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Facile access to some chiral building blocks. Synthesis of verbalactone and exophilin A

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ABSTRACT

D-Glucono-1,5-lactone, an inexpensive carbohydrate, was elaborated into chiral building blocks readily applicable in synthesis via practical routes without involving any expensive reagents or tedious operations. Application of such chiral building blocks in total synthesis is then exemplified through construction of verbalactone and exophilin A. The latter compound has not been synthesized to date.

1. Introduction

D-Glucono-1,5-lactone (**1**) is an inexpensive and readily available carbohydrate compound containing four well-defined stereogenic centers. However, up to now use of this compound as a chiral pool appears to be limited mainly to those syntheses where the molecular architecture of **1** could be incorporated as a whole into the target structures without selective elimination of and complete differentiation between the hydroxyl groups.[1] Examples[2] of elaboration of **1** into compounds possible to be directly used in synthesis are also known, but relatively scant to date. Herein we wish to report a few more ways to make use of **1**, which provide facile access to several flexible chiral building blocks.

Compound **2**[3] is one of the exploitable intermediates we found in the literature, which can be readily prepared using Pedersen's[4] five-step practical sequence without recourse to chromatographic purification. Perhaps because its structure still carries a carbohydrate look and its preparation was 'hidden' among many other typical manipulations of carbohydrate chemistry,[5] up to now the potential of **2** as a precursor for various chiral building blocks does not seem to have been broadly recognized by the synthetic community.

2. Results and discussions

The first chiral building blocks we prepared in this work are **5** and **8** (Scheme 1), a pair of epoxides initially introduced in 1995 by Mulzer[6] and co-workers. These compounds are apparently rather useful in synthesis. However, to date no records on their applications can be found in the literature presumably because of lack of facile access.

Our route to **5** and **8** is shown in Scheme 1. The precursor **2** was prepared[7] by the method of Pedersen[4] in 79% overall yield by just one crystallization at the end of the sequence. Compound **2** was then readily reduced with $NaBH_4$ in MeOH at ambient temperature, giving triol **3** (Scheme 1). The primary hydroxyl group selectively tosylated under the conditions of Martinelli[8,9] led to monotosylate **4**. Finally, treatment with K_2CO_3/MeOH gave epoxide **5**.[6]

The configuration at the C-2 could also be inverted to give a chiral building block containing a hidden 1,3-*syn* diol motif. In this case, the C-2 hydroxyl group in **2** was first mesylated under carefully controlled conditions (MsCl/Py/0 °C). The resultant crude mesylate **6** was reduced with $NaBH_4$ in MeOH at ambient temperature to yield diol-mesylate **7**, which was not stable and underwent spontaneous cyclization to afford the desired epoxide **8** in 86% overall yield from **2**.[6] It is noteworthy that in both cases throughout the whole synthesis only one chromatography was needed at the end of the sequence.

Once being brought to a new perspective of readily applicable chiral building blocks rather than merely an individual

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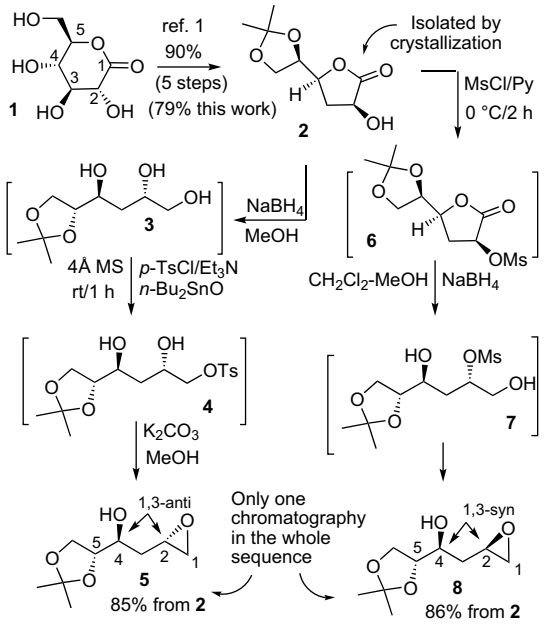
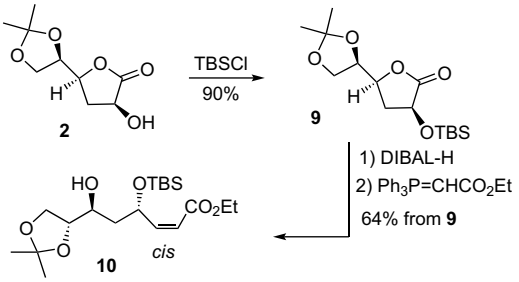


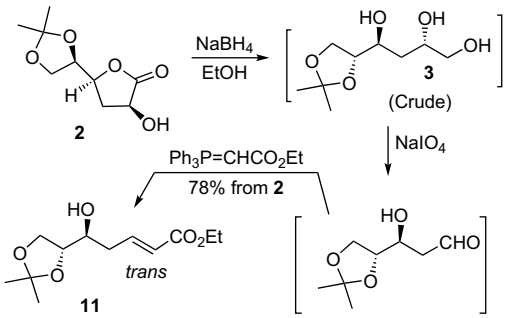
Scheme 1.

intermediate involved in a particular synthesis, other potential ways of elaboration of **2** are not difficult to design through selective reaction at either the lactone or the free hydroxyl group. Two of such possibilities are illustrated below. Thus, protection of the hydroxyl group with TBSCl (*tert*-butyldimethylsilyl chloride) followed by partial reduction of the lactone and chain extension using a Wittig reaction led to *cis*[10] alkene **10** (Scheme 2).



Scheme 2.

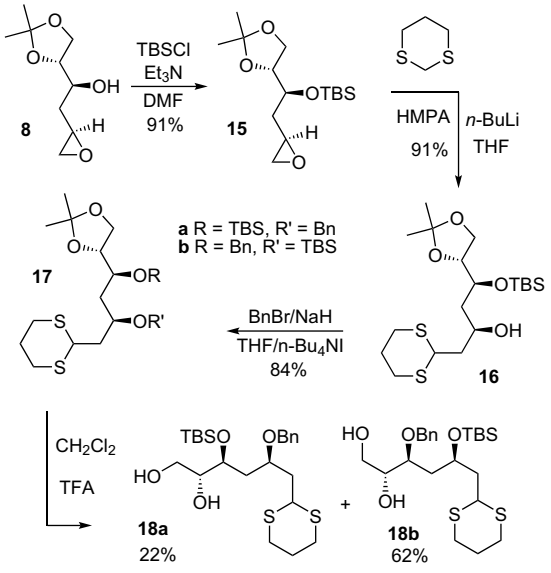
Alternatively, the crude triol **3** in the $NaBH_4$ reduction of **2** mentioned above could be converted into **11** by oxidative cleavage of the vicinal diol with $NaIO_4$ in $MeOH/H_2O$ followed by a Wittig reaction with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 (Scheme 3).



Scheme 3.

To exemplify the potential utility of these readily accessible enantiopure building blocks, one of them (**8**) was elaborated into precursors to (3*R*,5*R*)-3-hydroxy-5-decanoate, a structural unit common to (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide[11,12] (**12**), verbalactone[12] (**13**), and exophilin A[13] (**14**). Compound **12**, the simplest member of these three natural products, is a potent HMG-CoA reductase inhibitor. The dimer (verbalactone) has been shown to possess antibacterial activity. Exophilin A is also an antibacterial, which to date has never been synthesized yet.

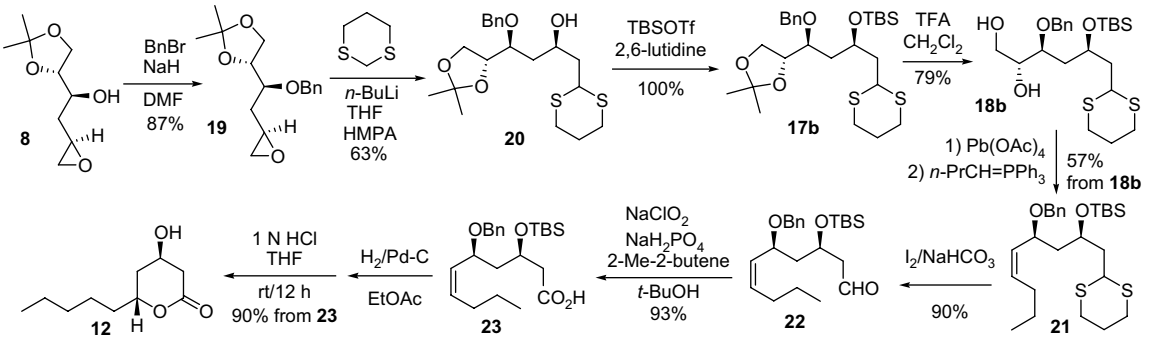
The elaborations began with introduction of a dithiane functionality at the epoxide end after masking the hydroxyl group in **8** with TBSCl (Scheme 4). The newly formed hydroxyl group in **16** was then protected as a Bn ether by treatment with NaH/BnBr. The product **17** turned out to be a mixture of two inseparable isomers. Interestingly, after removal of the acetonide group, the two resulting diols could be completely separated on silica gel giving **18a** and **18b** in an about 1:3 ratio. These results revealed that the silyl protecting group in the present case was apparently too labile to migration. The order of introducing the protecting groups was therefore reversed later.



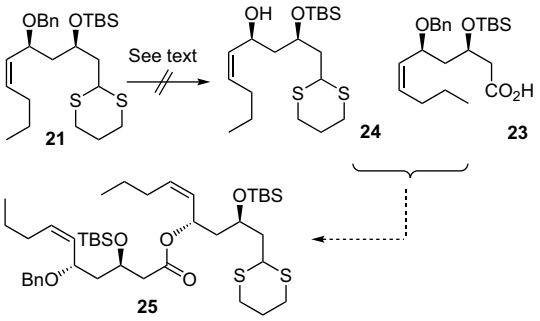
Scheme 4.

