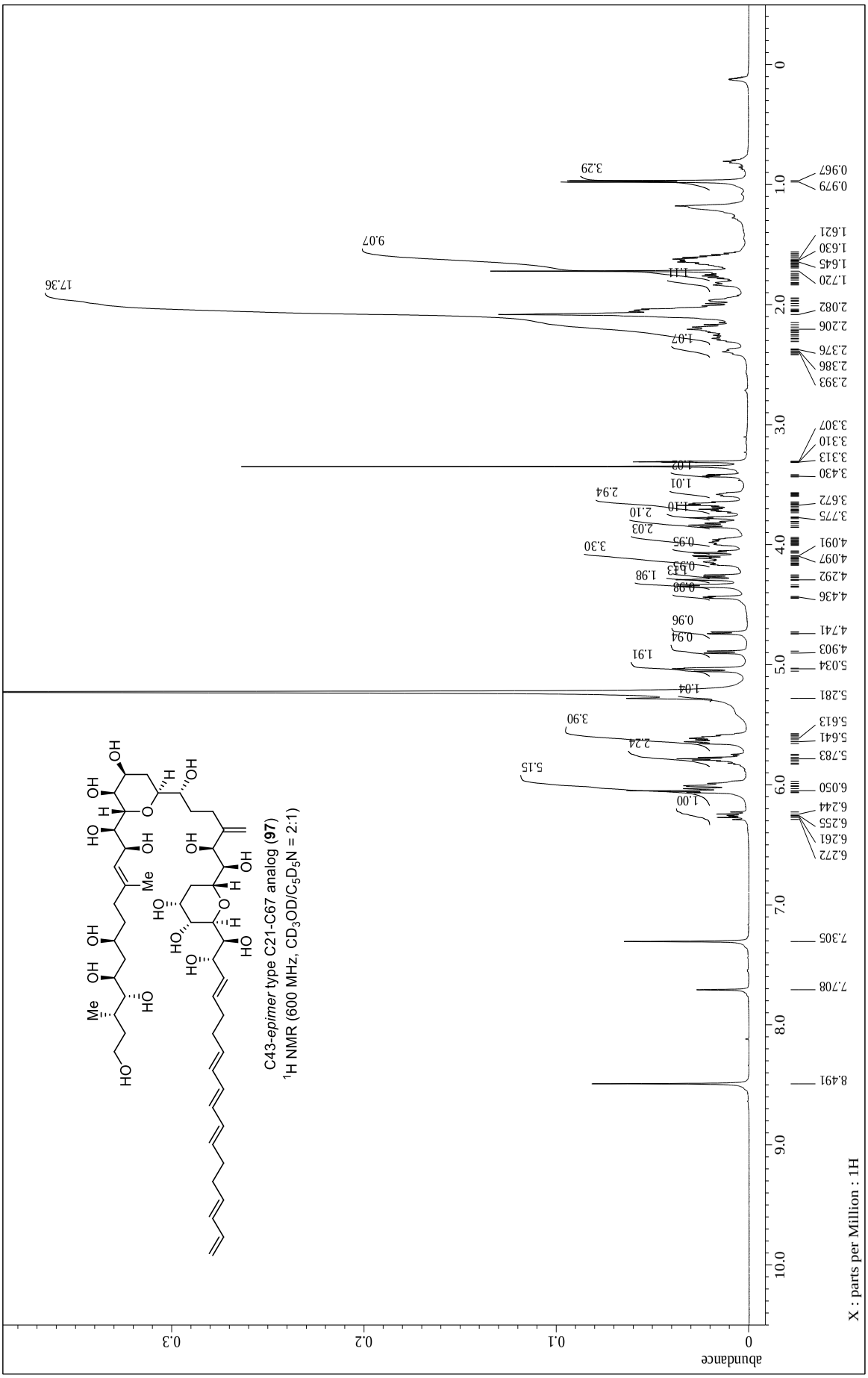

HSQC (600 MHz, C6D6)
99
PMBO
TBSO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
Me
I
H
H
H
O
O
O
O
O
O
O
Y : parts per Million : 13C
X : parts per Million : 1H
abundance
abundance
0.91
0.98
3.03
1.14
2.07
8.33
3.24

