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Asymmetric Total Syntheses of Two Possible Diastereomers of Gliomasolide E and Its Structural Elucidation

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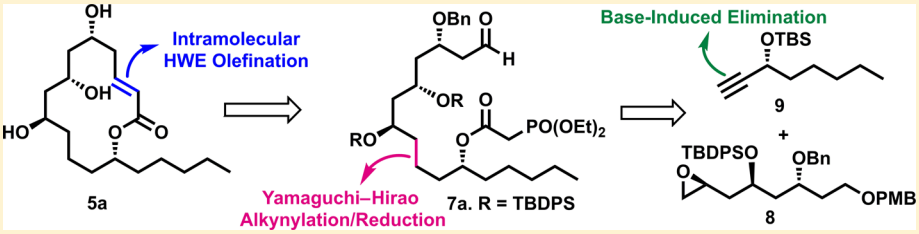
Supporting Information



ABSTRACT: The first total syntheses of two possible diastereomers of gliomasolide E, a 14-membered macrolides isolated from the marine sponge *Phakellia fusca* Thiele, which was collected from the South China Sea, is reported. Highlights of the synthesis include macrolactonization through intramolecular Horner–Wadsworth–Emmons olefination, Yamaguchi–Hirao alkynylation, and base-induced elimination reactions for propargyl alcohol synthesis as the key reactions. Detailed comparison of their ^{1}H and ^{13}C NMR (1D and 2D NMR data) and specific rotation with those of the natural product revealed that the absolute stereochemistry of gliomasolide E should be (2*E*,5*R*,7*R*,9*R*,13*R*).

INTRODUCTION

Gliomasolides A–E (**1**–**5**) (Figure 1) are 14-membered macrolides isolated from a sponge-derived fungus *Gliomastix* sp. ZSDS1-F7–2 and from the South China Sea marine sponge *Phakellia fusca* Thiele by Xu et al.[1,2] While a plethora of polyketide macrolactones resulting from the propionate aldol reaction are known in literature, macrolactones devoid of the methyl group are rare in nature. It was shown that gliomasolide A exhibits moderate in vitro inhibitory activity (IC_{50} 10.1 μM) against HeLa (human epithelial carcinoma cell line) cells. While the structure and absolute stereochemistry of gliomasolides was established by extensive NMR studies, stereochemistry of the C9 stereocenter in gliomasolide E left unassigned. Architecturally, gliomasolide E (**5**) features a 14-membered macrolactone, (*E*)-α,β-unsaturated ester, a lipophilic *n*-pentyl substitution and four oxygenated methine carbons. The stereochemistry (2*E*,5*R*,7*R*,13*R*) of **5**, being identical with that of **3**, was assumed by the biogenetic viewpoint and the proton coupling constant of $J_{2,3}$ (16.0 Hz). However, the stereochemistry at C9 position, which is a stereocenter remote from the C1 and C13 positions, was left undetermined.[2]

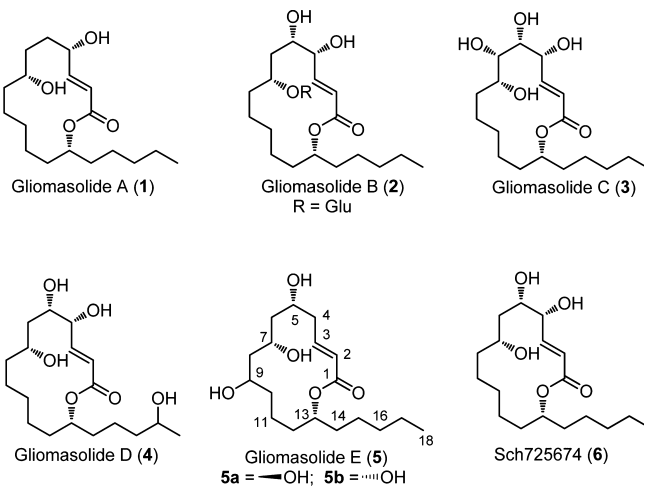


Figure 1. Structure of gliomasolides A–E (**1**–**5**) and sch-725674 (**6**).

A solitary report on the synthesis of gliomasolide C was disclosed by Reddy's group,[3c] while a handful of syntheses were reported for a closely related macrolide natural product Sch725674,[3] gloeosporone[4] and others.[5] Coupled with our own group efforts in the synthesis of varied bioactive macrolides,[6] and the synthetic challenge to resolve the stereochemistry of the unassigned center prompted us to embark on the total synthesis of gliomasolide E (**5**). Herein, we report the first asymmetric total synthesis of two possible diastereomers (**5a**) and (**5b**) (Figure 1) of gliomasolide E and comparison of their spectroscopic data with that reported for

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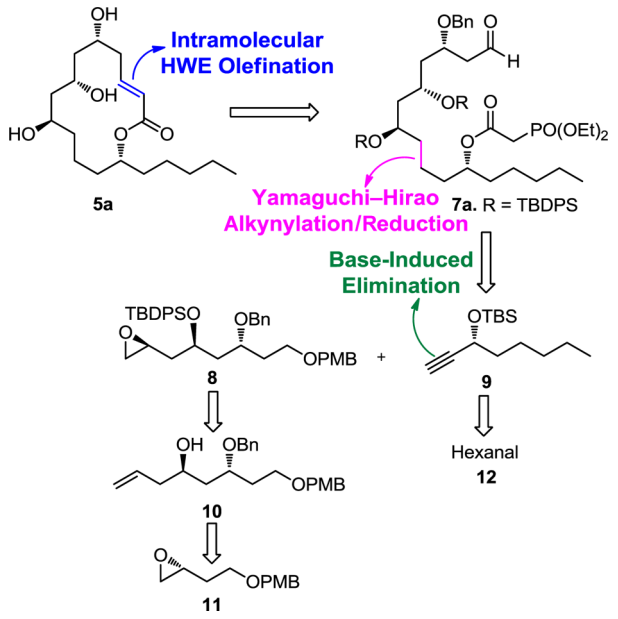
the natural product, thus ascertaining the stereochemistry of gliomasolide E.

Retrosynthetic analysis of gliomasolide E (**5a**) is outlined in Scheme 1. We envisaged the formation of the macrolactone of

Scheme 1. Retrosynthetic Analysis



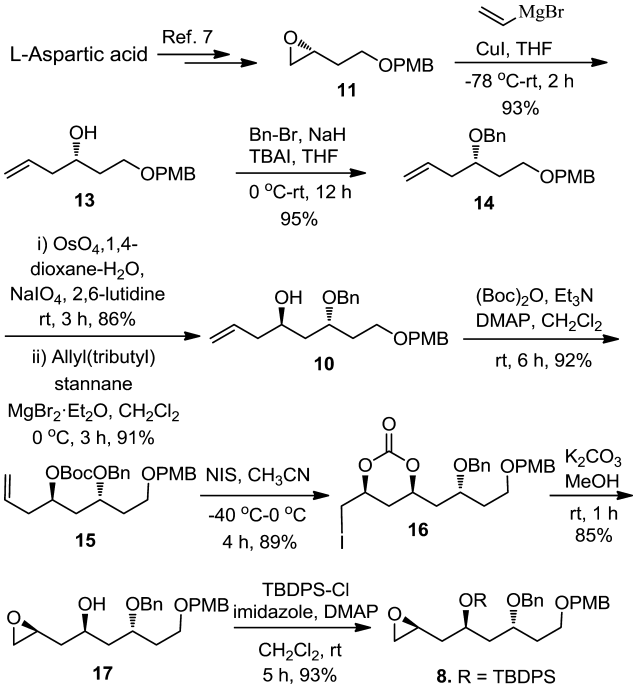
5a and its 9-epimer **5b** by a late stage intramolecular macrocyclization using Horner–Wadsworth–Emmons olefination[7] as the key step. The precursor **7a** could be accessible from epoxide **8** and alkyne **9** via Yamaguchi–Hirao alkynylation.[8] The epoxide fragment **8** could be obtained from homoallylic alchol **10** by employing Bartlett–Smith iodocarbonate cyclization[9] reaction, which in turn could be prepared from chiral epoxide **11**. The alkyne fragment **9** could be generated by utilizing base-induced protocol on corresponding epoxy alcohol, which could be easily attainable from commercially available *n*-hexanal (**12**).

RESULTS AND DISCUSSION

The synthesis commenced with the preparation of the epoxide intermediate **8** which is outlined in Scheme 2. Enantiopure epoxide **11**, prepared from commercially available L-aspartic acid in three steps following literature protocol,[10] was treated with vinylmagnesium bromide in the presence of CuI at −78 °C to furnish optically active homoallylic alcohol **13** in 93% yield.[11]

Protection of the hydroxy group as its benzyl ether with benzyl bromide and NaH in the presence of *tetra*-butyl ammonium iodide (TBAI) afforded compound **14** in 95% yield. One-pot oxidative cleavage of the terminal double bond present in **14** using Jin's protocol[12] afforded the corresponding unstable aldehyde, which was immediately subjected to chelation-controlled diastereoselective allylation[13] by treatment with allyl(tributyl)stannane in the presence of $MgBr_2{\cdot}Et_2O$ to obtain homoallyl alcohol **10** in 91% yield as the only stereoisomer. The stereochemical assignment of the secondary hydroxy bearing center was achieved following modified Mosher's method.[14] Accordingly, compound **10** was converted to its (*S*)- and (*R*)-(MTPA) ester with α-methoxy-α-(trifluoromethyl)-phenyl acetic acid which showed negative chemical shift

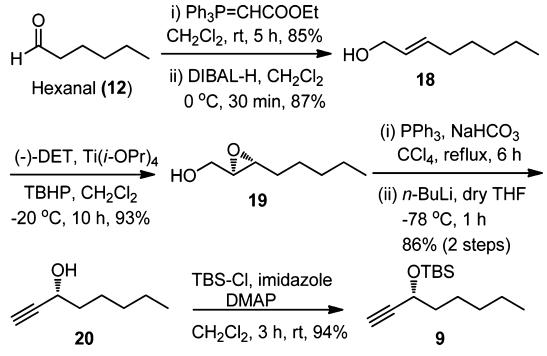
Scheme 2. Synthesis of the Epoxide Fragment 8



differences ($\Delta\delta = \delta_S - \delta_R$) for protons on C5 through C8 while protons on C1 through C3 showed positive differences, which is consistent with C4 bearing an *R*-configuration. After confirming the stereocenter, compound **10** was treated with di-*tert*-butyl carbonate[15] in the presence of DMAP to form the homoallyl *tert*-butyl-carbonate **15** in 92% yield. The next stereogenic center with the desired stereochemistry was achieved via Bartlett–Smith iodo-carbonate cyclization protocol.[7] Accordingly, treatment of compound **15** with *N*-iodosuccinimide in CH_3CN at 0 °C, produced the desired iodo-carbonate derivative **16** in 89% yield as the only product. The iodo derivative **16** on treatment with K_2CO_3 in methanol at room temperature underwent rapid hydrolysis and facile epoxidation to obtain the epoxy alcohol **17** in 85% yield. The secondary alcohol was protected as its silyl ether using TBDPSCl and imidazole in CH_2Cl_2 at 0 °C to afford epoxide fragment **8** in 93% yield.

