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Studies on the Synthesis of Apoptolidin: Progress on the Stereocontrolled Assembly of the Pseudo Aglycone of Apoptolidin

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Progress on a stereocontrolled total synthesis of the pseudo aglycone of apoptolidin (**2**) starting from (*S*)-epichlorohydrin is reported. The lower C(12)–C(28) fragment (**4**) was derived by consecutive stereoselective aldol reactions and extended using a Suzuki cross-coupling reaction. Studies on glycoysl-ation of the C9 hydroxy group are also described.

Introduction

Polyketide-derived secondary metabolites have long served as a source of structurally diverse and biologically active natural products.[1] In the course of screening soil microorganisms for cell-specific apoptosis inducing agents Hayakawa and co-workers isolated the polyketide natural product apoptolidin from *Nocardiopsis* sp.[2,3] Apoptolidin induced programmed cell death in E1A transformed rat glia cells but not normal cells. In 2001 Khosla and Salomon, utilizing a combination of molecular- and cellular-based assays, correlated this cell-specific activity to the inhibition of mitochondrial F_0F_1-ATPase by apoptolidin.[4] Structurally, apoptolidin features an unsaturated 20-membered macrolide, a six-membered hemiketal and three hexose sugars (Figure 1). The combined complex molecular structure and selective cytotoxic profile of apoptolidin identified it as a target for total synthesis.[5] In 2001 Koert reported the synthesis of apoptolidinone[6] and later the same year Nicolaou

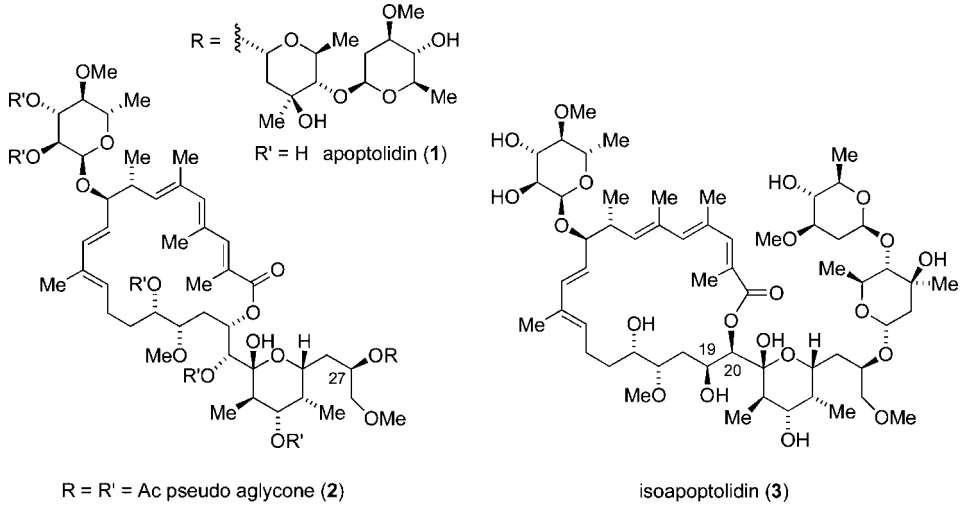

Figure 1. Structure of apoptolidin (**1**), pseudo aglycone (**2**) and isoapoptolidin (**3**).

described the total synthesis of apoptolidin.[7] Three years later the Koert group described the total synthesis of apoptolidin[8] and our group reported the second synthesis of the aglycon apoptolidinone.[9]

The first total synthesis of apoptolidin reported by the Nicolaou group[7] and other recent work[10] demonstrated

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apoptolidin to be a rather labile compound that undergoes a base-induced acyl migration from a hydroxy group located at C19 to the neighboring C20 hydroxy group to produce isoapoptolidin (**3**), a compound possessing diminished activity against mitochondrial F_0F_1-ATPase.[10a] Peracetylation of apoptolidin followed by brief acidic methanolysis and acetylation of the C27 hydroxy group led to the isolation of a pseudo aglycon of apoptolidin (**2**), a compound that showed no propensity to decompose under either acidic or basic conditions.[10b] As a prelude to the total synthesis of apoptolidine we pursued the chemical synthesis of **2**. Herein we report a summary of these investigations that led to the eventual completion of apoptolidinone as described elsewhere.[9]

Results and Discussion

Our primary synthetic strategy divided the target compound **2** into three fragments: **4** (C12–C28), **5** (C6–C11) and **6** (C5–C1) (Figure 2). These fragments would be coupled using metal-catalyzed cross-coupling reactions (**a**–**c**, Scheme 1)[11] and a Yamaguchi esterification (**d**).[12] Our attention was turned toward the stereocontrolled assembly of the most complex fragment C12–C28 (**4**) (Figure 2). Here, we desired to produce a product with the C19 and C27 hydroxy groups uniquely protected as TBS ethers, easily distinguished from the remaining acetate groups. To this end we anticipated that selective removal of the TES groups of intermediate **7** followed by peracetylation would provide the bis-TBS ether **4**. Key to the assembly of ketone **7** would be establishment of the C19 to C23 stereochemical array, which we planned to introduce in the course of two stereoselective aldol reactions.

The synthesis of aldehyde **10** began with the dithiane opening of (*R*)-glycidol methyl ether, the resulting adduct was subsequently converted to the aldehyde **11** following hydroxy group protection and dithiane hydrolysis (Scheme 1).[13] Condensation of **11** with the titanium enolate derived from the acyloxazolidinethione **12** afforded the aldol adduct **13** in excellent yield (85–90%) and stereoselectivity (>95% *de*).[14] Silylation of aldol adduct **13** was followed by reduction and oxidation to afford the aldehyde **10** in seven steps from commercially available glycidol methyl ether and 40–48% overall yield.

The assembly of aldehyde **8** began with the reaction of (*S*)-epichlorohydrin[15a] and the anion derived from 1,3-dithiane to give epoxide **14** in 62–75% yield (Scheme 2).[15] Epoxide **14** was opened with sodium *p*-methoxybenzylalkoxide and the resulting secondary alcohol methylated. Oxidative removal of the PMB group afforded a primary alcohol that was oxidized under Swern conditions to provide α-methoxyaldehyde **15**. The remaining five carbons of aldehyde **8** were introduced by chelation-controlled addition of a Grignard reagent derived from bromide **16** produced from dihydrofuran following Kocienski's procedure[16] as described by Koert during the course of his synthesis of apoptolidinone.[6] Silylation of the addition product gave a single isomer in 45–60% yield. Tin–iodine exchange followed by dithiane hydrolysis completed the

