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Graphical Abstract

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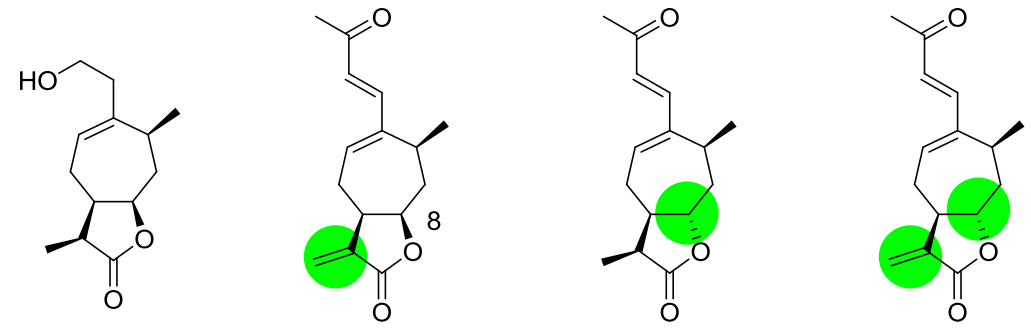

(+)-sundiversifolide (+)-8-*epi*-xanthatin (-)-dihydroxanthatin (-)-xanthatin

Total Synthesis of Xanthanolides

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Abstract

The total synthesis and determination of the absolute configuration of (+)- and (-)-sundiversifolide have been achieved via intramolecular acylation and Wittig lactonization as the key steps. The xanthanolide sesquiterpene lactones, 8-*epi*-xanthatin (**1**), dihydroxanthatin (**2**), and xanthatin (**3**) were also prepared, starting from a common intermediate derived from the synthesis of sundiversifolide.

Keywords: Xanthanolides, Natural products, Sesquiterpene lactones, Total synthesis

1. Introduction

The xanthanolide sesquiterpene lactones are a class of natural products isolated from the plants of the genus *Xanthium* (family Compositae). They have a bicyclic 5,7-fused ring system, and are known to exhibit allelopathic,[1] antitumor,[2] antimalarial,[3] and antimicrobial activity.[4] Accordingly, their intriguing biological profile has attracted the interest of medicinal chemists and biochemists as well as organic chemists. An efficient synthesis of these sesquiterpenes therefore would be extremely useful in order to identify biological targets and develop related drugs. Xanthatin (**3**), isolated from *Xanthium strumarium*[5] and other *Xanthium* families, has shown potent antibacterial activity against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*.[6] 8-*epi*-Xanthatin (**1**), which is found in the extracts of the aerial parts of various species in the genus *Xanthium*,[7] has also been

reported to exhibit antitumor activity[2a] and *in vitro* inhibitory activity on farnesyltransferase,[2d] insect development,[7b] and auxin-induced growth of sunflower hypocotyls.[1b,1c] In spite of these attractive bioactivities, only a few synthetic studies of the xanthanolides and their related natural products have been reported.[8,9] Recently, we have achieved an efficient total synthesis of a dinorxanthanolide, (+)-sundiversifolide (**4**),[9b] which was isolated from the exudate of germinating sunflowers (*Helianthus annuus* L.) as an allelopathic compound,[1a] via a novel construction of the seven-membered carbocycle by an intramolecular acylation and a one-pot Wittig-lactonization as the key steps. This synthesis afforded useful intermediates having a bicyclic 5,7-fused ring system for the synthesis of the xanthanolides. Herein, we report the total synthesis of (+)-8-*epi*-xanthatin (**1**), (-)-dihydroxanthatin (**2**), and (-)-xanthatin (**3**) starting from the common key intermediate **5** as well as full details of the total synthesis of (+)-sundiversifolide.

Figure 1.

2. Results and discussion

2.1. Synthesis of sundiversifolide and the key intermediate for the xanthanolides

Our synthetic strategy for the key intermediate **5** is illustrated in Scheme 1. The γ-lactone moiety would be formed by acylation-olefination of the hydroxyketone **6**, followed by hydrogenation. The vinyl side chain on C-1 would then be introduced by alkylation of the ketone **7**. The seven-membered ring construction is much more challenging than the six-membered ring, due to the entropically unfavorable ring size and/or non-bonded interactions in the transition state. To overcome these issues, we envisioned an intramolecular acylation of a carbanion on the γ-lactone **9** leading to the 8-oxabicyclo[3.2.1]octane skeleton **8** via a six-membered ring formation. Since the fused oxabicycle **8** is a hemiacetal, the hydroxycycloheptanone **7** would be easily provided. The relevant strategy has been reported by Molander and coworkers utilizing SmI_2.[10] The asymmetric centers on **9** would be obtained by a diastereoselective alkylation using the chiral oxazolidinone **11**, followed by stereocontrolled dihydroxylation of the resulting **10**.

Scheme 1.

The alkylating reagent **12** was prepared from 3-butyn-1-ol in five steps via protection, hydroxymethylation, hydroalumination-protonation, and mesylation-iodination. The diastereoselective alkylation of Evans' oxazolidinone **11** with **12** provided **13** in good yield with excellent stereoselectivity.[11] The stereocontrolled dihydroxylation of **13** with AD-mix-β®[12] was accompanied by spontaneous lactonization of the intermediate diol to afford the lactone **14** as a single isomer. Protection of the secondary alcohol with MOMCl and deprotection of the TBDPS

ether with TBAF in THF,[13] followed by mesylation-iodination, furnished the iodolactone **17** in good yield (Scheme 2).

Scheme 2.

The pivotal intramolecular acylation forming the seven-membered ring was first attempted with SmI_2 under various conditions and resulted in no reaction. Instead, lithiation of the iodide **17** using *t*-BuLi successfully provided the seven-membered ring in excellent yield.[13] The NMR spectra showed that the product is in equilibrium between the hemiacetal **18** and the cycloheptanone **19** in $CDCl_3$. Treatment of the product with TBDPSCl and imidazole gave the trisubstituted cycloheptanone **20** in good yield (Scheme 3).

Scheme 3.

With the seven-membered skeleton in hand, we next attempted the introduction of the vinyl unit along with the formation of the C1-C5 endocyclic-olefin (Scheme 4). The vinyl Grignard reagent added stereoselectively to the ketone to give **21** in good yield as a single isomer. According to the conformational analysis of **20**,[14] the nucleophile would attack the α-face as an equatorial attack (Figure 2). Attempts to dehydrate with thionyl chloride gave the chlorinated compound **22** via an S_N2' reaction, and the Burgess reagent resulted in formation of the oxabicyclic compound **23**.

Scheme 4.

Figure 2.

We then tried the enol triflation of the ketone **20** which gave only recovered starting material, but the Shapiro reaction of the corresponding *p*-toluenesulfonyl hydrazone **24** afforded the alkenyl iodide **25** in 77% yield after trapping of the alkenyllithium with iodine. Stille coupling with **25** and tributylvinyltin provided the vinylcycloheptene **26**. Since we first intended to achieve the synthesis of sundiversifolide, the vinyl compound **26** was subjected to hydroboration with thexylborane to provide primary alcohol **27** after oxidative treatment. After protection of the hydroxyl group, deprotection of the MOM ether was attempted by using various kinds of acid, but resulted in low yield, and the oxabicyclic compound **30** was again obtained. The tertiary carbocation at C-1 would be easily generated to form this product.

Scheme 5.

In place of the MOM ether, a TBS ether was selected as the protecting group of the hydroxyl group at C-7. Treatment of **14** with TBSCl gave **31**, the primary TBDPS ether of which should be selectively deprotected. Although the usual protocol (TBAF, AcOH in THF)[15] gave mainly the diol **37**, in the presence of CH_2Cl_2 as a co-solvent,[16] the desired partially deprotected alcohol **32** was obtained in good yield. However, on a scale larger than 10 g of substrate, the yield of **32** decreased to 60% and more of the diol **37** was generated. The alcohol **32** was converted into the iodide **33** quantitatively. The diol **37** also can be transformed into the iodide **33** via selective iodination followed by protection of the secondary alcohol with TBSOTf. The iodide **33** was treated with *t*-BuLi to afford the hemiacetal **34** and the cycloheptanone **35** in excellent yield. Although MOMCl reacted with the hydroxyl groups on both **34** and **35**, TBDPSCl protected only the secondary alcohol of **35** to afford **36** in good yield (Scheme 6).

Scheme 6.

The Shapiro reaction was carried out on the corresponding hydrazone **37** to give the doubly iodinated compound **38** in low yield after treatment with iodine.

Scheme 7.

Hence, we then attempted the nucleophilic vinylation of **36** with a Grignard reagent as in the previous case.[17] Vinylmagnesium bromide added to the ketone to afford the adduct **39** in excellent yield as a single isomer. Since dehydration of the tertiary alcohol of **39** to afford the endocyclic-olefin was unsuccessful at this stage as shown in Scheme 8, we decided to assemble the lactone first. Selective deprotection of the TBS group of **39**, TPAP oxidation of **40**, and removal of the TBDPS group of **41** provided the hydroxy hemiacetal **42** in nearly quantitative yield. We next tried to construct the lactone moiety from **42**, which is equivalent to an α-hydroxyketone. In order to carry out the intramolecular Horner-Emmons reaction, condensation with the carboxylic acid of the phosphonate ($(EtO)_2P(O)CH(CH_3)CO_2H$) and **42** gave a 1:1 mixture of **43** and **44**. On the contrary, reaction of **42** with the Wittig reagent ($Ph_3P=C(CH_3)CO_2C_2H_5$) under reflux in xylene for 9 hours directly provided the butenolide **46** in 91% yield, the structure of which was unambiguously assigned by X-ray diffraction study. In contrast to Garner's report on the Wittig reaction of α-hydroxy ketones giving *E*-olefins,[18] this reaction was exclusively *Z*-selective. The mechanism of this direct lactonization could be postulated as transesterification giving the intermediate **45**, followed by intramolecular olefination, because the ketone in **42** was masked by hemiacetalization.

The reaction using the Wittig reagents with the trifluoroethyl ester (R = CH_2CF_3) and the phenyl ester (R = Ph), which have better leaving groups, was completed in only 4 hours (92% yield) and 2.5 hours (74% yield), also suggesting that the intramolecular olefination had occurred (Scheme 8).
With the carbon skeleton in hand, we then investigated the less substituted endocyclic alkene formation. Dehydration using MsCl/Et_3N gave the S_N2' products **47** and not the desired compound.

Scheme 8.

Since the double bond on the allylic alcohol had to be protected prior to dehydration, **46** was treated with mCPBA to give the epoxide **48**, which was subjected to hydrogenation with the nickel boride reagent derived from $NiCl_2$ and $NaBH_4$[19] to afford a separable mixture of **49** (81%) and its C11-epimer (14%). After numerous attempts, the best results for a kinetically controlled dehydration of **49** were obtained using a protocol involving slow addition of a solution of freshly distilled $SOCl_2$ (2 equiv.) and pyridine (4 equiv.) in CH_2Cl_2 at -20 ºC. Under these conditions, the desired endocyclic alkene **50** was successfully obtained in yields ranging of 68-87%. Finally, the epoxide in **50** was regioselectively reduced with $NaBH_3CN$ in the presence of ZnI_2[20] to provide sundiversifolide (**4**) in 85% yield. The synthetic **4** {$[\alpha]^{22}_D$ = +33.0 (c 0.44, $CHCl_3$)} was found to be identical to the natural **4** according to spectroscopic properties (^{1}H and ^{13}C NMR, IR, and MS) (Scheme 9). Since the optical rotation data of the natural product has not been reported due to a limited amount of the natural product, the enantiomer *ent*-**1** {$[\alpha]^{22}_D$ = -33.7 (c 0.46, $CHCl_3$)} was synthesized in a similar manner, using the chiral oxazolidinone derived from *L*-Phe in the asymmetric alkylation and AD-mix-$\alpha^{®}$ in the asymmetric dihydroxylation, which also gave a single isomer. HPLC analysis using chiral column (Daicel Chiralpak IA, detector: UV 207 nm, hexane/isopropanol 93:7, flow = 1.0 ml/min; (-)-sundiversifolide t_r = 31 min; (+)-sundiversifolide t_r = 38 min, 30 °C) indicated that the natural **4** is identical with the synthetic (+)-**4** (Figure 3). This study therefore determined that the absolute configuration of the naturally occurring sundiversifolide isolated from the sunflower is that shown in **1**.

Scheme 9.

Figure 3.

2.2. Synthesis of (+)-8-*epi*-xanthatin (1)

The key intermediate **5** for construction of xanthanolide has a *cis*-fused cycloheptene-γ-butyrolactone skeleton bearing a vinyl substituent, which has been converted into the

butenone moiety via cross metathesis.[8] Attempts to reduce the epoxide in **50** to an alkene using SmI_2[21] or P_2I_4[22] resulted in a complex mixture, but KSeCN successfully reduced the epoxide to give **5** in good yield (Scheme 10).[23] With the key intermediate in hand, we tried to convert **5** to xanthanolides. In order to prepare 8-*epi*-xanthatin (**1**) from **5**, conversion of the α-methyl group on the γ-butyrolactone into an *exo*-methylene was examined. According to Ando's protocol,[24] bromination at C-11 was employed with LDA/CBr_4 to give a 1:1.4 diastereomeric mixture of **51** and **52**, the stereochemistry of which was determined by NOE experiments as shown in Scheme 10. After separation of these diastereomers, each isomer was subjected to dehydrobromination with base. The α-bromo isomer **51** was easily converted into the desired *exo*-olefin **53** by using TBAF in THF. The β-bromo isomer **52**, on the other hand, after being treated with various bases (TBAF, KHMDS, DBU, or Triton B) only gave the conjugated *endo*-olefin **55**, probably due to the *anti*-periplanar relationship between the bromide and the β-proton on C-11. Thus, for isomerization of **52** to **51**, formation of the enolate of **52** via lithium-halogen exchange, followed by bromination, was attempted using *n*-, *sec*- or *tert*-butyllithium, but the desired bromo lactone **51** was not obtained. Unexpectedly, LDA worked well to generate the enolate **56** via lithium-halogen exchange, affording a 1:1.4~1:2.5 mixture of **51** and **52** after bromination by CBr_4. Finally, **53** was subjected to cross metathesis[8] using the 2nd generation Hoveyda-Grubbs catalyst (**54**)[25] to give 8-*epi*-xanthatin (**1**) in good yield. The spectra of the synthetic **1** were identical with those of the natural compound.[8a]

Scheme 10.