As shown in Scheme 5, benzyl protection followed by the opening of the epoxy ring with 1,3-dithiane gave alcohol **20**. The subsequent silylation and hydrolysis of the acetonide afforded diol **18b**. It is noteworthy that use of TBSCl to replace TBSOTf here led to a rather sluggish reaction and more than 10 mol equiv of TBSCl must be used to ensure a complete silylation. Oxidative cleavage of the vicinal diol provided an intermediate aldehyde, which on reaction with the butyl Wittig reagent[14a] gave *cis*[14b] alkene **21**. The thiol protecting group was then hydrolyzed and the resulting aldehyde **22** was oxidized with $NaClO_2$[15] to afford acid **23**. Finally, removal of the benzyl group and saturation of the C–C double bond by H_2/Pd–C followed by removal of the TBS ether provided the **12**, which showed spectroscopic data consistent with those reported in the literature.

The synthesis of verbalactone requires connection of two units of the above-mentioned fragments. As we had already obtained acid **23**, the most straightforward approach to the dimmer framework appeared to be a coupling of **23** with **24** (Scheme 6). Unfortunately, removal of the benzyl group in **21** turned out to be extremely difficult presumably because of the presence of the thiol acetal functionality.

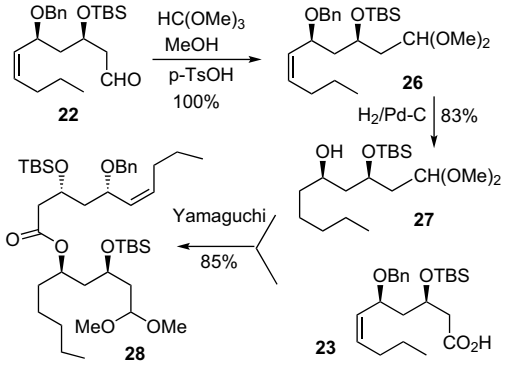


Scheme 5.



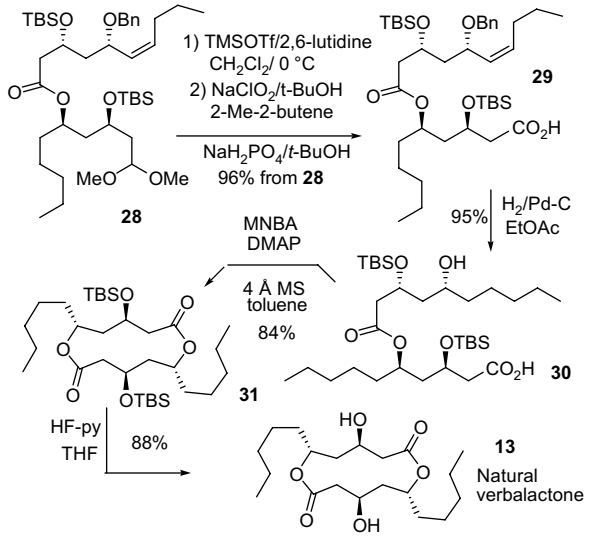
Scheme 6.

To get around this problem, the thioacetal functionality was replaced by dimethyl acetal before execution of the remaining steps. In the event, the aforementioned aldehyde **22** was converted[16] into the corresponding dimethyl acetal by careful treatment with $HC(OMe)_3$/MeOH/*p*-TsOH.[17] The resulting **26** was debenzylated with concurrent hydrogenation of the C–C double bond, giving alcohol **27** smoothly. With a free hydroxyl group ready for coupling with **23**, a Yamaguchi[18] esterification (trichlorobenzoyl chloride/DMAP/Et_3N) was performed, which resulted in the desired **28** in 85% yield (Scheme 7).



Scheme 7.

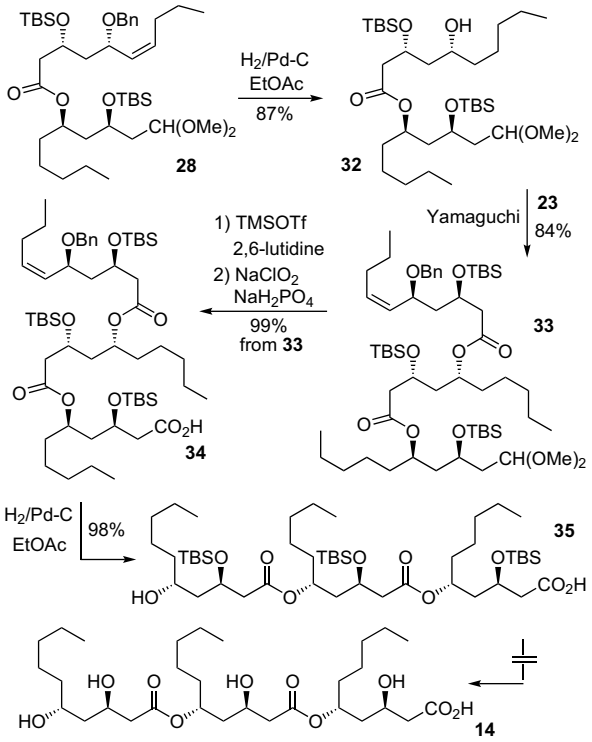
Further elaboration of **28** into natural verbalactone **13** is depicted in Scheme 8. To reach the dilactone architecture, the dimethyl acetal terminal must be transformed into a carboxylic acid while the benzyl protected hydroxyl group must be freed. Perhaps because of the presence of too many acid-sensitive functionalities in the molecule, hydrolysis of the acetal into the corresponding aldehyde was not so facile as expected. Under mild conditions (e.g., *p*-TsOH/acetone–H_2O) essentially no reaction took place. Use of more forcing conditions led to complicated product mixtures. Finally, the problem was solved by using the conditions developed by Fujioka and Kita[19] (TESOTf or TMSOTf/2,6-lutidine/CH_2Cl_2), which gave a clean conversion with either TESOTf or TMSOTf as the silylation agent.



Scheme 8.

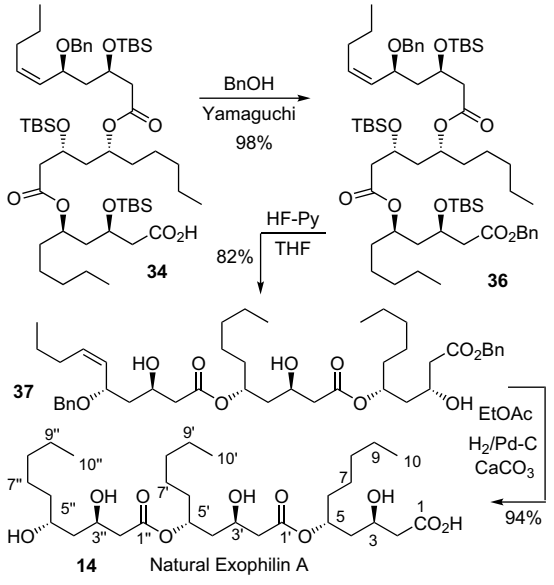
The intermediate aldehyde was immediately oxidized with $NaClO_2$ in the presence of NaH_2PO_4 and 2-methyl-2-butene, providing the acid **29** in 96% yield over the two steps. The benzyl protecting group was then removed by treatment with H_2/Pd–C, with the C–C double bond saturated at the same time. Because in our previous[20] investigations involving closing medium-size lactone rings the MNBA (2-methyl-6-nitrobenzoic anhydride) method developed by Shiina[21] often gave better results than other alternatives, in this work we also used this protocol. Thus, treatment of **30** with MNBA/DMAP led to the desired dilactone **31** in 84% yield. Finally, the TBS protecting groups were cleaved with HF·Py/THF, giving verbalactone **13** in 88% yield with the spectroscopic data consistent with those reported in the literature. It is noteworthy that use of TBAF (tetrabutyl-ammonium fluoride) here led to a complex product mixture.

Construction of the trimer structure started with debenzylation of **28**. As shown in Scheme 9, treatment with H_2 over 10% Pd–C gave alcohol **32** in 87% yield. Acid **23** was then connected to **32** using a Yamaguchi esterification. Modification of the acetal terminal was performed in the same fashion as for converting **28** into **29**. Thus, exposure of **33** to TMSOTf/2,6-lutidine followed by $NaClO_2$ oxidation afforded the desired acid **34**. Removal of the benzyl group and saturation of the C–C double bond resulted in the hydroxyl acid **35**.



Scheme 9.

Up to this point it seemed that the end product exophilin A was just one step away. However, removal of the TBS groups, which in many cases is quite facile, turned out to be an impossible task here. We tried many sets of conditions, including TBAF/THF, TBAF/HOAc/THF, HF·Py/THF, concd HCl/THF, TMSCl/KF·H_2O/MeCN,[22] HF (48%)/MeCN, $TiCl_4$/$MeNO_2$/CH_2Cl_2,[23] and TAS-F (tris(diethyl-amino)-sulfonium difluorotrimethylsilicate)/DMF[24] without success. In most cases, the TBS groups in the substrate were not completely removed. The high polarity and water solubility of **14** made it extremely difficult to monitor the progress of the deprotection reaction and to isolate **14** in high purity. These factors prompted us to adopt a different strategy (Scheme 10), in which acid **34** was masked as a benzyl ester before cleaving the TBS groups. The C–C double bond and the benzyl group on the allylic hydroxyl group



Scheme 10.

Table 1
Comparison of ^{13}C NMR δ data recorded in $CDCl_3/CD_3OD$ (1:3)

Carbons (Ref. 13)	Natural **14** (Ref. 13) (125 MHz)	Synthetic **14** (this work) (100 MHz)
1, 1′, 1″	172.9, 172.9, 172.9	172.95, 172.87, 172.87
2, 2′, 2″	43.5, 43.3, 43.3	43.14, 43.10, 43.10
3, 3′, 3″	66.5, 66.7, 69.0	66.4, 66.9, 69.4
4, 4′, 4″	41.8, 41.9, 43.7	41.4, 41.7, 43.4
5, 5′, 5″	73.4, 73.4, 71.8	73.4, 73.4, 72.1
6, 6′, 6″	35.0, 35.0, 38.4	35.0, 35.0, 38.2
7, 7′, 7″	25.6, 25.6, 25.8	25.4, 25.4, 25.6
8, 8′, 8″	32.4, 32.4, 32.7	32.1, 32.1, 32.4
9, 9′, 9″	23.3, 23.4, 23.4	23.0, 23.2, 23.2
10, 10′, 10″	14.4, 14.4, 14.4	14.45, 14.41, 14.41

The assignments of the carbons are taken from Ref. 13. For the position numbering of **14**, see the structure in Scheme 10.

also remained. With these changes, the desilylation product **37** became much less polar and less water-soluble than **35** and thus made the isolation as well as spectral assignments much more executable. Finally, saturation of the C–C double bond and cleavage of the benzyl groups were realized cleanly in a one-pot manner by treatment with H_2 over 10% Pd–C in the presence of $CaCO_3$.

