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Synthesis and biological evaluation of analogs of altohyrtin C (spongistatin 2)

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Abstract

Several structural analogs that contain only part of the altohyrtin structure have been prepared and compared with synthetic altohyrtin C (**2**) for in vitro cytotoxicity against human colon (HCT116) and ovarian (A2780) cell lines. Whereas altohyrtin C was found to be exceedingly potent against these lines (IC_{50}=0.0003 μM), analogs **3**–**5** were >27,000-fold less potent (IC_{50}>8 μM). Analogs **6** and **7** also demonstrated weak cytotoxicity with IC_{50} values for the HCT116 and A2780 cells of 4.8 μM and 2.4 μM, respectively, for **6**.

1. Introduction

The spongipyran natural products are a family of potent cytotoxins that were isolated and characterized in the early 1990s by the research groups of Pettit (spongistatins),[1,2] Kitagawa (altohyrtins),[3–5] and Fusetanai (cinachyrolides).[6] Two members of this unusual family of compounds are **1** and **2**, altohyrtin A (spongistatin 1) and altohyrtin C (spongistatin 2). The antitumor activity of these compounds has been described as 'probably the best to date in the NCI's evaluation programs.'[7] Altohyrtin A (spongistatin 1), the most active member, has an average IC_{50} of 0.13 nM against the NCI's panel of 60 cancer cell lines and is even more active against certain cell lines in the panel.[8] Although the mechanism of this cytotoxicity has not been determined, it has been established that the altohyrtins inhibit tubulin polymerization and bind at a unique site on the tubulin dimer.[8]

The spongistatins are rather complex molecules, and it is not known which part of the structure is involved in binding to the microtubules and which portions might play mainly an organzational role, holding the actual binding region in an optimum conformation for efficient binding (Fig. 1). There is some suggestion that the portion of the molecule comprising rings E and F and the diene side chain might be involved in binding, since there is a 10-fold difference in potency associated with substitution at C50 (i.e., altohyrtin A, with Cl at C50, is 10 times more potent than altohyrtin C, which has H at this position).[1,2]

Smith and Lin have reported two simplified analogs having only the F ring and the C44–C51 side chain and report that these analogs are active against several cultured cancer cell lines at the micromolar level.[9] It has also been found that dehydration of the ring E secondary alcohol in either the altohyrtin A or altohyrtin C series results in a 10-fold increase in potency against some cell lines.[10,11] It was further noted by Paterson and co-workers that a full altohyrtin analog, but lacking carbons 47–51, is dramatically less potent than altohyrtin

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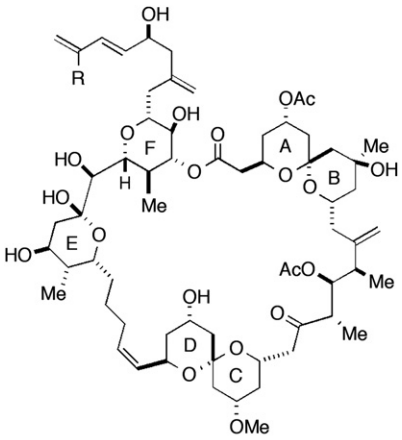


Figure 1.

A or altohyrtin C.[11b] Against this background, we set out to prepare several simplified altohyrtin analogs that include two to four of the original six altohyrtin ring systems and a linear polymethylene hydrocarbon chain to substitute for the missing ring systems. Through this procedure, we hoped to generate altohyrtin analogs retaining the potency of the parent compound, but lacking the synthetic complexity. The identification of potent analogs would not only present synthetically accessible pharmaceutical targets, but it would also elucidate the most important structural motifs of altohyrtin for microtubule binding.

For example, compounds **3** and **4**, which lack C1–C28 completely, lactone **5**, in which the two spiroketals and their associated functionality are replaced by a simple polymethylene linker, were synthesized. Lactone **6**, which contains all of the altohyrtin structure except the ring C/D spiroketal and the functionality in the C13–C17 region, and lactone **7**, which contains all of the altohyrtin structure except the E and F rings, were also synthesized (Fig. 2). In this article, we report the preparation and biological evaluation of these five synthetic analogs. As will be seen, we were quite surprised to find that none of the compounds show any significant activity in a number of cell lines.

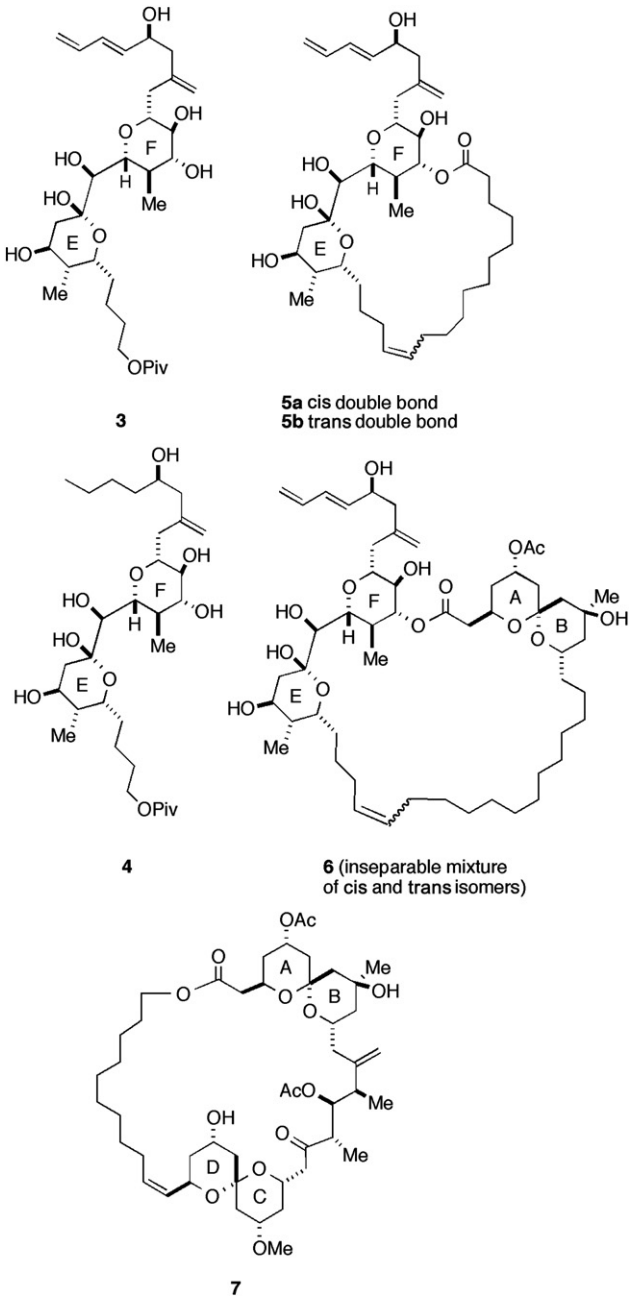
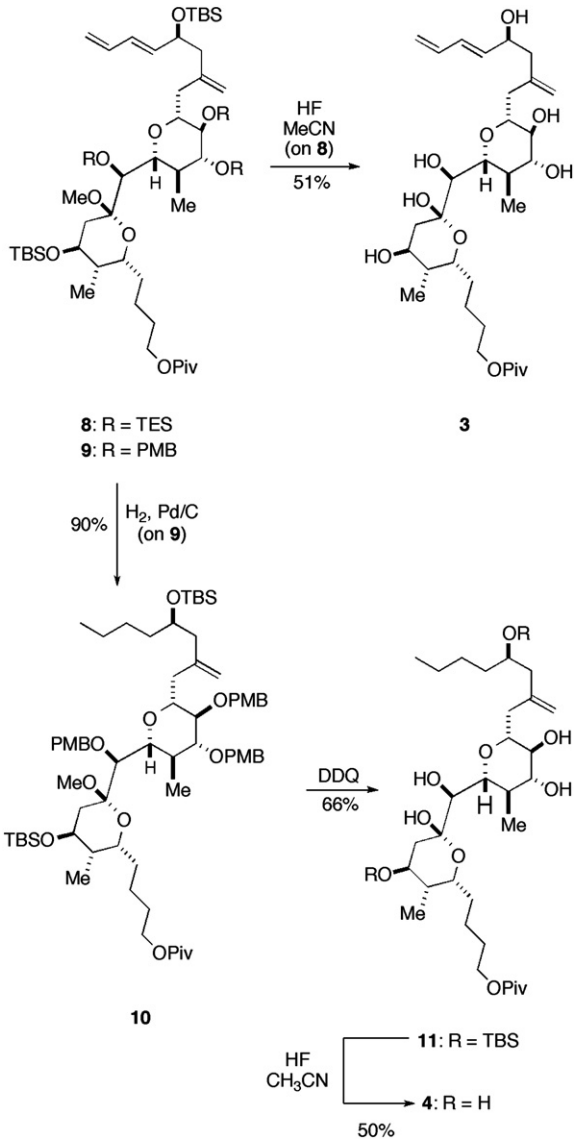


Figure 2.

Compound **3**, comprising the C29–C51 portion of spongistatin 2 was prepared by deprotection (HF in acetonitrile) of the previously reported[10] synthetic intermediate **8**. For preparation of tetrahydro analog **4**, the tris-*p*-methoxybenzyl ether **9** was selectively hydrogenated to provide tetrahydro derivative **10**, which was oxidatively deprotected to obtain **11**. Desilylation of **11** provided analog **4** (Scheme 1).

As shown in Scheme 2, phosphonium salt **12**[10] was treated with methyllithium to obtain the corresponding Wittig reagent, which was coupled with ester-aldehyde **13**, prepared from cyclododecanone as shown in the inset. Alkene **14** was obtained as a 3:1 mixture of cis and trans isomers. Reaction with tetra-*n*-butylammonium flouride in tetrahydrofuran removed the triisopropylsilyl group and the two triethylsilyl groups from the F ring to provide the corresponding dihydroxy acid. This material was cyclized under Yamaguchi's conditions[12] to obtain lactones **15** in 43% yield for the three steps. The geometric isomers were separated by preparative HPLC to obtain pure samples of isomers **15a** and **15b**. The separated isomers were each deprotected by treatment with HF in acetonitrile to acquire geometrically homogeneous samples of lactones **5a** and **5b**.

The synthesis of analog **6** began (Scheme 3) by benzylation of with 1,12-dodecanediol to obtain mono-ether **16**, which was converted into iodide **17** by treatment with triphenylphosphine and iodine.[13] Displacement of the primary iodide with triphenylphosphine resulted in almost quantitative conversion into the phosphonium salt **18**.



Scheme 1.

Salt **18** was deprotonated and the resulting ylide coupled with the previously described aldehyde **19**[14] to obtain exclusively the *cis*-alkene **20** in 44% yield. The *tert*-butyl ester **20** was converted into the corresponding triisopropylsilyl ester **21** by treatment with TMS-triflate followed by triisopropylsilylchloride in 87% overall yield for the two steps. Treatment of **21** with hydrogen over palladium on charcoal saturated the double bond and removed the benzyl group, giving primary alcohol **22**, which was oxidized by the Moffat–Swern procedure[15] to obtain aldehyde **23** (Scheme 4).

As shown in Scheme 5, the previously described phosphonium salt **12** was deprotonated with methyllithium in tetrahydrofuran and the resulting ylide was treated with aldehyde **23** to obtain alkene **24** as a 3:1 mixture of cis and trans double bond isomers. Treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran at 0 °C cleaved the TIPS ester and removed the two TES groups on ring E. The resulting dihydroxy acid was lactonized by the Yamaguchi procedure[12] to obtain lactone **25**, still as a mixture of cis and trans isomers. Global deprotection was accomplished by treatment of **25** with HF in acetonitrile, yielding analog **6**.