2.3. Synthesis of (-)-dihydroxanthatin (2)

In order to synthesize dihydroxanthatin (**2**) from the intermediate **5**, a stereochemical inversion at C-8 was necessary. As we reported in the synthesis of diversifolide,[9d] the lactone moiety was opened by diethylamine and aluminum trichloride to give the hydroxy amide **57** quantitatively. Since the inversion at C-8 by the Mitsunobu reaction was unsuccessful, probably due to steric reasons,[26] the oxidation-reduction protocol was examined. TPAP oxidation of the secondary alcohol at C-8, followed by thermodynamically controlled reduction with SmI_2,[27] provided a 4:1 mixture of the desired *trans*-isomer **59** and the *cis*-isomer **57**, quantitatively. After separation of these isomers, the *trans*-isomer **59** was cyclized by acid to furnish the *trans*-fused lactone **60**, which was subjected to cross metathesis with methyl vinyl ketone as described previously to yield (-)-dihydroxanthatin (**2**). All the spectra were identical with those of the reported compound.[8c]

Scheme 11.

2.4. Synthesis of (-)-xanthatin (3)

Xanthatin (**3**) could be synthesized by "dehydrogenation" of the methyl moiety on dihydroxanthatin (**2**). According to the procedure described above, the precursor **60** was deprotonated by LDA, followed by bromination with CBr_4, to give selectively the brominated compound **61** with the undesired stereochemistry.[28] The elimination reaction with base (TBAF, KHMDS) resulted in the formation of the endo-olefin **62**, as was seen with **52** (Scheme 10). LDA induced lithiation to give the lithium enolate. Since the *trans*-fused lactone would have a planar structure, bromination would occur from the β-face of the enolate rather than the α-face to avoid steric hindrance with H-7. We then decided to carry out the stereochemical inversion of C-8 in **53**, since it already had the *exo*-methylene on the lactone. According to the stereochemical inversion procedure described above, the lactone was opened to give the hydroxy amide **63**, which was oxidized by TPAP to afford the ketone **64**. This compound was treated with SmI_2 in the same way, but gave **66**, resulting from reduction of the enoate as well as the ketone. After screening several reducing reagents, we found that DIBAL reduced only the ketone to give a 1:1.2 ratio of the epimers (**65**:**63**). After lactonization with acid, cross metathesis was employed to provide (-)-xanthatin (**3**) (Scheme 12). The spectra of the synthetic **3** were identical with those of the reports.[29]

Scheme 12.

3. Conclusion

We have achieved the total synthesis of 8-*epi*-xanthatin (**1**), dihydroxanthatin (**2**), and xanthatin (**3**) starting from a common intermediate, prepared according to our original method, including an intramolecular acylation and a one-pot Wittig-lactonization, used in the synthesis of sundiversifolide. Since these xanthanolides have shown promising bioactivity, this work would be useful for the preparation of these compounds and the development of novel bioactive compounds derived from the natural products.

4. Experimental

4.1. General Procedures

^{1}H-NMR and ^{13}C-NMR spectra were measured in a $CDCl_3$ solution using JEOL JNM AL-400, (^{1}H-NMR at 400 MHz, ^{13}C-NMR at 100 MHz) and a JNM ECA-600 spectrometer (^{1}H NMR at 600 MHz, ^{13}C-NMR at 150 MHz) as the reference standards (^{1}H NMR at 0.00 ppm (TMS), ^{13}C-NMR at

77.0 ppm ($CDCl_3$)) unless otherwise noted. Chemical shifts are reported in ppm. Peak multiplicities used the following abbreviation: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on JASCO FT/IR-410 and Shimazu FT/IR-8300 spectrometers. Mass spectra and high resolution mass spectra were obtained on JMS-K9, JMS-AMSUN200/300, JMS-SX102A, JMS-DX303, and Waters LCT Premier mass spectrometers. Elemental analyses were performed with a Yanaco MT-3, MT-5, MT-6 CHN-Corde. Melting points were measured with a Yanaco MP-500D apparatus and a Seki Technotron Corp. Opti Melt MPA 100 apparatus and are uncorrected. Optical rotations were recorded on JASCO P-1010 and HORIBA SEPA-200. Analytical TLC was performed on precoated plates (0.25 mm, silica gel Merck 60 F_{254}). Column chromatography was performed on silica gel (Kanto Chemical Co., Inc.). Preparative HPLC was performed on Kanto Mightysil Si60 and Merck LiChrosorb Si60, and performed with a gradient solvent system of hexane and ethyl acetate and a UV detector at 254 nm. All reactions were performed under argon or nitrogen atmosphere unless otherwise noted, and dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Inc., and the other solvents were distilled. Unless otherwise noted, reagents were obtained from chemical sources and used without further purification.

4.2. Synthesis of sundiversifolide (4)

4.2.1. (*E*)-5-(*tert*-Butyldiphenylsiloxy)-1-iodo-2-pentene **12**. To a solution of 5-(*tert*-butyldiphenylsiloxy)pent-2-en-1-ol (5.00 g, 14.7 mmol)[30] in CH_2Cl_2 (150 mL) at 0 ºC were added Et_3N (5.1 mL, 36.7 mmol) and MsCl (2.3 mL, 29.4 mmol). The mixture was stirred for 0.5 h at room temperature, and then cooled to 0 ºC. After addition of H_2O, the resulting mixture was extracted with CH_2Cl_2, washed with 5% HCl, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The crude product was dissolved in acetone (150 mL), and NaI (6.60 g, 44.0 mmol) was added. The resulting suspension was stirred for 0.5 h at room temperature, and the solvent was removed *in vacuo*. After addition of H_2O, the mixture was extracted with CH_2Cl_2, washed with saturated aqueous $Na_2S_2O_4$ and brine, and dried over Na_2SO_4. After the mixture was evaporated, the residue was purified by silica gel column chromatography (10% EtOAc-hexane) to give **12** as a yellow oil (6.53 g, 99%). ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.06 (s, 9H), 2.28 (dt, *J* = 6.6, 6.6 Hz, 2H), 3.70 (t, *J* = 6.6 Hz, 2H), 3.86 (d, *J* = 7.4 Hz, 2H), 5.72 (dt, *J* = 6.6, 15.2 Hz, 1H), 5.78 (dt, *J* = 7.4, 15.2 Hz, 1H), 7.47 (m, 6H), 7.70 (m, 4H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 6.4 (t), 19.3 (s), 26.9 (q), 35.4 (t), 63.1 (t), 127.5 (d), 129.5 (d), 129.7 (d), 131.5 (d), 133.7 (s), 135.5 (d). IR (KBr, neat): 3070, 3048, 2955, 2930, 2857, 1471, 1427 cm^{-1}. MS (FAB) m/z: 473 (M^++Na), 135 (100%); HRMS (FAB) Calcd for $C_{21}H_{27}IOSiNa$ (M^++Na) 473.0774, Found: 473.0784.

4.2.2. (*4R,2'S*)-4-Benzyl-3-[7'-(*tert*-butyldiphenylsiloxy)-2'-methylhept-4'-enoyl]oxazolidin-2-one

13. To a solution of diisopropylamine (1.08 mL, 7.73 mmol) in THF (21 mL) at -78 ºC was added BuLi in pentane (1.55 M, 4.9 mL, 7.73 mmol). The mixture was stirred for 20 min at -78 ºC, and a solution of **11** (1.50 g, 6.44 mmol) in THF (10 mL) was added. After the reaction stirred for 1 h at -78 ºC, a solution of **6** (4.35 g, 9.66 mmol) in THF (10 mL) was added to the mixture, which was stirred for 6 h at -40 ºC. After addition of saturated aqueous NH_4Cl (3 mL), the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (30% EtOAc-hexane) to give **13** as a colorless oil (3.29 g, 92%, >99%d.e.). $[\alpha]_D^{26.4}$ -20.1 (*c* 1.07, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +20.37 (*c* 1.08, $CHCl_3$). ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.17 (d, *J* = 6.8 Hz, 3H), 2.18 (ddd, *J* = 7.2, 7.2, 12.8 Hz, 1H), 2.28 (dt, *J* = 6.4, 6.4 Hz, 2H), 2.48 (ddd, *J* = 6.4, 6.4, 12.8 Hz, 1H), 2.65 (dd, *J* = 10.4, 12.8 Hz, 1H), 3.26 (dd, *J* = 2.8, 12.8 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.81 (tq, *J* = 6.8, 6.8 Hz, 1H), 4.13 (dd, *J* = 3.2, 7.6, 10.4 Hz, 1H), 5.47 (dt, *J* = 6.4, 14.8 Hz, 1H), 5.54 (ddd, *J* = 7.2, 6.4, 14.8 Hz, 1H), 7.20-7.40 (m, 11H), 7.64-7.70 (m, 4H). ^{13}C-NMR (100MHz, $CDCl_3$) δ: 16.4 (q), 19.2 (s), 26.9 (q), 36.6 (t), 36.9 (t), 37.6 (d), 38.1 (t), 55.3 (d), 63.8 (t), 66.0 (t), 127.2 (d), 127.5 (d), 127.6 (d), 128.8 (d), 129.3 (d), 129.4 (d), 133.9 (s), 135.4 (s), 135.5 (d), 152.9 (s), 176.5 (s). IR (KBr, neat): 2931, 2858, 1781, 1698 cm^{-1}. MS (FAB) m/z: 578 (M^++Na), 135 (100%). HRMS (FAB) Calcd for $C_{13}H_{43}NO_4SiNa$ (M^++Na) 556.2883, Found: 556.2888.

4.2.3. (*3S,5R,1'R*)-5-[3'(*tert*-Butyldiphenylsiloxy)-1'-hydroxypropyl-3-methyldihydrofuran-2-one **14.** To a solution of AD-mix β® (16.33 g) in 50% *t*BuOH/H_2O (30 mL) was added $MeSO_2NH_2$ (1.00 g, 10.4 mmol), and the mixture was stirred for 0.5 h at room temperature. The resulting mixture was cooled to 0 ºC, and a solution of **13** (2.33 g, 4.17 mmol) in 50% *t*-BuOH/H_2O (30 mL) was added. The mixture was stirred for 10 h at 0 ºC, and Na_2SO_3 (3.15 g, 25.06 mmol) was added. The resulting mixture was stirred for 0.5 h at room temperature, extracted with $CHCl_3$ (100 mL), and the combined organic layer was washed with sat. $NaHCO_3$ aq (50mL), brine (50mL), and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (30% EtOAc-hexane) to give **14** (1.67 g, 97%): colorless needles (benzene-hexane): mp 93 ºC. $[\alpha]_D^{26}$ -33.19 (*c* 0.97, $CHCl_3$). ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.68 (ddt, *J* = 3.2, 3.2, 14.8 Hz, 1H), 1.94 (m, 1H), 1.96 (m, 1H), 2.44 (ddd, *J* = 3.6, 9.6, 12.4 Hz, 1H), 2.89 (td, *J* = 7.2, 12.4 Hz, 1H), 3.94 (m, 1H), 4.39 (dt, *J* = 3.6, 8.4 Hz, 1H), 7.26-7.47 (m, 6H), 7.66-7.68 (m, 4H). ^{13}C-NMR (100MHz, $CDCl_3$) δ: 16.3 (q), 19.1 (s), 26.8 (q), 32.5 (t), 34.1 (t), 62.5 (t), 73.1 (d), 80.2 (d), 127.2 (d), 127.7 (d), 129.7 (d), 132.6 (s), 132.9 (s), 135.4 (d), 180.4 (s). IR ($CHCl_3$): 3459, 1769 cm^{-1}; MS (FAB) m/z: 435 (M^++Na, 100%). Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.86; H, 7.82. Found: C, 69.72; H, 7.85.

4.2.4.

(*3S,5R,1'R*)-5-[1-(*tert*-Butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)propyl]-3-methyldihydrofuran-2-one **31.** To a solution of **14** (1.37 g, 3.33 mmol) in CH_2Cl_2 (6.7 mL) were added imidazole (793 mg, 11.7 mmol), 4-DMAP (40.3 mg, 0.33 mmol), and TBSCl (1.50 g, 9.99 mmol) at room temperature. The mixture was heated for 10 h under reflux. After addition of water, the resulting mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (10-30% EtOAc-hexane) to give **31** as a colorless oil (1.75 g, quant.). $[\alpha]_D^{26}$ –15.6 (c = 1.16, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +13.09 (c = 0.84, $CHCl_3$). ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.09 (s, 3H), 0.86 (s, 9H), 1.05 (s, 9H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.66-1.74 (m, 1H), 1.78-1.89 (m, 2H), 2.21 (ddd, *J* = 4.4 Hz, 9.2 Hz, 12.8 Hz, 1H), 2.65-2.75 (m, 1H), 3.76 (t, *J* = 6.0 Hz, 2H), 3.92 (dt, *J* = 4.0 Hz, 6.4 Hz, 1H), 4.43 (dt, *J* = 4.4 Hz, 8.4 Hz, 1H), 7.36-7.46 (m, 6H), 7.64 (dd, *J* = 1.2 Hz, 6.4 Hz, 4H). ^{13}C-NMR (100MHz, $CDCl_3$) δ : -4.5 (q), -4.4 (q), 16.6 (q), 18.1 (s), 19.2 (s), 25.9 (q), 26.9 (q), 32.2 (t), 34.3 (d), 35.7 (t), 60.1 (t), 71.5 (d), 79.1 (d), 127.6 (d), 129.6 (d), 129.7 (d), 133.4 (s), 133.5 (s), 135.4 (d), 180.1 (s). IR (KBr, neat): 1779 cm^{-1}. MS (EI) m/z: 526 (M^+), 135 (100%). HRMS (EI) Calcd for $C_{30}H_{46}O_4Si_2$ (M^+) 526.2935, Found: 526.2915.