The spectroscopic data of **14** thus obtained were consistent with those reported for natural **14**, confirming that the relative and absolute configurations of natural **14** are indeed as assigned in the literature. The ^{13}C NMR data comparison is given in Table 1.

3. Conclusions

In summary, facile access to two potentially very useful[25] chiral building blocks **5** and **8** (Mulzer's epoxides) has been developed with inexpensive and readily available D-glucono-1,5-lactone as the starting material via the known yet almost 'forgotten' **2**. Although formally the overall sequences are one step longer than those in the literature[6] (seven or eight steps from **1** vs six or seven steps from D-mannitol), all the transformations are very easy to perform. Besides, the whole syntheses require only one crystallization and one chromatography (at the end of each sequence) to give the end products in 64–65% overall yields, comprising a highly practical approach to the synthesis of the epoxides. That no expensive reagents were involved is also an added merit. Other ways of exploiting **2** in the present context are also illustrated. Potential utilities of these chiral building blocks are exemplified by elaboration of **8** into natural products **12**, **13**, and **14**. The first synthesis of **14** presented here may also serve as a direct proof of the structure previously assigned to the natural product.

4. Experimental

4.1. General

Unless otherwise stated, the ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruker Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR spectrometer. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. Optical rotations were recorded on a Jasco P-1030 polarimeter. Dry THF was distilled from Na/Ph_2CO under argon prior to use. Dry CH_2Cl_2 and pyridine were distilled over CaH_2 under N_2 prior to use. Dry HMPA was stirred with CaH_2 at ambient temperature for a few days, distilled under reduced pressure and kept over activated 4 Å molecular sieves. PE (chromatography eluent) stands for petroleum ether (bp 60–90 °C). DMF stands for *N*,*N*′-dimethylformamide. Molecular sieves (4 Å) were activated by heating 3×1 min (with the moisture briefly

ventilated between the heating sessions by opening the oven door) in a 700 W household microwave oven using ca. 75% of the full power.

4.2. Synthesis of epoxide 5 from 2

$NaBH_4$ (454 mg, 12 mmol) was added in portions to a solution of **2** (2.020 g, 10 mmol) in MeOH (50 mL) stirred at 0 °C. After completion of the addition, the cooling bath was removed and the stirring was continued at ambient temperature until TLC showed a complete reaction. The mixture was concentrated on a rotary evaporator and then co-evaporated 5–7 times with MeOH to give crude **3** as a yellowish sticky oil, which was directly dissolved in THF (50 mL). To this solution were added *n*-Bu_2SnO (72 mg, 0.3 mmol), activated 4 Å MS (1.5 g), Et_3N (1.54 mL, 11 mmol), and *p*-TsCl (1.904 g, 10 mmol). The mixture was stirred at ambient temperature for ca. 1 h, when TLC showed completion of the reaction. The solids were filtered off through a short pad of Celite. The filtrate was concentrated on a rotary evaporator. The residue was dissolved in MeOH (40 mL). With cooling (0 °C) and stirring, powdered K_2CO_3 (495 mg, 5.0 mmol) was added. The mixture was stirred at ambient temperature for 2 h. Water (10 mL) was added. The mixture was concentrated by rotary evaporation. The residue was extracted with EtOAc (3×50 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography on silica gel (1:2 EtOAc/petroleum ether) gave **5** as a colorless oil (1.599 g, 8.5 mmol, 85% from **2**). $[\alpha]_D^{24}$ −5.1 (*c* 1.2, $CHCl_3$) (lit.[6] $[\alpha]_D^{20}$ −2.6 (*c* 0.8, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05–3.88 (m, 2H), 3.85–3.74 (m, 2H), 3.12–3.04 (m, 1H), 3.00 (d, *J*=3.9 Hz, 1H, OH), 2.73 (t, *J*=4.4 Hz, 1H), 2.50 (dd, *J*=5.1, 3.1 Hz, 1H), 1.75 (ddd, *J*=14.4, 8.9, 3.7 Hz, 1H), 1.47 (ddd, *J*=14.3, 7.1, 3.6 Hz, 1H), 1.33 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.0, 78.1, 68.9, 65.2, 49.6, 47.0, 35.3, 26.3, 24.9.

4.3. Synthesis of epoxide 8 from 2

MsCl (0.15 mL, 2.0 mmol) was added dropwise to a solution of **2** (202 mg, 1.0 mmol) in pyridine (0.5 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred at the same temperature for 2 h. Ice-cold water (5.0 mL) was added. The white precipitates formed (crude **6**) were collected by filtration and immediately dissolved in 1:1 CH_2Cl_2/MeOH (1.0 mL). The resultant solution of **6** was cooled to −5 °C (ice–NaCl bath). $NaBH_4$ (56 mg, 1.5 mmol) was added. The stirring was then continued at the ambient temperature for 12 h. Water (10 mL) was added. The mixture was extracted with Et_2O (3×20 mL). The combined ethereal phases were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (1:2 EtOAc/petroleum ether) on silica gel afforded **8** as a colorless oil (162 mg, 0.861 mmol, 86% from **2**). $[\alpha]_D^{26}$ +18.8 (*c* 1.0, $CHCl_3$) (lit.[6] $[\alpha]_D^{20}$ +9.6 (*c* 0.8, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10–3.88 (m, 4H), 3.20–3.08 (m, 1H), 2.80 (t, *J*=4.5 Hz, 1H), 2.54 (dd, *J*=5.0, 2.5 Hz, 1H), 2.45 (br s, OH), 2.10–1.95 (m, 1H), 1.55–1.40 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.0, 78.2, 70.1, 65.5, 50.2, 46.4, 35.7, 26.4, 25.0.

4.4. TBS protection of 2 (9)

To a solution of **2** (242 mg, 1.198 mmol) in dry CH_2Cl_2 (5.0 mL) stirred in an ice-water bath were added in turn Et_3N (0.42 mL, 2.995 mmol), TBSCl (460 mg, 3.056 mmol), and DMAP (20 mg, 0.164 mmol). The mixture was stirred at ambient temperature overnight. Water (5 mL) was added. The mixture was extracted with EOAc (2×20 mL). The combined organic phases were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (1:12 EtOAc/PE) on silica gel afforded **9** as a sticky yellowish oil (341 mg, 1.078 mmol, 90%). $[\alpha]_D^{24}$ −4.3 (*c* 4.85, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.45 (dd, *J*=9.8, 8.3 Hz, 1H), 4.19 (dt, *J*=9.3, 6.4 Hz, 1H), 4.14–4.03 (m, 2H), 3.89 (dd, *J*=11.8, 7.7 Hz, 1H), 2.62 (ddd, *J*=13.9, 8.2, 5.8 Hz, 1H), 2.12–1.97 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 109.9, 77.3, 77.1, 68.6, 66.7, 35.1, 26.6, 25.5, 24.9, 18.1, −4.8, −5.4; FTIR (film): 2954, 2932, 2858, 2887, 1794, 1473, 1373, 1382, 1259, 1154, 1064, 1007, 840, 781 cm^{-1}; ESIMS *m*/*z* 339.0 ($[M+Na]^+$). ESIHRMS calcd for $C_{15}H_{28}O_5SiNa$ ($[M+Na]^+$): 339.1598; found: 339.1602.

4.5. Synthesis of 10 from 9

DIBAL-H (1.0 M, in cyclohexane, 1.2 mL, 1.2 mmol) was added to a solution of **9** (221 mg, 0.698 mmol) in dry CH_2Cl_2 (5.0 mL) stirred at −78 °C under N_2. The mixture was stirred at the same temperature until TLC showed completion of the reduction. A solution of $Ph_3P{=}CHCO_2Et$ (610 mg, 1.748 mmol) in dry CH_2Cl_2 (2.0 mL) was introduced dropwise. The mixture was stirred at ambient temperature overnight. Aq satd potassium sodium tartrate (5.0 mL) was added. The mixture was stirred for 2 h before being extracted with EtOAc (2×20 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (1:8 EtOAc/petroleum ether) on silica gel gave **10** as a sticky yellowish oil (170 mg, 0.447 mmol, 64% from **9**). $[\alpha]_D^{26}$ −17.2 (*c* 1.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.33 (dd, *J*=11.7, 7.8 Hz, 1H), 5.74 (dd, *J*=11.7, 1.5 Hz, 1H), 5.65–5.57 (m, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 4.05–3.85 (m, 4H), 3.29 (br s, OH), 1.92 (ddd, *J*=14.3, 6.7, 2.1 Hz, 1H), 1.63 (ddd, *J*=13.9, 10.2, 3.5 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 152.9, 118.3, 109.1, 78.9, 69.2, 67.8, 66.0, 60.4, 40.0, 26.6, 25.8 (3C's), 25.4, 18.0, 14.2, −4.7, −5.1; FTIR (film): 3504, 2930, 2857, 1721, 1648, 1464, 1256, 1190, 1066, 837, 779 cm^{-1}; ESIMS *m*/*z* 411.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{19}H_{36}O_6SiNa$ ($[M+Na]^+$): 411.2173; found: 411.2170.