As outlined in Scheme 3, the synthesis of the second fragment **9** started with the transformation of commercially available hexanal (**12**) into the allylic alcohol **18** in two steps.[16] The first step was two carbon homologation of hexanal (**12**) using (ethoxycarbonylmethylene) triphenylphosphorane in

Scheme 3. Synthesis of the Fragment 9



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CH_2Cl_2 to furnish α,β-unsaturated ester with *E*-configuration in 85% yield, followed by reduction with DIBAL-*H* in CH_2Cl_2 to obtain the corresponding allylic alcohol **18** in 87% yield. The Sharpless asymmetric epoxidation[17] of (*E*)-2-octenol (**18**) using (−)-DET and $Ti(^iPrO)_4$ in CH_2Cl_2 at −20 °C furnished epoxy alcohol **19**[18] in 93% yield. Compound **19** was converted to the corresponding (chloromethyl)oxirane using CCl_4−Ph_3P under reflux conditions followed by Yadav's protocol of base-induced elimination reaction[9] to afford the chiral propargylic alcohol **20**[19] in 81% yield over two steps. The alkynol **20** was treated with TBSCl and imidazole in CH_2Cl_2 to furnish silyl ether **9**[20] in 94% yield.

Having secured both the coupling partners **8** and **9**, the stage was set to examine the opening of epoxide **8** with the alkyne **9** under the Yamaguchi−Hirao protocol[8] (Scheme 4). Accordingly, treatment of alkyne **9** with *n*-BuLi followed by addition to epoxide **8** with $BF_3{\cdot}Et_2O$ (in a separate round bottomed flask) in THF afforded the homopropargyl alcohol **21** in 85% yield. The hydroxy functionality of homopropargyl alcohol **21** was protected as its TBDPS ether with TBDPS-Cl and imidazole in CH_2Cl_2 to obtain compound **22** in 91% yield. The TBS group in compound **22** was selectively removed by using PPTS in methanol and subsequent diimide-mediated[21] reduction of triple bond using $TsNHNH_2$ furnished saturated alcohol **23a** in 86% yield over two steps. The free hydroxy group in compound **23a** was then coupled with 2-(diethoxyphosphoryl)acetic acid[22,23] using *N*,*N*′-Dicyclohexylcarbodiimide (DCC) to afford the phosphonoester **24a** in 87% yield. Oxidative removal of PMB ether by treating with ceric ammonium nitrate (CAN) provided penultimate alcohol **25a**. Oxidation of the primary alcohol **25a** with Dess−Martin periodinane (DMP)[24] furnished macrocyclization precursor phosphonate-aldehyde **7a**, which was immediately subjected to an intramolecular Horner−Wadsworth−Emmons reaction under Masamune−Roush conditions[25] (LiCl, DBU, MeCN, rt, 12 h) to establish the desired 14-membered macrolactone **26a** as a sole *E*-olefinic isomer in 80% yield. Global deprotection[26] was achieved by treating **26a** with excess $TiCl_4$ in CH_2Cl_2 to complete the total synthesis of **5a** in 75% yield.

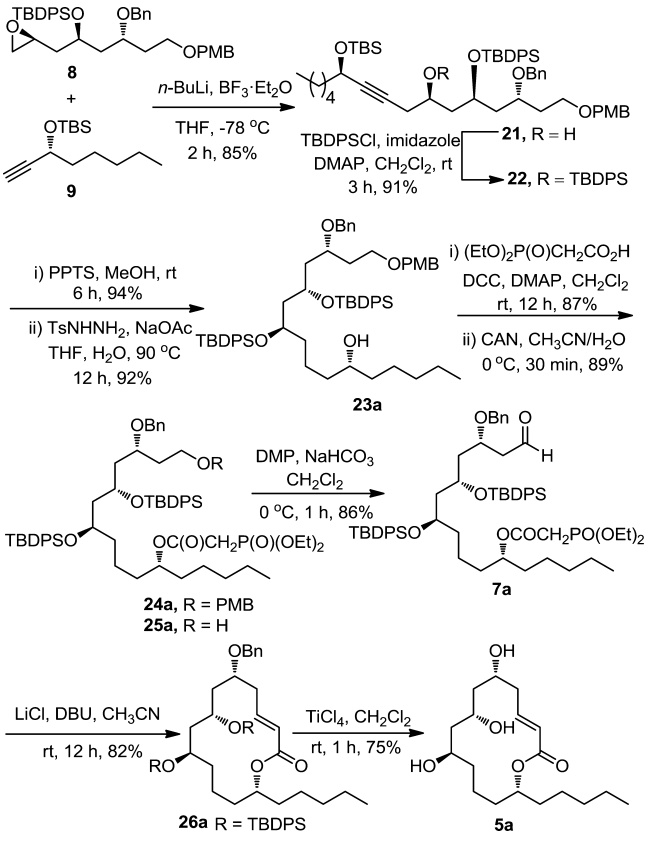
After achieveing the synthesis of **5a**, total syntheis of **5b** was initiated. For the same, the alkyne **21** was reduced to alkane **27** in 90% yield by treating excess diimide[21] as explained earlier (Scheme 5). Mitsunobu inversion[27] of the secondary alcohol (C9) group present in **27** using benzoic acid, Ph_3P and DIAD in THF at 0 °C followed by hydrolysis under basic conditions (K_2CO_3, MeOH) afforded the required alcohol **28** in 70% yield over two steps.

The hydroxy group present in **28** was protected as its TBDPS ether in 93% yield and subsequent selective deprotection of TBS group using PPTS provided phosphonate ester precursor **23b** in 92% yield. Following similar sequence of reactions (five steps) as reported in Scheme 4 for the synthesis of **5a**, macrolactone **5b** was obtained.

Having completed the total syntheses of **5a** and **5b**, the structures were established by ^1H NMR and ^{13}C NMR data (600 MHz, CD_3OD) and the data of **5a** were found to be in full agreement with those reported for the natural product.[2] On the other hand, the ^1H and ^{13}C NMR data of **5b** were clearly different from those of the natural product.[2] The selected chemical shift difference between the natural product and the synthetic products **5a** and **5b** are described in Table 1.

Significant deviations between the natural product and the synthetic **5b** were observed at the C3, C4, C7, C10, and C13 positions in the ^1H NMR data and at the C3, C4, C6, C7, C8, C10, C13, and C17 positions in the ^{13}C NMR data. The measured specific rotation of the synthetic **5a**, $[\alpha]_D^{25}$ − 92.7 (*c* 0.15, CH_3OH) was consistent with the sign of the specific

Scheme 4. Synthesis of the Macrocycle 5a through Intramolecular Horner−Wadsworth−Emmons Olefination



Scheme 5. Synthesis of the Macrocycle 5b

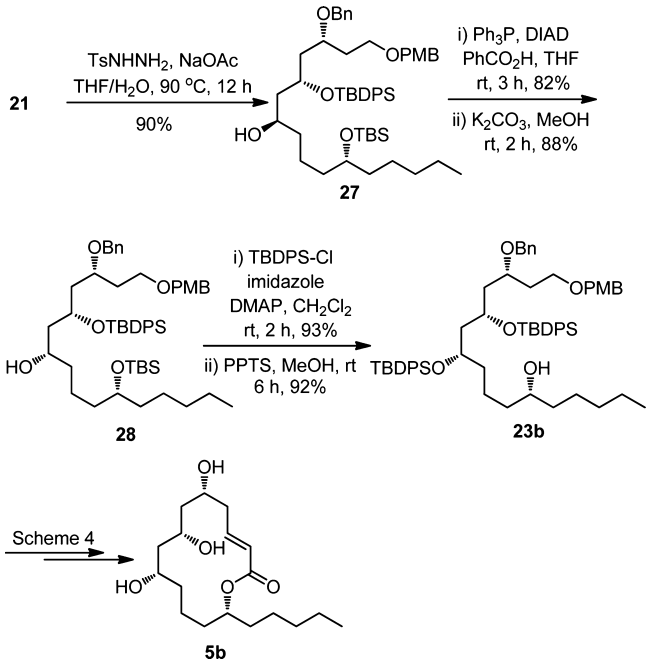


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Table 1. Selected Chemical Shift Difference in ppm between Natural Gliomasolide E and the Synthetic Products 5a and 5b in the ^{1}H and ^{13}C NMR (CD_3OD)[a]

	synthetic **5a** (9*R*) ^{1}H NMR	synthetic **5b** (9*S*) ^{1}H NMR	synthetic **5a** (9*R*) ^{13}C NMR	synthetic **5b** (9*S*) ^{13}C NMR
position	$\Delta\delta_{N-S}$	$\Delta\delta_{N-S}$	$\Delta\delta_{N-S}$	$\Delta\delta_{N-S}$
3	0.01	0.21	0.0	1.2
4	0.02	−0.20	0.0	2.4
	0.02	−0.06		
6	0.00	0.30	0.0	−2.9
	0.00			
7	0.02	−0.03	0.1	1.8
8	0.03	−0.17	0.0	3.2
	0.02			
10	0.02	−0.19	0.1	0.5
	0.02			
13	0.01	0.71	0.1	0.9
17	0.01	0.08	0.0	−1.0

[a]NMR spectra of the natural product and the synthetic products were recorded at 600 MHz (150 MHz). Chemical shifts are reported in ppm with reference to the residual solvent. δ_N and δ_S are chemical shifts of the natural product and the synthetic product, respectively.

rotation of the natural product, $[\alpha]_D^{25}$ − 174 (*c* 0.15, CH_3OH).[2] The assignment of protons and carbons were made with the help of 2D NMR (TOCSY, NOESY, HSQC and HMBC) experiments. In **5a**, the coupling between H2/H3 (J = 16.1 Hz) shows that these protons are antiperiplanar arrangement and the characteristic NOE correlation between H3/H7, H3/H5, H3/H9 and H2/H4 H2/H4′ confirmed the assigned structure where as in case of **5b**, NOE correlation between H3/H9 was absent (Figure 2). The energy minimized structure as shown in Figure 2 is also in agreement with the assigned structures and stereochemistry proposed for the compounds **5a** and **5b** from NMR data. Therefore, the absolute configuration of gliomasolide E was elucidated to be (2*E*,5*R*,7*R*,9*R*,13*R*) as depicted in **5a**.