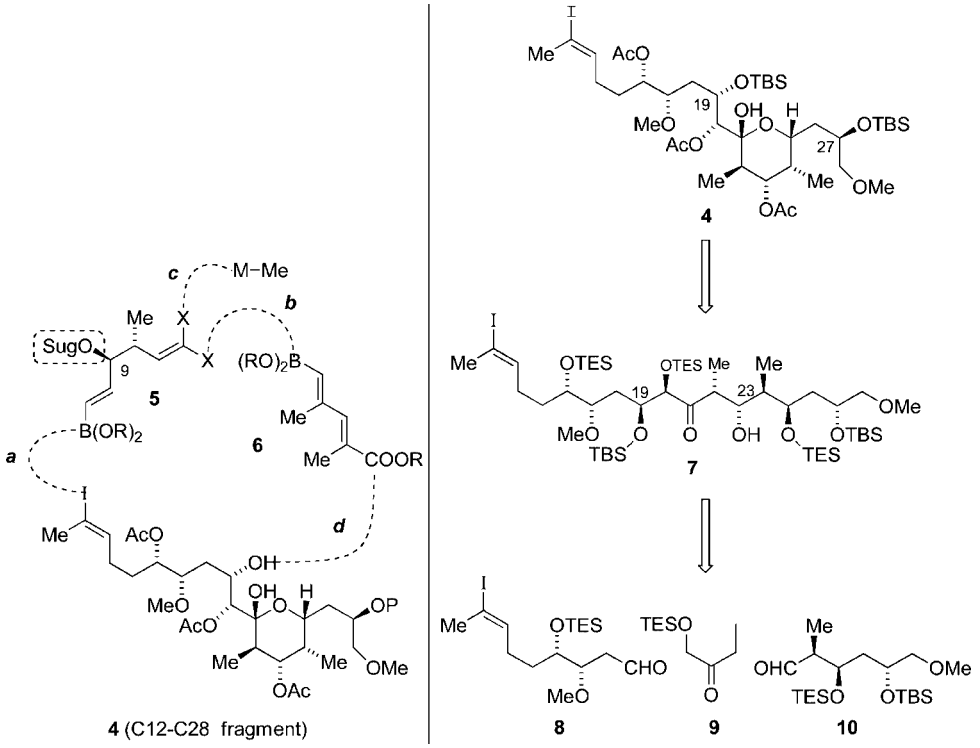
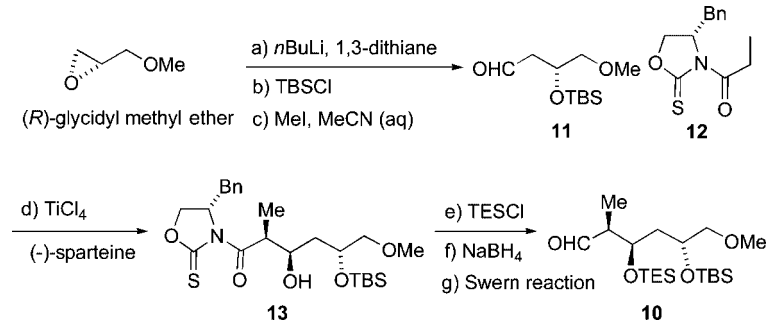


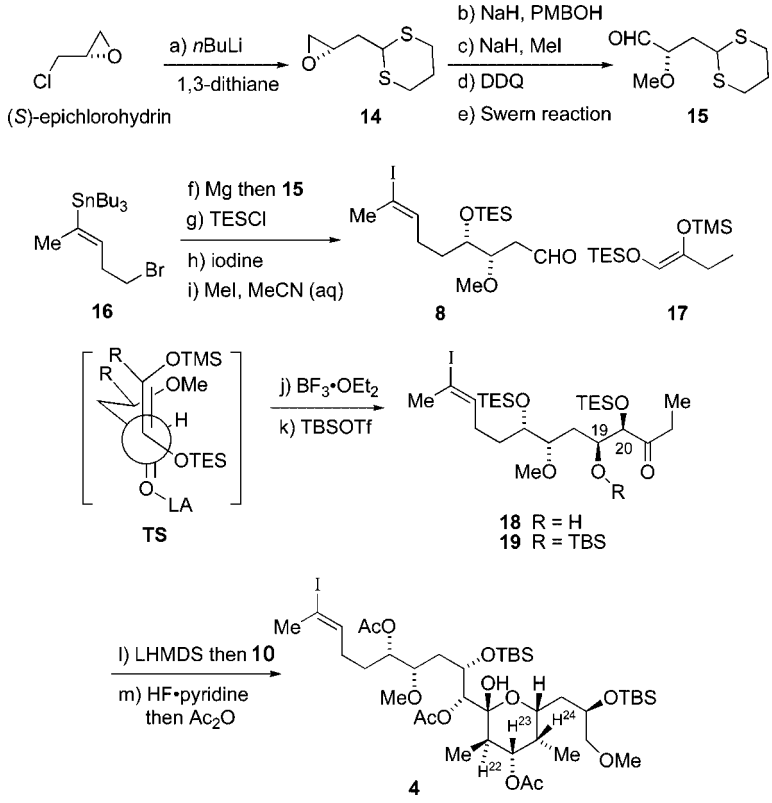
Figure 2. Retrosynthetic analysis of the pseudo aglycone of apoptolidin (**2**) and C12–C28 fragment (**4**).



Scheme 1. Reagents; (a) 1,3-dithiane, *n*BuLi, THF, –40 °C (90–95%). (b) TBSCl, ImH, CH_2Cl_2, room temp. (90–95%). (c) MeI, K_2CO_3, MeCN/H_2O (10:1), 40 °C (90%). (d) $TiCl_4$, (–)-sparteine, CH_2Cl_2, –78 °C (90–95%). (e) TESCl, imid., DMF, 0 °C (90–95%). (f) $NaBH_4$, MeOH, room temp. (68%). (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C (88%).

synthesis of aldehyde **8**.[13] The synthesis of aldehyde **8** required nine steps starting from (*S*)-epichlorohydrin and proceeded in 10–19% overall yield.

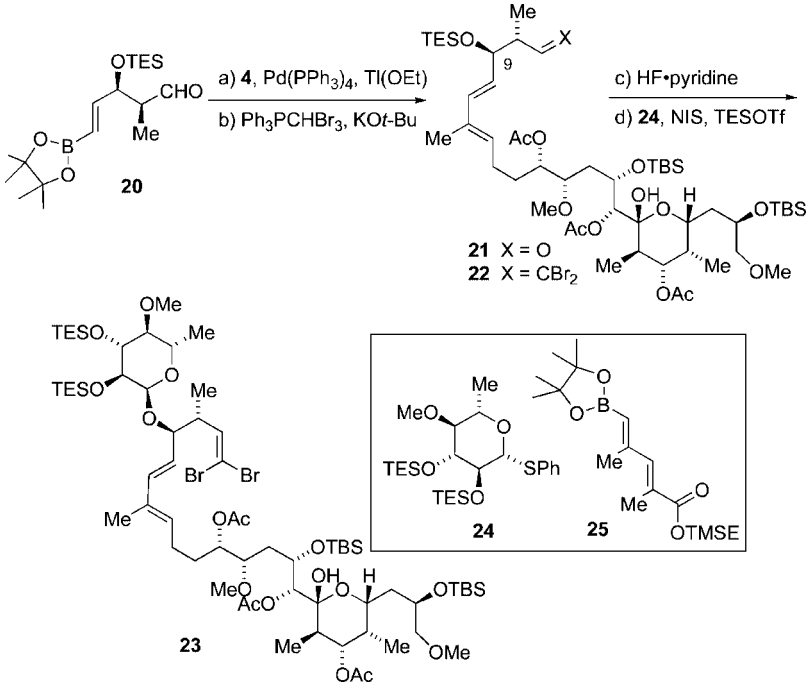
The first of two key aldol reactions was effected by reacting Z-silyl enol ether **17** derived from ketone **9** (Figure 2) [$LiN(SiMe_2Ph)_2$, THF, –78 °C then TMSCl] with aldehyde **8** on treatment with boron trifluoride–diethyl ether. Ketone **9** is derived from commercially available 1,2-butanediol in two steps. According to the precedent set by Evans and coworkers[17] we anticipated Mukaiyama aldol reaction between the aldehyde **8** and the silyl enol ether **17** would proceed by way of an extended Felkin–Anh transition state to give β-hydroxy ketone **18** as the major product. Ketone **19** was obtained as a major stereoisomer (4:1 ratio of isomers) following silylation of the aldol adduct **18**. The assigned relative stereochemistry of aldol adduct **18** rested on the observed coupling constant of the aldol product ($J_{19,20}$ = 3.5 Hz)[18] and the 1,3-asymmetric induction model proposed by Evans for β-methoxy aldehydes.[17] A second aldol followed kinetic deprotonation (LHMDS, THF, –78 °C) of **19** and condensation of the resulting Z-enolate with aldehyde **10** to give a single *syn* isomer as judged by ^1H NMR



