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Stereoselective Synthesis of the C31–C41 Spirolactam Fragment of Sanglifehrin A

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A stereoselective synthesis of the spirolactam fragment (C31–C41) of a highly-potent immunosuppressant sanglifehrin A is described. The key steps involved in this synthesis are a desymmetrization protocol, Sharpless asymmetric epoxidation, Crimmins *syn* aldol reaction, Barton–McCombie deoxygenation, and acid-mediated spirolactamization.

Introduction

The highly-potent immunosuppressive natural product sanglifehrin A (**1**) (Figure 1), isolated from *Streptomyces* flaveolus (A92-308110), was found in soil samples collected at Dembo-Bridge, Malawi, by a group of scientists from Novartis. Sanglifehrin A acts as a potent inhibitor of the mitochondrial permeability transition and reperfusion injury of the heart through binding to cyclophilin D at a different site from cyclosporine A.[1] It has high affinity towards cyclophilin A and also inhibits nitrogen-induced B-cell proliferation without influencing T-cell receptor-mediated cytokine production.[2] It was found to exhibit significant biological properties like strong cyclophilin A binding (20-fold higher affinity than cyclosporin) and immunosuppressive activity (10-fold less potent than cyclosporin). It has a complex molecular structure consisting of a 22-membered macrocyclic ring in combination with a highly-substituted spirobicyclic [5.5] spirolactam subunit, and an unusual peptidic backbone.[3] Its molecular structure has been fully elucidated by spectroscopic and X-ray crystallographic techniques.[4] Unusual structural features, seventeen stereogenic centers, and sensitive functionalities coupled with its important biological activity make sanglifehrin A attractive to synthetic- and medicinal-chemistry research groups worldwide. Its first total synthesis was achieved by Nicolaou and co-workers in 1999 by using 3-pentanone as the starting material for the spirolactam fragment,[5] and

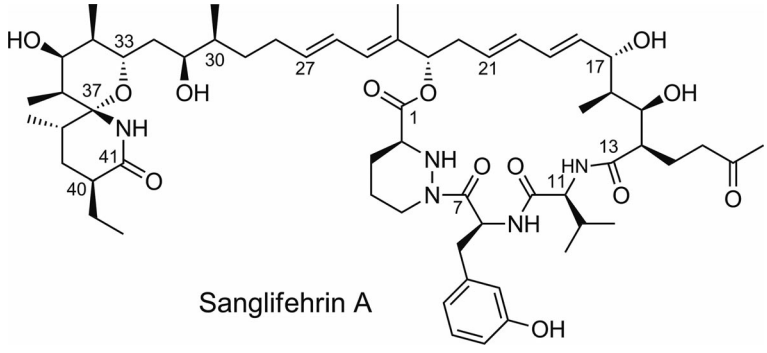

Figure 1. Structure of sanglifehrin A.

then Paquette et al.[6] reported the second total synthesis. Many other groups have also made attempts towards the synthesis of sanglifehrinA.[7] As part of our ongoing interest in the synthesis of spirocyclic natural products[8] and macrolides containing polypropionates by means of desymmetrization strategies,[9] the synthesis of sanglifehrin A (**1**) was chosen for investigation and this report describes a

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highly-stereoselective synthesis of the C31–C41 segment starting from bicyclic olefin **5** and substrate-controlled stereoselective transformations to create contiguous stereocenters.

The retrosynthetic analysis of sanglifehrin A, shown in Figure 2, explains the overall strategy involved in the present synthesis. Fragment **2** could be synthesized through intramolecular spirolactamization of key fragment **3** embedded with all of the required stereocenters of the spirolactam fragment. Fragment **3** in turn could be prepared starting from known triol **4**, which in turn could be easily obtained from **5**.

