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

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ABSTRACT: The first total syntheses of two possible diastereomers of gliomasolide E, a 14membered 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 are the key reactions. Detailed comparison of their ¹H and ¹³C NMR (1D and 2D 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*).

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. 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 (IC₅₀ 10.1 μ M) 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

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 gloeosporone⁴ and others.⁵ Coupled with our own efforts in the synthesis of varied bio-active 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 the natural product, thus ascertaining the stereochemistry of gliomasolide E.



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

Retrosynthetic analysis of gliomasolide E (**5a**) is outlined in Scheme 1. We envisaged the formation of the macrolactone of **5a** and its 9-epimer **5b** by a late stage intramolecular macrocyclization using Horner-Wadsworth-Emmons olefination⁷ 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 cyclization⁹ 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 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 protocol¹² afforded the corresponding unstable aldehyde, which was immediately subjected to chelation-controlled diastereoselective allylation¹³ by treatment with allyl(tributyl)stannane in presence of MgBr₂·Et₂O 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 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 carbonate¹⁵ in 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 CH₃CN at 0 °C, produced the desired iodo-carbonate derivative **16** in 89% yield as the only product. The iodo derivative **16** on treatment with K₂CO₃ 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 CH₂Cl₂ 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 CH₂Cl₂ to furnish α,β -unsaturated ester with *E*-configuration in 85% yield, followed by reduction with DIBAL-*H* in CH₂Cl₂ to obtain the corresponding allylic alcohol **Scheme 3. Synthesis of the Fragment 9**



18 in 87% yield. The Sharpless asymmetric epoxidation¹⁷ of (*E*)-2-octenol (**18**) using (–)-DET and Ti(^{*i*}PrO)₄ in CH₂Cl₂ at –20 °C furnished epoxy alcohol **19**¹⁸ in 93% yield. Compound **19** was converted to the corresponding (chloromethyl)oxirane using CCl₄-Ph₃P under reflux conditions followed by Yadav's protocol of base-induced elimination reaction⁹ to afford the chiral propargylic alcohol **20**¹⁹ in 81% yield over two steps. The alkynol **20** was treated with TBSCl and imidazole in CH₂Cl₂ 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 protocol⁸ (Scheme 4). Accordingly,

of epoxide **8** with the alkyne **9** under the Yamaguchi–Hirao protocol⁸ (Scheme 4). Accordingly, treatment of alkyne **9** with *n*-BuLi followed by addition to epoxide **8** with BF₃·Et₂O (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 CH₂Cl₂ to obtain compound **22** in 91% yield. The TBS group in compound **22** was selectively removed by using PPTS in methanol and subsequent diimide-mediated²¹ reduction of triple bond using TsNHNH₂ 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-

Scheme 4. Synthesis of the Macrocycle 5a through Intramolecular Horner-Wadsworth-



Emmons Olefination

Emmons reaction under Masamune–Roush conditions²⁵ (LiCl, DBU, MeCN, rt, 12 h) to establish the desired 14-membered macrolactone **26a** as a sole *E*-olefinic isomer in 80% yield. Global deprotection²⁶ was achieved by treating **26a** with excess TiCl₄ in CH₂Cl₂ to complete the total synthesis of **5a** in 75% yield.

After achieveing the synthesis of **5a**, total synthesis of **5b** was initiated. For the same, the alkyne **21** was reduced to alkane **27** in 90% yield by treating excess diimide²¹ as explained earlier (Scheme 5). Mitsunobu inversion²⁷ of the secondary alcohol (C9) group present in **27** using benzoic acid, Ph₃P and DIAD in THF at 0 °C followed by hydrolysis under basic conditions (K₂CO₃, MeOH) afforded the required alcohol **28** in 70% yield over two steps. Scheme **5. Synthesis of the Macrocycle 5b** OBn



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 ¹³C NMR data (600 MHz, CD₃OD) 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 ¹³C 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.