Attempted separation of the double bond isomers of **24**, **25**, and **6** by preparative HPLC was not successful.

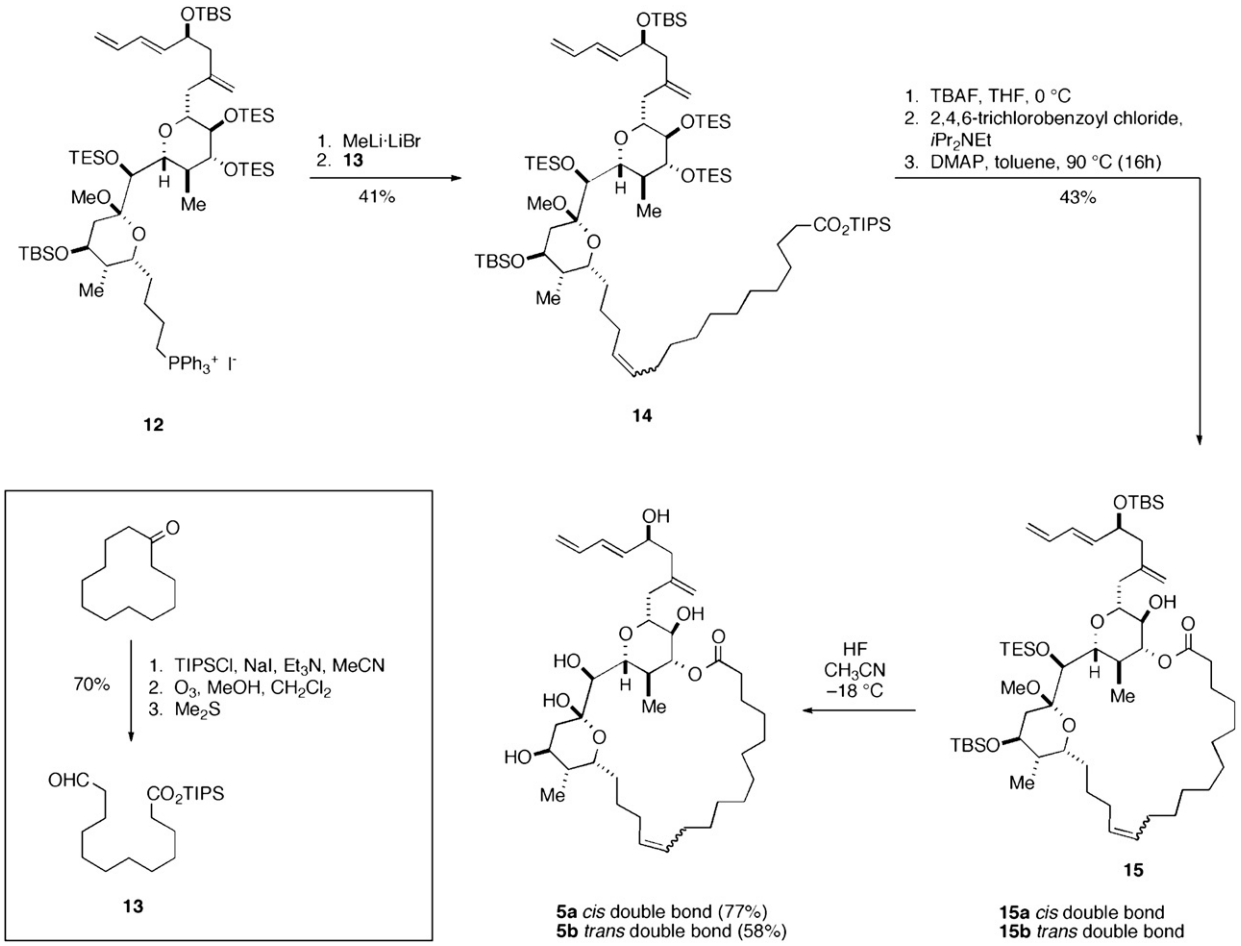
The synthesis of lactone **7** started from the TIPS protection of 1,10-dodecane diol to give the mono-protected TIPS ether **26** in 48% yield. The TIPS ether **26** was subsequently converted to iodide **27** in 82% yield, and reaction of **27** with triphenylphosphine provided the triphenylphosphonium iodide salt **28** in 80% yield. The TIPS ether phosphonium iodide salt **28** was deprotonated by LiHMDS in THF, and the previously described aldehyde **29**[10] was added to the ylide solution to obtain the Wittig product **30** in 41% yield as the *cis*-alkene isomer. The TIPS protecting groups were removed by treatment with TBAF to give lactone precursor **31** in 69% yield, and **31** was lactonized by the Yamaguchi procedure[12] to give lactone **32** in 18% yield. Lactone **32** was deprotected by treatment with HF in acetonitrile at −15 °C to give lactone **7** (Scheme 6).

2. Biological evaluation

In vitro cytotoxicity of synthetic altohyrtin C (**2**) and analogs **3**–**7** in human tumor cell lines was assessed as previously described using a tetrazolium-based colorimetric assay in which MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2*H*-tetrazolium, inner salt) is metabolically converted in live cells to a reduced form, which absorbs light at 492 nm.[16] IC_{50} values, defined as the concentration required to inhibit cell growth by 50%, were determined after 72-h drug exposures. Although altohyrtin C demonstrated very potent cytotoxicity against human colon (HCT116) and ovarian (A2780) cells (IC_{50} values of 0.0003 μM), analogs **3**–**5** were >27,000-fold less potent (IC_{50} values of >8 μM) than the parent compound. Analog **6** demonstrated weak cytotoxicity potency with IC_{50} values for the HCT116 and A2780 cells of 4.8 μM and 2.4 μM, respectively. Analog **7** also demonstrated weak cytotoxicity potency with IC_{50} values for the HCT116 and A2780 cells of 4.5 μM and 6.3 μM, respectively.

3. Conclusion

We have prepared several altohyrtin analogs (**3**–**7**) that include two to four of the original ring systems and a simple polymethylene hydrocarbon chain as a substitute for the ring systems that are absent. The biological tests indicate that none of the analogs **3**–**7** demonstrate significant cytotoxicity compared to the parent altohyrtin compounds. The results of this work suggest that all ring systems are necessary to confer potent cytotoxicity to the altohyrtin compound, and a simple polymethylene hydrocarbon substitute for two to four of the ring systems is not adequate to retain potent cytotoxycity in altohyrtin analogs.

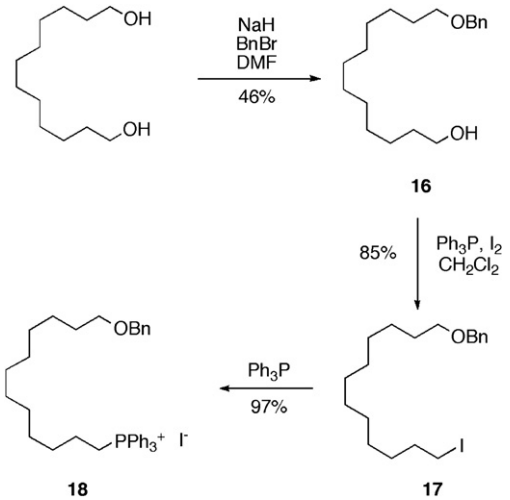


Scheme 2.

4. Experimental section

4.1. General

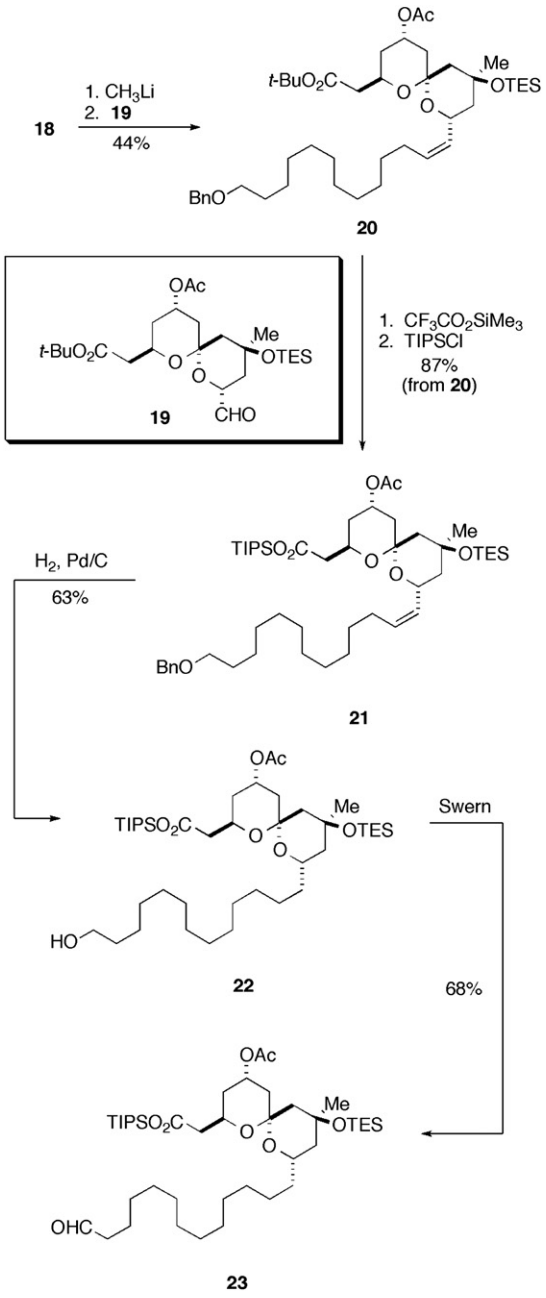
^{1}H NMR spectra were acquired at 400 MHz or 500 MHz on Bruker spectrometers. Chemical shifts (δ) are listed in parts per million against an internal reference. Coupling constants (J) are reported in Hertz, and the abbreviations for splitting include: s, single; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br, broad. ^{13}C NMR spectra were acquired on Bruker instruments at 125.8 MHz. Chemical shifts (δ) are listed in parts per million against solvent carbon peaks as an internal reference.



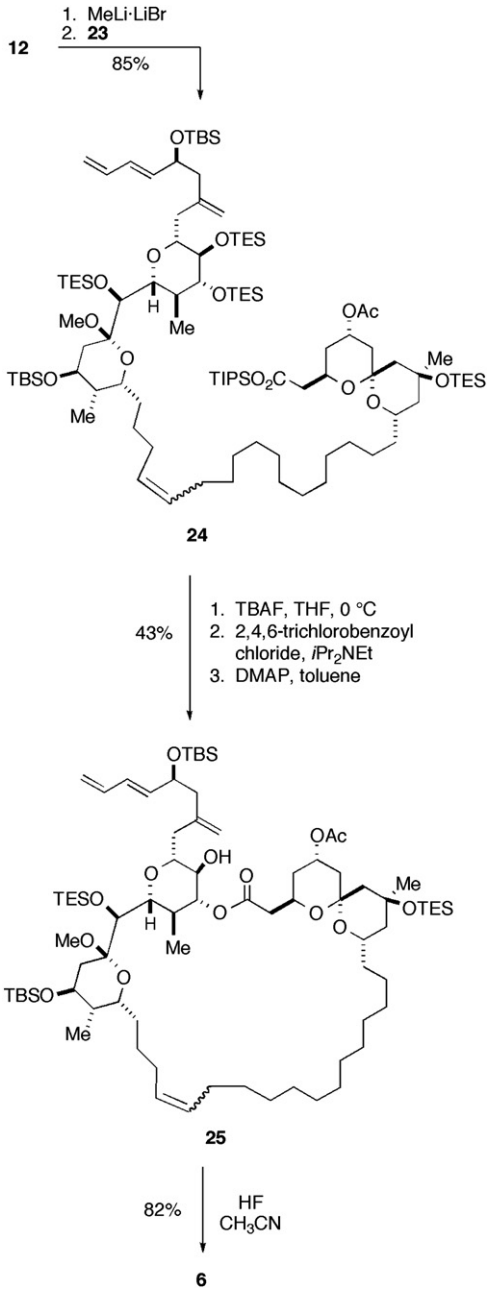
Scheme 3.