CONCLUSIONS

In summary, the total syntheses of two possible diastereomers of gliomasolide E have been achieved following macrolactonization through intramolecular Horner−Wadsworth−Emmons olefination, Yamaguchi−Hirao alkynylation, and base-induced elimination reaction for propargyl alcohol synthesis as the key steps. Detailed comparison of their ^{1}H and ^{13}C NMR data and specific rotation with those of the natural product revealed the absolute stereochemistry of gliomasolide E should be (2*E*,5*R*,7*R*,9*R*,13*R*). Following the same protocol, syntheses of other family members are in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. Experiments that required an inert atmosphere were carried out under argon in flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled over KOH. Commercially available reagents were used as received. Unless detailed otherwise, "workup" means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parentheses. If the reaction medium was acidic (basic), an additional washing with saturated aqueous $NaHCO_3$ solution (saturated aqueous NH_4Cl solution) was performed. Washing with brine, drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure followed by chromatography on a silica gel column (60−120 mesh) with the indicated eluent furnished the corresponding products. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (J) are reported in hertz (Hz). High resolution mass spectra were run by the electron impact mode (ESIMS, 70 eV) or by the FAB mode (*m*-nitrobenzyl alcohol matrix), using an orbitrap mass analyzer. IR data were measured with oily films on NaCl plates (oils) or KBr pellets (solids). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1} and were measured at 20 °C or otherwise mentioned. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad.

*(S)-1-((4-Methoxybenzyl)oxy)hex-5-en-3-ol (**13**).* To a solution of chiral epoxide 11 (10.0 g, 48.01 mmol) in dry THF (150 mL), CuI (0.91 g, 4.80 mmol) was added and the mixture was stirred at 25 °C for 30 min. It was cooled to −20 °C and vinyl magnesium bromide (96.03 mL, 1 M in THF, 96.03 mmol) was slowly added at the same temperature. It was allowed to stir for another 2 h at the same temperature. The reaction (monitored by TLC) was quenched with saturated aqueous NH_4Cl solution (100 mL) and diluted with ethyl acetate (100 mL). The two layers were separated and aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic

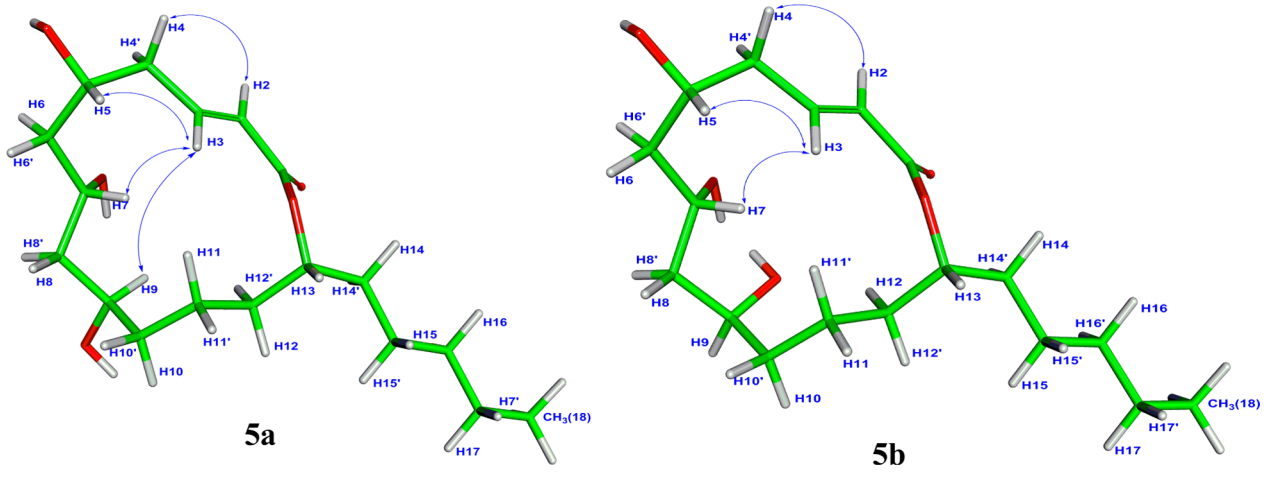

Figure 2. Energy minimized structure of **5a** and **5b** along with the characteristic NOE interactions.

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layer was washed with brine (2 × 200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product which was then purified by column chromatography over silica gel (ethyl acetate/hexane = 1:9) to afford the corresponding allylic alcohol 13 (10.55 g, 93%) as a colorless liquid. $[\alpha]_D^{20}$ − 8.5 (*c* 0.35, $CHCl_3$); IR (neat) ν 3439, 2926, 2861, 1612, 1513, 1452, 1247, 1090, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.88−5.78 (m, 1H), 5.13−5.06 (m, 2H), 4.45 (s, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.71−3.58 (m, 2H), 2.90 (br s, 1H), 2.24 (t, *J* = 6.3 Hz, 2H), 1.78−1.72 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 134.8, 129.9, 129.2, 117.4, 113.7, 72.8, 70.4, 68.5, 55.2, 41.8, 35.7 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{14}H_{20}O_3Na$ $[M + Na]^+$: 259.1305, found 259.1320.

*(S)-1-(((3-(Benzyloxy)hex-5-en-1-yl)oxy)methyl)-4-methoxybenzene (**14**).* To a suspension of NaH (5.17 g, 129.49 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (60 mL), was added dropwise a solution of homoallyl alcohol **13** (10.2 g, 43.16 mmol) in THF (100 mL) at 0 °C. To this reaction mixture, tetra-butyl ammonium iodide (catalytic) and benzyl bromide (7.69 mL, 64.74 mmol) were added subsequently and stirring was continued for 12 h at room temperature. The reaction mixture was quenched by small crushed ice flakes until a clear solution formed. The reaction mixture was extracted with ethyl acetate (3 × 100 mL). The organic extracts were washed with water (200 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents followed by purification of the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:19) afforded the product **14** (13.38 g, 95%) as a colorless liquid. $[\alpha]_D^{20}$ + 40.5 (*c* 0.60, $CHCl_3$); IR (neat) ν 3447, 2929, 2858, 1612, 1512, 1247, 1092, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.90−5.80 (m, 1H), 5.12−5.04 (m, 2H), 4.50 (q, *J* = 11.4 Hz, 2H), 4.40 (q, *J* = 11.4 Hz, 2H), 3.79 (s, 3H), 3.69−3.62 (m, 1H), 3.60−3.50 (m, 2H), 2.36−2.31 (m, 2H), 1.84−1.79 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 138.7, 134.6, 130.5, 129.2, 128.2, 127.7, 127.4, 117.1, 113.7, 75.5, 72.5, 71.2, 66.4, 55.1, 38.5, 34.3 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{26}O_3Na$ $[M + Na]^+$: 349.1774, found 349.1777.

*(4R,6R)-6-(Benzyloxy)-8-((4-methoxybenzyl)oxy)oct-1-en-4-ol (**10**).* To a stirred solution of alkene **14** (12.0 g, 36.76 mmol) in 1,4-dioxane/water (3:1; 100 mL), 2,6-lutidine (8.51 mL, 73.52 mmol), OsO_4 (0.18 g, 0.73 mmol) followed by $NaIO_4$ (31.45 g, 147.04 mmol) were sequentially added at room temperature and the reaction mixture was stirred for 3 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was quickly washed with 1 N HCl (2 × 50 mL) to remove excess 2,6-lutidine followed by brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by a short flash silica gel column chromatography (ethyl acetate/hexane = 1:9) to afford the corresponding aldehyde (10.38 g, 86%) as a colorless liquid, that was used immediately for the next reaction.

A solution of the above aldehyde (10.38 g, 31.60 mmol) in anhydrous CH_2Cl_2 (120 mL) was treated with $MgBr_2{\cdot}Et_2O$ (24.28 g, 94.82 mmol) and allyl(tributyl)stannane (12.24 mL, 37.92 mmol) at 0 °C and the mixture was stirred for 3 h. The mixture was then quenched with 2 M HCl solution (30 mL). The resultant mixture was warmed to room temperature and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane = 1:9) to afford homoallylic alcohol **10** (10.65 g, 91%) as a colorless liquid. $[\alpha]_D^{20}$ − 5.1 (*c* 0.56, $CHCl_3$); IR (neat) ν 3448, 2934, 2863, 1714, 1608, 1512, 1251, 1172, 1095, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.85−5.75 (m, 1H), 5.12−5.06 (m, 2H), 4.53 (q, *J* = 17.1, 11.3 Hz, 2H), 4.40 (d, *J* = 2.0 Hz, 2H), 3.97−3.87 (m, 1H), 3.80 (s, 3H), 3.58−3.48 (m, 2H), 2.23−2.18 (m, 2H), 2.04−1.95 (m, 1H), 1.86−1.69 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.2, 134.8, 130.3, 129.3, 128.3, 127.9, 127.6, 117.4, 113.7, 74.4, 72.6, 71.5, 67.7, 66.3, 55.2, 42.1, 39.7, 34.0 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{30}O_4Na$ $[M + Na]^+$: 393.2036, found 393.2041.