4.2.5. (*3S,5R,1'R*)-5-[1-(*tert*-Butyldimethylsiloxy)-3-hydroxypropyl]-3-methyldihydrofuran-2-one **32.** TBAF (1.0 M in THF, 0.02 mL, 0.02 mmol) and AcOH (0.01 mL, 0.019 mmol) were added to a solution of **31** (10 mg, 0.02 mmol) in THF (0.1 mL) and CH_2Cl_2 (0.1 mL). The resulting mixture was refluxed for 6 h, and saturated aqueous $NaHCO_3$ was added to neutralize the mixture to a pH of 7. The aqueous phase was saturated with NaCl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (30-75% EtOAc-hexane) to give **32** as a colorless oil (4.6 mg, 84%). $[\alpha]_D^{26}$ -23.7 (*c* 1.00, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +17.24 (*c* 1.45, $CHCl_3$). ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.68-1.76 (m, 2H), 1.84-1.97 (m, 2H), 2.28 (ddd, *J* = 4.4 Hz, 9.6 Hz, 13.2 Hz, 1H), 2.68-2.78 (m, 1H), 3.73-3.83 (m, 2H), 3.94 (dt, *J* = 6.4 Hz, 10.8 Hz, 1H), 4.55 (dt, *J* = 4.4 Hz, 8.8 Hz, 1H). ^{13}C-NMR (100MHz, $CDCl_3$) δ: -4.6 (q), -4.5 (q), 16.5 (q), 18.0 (s), 25.8 (q), 32.0 (t), 34.3 (d), 35.4 (t), 58.8 (t), 71.9 (d), 79.4 (d), 180.1 (s). IR (KBr, neat) 3444, 1770 cm^{-1}. MS (EI) m/z: 288 (M^+), 157 (100%). HRMS (EI) Calcd for $C_{14}H_{28}O_4Si$ (M^+) 288.1757, Found: 288.1744.

4.2.6. (*3S,5R,1'R*)-5-[1-(*tert*-Butyldimethylsiloxy)-3-iodopropyl]-3-methyldihydrofuran-2-one **33**. To a solution of **32** (3.70 g, 12.8 mmol) in CH_2Cl_2 (128 mL) were added Et_3N (3.6 mL, 25.6 mmol) and MsCl (1.9 mL, 19.2 mmol). The mixture was stirred for 30 min at room temperature, and then cooled to 0 ºC. Water was added to the resulting mixture, which was diluted with CH_2Cl_2. The

organic layer was washed with 5% aqueous HCl and saturated aqueous $NaHCO_3$, and was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was dissolved in acetone (128 mL). NaI 11.5 g, 76.8 mmol) was added to the resulting mixture, which was stirred for 0.5 h at room temperature. The solvent was removed and water was added. The resulting mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous $Na_2S_2O_4$ and brine, then dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography (10% EtOAc-hexane) to give a colorless oil **33** (5.10 mg, quant.). $[\alpha]_D^{26}$ -18.1 (*c* 1.06, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +18.62 (*c* 1.02, $CHCl_3$) ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.13 (s, 6H), 0.89 (s, 9H), 1.28 (d, *J* = 7.6 Hz, 3H), 1.90-2.01 (m, 2H), 2.08-2.16 (m, 1H), 2.30 (ddd, *J* = 4.4 Hz, 9.6 Hz, 12.8 Hz, 1H), 2.68-2.78 (m, 1H), 3.19-3.28 (m, 2H), 3.85 (dt, *J* = 4.4 Hz, 6.8 Hz, 1H), 4.47 (dt, *J* = 4.0 Hz, 8.0 Hz, 1H) ^{13}C-NMR (100MHz, $CDCl_3$) δ : -4.4 (q), -4.3 (q), 1.7 (t), 16.5 (q), 18.0 (s), 25.8 (q), 31.8 (t), 34.1 (d), 36.4 (t), 74.0 (d), 78.3 (d), 179.6 (s). IR (KBr, neat): 1774 cm^{-1}. MS (EI) m/z: 398 (M^+), 283 (100%). HRMS (EI) Calcd for $C_{14}H_{27}O_3SiI$ (M^+) 398.0774, Found: 398.0780.

4.2.7. (*1R,4R,5R,7S*)-4-(*tert*-Butyldimethylsilyloxy)-7-methyl-8-oxabicyclo[3.2.1]octan-1-ol **34.** To a solution of **33** (5.10 g, 12.8 mmol) in THF (213 mL) was added *t*-BuLi (1.45 M in pentane, 21.2 mL, 30.7 mmol) at -78 ºC. The mixture was stirred for 30 min, and saturated aqueous NH_4Cl was added. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (15% EtOAc-hexane) to give **34** (3.29 mg, 94%) as a colorless solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.03 (s, 1.5 H), 0.04 (s, 1.5 H), 0.155 (s, 1.5 H), 0.12 (s, 1.5 H), 0.86 (s, 4.5 H), 0.91 (s, 4.5 H), 1.00 (d, *J* = 6.8 Hz, 1.5 H), 1.10 (d, *J* = 6.8 Hz, 1.5 H), 1.43-1.52 (m, 2H), 1.69-1.85 (m, 2H), 1.94 (tt, *J* = 3.2 Hz, 14.4 Hz, 1H), 2.08-2.15 (m, 0.5 H), 2.34 (dd, *J* = 9.2 Hz, 13.2 Hz, 0.5 H), 2.36-2.43 (m, 0.5 H), 2.49 (dd, *J* = 3.6 Hz, 12.8 Hz, 0.5 Hz), 2.56 (s, 0.5 H), 2.70 (s, 0.5 H), 3.40 (dt, *J* = 3.6 Hz, 10.4 Hz, 0.5 H), 3.50 (ddd, *J* = 3.2 Hz, 7.6 Hz, 11.2 Hz, 0.5 H), 3.96-4.00 (m, 0.5 H). ^{13}C-NMR (100MHz, $CDCl_3$) δ : -4.7 (q), -4.7 (q), -4.6 (q), -4.1 (q), 17.3 (q), 17.6 (q), 18.0 (s), 25.8 (q), 27.1 (t), 29.7 (t), 32.5 (t), 35.3 (t), 36.5 (t), 36.6 (d), 37.6 (t), 41.7 (d), 68.0 (d), 76.0 (d), 76.4 (d), 78.6 (d), 104.1 (s), 214.0 (s). IR (0.2mm KBr, $CHCl_3$): 3590, 1701 cm^{-1}; MS (EI) m/z: 272 (M^+), 215 (100%); HRMS (EI) Calcd for $C_{14}H_{28}O_3Si$ (M^+) 272.1808, Found: 398.0780.

4.2.8. 5-(*tert*-Butyldimethylsiloxy)-4-(*tert*-butyldiphenylsiloxy)-2-methylcycloheptanone **36**. To a solution of **34** (11.4 mg, 0.04 mmol) in CH_2Cl_2 (0.08 mL) were added imidazole (5.1 mg, 0.07 mmol), 4-DMAP (catalytic amount), and TBDPSCl (0.01 mL, 0.05 mmol) at room temperature. The mixture was stirred for 2 d, and after addition of H_2O, the resulting mixture was extracted with

CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (3% EtOAc-hexane) to give a colorless oil **36** (20 mg, 94%). $[\alpha]_D^{26}$ –0.75 (c = 1.06, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$+0.96 (c 1.04, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: -0.31 (s, 3H), -0.20 (s, 3H), 0.77 (s, 9H), 1.05 (s, 9H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.59-1.69 (m, 2H), 1.98-2.06 (m, 1H), 2.28-2.35 (m, 2H), 2.51-2.60 (m, 1H), 2.72 (ddd, *J* = 3.2 Hz, 11.6 Hz, 12.8 Hz, 1H), 3.51 (dt, *J* = 2.4 Hz, 5.6 Hz, 1H), 3.94 (ddd, *J* = 2.0 Hz, 4.8 Hz, 7.2 Hz, 1H), 7.35-7.47 (m, 6H), 7.65 (dd, *J* = 1.2 Hz, 8.0 Hz, 4H). ^{13}C-NMR (100MHz, $CDCl_3$) δ: -5.1 (q), -5.0 (q), 17.9 (q), 18.2 (s), 19.2 (s), 25.7 (q), 27.2 (q), 27.2 (t), 32.1 (t), 36.6 (t), 42.6 (d), 71.7 (d), 74.8 (d), 127.6 (d), 127.7 (d), 129.7 (d), 129.7 (d), 133.8 (s), 133.9 (s), 135.7 (d), 135.8 (d), 213.5 (s). IR (KBr, neat) 1711 cm^{-1}; MS (EI) m/z: 510(M^+), 193 (100%); HRMS (EI) Calcd for $C_{30}H_{46}O_3Si_2$ (M^+) 510.2986, Found: 510.3013.

4.2.9. (*1S,2S,4R,5R*)-5-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-2-methyl-1-vinylcycloheptanol **39**. To a 1.0 M THF solution of vinylmagnesium bromide (3.5 mL, 3.51 mmol) was added **36** (0.89 g, 1.75 mmol) in THF (6.0 mL), and the mixture was refluxed for 6 h. After cooling to room temperature, the mixture was poured into 0.3M HCl at 0 ºC. The mixture was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (5% EtOAc-Hexane), to give **39** as a colorless oil (0.90 g, 96%). $[\alpha]_D^{26}$ -12.58 (*c* 1.04, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$+14.96 (c 1.47, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: -0.23 (s, 3H), -0.12 (s, 3H), 0.80 (s, 9H), 1.09 (s, 9H), 1.41-1.52 (m, 2H), 1.65-1.75 (m, 3H), 1.87 (m, 1H), 2.17 (m, 1H), 2.91 (s, 1H), 3.62 (m, 1H), 3.86 (m, 1H), 4.95 (dd, *J* = 1.6Hz, 10.8 Hz, 1H), 5.17 (dd, *J* = 1.6 Hz, 17.2 Hz, 1H), 5.77 (dd, *J* = 10.8 Hz, 17.2 Hz, 1H), 7.34-7.45 (m, 6H), 7.67-7.71 (m, 4H). ^{13}C-NMR (100MHz, $CDCl_3$) δ: -4.8 (q), -4.7 (q), 17.9 (q), 18.5 (s), 19.1 (s), 25.8 (q), 26.0 (t), 27.1 (q), 35.1 (t), 36.2 (t), 38.4 (d), 73.8 (d), 75.7 (s), 76.6 (d), 109.8 (t), 127.5 (d), 127.6 (d), 129.6 (d), 129.7 (d), 133.5 (s), 133.7 (s), 135.8 (d), 135.9 (d), 146.2 (d). IR (KBr, neat): 3464, 1704 cm^{-1}; MS (ESI) m/z: 561 (M^++Na); HRMS (ESI) Calcd for $C_{32}H_{50}O_3NaSi_2$ (M^++Na) 561.3196, Found: 561.3192.

4.2.10. (*1S,4R,5R,7S*)-5-(*tert*-Butyldiphenylsilyloxy)-7-methyl-1-vinylcycloheptane-1,4-diol **40**. To a solution of **39** (1.35 g, 1.61 mmol) in THF (14.2 mL) was added 6M HCl (1.8 mL). The mixture was stirred for 18 h at room temperature, and then extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (30% EtOAc-hexane) to give **40** as colorless needles (0.62 g, 91%): (EtOAc-hexane): mp 110 ºC; $[\alpha]_D^{25}$ -49.55 (c 1.12, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +53.19 (*c* 0.94, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ:

0.51 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 1.13 (m, 3H), 1.36 (m, 1H), 1.55-1.60 (m, 1H), 1.76-1.83 (m, 2H), 1.90 (m, 1H), 2.42 (s, 1H), 3.53 (m, 1H), 3.64 (m, 1H), 4.96 (dd, *J* = 1.2 Hz, 11.2 Hz, 1H), 5.079 (dd, *J* = 1.2 Hz, 17.2 Hz, 1H), 5.75 (dd, *J* = 11.2 Hz, 17.2 Hz, 1H), 7.40 (m, 6H), 7.66 (m, 4H). ^{13}C-NMR (150MHz, $CDCl_3$) δ: 16.1 (q), 19.3 (s), 25.3 (t), 27.0 (q), 35.5 (t), 35.7 (t), 36.5 (d), 75.5 (s), 78.5 (d), 81.1 (d), 110.9 (d), 127.6 (d), 127.8 (d), 129.7 (d), 129.8 (d), 133.7 (s), 135.6 (d), 135.7 (d), 145.3 (d). IR (0.1 mm NaCl, $CHCl_3$): 3427, 1633 cm^{-1}; MS (FAB) m/z: 425 (M^++1),; Anal. Calcd for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54. Found: C, 73.47; H, 8.49.