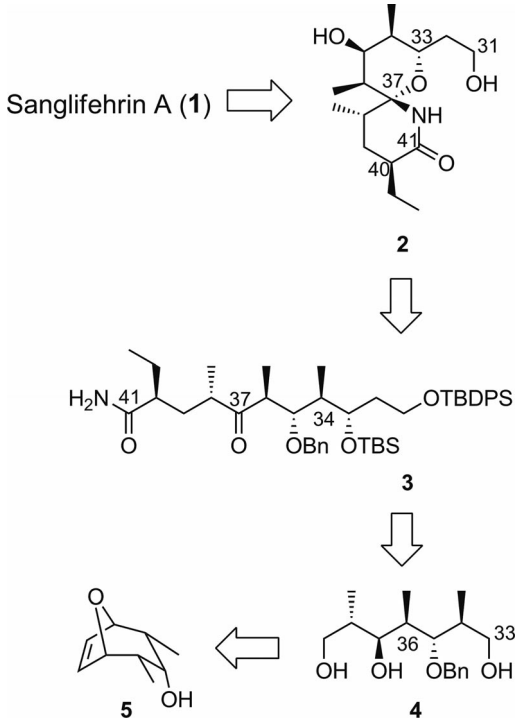


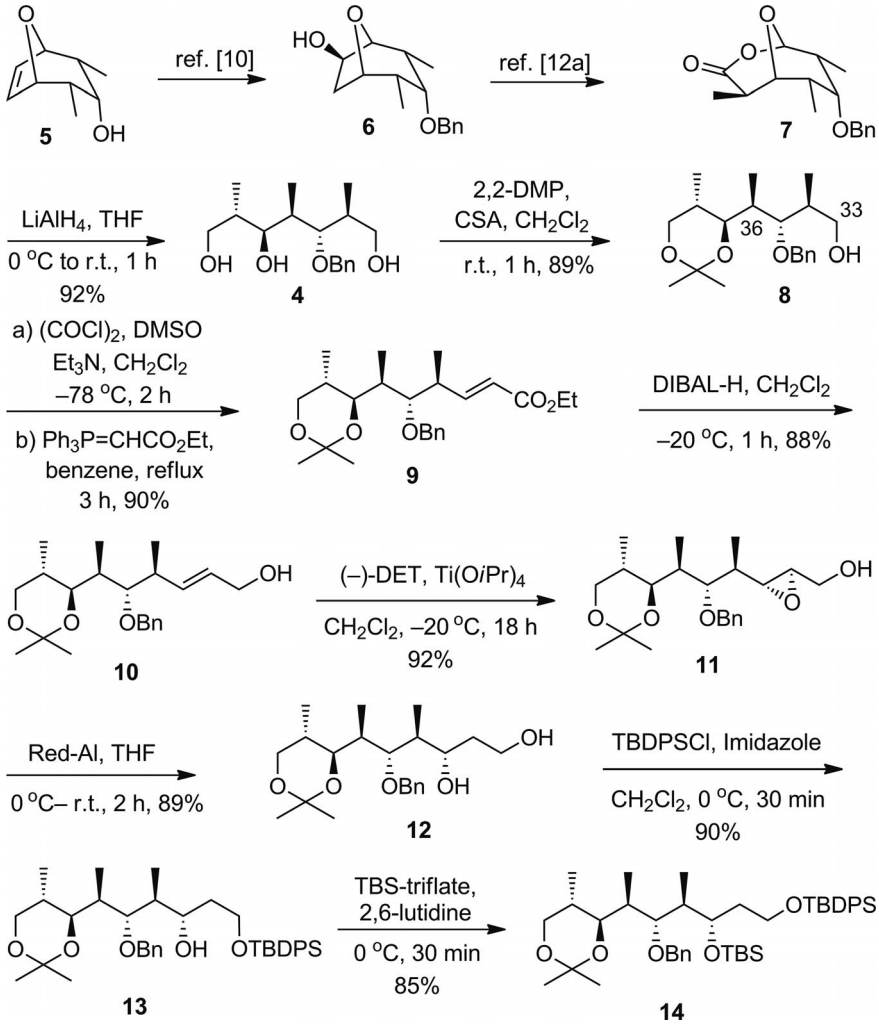
Figure 2. Retrosynthetic analysis.

