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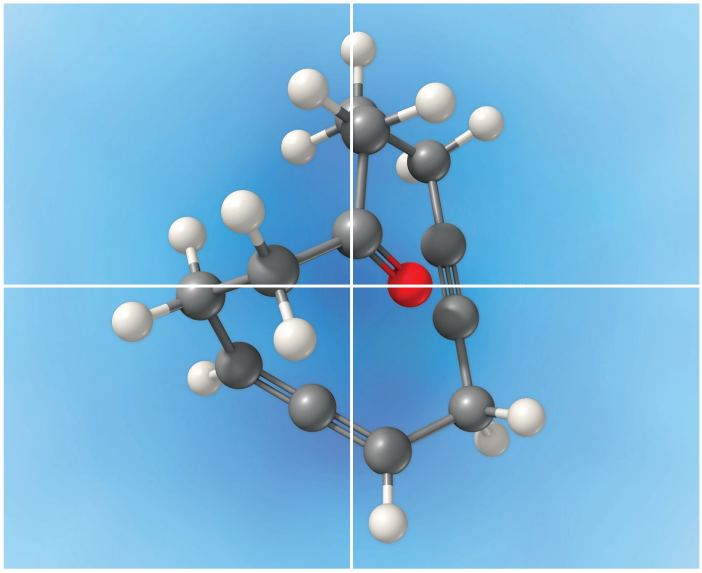

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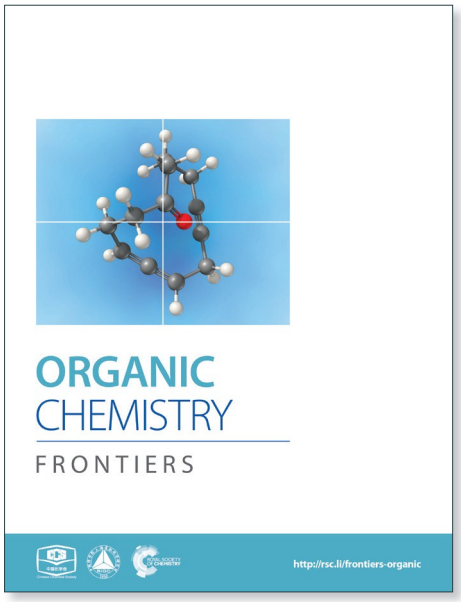

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ARTICLE

Studies towards the synthesis of the functionalized C3-C14 decalin framework of alchivemycin A ‡

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We report our synthetic studies towards the synthesis of the C3-C14 fragment of alchivemycin A. The synthesis featured an asymmetric alkylation with excellent diastereoselectivity and a one-pot Julia-Kocienski olefination with excellent *E*-selectivity. Intramolecular Diels-Alder reaction was employed to construct the highly functionalized *cis*-decalin framework. Interestingly, the stereochemical outcome was unexpected to generate two stereoisomers **20** and **21** instead of the desired *cis*-decalin **5**. Detailed mechanism for this transformation was discussed. These synthetic endeavors have offered us a number of crucial insights for the synthesis of the complex natural product alchivemycin A.

Introduction

Alchivemycins A (**1**) and B (**2**) are two novel 17-membered polycyclic polyketides recently isolated from the culture extract of a plant-derived actinomycete *Streptomyces* sp by Igarashi and co-workers in 2010[1] and 2013,[2] respectively (Fig. 1). Alchivemycin A (**1**) exhibits promising biological activities with potent antimicrobial activity against Gram-positive *Micrococcus luteus* (MIC = 50 nM) and remarkable inhibitory effects against tumor cell invasion (IC_{50} = 0.34 μM) without showing cytotoxic effects. The structure and relative stereochemistry of alchivemycin A (**1**) was assigned by spectroscopic analysis and X-ray crystallography.[1] Altogether, the potent biological activity, combined with the unique structure containing an unprecedented 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine heterocyclic ring as well as a highly functionalized *cis*-decalin (C3-C14 fragment), render it an ideal target for total synthesis.

To date, no total synthesis of alchivemycin A (**1**) or related synthetic studies towards its major fragment have been reported in the literature owing to the significant synthetic challenges underlying its complex structure[3]. Herein, we disclose our synthetic progress towards alchivemycin A, focusing on the construction of the C3-C14 fragment containing the highly functionalized *cis*-decalin.

Results and discussion

From a synthetic perspective, alchivemycin A possesses a considerable degree of structural complexity. Fifteen stereocenters are embedded within a 17-membered macrocycle featuring a novel 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine heterocyclic ring and a highly functionalized *cis*-decalin framework. For maximal synthetic convergency and stereocontrol, we envisioned that alchivemycin A **(1)** could be forged from C3-C14 ketone **4** and the C15-C30 phosphonate **3** (Fig. 2) through Horner-Wadsworth-Emmons (H-W-E)[4] olefination and Dieckmnann condensation. [5]

The proposed major C3-C14 fragment could be generated from compound **5** through a gold catalyzed alkyne hydration.[6] Initially, a transannular Diels-Alder (TADA) strategy was considered for the synthesis of the *cis*-decalin system, however, this approach was not pursued because it unfortunately provided an undesired diastereomer containing the C8 and C9 *syn*-substituted motif on the decalin ring in comound **5**.[7] We thus decided to install the *cis*-decalin through an intramolecular Diels-Alder (IMDA) reaction[8] from a linear precursor such as **6**, favoring the *exo*-selective cycloaddition. The desired D-A substrate was to be assembled through one-pot Wittig and Julia-Kocienski (J-K) olefinations of 2,4-*syn*-dimethyl aldehyde **7**[9]

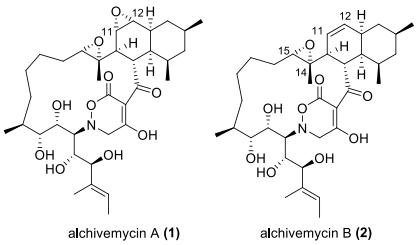

Fig. 1 Structures of alchivemycin A (**1**) and B (**2**).