Table 1. Selected Chemical Shift Difference in ppm between Natural Gliomasolide E and the Synthetic Products 5a and 5b in the ¹H and ¹³C NMR (CD₃OD)^{*a*}

Position	Synthetic	Synthetic	Synthetic	Synthetic
	5a (9 <i>R</i>)	5b (9 <i>S</i>)	5a (9 <i>R</i>)	5b (9 <i>S</i>)
	¹ H NMR	¹ H NMR	¹³ C NMR	¹³ C NMR
	$\Delta \delta_{N-S}$	$\Delta \delta_{N-S}$	$\Delta \delta_{N-S}$	$\Delta \delta_{N-S}$
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

"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.

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 ¹³C NMR data. The measured specific rotation of the synthetic **5a**, $[\alpha]_D^{25}$ –92.7 (*c* 0.15, CH₃OH) was consistent with the sign of the specific rotation of the natural product, $[\alpha]_D^{25}$ –174 (*c* 0.15, CH₃OH).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 anti-periplanar arrangement and the



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

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 (2E,5R,7R,9R,13R) 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 ¹H and ¹³C NMR data and specific rotation with those of the natural product revealed the absolute stereochemistry of gliomasolide E should be (2E,5R,7R,9R,13R). Following the same protocol, syntheses of other family members are in progress and will be reported in due course.

EXPERIMENTAL SECTION

General methods: Experiments which required an inert atmosphere were carried out under argon in flame-dried glassware. Et₂O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH₂. Tertiary amines were freshly distilled over KOH. Commercially available reagents were used as received. Unless detailed otherwise, "work-up" means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with saturated aqueous NaHCO₃ solution (saturated aqueous NH₄Cl solution) was performed. Washing with brine, drying over anhydrous Na₂SO₄ 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. ¹H and ¹³C 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

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were measured with oily films on NaCl plates (oils) or KBr pellets (solids). Specific optical rotations $[\alpha]_D$ are given in 10⁻¹ deg cm² 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, 1M 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 NH₄Cl solution (100 mL) and diluted with ethyl acetate (100 mL). The two layers were separated and aqueous layer extracted with ethyl acetate (2 \times 100 mL). The combined organic layer was washed with brine (2×200 mL), dried over anhydrous Na₂SO₄, 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. $\left[\alpha\right]_{D}^{20}$ -8.5 (c 0.35, CHCl₃); IR (neat): v 3439, 2926, 2861, 1612, 1513, 1452, 1247, 1090, 1032 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 C₁₄H₂₀O₃Na [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 Na₂SO₄. 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, CHCl₃); IR (neat): *v* 3447, 2929, 2858, 1612, 1512, 1247, 1092, 1033 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 C₂₁H₂₆O₃Na [M + Na]⁺: 349.1774, found: 349.1777.

(4*R*,6*R*)-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), OsO₄ (0.18 g, 0.73 mmol) followed by NaIO₄ (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 1N HCl (2 × 50 mL) to remove excess 2,6-lutidine followed by brine (2 × 100 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was

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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 CH₂Cl₂ (120 mL) was treated with MgBr₂·Et₂O (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 CH₂Cl₂ (3 × 60 mL). The combined organic layers were dried over anhydrous Na₂SO₄ 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, CHCl₃); IR (neat): *v* 3448, 2934, 2863, 1714, 1608, 1512, 1251, 1172, 1095, 1031 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 C₂₃H₃₀O₄Na [M + Na]⁺: 393.2036, found: 393.2041.

(*S*)-Mosher esters of alcohol (10a): To a solution of homoallylic alcohol 10 (15 mg, 0.04 mmol) in CH₂Cl₂ (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 NaHCO₃ solution (2 mL). Then the reaction mixture was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layer was dried over anhydrous Na₂SO₄, 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, CDCl₃): 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 Esters 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, CDCl₃): 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).