*(S)-Mosher Ester of Alcohol (**10a**).* To a solution of homoallylic alcohol **10** (15 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) were added *N*,*N*-dicyclohexylcarbodiimide (DCC) (15 mg, 0.07 mmol), (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*S*-MTPA) (14 mg, 0.06 mmol) and a catalytic amount of DMAP (3 mg) simultaneously. The reaction was stirred overnight at room temperature and quenched with saturated aqueous $NaHCO_3$ solution (2 mL). Then the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 19:1) to afford (*S*)-MTPA ester **10a** (19 mg, 83%) as a colorless liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.9, 2H), 7.39−7.27 (m, 8H), 7.22 (d, *J* = 8.6, 2H), 6.86 (d, *J* = 8.6, 2H), 5.74 (m, 1H), 5.46 (m, 1H), 5.10 (m, 1H), 5.07 (m, 1H), 4.44−4.30 (m, 4H), 3.80 (s, 1H), 3.56−3.50 (m, 3H), 3.48 (m, 1H), 3.46−3.40 (m, 2H), 2.47−2.41 (m, 2H), 1.84 (m, 1H), 1.79−1.69 (m, 3H).

*(R)-Mosher Ester of Alcohol (**10b**).* The reaction of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*R*-MTPA) with the alcohol 10 similarly afforded the (*R*)-MTPA ester **10b**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.8, 2H), 7.40−7.26 (m, 8H), 7.22 (d, *J* = 8.6, 2H), 6.85 (d, *J* = 8.6, 2H), 5.62 (m, 1H), 5.44 (m, 1H), 5.02 (m, 1H), 4.98 (m, 1H), 4.48−4.30 (m, 4H), 3.79 (s, 1H), 3.59 (m, 1H), 3.52 (m, 1H), 3.49−3.46 (3H), 3.43 (m, 1H), 2.46−2.30 (m, 2H), 1.90 (m, 1H), 1.84−1.71 (m, 3H).

*(4R,6R)-6-(Benzyloxy)-8-((4-methoxybenzyl)oxy)oct-1-en-4-yl tert-butyl carbonate (**15**).* To a stirred solution of alcohol **10** (7.50 g, 20.24 mmol) in anhydrous CH_2Cl_2 (80 mL), di-*tert*-butyl dicarbonate $[(Boc)_2O$; 13.95 mL, 60.73 mmol], followed by Et_3N (5.65 mL, 40.48 mmol) and DMAP (0.24 g, 2.02 mmol) were added at room temperature. After stirring for 6 h, the reaction was quenched with 5% aqueous $KHSO_4$ solution (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/hexane = 1:19) to give the Boc-protected compound **15** (8.76 g, 92%) as a colorless liquid. $[\alpha]_D^{20}$ − 19.2 (*c* 0.40, $CHCl_3$); IR (neat) ν 3420, 2977, 2934, 2863, 1736, 1513, 1278, 1251, 1166, 1094, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 7.25 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.83−5.72 (m, 1H), 5.11−4.99 (m, 2H), 4.45 (q, *J* = 16.1, 10.6, 2H), 4.41 (q, *J* = 14.0, 11.6, 2H), 3.80 (s, 3H), 3.74−3.66 (m, 1H), 3.60−3.48 (m, 2H), 2.38−2.33 (m, 2H), 1.91−1.79 (m, 2H), 1.77−1.73 (m, 2H), 1.47 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 153.1, 138.3, 133.3, 130.4, 129.1, 128.2, 128.0, 127.4, 117.8, 113.6, 81.5, 73.2, 73.1, 72.5, 72.0, 66.1, 55.1, 39.4, 39.2, 34.5, 27.7 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{28}H_{38}O_6Na$ $[M + Na]^+$: 493.2560, found 493.2568.

*(4S,6S)-4-((R)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butyl)-6-(iodomethyl)-1,3-dioxan-2-one (**16**).* To a stirred solution of carbonate **15** (8.50 g, 18.06 mmol) in acetonitrile (80 mL), was added *N*-iodosuccinimide (6.09 g, 27.09 mmol) at −40 °C. The resulting mixture was warmed up and stirred at 0 °C for 4 h. After completion of the reaction (monitored by TLC), it was quenched with aqueous $Na_2S_2O_3$ solution (30 mL), followed by of saturated aqueous $NaHCO_3$ solution (30 mL). Acetonitrile was removed under reduced pressure and the aqueous layer extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was quickly purified by flash column chromatography over silica gel (ethyl acetate/hexane = 2:3) to furnish the desired iodo-carbonate derivative **16** (8.68 g, 89%) as a colorless liquid, which was not very stable and used immediately.

*(2S,4R)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-1-((S)-oxiran-2-yl)hexan-2-ol (**17**).* To a solution of iodocarbonate **16** (8.50 g, 18.06 mmol) in MeOH (150 mL), K_2CO_3 (6.09 g, 27.09 mmol) was added and the resulting mixture was stirred at room temperature for 1 h.

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After completion of the reaction (monitored by TLC), MeOH was evaporated under reduced pressure. The residue was diluted with H_2O (40 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic phase was washed with brine (75 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which on purification by column chromatography over silica gel (ethyl acetate/hexane = 3:7) afforded the desired epoxy alcohol **17** (5.10 g, 85%) as a colorless liquid. $[\alpha]_D^{20}$ + 3.7 (*c* 0.32, $CHCl_3$); IR (neat) ν 3449, 2924, 2856, 1612, 1509, 1245, 1090, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.54 (q, *J* = 16.8, 11.3 Hz, 2H), 4.40 (d, *J* = 2.0 Hz, 2H), 4.16−4.10 (m, 1H), 3.95−3.89 (m, 1H), 3.79 (s, 3H), 3.59−3.49 (m, 2H), 3.09−3.04 (m, 1H), 2.76−2.74 (m, 1H), 2.49−2.46 (m, 1H), 2.05−1.96 (m, 1H), 1.88−1.80 (m, 2H), 1.73−1.58 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.1, 130.2, 129.3, 128.4, 127.9, 127.7, 113.7, 74.4, 72.6, 71.6, 66.7, 66.2, 55.2, 49.9, 46.5, 40.1, 40.0, 33.9 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{30}O_5Na$ $[M + Na]^+$: 409.2009, found 409.1984.

(((2S,4R)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-1-((S)-oxiran-2-yl)hexan-2-yl)oxy)(tert-butyl)diphenylsilane (***8***). To a stirred solution of alcohol 17 (4.50 g, 11.64 mmol) in CH_2Cl_2 (50 mL) under nitrogen atmosphere at room temperature, was added TBDPSCl (6.40 g, 23.28 mmol), imidazole (2.37 g, 34.93 mmol) and DMAP (0.14 g, 1.16 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion (monitored by TLC), the reaction was quenched with water (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography over silica gel (ethyl acetate/hexane = 1:9) to give **8** (6.76 g, 93%) as a colorless liquid. $[\alpha]_D^{20}$ + 12.6 (*c* 0.63, $CHCl_3$); IR (neat) ν 3447, 2930, 2856, 1616, 1512, 1247, 1106, 770, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.41−7.25 (m, 9H), 7.21(d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.36−4.30 (m, 3H), 4.18 (d, *J* = 11.2 Hz, 1H), 4.13−4.08 (m,1H), 3.79 (s, 3H), 3.64−3.58 (m, 1H), 3.48−3.36 (m, 2H), 3.08−3.03 (m, 1H), 2.64 (t, *J* = 4.7 Hz, 1H), 2.30 (q, *J* = 5.0, 2.7 Hz, 1H), 1.99−1.94 (m, 1H), 1.75−1.59 (m, 5H), 1.06 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.7, 135.9, 134.0, 130.5, 129.6, 129.2, 128.1, 127.5, 127.2, 113.6, 73.5, 72.5, 70.6, 69.0, 66.3, 55.2, 48.8, 46.4, 42.3, 39.8, 34.3, 26.9, 19.3 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{39}H_{48}O_5NaSi$ $[M + Na]^+$: 647.3163, found 647.3175.

(E)-Oct-2-en-1-ol (***18***). To a stirred solution of the commercially available hexanal (**12**) (6.0 g, 59.91 mmol) in CH_2Cl_2 (100 mL) was added (ethoxycarbonylmethylene) triphenylphosphorane (31.30 g, 89.86 mmol) at room temperature and stirred for 5 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography using (ethyl acetate/hexane = 1:19) to give pure α,β-unsaturated ester (9.02 g, 90%) as a colorless liquid. IR (neat) ν 3422, 2927, 2861, 1721, 1655, 1267, 1171, 1044, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.7, 7.0 Hz, 1H), 5.81 (dt, *J* = 15.7, 3.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.19 (dq, *J* = 7.1, 1.5 Hz, 2H), 1.46 (qt, *J* = 7.4 Hz, 2H), 1.35−1.27 (m, 7H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 149.3, 121.1, 60.0, 32.0, 31.2, 27.6, 22.3, 14.2, 13.8 ppm; CHN analysis calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; Found: C, 70.43; H, 10.71.