4.6. Synthesis of 11 from 2

$NaBH_4$ (56 mg, 1.5 mmol) was added in portion to a solution of **2** (841 mg, 4.16 mmol) in EtOH (14 mL) stirred at 0 °C. The mixture was stirred at ambient temperature overnight. Aq satd NaCl (5 mL) was added. The mixture was concentrated on a rotary evaporator. The residue was taken into MeOH, filtered (to remove the insolubles), and concentrated to give crude **3** as a white wax. A portion of this wax (177 mg, 0.86 mmol) was dissolved in MeOH (8.4 mL). To this solution was added a solution of $NaIO_4$ (277 mg, 1.29 mmol) in water (1.6 mL). The resultant milky suspension was stirred at ambient temperature for 2 h. Most of the MeOH was removed by rotary evaporation. The residue was partitioned between aq satd NH_4Cl (5 mL) and CH_2Cl_2 (20 mL). The phases were separated. The aqueous layer was back-extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent left a yellowish sticky oil (crude aldehyde, 117 mg, 0.73 mmol), which was dissolved in CH_2Cl_2 (3 mL) and treated with $Ph_3P{=}CHCO_2Et$ (509 mg, 1.46 mmol). The resultant clear bright yellow solution was stirred at ambient temperature overnight. The residue was partitioned between water (5 mL) and CH_2Cl_2 (20 mL). The phases were separated. The aqueous layer was back-extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:3 EtOAc/PE) on silica gel gave **11** as a yellowish sticky oil (164 mg, 0.671 mmol, 78% from **2**). $[\alpha]_D^{23}$ +4.6 (*c* 1.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (dt, *J*=15.6, 7.3 Hz, 1H), 5.94 (d, *J*=15.6 Hz, 1H), 4.16 (q, *J*=7.1 Hz, 2H), 4.05–3.95 (m, 2H), 3.93–3.86 (m, 1H),

3.85–3.75 (m, 1H), 2.50–2.40 (m, 1H), 2.39–2.24 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.25 (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 144.4, 124.1, 109.3, 78.1, 70.4, 65.3, 60.4, 36.0, 26.5, 25.2, 14.2; FTIR (film): 3468, 2986, 2932, 1720, 1655, 1460, 1372, 1063, 982, 850, 716 cm^{-1}; ESIMS m/z 267.2 ([M+Na]$^+$). ESIHRMS calcd for $C_{12}H_{20}O_5Na$ ([M+Na]$^+$): 267.1203; found: 267.1205.

4.7. Conversion of 8 to 15

A solution of **8** (1.112 g, 5.91 mmol), Et_3N (3.3 mL, 23.64 mmol), DMAP (219 mg, 1.77 mmol), and TBSCl (1.153 g, 7.69 mmol) in dry DMF (15 mL) was stirred at ambient temperature for 2 days before being diluted with water and extracted with Et_2O three times. The combined organic layers were washed in turn with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (20:1 PE/EtOAc) on silica gel gave **15** as a colorless oil (1.626 g, 5.38 mmol, 91%). $[\alpha]_D^{25}$ +35.2 (c 2.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14–4.03 (m, 2H), 3.92–3.84 (m, 2H), 3.13 (m, 1H), 2.77 (t, J=4.5 Hz, 1H), 2.48 (dd, J=5.0, 2.9 Hz, 1H), 1.86–1.72 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.09 (d, J=3.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.1, 78.4, 71.0, 66.7, 48.7, 46.8, 38.1, 26.7, 25.7, 25.3, 17.9, −4.3, −4.6; FTIR (film): 2955, 2930, 2858, 1265, 1075, 838, 777 cm^{-1}; ESIMS m/z 325.0 ([M+Na]$^+$). ESIHRMS calcd for $C_{15}H_{30}SiO_4Na$ ([M+Na]$^+$): 325.1805; found: 325.1809.

4.8. Conversion of 15 to 16

n-BuLi (1.6 M solution in hexanes, 6.6 mL, 10.59 mmol) was added to a solution of 1,3-dithiane (1.273 g, 10.59 mmol) in dry THF (15 mL) stirred at −78 °C under argon. After completion of the addition, the bath temperature was allowed to rise to 0 °C and kept at that temperature for 2 h before being re-cooled to −20 °C. A solution of **15** (1.153 g, 7.69 mmol) in dry HMPA (1.83 mL) and dry THF (15 mL) was added via a syringe to the above dithiane anion solution. The mixture was stirred at −20 °C for 3 h. Aq satd NH_4Cl was added, followed by Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined ethereal phases were washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (5:1 PE/EtOAc) on silica gel gave **16** as a colorless oil (2.943 g, 6.96 mmol, 91%). $[\alpha]_D^{25}$ +5.1 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (m, 1H), 4.06 (t, J=7.2 Hz, 1H), 3.96–4.02 (m, 1H), 3.86–3.95 (m, 2H), 2.91–2.77 (m, 4H), 2.09–2.30 (m, 1H), 1.85–1.95 (m, 2H), 1.80–1.85 (m, 1H), 1.70–1.80 (m, 1H), 1.45–1.55 (m, 1H), 1.50 (s, 3H), 1.34 (s, 3H), 0.86 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 109.1, 78.7, 69.5, 68.3, 65.4, 43.7, 43.1, 39.3, 30.4, 30.3, 26.6, 25.9, 25.8 (3C's), 25.3, 17.9, −4.3, −4.5; FTIR (film): 3476, 2931, 2856, 1472, 1423, 1370, 1252, 1068 cm^{-1}; ESIMS m/z 445.1 ([M+Na]$^+$). ESIHRMS calcd for $C_{19}H_{38}O_4S_2SiNa$ ([M+Na]$^+$): 445.1873; found: 445.1867.

4.9. Conversion of 16 to 18a and 18b

A solution of **16** (108 mg, 0.26 mmol) in dry THF (0.5 mL) was added to a suspension of NaH (60% suspension in mineral oil, 61 mg, 1.53 mmol, washed with hexanes prior to use in the reaction flask with all washings removed using a pipette) in dry THF (2 mL) stirred at −10 °C. The mixture was stirred at the same temperature for 30 min. BnBr (182 μL, 1.53 mmol) was introduced slowly. The stirring was continued at ambient temperature for 8 h before the excess hydride was destroyed by addition of a drop of MeOH. The insoluble substance was filtered off. The filtrate was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O. The combined organic layers were washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (30:1 PE/EtOAc) on silica gel afforded an inseparable mixture of **17a** and **17b** as a colorless oil (110 mg, 0.23 mmol, 84%).

A portion of the above mentioned mixture of **17a**/**17b** (2.149 g, 4.19 mmol) was dissolved in CH_2Cl_2 (140 mL) to which an aqueous solution of trifluoroacetic acid (0.5 g/mL, 4.84 mL) was added. The mixture was stirred at ambient temperature until TLC showed completion of the reaction. The mixture was partitioned between water and EtOAc. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (3:1 PE/EtOAc) afforded **18a** (427 mg, 0.90 mmol, 22% from **17**) and **18b** (1.219 g, 2.58 mmol, 62% from **17**) as colorless oils.

Data for **18a**: $[\alpha]_D^{26}$ 33.6 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 4.61 (d, J=10.8 Hz, 1H), 4.52 (d, J=10.8 Hz, 1H), 4.07 (t, J=6.9 Hz, 1H), 4.00–3.97 (m, 1H), 3.86–3.80 (m, 1H), 3.72–3.68 (m, 1H), 3.63–3.52 (m, 2H), 3.27–3.25 (br s, 1H), 2.86–2.82 (m, 4H), 2.23–2.21 (m, 1H), 2.11–1.85 (m, 5H), 1.77–1.69 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 137.6, 128.5 (2C's), 128.2 (2C's), 128.0, 73.5, 72.5, 71.5, 70.7, 63.6, 43.6, 40.2, 38.7, 30.53, 30.49, 25.81, 25.77 (3C's), 17.9, −4.2, −4.8; FTIR (film): 3429, 2928, 2897, 2855, 1471, 1423, 1388, 1361, 1255, 1082 cm^{-1}; ESIMS: m/z 495.3 ([M+Na]$^+$). ESIHRMS calcd for $C_{23}H_{40}O_4S_2SiNa$ ([M+Na]$^+$): 495.2030; found: 495.2027.

Data for **18b**: $[\alpha]_D^{25}$ −7.23 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.26 (m, 5H), 4.62 (d, J=11.4 Hz, 1H), 4.55 (d, J=11.4 Hz, 1H), 4.23 (dt, J=11.0, 6.2 Hz, 1H), 4.07 (t, J=7.4 Hz, 1H), 3.72–3.67 (m, 4H), 3.18 (br s, 1H), 2.87–2.79 (m, 4H), 2.30 (br s, 1H), 2.14–2.09 (m, 1H), 1.95–1.85 (m, 4H), 1.79–1.69 (m, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.6, 128.5 (2C's), 128.2 (2C's), 127.9, 77.7, 72.9, 72.5, 66.4, 63.4, 43.9, 42.3, 38.5, 30.4, 30.1, 25.9, 25.8 (3C's), 18.0, −4.3, −4.6; FTIR (film): 3446, 2951, 2928, 2897, 2855, 1471, 1458, 1422, 1388, 1361, 1257, 1077 cm^{-1}; ESIMS: m/z 495.2 ([M+Na]$^+$). ESIHRMS calcd for $C_{23}H_{40}O_4S_2SiNa$ ([M+Na]$^+$): 495.2030; found: 495.2026.

4.10. Conversion of 8 to 19

A solution of **8** (28.0 mg, 0.148 mmol) in dry DMF (0.2 ml) was added to a suspension of NaH (60% suspension in mineral oil, 5.0 mg, 0.11 mmol, washed with hexanes prior to use in the reaction flask with all washings removed using a pipette) in dry DMF (0.2 mL) stirred at −10 °C. After completion of the addition, the stirring was continued at ambient temperature for 30 min before benzyl bromide (20 μL, 0.17 mmol) was added dropwise. The mixture was stirred at ambient temperature for 8 h. The reaction mixture was partitioned between water and Et_2O. The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (13:1 PE/EtOAc) on silica gel gave **19** as a colorless oil (36 mg, 0.129 mmol, 87%). $[\alpha]_D^{25}$ +27.8 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.28 (m, 5H), 4.65 (d, J=11.4 Hz, 1H), 4.60 (d, J=11.4 Hz, 1H), 4.20–4.13 (m, 1H), 4.08 (dd, J=6.4, 5.9 Hz, 1H), 3.90 (dd, J=6.4, 5.9 Hz, 1H), 3.67–3.61 (m, 1H), 3.10–3.09 (m, 1H), 2.73 (t, J=5.1 Hz, 1H), 2.47 (dd, J=5.1, 2.8 Hz, 1H), 1.92–1.79 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.9, 128.2, 127.7 (2C's), 127.6 (2C's), 109.0, 77.5, 77.4, 72.1, 66.5, 49.2, 46.7, 34.3, 26.5, 25.1; FTIR (film): 2987, 2881, 1455, 1380, 1371, 1258, 1213, 1074 cm^{-1}; ESIMS m/z 301.2 ([M+Na]$^+$). EIHRMS calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1510.