4.2. Intermediate 3

Compound **8**[17] (40.1 mg, 34.3 μmol) was placed in a polypropylene vessel, and THF (0.5 mL) was added, followed by acetonitrile (0.5 mL). The mixture was cooled to −18 °C, and a solution of HF (3.0 mL, 5.0 M in acetonitrile) was added dropwise over 1 h. The reaction mixture was then stirred overnight while the temperature was maintained between −15 °C and −19 °C. The reaction was quenched at low temperature by the addition of triethylamine (2.0 mL) and the mixture was allowed to warm to rt, and was transferred to a separatory funnel with satd $NaHCO_3$ (20 mL) and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4, filtered, and concentrated to leave an oil. This material was purified by column chromatography (10% MeOH/CH_2Cl_2) and compound **3** was obtained as a foaming



Scheme 4.

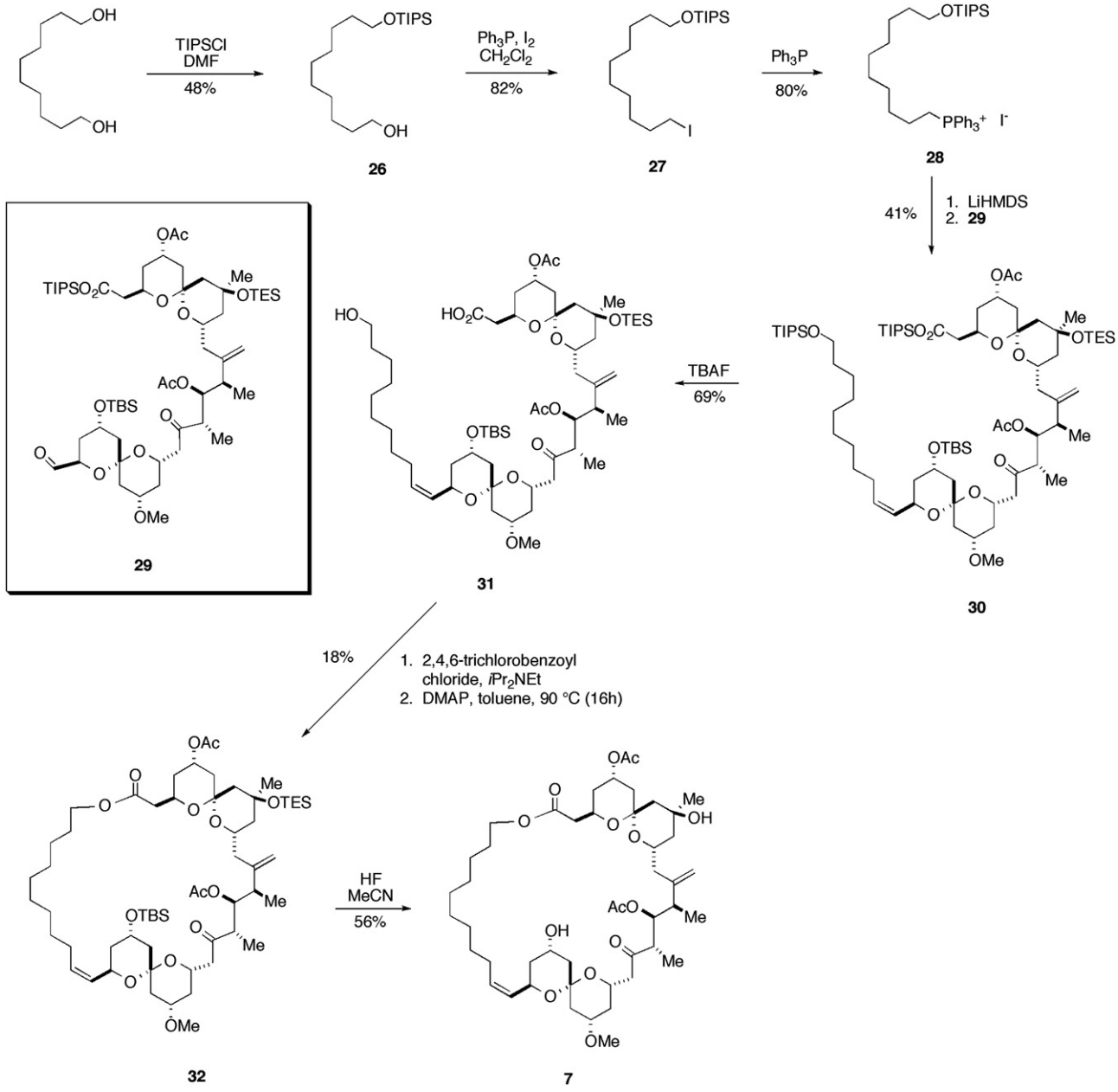


Scheme 5.

solid (10.2 mg, 51%). $[\alpha]_D$ +17.3 (*c* 0.78, CH_2Cl_2); IR: 3411, 2968, 2874, 1724, 1711 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 6.42–6.21 (m, 2H), 5.75 (dd, *J*=15.2, 6.4 Hz, 1H), 5.22 (dd, *J*=16.4, 1.6 Hz, 1H), 5.07 (dd, *J*=10.0, 1.2 Hz, 1H), 5.00 (d, *J*=2.0 Hz, 1H), 4.93 (s, 1H), 4.89 (s, 1H), 4.28–4.20 (m, 2H), 4.10–4.02 (m, 2H), 3.95 (d, *J*=9.2 Hz, 1H), 3.72–3.64 (m, 1H), 3.68 (d, *J*=9.6 Hz, 1H), 3.42–3.27 (m, 4H), 3.10 (t, *J*=9.4 Hz, 1H), 3.04–3.02 (m, 1H), 2.98 (t, *J*=8.8 Hz, 1H), 2.90 (d, *J*=10.0 Hz, 1H), 2.72 (d, *J*=14.4 Hz, 1H), 2.32–2.15 (m, 4H), 2.08 (dd, *J*=14.8, 10.4 Hz, 1H), 1.99–1.95 (m, 2H), 1.93 (dd, *J*=14.4, 2.0 Hz, 1H), 1.83–1.76 (m, 1H), 1.69–1.61 (m, 4H), 1.20 (s, 9H), 0.92 (d, *J*=6.8 Hz, 3H), 0.82 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ 178.1, 143.4, 137.1, 136.8, 130.0, 116.5, 114.4, 99.0, 80.2, 77.7, 77.0, 75.3, 72.1, 70.5, 70.2, 66.2, 64.0, 43.4, 39.1, 38.4, 37.6, 32.6, 31.8, 28.6, 26.6, 22.5, 11.7, 9.9; HRMS (electrospray) calcd for $C_{31}H_{52}O_{10}Li$ ($M+Li^+$) 591.3720, found 591.3717. Anal. Calcd for $C_{31}H_{52}O_{10}$: C 63.67, H 8.96. Found: C 63.52, H 9.21.

4.3. Intermediate **10**

Compound **9** (60 mg, 50.6 μmol) was dissolved in 20 mL of methanol. The flask was purged with nitrogen and the catalyst (10% Pd/C, 18 mg) was added. After purging with hydrogen, a balloon filled with hydrogen was placed on top of the



Scheme 6.

flask and the reaction mixture was stirred for 2 h at rt. Crude ^{1}H NMR showed that the starting material disappeared and the reaction mixture was filtered through a short silica gel pad. The silica gel pad was washed several times with methanol and the combined solution was concentrated under vacuum. The residue (54.2 mg, 90%) was used directly for the next step without further purification. $[\alpha]_D$ +10.6 (*c* 1.08, CH_2Cl_2); IR: 2953, 2932, 2857, 1729, 1613, 1514 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 7.40 (d, *J*=8.8 Hz, 2H), 7.34 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 6.84–6.77 (m, 6H), 5.11 (s, 2H), 5.03 (d, *J*=11.2 Hz, 1H), 4.97 (d, *J*=10.8 Hz, 1H), 4.90 (d, *J*=10.8 Hz, 1H), 4.71 (d, *J*=11.2 Hz, 1H), 4.61 (d, *J*=10.8 Hz, 1H), 4.51 (d, *J*=10.8 Hz, 1H), 4.34–4.31 (m, 1H), 4.07 (dt, *J*=6.0, 1.6 Hz, 2H), 4.11–3.94 (m, 2H), 3.71 (s, 1H), 3.61 (t, *J*=8.8 Hz, 1H), 3.37 (t, *J*=10.8 Hz, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 3.27 (s, 3H), 3.22 (s, 3H), 3.22–3.18 (m, 1H), 2.73 (d, *J*=14.4 Hz, 1H), 2.61 (dd, *J*=13.4, 5.4 Hz, 1H), 2.57 (dd, *J*=15.6, 4.0 Hz, 1H), 2.46 (dd, *J*=13.6, 8.0 Hz, 1H), 2.29 (dd, *J*=14.8, 9.6 Hz, 1H), 2.24–2.18 (m, 1H), 2.02 (d, *J*=15.6 Hz, 1H), 1.70–1.50 (m, 8H), 1.42–1.25 (m, 6H), 1.20 (s, 9H), 1.11 (s, 9H), 1.04 (s, 9H), 0.97–0.88 (m, 6H), 0.83 (d, *J*=6.4 Hz, 3H), 0.27 (s, 3H), 0.22 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 177.3, 159.5, 159.4, 144.0, 131.3, 131.2, 131.1, 130.1, 129.1, 129.0, 114.5, 113.7, 102.6, 86.8, 83.1, 79.6, 77.9, 76.2, 74.5, 74.5, 74.3, 70.7, 70.6, 66.8, 63.9, 54.4, 46.9, 45.1, 38.8, 38.5, 38.2, 36.4, 32.5, 31.2, 28.8, 27.5, 27.0, 25.9, 25.8, 23.0, 22.6, 18.0, 17.9, 14.1,

13.1, 10.1, −4.2, −4.5, −4.6, −4.8; HRMS (electrospray) calcd for $C_{68}H_{110}O_{13}Si_2Li$ ($M+Li^+$) 1197.7645, found 1197.7637. Anal. Calcd for $C_{68}H_{110}O_{13}Si_2$: C 68.53, H 9.30. Found: C 68.35, H 9.61.