To a stirred solution of the above α,β-unsaturated ester (8.6 g, 50.51 mmol) in anhydrous CH_2Cl_2 (75 mL) was added DIBAL-*H* (1.4 M solution in toluene 90.20 mL, 126.29 mmol) over a period of 15 min at 0 °C under nitrogen atmosphere. After 30 min of stirring at the same temperature, TLC was checked which showed complete consumption of starting material. It was quenched by slow addition of saturated solution of sodium potassium tartrate (80 mL), diluted with CH_2Cl_2 (75 mL) and allowed to stir at room temperature for another 2 h to get a clear two separated layers. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified on silica gel column chromatography (ethyl acetate/hexane = 1:9) to afford the desired allylic alcohol **18** (5.63 g, 87%) as a colorless liquid. IR (neat) ν 3383, 2925, 2859, 1457, 1085, 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73−5.57 (m, 2H), 4.08 (d, *J* = 5.6 Hz, 2H), 2.08−2.01 (m, 2H), 1.42−1.24 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 128.7, 63.6, 32.1, 31.3, 28.7, 22.4, 13.9 ppm; CHN analysis calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58; Found: C, 74.85; H, 12.49.

((2R,3R)-3-Pentyloxiran-2-yl)methanol (***19***). To a freshly flame-dried double necked round-bottom flask equipped with activated 4 Å molecular sieves (~13.0 g) and dry CH_2Cl_2 (180 mL) at −20 °C were added Ti(*i*-OPr)$_4$ (3.58 mL, 12.12 mmol), (−)-diethyl tartrate (2.48 mL, 14.54 mmol) and the mixture was stirred for 40 min. To this reaction mixture was added allylic alcohol **18** (5.18 g, 40.40 mmol) in an interval of 30 min and TBHP (10.77 mL, 64.60 mmol, 6.0 M solution in toluene) were added and stirring was continued until completion of the reaction. The reaction mixture was warmed to 0 °C and filtered through Celite pad. The filtrate was quenched with water (75 mL), 15% aqueous NaOH solution (15 mL) and stirred vigorously for 3 h. The biphasic solution was separated and aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in reduced pressure. The crude residue was purified by column chromatography (ethyl acetate/hexane = 1:4) to afford the pure epoxide **19** (5.41 g, 93%) as a colorless liquid. $[\alpha]_D^{20}$ + 17.1 (*c* 1.2, $CHCl_3$); IR (neat) ν 3414, 2927, 2862, 1461, 1076, 1030, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (dq, *J* = 12.6, 2.4 Hz, 1H), 3.65−3.59 (m, 1H), 2.96 (td, *J* = 5.6, 2.4 Hz, 1H), 2.92 (dt, *J* = 4.5, 2.5 Hz, 1H), 1.91 (t, *J* = 5.9 Hz, 1H, D_2O exchangeable), 1.60−1.55 (m, 2H), 1.51−1.40 (m, 2H), 1.36−1.29 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.7, 58.6, 56.0, 31.4, 25.4, 22.4, 13.8 ppm; CHN analysis calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18; Found: C, 66.75; H, 11.24.

(R)-Oct-1-yn-3-ol (***20***). To a stirred solution of epoxyalcohol **19** (5.10 g, 35.36 mmol) in CCl_4 (60 mL), was added Ph_3P (11.13 g, 42.43 mmol), $NaHCO_3$ (0.65 g, 7.78 mmol) and the resulting reaction mixture was refluxed for 6 h. The reaction mixture was then cooled to 0 °C, diluted with hexane (100 mL), and filtered through Celite pad. After evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane = 1:19) to afford crude chloroepoxide (5.80 g) which was contaminated with Ph_3P. This material was used in the next reaction without further purification.

n-BuLi (2.5 M solution in THF, 71.31 mL, 178.29 mmol) was added to a stirred solution of above chloroepoxide (5.80 g, 35.65 mmol) in THF (60 mL) at −78 °C. The reaction mixture was stirred at −78 °C for an additional 1 h. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous NH_4Cl solution (60 mL) and diluted with ethyl acetate (75 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (70 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:9) to give **20** (3.83 g, 86% over two steps) as a colorless liquid. $[\alpha]_D^{20}$ + 7.2 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (dt, *J* = 6.6, 2.0 Hz, 1H), 2.46 (d, *J* = 2.2 Hz, 1H), 1.88 (br s, 1H), 1.77−1.65 (m, 2H), 1.51−1.41 (m, 2H), 1.38−1.27 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.0, 72.6, 62.2, 37.5, 31.3, 24.6, 22.4, 13.9 ppm; CHN analysis calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18; Found: C, 76.45; H, 11.26.

(R)-tert-Butyldimethyl(oct-1-yn-3-yloxy)silane (***9***). To a stirred solution of propargyl alcohol **20** (3.70 g, 29.31 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C, was added imidazole (5.98 g, 87.95 mmol), TBS-Cl (8.79 g, 58.62 mmol) and DMAP (0.35 g, 2.93 mmol) sequentially. After stirring for 3 h at room temperature, water (50 mL) was added and diluted with CH_2Cl_2 (60 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layer was washed with brine (70 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to obtain compound **9** (6.76 g, 94%) as a colorless liquid. $[\alpha]_D^{20}$ + 14.5

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(c 0.92, $CHCl_3$); IR (neat) ν 3310, 2926, 2858, 1461, 1253, 1083, 838, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (dt, J = 6.4, 2.0 Hz, 1H), 2.37 (d, J = 2.0 Hz, 1H), 1.70−1.63 (m, 2H), 1.48−1.37(m, 2H), 1.36−1.24 (m, 4H), 0.91 (s, 9H), 0.89 (t, J = 6.9 Hz, 3H), 0.13 (s, 1H), 0.11 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.7, 71.8, 62.7, 38.5, 31.4, 25.7, 24.7, 22.5, 18.2, 13.9, −4.5, −5.0 ppm; ESI-MS: m/z = 242 $[M + H]^+$.

*(5R,7R,11R)-5-((R)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butyl)-2,2,13,13,14,14-hexamet-hyl-11-pentyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadec-9-yn-7-ol (**21**).* To a flame-dried round-bottom flask was charged with alkyne **9** (4.23 g, 17.60 mmol) in anhydrous THF (40 mL) and cooled to −78 °C. To this solution, n-BuLi (2.5 M in hexanes, 7.04 mL, 17.60 mmol) was added dropwise via syringe, warmed slowly to 0 °C. During this period, the reaction mixture turned to dark red in color. After 30 min, epoxide **8** (5.5 g, 8.80 mmol) in dry THF (40 mL) was slowly added followed by $BF_3.OEt_2$ (2.17 mL, 17.60 mmol) at −78 °C and stirred for an additional 1 h. After completion (monitored by TLC), the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL), diluted with ethyl acetate (100 mL) and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (ethyl acetate/hexane = 1:9) provided the desired secondary alcohol **21** (6.47 g, 85%) as a colorless liquid. $[\alpha]_D^{20}$ + 11.5 (c 0.80, $CHCl_3$); IR (neat) ν 3448, 2930, 2856, 1613, 1248, 1106, 833, 774, 702, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.42−7.27 (m, 7H), 7.25−7.22 (m, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.34−4.24 (m, 4H), 4.13−4.03 (m, 2H), 3.90−3.84 (m, 1H), 3.79 (s, 3H), 3.48−3.41 (m, 1H), 3.39−3.34 (m, 1H), 3.30−3.25 (m, 1H), 2.21 (dd, J = 6.1, 1.8 Hz, 2H), 1.89−1.55 (m, 8H), 1.43−1.23 (m, 6H), 1.03 (s, 9H), 0.89 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H), 0.09 (d, J = 10.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.4, 135.8, 134.0, 133.7, 130.5, 129.7, 129.6, 129.1, 128.2, 127.6, 127.5, 127.4, 113.6, 84.4, 80.4, 73.9, 72.5, 70.7, 70.2, 67.6, 66.2, 63.0, 55.2, 43.4, 42.6, 38.8, 34.1, 31.4, 27.9, 26.9, 25.8, 24.9, 22.5, 19.2, 18.2, 14.0, −4.9, −4.4 ppm; HRMS (ESI) m/z calcd. for $C_{53}H_{76}O_6NaSi_2$ $[M + Na]^+$: 887.5072, found 887.5067.

*(5R,9R,11S)-11-((R)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)-butyl)-9-((tert-butyldiphenylsilyl)oxy)-2,2,3,3,14,14-hexamethyl-5-pentyl-13,13-diphenyl-4,12-dioxa-3,13-disilapentadec-6-yne (**22**).* To a stirred solution of alcohol **21** (1.50 g, 1.73 mmol) in anhydrous CH_2Cl_2 (40 mL) under nitrogen atmosphere at room temperature, was added TBDPS-Cl (0.90 mL, 3.46 mmol), imidazole (0.35 g, 5.2 mmol) and DMAP (20 mg, 0.17 mmol) sequentially. The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the reaction was quenched with water (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to give compound **22** (1.74 g, 91%) as a colorless viscous liquid. $[\alpha]_D^{20}$ + 5.9 (c 0.36, $CHCl_3$); IR (neat) ν 3450, 2931, 2857, 1629, 1248, 1106, 772, 702, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.63−7.57 (m, 8H), 7.41−7.27 (m, 11H), 7.25−7.22 (m, 4H), 7.21 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.31 (q, J = 11.1, 21.6 Hz, 2H), 4.24−4.17 (m, 2H), 4.11−4.01 (m, 2H), 3.93−3.88 (m, 1H), 3.79 (s, 3H), 3.57−3.52 (m, 1H), 3.40−3.35 (m, 1H), 3.31−3.26 (m, 1H), 2.11−2.06 (m, 1H), 1.96−1.91 (m, 1H), 1.74−1.56 (m, 3H), 1.53−1.43 (m, 3H), 1.38−1.18 (m, 8H), 0.94 (s, 18H), 0.88−0.84 (m, 12H), 0.04 (d, J = 4.2 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 138.9, 135.9, 135.8, 135.4, 134.3, 134.2, 134.1, 133.7, 130.6, 129.5, 129.4, 129.1, 128.0, 127.5, 127.4, 127.1, 113.6, 84.0, 80.5, 73.6, 72.4, 70.6, 68.9, 68.6, 66.4, 63.1, 55.2, 44.2, 43.0, 38.9, 34.2, 31.5, 27.0, 26.9, 26.6, 25.8, 24.9, 22.6, 19.3, 19.1, 18.2, 14.0, −4.2, −4.9 ppm; HRMS (ESI) m/z calcd. for $C_{69}H_{94}O_6NaSi_3$ $[M + Na]^+$: 1125.6250, found 1125.6255.