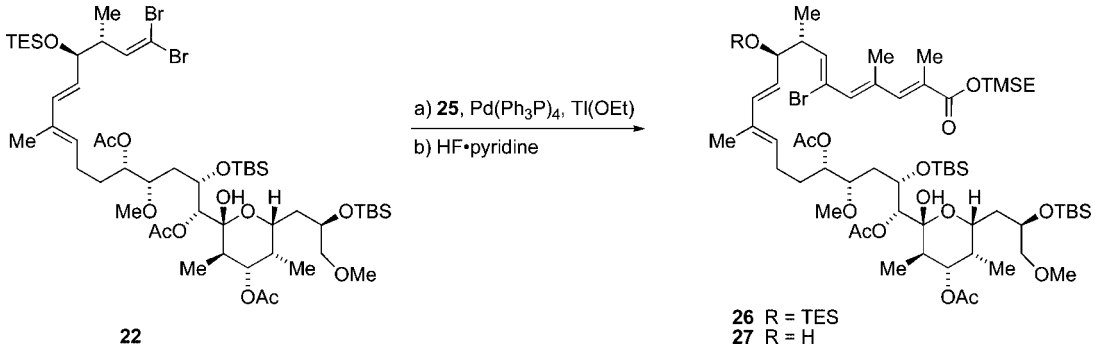
Scheme 2. Reagents: (a) 1,3-dithiane, *n*BuLi, THF, –40 °C to room temp. (76%). (b) NaH, PMBOH, DMF, 50 °C (69%). (c) MeI, NaH, THF, 0 °C (95%). (d) DDQ, CH_2Cl_2/H_2O (4:1), 0 °C (75%). (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C (81%). (f) **15**, Mg, 1,2-dibromoethane, Et_2O, –78 °C (60–70%). (g) TESCl, imid., CH_2Cl_2, room temp. (h) I_2, CH_2Cl_2, 0 °C (90%, two steps). (i) MeI, K_2CO_3, MeCN/pH 7 buffer (4:1), 28 °C (75%). (j) BF_3•OEt_2, CaH_2, CH_2Cl_2, –94 °C (69%). (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C (93%). (l) LHMDS, HMPA, **10**, THF, –78 °C (85%). (m) HF•pyr, pyr, THF, room temp. then Ac_2O, pyr., room temp. (64%).

analysis.[19] Removal of triethylsilyl ether groups followed by direct acetylation was performed in a single reaction vessel and gave hemiacetal **4** which exhibited $J_{22,23}$ = 11.5 Hz and $J_{23,24}$ = 4.5 Hz in the ^{1}H NMR spectrum in agreement with the assigned stereochemistry emerging from the second aldol condensation. This completed the synthesis of the C12–C28 fragment **4**.

In an earlier publication we described the synthesis of vinyl boronate **20** (Scheme 3) from an aldol condensation between 3-borylacrolein and the titanium enolate derived from the oxazolidinethione **12**.[20] Suzuki–Miyaura coupling of the vinyl boronate **20** and C12–C28 fragment **4** proceeded smoothly to give the aldehyde **21** in 88% yield.[11,21] Condensation of **21** with the phosphorus ylide derived from Ramirez salt afforded the dibromide **22**.[22] In preparation for a C9 glycosylation, removal of the triethylsilyl-protecting group was accomplished using HF·pyridine in 83% yield. Next, several methods were examined in order to effect α-selective glycosylation of the revealed C9 hydroxy group using various protected 6-deoxy glucose donors. Ultimately, the thioglycoside **24** proved to be the most effective donor and provided the α-glycoside **23** in 40–45% yield (α/β = 4:1) upon activation with NIS and TESOTf at low temperature.[23] Disappointingly, in contrast to earlier model studies,[20] all attempts to cross-couple the vinyl boronate **25** and the dibromide **23** failed. Assuming the sterically demanding C9 sugar unit was impeding productive coupling, we considered reversing the order of cross-coupling and glycosylation. To this end, we coupled the boronate **25** and the dibromide **22** under standard Suzuki–Miyaura reaction conditions [$Pd(PPh_3)_4$, TlOEt, THF/H_2O] to afford **26** (Scheme 4). While selective desilylation to **27** was successful, attempts to glycosylate **27** failed, perhaps due to the instability of the trienoate unit.



Scheme 3. Reagents: (a) **4**, [$Pd(Ph_3P)_4$], Tl(OEt), THF/H_2O (3:1), room temp. (88%). (b) Ph_3PCHBr_3, KO*t*Bu, THF, 0 °C (82%). (c) HF·pyridine, THF, 0 °C (80%). (d) **24**, NIS, TESOTf, CH_2Cl_2, 4-Å molecular sieves, –20 °C (45%).



Scheme 4. Reagents: (a) **25**, [$Pd(Ph_3P)_4$], Tl(OEt), THF/H_2O (3:1), room temp. (71%). (b) HF·pyridine, THF, 0 °C (66%).

Conclusions

Despite the fact we were unable to achieve our goal of assembling the targeted pseudo aglycon of apoptolidin (**2**), we did develop important reaction sequences that led to our eventual total synthesis of apoptolidinone.[9] Key reactions developed under this program include the preparation of fragments **8**–**10** and their coupling through application of substrate controlled aldol reactions (Scheme 2).

Experimental Section

General: All reactions were carried out under argon using dry glassware which had been flame-dried under a stream of nitrogen, unless otherwise noted. All necessary solvents were purified prior to use. Tetrahydrofuran was distilled from sodium/benzophenone and stored with 4-Å molecular sieves. Dichloromethane and toluene were distilled from calcium hydride and stored with 4-Å molecular sieves. Pyridine and triethylamine were distilled from calcium hydride and stored with sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded with a 500 or 400 MHz spectrometer at ambient temperature. ^{1}H and ^{13}C NMR spectroscopic data are reported as δ values relative to tetramethylsilane. Infrared spectra were recorded with Thermo Electron Corporation Nicolet IR100 spectrometer. Microwave reactions were run using a CEM Discover LabMate 300-watt laboratory microwave reactor. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center by Dr. Shane Tichy on an API QSTAR Pulsar Instrument.

Aldehyde 11: To a solution of dithiane (3.91 g, 12.1 mmol) in CH_3CN/H_2O (132 mL, 10:1) was added K_2CO_3 (3.34 g, 24.2 mmol), followed by iodomethane (17.2 g, 121 mmol). The slurry was stirredat 40 °C for 8 h, then saturated $NaHCO_3$ (40 mL) was added. The aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 40:1) to afford 2.54 g (90%) of the aldehyde **11** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.75 (t, J = 2.5 Hz, 1 H), 4.28 (quintet, J = 5.5 Hz, 1 H), 3.36 (dd, J = 9.5, 5.0 Hz, 1 H), 3.30 (s, 3 H), 3.26 (dd, J = 9.5, 5.5 Hz, 1 H), 2.54 (ddq, J = 16.0, 5.5, 2.5 Hz, 2 H), 0.82 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.4, 76.5, 67.2, 59.1, 48.7, 25.7, 18.0, –4.5, –5.0. HRMS (ESI): m/z = 233.1590 ([M + H]$^+$ calculated for $C_{11}H_{25}O_3Si$: 233.1573).