4.11. Conversion of 19 to 20

n-BuLi (1.6 M solution in hexanes, 213 μL, 0.34 mmol) was slowly added to a solution of 1,3-dithiane (41 mg, 0.34 mmol) in dry THF

(0.6 mL) stirred at −78 °C under argon. After completion of the addition, the cooling bath was allowed to warm up to 0 °C. The mixture was stirred at that temperature for 2 h before the bath was re-cooled to −78 °C. A solution of **19** (55 mg, 0.198 mmol) in dry HMPA (59 μL) and dry THF (0.4 mL) was then introduced. The mixture was stirred at −20 °C for 3 h. Aq satd NH_4Cl was added, followed by Et_2O. The phases were separated. The aqueous phase was back-extracted with Et_2O. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5:1 PE/EtOAc) on silica gel afforded **20** as a white solid (50 mg, 0.125 mmol, 63%). Mp 89–90 °C. $[\alpha]_D^{24}$ −12.0 (*c* 3.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 5H), 4.68 (d, *J*=11.2 Hz, 1H), 4.52 (d, *J*=11.2 Hz, 1H), 4.21–4.16 (m, 1H), 4.12–4.06 (m, 1H), 3.99–3.94 (m, 1H), 3.80 (t, *J*=7.0 Hz, 1H), 3.75–3.70 (m, 1H), 3.30 (s, 1H), 2.81–2.68 (m, 4H), 2.02–1.97 (m, 1H), 1.82–1.71 (m, 3H), 1.59 (m, 2H), 1.35 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 137.4, 128.2, 127.6 (2C's), 127.5 (2C's), 108.9, 77.8, 77.6, 72.6, 66.1, 65.5, 43.4, 42.7, 38.2, 30.0, 29.7, 26.1, 25.6, 24.8; FTIR (film): 3485, 2984, 2899, 1497, 1422, 1370, 1154, 1093, 845 cm^{-1}; ESIMS: *m*/*z* 421.2 ($[M+Na]^+$). ESIHRMS calcd for $C_{20}H_{30}O_4S_2Na$ ($[M+Na]^+$): 421.1478; found: 421.1486.

4.12. Conversion of 20 to 17b

2,6-Lutidine (20 μL, 0.176 mmol) was slowly added to a solution of **20** (14 mg, 0.035 mmol) in dry CH_2Cl_2 (0.35 mL) stirred at 0 °C under argon, followed by TBSOTf (24 μL, 0.105 mmol, dropwise). The mixture was stirred at 0 °C for 2 h. Water was added, followed by Et_2O. The phases were separated and the aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography (14:1 PE/EtOAc) afforded **17b** (18 mg, 0.035 mmol, 100%). $[\alpha]_D^{24}$ −23.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 4.69 (d, *J*=11.2 Hz, 1H), 4.60 (d, *J*=11.2 Hz, 1H), 4.23–4.20 (m, 1H), 4.15–4.10 (m, 2H), 4.04–3.99 (m, 1H), 3.88–3.83 (m, 1H), 3.68–3.65 (m, 1H), 2.87–2.75 (m, 4H), 2.12–2.07 (m, 1H), 2.03–1.92 (m, 1H), 1.89–1.80 (m, 2H), 1.75–1.70 (m, 2H), 1.61 (s, 3H), 1.42 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 138.3, 128.3 (2C's), 127.9 (2C's), 127.6, 109.1, 78.1, 75.9, 73.1, 66.0, 65.8, 43.9, 42.5, 39.5, 30.0, 29.9, 26.5, 26.0, 25.8 (3C's), 25.3, 18.0, −4.4, −4.7; FTIR (film): 2930, 2856, 1472, 1380, 1257, 1066, 837 cm^{-1}; ESIMS: *m*/*z* 535.4 ($[M+Na]^+$). ESIHRMS calcd for $C_{26}H_{44}O_4S_2SiNa$ ($[M+Na]^+$): 535.2342; found: 535.2342.

4.13. Conversion of 17b to 18b

F_3CCO_2H (0.5 g/mL aqueous solution, 40 μL, 0.175 mmol) was added dropwise to a solution of **17b** (18 mg, 0.035 mmol) in CH_2Cl_2 (1 mL) stirred at ambient temperature until TLC showed completion of the reaction. The mixture was partitioned between water and EtOAc. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (3:1 PE/EtOAc) afforded **18b** as a colorless oil (13 mg, 0.0275 mmol, 79%). Data for **18b**: given in Section 4.9.

4.14. Conversion of 18b to 21

Powdered Na_2CO_3 (145 mg, 1.372 mmol) was added to a solution of **18b** (162 mg, 0.343 mmol) in anhydrous CH_2Cl_2 (1.0 mL) stirred at 0 °C, followed by $Pb(OAc)_4$ (198 mg, 0.446 mmol). The mixture was stirred at 0 °C for 1 h before being filtered through a short pad of silica gel. The filtrate was partitioned between aq satd $NaHCO_3$ and Et_2O. The aqueous layer was back-extracted with Et_2O. The combined organic phases were washed in turn with water and brine, and finally dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left the crude aldehyde as a colorless oil, which was used directly in the next step.

n-BuLi (2.5 M solution in hexanes, 0.55 mL, 1.37 mmol) was added via a syringe to a solution of *n*-$BuPPh_3Br$ (546 mg, 1.37 mmol) in dry THF (15 mL) stirred at −78 °C under argon. After completion of the addition, the bath temperature was allowed to rise to −20 °C and kept at that temperature for 30 min before being re-cooled to −78 °C. A solution of the above-obtained crude aldehyde in dry THF (1.5 mL) was then introduced. The mixture was stirred while the bath was allowed to warm slowly to the ambient temperature. The stirring was then continued at ambient temperature overnight. The mixture was partitioned between aq satd NH_4Cl and Et_2O. The phases were separated. The organic layer was washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (60:1 PE/EtOAc) on silica gel afforded **21** as a colorless oil (95 mg, 0.198 mmol, 57% from **18b**). $[\alpha]_D^{25}$ −32.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 5.57 (dt, *J*=11.0, 7.5 Hz, 1H), 5.33 (dd, *J*=11.0, 9.3 Hz, 1H), 4.52 (d, *J*=11.7 Hz, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 4.28–4.14 (m, 3H), 2.88–2.76 (m, 4H), 2.08–1.84 (m, 7H), 1.59–1.53 (m, 1H), 1.40 (dt, *J*=14.7, 7.4 Hz, 1H), 0.91 (t, *J*=7.3 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 133.0, 130.7, 128.3 (2C's), 127.8 (2C's), 127.3, 71.0, 69.9, 66.2, 44.1, 43.7, 42.4, 30.6, 30.0, 29.9, 26.1, 25.9 (3C's), 22.9, 18.0, 13.8, −4.3, −4.6; FTIR (film): 2955, 2897, 1471, 1462, 1423, 1256, 1082 cm^{-1}; ESIMS *m*/*z* 503.4 ($[M+Na]^+$). ESIHRMS calcd for $C_{26}H_{44}SiO_2S_2Na$ ($[M+Na]^+$): 503.2444; found: 429.2448.

4.15. Conversion of 21 to 22

Powdered $NaHCO_3$ (80 mg, 0.952 mmol) was added to a solution of **21** (54 mg, 0.113 mmol) in 5:1 (v/v) acetone/H_2O (1.2 mL) stirred at 0 °C, followed by solid I_2 (229 mg, 0.902 mmol, in small portions). The mixture was stirred at ambient temperature overnight before being quenched by addition of aq satd $Na_2S_2O_3$ (2 mL). The mixture was extracted with Et_2O (3×15 mL). The combined organic layers were washed in turn with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (60:1 PE/EtOAc) on silica gel gave aldehyde **22** as a colorless oil (40 mg, 0.102 mmol, 90%). $[\alpha]_D^{26}$ −44.8 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73–9.71 (m, 1H), 7.34–7.26 (m, 5H), 5.59 (dt, *J*=10.7, 7.4 Hz, 1H), 5.34 (dd, *J*=11.7, 9.2 Hz, 1H), 4.56 (d, *J*=12.0 Hz, 1H), 4.45–4.35 (m, 1H), 4.26 (d, *J*=12.0 Hz, 1H), 4.28–4.20 (m, 1H), 2.52–2.47 (m, 2H), 2.05–1.93 (m, 3H), 1.63–1.59 (m, 1H), 1.44–1.37 (m, 2H), 0.92 (t, *J*=7.2 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 202.4, 138.6, 133.4, 130.3, 128.3 (2C's), 127.7 (2C's), 127.5, 70.5, 69.7, 65.5, 50.3, 43.5, 29.8, 25.7 (3C's), 22.8, 17.9, 13.8, −4.4, −4.8; FTIR (film): 2957, 2896, 1728, 1455, 1256, 1090 cm^{-1}; ESIMS *m*/*z* 413.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{23}H_{38}SiO_3Na$ ($[M+Na]^+$): 413.2482; found: 413.2489.

4.16. Conversion of 22 to 23

A solution of NaH_2PO_4 (584 mg, 4.867 mmol) in water (5.8 mL) was added to a solution of aldehyde **22** (171 mg, 0.438 mmol) and 2-methyl-2-butene (1 mL) in *t*-BuOH (11.7 mL) stirred at ambient temperature, followed by a solution of $NaClO_2$ (123 mg, 1.36 mmol, dropwise) in water (4.7 mL). After completion of the addition, the stirring was continued at ambient temperature until TLC showed completion of the oxidation (ca. 2 h). The mixture was acidified to pH 3 with 1 N HCl and extracted with Et_2O. The ethereal phase was washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude residue was

chromatographed on silica gel (5:1 PE/EtOAc) to afford **23** as a colorless oil (165 mg, 0.405 mmol, 93%). $[\alpha]_D^{26}$ −34.7 (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 5.61 (dt, *J*=10.8, 7.5 Hz, 1H), 5.34 (dd, *J*=11.8, 9.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.34–4.28 (m, 2H), 4.30 (d, *J*=12.0 Hz, 1H), 2.57 (dd, *J*=15.0, 4.9 Hz, 1H), 2.46 (dd, *J*=15.0, 4.9 Hz, 1H), 2.06–1.90 (m, 3H), 1.68–1.59 (m, 1H), 1.46–1.34 (m, 2H), 0.92 (t, *J*=7.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.7, 138.5, 133.5, 130.2, 128.4 (2C's), 127.9 (2C's), 127.5, 70.7, 69.8, 66.8, 42.9, 41.7, 29.8, 25.8 (3C's), 22.8, 17.9, 13.8, −4.5, −4.9; FTIR (film): 2925, 2854, 1712, 1463, 1256, 1087 cm^{-1}; ESIMS *m*/*z* 429.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{23}H_{38}SiO_4Na$ ($[M+Na]^+$): 429.2432; found: 429.2429.