4.2.11. (*1S,2R,4S,5S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-methyl-5-vinyl-8-oxabicyclo[3.2.1]octan-1-ol **41.** To a solution of **40** (0.62 g, 1.46 mmol) in CH_2Cl_2 (10 mL) were added 4-methylmorpholine *N*-oxide (0.85 g, 7.30 mmol) and MS4A (0.73 g). The mixture was stirred at room temperature for 10 min, and tetrapropylammonium perruthenate (0.02 g, 0.07 mmol) was added. The mixture was stirred for 1 h, and filtered through a pad of Celite. The solvent was removed from the filtrate and the crude product was purified with column chromatography (30% EtOAc-hexane) to give **41** as a colorless oil (0.61 g, quant.). $[\alpha]_D^{25}$ -40.62 (*c* 1.35, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +54.54 (*c* 0.33, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.09 (s, 9H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.46 (m, 2H), 1.69-1.95 (m, 5H), 3.72 (s, 1H), 3.77 (m, 1H), 5.04 (dd, *J* = 1.48 Hz, 11 Hz, 1H), 5.23 (dd, *J* = 1.48 Hz, 17.5 Hz, 1H), 5.93 (dd, *J* = 11 Hz, 17.5 Hz, 1H), 7.40 (m, 6H), 7.70 (m, 4H); ^{13}C-NMR (150MHz, $CDCl_3$) δ: 17.4 (q), 19.3 (s), 27.1 (q), 32.0 (t), 32.4 (t), 34.3 (t), 35.5 (d), 72.2 (d), 85.2 (s), 104.3 (s), 112.0 (t), 127.7 (d), 127.9 (d), 129.8 (d), 129.9 (d), 133.1 (s), 133.4 (d), 135.8 (d), 136.2 (d), 141.3 (d); IR (KBr neat): 3551 cm^{-1}; MS (FAB) m/z: 422 (M^+): HRMS (FAB) Calcd for $C_{26}H_{34}O_3Si$ (M^++Na) 422.2277, Found: 422.2278.

4.2.12. (*1S,2R,4S,5S*)-4-Methyl-5-vinyl-8-oxabicyclo[3.2.1]octane-1,2-diol **42.** To a solution of **41** (0.l6 g, 1.46 mmol) in THF (15 mL) was added TBAF (1.0M in THF, 1.7 mL). The mixture was stirred at room temperature for 30 min, and the solvent was removed in vacuo. The residue was purified with column chromatography (30-60% EtOAc-hexane) to give **42** as colorless needles (0.26 g, quant.). Colorless needles (EtOAc-hexane): mp 63-64 ºC; $[\alpha]_D^{25}$ –50.98 (c = 1.02, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +64.38 (c = 0.73, $CHCl_3$); 1H-NMR (400MHz, $CDCl_3$) δ: 1.11 (d, *J* = 7.2 Hz, 3H), 1.60 (m, 1H), 1.76 (m, 1H), 1.84-2.00 (m, 4H), 2.04 (m, 1H), 2.16 (m, 1H), 3.60 (m, 1H), 3.88 (s, 1H), 5.08 (dd, *J* = 1.2 Hz, 11.2 Hz, 1H), 5.26 (dd, *J* = 1.2 Hz, 18 Hz, 1H), 5.90 (dd, *J* = 11.2 Hz, 18 Hz); ^{13}C-NMR (150MHz, $CDCl_3$) δ : 18.1 (q), 32.1 (t), 32.9 (t), 34.4 (t), 35.1 (d), 70.9 (d), 85.4 (s), 104.5 (s), 112.1 (t), 140.5 (d); IR (0.1 mm NaCl, $CHCl_3$) : 3537 cm^{-1}; MS (FAB) m/z : 185 (M^++1), 154 (100%); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.11; H, 8.72.

4.2.13.

(*6S,7S,8aR*)-6-Hydroxy-3,7-dimethyl-6-vinyl-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[b]furan-2-one **46.** To a solution of **42** (0.10 g, 0.54 mmol) in xylene (10.8 mL) was added the Wittig reagent ($Ph_3PC(CH_3)CO_2CH_2CF_3$, 1.80 g, 4.32 mmol). The resulting mixture was refluxed for 4 h. The solvent was removed and the crude residue was purified with column chromatography (50% EtOAc-hexane) to give **46** as colorless prisms (0.112 g, 92%): (EtOAc-hexane): mp 151 ºC; $[\alpha]_D^{25}$ -140.27 (*c* 1.08, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ +133.11 (*c* 1.54, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.93 (d, *J* = 6.8 Hz, 3H), 1.61 (m, 1H), 1.775 (m, 1H), 1.779 (s, 3H), 1.86 (m, 2H), 2.11 (m, 1H), 2.53 (m, 1H), 2.89 (m, 1H), 4.87 (bd, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 10.8 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 5.93 (dd, *J* = 10.8 Hz, 17.6 Hz, 1H); ^{13}C-NMR (150MHz, $CDCl_3$) δ: 8.2 (q), 17.1 (q), 20.8 (t), 36.0 (t), 36.3 (t), 39.9 (d), 75.3 (s), 82.1 (d), 110.4 (t), 120.8 (d), 146.3 (d), 164.8 (s), 174.5 (s). IR ($CHCl_3$): 3471, 1741, 1672 cm^{-1}. MS (EI) m/z: 222 (M^+), 204 (100%); Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.05; H, 8.12. CCDC-629263 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts.retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

4.2.14.

(*6R,7S,8aR*)-6-Hydroxy-3,7-dimethyl-6-(oxiran-2-yl)-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[b]furan-2-one **48.** To a solution of **46** (50 mg, 0.22 mmol) in CH_2Cl_2 (2.2 mL) was added *m*-chloroperbenzoic acid (155.3 mg, 0.90 mmol). The mixture was stirred for 10 h at room temperature, and then saturated aqueous $NaHCO_3$ and brine were added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed and the crude residue was purified with column chromatography (60% EtOAc-hexane) to give **48** (50.2 mg, 96%) as colorless prisms; (CH_2Cl_2-hexane); mp. 220 ºC; $[\alpha]_D^{22}$ –99.25 (c = 1.35, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.01 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 1H), 1.67 (ddd, *J* = 11.2 Hz, 12 Hz, 14 Hz, 1H), 1.77 (s, 3H), 1.81-1.89 (m, 2H), 2.59 (m, 1H), 2.81 (m, 1H), 2.91 (d, *J* = 4 Hz, 2H), 2.98 (t, *J* = 4 Hz, 1H), 4.89 (bd, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100MHz, $CDCl_3$) δ: 8.3 (q), 16.7 (q), 20.7 (t), 34.0 (t), 36.7 (t), 38.5 (d), 46.5 (t), 58.0 (d), 71.3 (s), 81.9 (d), 121.1 (s), 164.4 (s), 174.4 (s). IR ($CHCl_3$): 3018, 1743 cm^{-1}. MS (EI) m/z: 238 (M^+), 177 (100%); Anal. Calcd for $C_{13}H_{18}O_4$: C, 66.53; H, 7.61. Found: C, 65.26; H, 7.58.

4.2.15. (*3S,3aR,6R,7S,8aR*)-6-Hydroxy-3,7-dimethyl-6-(oxiran-2-yl)octahydro-2*H*-cyclohepta[*b*]furan-2-one **49.** To a suspension of **48** (139 mg, 0.58 mmol) and $NiCl_2$ (19 mg, 0.14 mmol) in MeOH (10 mL) was added $NaBH_4$ (88 mg, 2.34 mmol) at 0 ºC. The mixture was stirred at 0 ºC for 2 h, and then saturated aqueous NH_4Cl (5 mL) was added. The resulting mixture was diluted with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed

with brine and dried over $MgSO_4$. The solvent was removed and the crude residue was purified by HPLC (60% EtOAc-hexane) to give **49** as colorless prisms (114 mg, 81%, 4:1 mixture of diastereomers of the oxirane) and C11-isomer (14%). Major isomer of **49**: colorless prisms (CH_2Cl_2-hexane); mp 150 ºC; $[\alpha]_D^{22}$ -5.00 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.00 (d, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.45-1.59 (m, 2H), 1.72 (m, 3H), 2.02 (ddd, *J* = 7.6 Hz, 7.6 Hz, 8.0 Hz, 1H), 2.35 (ddd, *J* = 10.4 Hz, 11.2 Hz, 14.8 Hz, 1H), 2.58 (m, 1H), 2.78-2.87 (m, 3H), 2.93 (dd, *J* = 2.8 Hz, 5.2 Hz, 1H), 4.67 (ddd, *J* = 6.6 Hz, 12 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 11.1 (q), 17.3 (t), 17.8 (q), 33.2 (t), 34.5 (d), 38.9 (d), 40.9 (t), 43.4 (d), 45.1 (t), 58.3 (d), 71.2 (s), 80.8 (r), 179.1 (s). IR (0.1 mm NaCl, $CHCl_3$): 1762 cm^{-1}. MS (FAB) m/z: 241 (M^++1); Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.93; H, 8.36.

4.2.16. (*3S,3aR,7S,8aR*)-3,7-Dimethyl-6-(oxiran-2-yl)-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*] furan-2-one **50**. To a solution of **49** (3.0 mg, 0.0125 mmol) in CH_2Cl_2 (1.2 mL) was added dropwise a solution of freshly distilled thionyl chloride (1.8 μL, 0.025 mmol) and pyridine (4 μL) in CH_2Cl_2 (0.3 mL) at -20 ºC. The resulting mixture was stirred at -20 ºC for 10 min then saturated aqueous $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with aqueous $CuSO_4$ and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (20% EtOAc-hexane) to give **50** as a colorless oil (2.5 mg, 87%); Major isomer: mp. 71.5-72 ºC (hexane-EtOAc); $[\alpha]_D^{22}$ -16.22º (*c* 0.31, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.16 (d, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.95-2.19 (m, 4H), 2.47 (dd, *J* = 6.4 Hz, 3.2 Hz, 1H), 2.48 (m, 1H), 2.73 (m, 1H), 2.83 (m, 1H), 2.91 (dd, *J* = 6.4 Hz, 4.4 Hz, 1H), 3.23 (bs, 1H), 4.65 (m, 1H), 5.73 (bd, *J* = 9.6 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ : 10.6 (q), 21.0 (q), 31.8 (t), 36.9 (d), 38.9 (d), 42.3 (t), 50.4 (d), 52.7 (d), 53.2 (d),80.1 (t), 121.4 (d), 141.2 (s), 178.8 (s). IR (NaCl, neat): 1770 cm^{-1}. MS (EI) m/z: 222 (M^+), 60 (100%); HRMS (EI) Calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, Found: 222.1258.

4.2.17. Sundiversifolide (**4**). To a solution of **50** (18.6 mg, 0.0837 mol) in CH_2Cl_2 (1.5 mL) and THF (0.1 mL) was added ZnI_2 (80.1 mg, 0.25 mmol) and $NaBH_3CN$ (16.5 mg, 0.25 mmol). The mixture was stirred for 2 h at room temperature, and 1M aqueous HCl (0.1 mL) was added at 0 ºC. The resulting mixture was saturated with NaCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (70% EtOAc-hexane) to give **4** as a colorless solid (15.9 mg, 85%). mp. 42-47 ºC; $[\alpha]_D^{20}$ +33.0 (*c* 0.44, $CHCl_3$), enantiomer; $[\alpha]_D^{20}$ -33.7º (*c* 0.46, $CHCl_3$); ^{1}H-NMR (400MHz, CD_3OD) δ: 1.11 (d, *J* = 7.3 Hz, 3H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.87-1.99 (m, 2H), 2.01-2.04 (m, 2H), 2.10-2.23 (m, 2H), 2.72-2.80 (m, 1H), 2.86-2.94 (m, 1H), 3.50-3.63 (m, 2H), 4.67-4.73 (m, 1H), 5.53-5.55 (m, 1H). ^{13}C-NMR (150MHz, CD_3OD) δ: 10.9, 21.8, 22.8, 33.9, 38.2, 40.1, 41.2, 43.5,

62.1, 82.5, 125.3, 143.6, 181.8; IR (neat): 3415, 1651, 1732 cm^{-1}. HRMS (EI) Calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, Found 224.1405.

4.3. Synthesis of 5

4.3.1. (3*S*,3a*R*,7*S*,8a*R*)-3,7-Dimethyl-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one **5.** To a solution of the epoxide **50** (6.2 mg, 27.9 μmol) in H_2O/methanol (1:10, 0.3 mL) was added potassium selenocyanate (16.1 mg, 111.6 μmol). The mixture was stirred for 10 h at room temperature. The reaction was filtered, diluted with water, and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (10% EtOAc/Hex) to give **5** (5.2 mg, 90%) as colorless prisms: mp 53.0-54.0 ºC (EtOAc-Hex); $[\alpha]_D^{21}$ -21.21 (*c* 0.33, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.19 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 4.8 Hz, 3H), 1.98-2.05 (m, 2H), 2.16 (ddd, *J* = 13.8 Hz, 5.4 Hz, 3.6 Hz, 1H), 2.43-2.48 (m, 1H), 2.71-2.86 (m, 3H), 4.63 (ddd, *J* = 11.4 Hz, 7.2 Hz, 3.6 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 5.74 (dd, *J* = 9.0 Hz, 5.4 Hz, 1H), 6.17 (dd, *J* = 17.4 Hz, 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 12.2 (q), 21.7 (q), 22.2 (t), 31.1 (d), 36.7 (t), 38.1 (d), 40.5 (d), 80.5 (d), 111.9 (t), 127.1 (d), 139.8 (d), 144.2 (s), 179.6 (s); IR (KBr): 2933, 1743 cm^{-1}; MS (EI) m/z: 206 (M^+), 91 (100%); HRMS (EI) calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1311.