*(6R,10R,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenyl-silyl)oxy)-16-((4-methoxybenzyl)oxy)hexadecan-6-ol (**23a**).* Pyridinium p-toluenesulfonate (PPTS, 0.46 g, 1.83 mmol) was added to a solution of the trisilylether **22** (1.35 g, 1.22 mmol) in MeOH (70 mL). The mixture was stirred at room temperature for 6 h. After completion of the reaction (TLC monitoring), saturated aqueous $NaHCO_3$ solution (25 mL) was added, and the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (40 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined extract was dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:9) to obtain propargyl alcohol (1.13 g, 94%) as a colorless liquid. $[\alpha]_D^{20}$ + 18.0 (c 0.20, $CHCl_3$); IR (neat) ν 3448, 2931, 2857, 1614, 1247, 1107, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.67−7.62 (m, 4H), 7.59−7.51 (m, 4H), 7.43−7.26 (m, 13H), 7.24−7.19 (m, 4H), 7.15 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 4.38−4.18 (m, 4H), 4.08−3.99 (m, 2H), 3.87−3.80 (m, 1H), 3.77 (s, 3H), 3.56−3.48 (m, 1H), 3.47−3.39 (m, 1H), 3.35−3.29 (m, 1H), 2.75 (d, J = 5.0, 1H), 2.10 (d, J = 4.4, 1H), 2.02−1.75 (m, 4H), 1.54−1.45 (m, 4H), 1.40−1.20 (m, 6H), 1.01 (s, 9H), 0.91 (s, 9H), 0.88 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.6, 135.8, 134.2, 134.1, 133.8, 130.0, 129.4, 128.1, 127.6, 127.5, 127.4, 127.3, 113.6, 84.1, 80.7, 73.1, 72.5, 70.6, 68.4, 66.2, 61.9, 55.1, 53.3, 43.2, 42.6, 37.7, 34.1, 31.5, 26.9, 25.7, 24.9, 22.5, 19.2, 14.0 ppm; HRMS (ESI) m/z calcd. for $C_{63}H_{80}O_6NaSi_2$ $[M + Na]^+$: 1011.5385, found 1011.5394.

To a flask charged with above propargylic alcohol (0.80 g, 0.80 mmol) and tetrahydrofuran (50 mL) was added p-toluenesulfonyl hydrazide (1.5 g, 8.08 mmol) in one portion. The flask was fitted with a reflux condensor and warmed to reflux (bath temperature 90 °C). A solution of NaOAc (0.99 g, 12.12 mmol) in H_2O (50 mL) was added by a syringe pump over 2 h and stirred for 12 h. After completion of the reaction (monitored by TLC), the mixture was then cooled to room temperature and diluted with ethyl acetate (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined extracts were dried over Na_2SO_4, concentrated and purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:9) to afford saturated alcohol **23a** (0.74 g, 92%) as a colorless viscous liquid. $[\alpha]_D^{20}$ + 10.0 (c 0.52, $CHCl_3$); IR (neat) ν 3452, 2931, 2857, 1616, 1247, 1107, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.66−7.55 (m, 8H), 7.41−7.26 (m, 12H), 7.25−7.22 (m, 3H), 7.26 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 4.39−4.10 (m, 4H), 4.02−3.89 (m, 2H), 3.78 (s, 3H), 3.56−3.49 (m, 1H), 3.43−3.36 (m, 1H), 3.35−3.27 (m, 1H), 3.21−3.14 (m, 1H), 1.85−1.75 (m, 2H), 1.69−1.45 (m, 12H), 1.36−1.27 (m, 6H), 0.99 (s, 9H), 0.93 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.8, 135.9, 135.8, 134.7, 134.4, 134.3, 134.2, 130.5, 129.4, 129.3, 129.2, 128.1, 127.6, 127.4, 127.3, 127.2, 113.6, 73.5, 72.5, 71.5, 70.6, 70.3, 68.8, 66.3, 55.2, 44.0, 42.9, 37.5, 37.2, 35.5, 34.4, 31.9, 29.6, 27.0, 26.9, 25.3, 22.6, 20.2, 19.2, 14.0 ppm; HRMS (ESI) m/z calcd. for $C_{63}H_{84}O_6NaSi_2$ $[M + Na]^+$: 1015.5698, found 1015.5702.

*(6R,10R,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenyl-silyl)oxy)-16-((4-methoxybenzyl)oxy)hexadecan-6-yl-2-(diethoxy-phosphoryl)acetate (**24a**).* To a stirred solution of 2-(diethoxyphosphoryl)acetic acid (0.19 g, 0.98 mmol) and DCC (0.29 g, 1.43 mmol) in CH_2Cl_2 (10 mL), was added DMAP (0.04 g, 0.32 mmol) at room temperature. The mixture was stirred for 15 min before a solution of **23a** (0.65 g, 0.65 mmol) in CH_2Cl_2 (10 mL) was added at room temperature. The mixture was stirred at room temperature for 12 h. After completion of the reaction (TLC monitoring), the mixture was quenched with H_2O (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was dried (Na_2SO_4), concentrated and the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 3:7) to furnish compound **24a** (0.76 g, 87%) as a colorless liquid. $[\alpha]_D^{20}$ + 8.3 (c 0.50, $CHCl_3$); IR (neat) ν 3446, 3067, 2933, 2858, 1732, 1464, 1270, 1108, 1054, 1030, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.63−7.55 (m, 8H), 7.40−7.26 (m, 13H), 7.25−7.23 (m, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 6.4 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.69−4.63 (m, 1H), 4.35−4.22 (m, 3H), 4.18−4.10 (m, 5H), 4.03−3.96 (m, 1H),

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3.93−3.86 (m, 1H), 3.79 (s, 3H), 3.55−3.48 (m, 1H), 3.41−3.36 (m, 1H), 3.33−3.25 (m, 1H), 2.84 (d, J = 2.1 Hz, 1H), 2.79 (d, J = 2.2 Hz, 1H), 1.83−1.72 (m, 2H), 1.62−1.45 (m, 6H), 1.34−1.15(m, 18H), 0.97 (s, 9H), 0.94 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 159.0, 138.8, 135.9, 135.8, 134.5, 134.2, 130.6, 129.4, 129.1, 128.1, 127.4, 127.1, 113.6, 75.7, 73.7, 72.4, 70.6, 70.5, 68.8, 66.3, 62.5, 62.4, 55.2, 44.7, 43.1, 35.9, 35.0, 34.3, 33.8, 33.6, 33.5, 31.7, 29.6, 27.0, 26.9, 24.6, 22.5, 20.4, 19.2, 16.3, 16.2, 14.0 ppm; HRMS (ESI) m/z calcd. for $C_{69}H_{95}O_{10}NaPSi_2$ $[M + Na]^+$: 1193.6093, found 1193.6073.

*(6R,10R,12S,14S)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)oxy)-16-oxohexadecan-6-yl 2-(diethoxyphosphoryl)acetate (**25a**).* To a stirred solution of **24a** (0.54 g, 0.46 mmol) in CH_3CN/H_2O (9:1) (20 mL) was added ceric ammonium nitrate (CAN, 0.50 g, 0.92 mmol) at 0 °C, and the mixture was stirred for 30 min. After completion (monitored by TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was filtered through Celite pad, organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:1) to afford corresponding primary alcohol **25a** (0.43 g, 89%) as a colorless liquid. $[\alpha]_D^{20}$ + 5.3 (c 0.88, $CHCl_3$); IR (neat) ν 3446, 2931, 2857, 1732, 1633, 1269, 1108, 1052, 1027, 7034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.55 (m, 8H), 7.42−7.27 (m, 15H), 7.17 (dd, J = 7.9, 1.5 Hz, 2H), 4.73−4.66 (m, 1H), 4.27−4.19 (m, 2H), 4.17−4.08 (m, 6H), 4.01−3.94 (m, 1H), 3.90−3.84 (m, 1H), 3.56−3.42 (m, 2H), 2.86 (d, J = 1.5 Hz, 1H), 2.82 (d, J = 1.5 Hz, 1H), 1.83−1.56 (m, 4H), 1.50−1.10 (m, 22H), 0.99 (s, 9H), 0.93 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 138.2, 135.8, 134.4, 134.3, 134.1, 133.9, 129.5, 129.4, 128.2, 127.6, 127.4, 75.9, 75.4, 70.6, 70.3, 68.6, 63.6, 63.5, 62.5, 62.4, 59.8, 44.2, 42.2, 36.0, 35.7, 34.9, 33.9, 33.8, 33.6, 31.6, 29.6, 27.0, 26.9, 24.6, 22.5, 20.2, 19.3, 19.2, 16.3, 16.2, 16.1, 16.0, 14.0 ppm; HRMS (ESI) m/z calcd. for $C_{61}H_{87}O_9NaPSi_2$ $[M + Na]^+$: 1073.5518, found 1073.5525.

*(6R,10R,12S,14S)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)oxy)-16-oxohexadecan-6-yl 2-(diethoxyphosphoryl)acetate (**7a**).* To a stirred solution of above alcohol **25a** (0.32 g, 0.30 mmol) and solid anhydrous $NaHCO_3$ (0.1 g, 1.21 mmol) in CH_2Cl_2 (10 mL), Dess−Martin periodinane (DMP) (0.26 g, 0.60 mmol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h. After completion of the reaction (monitored by TLC), it was filtered through Celite pad and thoroughly washed with CH_2Cl_2 (20 mL). Organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (ethyl acetate/hexane = 3:7) to afford aldehyde **7a** (0.27, 86%) as a colorless liquid, that was immediately used in the next step.