Aldol 13: To a solution of the acyloxazolidinethione **12** (1.12 g, 4.48 mmol) in DCM (20 mL) at 0 °C was added a solution of $TiCl_4$ (4.48 mL, 1 M in DCM). The solution was stirred for 15 min before the addition of (–)-sparteine (1.32 mL, 5.76 mmol). After 15 min, the reaction mixture was cooled to –78 °C, and the aldehyde **11** (0.990 g, 4.27 mmol) in DCM (4 mL) was added via cannula. After being stirred for 1 h at –78 °C and an additional 1 h at 0 °C, the reaction was quenched with saturated NH_4Cl (15 mL) and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 6:1) to afford 1.95 g (95%) of the alcohol **13** as a colorless oil. $[\alpha]_D^{25}$ = +52.5 (c = 4.4, $CHCl_3$). IR ($CHCl_3$) 2960, 2851, 1695, 1367, 1185 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 4.98–4.94 (m, 1 H), 4.71 (dq, J = 7.0, 4.0 Hz, 1 H), 4.35–4.28 (m, 3 H), 4.10 (quintet, J = 5.0 Hz, 1 H), 3.56 (s, 1 H), 3.44–3.29 (m, 3 H), 3.37 (s, 3 H), 2.77 (dd, J = 13.0, 10.0 Hz, 1 H), 1.83–1.77 (m, 1 H), 1.65 (ddd, J = 14.0, 6.0, 1.5 Hz, 1 H), 1.32 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.4, 177.3, 135.5, 129.6, 129.2, 127.6, 70.4, 69.9, 68.9, 60.6, 59.4, 43.4, 38.6, 37.8, 26.1, 18.3, 11.0, –4.3, –4.7. HRMS (ESI): m/z = 482.2402 ([M + H]$^+$ calculated for $C_{24}H_{40}NO_5SSi$: 482.2396).

Aldehyde 10: To a solution of $(COCl)_2$ (0.043 mL, 0.493 mmol) in DCM (1 mL) was added DMSO (0.070 mL, 0.986 mmol). The resulting mixture was stirred at –78 °C for 15 min before alcohol (125 mg, 0.308 mmol) in DCM (1 mL) was added. The mixture was stirred 15 min at –78 °C, and Et_3N (0.216 mL, 1.54 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for another 15 min before it was warmed to 0 °C for 45 min. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with 0.1 N HCl (20 mL), H_2O (15 mL), saturated $NaHCO_3$ (15 mL), H_2O (15 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 20:1) to afford 0.11 g (88%) of aldehyde **10** as a colorless oil: $[\alpha]_D^{25}$ = +26.3 (c = 6.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2953, 2873, 1709, 1462, 1251 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 4.31–4.28 (m, 1 H), 3.89–3.85 (m, 1 H), 3.30 (dd, J = 5.5, 2.0 Hz, 2 H), 3.33 (s, 3 H), 2.52 (dq, J = 7.0, 3.5 Hz, 1 H), 1.68–1.65 (m, 2 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.96 (t, J = 8.0 Hz, 9 H), 0.89 (s, 9 H), 0.62 (q, J = 8.0 Hz, 6 H), 0.10 (s, 3 H), 0.09 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.5, 77.8, 70.1, 69.5, 59.1, 52.4, 40.3, 26.1, 18.4, 8.1, 7.1, 5.4, –3.7, –4.4. HRMS (ESI) m/z = 427.2664 ([M + Na]$^+$ calculated for $C_{20}H_{44}NaO_4Si_2$: 427.2676).

Dithiane 14: To a solution of 1,3-dithiane (4.29 g, 35.7 mmol) in THF (75 mL) at –40 °C was slowly added nBuLi (15.5 mL, 2.30 M in hexanes). The resulting solution was stirred 1 h at –40 °C, and (*S*)-epichlorohydrin (3.00 g, 32.4 mmol) was then added neat dropwise. The reaction mixture was stirred at –40 °C for 30 min and then slowly warmed to room temperature over 2 h. After stirring at room temperature for 16 h, the reaction was quenched with H_2O (30 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to afford 4.32 g (76%) of the epoxide **14** as a colorless oil: $[\alpha]_D^{25}$ –5.8 (c = 5.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2989, 2902, 1593, 1425, 1280, 909 cm^{-1}. ^{1}H NMR (500 MHz, C_6D_6): δ = 3.99 (dd, J = 9.0, 5.5 Hz, 1 H), 2.97–2.93 (m, 1 H), 2.33–2.21 (m, 5 H), 2.03 (dd, J = 5.0, 2.5 Hz, 1 H), 1.84–1.70 (m, 2 H), 1.55–1.46 (m, 1 H), 1.38–1.32 (m, 1 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 49.1, 46.8, 44.9, 39.0, 30.2, 29.9, 25.7. HRMS (FAB): m/z = 177.0401 ([M + H]$^+$ calculated for $C_7H_{13}S_2O$: 177.0408).

Aldehyde 15: To a solution of $(COCl)_2$ (0.242 mL, 2.77 mmol) in DCM (6 mL) was added a solution of DMSO (0.393 mL, 5.54 mmol) in DCM (2 mL). The resulting mixture was stirred at –78 °C for 15 min before alcohol (0.36 g, 1.73 mmol) in DCM (1 mL) was added. The mixture was stirred 15 min at –78 °C, and iPr$_2$NEt (1.50 mL, 8.65 mmol) was added dropwise. The reaction

mixture was stirred at –78 °C for another 15 min before it was warmed to 0 °C for 45 min. The reaction was quenched with H_2O (10 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were washed with 0.1 N HCl (5 mL), H_2O (10 mL), saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 5:1) to afford 0.288 g (81%) of the aldehyde **15** as a colorless oil: $[\alpha]_D^{25}$ = –36.5 (*c* = 3.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3418, 2931, 2902, 2822, 1724, 1418, 1113 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 9.37 (d, *J* = 1.5 Hz, 1 H), 4.05 (t, *J* = 7.0 Hz, 1 H), 3.54 (ddd, *J* = 8.0, 5.0, 1.5 Hz, 1 H), 2.99 (s, 3 H), 2.30–2.22 (m, 2 H), 2.19–2.13 (m, 2 H), 2.09–2.00 (m, 2 H), 1.48–1.36 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 201.7, 82.6, 57.9, 41.7, 36.2, 28.6, 28.5, 25.6. HRMS (ESI): *m*/*z* = 207.0514 ($[M + H]^+$ calculated for $C_8H_{15}O_2S_2$: 207.0514).

Aldehyde 8: To a solution of dithiane (0.80 g, 1.55 mmol) in MeCN/pH 7 buffer (60 mL, 4:1) at 0 °C was added K_2CO_3 (0.536 g, 3.88 mmol) and MeI (0.965 mL, 15.5 mmol) in 5 min. The reaction mixture was warmed to 26.5 °C and stirred 48 h. The reaction mixture was diluted with EtOAc (50 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 25:1) to afford 0.50 g (75%) of the aldehyde **8** as a colorless oil: $[\alpha]_D^{25}$ = –15.0 (*c* = 4.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2953, 2873, 1724, 1455, 1375, 1113, 742 cm^{-1}. ^1H NMR (500 MHz C_6D_6): δ = 9.47 (s, 1 H), 6.14–6.10 (m, 1 H), 3.68–3.62 (m, 2 H), 3.04 (s, 3 H), 2.31 (ddt, *J* = 12.0, 3.5, 1.0 Hz, 1 H), 2.16–2.12 (m, 1 H), 2.11 (s, 3 H), 2.04–1.96 (m, 1 H), 1.79–1.71 (m, 1 H), 1.54–1.47 (m, 1 H), 1.16–1.09 (m, 1 H), 0.90 (t, *J* = 8.0 Hz, 9 H), 0.50 (q, *J* = 8.0 Hz, 6 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 119.2, 141.0, 93.9, 78.8, 71.3, 57.5, 43.6, 30.9, 27.3, 27.2, 6.9, 5.2. HRMS (ESI): *m*/*z* = 427.1131 ($[M + H]^+$ calculated for $C_{16}H_{32}IO_3Si$: 427.1166).