4.4. Synthesis of (+)-8-*epi*-xanthatin (1)

4.4.1. (3*R*,3a*S*,7*S*,8a*R*)-3-Bromo-3,7-dimethyl-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta [*b*]furan-2-one **51.** To a solution of **5** (70.0 mg, 0.34 mmol) in THF (3.4 mL) was added LDA (0.61 M) (0.72 mL, 0.44 mmol) at -78 °C. The mixture was stirred for 1 h at -78 °C, and then CBr_4 (225 mg, 0.68 mmol) in THF (1.0 mL) was added dropwise at -78 °C. After 20 min at -78 °C, the reaction was quenched with aqueous saturated NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (5% EtOAc/Hex) to give **51** (37.4 mg, 39%) as a colorless oil and **52** (53%) as a white solid.

51: $[\alpha]_D^{25}$ -44.4 (*c* 0.27, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.19 (d, *J* = 7.2 Hz, 3H), 1.87 (s, 3H), 2.00-2.06 (m, 1H), 2.15-2.24 (m, 2H), 2.37-2.42 (m, 1H), 2.67-2.73 (m, 1H), 3.10 (ddd, *J* = 13.2 Hz, 7.2 Hz, 3.0 Hz, 1H), 4.94 (ddd, *J* = 11.4 Hz, 6.6 Hz, 4.8 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 5.13 (d, *J* = 18.0 Hz, 1H), 5.73 (dd, *J* = 9.0 Hz, 4.2 Hz, 1H), 6.17 (dd, *J* = 18.0 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz,$CDCl_3$) δ: 22.1 (q), 22.9 (t), 24.1 (q), 30.9 (d), 35.8 (t), 52.5 (d), 57.3 (s), 79.4 (d), 112.8 (t), 125.2 (d), 139.6 (d), 145.2 (s), 174.3 (s); IR ($CHCl_3$): 2958, 1774, 1207 cm^{-1}; MS (EI) m/z: 286 ($[M+H]^+$), 284 ($[M-1]^+$), 79 (100%); HRMS (EI) calcd for $C_{13}H_{17}O_2Br$: 284.0412, found: 284.0411.

52: mp 86-87.5 ºC; $[\alpha]_D^{25}$ -16.7 (*c* 0.18, $CHCl_3$); ^{1}H-NMR (600 MHz,$CDCl_3$) δ: 1.19 (d, *J* = 6.6 Hz, 3H), 1.93 (s, 3H), 2.16 (ddd, *J* = 14.4 Hz, 7.8 Hz, 1.8 Hz, 1H), 2.25 (ddd, *J* = 13.8 Hz, 9.0 Hz, 4.8 Hz, 1H), 2.43-2.49 (m, 2H), 2.79-2.88 (m, 2H), 4.51 (ddd, *J* = 12.6 Hz, 8.4 Hz, 1.8 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 5.15 (d, *J* = 17.4 Hz, 1H), 5.74 (dd, *J* = 9.0 Hz, 6.0 Hz, 1H), 6.16 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.2 (q), 25.9 (t), 27.8 (q), 31.2 (d), 33.0 (t), 47.1 (d), 58.5 (s), 79.1 (d), 112.0 (t), 125.5 (d), 139.6 (d), 143.9 (s), 174.8 (s); IR ($CHCl_3$): 2941, 1762, 1236, 1209, 1105, 979 cm^{-1}; MS (EI) m/z: 286 ($[M+H]^+$), 284 ($[M-1]^+$), 91 (100%); HRMS (EI) calcd for $C_{13}H_{17}O_2Br$: 284.0412, found: 284.0417.

*Conversion of **52** to **51***: To a solution of **52** (7.7 mg, 27.0 μmol) in THF (300 μL) was added LDA (0.61 M, 66 μL, 40.5 μmol) at -78 °C. The mixture was stirred for 1 h at -78 °C, then CBr_4 (17.9 mg, 54 μmol) in THF (200 μL) was added dropwise at -78 °C. After 20 min at -78 °C, the reaction was quenched with aqueous saturated NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, then dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (5% EtOAc/Hex) to give **51** (3.3 mg, 43%) as a colorless oil and **52** (4.4 mg, 57%) as a white solid.

4.4.2. (3a*R*,7*S*,8a*R*)-7-methyl-3-methylene-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*] furan-2-one **53.** To a solution of **51** (3.9 mg, 13.7 μmol) in THF (0.35 mL) was added TBAF (1.0 M, 27.4 μl, 27.4 μmol) at room temperature. The reaction was stirred for 30 min at room temperature before the reaction was quenched with aqueous saturated NH_4Cl. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (10% AcOEt/Hex) to give **53** (2.8 mg) as colorless needles: mp 74.5-75.5 ºC (EtOAc-Hex); $[\alpha]_D^{25}$ +14.8 (*c* 0.27, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.6 Hz, 3H), 1.84-1.90 (m, 1H), 2.13 (ddd, *J* = 13.8 Hz, 7.2 Hz, 2.4 Hz, 1H), 2.37 (ddd, *J* = 13.8 Hz, 8.4 Hz, 4.8 Hz, 1H), 2.51 (ddd, *J* = 13.8 Hz, 13.8 Hz, 6.0 Hz, 1H), 2.80-2.87 (m, 1H), 3.36-3.42 (m, 1H), 4.66 (ddd, J_1 = 12.0 Hz, 8.4 Hz, 2.4 Hz, 1H), 5.00 (d, *J* = 11.4 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 5.54 (d, *J* = 3.0 Hz, 1H), 5.77 (dd, *J* = 9.0 Hz, 6.6 Hz, 1H), 6.16 (dd, *J* = 17.4 Hz, 11.4 Hz, 1H), 6.29 (d, 1H, *J* = 3.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.5 (q), 26.3 (t), 31.3 (d), 36.4 (t), 41.6 (d), 78.8 (d), 112.1 (t), 122.1 (d), 126.4 (s), 138.6 (d), 139.6 (d), 143.9 (s), 170.2 (s); IR ($CHCl_3$): 2931, 1747, 1272, 977 cm^{-1}; MS (EI) m/z: 204 (M^+), 93 (100%); HRMS (EI) calcd for $C_{13}H_{16}O_2$: 204.1150, found: 204.1153.

4.4.3. (+)-8-*epi*-Xanthatine **1**. To a solution of **53** (1.7 mg, 8.3 μmol) in dry CH_2Cl_2 (1.5 mL), the 2nd generation Hoveyda-Grubbs catalyst **54** (0.5 mg, 0.83 μmol) was added. Freshly distilled methyl vinyl ketone (13.4 μl, 166.4 μmol) was added to the mixture using a syringe pump over 8 h at 45 °C. Upon completion, the mixture was cooled to room temperature before DMSO (15.0 μl) was added.

After 6 h at room temperature, the mixture was evaporated, and the residue was purified by silica gel column chromatography (30% EtOAc/Hex) to give 8-*epi*-xanthatin (**1**) (1.7 mg, 85%) as a colorless oil. $[\alpha]_D^{23}$ +44.0 (*c* 0.25, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.6 Hz, 3H), 1.88-1.94 (m, 1H), 2.17 (ddd, *J* = 13.8 Hz, 7.2 Hz, 2.4 Hz, 1H), 2.30 (s, 3H), 2.57-2.65 (m, 1H), 2.50 (ddd, *J* = 13.8 Hz, 9.0 Hz, 4.8 Hz, 1H), 2.61 (ddd, *J* = 13.8 Hz, 13.8 Hz, 6.0 Hz, 1H), 2.80-2.86 (m, 1H), 3.39-3.44 (m, 1H), 4.65 (ddd, *J* = 12.0 Hz, 8.4 Hz, 2.4 Hz, 1H), 5.57 (d, *J* = 2.4 Hz, 1H), 6.13 (d, *J* = 16.2 Hz, 1H), 6.20 (dd, *J* = 9.0 Hz, 6.0 Hz, 1H), 6.32 (d, *J* = 3.6 Hz, 1H), 6.97 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.5 (q), 27.0 (q), 27.7 (d), 31.7 (q), 36.3 (t), 41.1 (d), 78.2 (d), 122.5 (t), 125.8 (d), 135.7 (d), 138.1 (s), 142.9 (s), 146.4 (d), 169.8 (s), 198.5 (s); IR ($CHCl_3$): 3018, 1758, 1668, 1593, 1274, 1207 cm^{-1}; MS (FAB) m/z: 247 ($[M+H]^+$); HRMS (FAB) calcd for $C_{15}H_{19}O_3$ ($[M+H]^+$): 247.1334, found: 247.1337.

4.5. Synthesis of (-)-dihydroxanthatin (2)

4.5.1. (*S*)-*N*,*N*-Diethyl-2-((1*R*,5*S*,7*R*)-7-hydroxy-5-methyl-4-vinylcyclohept-3-enyl)propanamide **57.** To a solution of **5** (20.0 mg, 97.9 μmol) in CH_2Cl_2 (1.0 mL) were added $AlCl_3$ (39.1 mg, 293.7 μmol) and Et_2NH (30.6 mL, 293.7 μmol) at room temperature. After 30 min at room temperature, the reaction was quenched with 1 M HCl, whereupon the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (50% AcOEt/Hex) to give **57** (27.4 mg) as a colorless oil. $[\alpha]_D^{23}$ -75.0 (*c* 0.40, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.12-1.20 (m, 6H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.72 (dd, *J* = 15.0 Hz, 9.0 Hz, 1H), 1.82 (dt, *J* = 15.0 Hz, 3.6 Hz, 1H), 1.86 (bs, 1H), 1.93-1.97 (m, 1H), 2.02 (dt, *J* = 15.0 Hz, 5.4 Hz, 1H), 2.61 (ddd, *J* = 15.6 Hz, 11.4 Hz, 4.8 Hz, 1H), 2.75-2.84 (m, 2H), 3.30-3.45 (m, 4H), 4.31 (bs, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 5.07 (d, *J* = 16.8 Hz, 1H), 5.78 (dd, *J* = 9.0 Hz, 4.2 Hz, 1H), 6.21 (dd, *J* = 16.8 Hz, 10.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 13.1 (q), 15.0 (q), 15.9 (q), 19.8 (t), 26.0 (t), 30.6 (d), 38.2 (d), 40.0 (t), 40.6 (t), 42.1 (t), 43.9 (q), 71.5 (d), 109.6 (d), 131.3 (d), 140.5 (d), 145.8 (s), 176.1 (s); IR ($CHCl_3$): 2985, 2358, 1731, 1618, 1462, 1434 cm^{-1}; MS (FAB) m/z: 280 ($[M+H]^+$); 280 (100%); HRMS (FAB) calcd for $C_{17}H_{30}NO_2$ ($[M+H]^+$): 280.2277, found: 280.2276.

4.5.2. (*S*)-*N*,*N*-Diethyl-2-((1*R*,5*S*)-5-methyl-7-oxo-4-vinylcyclohept-3-enyl)propanamide **58**. To a solution of **57** (12.3 mg, 44.0 μmol) in CH_2Cl_2 (0.44 mL) were added *N*-methylmorpholine oxide (NMO, 25.8 mg, 0.22 mmol) and MS4A (22 mg) at room temperature. After 10 min at room temperature, tetrapropylammonium perruthenate (TPAP, 1.5 mg, 4.4 μmol) was added. After 30 min, the mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (40% AcOEt/Hex) to give **58** (9.9 mg, 81%) as a colorless oil. $[\alpha]_D^{23}$ +44.9 (*c* 0.29,

$CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.06 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 6.6 Hz, 3H), 2.06 (ddd, *J* = 16.2 Hz, 12.0 Hz, 6.6 Hz, 1H), 2.28 (ddd, *J* = 15.0 Hz, 9.6 Hz, 3.6 Hz, 1H), 2.63 (d, *J* = 6.0 Hz, 2H), 2.84 (ddd, *J* = 12.6 Hz, 10.2 Hz, 3.6 Hz, 1H), 3.00-3.07 (m, 2H), 3.32-3.45 (m, 4H), 4.96 (d, *J* = 10.8 Hz, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 5.83 (dd, *J* = 9.0 Hz, 4.8 Hz, 1H), 6.23 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 13.2 (q), 15.1 (q), 17.2 (d), 18.4 (t), 27.9 (t), 29.8 (d), 36.4 (d), 40.6 (t), 42.2 (t), 49.1 (t), 56.2 (d), 111.0 (t), 129.7 (d), 140.2 (d), 145.0 (q), 174.2 (q), 212.3 (q); IR ($CHCl_3$): 2975, 1701, 1627, 1463, 1220 cm^{-1}; MS (FAB) m/z: 278 ($[M+H]^+$); HRMS (FAB) calcd for $C_{17}H_{28}NO_2$ ($[M+H]^+$): 278.2120, found: 278.2117.

4.5.3. (*S*)-*N*,*N*-Diethyl-2-((1*R*,5*S*,7*S*)-7-hydroxy-5-methyl-4-vinylcyclohept-3-enyl)propanamide **59.** To a solution of **58** (2.0 mg, 7.2 μmol) in THF (0.8 mL) were added Et_3N (5.0 μL, 36 μmol), H_2O (1 μL, 45 μmol) and SmI_2 (0.1 M in THF, 180 μl, 18.0 μmol) at 0 °C. The mixture was stirred for a few seconds at 0 °C, whereupon the reaction was quenched with saturated aqueous NH_4Cl, and then extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (50% AcOEt/Hex) to give **59** (1.6 mg, 80%) and the C8-isomer (20%) as colorless oils. *Major isomer* **59**: $[\alpha]_D^{23}$ -80.0 (*c* 0.25, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.11-1.23 (m, 6H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.59-1.69 (m, 2H), 2.00-2.38 (m, 1H), 2.40 (ddd, *J* = 16.2 Hz, 12.0 Hz, 4.8 Hz, 1H), 2.78 (ddd, *J* = 14.4 Hz, 7.2 Hz, 2.4 Hz, 1H), 2.87-2.92 (m, 1H), 3.28-3.36 (m, 2H), 3.39-3.399 (m, 2H), 3.95-3.99 (m, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 5.15 (d, *J* = 17.4 Hz, 1H), 5.16 (s, 1H), 5.72 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 6.21 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 12.7 (q), 13.0 (q), 14.9 (q), 17.1 (q), 28.6 (d), 31.1 (t), 40.9 (t), 41.5 (d), 42.0 (t), 42.5 (t), 46.5 (d), 69.5 (d), 110.2 (t), 129.3 (d), 140.1 (d), 146.7 (s), 177.1 (s); IR ($CHCl_3$): 2974, 2933, 1608, 1456 cm^{-1}; MS (FAB) m/z: 280 ($[M+H]^+$); HRMS (FAB) calcd for $C_{17}H_{30}NO_2$ ($[M+H]^+$): 280.2277, found: 280.2276.