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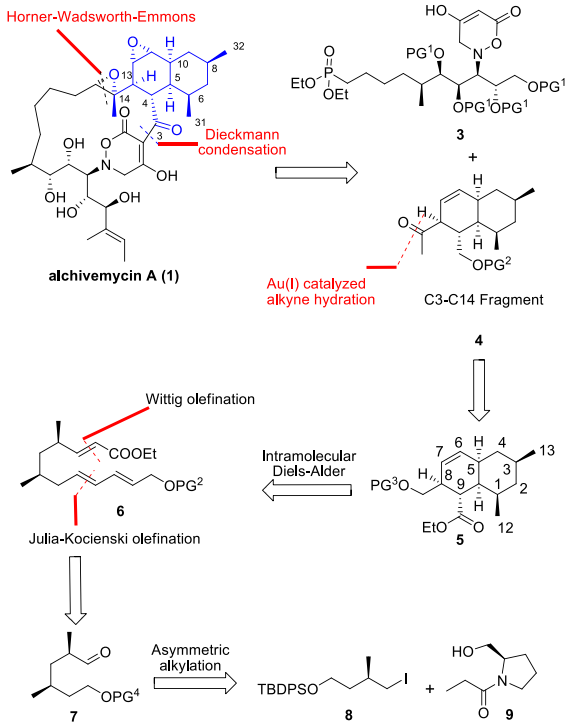


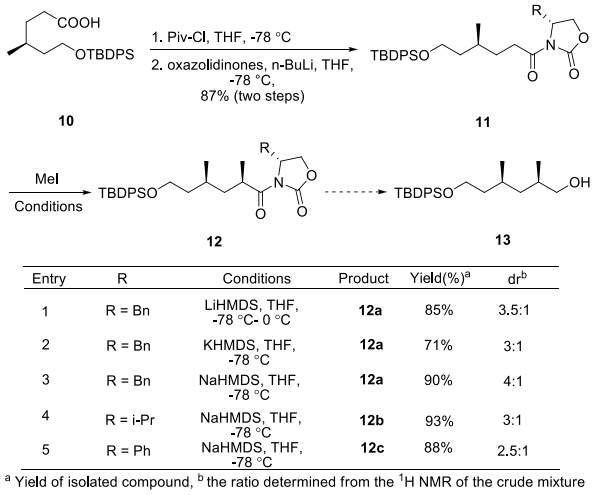
Fig. 2 Retrosynthetic analysis for alchivemycin A.

which in turn was planned to arise from the asymmetric alkylation of known compound **9**.

The synthesis began with recognizing that the 1, 3-*cis*-dimethyl **13** (a potential precursor to **7**) could be accessed from the diastereoselective methylation and subsequent reduction of compound **11**, using Evans' oxazolidinone auxiliary as the chiral source (Scheme 1). The amide **11** was prepared according to literature procedure from the known acid **10**.[10] Unfortunately, under various conditions, the substrate modified with different chiral oxazolidinones and treated with methyl iodide failed to afford any useful level of diastereoselectivity, based on ^{1}H-NMR analysis of the inseparable mixture.

In view of these results, a revised strategy was required for the stereocontrolled synthesis. Accordingly, a new approach was envisaged using the known iodide **8**[11] and the L-prolinol *N*-propionamide **9**[12] which were derived from (*R*)-methylsuccinic acid and L-prolinol, respectively. With **8** and **9** in hand, the asymmetric alkylation was then re-investigated. To our delight, the reaction proceeded smoothly using Evans' protocol[13] to afford the desired product **14** in good yield and excellent diastereoselectivity (91:9 ratio of 2*R*- and 2*S*-diastereomers as determined by ^{1}H-NMR) (Scheme 2). Conversion of the chiral auxiliary to the corresponding alcohol was then required. Excess $LiEt_3BH$[12] in THF led to epimerization of the substrate (5:1 dr). However, the chiral substituent was smoothly removed by reduction using LiH_2NBH_3 in THF at room temperature[14] to provide the alcohol **13** without epimerization. Compound **13** was further subjected to a Swern oxidation/Wittig reaction sequence to afford the α, β-conjugated ester **15** in excellent yield (83%, over two steps).