4.4. Intermediate **11**

To a solution of compound **10** (99 mg, 83.1 μmol) in CH_2Cl_2 (10 mL) and pH 7 aqueous phosphate buffer solution (1 mL) was added DDQ (75 mg, 0.33 mmol). The reaction mixture was stirred vigorously for 1 h at rt, and the color of the mixture changed from green to yellow. A solution of satd $NaHCO_3$ was then added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography on silica gel (50% EtOAc/hexanes) to afford the product as a colorless oil (45 mg, 66%). $[\alpha]_D$ +7.7 (*c* 0.31, CH_2Cl_2); IR: 3458, 2954, 2932, 2858, 1730 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 5.28 (s, 1H), 5.07 (d, J=12.0 Hz, 2H), 4.50 (t, J=5.4 Hz, 1H), 4.04 (t, J=6.4 Hz, 1H), 4.06–3.95 (m, 2H), 3.90 (d, J=2.8 Hz, 1H), 3.79 (d, J=10.4 Hz, 1H), 3.67 (d, J=7.6 Hz, 1H), 3.57 (t, J=8.8 Hz, 1H), 3.20–3.10 (m, 2H), 2.93 (s, 1H), 2.88 (d, J=14.8 Hz, 1H), 2.74 (d, J=8.0 Hz, 1H), 2.58 (s, 1H), 2.51 (dd, J=13.4, 5.4 Hz, 1H), 2.39 (dd, J=13.6, 7.6 Hz, 1H), 2.26 (dd, J=14.8, 10.0 Hz, 1H), 2.16–1.99 (m, 3H), 1.70–1.50 (m, 8H), 1.42–1.25 (m, 6H), 1.20 (s, 9H), 1.06 (s, 9H), 1.05–1.00 (m, 5H), 0.99 (s, 9H), 0.81 (d, J=7.2 Hz, 3H), 0.24 (s, 3H), 0.19 (s, 3H), 0.12 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 177.5, 144.1, 114.4, 98.5, 79.3, 79.0, 77.7, 75.5, 74.0, 72.5, 70.9, 65.9, 63.9, 44.7, 38.7, 38.5, 38.3, 37.8, 36.5, 32.8, 31.7, 28.6, 27.4, 27.0, 25.9, 25.6, 22.9, 22.3, 18.0, 17.8, 14.1, 12.6, 10.2, −4.2, −4.6, −5.0, −5.1; HRMS (electrospray) calcd for $C_{43}H_{84}O_{10}Si_2Li$ ($M+Li^+$) 823.5763, found 823.5789. Anal. Calcd for $C_{43}H_{84}O_{10}Si_2$: C 63.19, H 10.36. Found: C 62.95, H 10.41.

4.5. Intermediate **4**

Compound **11** (23 mg, 28.1 μmol) was placed in a polypropylene vessel, and THF (0.5 mL) was added followed by acetonitrile (0.5 mL). The mixture was cooled to −18 °C, and then a solution of HF (2.0 mL, 5.0 M in acetonitrile) was added dropwise over 1 h. The reaction mixture was then stirred overnight while the temperature was maintained between −15 °C and −19 °C. The reaction was quenched at low temperature by the addition of triethylamine (2.0 mL) and then allowed to warm to rt. The mixture was transferred to a separation funnel with satd $NaHCO_3$ (20 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to leave an oil. The residue was purified by column chromatography (10% MeOH/CH_2Cl_2) and the product was obtained as a foaming solid (8.3 mg, 50%). $[\alpha]_D$ +21.4 (*c* 0.14, CH_2Cl_2); IR: 3409, 2957, 2871, 1727 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 5.00 (d, J=2.4 Hz, 1H), 4.91 (m, 1H), 4.87 (m, 1H), 4.24 (td, J=7.8, 2.4 Hz, 1H), 4.07 (td, J=6.4, 0.8 Hz, 2H), 3.95 (d, J=9.2 Hz, 1H), 3.73–3.62 (m, 2H), 3.68 (d, J=11.6 Hz, 1H), 3.42–3.31 (m, 3H), 3.25 (d, J=4.8 Hz, 1H), 3.10 (td, J=9.4, 4.8 Hz, 1H), 2.97 (td, J=8.8, 3.6 Hz, 1H), 2.89 (d, J=10.4 Hz, 1H), 2.71 (d, J=14.8 Hz, 1H), 2.65 (d, J=5.2 Hz, 1H), 2.21 (s, 2H), 2.16 (t, J=6.4 Hz, 1H), 2.06 (dd, J=15.0, 10.2 Hz, 1H), 2.00–1.90 (m, 3H), 1.82–1.70 (m, 1H), 1.70–1.62 (m, 4H), 1.56–1.42 (m, 7H), 1.20 (s, 9H), 0.95–0.89 (m, 6H), 0.82 (d, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ 178.1, 144.5, 113.7, 99.0, 80.1, 77.7, 77.1, 75.3, 72.1, 70.5, 69.7, 66.2, 64.0, 43.9, 39.0, 38.4, 37.6, 37.5, 36.7, 32.6, 31.8, 28.6, 27.6, 26.6, 26.5, 22.5, 13.5, 11.7, 9.9; HRMS (electrospray) calcd for $C_{31}H_{56}O_{10}Li$ ($M+Li^+$) 595.4033, found 595.4039. Anal. Calcd for $C_{31}H_{56}O_{10}$: C 63.24, H 9.59. Found: C 62.98, H 9.79.

4.6. Intermediate **13**

To a cooled (0 °C) solution of cyclododecanone (5.0 g, 27.5 mmol) in acetonitrile (40 mL) was added triethylamine (4.8 mL, 34.3 mmol) followed by TIPSCl (7.3 mL, 34.3 mmol). Then NaI (5.1 g, 34.3 mmol) was added and the reaction mixture turned pink-white and a copious precipitate appeared. The reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with satd $NaHCO_3$ solution and the resulting mixture was extracted with hexanes. The organic layers were combined and washed with brine, dried over anhydrous K_2CO_3, filtered, and concentrated. The residue was used directly for ozonolysis without further purification.

The crude silyl enol ether was dissolved in methanol (50 mL) and dichloromethane (40 mL), and the mixture was cooled to −78 °C. To the mixture was added dimethyl sulfide (4 mL) and ozone was bubbled into the mixture for 1 h. The ozone flow was stopped after the color of the mixture turned to blue, the resulting mixture was warmed to rt, and the solvent was removed under vacuum. The residue was purified by column chromatography (20% EtOAc/hexanes) to give the desired aldehyde **13** (7.1 g, 70% for two steps) as a colorless oil. ^1H NMR (400 MHz, C_6D_6): δ 9.40 (s, 1H), 2.30 (t, J=7.4 Hz, 2H), 1.92 (td, J=7.2, 1.2 Hz, 2H), 1.72–1.65 (m, 2H), 1.40–1.20 (m, 17H), 1.18 (d, 18H); ^{13}C NMR (125 MHz, C_6D_6): δ 200.4, 172.9, 43.5, 35.6, 29.5, 29.4, 29.3, 29.2, 29.1, 25.3, 21.9, 17.7, 12.0.

4.7. Intermediate **14**

To a cooled (−78 °C) solution of Wittig salt **12**[18] (252 mg, 0.17 mmol) in THF (2 mL) was added dropwise a 1.4 M solution of MeLi·LiBr in ether (115 μL). The color of the solution turned orange-red immediately. After stirring for 30 min, a solution of aldehyde **13** (77 mg, 0.21 mmol) in THF (1 mL) was added dropwise. The flask containing the aldehyde was rinsed with an additional 1 mL of THF, which was added to the reaction mixture. The color of the reaction faded immediately to pale yellow upon the addition of the aldehyde. The reaction mixture was stirred for 1 h at −78 °C, warmed slowly to rt, and quenched with satd NH_4Cl solution. The mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (10% EtOAc/hexanes) to give the desired product (100 mg, 41%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 6.50–6.34 (m, 2H), 5.93 (dd, J=14.0, 6.0 Hz, 1H), 5.66–5.52 (m, 2H), 5.30–5.01 (m, 4H), 4.49 (q, J=6.8 Hz, 1H), 4.35 (m, 1H), 3.99–3.97 (m, 1H). 3.93 (s, 1H), 3.68–3.48 (m, 4H), 3.21 (s, 3H), 2.75 (d, J=12.8 Hz, 1H), 2.72–2.56 (m, 2H), 2.48–2.08 (m, 8H), 2.02–2.00 (m, 1H), 1.82–1.78 (m, 3H), 1.69–1.60 (m, 3H), 1.45–1.28 (m, 12H), 1.28–1.10 (m, 72H), 0.90–0.82 (m, 21H), 0.29 (s, 3H), 0.24 (s, 3H), 0.20 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6): δ 172.9, 144.1, 137.4, 136.7, 130.8 (trans), 130.1 (cis), 130.0, 129.6 (cis), 116.3, 114.9, 101.2, 81.0, 80.4, 77.5, 77.1, 72.1, 71.3, 70.9, 68.3, 67.0, 66.8 (trans), 46.8, 46.6, 40.1, 40.0 (trans), 38.7, 38.6 (trans), 35.6, 32.9 (trans), 32.8, 32.6, 32.3, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.5, 27.4, 26.5, 26.4 (trans), 25.9, 25.8, 25.3, 18.2, 18.0, 17.8, 15.8, 12.0, 10.4, 7.2, 7.1, 7.0, 5.8, 5.7, −4.3, −4.4. −4.8, −4.9; LRMS (FAB, low resolution) calcd for $C_{78}H_{156}O_{10}Si_6$ (M+H$^+$) 1422.1, found 1422.2.

4.8. Lactones **15**

To a cooled (0 °C) solution of the Wittig product **14** (23 mg, 16.2 μmol) in THF (2 mL) was added a 1.0 M solution of TBAF in THF (50 μL, 50.2 μmol) dropwise. The mixture was stirred for 2 h at 0 °C, quenched with satd NH_4Cl solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (75% EtOAc/hexanes) to give the desired carboxylic acid intermediate (12 mg, 70%) as a colorless oil. IR: 3384, 2928, 2855, 1710 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 6.42–6.30 (m, 2H), 5.83 (dd, J=14.2, 6.6 Hz, 1H), 5.60–5.47 (m, 2H), 5.24–4.96 (m, 4H), 4.42 (q, J=6.4 Hz, 1H), 4.28–4.20 (m, 1H), 3.95–3.93 (m, 1H), 3.89 (s, 1H), 3.39–3.33 (m, 1H), 3.32 (d, J=10.4 Hz, 1H), 3.27 (t, J=8.8 Hz, 1H), 3.13 (s, 3H), 3.11–3.07 (m, 1H), 2.77 (d, J=12.0 Hz, 1H), 2.59 (dd, J=13.6, 7.6 Hz, 1H), 2.51 (dd, J=13.6, 6.0 Hz, 1H), 2.37 (dd, J=14.2, 7.8 Hz, 1H), 2.32 (dd, J=15.2, 3.6 Hz, 1H), 2.22–2.04 (m, 6H), 1.90–1.61 (m, 4H), 1.58–1.01 (m, 55H), 0.98 (d, J=7.2 Hz, 3H), 0.86–0.75 (m, 6H), 0.25 (s, 3H), 0.19 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 178.8, 143.7, 137.5, 136.7, 130.7 (trans), 130.2 (trans), 130.1, 130.0 (cis), 129.6 (cis), 116.4, 115.1, 101.2, 79.0, 78.5, 78.4, 75.4, 72.6, 70.9, 67.0, 66.8 (trans), 46.6, 46.2, 39.2, 38.8, 38.7, 33.8, 32.9 (trans), 32.8, 32.7, 32.3, 30.1 (trans), 30.0, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 27.5, 27.4, 26.6, 26.4 (trans), 25.9, 25.8, 24.7, 18.2, 18.0, 13.5, 10.4, 7.2, 5.8, −4.3, −4.4. −4.8, −4.9; LRMS (electrospray) calcd for $C_{57}H_{108}O_{10}Si_3$ (M) 1035.72, found 1036.73. Anal. Calcd for $C_{57}H_{108}O_{10}Si_3$: C 65.97, H 10.49. Found: C 65.76, H 10.52.

To a flask containing the aforementioned acid (50 mg, 48.2 μmol) was added a 0.4 M solution of *N*,*N*-diisopropylethylamine in toluene (3.6 mL, 1.45 mmol) followed by 0.4 M 2,4,6-trichlorobenzoyl chloride in toluene (2.4 mL, 0.96 mmol). The reaction mixture was stirred for 3 h at rt and then diluted with toluene (20 mL), and added over a 24 h period (via syringe pump) to a solution of DMAP (295 mg, 2.41 mmol) in toluene (50 mL), heated in an oil bath set at 90 °C. A white precipitate was observed. Upon completion of the addition, the flask in which the mixed anhydride formed was rinsed with toluene (3 mL) and this rinse was added to the DMAP solution over 12 h. After cooling to rt, the mixture was washed with satd $NaHCO_3$ (50 mL) and then with brine (50 mL). The aqueous phases were back-extracted with EtOAc and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (20% EtOAc/hexanes) to give the desired product (30 mg, 61%) as a colorless oil.