Results and Discussion

As mentioned in Scheme 1, key fragment **3**, which contains all the required stereocenters of spirolactam **2**, was prepared mainly through desymmetrization of bicyclic olefin **5** by using Brown's chiral hydroboration with (+)-diisopinocamphenylborane.[10] Chiral bicyclic alcohol **6** was converted into *exo*-alkylated bicyclic lactone **7** by pyridinium-chlorochromate-mediated oxidation reaction, Baeyer-Villiger reaction,[11] and alkylation reaction with MeI. The reductive opening of *exo*-alkylated bicyclic lactone **7** with lithium aluminium hydride afforded triol **4**,[12] which has been used as a main building block in the synthesis of many natural products containing polypropionate units in our laboratory.[9] Triol **4** was converted into corresponding acetonide **8** by using 2,2-dimethoxypropane and a catalytic amount of camphor sulfonic acid (CSA).[13] The resulting free hydroxy group from a Swern oxidation reaction followed by condensation with $Ph_3P{=}CHCO_2Et$ in benzene furnished compound **9** in 90% yield. The α,β-unsaturated ester upon treatment with diisobutylaluminium hydride (DIBAL-H) afforded allyl alcohol compound **10** in 88% yield. Allylic alcohol **10** under Sharpless asymmetric epoxidation reaction conditions was smoothly converted into epoxide **11** (92% yield, 97% *de*), which was regioselectively opened with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in tetrahydrofuran (THF) to afford 1,3-diol product **12** exclusively in 89% yield.[14] The primary hydroxy group was selectively silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl), and the secondary alcohol further protected as its *tert*-butyldimethylsilyl (TBDMS) ether by using TBDMS trifluoromethanesulfonate (OTf) [15] and 2,6-lutidine to furnish fully-protected compound **14** in 77% yield over two steps.

Selective deprotection of the acetonide group of **14** in the presence of silyl groups by using $CuCl_2{\cdot}2H_2O$ in CH_3CN at 0 °C gave **15** in 90% yield.[16] The 1,3-diol was protected as its *p*-methoxybenzyl ether (PMB) acetal with anisaldehyde dimethyl acetal in the presence of a catalytic amount of CSA to furnish **16** in 92% yield, which on subsequent regioselective acetal cleavage with DIBAL-H at –15 °C in CH_2Cl_2 afforded **17** in 94%.[17] Further, the alcohol, on oxidation with Dess–Martin periodinane[18] at 0 °C, furnished an aldehyde that after aldol reaction with the chlorotitanium enolate of *N*-acyloxazolidinethione, (–)-sparteine at 0 °C gave aldol adduct **18** in 85% yield (> 98:2).[19] The chiral auxiliary was reductively removed with $NaBH_4$ to form 1,3-diol **19** in 89% yield (Scheme 2).[20] The primary alcohol was protected as triethylsilyl (TES) ether **20** in 86% yield, and the secondary alcohol was converted into xanthate **21** in 94% yield by using NaH, CS_2 and MeI. The xanthate was treated with Bu_3SnH and a catalytic amount of azobisisobutyronitrile (AIBN) in toluene under Barton–McCombie deoxygenation reaction conditions to obtain required compound **22** in 87% yield.[21] The selective deprotection of the TES group was successfully achieved with *p*-toluenesulfonic acid (*p*-TSA; catalytic amount) in CH_2Cl_2 to give **23** in 84% yield. Alcohol **23** was converted into the corresponding acid by following a two-step sequence. The alcohol was converted into an aldehyde by Dess–Martin periodinane followed by a Pinnick oxidation to furnish desired acid **24** in 85% yield over two steps.[22]

Our next task was spirolactamization of compound **3**, which could be obtained from acid **24** (Scheme 3). Furthermore, the acid was converted into amide **25** in 85% yield by using ethyl chloroformate followed by aqueous NH_3. The PMB group was selectively deprotected by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under standard conditions to afford secondary alcohol **26** in 96% yield. Oxidation of the secondary alcohol with Dess–Martin periodinane afforded keto compound **3** in 83% yield. The cleavage of the silyl group present in the keto compound with HF in CH_3CN followed by cyclization furnished spirolactam fragment **27** with the natural configuration at C37 with high fidelity in 80% yield. Finally, depro-



Scheme 1. Synthesis of intermediate **14**.

tection of the benzyl ether with $Pd(OH)_2$ in MeOH under a hydrogen atmosphere provided diol **2** in 86% yield. The spectral (^1H, ^{13}C NMR, and IR) and analytical data {$[\alpha]_D^{27}$ = –57.4 (c = 0.45, $CHCl_3$)} of spiro fragment **2** were in good agreement with the reported values.[5c]