(4*R*,6*R*)-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 CH₂Cl₂ (80 mL), di-*tert*butyl dicarbonate [(Boc)₂O; 13.95 mL, 60.73 mmol], followed by Et₃N (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 KHSO₄ solution (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ 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. [α]_D²⁰ –19.2 (*c* 0.40, CHCl₃); IR (neat): *v* 3420, 2977, 2934, 2863, 1736, 1513, 1278, 1251, 1166, 1094, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 C₂₈H₃₈O₆Na [M + Na]⁺: 493.2560, found: 493.2568.

(45,65)-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 Na₂S₂O₃ solution (30 mL), followed by of saturated aqueous NaHCO₃ solution (30 mL). Acetonitrile was removed under reduced pressure and the aqueous layer extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ 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.

(2*S*,4*R*)-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), K₂CO₃ (6.09 g, 27.09 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), MeOH was evaporated under reduced pressure. The residue was diluted with H₂O (40 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic phase was washed with brine (75 mL), dried over anhydrous Na₂SO₄ 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. [α]_D²⁰ +3.7 (*c* 0.32, CHCl₃); IR (neat): *v* 3449,

2924, 2856, 1612, 1509, 1245, 1090, 1033 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 C₂₃H₃₀O₅Na [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 CH₂Cl₂ (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 Na₂SO₄, 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, CHCl₃); IR (neat): v 3447, 2930, 2856, 1616, 1512, 1247, 1106, 770, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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 = 3.08)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; ¹³C NMR (100 MHz, CDCl₃): 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 C₃₉H₄₈O₅NaSi [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 CH_2Cl_2 (100) mL) was added (ethoxycarbonylmethylene) 59.91 mmol) in g, 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): v 3422, 2927, 2861, 1721, 1655, 1267, 1171, 1044, 758 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 C₁₀H₁₈O₂: C, 70.55; H, 10.66; Found: C, 70.43; H, 10.71.

To a stirred solution of the above $\alpha_s\beta$ -unsaturated ester (8.6 g, 50.51 mmol) in anhydrous CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ 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): *v* 3383, 2925, 2859, 1457, 1085, 974 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): δ 133.3,

128.7, 63.6, 32.1, 31.3, 28.7, 22.4, 13.9 ppm; CHN analysis calcd. For C₈H₁₆O: 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 CH₂Cl₂ (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 till 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 Na₂SO₄ 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, CHCl₃); IR (neat): v 3414, 2927, 2862, 1461, 1076, 1030, 884 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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, D₂O 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; ¹³C NMR (100 MHz, CDCl₃): δ 61.7, 58.6, 56.0, 31.4, 25.4, 22.4, 13.8 ppm; CHN analysis calcd. For C₈H₁₆O₂: 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 CCl₄ (60 mL), was added Ph_3P (11.13 g, 42.43 mmol), NaHCO₃ (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

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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 NH₄Cl 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 Na₂SO₄, 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 colourless liquid. [α]_D²⁰ +7.2 (*c* 0.80, CHCl₃); ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): δ 85.0, 72.6, 62.2, 37.5, 31.3, 24.6, 22.4, 13.9 ppm; CHN analysis calcd. For C₈H₁₄O: 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 CH₂Cl₂ (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 CH₂Cl₂ (60 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 × 60 mL). The combined organic layer was washed with brine (70 mL), dried over anhydrous Na₂SO₄ 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 (*c* 0.92, CHCl₃); IR (neat): *v* 3310, 2926, 2858, 1461, 1253, 1083, 838, 775 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 (2.5M in hexanes, 7.04 mL, 17.60 mmol) was added drop-wise 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 BF₃.OEt₂ (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 NH₄Cl 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 $(3 \times 75 \text{ mL})$. The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, 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, CHCl₃); IR (neat): v 3448, 2930, 2856, 1613, 1248, 1106, 833, 774, 702, 505 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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; ¹³C

NMR (100 MHz, CDCl₃): 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 C₅₃H₇₆O₆NaSi₂ [M + Na]⁺: 887.5072, found: 887.5067