The mixture of isomers was further purified by preparative HPLC (98.5% hexanes/isopropanol) to give the cis isomer (16 mg) and the trans isomer (5 mg) separately.

4.8.1. Cis isomer ***15a***

$[\alpha]_D$ +25.7 (*c* 0.4, CH_2Cl_2); IR: 2928, 2855, 1717 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 6.40–6.28 (m, 2H), 5.81 (dd, J=14.4, 6.0 Hz, 1H), 5.49–5.40 (m, 2H), 5.22–5.08 (m, 3H), 4.98–4.94 (m, 1H), 4.66 (t, J=9.6 Hz, 1H), 4.43 (q, J=6.4 Hz, 1H), 4.28 (d, J=10.4 Hz, 1H), 3.91 (br s, 2H), 3.45 (t, J=9.0 Hz, 1H), 3.39 (d, J=10.8 Hz, 1H), 3.27 (td, J=8.6, 2.4 Hz, 1H), 3.22 (s, 3H), 2.91 (d, J=13.6 Hz, 1H), 2.78–2.63 (m, 2H), 2.59 (dd, J=13.4, 7.4 Hz, 1H), 2.51 (dd, J=13.2, 6.0 Hz, 1H), 2.36 (dd, J=14.4, 8.0 Hz, 1H), 2.27 (dd, J=15.2, 3.6 Hz, 1H), 2.23–1.92 (m, 6H), 1.80 (d, J=15.2 Hz, 1H), 1.62–1.42 (m, 6H), 1.40–1.18 (m, 18H), 1.14–1.04 (m, 26H), 0.93 (d, J=7.2 Hz, 3H), 0.84–0.72 (m, 6H), 0.50 (br s, 1H), 0.25 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 175.2, 143.4, 137.6, 136.8, 130.3, 130.0, 129.4, 116.4, 115.1, 101.2, 81.5, 79.4, 77.6, 73.6, 72.6, 72.4, 71.0, 69.5, 47.5, 46.6, 39.9, 38.6, 37.5, 34.7, 32.8, 31.1, 30.9, 30.2, 30.0, 29.7, 29.2, 29.1, 28.9, 28.7, 28.5, 25.9, 25.9, 25.8, 25.4, 18.2, 18.1, 14.7, 14.1, 10.7, 7.2, 6.0, −4.3, −4.4, −4.8, −4.9; LRMS (electrospray) calcd for $C_{57}H_{106}O_9Si_3Na$ (M+Na$^+$) 1041.7, found 1041.7.

4.8.2. Trans isomer ***15b***

$[\alpha]_D$ +20.5 (*c* 0.2, CH_2Cl_2); IR: 2928, 2855, 1717 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 6.40–6.28 (m, 2H), 5.81 (dd, J=14.4, 6.4 Hz, 1H), 5.59–5.53 (m, 2H), 5.20–5.06 (m, 3H), 4.97–4.94 (m, 1H), 4.75 (t, J=9.8 Hz, 1H), 4.43 (q, J=6.4 Hz, 1H), 4.38–4.30 (m, 1H), 3.93 (m, 1H), 3.91 (s, 1H), 3.49–3.42 (m, 1H), 3.45 (d, J=10.8 Hz, 1H), 3.34 (td, J=8.8, 2.4 Hz, 1H), 3.24 (s, 3H), 2.90 (d, J=14.8 Hz, 1H), 2.59 (dd, J=13.4, 7.4 Hz, 1H), 2.51 (dd, J=13.4, 5.8 Hz, 1H), 2.35 (dd, J=14.4, 8.0 Hz, 1H), 2.42–2.28 (m, 3H), 2.22 (dd, J=15.2, 3.6 Hz, 1H), 2.23–1.98 (m, 6H), 1.85 (d, J=15.2 Hz, 1H), 1.67–1.50 (m, 6H), 1.41–1.18 (m, 18H), 1.12–1.02 (m, 26H), 0.94 (d, J=7.2 Hz, 3H), 0.83–0.72 (m, 6H), 0.24 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 175.0, 143.4, 137.6, 136.8, 131.2, 130.0, 129.8, 116.4, 115.1, 101.0, 81.2, 79.3, 77.5, 73.6, 73.1, 72.5, 71.3, 67.8, 48.0, 46.5, 39.4, 38.6, 37.8, 34.3, 33.0, 32.8, 31.5, 31.0, 30.7, 30.1, 29.9, 29.8, 29.4, 29.3, 28.7, 27.1, 25.9, 25.8,

25.4, 18.2, 18.1, 14.6, 10.8, 7.2, 5.9, −4.3, −4.4. −4.8, −4.9; LRMS (electrospray, low resolution) calcd for $C_{57}H_{106}O_9Si_3Na$ ($M+Na^+$) 1041.7, found 1041.7.

4.9. Lactone *5a*

The cis isomer of macrolactone **15** (8.0 mg, 7.85 μmol) was placed in a polypropylene vessel, and then THF (0.2 mL) was added followed by acetonitrile (0.2 mL). The mixture was cooled to −18 °C, and a solution of HF (0.55 mL, 5.0 M in acetonitrile) was added dropwise over 1 h. The reaction mixture was stirred overnight while the temperature was maintained between −15 °C and −19 °C. The reaction was then quenched at low temperature by the addition of triethylamine (1.0 mL). The resulting mixture was allowed to warm to rt, transferred to a separation funnel with satd $NaHCO_3$ (20 mL), and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to leave an oil. The residue was purified by column chromatography (75% EtOAc/hexanes) and the product was obtained as a foaming solid (4.9 mg, 77%). $[\alpha]_D$ +25.3 (*c* 0.19, CH_2Cl_2); IR: 3412, 2926, 2854, 1736, 1715 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 6.32−6.18 (m, 2H), 5.61 (dd, *J*=15.0, 6.0 Hz, 1H), 5.57−5.47 (m, 2H), 5.12 (dd, *J*=16.0, 1.5 Hz, 1H), 4.97 (dd, *J*=9.5, 1.5 Hz, 1H), 4.90 (d, *J*=7.0 Hz, 1H), 4.89 (s, 2H), 4.57 (dd, *J*=10.5, 9.0 Hz, 1H), 4.37 (d, *J*=10.0 Hz, 1H), 4.25 (br s, 2H), 4.16 (q, *J*=6.5 Hz, 1H), 3.87 (d, *J*=10.5 Hz, 1H), 3.82 (br s, 1H), 3.48 (td, *J*=10.0, 2.0 Hz, 1H), 3.45−3.40 (m, 1H), 3.39 (br s, 1H), 3.26 (t, *J*=9.0 Hz, 1H), 2.87 (d, *J*=15.0 Hz, 1H), 2.41−2.33 (m, 1H), 2.30−2.20 (m, 3H), 2.18−1.92 (m, 9H), 1.76−1.67 (m, 1H), 1.57−1.41 (m, 4H), 1.40−1.08 (m, 16H), 0.84 (d, *J*=6.5 Hz, 3H), 0.64 (d, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 176.6, 142.9, 136.6, 136.5, 130.6, 130.3, 129.5, 128.8, 117.1, 115.3, 98.9, 81.8, 79.8, 78.4, 73.9, 72.8, 70.9, 70.8, 67.5, 43.8, 39.3, 38.6, 36.0, 34.0, 32.9, 32.4, 30.5, 30.0, 29.2, 28.5, 28.2, 28.1, 28.0, 27.8, 27.5, 26.9, 23.4, 12.6, 10.9; HRMS (FAB) calcd for $C_{38}H_{62}O_9Li$ ($M+Li^+$) 669.4558, found 669.4554.

4.10. Lactone *5b*

The trans isomer of lactone **15** (4.0 mg, 3.93 mmol) was deprotected following the foregoing procedure and the final product was obtained as a foaming solid (1.5 mg, 58%). $[\alpha]_D$ +26.7 (*c* 0.075, CH_2Cl_2); IR: 3405, 2926, 2854, 1736, 1716 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.43−6.25 (m, 2H), 5.72−5.61 (m, 3H), 5.23 (d, *J*=16.4 Hz, 1H), 5.09 (d, *J*=9.6 Hz, 1H), 4.99 (d, *J*=10.4 Hz, 1H), 4.98 (s, 2H), 4.81 (dd, *J*=10.4, 9.2 Hz, 1H), 4.55−4.35 (m, 2H), 4.23 (q, *J*=6.4 Hz, 1H), 4.04 (d, *J*=10.4 Hz, 1H), 3.94 (br s, 1H), 3.60 (td, *J*=9.6, 2.0 Hz, 1H), 3.49 (br s, 1H), 3.31 (t, *J*=9.2 Hz, 1H), 2.92 (d, *J*=14.8 Hz, 1H), 2.85 (br s, 1H), 2.45−2.23 (m, 6H), 2.18−2.08 (m, 6H), 2.07−1.96 (m, 2H), 1.87−1.79 (m, 1H), 1.57−1.50 (m, 4H), 1.49−1.10 (m, 16H), 0.93 (d, *J*=6.8 Hz, 3H), 0.77 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 175.5, 142.9, 136.5, 136.4, 130.9, 130.7, 129.8, 117.2, 115.4, 98.9, 80.6, 80.0, 78.3, 73.9, 72.7, 70.9, 70.8, 67.3, 43.7, 39.4, 38.9, 36.1, 33.9, 33.6, 33.0, 32.3, 31.6, 30.2, 30.0, 29.9, 29.3, 28.2, 28.0, 27.5, 27.4, 27.2, 23.5, 12.4, 10.9; HRMS (FAB) calcd for $C_{38}H_{62}O_9Li$ ($M+Li^+$) 669.4558, found 669.4554.

4.11. 1,12-Dodecanediol, monobenzyl ether (*16*)

To a heterogeneous solution of 1,12-dodecanediol (5.0 g, 25 mmol) in DMF was added a dispersion of NaH (60% by weight) in mineral oil (1.09 g, 27 mmol) with stirring at rt. Virtually no gas evolution was observed. To this heterogeneous reaction mixture, benzyl bromide (3.0 mL, 25 mmol) was added and the reaction was stirred 12 h by which time the reaction solution had become homogeneous. The reaction solution was slowly added into 100 mL of water and extracted with 100 mL of diethyl ether. The organic layer was washed with 100 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting products were purified by column chromatography (SiO_2, 15% EtOAc/hexanes) to afford the monobenzyl ether (**16**) as a white solid (3.34 g, 46%). ^1H NMR (400 MHz, CD_3Cl): δ 7.45−7.21 (m, 5H), 4.50 (s, 2H), 3.63 (t, *J*=6.8, 2H), 3.47 (t, *J*=6.8, 2H), 2.10 (br s, 1H), 1.62 (p, *J*=6.8, 2H), 1.56 (p, *J*=7.2, 2H), 1.44−1.22 (m, 16H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 138.6, 128.3, 127.6, 127.4, 126.9, 72.8, 70.5, 63.0, 32.7, 29.7, 29.5, 29.4 (br), 29.3 26.1, 25.7; HRMS (FAB) *m/z* calcd for $C_{19}H_{33}O_2$ $(M+H)^+$ 293.2481, found 293.2482.