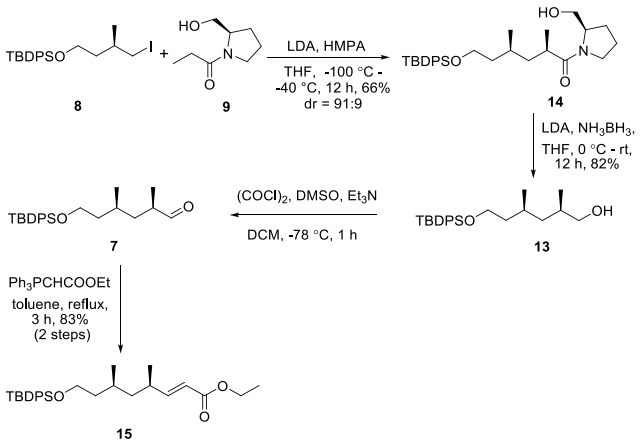
Our initial attempt at the synthesis of the Diels-Alder precursor began with ester **15**. Desilylation of **15** with triethylamine



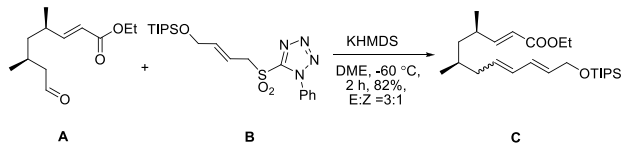
Entry	R	Conditions	Product	Yield(%)[a]	dr[b]
1	R = Bn	LiHMDS, THF, -78 °C- 0 °C	**12a**	85%	3.5:1
2	R = Bn	KHMDS, THF, -78 °C	**12a**	71%	3:1
3	R = Bn	NaHMDS, THF, -78 °C	**12a**	90%	4:1
4	R = i-Pr	NaHMDS, THF, -78 °C	**12b**	93%	3:1
5	R = Ph	NaHMDS, THF, -78 °C	**12c**	88%	2.5:1

[a] Yield of isolated compound, [b] the ratio determined from the ^{1}H NMR of the crude mixture

Scheme 1 Attempted synthesis of the intermediate **13.**



Scheme 2 Synthesis of the intermediate **15.**



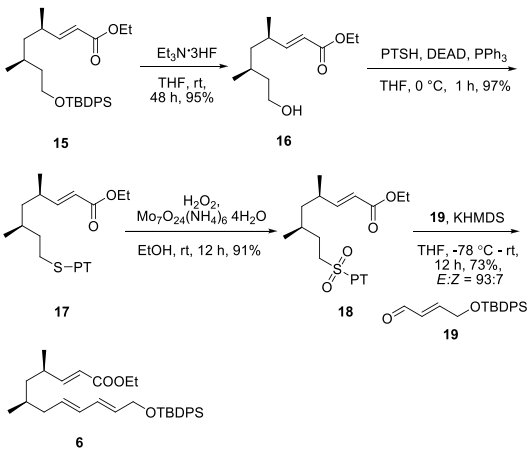
Scheme 3 Attempt to synthesize the Diels-Alder precursor.

and subsequent oxidation with Dess-Martin periodinane set the stage for the J-K olefination.[15] Treatment of the aldehyde **A** with allylic sulfone **B** afforded a 1.5:1 inseparable mixture of *E/Z* isomers of **C** using the Barbier-type J-K protocol. The use of a more polar solvent such as DME led to the formation of an improved 3:1 mixture (Scheme 3).

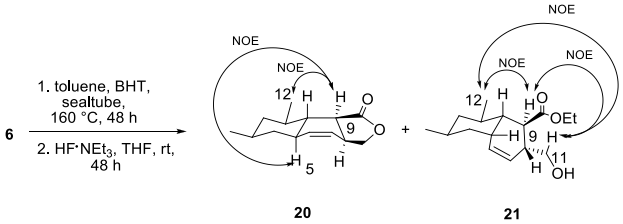
Considering that the allylic sulfone **B** and the α-nonbranched aldehyde **A** may not be the optimal substrates for the *E*-selective olefination,[16] we attempted the reaction with an alternative substrate pair:[17] the known conjugated aldehyde **19**[18] and heteroarylsulfone **18** (PT = phenyltetrazolyl). The sulfone **18** was prepared from the primary alcohol **16** employing a sequence of Mitsunobu thioetherification and molybdenum-

catalyzed sulfide oxidation. Gratifyingly, the coupling of **18** and **19** through one-pot J-K olefination furnished the desired (*E/E/E*)-triene substrate **6** in good yield and with excellent *E/Z*-selectivity (93:7) using the Barbier-type J-K protocol (Scheme 4).

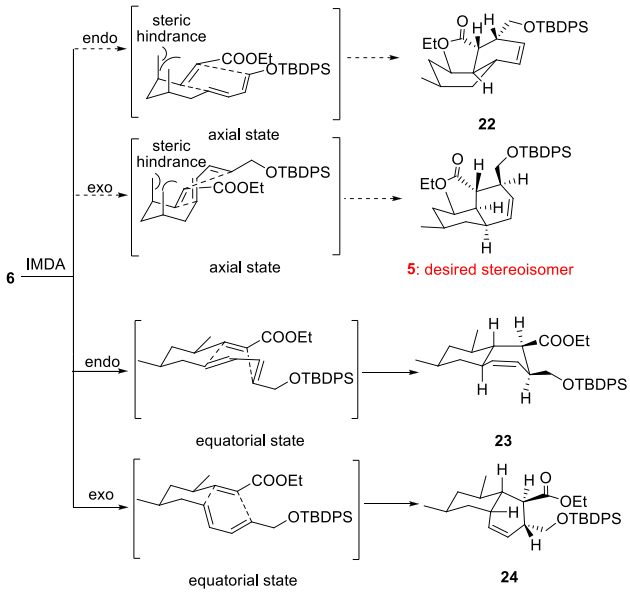
With triene **6** in hand, we began to further investigate the crucial IMDA reaction. The ester **6** underwent thermally promoted IMDA cycloaddition in toluene to afford mixtures of the adducts which could not be directly separated by chromatography, but they could be separated chromatographically upon desilylation with triethylamine trihydrofluoride to afford the lactone and the primary alcohol in 30% and 45% yield over two steps (Scheme 5). The lactone were identified as *trans*-fused bicyclic product **20** based on the cross peaks between H12-H9 and -H5 in the NOE experiments. The NOE experiment performed on another isomer revealed the cross peaks between H12-H9 and -H11 surporting the *cis*-fused primary alcohol **21** as the *exo* adduct, while the desired *cis*-fused decalin **5** required for alchivemycin A was not observed. From the IMDA reaction of triene **6**, we expected four distinct decalin diastereomers from four possible transition states (Scheme 6). The cycloadducts **20** and **21** was generated through the equatorial state as the *endo* and *exo* products, respectively. The desired isomer **5** would form from the axial state with high energy which creates a severe 1, 3-diaxial methyl interaction. The observed stereochemical outcome was consistent with Lee's finding[19].We envisioned that an organocatalytic process or elevated reaction temperature could overcome the inherent substrate selectivity of this structure and favor the adduct **5** which was in the structure of alchivemycin A. The conditions