4.17. Conversion of 23 to 12

A mixture of **23** (36 mg, 0.089 mmol) and 10% Pd–C (75 mg) in EtOAc (7 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed completion of the reaction. The solids were filtered off (washing with EtOAc). The combined filtrate/washings were concentrated on a rotary evaporator. The residue was directly dissolved in THF (2 mL) to which 1 N HCl (2.0 mL) was added. The mixture was stirred at ambient temperature for 12 h. Aq satd $NaHCO_3$ (5.0 mL) was added. The mixture was extracted with Et_2O three times. The combined organic phases were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:2 EtOAc/PE) afforded the known lactone **12** as a colorless oil (15 mg, 0.080 mmol, 90% from **23**). $[\alpha]_D^{25}$ +36.6 (*c* 0.53, $CHCl_3$) (lit.[12b] $[\alpha]_D^{25}$ +18 (*c* 0.9, $CHCl_3$); lit.[12e] $[\alpha]_D^{20}$ +20.3 (*c* 0.5, $CHCl_3$); lit.[13] $[\alpha]_D^{26}$ +37.6 (*c* 0.31, $CHCl_3$)). ^1H NMR (400 MHz, CDCl3): δ 4.65–4.70 (m, 1H), 4.34–4.39 (m, 1H), 2.72 (dd, *J*=7.4, 5.2 Hz, 1H), 2.61 (ddd, *J*=17.4, 3.9, 1.5 Hz, 1H), 2.30 (br s, 1H, –OH), 1.92–1.98 (m, 1H), 1.68–1.76 (m, 2H), 1.54–1.61 (m, 1H), 1.34–1.50 (m, 2H), 1.25–1.33 (m, 4H), 0.89 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 75.9, 62.7, 38.6, 35.9, 35.4, 31.5, 24.5, 22.5, 13.9; FTIR (film): 3435, 2925, 2855, 1717, 1458, 1257, 1068, 1037 cm^{-1}; EIMS *m*/*z* (%) 186 (M^+, 0.05), 115 (56), 97 (73), 89 (18), 73 (68); EIHRMS calcd for $C_{10}H_{16}O_2$ [$(M-H_2O)^+$]: 168.1150; found: 168.1154.

4.18. Conversion of 22 to 26

A solution of *p*-TsOH in MeOH (1 mg/mL, 0.95 mL) was added to a solution of **22** (270 mg, 0.691 mmol) in $HC(OMe)_3$ (2.73 mL) stirred at ambient temperature. After completion of the addition, the stirring was continued at the same temperature for 1 h. Aq satd $NaHCO_3$ was introduced. The resulting mixture was extracted with Et_2O three times. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (30:1 PE/EtOAc) on silica gel afforded **26** as a colorless oil (301 mg, 0.691 mmol, 100%). $[\alpha]_D^{24}$ −34.4 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.25 (m, 5H), 5.58 (dt, *J*=11.3, 6.8 Hz, 1H), 5.33 (dd, *J*=11.3, 9.3 Hz, 1H), 4.55 (t, *J*=3.1 Hz, 1H), 4.54 (d, *J*=11.2 Hz, 1H), 4.29 (d, *J*=11.2 Hz, 1H), 4.28–4.25 (m, 1H), 4.06–4.00 (m, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 2.05–2.00 (m, 2H), 1.90–1.84 (m, 2H), 1.71 (ddd, *J*=13.8, 8.5, 4.3 Hz, 1H), 1.57 (ddd, *J*=13.8, 8.5, 3.8 Hz, 1H), 1.40 (m, 2H), 0.91 (t, *J*=7.2 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 132.9, 130.9, 128.2 (2C's), 127.7 (2C's), 127.3, 102.2, 71.2, 69.9, 66.4, 52.7, 52.6, 43.8, 40.0, 29.9, 25.9 (3C's), 22.9, 18.0, 13.8, −4.2, −4.7; FTIR (film): 3470, 2930, 2858, 1471, 1387, 1256, 1128 cm^{-1}; ESIMS *m*/*z* 459.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{25}H_{44}SiO_4Na$ ($[M+Na]^+$): 459.2901; found: 459.2910.

4.19. Conversion of 26 to 27

A mixture of the ester **26** (650 mg, 1.49 mmol) and 10% Pd–C (250 mg) in EtOAc (7 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed completion of the reaction. The solids were then filtered off (washing with EtOAc). The combined filtrate/washings were concentrated on a rotary evaporator to afford **27** as a colorless oil (431 mg, 1.24 mmol, 83%). $[\alpha]_D^{23}$ +8.98 (*c* 5.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.45 (t, *J*=5.6 Hz, 1H), 3.98 (t, *J*=6.4 Hz, 1H), 3.68 (s, 1H), 3.27 (s, 6H), 2.72 (br s, 1H, –OH), 1.78 (t, *J*=5.9 Hz, 2H), 1.60–1.53 (m, 2H), 1.42–1.26 (m, 8H), 0.86–0.90 (m, 12H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.0, 69.9, 68.8, 52.8, 52.6, 44.1, 40.6, 37.9, 31.9, 25.8 (3C's), 25.1, 22.6, 17.8, 14.0, −4.46, −4.57; FTIR (film): 3470, 2930, 2858, 1471, 1387, 1256, 1128 cm^{-1}; ESIMS *m*/*z* 371.2 ($[M+Na]^+$). ESIHRMS calcd for $C_{18}H_{40}SiO_4Na$ ($[M+Na]^+$): 371.2588; found: 371.25897.

4.20. Coupling of 23 with 27 leading to 28

2,4,6-Trichlorobenzoyl chloride (141 μL, 0.902 mmol) was slowly added to a solution of alcohol **27** (141 mg, 0.404 mmol), acid **23** (164 mg, 0.404 mmol), DMAP (235 mg, 1.92 mmol), and powdered/activated 4 Å molecular sieves (200 mg) in dry CH_2Cl_2 (14 mL) stirred at ambient temperature under argon. After completion of the addition, the stirring was continued at ambient temperature until TLC showed completion of the reaction (ca. 20 h). The mixture was diluted with Et_2O, washed in turn with aq satd $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (40:1 PE/EtOAc) on silica gel afforded **28** as a colorless oil (254 mg, 0.345 mmol, 85%). $[\alpha]_D^{28}$ −19.5 (*c* 2.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.23 (m, 5H), 5.58 (dt, *J*=10.8, 7.6 Hz, 1H), 5.33 (dd, *J*=10.8, 9.2 Hz, 1H), 4.93–4.95 (m, 1H), 4.53 (d, *J*=12.3 Hz, 1H), 4.52 (t, *J*=6.0 Hz, 1H), 4.30 (d, *J*=12.3 Hz, 1H), 4.29–4.35 (m, 2H), 3.83 (m, 1H), 3.28 (s, 6H), 2.47 (dd, *J*=10.8, 8.4 Hz, 1H), 2.20 (dd, *J*=10.8, 8.4 Hz, 1H), 2.06–1.87 (m, 3H), 1.87–1.65 (m, 5H), 1.56–1.52 (m, 2H), 1.40 (m, 2H), 1.34–1.20 (m, 6H), 0.91 (t, *J*=7.3 Hz, 6H), 0.87 (m, 18H), 0.06 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 138.9, 133.3, 130.6, 128.2 (2C's), 127.7 (2C's), 127.3, 101.6, 71.3, 70.8, 69.6, 66.6, 66.2, 52.5, 52.1, 43.0, 42.1, 41.8, 39.5, 34.6, 31.7, 29.9, 25.8 (6C's), 24.8, 22.9, 22.5, 18.0 (2C's), 14.0, 13.8, −4.4, −4.5, −4.6, −4.7; FTIR (film): 2929, 2857, 1735, 1471, 1463, 1388, 1257, 1083 cm^{-1}; ESIMS *m*/*z* 759.6 ($[M+Na]^+$). ESIHRMS calcd for $C_{41}H_{76}Si_2O_7Na$ ($[M+Na]^+$): 759.5022; found: 759.5015.

4.21. Conversion of 28 to 29

2,6-Lutidine (107 μL, 0.921 mmol) was added to a solution of **28** (113 mg, 0.154 mmol) in CH_2Cl_2 (1.5 mL) stirred at 0 °C under argon, followed by TMSOTf (117 μL, 0.616 mmol). The mixture was stirred at the same temperature for 3 h before H_2O (25 μL) was introduced. The stirring was continued for another 45 min. The mixture was extracted with Et_2O, washed in turn with aq satd $CuSO_4$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator gave the crude intermediate aldehyde, which was directly dissolved in *t*-BuOH (4 mL). To this solution were added in turn a solution of NaH_2PO_4 (200 mg, 1.67 mmol) in water (2.0 mL), 2-methyl-2-butene (0.36 mL), and a solution of $NaClO_2$ (43 mg, 0.475 mmol, dropwise) in water (1.7 mL). The mixture was then stirred at ambient temperature until TLC showed completion of the reaction (ca. 5 h). The mixture was acidified to pH 3 with 1 N HCl, extracted twice with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent by rotary evaporation, the crude residue was chromatographed on silica gel (1:60 MeOH/CH_2Cl_2) to afford **29** as a colorless oil (105 mg, 0.148 mmol, 96% from **28**). $[\alpha]_D^{26}$ −22.3 (*c* 1.7, $CHCl_3$). ^1H NMR

(400 MHz, $CDCl_3$): δ 7.30–7.26 (m, 5H), 5.59 (dt, J=10.8, 7.6 Hz, 1H), 5.33 (dd, J=10.8, 9.2 Hz, 1H), 4.95–4.92 (m, 1H), 4.52 (t, J=6.0 Hz, 1H), 4.54 (d, J=12 Hz, 1H), 4.34–4.27 (m, 1H), 4.30 (d, J=12 Hz, 1H), 4.16–4.13 (m, 1H), 2.58–2.38 (m, 4H), 2.06–1.76 (m, 5H), 1.68–1.61 (m, 1H), 1.52–1.49 (m, 2H), 1.39–1.35 (m, 2H), 1.28–1.26 (m, 6H), 0.91 (t, J=7.6 Hz, 6H), 0.85 (s, 9H), 0.82 (s, 9H), 0.06 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.2, 138.8, 133.4, 130.6, 128.2 (2C's), 127.7 (2C's), 127.3, 71.0, 70.8, 69.7, 66.6, 66.4, 43.0, 42.0, 41.6, 41.5, 34.5, 31.7, 29.9, 25.8 (6C's), 24.8, 22.9, 22.5, 18.0, 17.9, 14.0, 13.8, −4.56 (2C's), −4.6, −4.6, −4.9; FTIR (film): 2956, 1735, 1713, 1463, 1256, 1086 cm^{-1}; ESIMS: m/z 729.4 ($[M+Na]^+$). ESIHRMS calcd for $C_{39}H_{70}Si_2O_7Na$ ($[M+Na]^+$): 729.4552; found: 729.4563.