*(6R,8S,10R,14R,E)-6-(Benzyloxy)-8,10-bis((tert-butyldiphenylsilyl)oxy)-14-pentyloxacyclotetradec-3-en-2-one (**26a**).* The above obtained aldehyde **7a** (0.25 g, 0.23 mmol) in acetonitrile (200 mL) was added LiCl (0.15 g, 3.57 mmol) at room temperature. After 30 min, a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.07 mL, 0.47 mmol) in acetonitrile (100 mL) was added dropwise. After being stirred at room temperature for 12 h, the reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and brine (30 mL). The organic solvent was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layer were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:9) to yield macrolide **26a** (0.17 g, 82%) as a colorless viscous liquid. $[\alpha]_D^{20}$ + 6.2 (c 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 6.7 Hz, 4H), 7.59 (d, J = 6.7 Hz, 4H), 7.44−7.27 (m, 15H), 7.22 (d, J = 6.8 Hz, 2H), 6.22−6.14 (m, 1H), 5.54 (d, J = 15.5 Hz, 1H), 4.76−4.69 (m, 1H), 4.37(q, J = 11.7, 2.5 Hz, 2H), 4.25−4.17 (m, 1H), 4.14−4.09 (m, 1H), 3.67−3.60 (m, 1H), 3.11−3.04 (m, 1H), 2.44−2.36 (m, 1H), 1.88−1.81 (m, 1H), 1.70−1.47 (m, 8H), 1.35−1.25 (m, 10H), 1.02 (s, 9H), 0.90 (t, J = 7.0, 3H), 0.87 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 144.1, 138.1, 135.9, 135.8, 134.5, 134.4, 134.3, 133.4, 129.8, 129.5, 129.4, 128.3, 127.6, 127.4, 125.1, 77.1, 75.6, 70.7, 69.4, 67.4, 53.3, 45.7, 41.7, 39.0, 35.2, 35.1, 34.8, 31.7, 29.6, 27.0, 26.9, 25.1, 22.5, 19.3, 19.1, 14.0 ppm; HRMS (ESI) m/z calcd. for $C_{57}H_{74}O_5NaSi_2$ $[M + Na]^+$: 917.4967, found 917.4981.

*(6R,8R,10R,14R,E)-6,8,10-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (**5a**).* To a stirred solution of compound **26a** (100 mg, 0.11 mmol) in CH_2Cl_2 (10 mL), $TiCl_4$ (3.35 mL, 3.35 mmol, 1 m in CH_2Cl_2) was added at 0 °C and the reaction mixture stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), it was quenched with a saturated aqueous $NaHCO_3$ solution (15 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which on purification by column chromatography over silica gel (ethyl acetate/hexane = 19:1) furnished compound **5a** (27 mg, 75%) as a white amorphous powder. $[\alpha]_D^{25}$ − 92.5 (c 0.18, CH_3OH); IR (neat) ν 3361, 2926, 2856, 1716, 1647, 1458, 1054, 861 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 6.97 (ddd, J = 16.1, 10.0, 6.5 Hz, 1H), 5.91 (d, J = 15.7 Hz, 1H), 4.04−3.98 (m, 1H), 3.85−3.79 (m, 1H), 3.78−3.73 (m, 1H), 2.59−2.52 (m, 1H), 2.48−2.41 (m, 1H), 1.95−1.88 (m, 1H), 1.83−1.76 (m, 1H), 1.75−1.67 (m, 1H), 1.66−1.50 (m, 4H), 1.49−1.38 (m, 2H), 1.34−1.23 (m, 9H), 0.88 (t, J = 6.8, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 168.3, 147.2, 125.5, 77.4, 69.9, 69.1, 68.2, 43.8, 43.2, 41.8, 36.5, 36.0, 33.6, 32.5, 25.9, 23.4, 21.7, 14.3 ppm; HRMS (ESI) m/z calcd. for $C_{18}H_{32}O_5Na$ $[M + Na]^+$: 351.2142, found 351.2120.

*(5R,7R,11R)-5-((R)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butyl)-2,2,13,13,14,14-hexamethyl-11-pentyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecan-7-ol (**27**).* To a flask charged with homopropargylic alcohol **21** (4.0 g, 4.62 mmol) and tetrahydrofuran (100 mL) was added p-toluenesulfonyl hydrazide (8.60 g, 46.22 mmol) in one portion. The flask was fitted with a reflux condensor and warmed to reflux (bath temperature 90 °C). A solution of NaOAc (5.68 g, 69.33 mmol) in H_2O (100 mL) was added by a syringe pump over 5 h and stirred for 12 h. After completion of the reaction (TLC monitoring), the mixture was then cooled to room temperature and diluted with ethyl acetate (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, concentration under reduced pressure and purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:9) to obtain saturated alcohol **27** (3.60 g, 90%) as a colorless viscous liquid. $[\alpha]_D^{20}$ + 9.5 (c 0.4, $CHCl_3$); IR (neat) ν 3448, 2931, 2857, 1460, 1248, 1101, 827, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.43−7.26 (m, 7H), 7.25−7.22 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 7.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.35−4.25 (m, 3H), 4.13−4.03 (m, 2H), 3.80 (s, 3H), 3.75−3.67 (m, 1H), 3.62−3.54 (m, 1H), 3.41−3.30 (m, 2H), 3.28−3.22 (m, 1H), 1.86−1.78 (m, 2H), 1.65−1.49 (m, 6H), 1.42−1.20 (m, 12H), 1.03 (s, 9H), 0.90−0.86 (m, 12H), 0.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.3, 135.8, 134.1, 133.7, 130.5, 129.7, 129.6, 129.1, 128.2, 127.7, 127.6, 127.5, 127.4, 113.7, 74.1, 72.5, 72.2, 71.2, 70.8, 69.4, 66.2, 55.2, 44.7, 42.9, 38.1, 37.1, 36.9, 34.2, 32.0, 26.9, 25.9, 24.9, 22.6, 21.1, 19.2, 18.1, 14.0, −4.3, −4.4 ppm; HRMS (ESI) m/z calcd. for $C_{53}H_{80}O_6NaSi_2$ $[M + Na]^+$: 891.5385, found 891.5371.

*(5S,7S,11R)-5-((R)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butyl)-2,2,13,13,14,14-hexamethyl-11-pentyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecan-7-yl benzoate (**28**).* To Triphenylphosphine (1.50 g, 5.75 mmol), diisopropyl azodicarboxylate (1.13 mL, 5.75 mmol), and benzoic acid (0.70 g, 5.75 mmol) were added with stirring to a cooled (0 °C) solution of compound **27** (2.50 g, 2.87 mmol) in THF (30 mL). The reaction mixture was then stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (60 mL) and quenched with saturated aqueous $NaHCO_3$ solution (30 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The

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residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:19) to provide the benzoate (2.30 g, 82%) as a light yellow liquid. $[\alpha]_D^{20}$ − 3.1 (*c* 0.36, $CHCl_3$); IR (neat) ν 3452, 2930, 2857, 1717, 1463, 1272, 1250, 1107, 829, 706, 504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.97 (d, *J* = 7.9 Hz, 2H), 7.71 (d, *J* = 6.7 Hz, 2H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.58−7.54 (m, 1H), 7.44−7.32 (m, 6H), 7.33−7.13 (m, 9H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.23−5.18 (m, 1H), 4.39−4.28 (m, 3H), 4.19−4.11 (m, 1H), 4.06−3.98 (m, 1H), 3.84 (s, 3H), 3.63−3.53 (m, 2H), 3.44−3.38 (m, 1H), 3.35−3.28 (m, 1H), 2.04−1.96 (m, 1H), 1.91−1.80 (m, 2H), 1.75−1.68 (m, 1H), 1.47−1.22 (m, 15H), 1.05 (s, 9H), 0.89 (s, 9H), 0.87 (t, *J* = 8.6 Hz, 3H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 159.0, 138.7, 135.8, 134.3, 133.5, 132.5, 130.7, 130.6, 129.5, 129.1, 128.1, 127.4, 127.2, 113.6, 73.9, 72.5, 72.4, 72.0, 70.6, 68.7, 66.2, 55.2, 43.2, 42.5, 37.0, 36.9, 34.6, 34.1, 32.0, 29.6, 26.9, 25.9, 24.9, 22.6, 20.7, 19.3, 18.0, 14.0, −4.4 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{60}H_{84}O_7NaSi_2$ $[M + Na]^+$: 995.5647, found 995.5643.

The above benzoate (2.00 g, 2.05 mmol) was dissolved in methanol (30 mL). Potassium carbonate (0.14 g, 1.02 mmol) was then added and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), methanol was removed under reduced pressure and the crude product was dissolved in water (20 mL). The aqueous layer was then extracted with ethyl acetate (3 × 40 mL). The organic layer was dried over $NaSO_4$, concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:9) to provide the compound **28** (1.57 g, 88%) as a colorless liquid. $[\alpha]_D^{20}$ − 12.3 (*c* 0.10, $CHCl_3$); IR (neat) ν 3448, 2931, 2857, 1460, 1248, 1101, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.44−7.31 (m, 7H), 7.25−7.22 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.12 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.34−4.22 (m, 3H), 4.13−4.04 (m, 2H), 3.92−3.84 (m, 1H), 3.79 (s, 3H), 3.63−3.53 (m, 1H), 3.39−3.24 (m, 3H), 1.75−1.46 (m, 6H), 1.44−1.21 (m, 14H), 1.05 (s, 9H), 0.88 (m, 12H), 0.03 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 138.4, 136.0, 135.9, 133.5, 133.2, 130.5, 129.8, 129.1, 128.1, 127.6, 127.3, 113.7, 73.7, 72.5, 72.3, 70.8, 70.6, 68.4, 66.1, 55.2, 42.4, 41.3, 38.1, 37.3, 37.0, 34.0, 32.0, 26.9, 24.9, 22.6, 21.4, 19.1, 18.1, 14.0, −4.3, −4.4 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{53}H_{80}O_6NaSi_2$ [$[M + Na]^+$: 891.5385, found 891.5386.