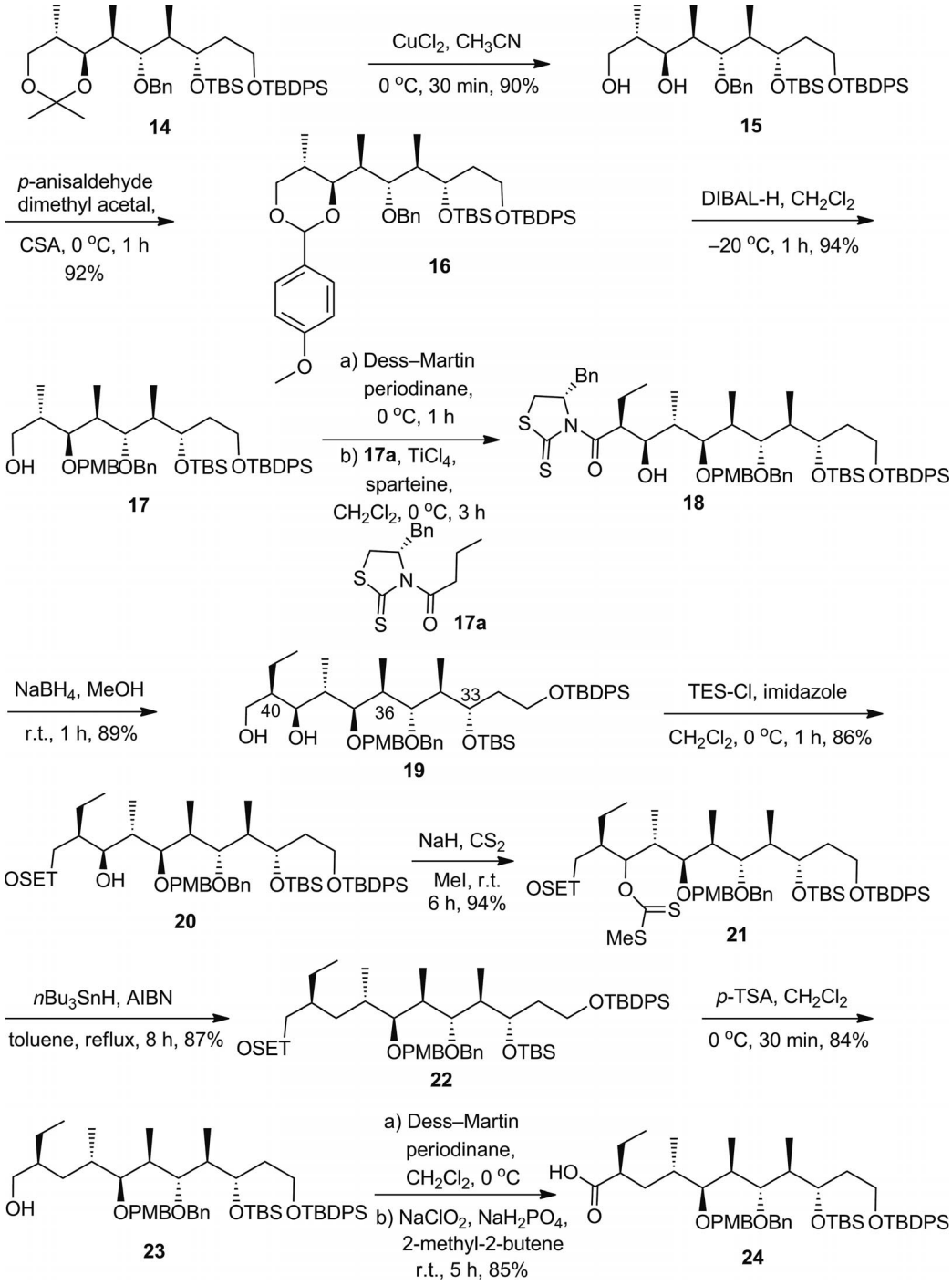
Conclusions

In conclusion, we have developed an efficient and highly-stereoselective synthesis for the spirolactam segment of the extremely potent immunosuppressant sanglifehrin A. The synthesis of the C31–C41 fragment of sanglifehrin A (**1**) was successfully accomplished by following our own desymmetrization strategy, followed by Sharpless asymmetric epoxidation reaction, Crimmins *syn* aldol reaction, Barton–McCombie deoxygenation reaction, and spirolactamization under aqueous HF conditions in a 21-step longest linear sequence with 6.3% overall yield starting from known triol **4**. Attempts toward the peptide macrolactone core and coupling with the spirolactam segment to synthesize sanglifehrin A is in progress and will be reported in due course.