(5R,9R,11S)-11-((R)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butyl)-9-((tert-

butyldiphenyl- silyl)oxy)-2,2,3,3,14,14-hexamethyl-5-pentyl-13,13-diphenyl-4,12-dioxa-3,13disilapentadec-6-yne (22): To a stirred solution of alcohol 21 (1.50 g, 1.73 mmol) in anhydrous CH₂Cl₂ (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 Na₂SO₄, 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. $\left[\alpha\right]_{D}^{20}$ +5.9 (c 0.36, CHCl₃); IR (neat): v 3450, 2931, 2857, 1629, 1248, 1106, 772, 702, 506 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 C₆₉H₉₄O₆NaSi₃ [M + Na]⁺: 1125.6250, found: 1125.6255.

(6R,10R,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)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 tri-silvlether 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 NaHCO₃ 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 Na₂SO₄, 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, CHCl₃); IR (neat): v 3448, 2931, 2857, 1614, 1247, 1107, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃); 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; ¹³C NMR (100 MHz, CDCl₃): 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 H₂O (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 Na₂SO₄, 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. $\left[\alpha\right]_{D}^{20}$ +10.0 (c 0.52, CHCl₃); IR (neat): v 3452, 2931, 2857, 1616, 1247, 1107, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 C₆₃H₈₄O₆NaSi₂ [M + Na]⁺: 1015.5698, found: 1015.5702.

(6R,10R,12S,14R)-14-(Benzyloxy)-10,12-bis((*tert*-butyldiphenylsilyl)oxy)-16-((4-methoxybenzyl)oxy)hexadecan-6-yl-2-(diethoxyphosphoryl)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 CH₂Cl₂ (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 CH₂Cl₂ (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 H₂O (20 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layer

was dried (Na₂SO₄), 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, CHCl₃); IR (neat): *v* 3446, 3067, 2933, 2858, 1732, 1464, 1270, 1108, 1054, 1030, 738 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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), 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; ¹³C NMR (100 MHz, CDCl₃): 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 C₆₉H₉₅O₁₀NaPSi₂ [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 CH₃CN/H₂O (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 NaHCO₃ solution (20 mL). The mixture was filtered through Celite pad, organic layer separated and the aqueous layer extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layer were washed with H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄), 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. [α]_D²⁰ +5.3 (*c* 0.88, CHCl₃); IR (neat) : *v* 3446, 2931, 2857, 1732, 1633, 1269, 1108, 1052, 1027, 7034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 for C₆₁H₈₇O₉NaPSi₂ [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 NaHCO₃ (0.1 g, 1.21 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (20 mL). Organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layer was dried over anhydrous Na₂SO₄, 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-pentyloxa

cyclotetradec-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 NH₄Cl 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 Na₂SO₄, 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. [α]_D²⁰ +6.2 (*c* 0.97, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 for C₃₇H₇₄O₅NaSi₂ [M + Na]⁺: 917.4967, found: 917.4981.

(6*R*,8*R*,10*R*,14*R*,*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 CH₂Cl₂ (10 mL), TiCl₄ (3.35 mL, 3.35 mmol, 1 m in CH₂Cl₂) 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 NaHCO₃ solution (15 mL). The organic phase was separated and the aqueous phase extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried with anhydrous Na₂SO₄ 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, CH₃OH); IR (neat): *v* 3361, 2926, 2856, 1716, 1647, 1458, 1054, 861 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): 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; ¹³C NMR (75 MHz, CD₃OD): 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 for C₁₈H₃₂O₅Na [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 H₂O (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 \times 100 mL). The combined organic extracts were dried over Na₂SO₄, 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, CHCl₃); IR (neat): v 3448, 2931, 2857, 1460, 1248, 1101, 827, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 for C₅₃H₈₀O₆NaSi₂ [M + Na]⁺: 891.5385, found: 891.5371.