Scheme 4 Synthesis of the Diels-Alder precursor **6**.

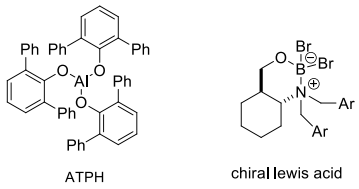


Scheme 5 IMDA and deprotection reation of **6.**



Entry	Reagents and Conditions[a]	**22** : **5** : **23** : **24**[b]
1	1,2-Dichlorobenzene, BHT, sealtube, 220 °C, 72 h	0 : 0 : 1: 1.5
2	DMSO, BHT, 160 °C, 12 h	Decomposed
3	ATPH, Tolene, 100 °C, 12 h	0 : 0 : 1 : 1
4	chiral lewis acid, DCM, -78 °C, 12 h	0 : 0 : 1 : 0
5	neat, -20 °C, 72 h	0 : 0 : 1 : 0

[a] Unless otherwise specified all reacitons were run at 0.02 M. ATPH and BHT was used in 2 equiv and 0.2 equiv amounts. Chiral lewis acid was used in 0.1 equiv amounts. [b] the ratio determined from the 1H NMR of the crude mixture.



Scheme 6 Possible transition states and conditions evaluation for the IMDA reaction of **6.** The terms axial and equatorial refer to the relative orientation of the methyl group at C1 and C3.

of the IMDA reaction were extensively evaluated (Scheme 6). Treatment of ester **6** in dichlorobenzene at 220 ℃ affords 1:1.5 mixtures of compound **23** and **24** (Scheme 6, entry 1). When the reaction solution was heated in trichlorobenzene at 240 ℃[20], the ratio did not further improve, and in fact some decomposition of substrate was observed (data not shown). The ethyl ester decomposed when the reaction was heated in DMSO (Scheme 6, entry 2). Bulky Lewis acids[21] like aluminum tris(2,6-diphenylphenoxide) (ATPH) and chiral Lewis acids[22] such as cationic oxazaborinane, known to promote the *exo*-selective D-A reaction were also evaluated but led only to a 1:1 ratio of compound **23** and **24** or compound **23** (Scheme 6, entry 3 and 4, respectively). The D-A reaction under neat conditions afforded the undesired *endo* adduct compound **23** as the sole product (Scheme 6, entry 5). Unfortunately, elevated reaction temperature or using lewis acid could not afford the desire adduct **5** based on the ^{1}H-NMR of the crude mixture which was presumably due to the high energy of the transition state when

the both methyl at the axial position. In light of these results, a revised strategy was required to construct the *cis*-decalin **5**. Based on the study of Roush group[8], the *Z* dienophile facilitate the formation of the *cis*-decalin. It is a good strategy to synthesize the 9-*epi*-**5** followed by epimerization under basic conditions to provide compound **5**. However, in Lee's doctoral dissertation[19], they have changed the structure of **6** to *(E, E, Z)*-triene and examined the IMDA reaction. Unfortunately they observed that the reaction only afforded the undesired *trans*-decalin rather than the 9-*epi*-**5**. Eventually, the chiral auxiliary approach was proposed in which the Evans oxazolidinones was employed as chiral auxiliary to obtain the desired *exo*-axial cycloadducts[23] and the preparation of the precursor of the IMDA with the chiral auxiliary is ongoing.

Conclusions

We have reported our synthetic endeavors towards the synthesis of the C3-C14 fragment of alchivemycin A. The synthesis relies on an asymmetric alkylation and a one-pot *E*-selective J-K olefination. Although the decalin containing the relative stereochemistry required for alchivemycin A was not obtained under various conditions, the ready access to compound **20**, which is a common structural motif in the related polyketide, would facilitate synthetic endeavors toward other natural products[24]. The alternative strategy to construct the *cis*-decalin of alchivemycin A is currently underway in our laboratory and will be reported in due course.