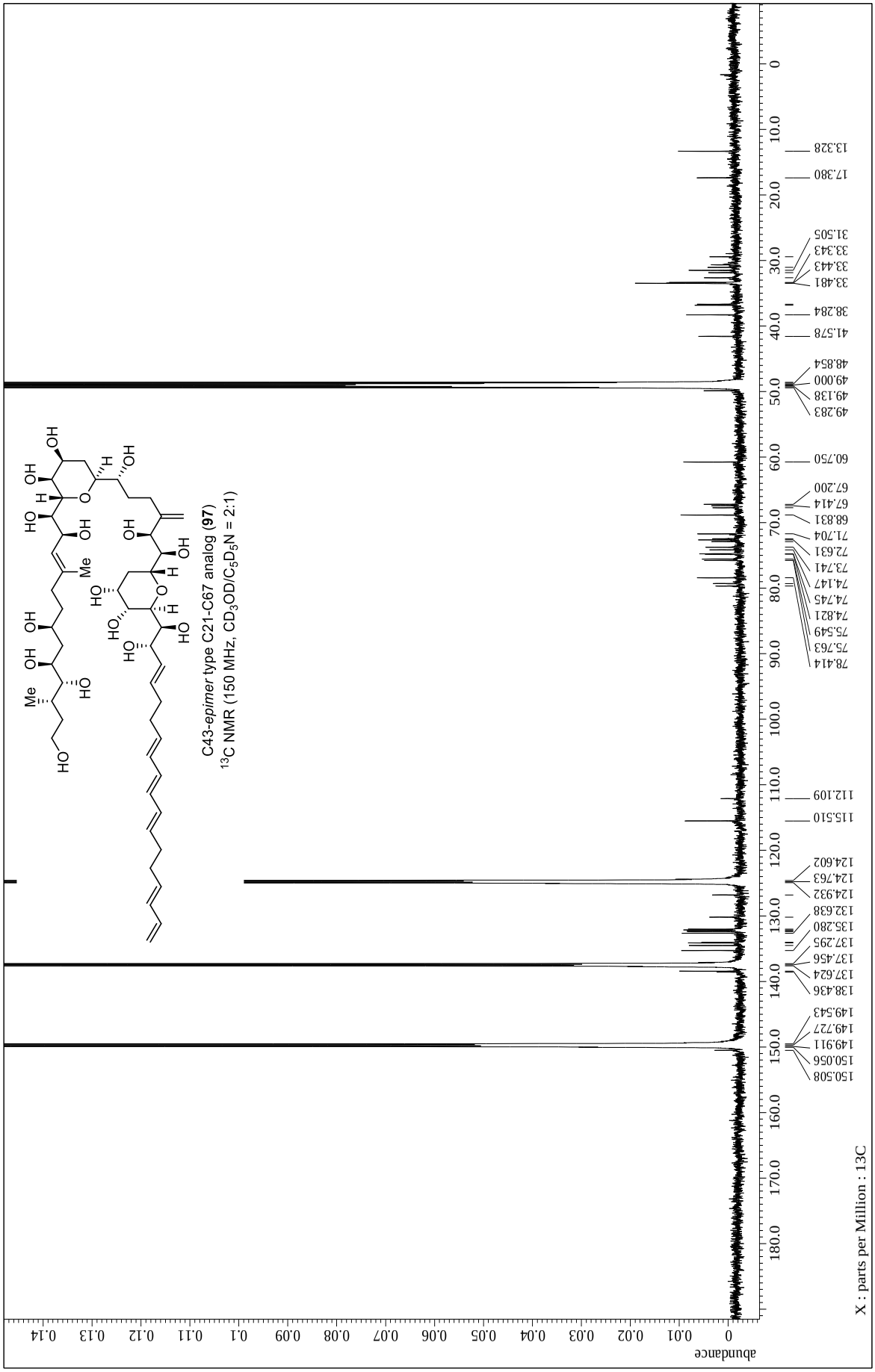

abundance
X : parts per Million : 1H
126
TBSO
TBS
OTBS
Me
TBSO
PMBO
TBSO
TBSO
TBSO
TBSO
OTBS
OTBS
OTBS
Me
O
H
86.72
106.14
4.93
9.27
15.20
8.47
1.99
0.85
3.04
4.93
1.01
0.95
1.01
2.10
2.09
7.308
7.293
7.160
6.881
6.867
5.641
5.627
5.477
5.194
5.031
5.016
4.542
4.466
4.347
4.265
4.115
4.095
4.084
3.688
3.383
3.360
3.332
2.691
2.542
2.121
2.114
2.108
2.028
1.866
1.634
1.369
1.323
1.145
1.082
1.022
0.345
0.336
0.299
0.292
0.284
0.278
0.244
0.223
0.121