4.12. 12-Iodododecanol, benzyl ether (*17*)[13]

To 20 mL of CH_2Cl_2 was added triphenylphosphine (3.61 g, 13.8 mmol), imidazole (0.94 g, 13.8 mmol) and iodine (3.49 g, 13.8 mmol). To this prepared reaction mixture was added a solution of **3** (3.35 g, 11.5 mmol) in 36 mL of CH_2Cl_2, and the resulting solution was stirred for 1 h. The solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford **17** as a colorless oil (3.8 g, 86%). ^1H NMR (400 MHz, CD_3Cl): δ 7.36−7.28 (m, 5H), 4.52 (s, 2H), 3.48 (t, *J*=6.8, 2H), 3.19 (t, *J*=6.8, 2H), 1.82 (p, *J*=7.2, 2H), 1.63 (p, *J*=6.8, 2H), 1.39−1.28 (m, 16H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 138.6, 128.3, 127.5, 127.4, 72.8, 70.4, 33.5, 30.4, 29.7, 29.6, 29.5, 29.4 (br), 29.3, 28.5, 26.1, 7.23; HRMS (EI) *m/z* calcd for $C_{19}H_{32}OI$ $(M+H)^+$ 403.1498, found 403.1482.

4.13. Wittig salt *18*

Triphenylphosphine (0.507 g, 1.9 mmol) was dissolved in $^iPr_2NEt$ (0.35 mL, 2 mmol) and 3 mL of acetonitrile, and iodide **17** (0.26 g, 0.67 mmol) was added to this solution in a screw-cap vial. The vial was sealed and heated to 80−90 °C overnight. The solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2, 5% MeOH/EtOAc) to afford **18** as a yellow oil (0.34 g, 81%). ^1H NMR (400 MHz, CD_3Cl): δ 7.8−7.67 (m, 15H), 7.32−7.23 (m, 5H), 4.47 (s, 2H), 3.62 (br s, 2H), 3.44 (t, *J*=6.8, 2H), 1.62−1.56 (m, 6H), 1.36−1.17 (m, 14H).

4.14. Intermediate **20**

To a solution of Wittig salt **18** (1.85 g, 2.85 mmol) in 16 mL of THF cooled to −78 °C was added a 1.6 M solution of MeLi (1.8 mL, 2.88 mmol), whereupon the solution changed from colorless to bright orange. After stirring at −78 °C for 30 min, a solution of aldehyde **19**[19] (1.2 g, 2.4 mmol) in 18 mL of THF was added whereupon the solution became colorless. The solution was allowed to warm to rt, and was diluted with 100 mL of diethyl ether and treated with 60 mL of satd NH_4Cl. The organic layer was separated and washed with 100 mL of satd NaCl, dried over Na_2SO_4 and concentrated in vacuo to give a crude product that was purified by column chromatography (SiO_2, 10% EtOAc to 30% EtOAc/hexanes) to afford **20** as a colorless oil (0.81 g, 44%). ^{1}H NMR (400 MHz, CD_3Cl): δ 7.34−7.26 (m, 5H), 5.45 (ddd, J=10.8, 3.6, 1H), 5.36 (t, J=10.8, 1H), 4.99−4.96 (m, 1H), 4.88 (t, J=10, 1H), 4.50 (s, 2H), 4.39−4.30 (m, 1H), 3.46 (t, J=6.8, 2H), 2.40 (dd, J=15.6, 4.8, 1H), 2.28 (dd, J=15.6, 9.2, 1H), 2.21−2.10 (m, 2H), 2.01 (s, 3H), 1.95−1.70 (m, 3H), 1.68−1.50 (m, 6H), 1.44 (s, 9H), 1.39−1.20 (m, 17H), 1.19 (s, 3H), 0.98 (t, J=8.0, 9H), 0.55(q, J=8.0, 6H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 171.1, 170.1, 138.6, 131.8, 130.5, 128.3, 127.5, 127.4, 96.9, 80.3, 72.8, 70.5, 70.2, 67.3, 62.1, 61.4, 47.1, 45.1, 41.8, 38.3, 33.9, 31.9, 31.6, 29.9, 29.8, 29.7, 29.6, 29.5, 28.1, 27.9, 26.2, 22.6, 21.4, 14.1, 7.3, 6.9; HRMS (EI) *m/z* calcd for $C_{44}H_{74}SiO_8Li$ $(M+Li)^+$ 765.5310, found 765.5313.

4.15. Intermediate **21**

To the *tert*-butyl ester **20** (0.52 g, 0.68 mmol) in 7.0 mL of CH_2Cl_2 was added 2,6-lutidine (0.82 mL, 7.1 mmol) and TMS-triflate (0.40 mL, 2.2 mmol). The solution was allowed to stir overnight after which time the solution was added to 50 mL of diethyl ether, washed with 20 mL of 1 M $KHSO_4$, dried over Na_2SO_4 and concentrated in vacuo. To the crude carboxylic acid dissolved in 2.0 mL of CH_2Cl_2 was added triethylamine (0.2 mL, 1.43 mmol) followed by triisopropylsilylchloride (0.2 mL, 0.93 mmol). The solution was stirred for 1 h after which time it was poured into 40 mL of diethyl ether and washed with 20 mL of 1 M $KHSO_4$, followed by 20 mL of a satd $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a crude product that was purified by column chromatography (SiO_2, 10% EtOAc/hexanes) to afford **21** as a colorless oil (0.51 g, 87%). ^{1}H NMR (400 MHz, CD_3Cl): δ 7.33−7.24 (m, 5H), 5.45 (ddd, J=10.8, 3.6, 1H), 5.36 (t, J=10.8, 1H), 4.99−4.95 (m, 1H), 4.88 (t, J=9.2, 1H), 4.50 (s, 2H), 4.42−4.38 (m, 1H), 3.46 (t, J=6.8, 2H), 2.79 (dd, J=15.6, 4.0, 1H), 2.42 (dd, J=15.6, 10.4, 1H), 2.10−1.91 (m, 7H), 1.74 (d, J=14.4, 1H), 1.62 (p, J=6.4, 2H), 1.52−1.49 (m, 3H), 1.40−1.26 (m, 21H), 1.20 (s, 3H), 1.08−1.05 (m, 18H), 0.95(t, J=8.0, 9H), 0.55(q, J=8.0, 6H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 171.0, 170.6, 138.7, 131.3, 130.6, 128.3, 127.5, 127.4, 96.9, 72.8, 70.5, 70.2, 67.1, 62.2, 61.4, 47.0, 45.1, 42.4, 38.1, 34.2, 31.9, 29.9, 29.8, 29.7, 29.6 (br), 29.5, 27.9, 26.1, 21.3, 17.7, 11.9 7.2, 6.9; HRMS (FAB) *m/z* calcd for $C_{49}H_{86}Si_2O_8Li$ $(M+Li)^+$ 865.6021, found 865.6010.

4.16. Intermediate **22**

To 10 mL of THF in a 100-mL round-bottomed flask was added compound **21** (0.32 g, 0.47 mmol) and 5 mol % Pt on carbon (0.30 g). The flask was purged under high vacuum and backfilled with hydrogen gas from a balloon four times. The suspension was allowed to stir under hydrogen at atmospheric pressure and monitored by TLC. After 4 h, the reaction mixture was filtered, through a medium glass filter. The solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2, 15% EtOAc to 30% EtOAc/hexanes) to afford **22** as a colorless oil (0.18 g, 63%). ^{1}H NMR (400 MHz, CD_3Cl): δ 5.05−5.01 (m, 1H), 4.38−4.33 (m, 1H), 3.98−3.96 (m, 1H), 3.63 (t, J=6.8, 2H), 2.76 (dd, J=15.2, 3.6, 1H), 2.38 (dd, J=15.2, 10.4, 1H), 2.0 (s, 3H), 2.98−2.93 (m, 1H), 2.89−83 (m, 1H), 1.75−1.70 (m, 2H), 1.68−1.50 (m, 6H), 1.40−1.21 (m, 26H), 1.18 (s, 3H), 1.09−1.05 (m, 18H), 0.95 (t, J=8.0, 9H), 0.55 (q, J=8.0, 6H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 170.9, 170.8, 96.7, 70.4, 67.2, 65.5, 63.0, 61.3, 47.5, 45.0, 42.6, 38.2, 35.8, 34.2, 32.8, 32.1, 31.6, 30.2, 29.9, 29.8, 29.7 (br), 29.6, 29.4, 25.9, 25.8, 25.7, 22.6, 21.4, 17.7, 14.1, 11.9, 7.2, 6.8; HRMS (FAB) *m/z* calcd for $C_{42}H_{82}Si_2O_8Li$ $(M+Li)^+$ 777.5708, found 777.5688.

4.17. Intermediate **23**

To a solution of DMSO (0.90 mL, 12 mmol) in 10.0 mL of dry CH_2Cl_2 cooled to −78 °C was added oxalyl chloride (0.50 mL, 5.7 mmol). After stirring the mixture for 15 min at −78 °C, a solution of compound **22** (0.28 g, 0.36 mmol) in 10.0 mL of dry CH_2Cl_2 was slowly added. The mixture was stirred for an additional 45 min at −78 °C and Et_3N (2.1 mL, 15 mmol) was added. The resulting mixture was allowed to warm to rt and poured into 150 mL of diethyl ether, and then washed with 100 mL of satd $NaHCO_3$. The organic layer was then washed with 100 mL of 1 M $KHSO_4$ followed by 100 mL of satd $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (SiO_2, 15% EtOAc/hexanes) to afford **23** as a colorless oil (0.19 g, 68%). ^{1}H NMR (400 MHz, CD_3Cl): δ 9.74−9.72 (m, 1H), 5.04−5.02 (m, 1H), 4.34−4.29 (m, 1H), 3.93−3.89 (m, 1H), 2.75 (dd, J=15.2, 3.6, 1H), 2.38 (m, 3H), 2.02 (m, 4H), 1.85 (d, J=14.8, 1H), 1.73 (d, J=14.0, 1H), 1.60 (m, 6H), 1.23 (m, 24H), 1.19 (s, 3H), 1.03 (m, 18H), 0.92 (t, J=8.0, 9H), 0.52 (q, J=8.0, 6H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 202.8, 170.8, 170.7, 96.7, 70.4, 67.1, 65.5, 61.3, 60.32, 47.4, 45.0, 43.9, 42.6, 38.1, 35.7, 34.2, 32.0, 31.5, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 25.7, 22.6, 22.0, 21.4, 17.7, 17.3, 11.9, 7.2, 6.8; HRMS (FAB) *m/z* calcd for $C_{42}H_{80}Si_2O_8Li$ $(M+Li)^+$ 775.5551, found 775.5552.