4.22. Conversion of 29 to 30

A mixture of **29** (27 mg, 0.038 mmol) and 10% Pd–C (250 mg) in EtOAc (0.4 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed completion of the reaction. The solids were filtered off (washing with EtOAc). The combined filtrate/washings were evaporated under reduced pressure to afford **30** as a colorless oil (22 mg, 0.036 mmol, 95%). $[\alpha]_D^{27}$ +1.89 (c 1.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.97–4.95 (m, 1H), 4.32–4.31 (m, 1H), 4.17–4.14 (m, 1H), 3.75–3.73 (m, 1H), 2.50–2.46 (m, 4H), 1.90–1.80 (m, 1H), 1.79–1.71 (m, 2H), 1.56–1.40 (m, 3H), 1.36–1.23 (m, 12H), 1.04–0.85 (m, 24H), 0.14–0.07 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.9, 170.8, 71.4, 70.3, 69.1, 66.4, 43.9, 43.3, 41.6, 41.5, 37.6, 34.5, 31.9, 31.6, 25.7 (3C's), 25.67 (3C's), 25.1, 24.8, 22.6, 22.5, 17.9, 17.8, 14.0, 13.9, −4.4, −4.6, −4.8, −4.9; FTIR (film): 3437, 2956, 1716, 1471, 1256, 1085 cm^{-1}; ESIMS: m/z 641.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{32}H_{66}Si_2O_7Na$ ($[M+Na]^+$): 641.4245; found: 641.4257.

4.23. Conversion of 30 to 31

A solution of MNBA (42 mg, 0.122 mmol), DMAP (47 mg, 0.483 mmol), and powdered/activated 4 Å molecular sieves (450 mg) in dry toluene (28 ml) was stirred at ambient temperature for 10 min. A solution of hydroxyl acid **30** (50 mg, 0.081 mmol) in dry toluene (12.5 mL) was added slowly (via a syringe driven by a syringe pump over 5 h). After completion of the addition, the stirring was continued at ambient temperature for 24 h. The mixture was diluted with Et_2O, washed in turn with aq satd $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (1:60 PE/EtOAc) on silica gel afforded dilactone **31** as a colorless oil (41 mg, 0.068 mmol, 84%). $[\alpha]_D^{25}$ −56.7 (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.77–4.70 (m, 2H), 4.40–4.34 (m, 2H), 2.63 (dd, J=13.6, 2.4 Hz, 2H), 2.40 (dd, J=13.6, 2.4 Hz, 2H), 1.95 (ddd, J=14.4, 10.1, 4.7 Hz, 2H), 1.76 (ddd, J=14.4, 8.2, 3.5 Hz, 2H), 1.71–1.67 (m, 2H), 1.52–1.46 (m, 2H), 1.31–1.26 (m, 12H), 0.91 (s, 18H), 0.87 (t, J=6.6 Hz, 6H), 0.13 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.4 (2C's), 72.3 (2C's), 66.5 (2C's), 45.5 (2C's), 42.4 (2C's), 34.2 (2C's), 31.6 (2C's), 25.8 (6C's), 24.6 (2C's), 22.5 (2C's), 18.0 (2C's), 13.9 (2C's), −4.69 (2C's), −4.73 (2C's); FTIR (film): 2956, 1744, 1463, 1281, 1252, 1085 cm^{-1}; ESIMS: m/z 623.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{32}H_{64}Si_2O_6Na$ ($[M+Na]^+$): 623.4134; found: 623.4141.

4.24. Conversion of 31 to verbalactone 13

HF·Py (Aldrich, containing ~70% HF and 30% Py, 0.36 mL) was added to a solution of **31** (28 mg, 0.047 mmol) in THF (1.0 mL) stirred at ambient temperature in a plastic (Nalgene) bottle. After completion of the addition, the stirring was continued for another 2 h. Aq satd $NaHCO_3$ was introduced, followed by EtOAc. The phases were separated. The aqueous phase was back-extracted with EtOAc. The combined organic layers were washed in turn with aq satd $CuSO_4$, aq satd $NaHCO_3$, water, and brine before being dried over anhydrous Na_2SO_4. After removal of the solvent by rotary evaporation, the crude residue was chromatographed on silica gel (9:2 PE/EtOAc) to afford natural verbalactone **13** as a colorless oil (15 mg, 0.040 mmol, 88%). $[\alpha]_D^{27}$ +8.7 (c 1.0, $CHCl_3$) (lit.[12a] $[\alpha]_D^{25}$ +7.3 (c 0.9, $CHCl_3$); lit.[12b] $[\alpha]_D^{25}$ +6.2 (c 0.9, $CHCl_3$); lit.[12e] $[\alpha]_D^{20}$ +8.5 (c 0.5, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$): δ 4.95–4.98 (m, 2H), 4.06–4.08 (m, 2H), 3.73 (br s, 2H, 2OH's), 2.67 (d, J=4.5 Hz, 4H), 2.08 (ddd, J=3.2, 10.2, 15.3 Hz, 2H), 1.97 (dt, J=15.3, 4.3 Hz, 2H), 1.48–1.61 (m, 4H), 1.50–1.59 (m, 12H), 0.89 (t, J=7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.9, 72.5, 64.5, 39.4, 38.2, 35.4, 31.7, 25.5, 22.5, 13.9; FTIR (film): 3448, 2956, 1736, 1466, 1281, 1117 cm^{-1}; ESIMS: m/z 395.0 ($[M+Na]^+$). ESIHRMS calcd for $C_{20}H_{36}O_6Na$ ($[M+Na]^+$): 395.2404; found: 395.2398.

4.25. Conversion of 28 to 32

A mixture of **28** (61 mg, 0.0083 mmol) and 10% Pd–C (84 mg) in EtOAc (0.6 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed completion of the reaction. The solids were filtered off (washing with EtOAc). The combined filtrate/washings were evaporated under reduced pressure to afford **32** as a colorless oil (47 mg, 0.072 mmol, 87%). $[\alpha]_D^{27}$ +0.16 (c 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 5.00–4.96 (m, 1H), 4.55–4.51 (dd, J=6.7, 4.5 Hz, 1H), 4.34–4.29 (m, 1H), 3.85–3.80 (m, 1H), 3.73 (m, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 3.0 (s, 1H), 2.58–2.46 (m, 2H), 1.84–1.47 (m, 8H), 1.42–1.35 (m, 2H), 1.29–1.26 (m, 12H), 0.89 (s, 24H), 0.13 (d, J=4.3 Hz, 6H), 0.06 (d, J=2.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.7, 101.6, 71.7, 69.3, 66.1, 52.6, 52.3, 44.0, 43.6, 41.9, 39.4, 37.7, 34.7, 31.9, 31.7, 25.8, 26.0–25.5 (6C's, not well-resolved), 25.1, 24.8, 22.6, 22.5, 18.0, 17.8, 14.1, 14.0, −4.3, −4.4, −4.7, −4.8; FTIR (film): 3501, 2956, 2930, 2858, 1734, 1471, 1387, 1363, 1313, 1257, 1082 cm^{-1}; ESIMS: m/z 671.5 ($[M+Na]^+$). ESIHRMS calcd for $C_{34}H_{72}Si_2O_7Na$ ($[M+Na]^+$): 671.4709; found: 671.4715.

4.26. Conversion of 32 to 33

2,4,6-Tichlorobenzoyl chloride (114 μL, 0.729 mmol) was added slowly to a solution of **32** (134 mg, 0.330 mmol), **23** (134 mg, 0.330 mmol), DMAP (189 mg, 1.55 mmol), and powdered/activated 4 Å molecular sieves (300 mg) in dry CH_2Cl_2 (11 mL) stirred at ambient temperature under argon. After completion of the addition, the stirring was continued at ambient temperature until TLC showed completion of the reaction (ca. 20 h). The mixture was diluted with Et_2O, washed in turn with aq satd $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (40:1 PE/EtOAc) on silica gel afforded **33** as a colorless oil (287 mg, 0.277 mmol, 84%). $[\alpha]_D^{20}$ −16.6 (c 1.14, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.47–7.39 (m, 5H), 5.79–5.70 (dt, J=11.1, 7.5 Hz, 1H), 5.47 (dd, J=11.1, 10.0 Hz, 1H), 5.14–5.04 (m, 2H), 4.67 (t, J=5.6 Hz, 1H), 4.58 (d, J=10.8 Hz, 1H), 4.37–4.25 (m, 2H), 4.32 (d, J=10.8 Hz, 1H), 4.14–4.11 (m, 1H), 3.84–3.80 (m, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.66–2.55 (m, 4H), 2.05–2.00 (m, 2H), 2.00–1.76 (m, 4H), 1.73–1.65 (m, 4H), 1.60–1.48 (m, 4H), 1.44–1.36 (m, 2H), 1.35–1.20 (m, 12H), 0.91 (t, J=7.8 Hz, 9H), 0.90–0.88 (m, 27H), 0.08–0.06 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.6, 138.8, 133.4, 130.5, 128.2 (2C's), 127.7 (2C's), 127.3, 101.5, 71.4, 71.2, 70.7, 69.6, 66.6, 66.2, 66.1, 52.5, 52.2, 43.0, 42.0 (2C's), 41.8, 41.3, 39.4, 34.6, 34.2, 31.8, 31.7, 29.9, 26.1–25.6 (9C's, not well-resolved), 24.8, 24.7, 22.9, 22.5 (2C's), 17.9 (3C's), 14.0 (2C's), 13.8, −4.4, −4.6 (2C's), −4.7 (2C's), −4.8; FTIR (film): 2928, 2857, 1736, 1472, 1387, 1258, 1074 cm^{-1}; ESIMS: m/z 1059.8 ($[M+Na]^+$). ESIHRMS calcd for $C_{57}H_{108}Si_3O_{10}Na$ ($[M+Na]^+$): 1059.7143; found: 1059.7160.