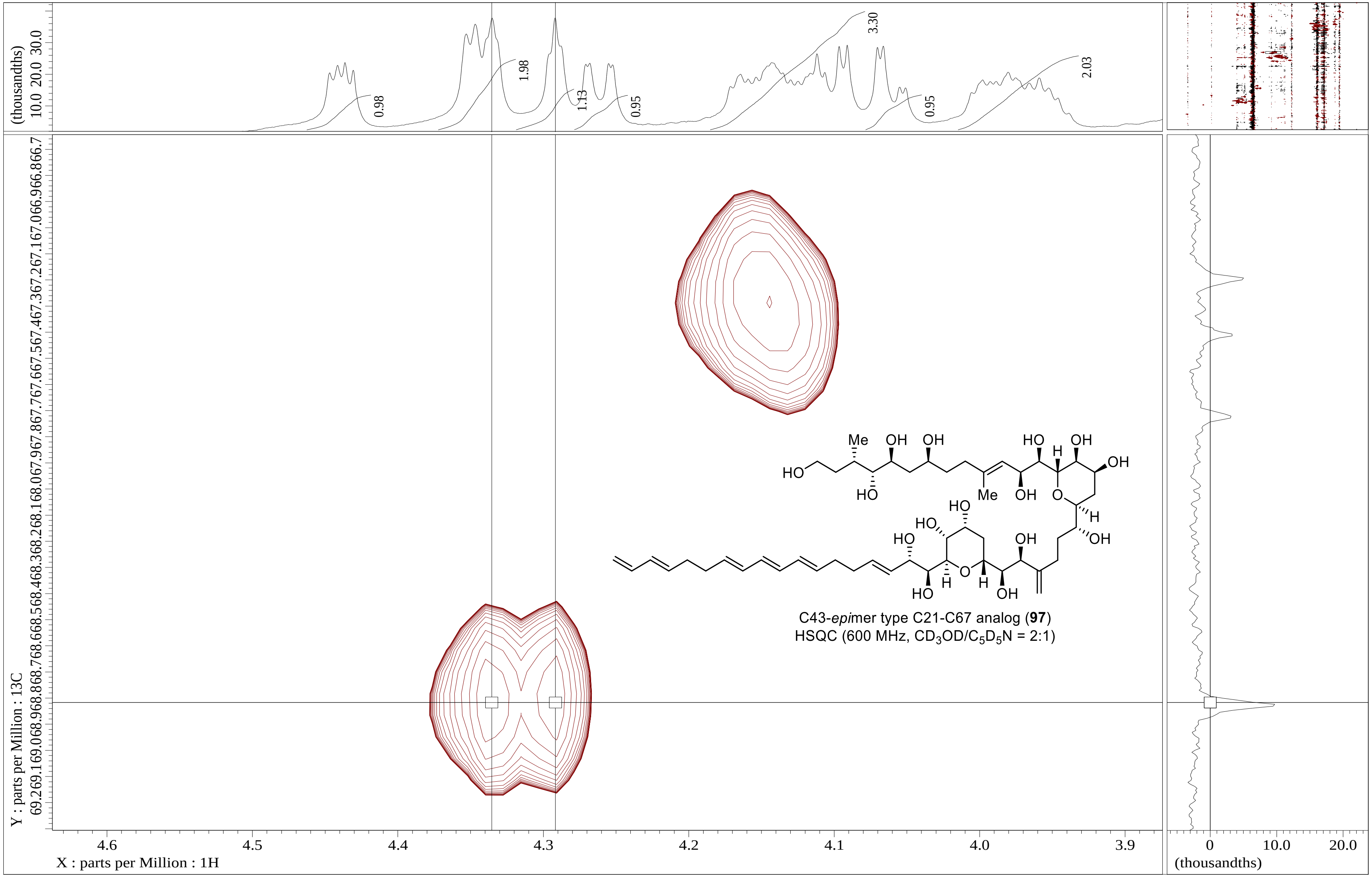
126
^{13}C NMR (150 MHz, C_6D_6)
abundance
X : parts per Million : 13C
159.714
149.594
143.188
128.223
128.060
127.897
122.794
119.404
113.956
111.572
84.035
82.101
80.445
73.752
73.513
71.961
70.295
61.381
54.746
41.590
26.615
26.558
26.520
26.424
26.366
26.251
18.697
18.649
18.592
18.429
-3.047
-3.335
-3.651
-3.880
-4.014
-4.043
-4.120
-4.215
-5.001
-5.068