Aldol 18: To a solution of the aldehyde **8** (0.45 g, 1.06 mmol) and the silyl enol ether **17** (0.871 g, 3.18 mmol) in DCM (16 mL) at 0 °C was added CaH_2 (0.050 g). The suspension was stirred 10 min at 0 °C before being cooled to –94 °C. A solution of $BF_3{\cdot}OEt_2$ in DCM (2.12 mL, 1.06 mmol) was added dropwise via syringe. After stirring at –94 °C for 15 min, the reaction was quenched with H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 25:1 to 20:1) to afford 0.46 g (69%) of aldol products **18** as a 4:1 mixture of isomers. The product can be further purified through preparative HPLC (2–6% EtOAc in hexanes as eluent) to afford the single isomer as a colorless oil: $[\alpha]_D^{25}$ = –8.2 (*c* = 3.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3476, 2953, 2865, 1716, 1455, 1404, 1367, 1236, 1098, 742 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 6.15 (tq, *J* = 7.0, 1.0 Hz, 1 H), 4.19–4.14 (m, 1 H), 4.02 (d, *J* = 3.5 Hz, 1 H), 3.82 (quintet, *J* = 4.0 Hz, 1 H), 3.59 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1 H), 3.25 (s, 3 H), 2.59 (d, *J* = 8.5 Hz, 1 H), 2.51–2.36 (m, 2 H), 2.13 (s, 3 H), 2.10–2.08 (m, 1 H), 1.90–1.81 (m, 2 H), 1.66 (tq, *J* = 9.5, 3.5 Hz, 1 H), 1.56 (ddd, *J* = 12.5, 9.5, 2.0 Hz, 1 H), 1.41–1.34 (m, 1 H), 0.99 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 8.0 Hz, 9 H), 0.88 (t, *J* = 8.0 Hz, 9 H), 0.58 (dq, *J* = 8.0, 2.0 Hz, 6 H), 0.49 (q, *J* = 8.0 Hz, 6 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 212.2, 141.2, 93.9, 81.7, 80.7, 71.4, 70.5, 58.2, 33.4, 32.1, 31.0, 27.4, 27.3, 7.2, 7.0, 6.8, 5.3, 5.0. HRMS (ESI): *m*/*z* = 629. 2553 ($[M + H]^+$ calculated for $C_{26}H_{54}IO_5Si_2$: 629.2555).

Aldol 19: To a solution of alcohol **18** (0.085 g, 0.135 mmol) in DCM (2 mL) at –78 °C was added 2,6-lutidine (0.11 mL, 0.945 mmol) dropwise. The resulting solution was stirred at –78 °C for 5 min and TBSOTf (0.186 mL, 0.812 mmol) was added. The mixture was stirred at –78 °C for 4 h, and then quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatograph (hexane/EtOAc, 60:1) to afford 0.093 g (93%) of the ether **19** as a colorless oil: $[\alpha]_D^{25}$ = –37.8 (*c* = 3.8, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3016, 2853, 2924, 2878, 1716, 1459, 1413, 1379, 1252, 1120, 1005 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 6.12 (t, *J* = 7.0 Hz, 1 H), 4.37 (d, *J* = 3.5 Hz, 1 H), 4.27 (dt, *J* = 8.5, 4.0 Hz, 1 H), 3.84 (m, 1 H), 3.43 (ddd, *J* = 10.0, 3.0, 1.0, 1 H), 3.19 (s, 3 H), 2.74 (dq, *J* = 17.5, 7.5, 1 H), 2.49 (dq, *J* = 18.0, 7.5 Hz, 1 H), 2.14 (s, 3 H), 2.12–2.00 (m, 2 H), 1.92–1.84 (m, 1 H), 1.67–1.61 (m, 2 H), 1.10 (t, *J* = 7.5 Hz, 3 H), 1.02 (s, 9 H), 0.99 (t, *J* = 8.0 Hz, 9 H), 0.98 (t, *J* = 8.0 Hz, 9 H), 0.62 (q, *J* = 8.0 Hz, 6 H), 0.59 (q, *J* = 8.0 Hz, 6 H), 0.21 (s, 3 H), 0.18 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 210.1, 141.1, 94.0, 81.1, 79.7, 72.1, 70.8, 56.3, 33.6, 31.5, 30.9, 27.4, 27.3, 26.1, 18.2, 7.4, 7.1, 7.0, 5.4, 5.2, –3.9, –4.5. HRMS (ESI): *m*/*z* = 743.3405 ($[M + H]^+$ calculated for $C_{32}H_{68}IO_5Si_2$: 743.3335).

Ketone 7: To a solution of LHMDS (0.262 mL, 1.0 M in THF) in THF (1 mL with 0.046 mL HMPA) at –78 °C was added ketone **19** (0.065 g, 0.0876 mmol) in THF (1 mL) via cannula. The resulting solution was stirred at –78 °C for 2 h before aldehyde **10** (0.106 g, 0.262 mmol) was added via cannula. The reaction stirred at –78 °C for 1 h and quenched with saturated NH_4Cl (5 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 25:1) to afford 0.085 g (85%) of alcohol **7** as a colorless oil: $[\alpha]_D^{25}$ = –47.6 (*c* = 1.5, $CHCl_3$). IR ($CHCl_3$) 3461, 2956, 2878, 1725, 1706, 1459, 1258, 1116 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 6.12 (tq, *J* = 7.5, 1.5 Hz, 1 H), 4.76 (d, *J* = 4.0 Hz, 1 H), 4.54 (t, *J* = 6.5 Hz, 1 H), 4.36 (dt, *J* = 10.0, 3.5 Hz, 1 H), 4.09–4.04 (m, 1 H), 3.85 (quintet, *J* = 4.0 Hz, 1 H), 3.77 (s, 1 H), 3.46 (ddd, *J* = 11.0, 4.0, 2.0 Hz, 1 H), 3.35–3.30 (m, 1 H), 3.24 (s, 3 H), 3.09 (s, 3 H), 2.16 (s, 3 H), 2.06–1.96 (m, 2 H), 1.94–1.85 (m, 2 H), 1.65–1.59 (m, 1 H), 1.45–1.38 (m, 1 H), 1.29 (d, *J* = 6.5 Hz, 3 H), 1.07 (t, *J* = 8.0 Hz, 9 H), 1.06 (t, *J* = 8.0 Hz, 9 H), 1.03–0.99 (m, 30 H), 0.76–0.70 (m, 12 H), 0.60 (q, *J* = 8.0 Hz, 6 H), 0.27 (s, 3 H), 0.21 (s, 6 H), 0.17 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 214.0, 141.1, 94.0, 80.1, 79.3, 77.7, 73.2, 71.7, 70.9, 70.6, 70.2, 58.5, 56.3, 45.0, 40.9, 40.7, 32.0, 31.1, 27.4, 27.3, 26.1, 16.1, 18.4, 18.3, 10.5, 8.2, 7.2, 7.0, 5.6, 5.4, 5.2, –3.2, –3.7, –4.4, –4.6. HRMS (ESI) *m*/*e* 1147.6201 ($[M + H]^+$ calculated for $C_{52}H_{112}IO_9Si_5$: 1147.6198).