(5*S*,7*S*,11*R*)-5-((*R*)-2-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butyl)-2,2,13,13,14,14-hexa

methyl-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 NaHCO₃ 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 Na₂SO₄. filtered, and concentrated. The 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. $\left[\alpha\right]_{D}^{20}$ -3.1 (c 0.36, CHCl₃); IR (neat): v 3452, 2930, 2857, 1717, 1463, 1272, 1250, 1107, 829, 706, 504 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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,

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-4.4 ppm; HRMS (ESI) m/z calcd. For for C₆₀H₈₄O₇NaSi₂ [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 NaSO₄, 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, CHCl₃); IR (neat): v 3448, 2931, 2857, 1460, 1248, 1101, 827 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 for $C_{53}H_{80}O_6NaSi_2$ [[M + Na]⁺: 891.5385, found: 891.5386.

(6*R*,10*S*,12*S*,14*R*)-14-(Benzyloxy)-10,12-bis((*tert*-butyldiphenylsilyl)oxy)-16-((4-methoxy benzyl)oxy)hexadecan-6-ol (23b): To a stirred solution of alcohol 28 (1.40 g, 1.61 mmol) in anhydrous CH₂Cl₂ (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 CH₂Cl₂ (3 × 40 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:19) to give tri-silylether compound (1.65 g, 93%) as a colorless liquid. $[\alpha]_D^{20}$ –5.1 (*c* 0.20, CHCl₃); IR (neat): *v* 3448, 2924, 2854, 1740, 1461, 1108, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 for C₆₉H₉₈O₆NaSi₃ [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 tri-silylether (1.2 g, 1.08 mmol) in MeOH (50 mL). The mixture was stirred at room temperature for 6 h. Saturated aqueous NaHCO₃ 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 Na₂SO₄, 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, CHCl₃); IR (neat): *v* 3452, 2931, 2857, 1616, 1247, 1107, 741 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 for C₆₃H₈₄O₆NaSi₂ [M + Na]⁺: 1015.5698, found: 1015.5699.

(6*R*,10*S*,12*S*,14*R*)-14-(Benzyloxy)-10,12-bis((*tert*-butyldiphenylsilyl)oxy)-16-((4-methoxy bennzyl)oxy)hexadecan-6-yl 2-(diethoxyphosphoryl)acetate (24b): Procedure is same as for 24a. $[\alpha]_D^{20}$ –3.2 (*c* 1.56, CHCl₃); IR (neat): *v* 3446, 3067, 2933, 2858, 1732, 1464, 1270, 1108, 1054, 1030, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 for C₆₉H₉₅O₁₀NaPSi₂ [[M + Na]⁺: 1193.6093, found: 1193.6092.

(6R,10S,12S,14R)-14-(Benzyloxy)-10,12-bis((tert-butyldiphenylsilyl)oxy)-16-

hydroxyhexa- decan-6-yl 2-(diethoxyphosphoryl)acetate (25b): Procedure is same as for 25a. $[\alpha]_D^{20}$ +10.7 (*c* 0.32, CHCl₃); IR (neat): *v* 3446, 2931, 2857, 1732, 1633, 1269, 1108, 1052, 1027 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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 for C₆₁H₈₇O₉PSi₂ [M + H]⁺: 1051.5699, found: 1051.5701.

(6*R*,8*S*,10*S*,14*R*,*E*)-6-(Benzyloxy)-8,10-bis((*tert*-butyldiphenylsilyl)oxy)-14-pentyloxacyclo tetradec-3-en-2-one (26b): Procedure is same as for 26a. $[α]_D^{20}$ –54.4 (*c* 1.10, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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; ¹³C NMR (125 MHz, CDCl₃): 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 for C₅₇H₇₄O₅NaSi₂ [M + Na]⁺:917.4967, found: 917.4962.

(6*R*,8*R*,10*S*,14*R*,*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, CH₃OH); IR (neat): *v* 3381, 2924, 2859, 1713, 1656, 1447, 1173, 1053, 889, 616 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): 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; ¹³C NMR (75 MHz, CD₃OD): 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 for C₁₈H₃₂O₅Na [M + Na]⁺: 351.2142, found: 351.2130.

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Supporting Information Available: Copies of ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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