(6R,10S,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)oxy)-16-((4-methoxybenzyl)oxy)hexadecan-6-ol (***23b***). To a stirred solution of alcohol **28** (1.40 g, 1.61 mmol) in anhydrous CH_2Cl_2 (40 mL) under nitrogen atmosphere at room temperature, was added TBDPS-Cl (0.83 mL, 3.22 mmol), imidazole (0.33 g, 4.83 mmol) and DMAP (0.02 g, 0.16 mmol) sequentially. The reaction mixture was stirred at room temperature for 2 h. After completion the reaction (monitored by TLC), it was quenched with water (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:19) to give trisilylether compound (1.65 g, 93%) as a colorless liquid. $[\alpha]_D^{20}$ − 5.1 (*c* 0.20, $CHCl_3$); IR (neat) ν 3448, 2924, 2854, 1740, 1461, 1108, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73−7.70 (m, 1H), 7.64−7.56 (m, 8H), 7.42−7.27 (m, 12H), 7.25−7.21 (m, 2H), 7.09−7.02 (m, 2H), 6.87 (d, *J* = 11.2 Hz, 2H), 4.42−4.34 (m, 2H), 4.25 (d, *J* = 11.3 Hz, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.84−3.77 (m, 4H), 3.73−3.60 (m, 1H), 3.58−3.48 (m, 1H), 3.47−3.36 (m, 2H), 3.35−3.26 (m, 1H), 1.71−1.46 (m, 10H), 1.38−1.13 (m, 10H), 0.95 (s, 18H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), −0.02 (d, *J* = 11.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.8, 135.8, 134.5, 134.4, 134.2, 134.1, 130.6, 129.4, 129.3, 129.1, 128.1, 127.4, 127.2, 127.1, 113.7, 73.5, 72.5, 72.3, 71.0, 68.6, 66.4, 55.2, 46.0, 42.6, 37.4, 37.0, 36.4, 34.4, 32.1, 27.0, 25.9, 24.8, 22.6, 20.8, 19.2, 18.1, 14.0, −4.3, −4.4 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{69}H_{98}O_6NaSi_3$ $[M + Na]^+$: 1129.6560, found 1129.6563.

Pyridinium *p*-toluenesulfonate (PPTS, 0.40 g, 1.62 mmol) was added to a solution of the above trisilylether (1.2 g, 1.08 mmol) in MeOH (50 mL). The mixture was stirred at room temperature for 6 h. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and the resulting solution was washed with brine (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4, removed under reduced pressure and purified by flash chromatography over silica gel (ethyl acetate/hexane = 1:9) to give compound **23b** (0.99 g, 92%) as a colorless liquid. $[\alpha]_D^{20}$ − 5.0 (*c* 1.28, $CHCl_3$); IR (neat) ν 3452, 2931, 2857, 1616, 1247, 1107, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64−7.56 (m, 9H), 7.42−7.27 (m, 12H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.05−7.03 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.39 (q, *J* = 11.5 Hz, 7.9 Hz, 2H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.05 (d, *J* = 11.2 Hz, 1H), 3.86−3.81 (m, 1H), 3.80 (s, 3H), 3.73−3.67 (m, 1H), 3.56−3.49 (m, 1H), 3.45−3.38 (m, 1H), 3.36−3.27 (m, 2H), 1.74−1.63 (m, 3H), 1.37−1.21 (m, 10H), 1.18−1.01 (m, 7H), 0.96 (s, 9H), 0.95 (s, 9H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.8, 135.8, 134.5, 134.4, 134.2, 134.0, 130.6, 129.4, 129.3, 129.1, 128.0, 127.4, 127.3, 127.1, 113.7, 73.6, 72.5, 71.4, 70.8, 68.5, 66.4, 55.2, 45.9, 42.6, 37.2, 37.1, 35.8, 34.4, 31.9, 26.9, 25.2, 22.6, 20.5, 19.2, 14.0 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{63}H_{84}O_6NaSi_2$ $[M + Na]^+$: 1015.5698, found 1015.5699.

(6R,10S,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)oxy)-16-((4-methoxybenzyl)oxy)hexadecan-6-yl 2-(diethoxyphosphoryl)acetate (***24b***). Procedure is same as for **24a**. $[\alpha]_D^{20}$ − 3.2 (*c* 1.56, $CHCl_3$); IR (neat) ν 3446, 3067, 2933, 2858, 1732, 1464, 1270, 1108, 1054, 1030, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.54 (m, 9H), 7.42−7.27 (m, 12H), 7.25−7.22 (m, 2H), 7.05−7.02 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.75−4.68 (m, 1H), 4.39 (q, *J* = 11.5, 5.5 Hz, 2H), 4.27 (d, *J* = 11.2 Hz, 2H), 4.19−4.10 (m, 4H), 4.06 (d, *J* = 11.2 Hz, 2H), 3.80 (s, 3H), 3.79−3.73 (m, 1H), 3.71−3.64 (m, 1H), 3.54−3.47 (m, 1H), 3.44−3.37 (m, 1H), 2.89 (d, *J* = 2.8 Hz, 1H), 2.83 (d, *J* = 2.9 Hz, 1H), 1.71−1.51 (m, 8H), 1.44−1.35 (m, 2H), 1.35−1.29 (m, 6H), 1.28−1.09 (m, 10H), (0.95 (s, 9H), 0.94 (s, 9H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 159.0, 138.8, 135.8, 134.4, 134.3, 134.1, 134.0, 130.6, 129.5, 129.4, 129.3, 129.1, 128.0, 127.4, 127.3, 127.1, 113.7, 75.7, 73.6, 72.5, 70.8, 70.7, 68.5, 66.4, 62.5, 62.4, 55.2, 46.0, 42.6, 35.9, 35.0, 34.4, 33.8, 33.7, 31.7, 26.9, 24.6, 22.5, 20.4, 19.2, 16.3, 16.2, 14.0 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{69}H_{95}O_{10}NaPSi_2$ [$[M + Na]^+$: 1193.6093, found 1193.6092.

(6R,10S,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)oxy)-16-hydroxyhexadecan-6-yl 2-(diethoxyphosphoryl)acetate (***25b***). Procedure is same as for **25a**. $[\alpha]_D^{20}$ + 10.7 (*c* 0.32, $CHCl_3$); IR (neat) ν 3446, 2931, 2857, 1732, 1633, 1269, 1108, 1052, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.55 (m, 9H), 7.44−7.29 (m, 12H), 7.26−7.23 (m, 2H), 7.10−7.06 (m, 2H), 4.76−4.70 (m, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.22−4.07 (m, 5H), 3.81−3.72 (m, 1H), 3.66−3.58 (m, 2H), 3.57−3.46 (m, 2H), 2.89 (d, *J* = 2.0 Hz, 1H), 2.84 (d, *J* = 2.2 Hz, 1H), 1.72−1.53 (m, 4H), 1.44−1.15 (m, 22H), 0.96 (s, 18H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 138.2, 135.8, 134.3, 134.1, 134.0, 129.6, 129.5, 129.4, 129.2, 127.5, 127.4, 75.7, 75.5, 70.8, 70.7, 68.8, 63.6, 62.5, 60.3, 60.0, 45.9, 42.0, 36.3, 35.8, 35.0, 33.8, 33.7, 31.6, 26.9, 24.6, 22.5, 21.0, 20.5, 19.2, 16.3, 16.2, 16.1, 16.0, 14.1, 14.0 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{61}H_{87}O_9PSi_2$ $[M + H]^+$: 1051.5699, found 1051.5701.

(6R,8S,10S,14R,E)-6-(Benzyloxy)-8,10-bis((tert-butyldiphenylsilyl)oxy)-14-pentyloxacyclotetradec-3-en-2-one (***26b***). Procedure is same as for **26a**. $[\alpha]_D^{20}$ − 54.4 (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.74−7.71 (m, 2H), 7.66−7.56 (m, 6H), 7.46−7.27 (m, 17), 6.27−6.19 (m, 1H), 5.20 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.96−4.88 (m, 1H), 4.38 (q, 2H), 3.55−3.48 (m, 1H), 3.32−3.25 (m, 1H), 3.08−3.02 (m, 1H), 2.48−2.42 (m, 1H), 2.20−2.12 (m, 1H), 1.76−1.60 (m, 2H), 1.53−1.40 (m, 4H), 1.34−1.08 (m, 12H), 0.97−0.92 (m, 18H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 143.4, 138.6, 136.3, 136.1, 136.0, 135.9, 134.9, 134.5, 133.9, 133.6, 129.6, 129.5, 129.3, 128.3, 128.1, 127.6, 127.5, 127.4, 127.3, 127.2, 125.2, 75.9, 74.8, 72.4, 70.0, 66.7, 47.6, 37.0, 36.9, 35.8, 34.9, 32.6, 31.6, 29.6, 26.9, 26.8, 25.0, 23.2, 22.5, 19.4, 19.0, 14.0 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{57}H_{74}O_5NaSi_2$ $[M + Na]^+$: 917.4967, found 917.4962.

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*(6R,8R,10S,14R,E)-6,8,10-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (**5b**).* Procedure is same as for **5a**. $[\alpha]_D^{20}$ − 28.7 (*c* 0.08, CH_3OH); IR (neat) ν 3381, 2924, 2859, 1713, 1656, 1447, 1173, 1053, 889, 616 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 6.78 (ddd, *J* = 15.5, 10.6, 4.8 Hz, 1H), 6.03 (d, *J* = 15.7 Hz, 1H), 4.19−4.13 (m, 2H), 4.09−4.00 (m, 2H), 2.81−2.75 (m, 1H), 2.56−2.47 (m, 1H), 1.88−1.78 (m, 2H), 1.72−1.63 (m, 4H), 1.60−1.51 (m, 3H), 1.35−1.15 (m, 9H), 0.87 (t, *J* = 6.7, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 168.9, 146.1, 125.9, 78.6, 70.3, 69.6, 66.3, 46.5, 39.6, 39.5, 37.6, 35.8, 34.0, 32.4, 25.9, 24.3, 23.3, 14.2 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{32}O_5Na$ $[M + Na]^+$: 351.2142, found 351.2130.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02611.

Copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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