C12–C28 Fragment 4: To a solution of alcohol **7** (0.135 g, 0.118 mmol) in THF/MeCN (10 mL, 3:1) at 0 °C was added a solution of HF in pyridine (4 mL, prepared from 2 g of HF in pyridine, 2 mL pyridine and 10 mL THF). The resulting solution was stirred between 0 °C to 10 °C for 5 h. Pyridine (5 mL) was added to the reaction mixture, followed by Ac_2O (5 mL). The reaction was stirred at 5 °C for 4 h, and diluted with toluene. The solvent was removed in vacuo and the residue was diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 8:1) to afford 70 mg (64%) of triacetate **4** as a colorless oil: $[\alpha]_D^{25}$ = +26.0 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$) 3440, 2953, 2931, 2851, 1731, 1462, 1360, 1244, 1091, 1047 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 6.14 (tq, *J* = 7.5, 1.5 Hz, 1 H), 5.46 (dd, *J* = 11.5, 5.0 Hz, 1 H), 5.44 (d, *J* = 5.0 Hz, 1 H), 5.29 (d, *J* = 1.5 Hz, 1 H), 5.26 (dt, *J* = 10.0, 3.5 Hz, 1 H), 4.69 (d, *J* = 9.5 Hz, 1 H), 4.36 (dd, *J* = 8.5, 4.0 Hz, 1 H),

4.13–4.06 (m, 1 H), 3.43 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.27 (s, 3 H), 3.25 (dd, *J* = 9.0, 6.0 Hz, 1 H), 3.14 (dd, *J* = 9.0, 5.0 Hz, 1 H), 3.1 (s, 3 H), 2.25 (dd, *J* = 15.0, 11.0 Hz, 1 H), 2.20–2.08 (m, 3 H), 2.14 (s, 3 H), 1.98–1.87 (m, 3 H), 1.92(s, 3 H), 1.74–1.56 (m, 2 H), 1.63 (s, 3 H), 1.62 (s, 3 H), 1.46 (ddd, *J* = 14.0, 10.5, 2.0 Hz, 1 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 1.03 (s, 9 H), 0.93 (s, 9 H), 0.33 (s, 3 H), 0.32 (s, 3 H), 0.23 (s, 3 H), 0.11 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 170.1, 169.7, 169.3, 140.6, 102.0, 94.3, 78.5, 78.1, 75.1, 71.5, 71.2, 70.4, 69.5, 67.4, 58.9, 57.2, 39.4, 37.4. 34.5, 34.4, 37.7, 37.4, 27.3, 26.2, 25.8, 21.0, 20.5, 20.3, 18.4, 18, 11.9, 5.8, –3.3, –4.0, –4.0, –5.2. HRMS (ESI): *m*/*z* = 953.3709 ([M + Na]$^+$ calculated for $C_{40}H_{75}INaO_{12}Si_{12}$: 953.3739).

Aldehyde 21: To a solution of acetate **4** (0.10 g, 0.107 mmol) and boronic ester **20** (0.080 g, 0.225 mmol) in THF/H_2O (3.6 mL, 3:1, degassed) at room temperature was added [Pd(Ph_3P)$_4$] (0.012 g, 0.011 mmol). The resulting yellow solution was stirred 5 min before TlOEt (0.011 mL, 0.161 mmol) was added via syringe. The reaction was stirred for 40 min and quenched with 1 N $NaHSO_4$ (4 mL). The mixture was filtered through Celite and rinsed with EtOAc (60 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford 0.098 g (88%) of aldehyde **21** as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6): δ = 9.68 (d, *J* = 1.0 Hz, 1 H), 6.25 (d, *J* = 15.5 Hz, 1 H), 5.53 (dd, *J* = 16.0, 7.0 Hz, 1 H), 5.52–5.49 (m, 2 H), 5.47 (t, *J* = 4.5 Hz, 1 H), 5.37 (dt, *J* = 10.0, 3.5 Hz, 1 H), 5.32 (s, 1 H), 4.71 (d, *J* = 9.0 Hz, 1 H), 4.47 (dd, *J* = 6.5, 3.5 Hz, 1 H), 4.42 (dd, *J* = 9.0, 5.5 Hz, 1 H), 4.19–4.16 (m, 1 H), 3.51 (dd, *J* = 10.5, 3.5 Hz, 1 H), 3.33 (s, 3 H), 3.29 (dd, *J* = 9.0, 6.5 Hz, 1 H), 3.19 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.12 (s, 3 H), 2.37–2.15 (m, 6 H), 1.94 (s, 3 H), 1.86–1.74 (m, 2 H), 1.68 (s, 3 H), 1.66 (s, 3 H), 1.64 (s, 3 H), 1.24 (d, *J* = 6.5 Hz, 3 H), 1.06 (s, 9 H), 1.05 (q, *J* = 8.0 Hz, 6 H), 0.97 (t, *J* = 8.0 Hz, 9 H), 0.95 (s, 9 H), 0.57 (q, *J* = 8.0 Hz, 9 H), 0.36 (s, 3 H), 0.35 (s, 3 H), 0.26 (s, 3 H), 0.14 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 202.6, 169.9, 169.6, 169.2, 136.0, 133.8, 132.4, 127.5, 101.9, 78.4, 78.0, 75.0, 73.9, 71.4, 71.2, 70.4, 69.5, 67.3, 58.7, 57.1, 53.2, 39.3, 37.4, 34.5, 34.3, 28.0, 26.1, 25.7, 25.0, 20.9, 20.5, 20.2, 18.3, 17.9, 12.5, 11.9, 8.6, 7.0, 5.7, 5.2, –3.4, –4.0, –4.1, –5.3. HRMS (ESI): *m*/*z* = 1053.6058 ([M + Na]$^+$ calculated for $C_{52}H_{98}NaO_{14}Si_3$: 1053.6162).

Dibromide 22: To a suspension of Ph_3P–$CHBr_3$ (0.510 g, 0.99 mmol) in THF (10 mL) at 0 °C was added KO*t*Bu (0.055 g, 0.50 mmol). The resulting orange solution was stirred at 0 °C for 5 min and a solution of aldehyde **21** (0.085 g, 0.0825 mmol) in THF (2 mL) was added via cannula. The reaction mixture was stirred at 0 °C for 30 min and quenched with brine. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 10:1) to afford 0.080 g (82%) of dibromide **22** as a colorless oil: $[\alpha]_D^{25}$ = +6.7 (*c* = 2.2, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6): δ = 6.30 (d, *J* = 9.5 Hz, 1 H), 6.22 (d, *J* = 15.5 Hz, 1 H), 5.55 (dd, *J* = 15.5, 7.0 Hz, 1 H), 5.49 (t, *J* = 7.5 Hz, 1 H), 5.45 (dd, *J* = 11.5, 5.0 Hz, 1 H), 5.43 (d, *J* = 5.0 Hz, 1 H), 5.34 (td, *J* = 10.0, 3.5 Hz, 1 H), 5.30 (s, 1 H), 4.69 (d, *J* = 9.0 Hz, 1 H), 4.39 (dd, *J* = 9.0, 5.5 Hz, 1 H), 4.18–4.13 (m, 1 H), 4.07 (t, *J* = 5.5 Hz, 1 H), 3.50 (dd, *J* = 11.5, 4.0 Hz, 1 H), 3.33 (s, 3 H), 3.28 (dd, *J* = 9.0, 6.5 Hz, 1 H), 3.18 (dd, *J* = 9.0, 4.5 Hz, 1 H), 3.12 (s, 3 H), 2.80–2.61 (m, 1 H), 2.35–2.29 (m, 1 H), 2.28–2.13 (m, 4 H), 1.93 (s, 3 H), 1.94–1.89 (m, 1 H), 1.85–1.70 (m, 2 H), 1.69 (s, 3 H), 1.65 (s, 3 H), 1.63 (s, 3 H), 1.49 (ddd, *J* = 14.0, 10.5, 1.5 Hz, 1 H), 1.36–1.28 (m, 1 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.04 (d, *J* = 6.0 Hz, 3 H), 1.04 (s, 9 H), 0.99 (t, *J* = 8.0 Hz, 9 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.93 (s, 9 H), 0.59 (q, *J* = 8.0 Hz, 6 H), 0.33 (s, 3 H), 0.33 (s, 3 H), 0.24 (s, 3 H), 0.17 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 169.9, 169.6, 169.2, 141.7, 135.8, 133.9, 132.1, 128.2, 101.9, 88.7, 78.4, 78.0, 76.1, 75.0, 71.4, 71.1, 70.3, 69.5, 67.3, 58.7, 57.1, 45.7, 39.2, 37.3, 34.4, 34.2, 27.9, 26.1, 25.7, 25.0, 20.8, 20.4, 20.2, 18.3, 17.8, 13.7, 12.5, 11.8, 7.0, 5.7, 5.2, –3.3, –4.0, –4.0, –5.3. HRMS (ESI): *m*/*z* = 1191.4857 ([M + Li]$^+$ calculated for $C_{53}H_{98}Br_2LiO_{13}Si_3$: 1191.4842).