abundance
0
0.1
4.02
1.00
2.09
1.09
2.04
3.11
0.77
0.99
0.93
0.95
0.87
Y : parts per Million : 13C
72.0
73.0
74.0
75.0
76.0
77.0
78.0
79.0
80.0
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
X : parts per Million : 1H
0
10.0
(thousandths)
TBSO
TBS
Me
O
OTBS
TBSO
Me
H
O
OTBS
TBSO
PMBO
126
HSQC (600 MHz, C_6D_6)

S12
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H
7.160
5.640
5.627
5.475
5.192
5.059
5.044
4.504
4.470
4.331
4.085
3.885
3.697
3.689
3.682
3.673
2.588
2.575
2.553
2.502
2.491
2.115
2.104
1.881
1.640
1.637
1.627
1.404
1.362
1.107
1.080
1.072
1.020
0.341
0.326
0.323
0.308
0.281
0.277
0.121
0.118
1.03
1.01
1.00
0.99
2.94
2.02
2.06
0.83
4.96
3.90
1.90
0.92
2.01
6.06
15.24
9.06
1.60
107.60
69.95


C43-epimer type C21-C67 analog (97)
1H NMR (600 MHz, CD3OD/C5D5N = 2:1)
X : parts per Million : 1H
abundance


C43-epimer type C21-C67 analog (97)
13C NMR (150 MHz, CD3OD/C5D5N = 2:1)
abundance
X : parts per Million : 13C
150.508
150.056
149.911
149.727
149.543
138.436
137.624
137.456
137.295
135.280
132.638
124.932
124.763
124.602
115.510
112.109
78.414
75.763
75.549
74.821
74.745
74.147
73.741
72.631
71.704
68.831
67.414
67.200
60.750
49.283
49.138
49.000
48.854
41.578
38.284
33.481
33.443
33.343
31.505
17.380
13.328



C43-*epi*mer type C21-C67 analog (**97**)
HSQC (600 MHz, CD_3OD/C_5D_5N = 2:1)

(thousandths)
10.0
20.0
30.0
1.07
17.36
1.11
9.07
Y : parts per Million : 13C
30.0
31.0
32.0
33.0
34.0
35.0
36.0
37.0
38.0
39.0
40.0
41.0
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
X : parts per Million : 1H
0
10.0
20.0
(thousandths)
Me
OH
OH
HO
HO
HO
H
OH
OH
Me
OH
O
HO
HO
HO
H
OH
HO
H
O
H
OH
HO
C43-epimer type C21-C67 analog (97)
HSQC (600 MHz, CD3OD/C5D5N = 2:1)

Acknowledgments

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

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Finally, I would like to express to my father and mother 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 my time at Fukuoka so enjoyable. I wish everyone nothing but the best in future.

Yuma Wakamiya

Fukuoka, Japan
March 2020

List of Publications

1. “Synthesis and Stereochemical Revision of the C31–C67 Fragment of Amphidinol 3” Wakamiya, Y.; Ebine, M.; Murayama, M.; Omizu, H.; Matsumori, N.; Murata, M.; Oishi, T. *Angew. Chem. Int. Ed.* **2018**, *57*, 6060–6064.

2. “Synthesis of an Analog of Amphidinol 3 Corresponding to the C31–C67 Section” Koge, T.; Wakamiya, Y.; Ebine, M.; Oishi, T. *Heterocycles*. **2018**. *7*, 1197–1202.

3. “Total Synthesis of Amphidinol 3: A General Strategy for Synthesizing Amphidinol Analogs and Structure-Activity Relationship Study” Wakamiya, Y.; Ebine, M.; Matsumori, N.; Oishi, T. *J. Am. Chem. Soc.***2020**, in press.