Experimental section

General

^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a Varian 100 MHz spectrometer (with complete proton decoupling) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.26; ^{13}C, δ 77.00). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. Infrared spectra were recorded on a Thermo Fisher FT-IR200 spectrophotometer. High-resolution mass spectra were obtained at Peking University Mass Spectrometry Laboratory using a Bruker APEX Flash chromatography. The samples were analyzed by HPLC/MS on a Waters Auto Purification LC/MS system (3100 Mass Detector, 2545 Binary Gradient Module, 2767 Sample Manager, and 2998 Photodiode Array (PDA) Detector). The system was equipped with a Waters C18 5 μm SunFire separation column (150*4.6 mm), equilibrated with HPLC grade water (solvent A) and HPLC grade methanol (solvent B) with a flow rate of 1.0 mL/min at room temperature. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Silica gel column chromatography was performed using 200-400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. All reagents were used as supplied by J&K, Sigma-Aldrich, and Alfa Aesar Chemicals. Toluene, methylene chloride were distilled from calcium hydride; tetrahydrofuran were distilled from sodium/benzophenone ketyl prior to use. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

(*R*)-4-benzyl-3-((*S*)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhexanoyl)oxazolidin-2-one (11a) To a solution of acid **10** (0.30 g, 0.78 mmol) in THF (5 mL) was added pivaloylchloride (0.1 mL, 0.86 mmol) dropwise at -78 ℃. After being stirred 0 ℃ for 1 h, the precipitate formed. In another flask, to a solution of the oxazolidinone (0.20 g, 0.94 mmol) in THF (2 mL) was added n-BuLi in hexane (2.5 M, 0.94 mmol, 0.4 mL) dropwise at -78 ℃. The resulting solution was stirred at this temperature and the transferred into the freshly prepared anhydride in the other flask at -78 ℃. After being stirred at this temperature for 1 h, the reaction mixture was warmed to 0 ℃ and stirred for another 1 h. The reaction mixture was quenched with saturated NH_4Cl solution (2 mL). The resulting solution was extracted with EtOAc (10 mL × 3) and the combined extracts were washed with saturated NaCl solution (10 mL × 2), dried over anhydrous Na_2SO_4 and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1) to afford the amide **11a** (0.37 g, 87%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70-7.63 (m, 4H), 7.45-7.33 (m, 6H), 7.33-7.23 (m, 3H), 7.22-7.17 (m, 2H), 4.63-4.69 (m, 1H), 4.26-4.06 (m, 2H), 3.84 -3.63 (m, 2H), 3.29 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.09-2.80 (m, 2H), 2.74 (dd, *J* = 13.4, 9.7 Hz, 1H), 1.80-1.62 (m, 3H), 1.61-1.47 (m, 1H), 1.46-1.33 (m, 1H), 1.05 (s, 9H), 0.89 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 153.4, 135.5, 135.3, 134.0, 129.5, 129.4, 128.9, 127.6, 127.3, 66.1, 61.9, 55.1, 39.3, 37.9, 33.3, 31.3, 29.2, 26.9, 19.3, 19.2; **IR** (neat) ν_{max} 3070, 2958, 1787, 1703, 740 cm^{-1}; **HRMS** (ESI) [M + H$^+$] calculated for $C_{33}H_{42}NO_4Si$: 544.28776, found: 544.29006; **$[\alpha]^{20}_D$** -16.2 (*c* 1.3, $CHCl_3$).

(*R*)-3-((*S*)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhexanoyl)-4-isopropyloxazolidin-2-one (11b) yellow oil, yield = 81%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.47-7.33 (m, 6H), 4.53-4.36 (m, 1H), 4.33-4.12 (m, 2H), 3.78-3.62 (m, 2H), 3.01 (m, 1H), 2.90-2.74 (m, 1H), 2.45-2.27 (m, 1H), 1.74-1.59 (m, 1H), 1.57-1.45 (m, 3H), 1.45-1.35 (m, 1H), 1.05 (s, 9H), 0.94-0.82 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 154.0, 135.5, 134.0, 129.5, 127.6, 63.2, 62.0, 58.4, 39.3, 33.3, 31.5, 29.2, 29.1, 28.3, 26.8, 19.3, 19.3, 19.2, 18.0, 14.6; **IR** (neat) ν_{max} 3071, 1784, 1702, 739 cm^{-1}; **HRMS** (ESI) [M + H$^+$] calculated for $C_{29}H_{44}NO_3Si$: 496.28831, found: 496.28936; **$[\alpha]^{20}_D$** -25.3 (*c* 2.1, $CHCl_3$).

(*R*)-3-((*S*)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhexanoyl)-4-phenyloxazolidin-2-one (11c) yellow oil, Yield = 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78-7.56 (m, 4H), 7.48-7.16 (m, 11H), 5.37 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.63 (dd, *J* = 11.8, 5.8 Hz, 1H), 4.23 (dd, *J* = 8.9, 3.7 Hz, 1H), 3.72-3.52 (m, 2H), 3.02-2.78 (m, 2H), 1.71-1.49 (m, 3H), 1.37-1.27 (m, 1H), 1.00 (s, 9H), 0.80 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ

172.9, 153.6, 139.2, 135.5, 134.0, 129.5, 129.1, 128.6, 127.6, 125.9, 69.9, 62.0, 57.6, 39.3, 33.3, 31.1, 29.1, 29.0, 26.9, 26.8, 19.2, 19.2; **IR** (neat) ν_{max} 3070, 1789, 1710, 741, 707 cm^{-1}; **HRMS** (ESI) [M + H^+] calculated for $C_{32}H_{40}NO_4Si$: 530.27211, found: 530.27187; $[\alpha]^{20}_D$ -25.0 (*c* 1.4, $CHCl_3$).