Glycoside 23: To a solution of alcohol (0.008 g, 7.53 μmol) and glycosyl sulfide **24** (0.0075 g, 15.0 μmol) in DCM (1 mL) at –20 °C was added 4-Å molecular sieves. A solution of TESOTf in DCM (0.1 mL, 7.5 mmol) was then added dropwise. The resulting solution turned to pink and was quenched with saturated $Na_2S_2O_3$ after 10 min. The aqueous layer was extracted with DCM (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford 0.005 g (45%) of the *α*-glycoside **23** as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6): δ = 6.29 (d, *J* = 15.5 Hz, 1 H), 6.24 (d, *J* = 9.5 Hz, 1 H), 5.53–5.46 (m, 4 H), 5.38 (dt, *J* = 10.0, 3.5 Hz, 1 H), 5.33 (s, 1 H), 4.93 (d, *J* = 3.5 Hz, 1 H), 4.72 (d, *J* = 9.0 Hz, 1 H), 4.42 (dd, *J* = 9.5, 5.0 Hz, 1 H), 4.21–4.13 (m, 2 H), 4.08 (dd, *J* = 9.0, 6.0 Hz, 1 H), 3.89–3.85 (m, 1 H), 3.67 (dd, *J* = 9.5, 3.5 Hz, 1 H), 3.52 (dd, *J* = 11.5, 4.0 Hz, 1 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 3.29 (dd, *J* = 9.0, 6.5 Hz, 1 H), 3.21 (dd, *J* = 9.0, 4.5 Hz, 1 H), 3.14 (s, 3 H), 2.84–2.78 (m, 1 H), 2.67 (t, *J* = 9.0 Hz, 1 H) 2.36–2.16 (m, 5 H), 2.14–2.08 (m, 1 H), 1.96 (s, 3 H), 1.96–1.92 (m, 1 H), 1.84–1.70 (m, 2 H), 1.80 (s, 3 H), 1.66 (s, 3 H), 1.54–1.50 (m, 1 H), 1.40–1.28 (m, 6 H), 1.38 (d, *J* = 6.0 Hz, 3 H), 1.25 (d, *J* = 6.5 Hz, 3 H), 1.20–1.15 (m, 9 H), 1.09–1.06 (m, 18 H), 0.97–0.85 (m, 18 H), 0.68 (q, *J* = 8.0 Hz, 6 H), 0.36 (s, 3 H), 0.35 (s, 3 H), 0.26 (s, 3 H), 0.15 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 170.0, 169.6, 169.3, 141.0, 140.6, 133.7, 133.4, 130.6, 123.4, 102.0, 95.2, 89.5, 87.6, 78.4, 77.9, 75.0, 74.6, 74.5, 71.6, 71.1, 70.3, 69.6, 68.1, 67.3, 60.9, 58.8, 57.2, 43.8, 39.3, 37.4, 34.4, 34.3, 32.2, 30.1, 29.7, 26.1, 25.7, 23.0, 20.9, 20.4, 20.2, 18.6, 18.3, 17.9, 14.6, 14.3, 12.4, 11.8, 7.4, 7.2, 5.8, 5.4, –3.3, –4.0, –4.0, –5.3.

Triene 26: To a solution of the dibromide **22** (0.040 g, 0.0337 mmol) and the boronic ester **25** (0.060 g, 0.168 mmol) in THF/H_2O (1.6 mL, 3:1, degassed) at room temperature was added [Pd(Ph_3P)$_4$] (3.9 mg, 3.37 μmol). The resulting yellow solution was stirred 5 minutes before TlOEt (4.3 μL, 0.061 mmol) was added via syringe. The reaction was stirred for 3 h and quenched with 1 N $NaHSO_4$. The mixture was filtered through a Celite plug and washed with EtOAc (30 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 11:1) to afford 0.032 g (71%) of the trienoate **26** as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6): δ = 7.34 (s, 1 H), 6.29 (d, *J* = 15.5 Hz, 1 H), 6.17 (s, 1 H), 5.74 (dd, *J* = 9.0, 1.0 Hz, 1 H), 5.72 (dd, *J* = 15.5, 7.0 Hz, 1 H), 5.50 (t, *J* = 7.0 Hz, 1 H), 5.46 (dd, *J* = 11.5, 4.5 Hz, 1 H), 5.44 (d, *J* = 3.5 Hz, 1 H), 5.35 (dt, *J* = 9.5, 3.5 Hz, 1 H), 5.30 (s, 1 H), 4.70 (d, *J* = 9.0 Hz, 1 H), 4.40 (dd, *J* = 9.0, 5.5 Hz, 1 H), 4.27 (t, *J* = 8.5 Hz, 2 H), 4.20 (t, *J* = 6.5 Hz, 1 H), 4.18–4.13 (m,1 H), 3.51 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.33 (s, 3 H), 3.28 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.19 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.12 (s, 3 H), 3.11–3.06 (m, 1 H), 2.35–2.14 (m, 5 H), 2.05 (d, *J* = 1.0 Hz, 3 H), 1.93 (s, 3 H), 1.92–1.89 (m, 1 H), 1.86 (d, *J* = 1.0 Hz, 3 H), 1.84–1.75 (m, 2 H), 1.73 (s, 3 H), 1.65 (s, 3 H), 1.64 (s, 3 H), 1.53–1.47 (m, 1 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.16 (d, *J* = 6.5 Hz, 3 H), 1.05–1.01 (m, 21 H), 0.93 (s, 9 H), 0.93–0.89 (m, 3 H), 0.64 (dq, *J* = 8.0, 1.0 Hz, 6 H), 0.34 (s, 3 H), 0.33 (s, 3 H), 0.24 (s, 3 H), 0.14 (s, 3 H), –0.09 (s, 9 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 169.9, 169.6, 169.2, 168.0, 140.9, 136.5, 136.0, 135.9, 134.1,133.8, 132.0, 128.7, 128.4, 120.6, 101.9, 78.4, 78.0, 77.2, 75.0, 71.3, 71.1, 70.4, 69.5,

67.3, 62.8, 58.7, 57.1, 44.8, 39.3, 37.3, 34.5, 34.2, 28.0, 26.1, 25.7, 25.0, 20.9, 20.4, 20.2, 18.3, 18.1, 17.8, 17.5, 15.0, 14.3, 12.6, 11.8, 7.1, 5.7, 5.4, –1.7, –3.4, –4.1, –4.1, –5.3. HRMS (ESI): *m/z* = 1337.6980 ([M + Li]$^+$ calculated for $C_{65}H_{119}BrLiO_{15}Si_4$: 1337.6970).