4.27. Conversion of 33 to 34

2,6-Lutidine (188 μL, 1.618 mmol) was added to a solution of **33** (269 mg, 0.259 mmol) in dry CH_2Cl_2 (3 mL) stirred at 0 °C under argon, followed by TMSOTf (179 μL, 0.942 mmol). After completion of the addition, the stirring was continued at the same temperature for 3 h. Then H_2O (44 μL) was added. The resulting mixture was stirred for another 45 min before being extracted with Et_2O, washed in turn with aq satd $CuSO_4$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left crude intermediate aldehyde as an oil, which was directly dissolved in *t*-BuOH (7.8 mL). To this solution were added in turn a solution of NaH_2PO_4 (335 mg, 2.79 mmol) in water (3.7 mL), 2-methyl-2-butene (0.7 mL), and (dropwise) a solution of $NaClO_2$ (74 mg, 0.817 mmol) in water (3.3 mL). The stirring was continued at ambient temperature until TLC showed completion of the reaction (ca. 5 h). The mixture was acidified to pH 3 with 1 N HCl, extracted twice with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent on a rotary evaporator, the crude residue was chromatographed on silica gel (1:60 MeOH/CH_2Cl_2) to afford **34** as a colorless oil (259 mg, 0.257 mmol, 99% from **35**). $[\alpha]_D^{25}$ −16.2 (*c* 1.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.24 (m, 5H), 5.60 (dt, *J*=11.0, 7.5 Hz, 1H), 5.33 (dd, *J*=11.1, 9.2 Hz, 1H), 5.00–4.92 (m, 2H), 4.55 (d, *J*=11.6 Hz, 1H), 4.33–4.26 (m, 2H), 4.31 (d, *J*=11.6 Hz, 1H), 4.16–4.11 (m, 2H), 2.57–2.39 (m, 6H), 1.81–1.77 (m, 7H), 1.69–1.64 (m, 1H), 1.54–1.50 (m, 4H), 1.44–1.34 (m, 2H), 1.32–1.22 (m, 12H), 0.91 (t, *J*=7.0 Hz, 9H), 0.89–0.84 (m, 27H), 0.09–0.04 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 171.1, 170.7, 138.8, 133.4, 130.5, 128.2 (2C's), 127.7 (2C's), 127.3, 71.3, 71.1, 70.8, 69.6, 66.6, 66.4, 66.3, 43.0, 42.1 (2C's), 42.0, 41.4, 41.35, 34.5, 34.3, 31.7, 31.6, 29.9, 25.84 (3C's), 25.8 (3C's), 25.8 (3C's), 24.8 (2C's), 22.9, 22.53, 22.5, 18.0 (2C's), 17.9, 14.0, 13.99, 13.8, −4.5, −4.57, −4.59, −4.6, −4.7, −4.9; FTIR (film): 2956, 2930, 2858, 1736, 1714, 1471, 1463, 1388, 1256, 1086 cm^{-1}; ESIMS: *m*/*z* 1029.6 ([M+Na]$^+$). ESIHRMS calcd for $C_{55}H_{102}Si_3O_{10}Na$ ([M+Na]$^+$): 1029.6673; found: 1029.6664.

4.28. Conversion of 34 to 36

2,4,6-Trichlorobenzoyl chloride (63 μL, 0.403 mmol) was added slowly to a mixture of **34** (126 mg, 0.125 mmol), benzyl alcohol (163 μL, 1.583 mmol), DMAP (97 mg, 0.794 mmol), and powdered/activated 4 Å molecular sieves (200 mg) in dry CH_2Cl_2 (5 mL) stirred at ambient temperature under argon. After completion of the addition, the stirring was continued at the same temperature until TLC showed completion of the reaction (ca. 24 h). The mixture was diluted with Et_2O, washed successively with aq satd $NaHCO_3$, water, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (40:1 PE/EtOAc) on silica gel afforded **36** as a yellowish oil (134 mg, 0.122 mmol, 98%). $[\alpha]_D^{26}$ −15.7 (*c* 1.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.21 (m, 10H), 5.57 (dt, *J*=11.1, 7.4 Hz, 1H), 5.31 (dd, *J*=11.1, 9.1 Hz, 1H), 5.11 (d, *J*=12.4 Hz, 1H), 5.05 (d, *J*=12.4 Hz, 1H), 4.98–4.94 (m, 2H), 4.52 (d, *J*=12.2 Hz, 1H), 4.30–4.26 (m, 2H), 4.28 (d, *J*=12.2 Hz, 1H), 4.16–4.10 (m, 2H), 2.52–2.39 (m, 6H), 2.05–1.85 (m, 3H), 1.80–1.71 (m, 4H), 1.65–1.57 (m, 1H), 1.57–1.50 (m, 4H), 1.43–1.34 (m, 2H), 1.32–1.20 (m, 12H), 0.91–0.76 (m, 36H), 0.05–0.02 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.0, 170.6, 138.8, 135.8, 133.3, 130.5, 128.4 (2C's), 128.20 (2C's), 128.16 (2C's), 128.11, 127.6 (2C's), 127.3, 71.2, 71.18, 70.7, 69.6, 66.5, 66.48, 66.2, 66.1, 43.0, 42.0 (3C's), 41.5, 41.3, 34.3, 34.2, 31.8, 31.6, 29.9, 25.8 (3C's), 25.75 (3C's), 25.67 (3C's), 24.79, 24.76, 22.8, 22.5 (2C's), 17.9 (2C's), 17.86, 14.0 (2C's), 13.8, −4.58 (2C's), −4.62, −4.66, −4.79, −4.83; FTIR (film): 2928, 2857, 1736, 1460, 1379, 1257, 1083 cm^{-1}; MALDIMS: *m*/*z* 1119.7 ([M+Na]$^+$). MALDIHRMS calcd for $C_{62}H_{108}Si_3O_{10}Na$ ([M+Na]$^+$): 1119.7143; found: 1119.7142.

4.29. Conversion of 36 to 37

HF·Py (Aldrich, containing ~70% HF and 30% Py, 0.622 mL) was added to a solution of **36** (89 mg, 0.081 mmol) in THF (1.5 mL) stirred at ambient temperature in a plastic (Nalgene) bottle. After completion of the addition, the reaction mixture was stirred for 2 h at the same temperature. Aq satd $NaHCO_3$ was added, followed by EtOAc. The phases were separated. The aqueous phase was back-extracted with EtOAc. The combined organic layers were washed in turn with aq satd $CuSO_4$, satd aq $NaHCO_3$, water, and brine before being dried over Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (2:1 PE/EtOAc) afforded **37** as a colorless oil (50 mg, 0.066 mmol, 82%). $[\alpha]_D^{26}$ −10.0 (*c* 1.55, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3OD): δ 7.25–7.24 (m, 10H), 5.70 (dt, *J*=11.3, 7.1 Hz, 1H), 5.30 (dd, *J*=11.3, 9.4 Hz, 1H), 5.14–5.11 (m, 2H), 5.08–5.04 (m, 2H), 4.56 (d, *J*=11.7 Hz, 1H), 4.43–4.40 (m, 1H), 4.35 (d, *J*=11.7 Hz, 1H), 4.14–4.07 (m, 3H), 2.62–2.35 (m, 6H), 2.11–2.03 (m, 2H), 1.94–1.61 (m, 5H), 1.60–1.55 (m, 5H), 1.48–1.41 (m, 2H), 1.38–1.20 (m, 12H), 0.95–0.87 (m, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 173.03, 173.01, 172.97, 138.9, 137.5, 135.5, 130.5, 129.5 (2C's), 129.4 (2C's), 129.2 (2C's), 129.17, 129.0 (2C's), 128.6, 73.3 (2C's), 73.2, 70.8, 67.3, 67.02, 66.78, 66.74, 43.7 (2C's), 43.5, 43.2, 42.3, 42.15, 35.1, 32.80, 32.77, 30.9 (2C's), 25.9, 23.9, 23.7, 23.6 (2C's), 14.4 (2C's), 14.2; FTIR (film): 3466, 2956, 2860, 1731, 1456, 1165, 1070 cm^{-1}; ESIMS: *m*/*z* 790.2 ([M+Cl]$^-$). ESIHRMS calcd for $C_{44}H_{66}O_{10}Na$ ([M+Na]$^+$): 777.4548; found: 777.4559.

4.30. Conversion of 37 to exophilin A 14

A mixture of **37** (12 mg, 0.0159 mmol), powdered $CaCO_3$ (10 mg, 0.1 mmol), and 10% Pd–C (10 mg) in EtOAc (0.3 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed completion of the reaction. The solids were filtered off (washing with EtOAc). The combined filtrate/washings were concentrated to dryness on a rotary evaporator to afford exophilin A **14** as a colorless oil (9 mg, 0.015 mmol, 94%). $[\alpha]_D^{26}$ −15.8 (*c* 0.3, $CHCl_3$) (lit.[13] $[\alpha]_D^{26}$ −22.3 (*c* 1.0, $CHCl_3$)). ^{1}H NMR (300 MHz, 3:1 $CDCl_3$/CD_3OD): δ 5.02 (m, 2H), 4.22–4.16 (m, 2H), 4.12–4.08 (m, 1H), 2.48–2.31 (m, 6H), 1.80–1.73 (m, 2H), 1.65–1.62 (m, 2H), 1.60–1.51 (m, 6H), 1.40–1.35 (m, 2H), 1.28–1.15 (m, 18H), 0.87–0.78 (m, 9H). ^{13}C NMR (100 MHz, 3:1 $CDCl_3$/CD_3OD): δ 172.95, 172.87 (2C's), 73.4 (2C's), 72.1, 69.4, 66.9, 66.4, 43.4, 43.14, 43.10 (2C's), 41.7, 41.4, 38.2, 35.0 (2C's), 32.4, 32.1 (2C's), 25.6, 25.4 (2C's), 23.2 (2C's), 23.0, 14.45, 14.41 (2C's); FTIR (film): 3422, 2955, 2859, 1728, 1460, 1166, 1056 cm^{-1}; ESIMS: *m*/*z* 575.3 ([M−H]$^-$). ESIHRMS calcd for $C_{30}H_{56}O_{10}Na$ ([M+Na]$^+$): 599.3771; found: 599.3799.

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