4.18. Intermediate **24**

To a cooled (−78 °C) solution of Wittig salt **12** (250 mg, 0.17 mmol) in THF (2 mL) was added dropwise a 1.4 M solution of MeLi·LiBr in ether (126 mL). The color of the solution turned orange-red immediately. After stirring for 30 min, a solution of aldehyde **23** (185 mg, 0.24 mmol) in THF (1 mL) was added

dropwise. The flask containing the aldehyde was rinsed with an additional 1 mL of THF, which was added to the reaction mixture. The color of the reaction faded immediately to pale yellow upon the addition of the aldehyde. The reaction mixture was stirred for 1 h at −78 °C and then warmed slowly to rt. The reaction was quenched with satd NH_4Cl solution and the resulting mixture extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (20% EtOAc/hexanes) to give the desired product (210 mg, 85%) as a colorless oil. IR: 3424, 2928, 2855, 1737, 1713 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.47–6.34 (m, 2H), 5.94–5.83 (m, 1H), 5.64–5.50 (m, 2H), 5.30–5.00 (m, 5H), 4.72–4.62 (m, 1H), 4.49 (q, J=6.4 Hz, 1H), 4.38–4.28 (m, 1H), 4.27–4.15 (m, 1H), 3.98 (br s, 1H), 3.92 (s, 1H), 3.64–3.48 (m, 4H), 3.21 (s, 3H), 3.02 (dd, J=15.6, 4.0 Hz, 1H), 2.75 (d, J=12.8 Hz, 1H), 2.68 (dd, J=13.2, 6.0 Hz, 1H), 2.62–2.52 (m, 2H), 2.43–2.33 (m, 1H), 2.37 (dd, J=15.2, 3.6 Hz, 1H), 1.98 (s, 3H), 1.89–1.65 (m, 5H), 1.65–1.53 (m, 4H), 1.51–1.22 (m, 28H), 1.20–1.01 (m, 88H), 0.89–0.77 (m, 18H), 0.75–0.65 (m, 6H), 0.29 (s, 3H), 0.23 (s, 3H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6): δ 170.3, 169.5, 144.1, 137.4, 136.7, 130.8 (trans), 130.2 (trans), 130.1 (cis), 130.0, 129.6 (cis), 116.3, 114.8, 101.2, 96.8, 81.0, 80.4, 77.4, 77.1, 72.1, 71.3, 70.9, 70.4, 67.1, 66.9, 66.8 (trans), 65.2, 61.5, 47.3, 46.7, 46.6, 45.3, 42.5, 40.1, 39.9, 38.7, 38.6 (trans), 38.1, 36.1, 34.3, 32.9, 32.8, 32.6, 32.3 (trans), 31.9, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.4, 27.5, 27.4, 26.5, 25.9, 25.8, 20.9, 18.2, 18.0, 17.8, 15.8, 12.0, 10.4, 7.3, 7.2, 7.1, 7.0, 6.9, 5.2, 5.0, −4.3, −4.4. −4.8, −4.9; LRMS (FAB, low resolution) calcd for $C_{99}H_{194}O_{15}Si_7Li$ (M+Li^+) 1828, found 1827. Anal. Calcd for $C_{99}H_{194}O_{15}Si_7$: C 65.29, H 10.74. Found: C 65.44, H 10.79.

4.19. Lactone **25**

To a cooled (0 °C) solution of the Wittig product **24** (49 mg, 26.9 mmol) in THF (2 mL) was added a 1.0 M solution of TBAF in THF (83 mL, 83.4 mmol) dropwise. The mixture was stirred for 2 h at 0 °C, quenched with satd NH_4Cl solution, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (50% EtOAc/hexanes) to give the ring F desilylated material (23 mg, 60%) as a foaming solid. IR: 2952, 2876, 1737, 1722 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.48–6.38 (m, 2H), 5.90 (dd, J=14.0, 6.0 Hz, 1H), 5.66–5.57 (m, 2H), 5.30–5.01 (m, 5H), 4.69 (m, 1H), 4.50 (q, J=6.8 Hz, 1H), 4.40–4.27 (m, 2H), 4.03 (m, 1H), 3.98 (s, 1H). 3.48–3.39 (m, 1H), 3.42 (d, J=10.8 Hz, 1H), 3.31 (t, J=8.8 Hz, 1H), 3.23 (s, 3H), 3.13 (t, J=10.0 Hz, 1H), 2.83 (d, J=12.0 Hz, 1H), 2.74–2.56 (m, 3H), 2.46–2.36 (m, 3H), 2.25–2.05 (m, 5H), 2.04 (s, 3H), 1.98–1.61 (m, 11H), 1.59–1.35 (m, 22H), 1.32 (dd, J=14.8, 3.6 Hz, 1H), 1.25–1.05 (m, 50H), 0.94–0.84 (m, 6H), 0.76 (q, J=8.0 Hz, 6H), 0.33 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 174.1, 170.0, 143.8, 137.5, 136.8, 130.8 (trans), 130.4 (trans), 130.2 (cis), 130.1, 129.7 (cis), 116.5, 115.1, 101.4, 96.9, 78.9, 78.5, 78.4, 75.6, 72.6, 71.0, 70.9, 70.5, 67.2, 67.1, 65.2, 61.0, 47.4, 46.6, 46.2, 45.2, 40.1, 39.4, 38.8, 38.7, 38.1, 36.2, 33.9, 32.8, 32.0, 30.2, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.2, 27.6, 27.5, 26.5, 25.9, 25.8, 20.9, 18.2, 18.1, 13.5, 10.4, 7.3, 7.2, 6.9, 5.9, −4.3, −4.4. −4.7, −4.9; LRMS (FAB, low resolution) calcd for $C_{78}H_{146}O_{15}Si_4$ (M−H^+) 1435.3, found 1435.0. Anal. Calcd for $C_{78}H_{146}O_{15}Si_4$: C 65.22, H 10.25. Found: C 65.41, H 10.44.

To a flask containing the aforementioned carboxylic acid (55 mg, 38.3 mmol) was added a 0.4 M solution of *N*,*N*-diisopropylethylamine in toluene (2.9 mL, 1.15 mmol) followed by 0.4 M 2,4,6-trichlorobenzoyl chloride in toluene (1.9 mL, 0.77 mmol). The reaction mixture was stirred for 3 h at rt, then diluted with toluene (16 mL), added over a 24 h period (via syringe pump) to a solution of DMAP (244 mg, 1.91 mmol) in toluene (50 mL), and heated in an oil bath set at 90 °C. A white precipitate was observed. Upon completion of the addition, the flask in which the mixed anhydride formed was rinsed with toluene (3 mL) and this rinse was added to the DMAP solution over 12 h. After cooling to rt, the mixture was washed with satd $NaHCO_3$ (50 mL) and then with brine (50 mL). The aqueous phases were back-extracted with EtOAc and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (20% EtOAc/hexanes) to give the desired product (30 mg, 72%) as a colorless oil. IR: 2928, 2854, 1736 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.40–6.25 (m, 2H), 5.81 (dd, J=14.4, 6.4 Hz, 1H), 5.57–5.40 (m, 2H), 5.20–4.93 (m, 5H), 4.79 (t, J=9.6 Hz, 1H), 4.63–4.53 (m, 1H), 4.39 (q, J=6.4 Hz, 1H), 4.34–4.22 (m, 2H), 4.00–3.87 (m, 2H), 3.43–3.37 (m, 1H), 3.32 (d, J=10.4 Hz, 1H), 3.27–3.25 (m, 1H), 3.14 (s, 3H), 3.00–2.91 (m, 1H), 2.82 (d, J=13.6 Hz, 1H), 2.59–2.45 (m, 3H), 2.37–2.21 (m, 3H), 2.12–1.96 (m, 10H), 1.82–1.51 (m, 9H), 1.50–1.15 (m, 24H), 1.12–0.93 (m, 46H), 0.80–0.72 (m, 6H), 0.65–0.57 (m, 6H), 0.26 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 171.5, 169.6, 143.3, 137.5, 136.7, 130.6 (trans), 130.5 (trans), 130.0, 129.6 (cis), 116.3, 115.3, 101.2, 96.9, 80.8, 79.0, 77.9, 73.4, 72.7, 70.8, 70.7, 70.4, 67.5, 67.1, 66.6 (trans), 65.0, 61.2, 47.3, 46.7, 46.5 (trans), 46.3, 45.4, 41.5, 39.0, 38.9, 38.0, 37.3, 35.8, 34.5, 33.1, 32.4, 32.3, 31.9, 30.2, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.4, 29.2, 29.1, 28.6, 27.7, 27.3, 27.0, 26.1, 25.9, 25.8, 20.9, 18.1, 18.0, 13.7, 10.3, 7.2, 7.1, 6.9, 5.8, −4.4, −4.5, −4.8, −4.9; LRMS (FAB, low resolution) calcd for $C_{78}H_{144}O_{14}Si_4Li$ (M+Li^+) 1425, found 1425. Anal. Calcd for $C_{78}H_{144}O_{14}Si_4$: C 66.05, H 10.23. Found: C 65.71, H 10.43.

4.20. Lactones **6**

Lactone **25** (26 mg, 18.3 mmol) was placed in a polypropylene vessel, THF (0.5 mL) was added followed by acetonitrile (0.5 mL). The mixture was cooled to −18 °C, and a solution of HF (1.3 mL, 5.0 M in acetonitrile) was added dropwise over 1 h. The reaction mixture was then stirred overnight while the temperature was maintained between −15 °C and −19 °C. The reaction was quenched at low temperature by the addition of triethylamine (1.0 mL), the resulting mixture allowed to warm to rt, transferred to a separation funnel with satd $NaHCO_3$

(20 mL), and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to leave an oil. The residue was purified by column chromatography (75% EtOAc/hexanes) and the product was obtained as a white solid (14 mg, 82%). IR: 3421, 2925, 2854, 1737 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.49–6.29 (m, 2H), 5.73–5.68 (m, 1H), 5.66–5.49 (m, 2H), 5.41 (br s, 1H), 5.26 (d, J=16.4 Hz, 1H), 5.20–5.08 (m, 3H), 4.74 (t, J=10.8 Hz, 1H), 4.61–4.57 (m, 1H), 4.48 (br s, 1H), 4.25 (q, J=6.4 Hz, 1H), 4.18–4.11 (m, 1H), 3.96 (br s, 1H), 3.89 (d, J=10.0 Hz, 1H), 3.64 (t, J=9.2 Hz, 1H), 3.50–3.35 (m, 2H), 3.04 (d, J=15.2 Hz, 1H), 2.44–2.05 (m, 6H), 1.98 (s, 3H), 1.95–1.75 (m, 7H), 1.72–1.25 (m, 35H), 1.12 (dd, J=14.8, 3.6 Hz, 1H), 1.10–0.95 (m, 7H), 0.82 (d, J=7.2 Hz, 3H), 0.73 (d, J=6.4 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 171.4, 169.6, 143.3, 136.8, 136.7, 131.3 (trans), 130.7 (cis), 130.5, 129.8 (trans), 129.6 (cis), 116.9, 115.0, 99.3, 98.2, 80.8, 79.9, 77.7, 72.6, 72.4, 70.6, 70.5, 69.4, 67.1, 66.2, 66.0, 63.7, 45.3, 43.7, 43.3, 40.5, 39.6, 37.1, 36.7, 36.6, 36.2 (trans), 35.9, 33.7, 33.3, 33.0 (trans), 32.3 (trans), 32.1, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.6 (trans), 27.6, 27.4, 25.6, 25.5, 20.8, 11.8, 11.7 (trans), 10.4 (trans), 10.3; HRMS (FAB) calcd for $C_{53}H_{86}O_{14}Li$ ($M+Li^+$) 953.6175, found 953.6178. Anal. Calcd for $C_{53}H_{86}O_{14}$: C 67.20, H 9.15. Found: C 67.40, H 9.52.

4.21. 1,10-Decane diol, mono-TIPS ether (*26*)

To a solution of 1,10-decane diol (2.6 g, 15 mmol) in 25 mL of DMF was added imidazole (0.68 g, 10 mmol) followed by TIPSCl (2.14 mL, 10 mmol), and the solution was stirred for 2 h at rt. The solution was then added to 200 mL of diethyl ether, washed with 60 mL of aqueous 1 M $KHSO_4$ followed by 60 mL of satd K_2CO_3 and washed again with 60 mL of aqueous 1 M $KHSO_4$. The organics were dried over sodium sulfate, concentrated and purified by flash chromatography (20% EtOAc/hexanes) to give the product as a colorless oil (1.58 g, 48%). ^1H NMR (400 MHz, CD_3Cl): δ 3.67–3.61 (m, 4H), 1.57–1.51 (m, 5H), 1.27–1.19 (m, 12H), 1.10 (d, J=6.8 Hz, 21H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 63.4, 63.0, 32.9, 32.7, 29.6, 29.5, 29.4, 29.3, 25.8, 25.7 17.9, 11.9.