Alcohol 27: To a solution of the trienoate **26** (0.010 g, 0.0075 mmol) in THF (1 mL) at 0 °C was added a solution of HF in pyridine (0.4 mL, prepared from 2 g of HF pyridine, 2 mL pyridine and 10 mL THF). The reaction mixture was stirred at 0 °C for 2 h, and quenched with saturated $NaHCO_3$ (2 mL). The aqueous layer was extracted with EtOAc (3 × 6 mL) and the combined organic layers were washed with saturated $CuSO_4$ and brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to afford 0.006 g (66%) of alcohol **27** as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6): δ = 7.34 (s, 1 H), 6.27 (d, *J* = 16.0 Hz, 1 H), 6.15 (s, 1 H), 5.70 (dd, *J* = 9.0, 1.0 Hz, 1 H), 5.62 (dd, *J* = 15.5, 7.0 Hz, 1 H), 5.51 (t, *J* = 7.0 Hz, 1 H), 5.48 (dd, *J* = 11.5, 5.0 Hz, 1 H), 5.46 (d, *J* = 5.0 Hz, 1 H), 5.39 (dt, *J* = 10.0, 3.5 Hz, 1 H), 5.32 (s, 1 H), 4.71 (d, *J* = 9.0 Hz, 1 H), 4.41 (dd, *J* = 9.5, 4.5 Hz, 1 H), 4.28 (t, *J* = 8.5 Hz, 2 H), 4.19–4.14 (m, 1 H), 3.97 (t, *J* = 6.5 Hz, 1 H), 3.52 (dd, *J* = 16.0, 3.0 Hz, 1 H), 3.32 (s, 3 H), 3.30 (dd, *J* = 9.0, 6.5 Hz, 1 H), 3.20 (dd, *J* = 9.0, 4.5 Hz, 1 H), 3.13 (s, 3 H), 3.00–2.94 (m, 1 H), 2.37–2.16 (m, 5 H), 2.04 (d, *J* = 1.5 Hz, 3 H), 1.95 (s, 3 H), 1.95–1.91 (m, 1 H), 1.87–1.76 (m, 2 H), 1.80 (d, *J* = 1.0 Hz, 3 H), 1.73 (s, 3 H), 1.67 (s, 3 H), 1.65 (s, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H), 1.05 (s, 9 H), 0.96 (s, 9 H), 0.93–0.89 (m, 3 H), 0.35 (s, 3 H), 0.34 (s, 3 H), 0.25 (s, 3 H), 0.15 (s, 3 H), –0.80 (s, 9 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 170.0, 169.7, 169.3, 168.1, 140.9, 136.4, 136.2, 136.1, 134.1, 133.8, 132.2, 129.1, 128.4, 120.6, 102.0, 78.4, 78.0, 75.7, 75.0, 71.4, 71.1, 70.3, 69.6, 67.3, 62.9, 58.8, 57.2, 43.8, 39.2, 37.3, 34.5, 34.3, 30.1, 28.0, 26.1, 25.7, 25.0, 20.9, 20.5, 20.2, 18.3, 18.0, 17.9, 17.5, 14.7, 14.3, 12.6, 11.9, 5.7, –1.7, –3.3, –4.0, –4.1, –5.3.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full characterization data for all new compounds.

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[1] J. Staunton, K. J. Weissman, *Nat. Prod. Rep.* **2001**, *18*, 380–416.
[2] a) J. W. Kim, H. Adachi, K. ShinYa, Y. Hayakawa, H. Seto, *J. Antibiot.* **1997**, *50*, 628–630; b) Y. Hayakawa, J. W. Kim, H. Adachi, K. Shin-Ya, H. Fujita, H. Seto, *J. Am. Chem. Soc.* **1998**, *120*, 3524–3525.
[3] Recently Wender and co-workers identified apoptolidin B and C, see: P. A. Wender, M. Sukopp, K. Longcore, *Org. Lett.* **2005**, *7*, 3025–3028.
[4] a) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 14766–14771; b) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla, *Chemistry & Biology* **2001**, *8*, 71–80; c) A. R. Salomon, Y. B. Zhang, H. Seto, C. Khosla, *Org. Lett.* **2001**, *3*, 57–59.
[5] a) J. Schuppan, B. Ziemer, U. Koert, *Tetrahedron Lett.* **2000**, *41*, 621–624; b) G. A. Sulikowski, W. M. Lee, B. Jin, B. Wu, *Org. Lett.* **2000**, *2*, 1439–1442; c) K. Toshima, T. Arita, K. Kato, D. Tanaka, S. Matsumura, *Tetrahedron Lett.* **2001**, *42*, 8873–8876; d) K. Abe, K. Kato, T. Arai, M. A. Rahim, I. Sultana, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2004**, *45*, 8849–8853; e) W. D. Paquette, R. E. Taylor, *Org. Lett.* **2004**, *6*, 103–106.
[6] J. Schuppan, H. Wehlan, S. Keiper, U. Koert, *Angew. Chem. Int. Ed.* **2001**, *40*, 2063–2066.
[7] a) K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, H. X. Wei, B. Weyershausen, *Angew. Chem. Int. Ed.* **2001**, *40*, 3849–3854; b) K. C. Nicolaou, Y. W. Li, K. C. Fylaktakidou, H. J. Mitchell, K. Sugita, *Angew. Chem. Int. Ed.* **2001**, *40*, 3854–3857; c) K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H. X. Wei, P. Guntupalli, D. Hepworth, K. Sugita, *J. Am. Chem. Soc.* **2003**, *125*, 15433–15442; d) K. C. Nicolaou, Y. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou, A. O'Brate, *J. Am. Chem. Soc.* **2003**, *125*, 15443–15454.
[8] H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, R. Mahrwald, B. Ziemer, M. E. J. Garcia, U. Koert, *Angew. Chem. Int. Ed.* **2004**, *43*, 4597–4601.
[9] B. Wu, Q. Liu, G. A. Sulikowski, *Angew. Chem. Int. Ed.* **2004**, *43*, 6673–6675.
[10] a) P. A. Wender, A. V. Gulledge, O. D. Jankowski, H. Seto, *Org. Lett.* **2002**, *4*, 3819–3822; b) J. D. Pennington, H. J. Williams, A. R. Salomon, G. A. Sulikowski, *Org. Lett.* **2002**, *4*, 3823–3825.
[11] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
[12] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[13] M. Fetizon, M. Jurion, *J. Chem. Soc., Chem. Commun.* **1972**, *7*, 382–383.
[14] a) M. T. Crimmins, B. King, E. A. Tabet, *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884; b) M. T. Crimmins, B. King, E. A. Tabet, K. Chaudhary, *J. Org. Chem.* **2001**, *66*, 894–902.
[15] a) M. E. Furrow, S. E. Schaus, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 6776–6777; b) A. Kumar, P. L. Coe, A. S. Jones, R. T. Walker, J. Balzarini, E. De Clercq, *J. Med. Chem.* **1990**, *33*, 2368–2375.
[16] P. Kocienski, S. Wadman, K. Cooper, *J. Am. Chem. Soc.* **1989**, *111*, 2363–2365.
[17] a) D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343; b) D. A. Evans, M. J. Dart, J. L. Duffy, D. L. Rieger, *J. Am. Chem. Soc.* **1995**, *117*, 9073–9074.
[18] C. H. Heathcock, M. C. Pirrung, E. Sohn, *J. Org. Chem.* **1979**, *44*, 4294–4299.
[19] a) D. A. Evans, M. G. Yang, M. J. Dart, J. L. Duffy, *Tetrahedron Lett.* **1996**, *37*, 1957–1960; b) W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonowski, K. A. Scheidt, *J. Org. Chem.* **2002**, *67*, 4275–4283.
[20] B. Jin, Q. Liu, G. A. Sulikowski, *Tetrahedron* **2005**, *61*, 401–408.
[21] S. A. Frank, H. Chen, R. K. Kunz, M. J. Schnaderbeck, W. R. Roush, *Org. Lett.* **2000**, *2*, 2691–2694.
[22] P. Michel, D. Gennet, A. Rassat, *Tetrahedron Lett.* **1999**, *40*, 8575–8578.
[23] P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316.

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