(2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-1-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)-2,4-dimethylhexan-1-one (14) A solution of n-BuLi in hexane (2.5 M, 1.7 mL, 4.2 mmol) was added to a solution of *N, N* – diisopropylamine (0.7 mL, 5.0 mmol) in THF (6 mL) at -78 ℃. The resulting solution was warmed to 0 ℃ and stirred for 30 min at this temperature. To the LDA solution (0.5 M) was added amid **9**[11] (0.20 g, 1.28 mmol) and HMPA (1.1 mL, 6.3 mmol) in anhydrous THF (1.2 mL). The resulting solution was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to -100 ℃ and the iodide **8**[10b] (0.38 g, 0.84 mmol) in THF (1.4 mL) was added to the solution dropwise. After being warmed to −40 °C in 1 h, the reaction mixture was stirred at this temperature for 11 h and quenched with saturated NH_4Cl solution (5 mL). The resulting solution was extracted with EtOAc (20 mL × 3) and the combined extracts were washed with saturated NaCl solution (20 mL × 2), dried over anhydrous Na_2SO_4 and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 1/1) to afford 1, 3-dimethyl compound **14** (0.27 g, 66 %) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.57 (m, 4H), 7.52-7.32 (m, 6H), 5.26 (dd, *J* = 7.7, 2.3 Hz, 1H), 4.19-4.25 (m, 1H), 3.78-3.61 (m, 3H), 3.60-3.51 (m, 2H), 3.43-3.50 (m, 1H), 2.63 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.06-1.78 (m, 3H), 1.71-1.52 (m, 4H), 1.31-1.17 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 9H), 0.83 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.4, 135.5, 134.0, 129.5, 127.6, 67.9, 61.9, 61.1, 47.8, 41.2, 39.3, 35.6, 28.3, 27.4, 26.8, 24.5, 20.0, 19.2, 18.0; **IR** (neat) ν_{max} 3391, 1620, 1111, 739, 704 cm^{-1}; **HRMS** (ESI) [M + H^+] calculated for $C_{29}H_{44}NO_3Si$: 482.30850, found: 482.30939; $[\alpha]^{20}_D$ -21.7 (*c* 0.7, $CHCl_3$).

(2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol (13) A solution of n-BuLi in hexane (2.5 M, 0.16 mL, 0.41 mmol) was added to a solution of *N, N* – diisopropylamine (62 μL, 0.44 mmol) in THF (0.4 mL) at -78 ℃. The resulting solution was warmed to 0 ℃ and stirred for 30 min at this temperature. The LDA solution (0.7 M) was added to a solution of borane-ammonia complex (10 mg, 0.42 mmol) in THF (0.2 mL) at 0 ℃. The resulting mixture was stirred at 0 ℃ for 15 min, and then was warmed to rt for 15 min. After cooling the mixture to 0 ℃, a solution of compound **14** (50 mg, 0.10 mmol) was added slowly via syringe, and the resulting solution was stirred at rt for 12 h. The reaction mixture was cooled to 0 ℃ and then was quenched with saturated NH_4Cl solution and extracted with EtOAc (10 mL × 3), and the combined extracts were washed with saturated NaCl solution (5 mL × 2), dried over anhydrous Na_2SO_4 and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1) to afford primary alcohol **13** (33 mg, 82%) as a slightly yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78-7.54 (m, 4H), 7.35-7.45 (m, 6H), 3.76-3.65 (m, 2H), 3.49 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.36 (dd, *J* = 10.5, 6.7 Hz, 1H), 1.76-1.58 (m, 3H), 1.25-1.32 (m, 2H), 1.05 (s, 9H), 0.95 (dd, *J* = 14.0, 7.6 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.6, 134.0, 129.5, 127.6, 68.4, 62.0, 41.0, 39.1, 33.1, 26.9, 26.7, 20.4, 19.2, 17.1; **IR** (neat) ν_{max} 3352, 1111, 1041, 737, 702 cm^{-1}; **HRMS** (ESI) [M + Na^+] calculated for $C_{24}H_{36}NaO_2Si$: 407.23768, found: 407.23859; $[\alpha]^{20}_D$ +7.5 (*c* 0.2, MeOH).

(4*R*,6*S*,*E*)-ethyl-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoate (15) To a solution of oxalyl chloride (1.7 mL, 13 mmol) in DCM (82 mL) was added DMSO (1.0 mL, 14 mmol) in DCM (30 mL) at -78 ℃. After being stirred at this temperature for 5 min, the primary alcohol **13** (3.4 g, 8.9 mmol) in DCM (20 mL) was added dropwise. The resulting solution was stirred at this temperature for 15 min, and TEA (6.2 mL, 44 mmol) was added. The reaction mixture was stirred 10 min at -78 ℃, warmed to room temperature and diluted with ether (30 mL). The suspension was filtrated, and the filtrate was concentrated in vacuo to provide a crude residue, which was used directly in the next step. The crude aldehyde was redissolved in toluene (30 mL), and $Ph_3PCHCOOEt$ (4.0 g, 12 mmol) was added. After being stirred at reflux for 3 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 50/1) to afford the ester **15** (3.1 g, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76-7.59 (m, 4H), 7.48-7.32 (m, 6H), 6.80 (dd, *J* = 15.7, 8.4 Hz, 1H), 5.77 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.81-3.57 (m, 2H), 2.49-2.24 (m, 1H), 1.68-1.50 (m, 2H), 1.37-1.29 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.08-1.16 (m, 1H), 1.04 (s, 9H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.8, 154.4, 135.6, 135.5, 134.0, 134.0, 129.5, 127.6, 119.7, 77.3, 77.0, 76.7, 61.8, 60.1, 43.8, 39.8, 34.1, 27.0, 26.9, 26.8, 20.2, 19.3, 19.1, 14.3; **IR** (neat) ν_{max} 3070, 2960, 1722, 1652, 1180, 1112, 739 cm^{-1}; **HRMS** (ESI) [M + Na^+] calculated for $C_{28}H_{40}NaO_3Si$: 475.26389, found: 475.26484; $[\alpha]^{20}_D$ -8.4 (*c* 2.5, $CHCl_3$).