4.22. 10-Iododecanol, TIPS ether (*27*)

To a solution of triphenylphosphine (2.4 g, 9.2 mmol) in 50 mL of DCM was added imidazole (0.63 g, 9.2 mmol), iodine (2.34 g, 9.2 mmol), and the ether **26** (2.6 g, 7.7 mmol). The reaction was stirred for 3 h and then poured into 200 mL of ether and washed with 30 mL of aqueous 1 M $KHSO_4$, 30 mL of satd $NaHCO_3$, and 30 mL of brine. The organics were dried over sodium sulfate, concentrated, and the crude residue was purified by flash chromatography (5% EtOAc/hexanes) to give **27** (2.84 g, 82%). ^1H NMR (300 MHz, CD_3Cl): δ 3.66 (t, J=6.6 Hz, 2H), 3.18 (t, J=7.2 Hz, 2H), 1.82 (p, J=7.2 Hz, 2H), 1.58–1.51 (m, 2H), 1.37–1.28 (m, 12H) 1.11–1.05 (m, 21H); ^{13}C NMR (75.5 MHz, CD_3Cl): δ 63.7, 33.8, 33.2, 30.7, 29.8, 29.7, 29.6, 28.8, 26.0, 18.3, 12.2, 7.6.

4.23. Wittig salt *28*

In a 20 mL screw-cap vial, iodide **27** (0.28 g, 0.64 mmol) was added to a solution of triphenylphosphine (0.51 g, 1.9 mmol) and $^iPr_2NEt$ (0.32 mL, 1.8 mmol) in 3 mL of acetonitrile. The vial was flushed with nitrogen, sealed, and heated to 90 °C overnight. The solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2, 5% MeOH/EtOAc) to afford **28** as a yellow oil (0.36 g, 80%). ^1H NMR (400 MHz, CD_3Cl): δ 7.84–7.78 (m, 9H), 7.74–7.69 (m, 6H), 3.65–3.62 (m, 4H), 1.63–1.60 (m, 4H), 1.51–1.46 (m, 2H), 1.35–1.20 (m, 10H), 1.11–1.03 (m, 21H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 135.1, 133.7, 133.6, 130.6, 130.5, 118.7, 117.8, 63.5, 33.0, 30.5, 30.4, 29.5, 29.3, 29.1, 25.7, 22.6, 18.0, 11.9.

4.24. Intermediate *30*

Wittig salt (**28**) (0.1258 g, 0.177 mmol) was dissolved in a 10% HMPA solution in THF (1.7 mL), cooled to −78 °C, and LiHMDS (1.0 M, 177 μL, 0.177 mmol) was added, and the reaction was stirred for 30 min. To this stirred reaction was added aldehyde **29** (99 mg, 0.088 mmol) in THF (1.45 mL), and the reaction was allowed to warm to rt and stir overnight. The crude reaction mixture was poured into diethyl ether (10 mL) and washed with saturated ammonium chloride (10 mL), followed by water (10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate, concentrated in vacuo, and purified by flash chromatography (25 mL SiO_2, 30% EtOAc in hexanes) to give the product as the *cis*-alkene isomer (52 mg, 41%). ^1H NMR (400 MHz, CD_3Cl): δ 5.42–5.40 (m, 2H), 5.21–5.13 (m, 2H), 5.03–5.00 (m, 1H), 4.97 (s, 1H), 4.82 (s, 1H), 4.44–4.08 (m, 3H), 3.94–3.89 (m, 1H), 3.66 (t, J=6.8 Hz, 1H), 3.45–3.39 (m, 1H), 3.29 (s, 3H), 2.91–2.81 (m, 2H), 2.75–2.62 (m, 2H), 2.41–2.31 (m, 2H), 2.26 (d, J=6.8 Hz, 2H), 2.14–2.08 (m, 2H), 2.04–2.02 (m, 4H), 2.01 (s, 3H), 1.96–1.94 (m, 1H), 1.90 (s, 3H), 1.84–1.82 (m, 1H), 1.73–1.70 (m, 1H), 1.59–1.40 (m, 9H), 1.29–1.15 (m, 25H), 1.19 (s, 3H), 1.09–1.00 (m, 33H), 0.94 (t, J=8 Hz, 9H), 0.85–0.80 (m, 12H), 0.55–0.45 (m, 6H), 0.01–0.00 (m, 6H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 209.8, 171.0, 170.5, 169.2, 146.9, 131.6, 130.3, 113.6, 98.1, 96.8, 77.19, 74.1, 73.7, 70.4, 66.6, 66.1, 64.4, 64.3, 63.4, 62.4, 61.0, 55.5, 49.9, 47.6, 47.6, 45.1, 43.6, 42.2, 41.9, 38.9, 38.4, 37.8, 36.9, 34.8, 33.9, 33.0, 31.9, 29.7, 29.6, 29.5, 29.4, 28.1, 25.8, 21.5, 20.7, 18.0, 17.8, 13.4, 12.0, 11.9, 11.8, 7.3, 6.9, −4.9, −5.0.

4.25. Intermediate *31*

To a solution of TIPS ester (**30**) (19.5 mg, 0.014 mmol) in THF (2 mL) cooled to 0 °C was added a solution of TBAF in THF (1 M, 28 μL, 0.028 mmol), and the reaction was stirred for 2.5 h. The reaction solution was diluted in diethyl ether (10 mL) and washed with an aqueous solution of 10% $KHSO_4$ followed by brine. The organic layer was dried over sodium sulfate, concentrated and purified by flash column chromatography (SiO_2, 1:1 EtOAc/hexanes) to give alcohol **31** (10.5 mg, 69%). ^1H NMR (400 MHz, CD_3Cl): δ 9.1 (br s, 1H), 5.45–5.35 (m,

2H), 5.22–5.20 (m, 2H), 5.03–5.00 (m, 1H), 4.97–4.95 (m, 1H), 4.82–4.79 (m, 1H), 4.27–4.20 (m, 1H), 4.14–4.10 (m, 1H), 4.08–4.04 (m, 1H), 3.94–3.91 (m, 1H), 3.67–3.60 (m, 2H), 3.46–3.40 (m, 2H), 3.29 (s, 3H), 2.92–2.80 (m, 2H), 2.71–2.63 (m, 1H), 2.50–2.32 (m, 2H), 2.30–2.15 (m, 1H), 2.14–2.09 (m, 2H), 2.08–2.05 (m, 2H), 2.04 (s, 3H), 2.91 (s, 3H), 1.81–1.79 (m, 2H), 1.60–1.50 (m, 6H), 1.49–1.35 (m, 6H), 1.30–1.18 (m, 20H), 1.07–1.02 (m, 8H), 0.91 (t, J=8.0 Hz, 9H), 0.85 (s, 9H), 0.57 (q, J=7.6 Hz, 6H), 0.02–0.00 (m, 6H); ^{13}C NMR (100.6 MHz, CD_3Cl): δ 209.87, 170.9, 169.4, 146.8, 131.9, 130.3, 128.3, 98.1, 97.4, 77.2, 74.0, 73.7, 70.6, 66.2, 66.0, 64.4, 62.9, 62.2, 61.1, 55.4, 53.4, 47.5, 44.9, 43.5, 40.2, 38.8, 38.4, 37.2, 36.9, 34.8, 34.0, 32.5, 31.9, 29.5, 29.4, 29.3, 29.2, 27.8, 25.8, 25.6, 21.4, 20.7, 19.3, 17.9, 13.3, 11.8, 7.2, 6.6.

4.26. Lactone 32

To a flask containing alcohol **31** (25 mg, 0.023 mmol) was added triisopropylethylamine (1.7 mL, 0.4 M in toluene) followed by 2,4,6-trichlorobenzoyl chloride (1.13 mL, 0.4 M in toluene). The mixture was stirred for 3 h at rt. The mixture was diluted with toluene (13.5 mL) and slowly added (over 24 h) to a solution of DMAP (137 mg, 1.13 mmol) in toluene (24 mL). After cooling to rt, the mixture was washed with satd $NaHCO_3$ (50 mL) and then with brine (50 mL). The aqueous phases were back-extracted with EtOAc and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (20% EtOAc/hexanes) to give the desired lactone (4.5 mg, 18%) as a colorless oil. ^{1}H NMR (400 MHz, CD_3Cl): δ 5.51–5.50 (m, 1H), 5.39–5.32 (m, 1H), 5.25–5.20 (m, 1H), 5.02–5.00 (m, 1H), 4.91–4.89 (m, 1H), 4.78–4.75 (m, 1H), 4.25–4.20 (m, 1H), 4.19–4.00 (m, 4H), 3.95–3.91 (m, 1H), 3.49–3.45 (m, 1H), 3.28 (s, 3H), 3.07–2.90 (m, 2H), 2.72–2.62 (m, 3H), 2.53–2.50 (m, 1H), 2.35–2.30 (m, 1H), 2.10–2.03 (m, 2H), 2.02 (s, 3H), 1.95–1.90 (m, 1H), 1.88 (s, 3H), 1.81–1.75 (m, 1H), 1.70–1.65 (m, 1H), 1.62–1.50 (m, 10H), 1.35–1.20 (m, 20H), 1.19 (s, 3H), 1.11–1.07 (m, 7H), 0.93 (t, J=8.0 Hz, 9H), 0.86 (s, 9H), 0.55 (q, J=7.6 Hz, 6H), 0.02–0.00 (m, 6H).

4.27. Lactone 7

The reaction took place in a polypropylene reaction vessel. To a solution of lactone **32** (4.5 mg, 0.0041 mmol) in acetonitrile (100 μL) and THF (100 μL) cooled to −18 °C (methanol/ice bath) was added a solution of HF (290 μL of a 5 M solution prepared from 10 mL of 48% aqueous HF and 40 mL of acetonitrile) over a period of 1 h. The solution was stirred for 5 h between −15 °C and −18 °C. The reaction mixture was diluted with a mixture of EtOAc/DCM (2:1, 50 mL) and the organic phase was dried over Na_2SO_4, filtered, and concentrated. The resulting crude oil was purified by running two subsequent columns on silica using DCM→3% MeOH/DCM to afford lactone **7** (2 mg, 56%) as an oil. ^{1}H NMR (400 MHz, CD_3Cl): δ 5.45–5.40 (m, 1H), 5.35–5.31 (m, 1H), 5.23–5.19 (m, 1H), 5.04–4.98 (m, 2H), 4.80 (s, 1H), 4.23–4.20 (m, 2H), 4.10–4.00 (m, 4H), 3.91–3.85 (m, 1H), 3.49–3.40 (m, 2H), 3.32 (s, 3H), 2.95–2.90 (m, 2H), 2.71–2.65 (m, 1H), 2.60–2.55 (m, 1H), 2.45–2.40 (m, 1H), 2.36–2.30 (m, 1H), 2.22–2.17 (m, 2H) 2.11–2.06 (m, 1H), 2.05 (s, 3H), 1.95–1.91 (m, 1H), 1.90 (s, 3H), 1.65–1.50 (m, 16H), 1.16 (s, 3H), 1.25–1.10 (m, 26H), 1.08 (d, J=6.8 Hz, 3H), 0.87–0.80 (m, 3H); LRMS (electrospray) *m/e* calcd for $C_{47}H_{74}NaO_{14}$ $(M+Na)^+$ 885.5 (100%), 886.5 (50.8%), 887.5 (12.6%), found 885.5 (100%), 886.5 (54%), 887.5 (17%).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.065.

References and notes

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17. Compound **21** in Ref. 10.
18. Prepared as described in Ref. 10, by the reaction of iodide **23** with triphenylphosphine in acetonitrile.
19. Compound **29** in Ref. 14.