4.5.4. (3*S*,3a*R*,7*S*,8a*S*)-3,7-Dimethyl-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one **60**.[8c] To a solution of **59** (16.5 mg, 59.1 μmol) in THF (0.47 mL) was added 3 M HCl (0.11 mL). The mixture was refluxed for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The combined organic layers were washed with brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (10% AcOEt/Hex) to give **60** (10.5 mg, 86%) as colorless prisms. mp 82.5-83.5 ºC; $[\alpha]_D^{23}$ -103.1 (*c* 0.32, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.13 (d, *J* = 7.8 Hz, 3H), 1.22 (d, *J* = 7.8 Hz, 3H), 1.70 (ddd, *J* = 12.6 Hz, 12.6 Hz, 3.6 Hz, 1H), 2.07-2.16 (m, 2H), 2.28-2.34 (m, 2H), 2.69 (dq, *J* = 7.8 Hz, 7.8 Hz, 1H), 3.07 (ddq, *J* = 7.8 Hz, 4.2 Hz, 4.2 Hz, 1H), 4.53 (ddd, *J* = 12.6 Hz,

10.2 Hz, 3.0 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 5.81 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 6.23 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 10.2 (q), 18.4 (q),25.0 (t), 28.1 (d), 36.5 (t), 40.0 (d), 46.2 (d), 81.4 (d), 110.3 (t), 129.8 (d), 141.4 (d), 145.4 (s), 180.0 (s); IR (KBr): 2958, 2929, 1766, 1627, 1465, 1450, 1211, 1039, 989, 887 cm^{-1}; MS (EI) m/z: 206 (M^+), 79 (100%); HRMS (EI) calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1302.

4.5.5. (-)-Dihydroxanthatin **2**.[8c] To a solution of **60** (6.2 mg, 30 μmol) in dry CH_2Cl_2 (6.0 mL) were added the 2nd generation Hoveyda-Grubbs catalyst **54** (1.9 mg, 3.0 μmol), and freshly distilled methyl vinyl ketone (49 μL, 0.60 mmol). The mixture was stirred at 45 °C for 1 h. Upon completion, the mixture was evaporated, and the residue was purified by column chromatography (30% EtOAc/Hex) to give dihydroxanthatin (**2**) (6.6 mg, 89%) as colorless prisms. mp 121.0-124.0 ºC (CH_2Cl_2-hexane); $[\alpha]_D^{23}$ -75.0 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.15 (d, *J* = 7.8 Hz, 3H), 1.23 (d, *J* = 7.8 Hz, 3H), 1.72 (ddd, *J* = 12.6 Hz, 12.6 Hz, 3.6 Hz, 1H), 2.13 (dddd, 12.6 H, 12.6 Hz, 7.8 Hz, 2.4 Hz, 1H), 2.21 (ddd, 12.0 H, 12.0 Hz, 3.0 Hz, 1H), 2.30 (s, 3H), 2.35 (ddd, *J* =12.6 Hz, 4.2 Hz, 4.2 Hz, 1H), 2.45 (ddd, *J* = 16.2 Hz, 9.0 Hz, 2.4 Hz, 1H), 2.72 (dq, *J* = 7.8 Hz, 7.8 Hz, 1H), 3.05 (ddq, *J* = 7.8 Hz, 4.2 Hz, 4.2 Hz, 1H), 4.54 (ddd, *J* = 12.6 Hz, 10.8 Hz, 3.0 Hz, 1H), 6.18 (d, *J* = 16.2 Hz Hz, 1H), 6.25 (dd, *J* = 9.6 Hz, 3.0 Hz, 1H), 7.05 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 10.2 (q), 18.4 (q), 25.7 (t), 27.9 (q), 29.0 (d), 36.4 (t), 39.9 (d), 45.9 (d), 80.8 (d), 124.4 (d), 139.3 (d), 144.5 (s), 148.4 (d), 179.0 (s), 198.6 (s); IR (KBr): 2968, 1768, 1679, 1585, 1357, 1282, 1205, 1180, 981 cm^{-1}; MS (EI) m/z: 248 (M^+), 248 (100%); HRMS (EI) calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1417.

4.6. Synthesis of (-)-xanthatin (3)

4.6.1. N,N-Diethyl-2-((1*R*,5*S*,7*R*)-7-hydroxy-5-methyl-4-vinylcyclohept-3-enyl)acrylamide **63.** To a solution of **53** (6.4 mg, 31.3 μmol) in CH_2Cl_2 (0.5 mL) were added $AlCl_3$ (8.4 mg, 62.7 μmol) and Et_2NH (6.5 μl, 62.7 μmol) at 0 °C. The mixture was stirred for 30 min at RT, whereupon the reaction was quenched with 1 M HCl, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (50% AcOEt/Hex) to give **63 (**8.4 mg, 97%) as a colorless oil. $[\alpha]_D^{20}$ -58.3 (*c* 0.06, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.18 (t, *J* = 7.2 Hz, 6H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.78 (ddd, *J* = 14.4 Hz, 4.8 Hz, 2.4 Hz, 1H), 1.86 (ddd, *J* = 14.4 Hz, 9.6 Hz, 2.4 Hz, 1H), 2.07 (ddd, *J* = 14.4 Hz, 7.2 Hz, 7.2 Hz, 1H), 2.68 (bd, *J* = 12.0 Hz, 6H), 2.78 (ddd, *J* = 14.4 Hz, 14.4 Hz, 4.2 Hz, 1H), 2.83 (dq, *J* = 7.2 Hz, 7.2 Hz, 1H), 3.339 (dq, *J* = 14.4 Hz, 7.2 Hz, 1H), 3.343 (dq, *J* = 14.4 Hz, 7.2 Hz, 1H), 3.55 (dq, *J* = 14.4 Hz, 7.2 Hz, 2H), 4.15-4.17 (m, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.96 (bs, 1H), 5.126 (d, *J* = 16.8 Hz, 1H), 5.132 (s, 1H), 5.26 (s, m), 5.73 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 6.21 (dd, *J* = 16.8 Hz, 10.8 Hz,

1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 12.6 (q), 14.2 (q), 20.3 (q), 25.0 (t), 31.4 (d), 38.4 (t), 39.0 (t), 43.3 (t), 48.5 (d), 74.4 (d), 110.4 (t), 115.8 (t), 129.0 (d), 140.4 (d), 146.5 (s), 146.7 (s), 172.2 (s); IR ($CHCl_3$): 2927, 1596, 1458 cm^{-1}; MS (FAB) m/z: 278 ($[M+H]^+$); HRMS (FAB) calcd for $C_{17}H_{28}NO_2$ ($[M+H]^+$): 278.2120, found: 278.2120.

4.6.2. N,N-Diethyl-2-((1*R*,5*S*)-5-methyl-7-oxo-4-vinylcyclohept-3-enyl)acrylamide **64.** To a solution of **63** (7.1 mg, 25.6 μmol) in CH_2Cl_2 (0.3 mL) were added NMO (15.0 mg, 128.0 μmol) and MS4A (12.8 mg) at room temperature. The mixture was stirred for 10 min, and then TPAP (0.9 mg, 2.6 μmol) was added. The mixture was stirred for 30 min. After filtration, the filtrate was purified by silica gel column chromatography (40% AcOEt/Hex) to give **64** as a colorless oil. $[\alpha]_D^{20}$ +11.6 (*c* 0.17, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.15-1.17 (m, 9H), 2.43 (ddd, *J* = 15.6 Hz, 9.6 Hz, 4.2 Hz, 1H), 2.61 (dd, *J* = 10.8 Hz, 5.4 Hz, 1H), 2.75-2.80 (m, 1H), 2.92-3.01 (m, 2H), 3.4 (bs, 3H), 3.47 (dd, *J* = 13.2 Hz, 4.2 Hz, 4.2 Hz, 1H), 3.52 (bs, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 5.22 (s, 1H), 5.26 (d, *J* = 1.2 Hz, 1H), 5.86 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 6.20 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 12.6 (q), 14.2 (q), 20.0 (q), 27.6 (t), 31.2 (d), 38.8 (d), 43.0 (d), 47.3 (t), 57.1 (d), 111.8 (t), 115.3 (t), 128.4 (d), 139.7 (d), 142.9 (s), 144.6 (s), 170.3 (s), 210.3 (s); IR ($CHCl_3$): 2999, 1703, 1610, 1461 cm^{-1}; MS (FAB) m/z: 276 ($[M+H]^+$); HRMS (FAB) calcd for $C_{17}H_{26}NO_2$ ($[M+H]^+$): 276.1964, found: 276.1966.

4.6.3. (3a*R*,7*S*,8a*S*)-7-Methyl-3-methylene-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*] furan-2-one **67.** To a solution of **64** (4.4 mg, 16.0 μmol) in THF (0.3 mL) at 0 °C was added DIBAL-H (18.9 μL, 17.6 μmol). The resulting mixture was stirred for 0.5 h at room temperature, then cooled to 0 °C, whereupon water was added. The mixture was filtered and the filtrate was dried over $MgSO_4$. The crude product (a mixture of the diastereomers, **65**:**63** = 1:1.2) was used directly in the next step. **65**: $[\alpha]_D^{20}$ -141.7 (*c* 0.06, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.12 (d, *J* = 7.8 Hz, 3H), 1.18 (t, *J* = 6.6 Hz, 6H), 1.59-1.61 (m, 1H), 2.14 (ddd, *J* = 13.2 Hz, 4.8 Hz, 2.4 Hz, 1H), 2.17-2.22 (m, 2H), 2.27-2.33 (m, 1H), 2.93-2.96 (m, 1H), 3.40 (dd, *J* = 15.6 Hz, 1H), 2.61 (dd, *J* = 10.8 Hz, 5.4 Hz, 1H), 2.75-2.80 (m, 1H), 2.92-3.01 (m, 2H), 3.40 (dq, *J* = 14.4 Hz, 7.2 Hz, 2H), 3.49-3.57 (m, 2H), 3.9 (bt, *J* = 10.8 Hz, 1H), 4.64 (d, *J* = 3.0 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 5.15 (s, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 5.29 (s, 1H), 5.71 (dd, *J* = 9.6 Hz, 4.2 Hz, 1H), 6.22 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H).

To a solution of the diastereomeric mixture (**65** and **63**) (16.0 μmol) in THF (320 μL) was added 3M HCl (80 μL). The mixture was refluxed for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The combined organic layers were washed with brine, and dried over $MgSO_4$. After the mixture was evaporated, the residue was purified by silica gel column chromatography (10% AcOEt/Hex) to give **67** (1.3 mg, 27% for 2 steps) and **53** (33% for 2

steps) as colorless needles. **67**: mp 77.2-77.7 ºC (hexane); $[\alpha]_D^{23}$ -40.0 (*c* 0.05, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.14 (d, *J* = 7.8 Hz, 3H), 1.83 (ddd, *J* = 12.6 Hz, 12.6 Hz, 3.6 Hz, 1H), 2.14 (ddd, *J* = 16.2 Hz, 11.4 Hz, 3.6 Hz, 1H), 2.35 (ddd, *J* = 13.2 Hz, 4.2 Hz, 3.6 Hz, 1H), 2.51-2.56 (m, 1H), 2.67 (ddd, *J* = 16.2 Hz, 9.0 Hz, 2.4 Hz, 2H), 3.11 (dq, *J* = 3.6 Hz, 3.6 Hz, 1H), 4.29 (ddq, *J* = 12.6 Hz, 10.2 Hz, 2.4 Hz, 1H), 4.99 (d, *J* = 11.4 Hz, 1H), 5.20 (d, *J* = 17.4 Hz, 1H), 5.47 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.18 (d, *J* = 3.0 Hz, 1H), 6.26 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 18.9 (q), 26.6 (t), 28.3 (d), 36.7 (t), 47.9 (d), 82.1 (d), 110.7 (t), 118.6 (t), 128.9 (d), 139.7 (s), 141.5 (d), 145.7 (s), 170.1 (s); IR ($CHCl_3$): 3005, 1764, 1600 cm^{-1}; MS (EI) m/z: 204 (M^+), 204 (100%); HRMS (EI) calcd for $C_{13}H_{16}O_2$: 204.1150, found: 204.1151.