(4*R*,6*S*,*E*)-ethyl-8-hydroxy-4,6-dimethyloct-2-enoate (16) To a solution of ester **15** (1.2 g, 2.6 mmol) in THF (36 mL) was added triethylamine trihydrofluoride (5.2 mL, 32 mmol) at room temperature. The resulting solution was stirred at room temperature for 48 h and quenched with H_2O (10 mL). The reaction mixture was extracted with EtOAc (20 mL × 3), and the combined extracts were washed with saturated NaCl solution (10 mL × 2), dried over anhydrous Na_2SO_4 and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford primary alcohol **16** (0.54 g, 95%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 15.7, 8.5 Hz, 1H), 5.78 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.74-3.60 (m, 2H), 2.51-2.37 (m, 1H), 1.65-1.52 (m, 2H), 1.35-1.42 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22-1.13 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.3, 119.9, 60.9, 60.2, 43.9, 40.2, 34.2, 27.2, 20.4, 19.3, 14.3; **IR** (neat) ν_{max} 3440, 2961, 1721, 1651, 1041, 986 cm^{-1}; **HRMS** (ESI) [M + Na^+] calculated for $C_{12}H_{23}NaO_3$: 237.14612, found: 237.14621; $[\alpha]^{20}_D$ -21.5 (*c* 0.7, $CHCl_3$).

(4*R*,6*S*,*E*)-ethyl-4,6-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylthio)oct-2-enoate (17) To a solution of the primary alcohol **16** (30 mg, 0.14 mmol) in THF (2.3 mL) was added triphenylphosphine (92 mg, 0.35 mmol), 1-Phenyl-1*H*-tetrazole-5-thiol (50 mg, 0.28 mmol) and diethyl diazenedicarboxylate (60 μL, 0.35 mmol) at 0 ℃. The resulting yellow solution was stirred for 1 h at 0 ℃ and diluted with EtOAc (10 mL). The reaction mixture was quenched with saturated sodium bicarbonate solution (1 mL), and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined extracts were washed with saturated NaCl solution (5 mL × 2), dried over anhydrous Na_2SO_4 and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1) to afford thioether **17** (51 mg, 97%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67-7.44 (m, 5H), 6.78 (dd, *J* = 15.7, 8.5 Hz, 1H), 5.78 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.40-3.47 (m, 1H), 3.30-3.38 (m, 1H), 2.50-2.35 (m, 1H), 1.88-1.75 (m, 1H), 1.69-1.60 (m, 2H), 1.39-1.47 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25-1.17 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 154.3, 153.8, 133.7, 130.1, 129.8, 123.8, 120.1, 60.2, 43.2, 36.4, 34.1, 31.0, 29.9, 20.4, 18.9, 14.3; **IR** (neat) ν_{max} 2961, 1717, 1651, 1277, 986, 763 cm^{-1}; **HRMS** (ESI) [M + H$^+$] calculated for $C_{19}H_{27}N_4O_2S$: 375.18492, found: 375.18560; **[α]$^{20}_D$** +10.1 (*c* 0.7, $CHCl_3$).

(4*R*,6*S*,*E*)-ethyl-4,6-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)oct-2-enoate (18) To a solution of thioether **17** (0.39 g, 1.0 mmol) in ethanol (7.8 mL) were added ammonium molybdate tetrahydrate (0.12 g, 0.1 mmol) and hydrogen peroxide (30%, 1.2 mL, 10 mmol) at 0 ℃. The resulting suspension was stirred for 12 h and quenched with saturated sodium sulfite solution (3 mL). The reaction mixture was extracted with EtOAc (10 mL × 3). The combined extracts were washed with saturated NaCl solution (10 mL × 2), dried over anhydrous Na_2SO_4, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford sulfone **18** (0.39 g, 91%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 2H), 7.64-7.57 (m, 3H), 6.75 (dd, *J* = 15.7, 8.6 Hz, 1H), 5.79 (d, *J* = 15.7 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.83-3.61 (m, 2H), 2.50-2.37 (m, 1H), 2.01-1.89 (m, 1H), 1.83-1.71 (m, 1H), 1.68-1.61 (m, 1H), 1.53-1.59 (m, 1H), 1.37-1.45 (m, 1H), 1.32-1.26 (m, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 153.2, 133.0, 131.5, 129.7, 125.0, 120.5, 60.3, 54.1, 43.0, 34.1, 29.6, 28.8, 20.4, 18.7, 14.3; **IR** (neat) ν_{max} 2962, 1716, 1651, 1232, 1040, 765 cm^{-1}; **HRMS** (ESI) [M + H$^+$] calculated for $C_{19}H_{27}N_4O_4S$: 407.17475, found: 407.17459; **[α]$^{20}_D$** +5.8 (*c* 0.7, $CHCl_3$).