4.6.4. (-)-Xanthatin **3**.[29] To a solution of **67** (3.0 mg, 14.7 μmol) in dry CH_2Cl_2 (3.0 mL) were added the 2nd generation Hoveyda-Grubbs catalyst **54** (0.9 mg, 1.5 μmol), and freshly distilled methyl vinyl ketone (11.9 μL, 147 μmol). The mixture was stirred at 45 °C for 1 h. Upon completion, the mixture was evaporated, and the residue was purified by column chromatography (30% EtOAc/Hex) to give xanthatin (**3**) (3.0 mg, 83%) as colorless needles. mp 112.1-113.1 ºC (Et_2O-hexane); lit.[8d] mp 114.5-115.2 ºC (EtOH); $[\alpha]_D^{25}$ -20.0 (*c* 0.15, $CHCl_3$); lit.[8d] $[\alpha]_D$ -17.8 (*c* 0.14, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.17 (d, *J* = 7.8 Hz, 3H), 186 (ddd, *J* = 12.6 Hz, 12.6 Hz, 3.6 Hz, 1H), 2.22 (ddd, *J* = 12.6 Hz, 9.6 Hz, 3.6 Hz, 1H), 2.31 (s, 3H), 2.38 (ddd, *J* = 12.6 Hz, 4.2 Hz, 2.4 Hz, 1H), 2.53-2.58 (m, 1H), 2.80 (ddd, *J* = 16.2 Hz, 8.4 Hz, 2.4 Hz, 1H), 2.80-2.86 (m, 1H), 3.39-3.44 (m, 1H), 4.65 (ddd, *J* = 12.0 Hz, 8.4 Hz, 2.4 Hz, 1H), 3.09 (ddq, *J* = 8.4 Hz, 4.2 Hz, 4.2 Hz, 1H), 4.30 (ddd, *J* = 12.6 Hz, 9.6 Hz, 2.4 Hz, 1H), 5.49 (d, *J* = 3.0 Hz, 1H), 6.207 (d, *J* = 16.2 Hz, 1H), 6.212 (d, *J* = 3.0 Hz, 1H), 6.29 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 7.08 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 18.9, 27.2, 27.9, 29.2, 36.6, 47.5, 81.5, 119.0, 124.7, 138.1, 139.2, 144.8, 148.5, 169.7, 198.5; IR (KBr): 2927, 1760, 1685, 1587, 1402, 1353, 1247, 1178, 1137, 977 cm^{-1}; MS (EI) m/z: 246 (M^+), 91 (100%); HRMS (EI) calcd for $C_{15}H_{18}O_3$ (M^+): 246.1256, found: 246.1258.

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17. The keto group on **36** was inert to olefinations, such as the Wittig or the Peterson reactions, probably due to the steric hindrance of the TBS and TBDPS groups.
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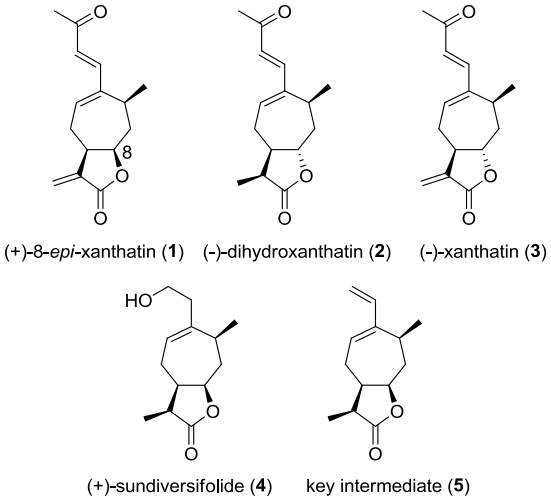


Figure 1. Xanthanolide natural products.

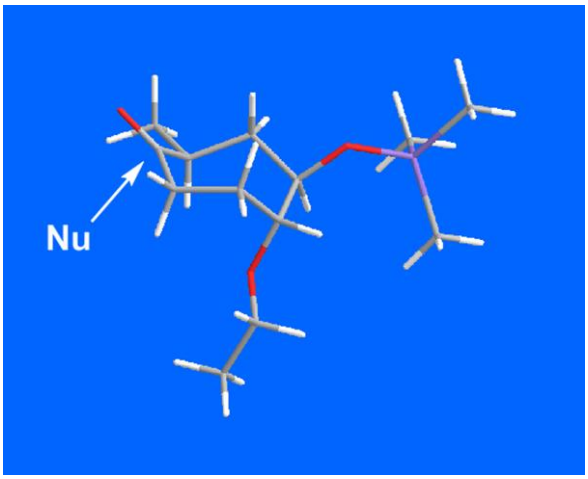


Figure 2. Calculated conformation of **20** (TBDPS group was replaced by TMS for simplification)

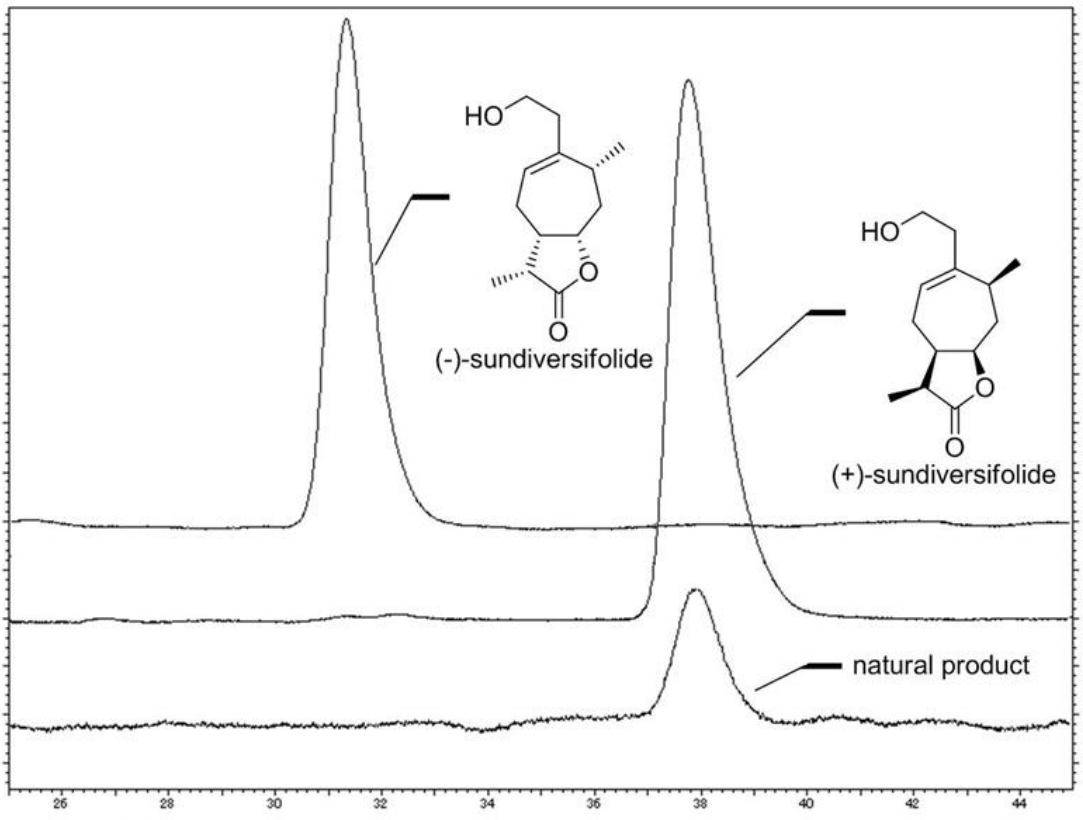
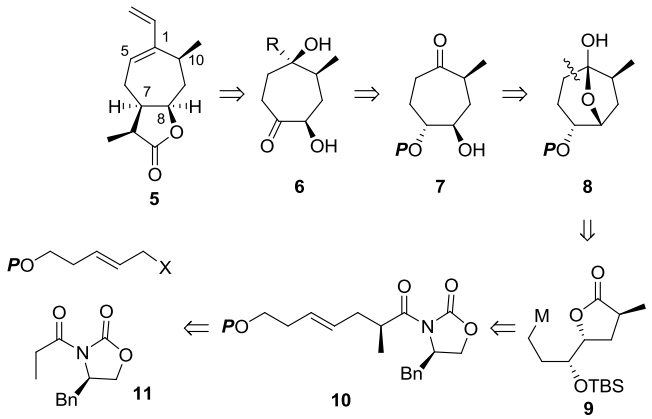
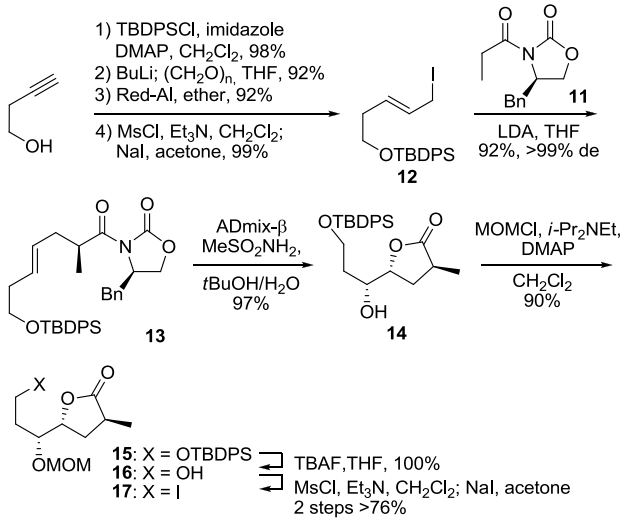


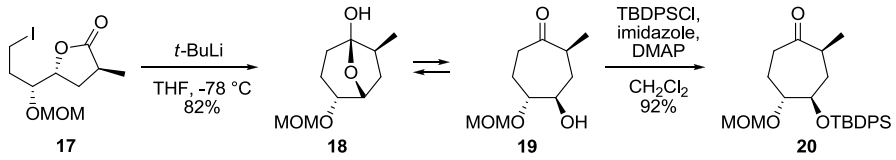
Figure 3. HPLC analysis of natural and unnatural sundiversifolide using a chiral column (Daicel Chiralpak IA, detector: UV 207 nm, hexane/isopropanol 93:7, flow = 1.0 ml/min; (-)-sundiversifolide t_r = 31 min; (+)-sundiversifolide t_r = 38 min, 30 °C)



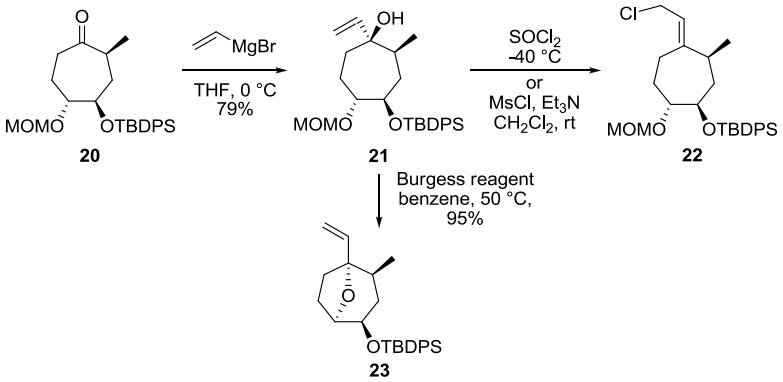
Scheme 1. Retro synthesis of the key intermediate for the xanthanolides.



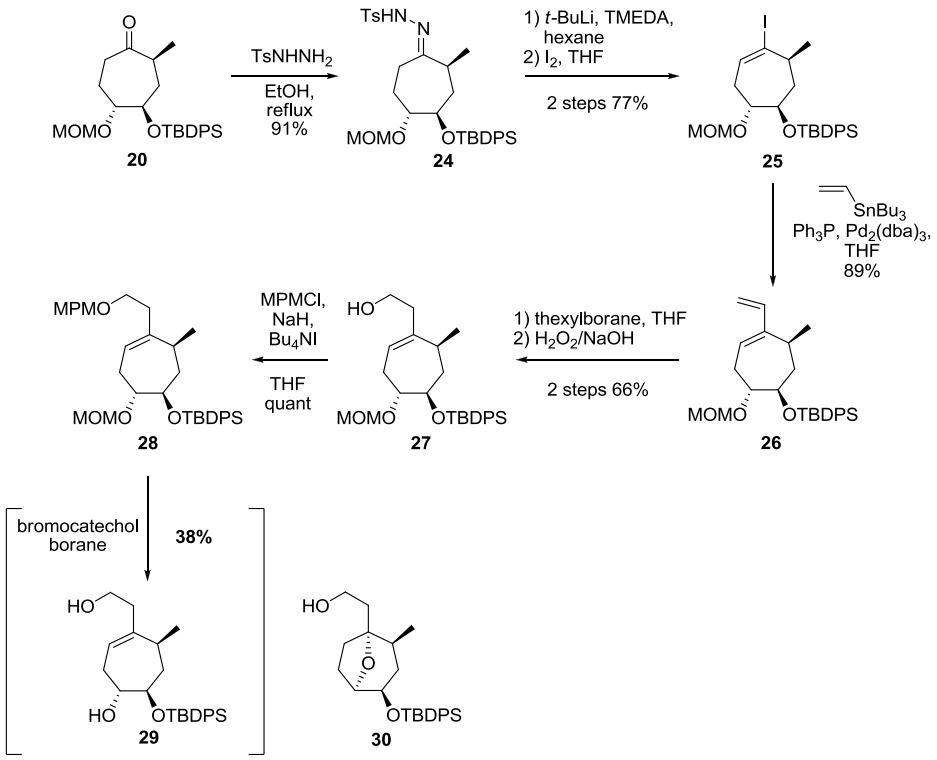
Scheme 2. Asymmetric synthesis of the γ-lactone **17**.