(2*E*,4*R*,6*R*,8*E*,10*E*)-ethyl-12-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyldodeca-2,8,10-trienoate (6) To a solution of sulfone **18** (0.20 g, 0.49 mmol) and aldehyde **19**[18] (0.32 g, 0.98 mmol) in THF (8 mL) was added KHMDS in toluene (0.7 M, 0.91 mL, 0.64 mmol) dropwise at -78 ℃. After being stirred at this temperature for 30 min, the reaction mixture was warmed to room temperature and stirred for 12 h before being quenched by addition of saturated NH_4Cl solution at 0 °C and then warmed to room temperature. The solution was extracted with EtOAc (5 mL × 3). The combined extracts were washed with saturated NaCl solution (5 mL × 2), dried over anhydrous Na_2SO_4, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 30/1) to afford triene **6** (0.20 g, 73%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85-7.56 (m, 4H), 7.54-7.31 (m, 6H), 6.81 (dd, *J* = 15.7, 8.3 Hz, 1H), 6.23 (dd, *J* = 15.2, 10.6 Hz, 1H), 6.02 (dd, *J* = 15.1, 10.7 Hz, 1H), 5.78 (d, *J* = 15.7 Hz, 1H), 5.71-5.53 (m, 2H), 4.23 (d, *J* = 5.0 Hz, 2H), 4.21-4.14 (m, 2H), 2.56-2.28 (m, 1H), 2.02-2.13 (m, 1H), 1.97-1.86 (m, 1H), 1.54-1.48 (m, 1H), 1.37-1.45 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.18-1.10 (m, 1H), 1.06 (s, 9H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9, 154.4, 135.6, 133.7, 132.3, 131.3, 130.1, 130.0, 129.6, 127.6, 119.8, 64.3, 60.2, 43.3, 40.6, 34.3, 30.7, 29.7, 26.8, 20.4, 19.2, 19.2, 14.3; **IR** (neat) ν_{max} 3071, 2959, 1721, 1652, 1113, 989, 704 cm^{-1}; **HRMS** (ESI) [M + Na$^+$] calculated for $C_{32}H_{44}NaO_3Si$: 527.29519, found: 527.29622; **[α]$^{20}_D$** +11.2 (*c* 0.5, $CHCl_3$).

(3*aR*,5*aS*,7*S*,9*R*,9*aR*,9*bS*)-7,9-dimethyl-3,3a,5a,6,7,8,9,9a-octahydronaphtho[2,1-c]furan-1(9b*H*)-one(20)

(1*S*,2*S*,4*aR*,6*S*,8*R*,8*aR*)-ethyl-2-(hydroxymethyl)-6,8 dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (21) In sealtube, to a solution of triene **6** (7.0 g, 14 mmol) in 1, 2-dichlorobenzene (0.7 L) was added BHT (0.62 g, 2.8 mmol). After being warmed to 220 ℃, the reaction mixture was stirred at this temperature for 72 h. The resulting brown solution was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1) to afford the mixture of two inseparable diastereomers which was redissolved in THF (155 mL). To the solution was added triethylamine trihydrofluoride (23 mL, 0.14 mol), and the reaction mixture was stirred for 48 h at room temperature before being quenched by H_2O (30 mL). The solution was extracted with EtOAc (70 mL × 3). The combined extracts were washed with saturated NaCl solution (20 mL × 2), dried over anhydrous Na_2SO_4, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1 to 4/1) to afford *exo* product **20** (1.78 g, 45%) as a colorless oil and the *endo* product **21** (0.98 g, 30%).

Compound 20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dt, *J* = 9.3, 2.9 Hz, 1H), 5.67-5.59 (m, 1H), 4.41 -4.33 (m, 1H), 4.23-4.26 (m, 1H), 2.92-2.99 (m, 1H), 2.71-2.62 (m, 1H), 1.96-1.84 (m, 1H), 1.77-1.65 (m, 2H), 1.59-1.48 (m, 1H), 1.46 -1.35 (m, 1H), 1.09-1.16 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.90-0.78 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.6, 139.1, 127.7, 71.6, 45.9, 44.8, 43.8, 40.7, 39.6, 38.4, 36.7, 32.2, 22.3, 20.1; **IR** (neat) ν_{max} 2965, 1756, 1441, 1203, 981 cm^{-1}; **HRMS** (ESI) [M + Na$^+$] calculated for $C_{14}H_{20}NaO_2$: 243.13555, found: 243.13516; **[α]$^{20}_D$** -10.4 (*c* 0.9, $CHCl_3$).

Compound 21: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54-5.64 (m, 2H), 4.30-4.02 (m, 2H), 3.69 (dd, *J* = 10.3, 6.5 Hz, 1H), 3.45-3.51 (m, 1H), 2.98 (t, *J* = 2.3 Hz, 1H), 2.71-2.79 (m, 1H), 2.52-2.26 (m, 1H), 1.75-1.64 (m, 2H), 1.62-1.44 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.13-1.20 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.69 (q, *J* = 11.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.3, 133.1, 125.4, 65.4, 60.6, 44.4, 43.0, 41.2, 40.0, 38.7, 32.7, 30.1, 27.8, 22.5, 20.2, 14.3; **IR** (neat)

ν_{max} 3362, 1730, 1456, 1375, 1182, 1031 cm^{-1}; **HRMS** (ESI) [M + H^+] calculated for $C_{16}H_{27}O_3$: 267.19547, found: 267.19504; $[\alpha]^{20}_D$ -8.9 (*c* 1.56, $CHCl_3$).

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