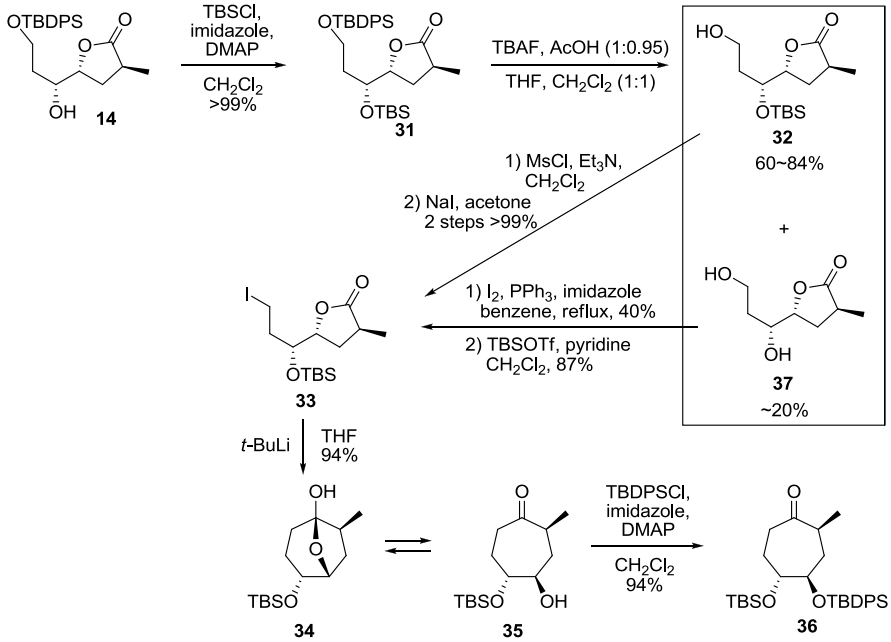
Scheme 3. Intramolecular acylation of the alkyllithium to give the cycloheptanone.


O
MgBr
THF, 0 °C
79%
OH
SOCl2
-40 °C
or
MsCl, Et3N
CH2Cl2, rt
Cl
MOMO
OTBDPS
20
21
22
Burgess reagent
benzene, 50 °C,
95%
O
OTBDPS
23

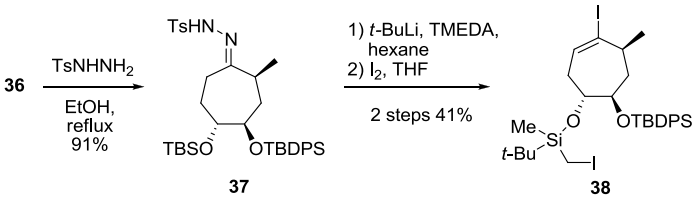
Scheme 4.


O
MOMO
OTBDPS
20
TsNHNH2
EtOH,
reflux
91%
TsHN
N
MOMO
OTBDPS
24
1) t-BuLi, TMEDA,
hexane
2) I2, THF
2 steps 77%
I
MOMO
OTBDPS
25
SnBu3
Ph3P, Pd2(dba)3,
THF
89%
MOMO
OTBDPS
26
1) thexylborane, THF
2) H2O2/NaOH
2 steps 66%
HO
MOMO
OTBDPS
27
MPMCl,
NaH,
Bu4NI
THF
quant
MPMO
MOMO
OTBDPS
28
bromocatechol
borane
38%
HO
HO
OTBDPS
29
HO
O
OTBDPS
30

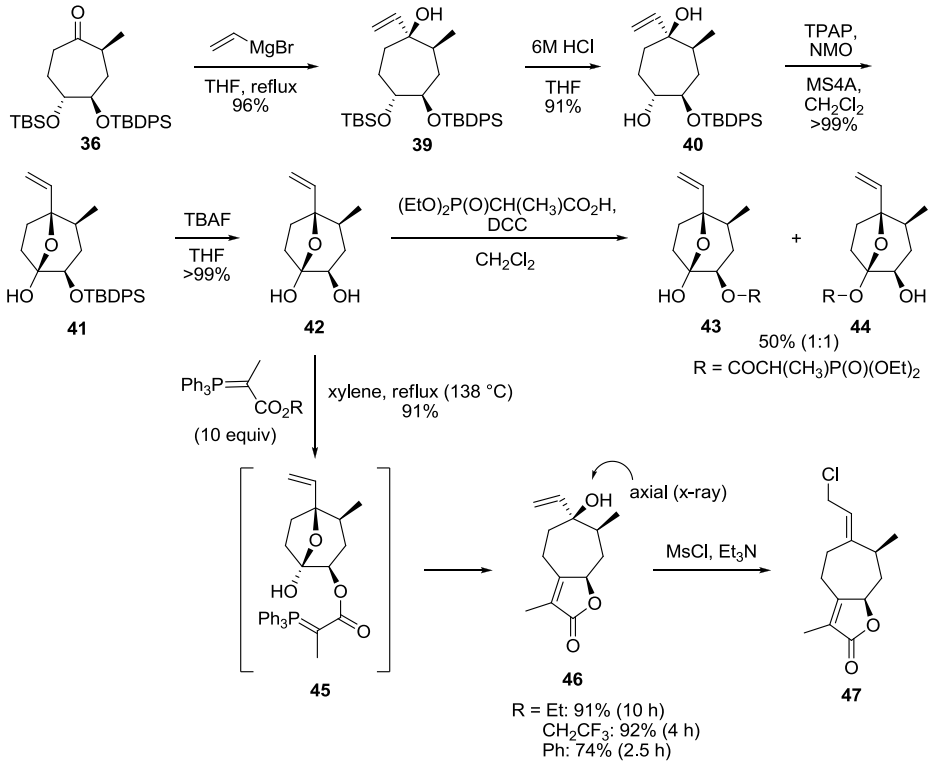
Scheme 5.


OTBDPS
O
O
OH
14
TBSCl,
imidazole,
DMAP
CH2Cl2
>99%
OTBDPS
O
O
OTBS
31
TBAF, AcOH (1:0.95)
THF, CH2Cl2 (1:1)
HO
O
O
OTBS
32
60~84%
1) MsCl, Et3N,
CH2Cl2
2) NaI, acetone
2 steps >99%
+
HO
O
O
OH
37
~20%
I
O
O
OTBS
33
1) I2, PPh3, imidazole
benzene, reflux, 40%
2) TBSOTf, pyridine
CH2Cl2, 87%
t-BuLi
THF
94%
OH
O
TBSO
34
O
TBSO
OH
35
TBDPSCl,
imidazole,
DMAP
CH2Cl2
94%
O
TBSO
OTBDPS
36

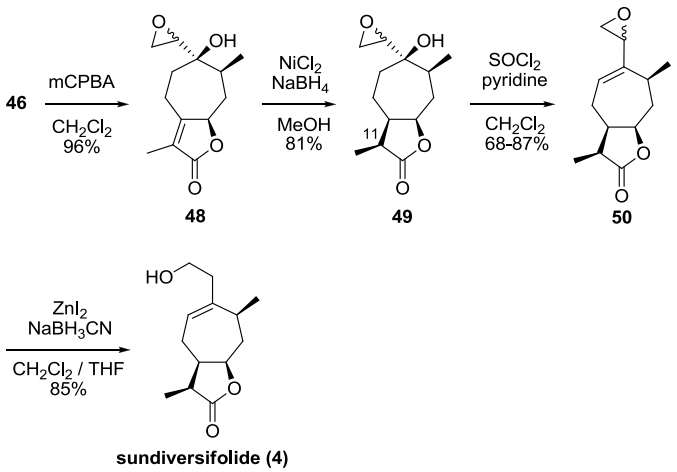
Scheme 6.


36
TsNHNH2
EtOH,
reflux
91%
TsHN
N
TBSO
OTBDPS
37
1) t-BuLi, TMEDA,
hexane
2) I2, THF
2 steps 41%
I
Me
Si
t-Bu
O
OTBDPS
38

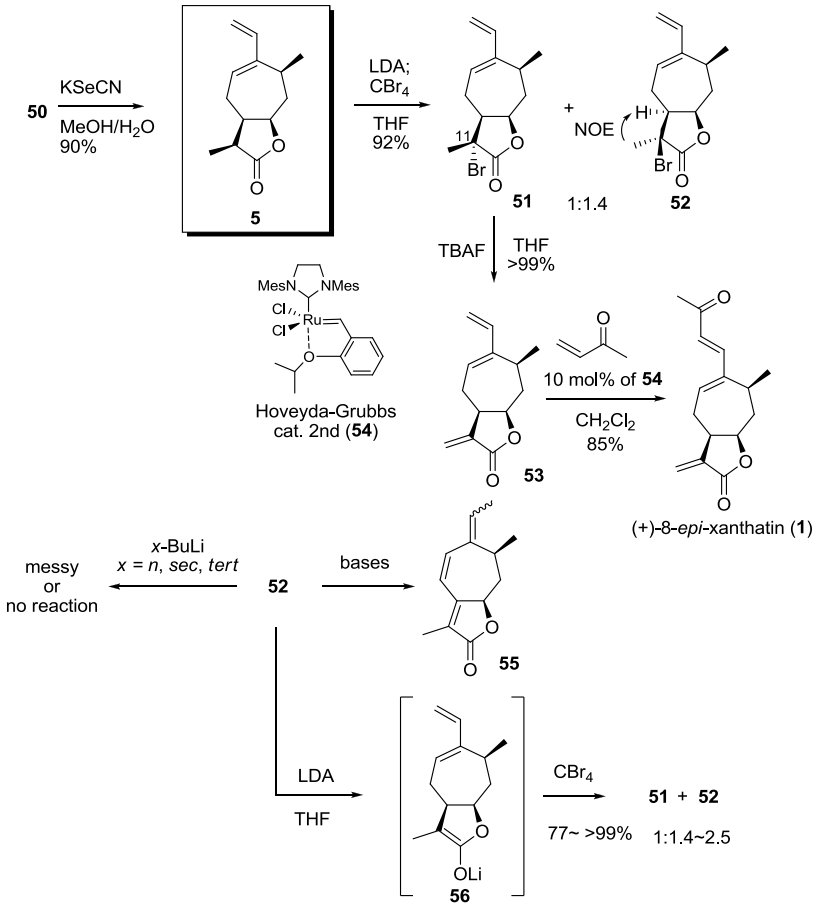
Scheme 7.


TBSO
OTBDPS
36
MgBr
THF, reflux
96%
OH
39
6M HCl
THF
91%
40
TPAP,
NMO
MS4A,
CH2Cl2
>99%
41
TBAF
THF
>99%
42
(EtO)2P(O)CH(CH3)CO2H,
DCC
CH2Cl2
43
44
50% (1:1)
R = COCH(CH3)P(O)(OEt)2
Ph3P
CO2R
(10 equiv)
xylene, reflux (138 °C)
91%
45
axial (x-ray)
MsCl, Et3N
46
R = Et: 91% (10 h)
CH2CF3: 92% (4 h)
Ph: 74% (2.5 h)
47

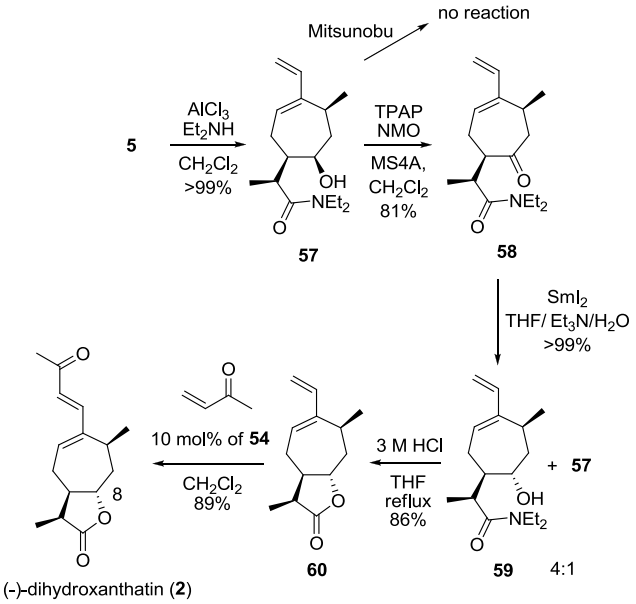
Scheme 8.



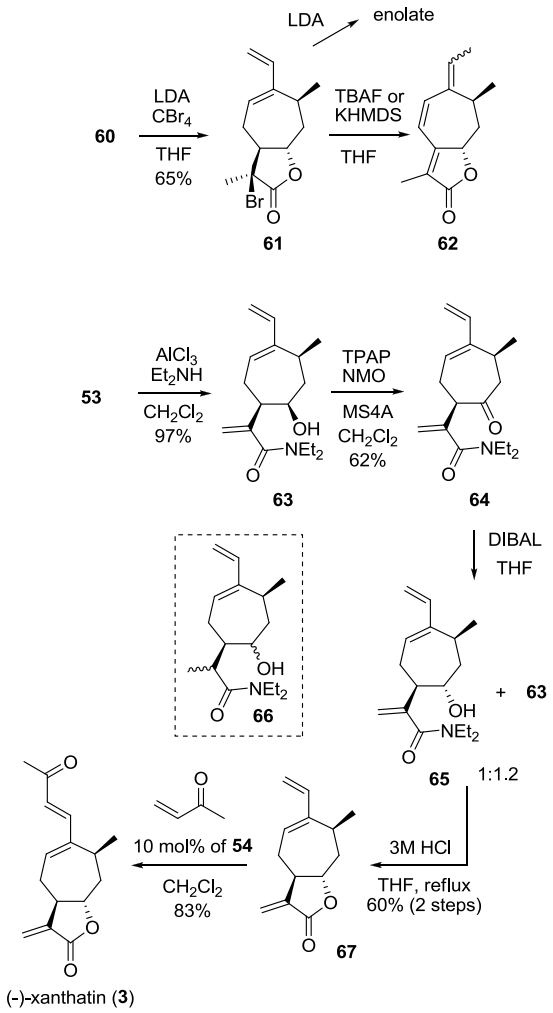
Scheme 9. Synthesis of sundiversifolide **(4)**



Scheme 10. Synthesis of (+)-8-*epi*-xanthatin (**1**)



Scheme 11. Synthesis of (-)-dihydroxanthatin (**2**)



Scheme 12. Synthesis of (-)-xanthatin (**3**)