Experimental Section

General Remarks: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven- or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexane from CaH_2; MeOH and EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). TOF analyzer technique was used for the HRMS measurement. ^1H and ^{13}C NMR chemical shifts are reported relative to tetramethylsilane. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad.

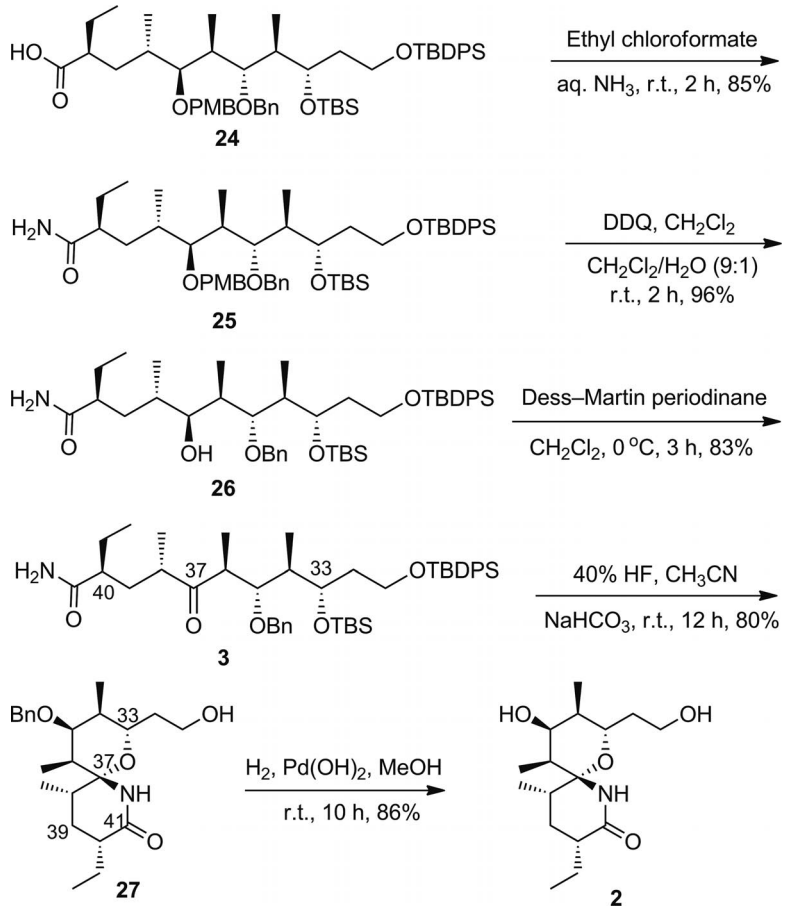
(2*S*,3*S*,4*R*,5*S*,6*S*)-5-(Benzyloxy)-2,4,6-trimethylheptane-1,3,7-triol (4): To an ice-cooled suspension of $LiAlH_4$ (5.1 g, 134.38 mmol) in THF (60 mL) at 0 °C, was added methylated lactone **7** (13.0 g, 44.82 mmol) in THF (50 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature. After complete conversion of the reaction (confirmed by TLC), it was again cooled to 0 °C and quenched with a saturated solution of Na_2SO_4 (60 mL). After stirring at room temperature for 5 h, the solid was filtered off through a pad of Celite and washed with ethyl



Scheme 2. Synthesis of intermediate **24**.

acetate (3 × 50 mL). The filtrate was dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane/ethyl acetate = 1:1) to afford triol **4** (12.2 g, 92%) as a viscous liquid. $[\alpha]_D^{27}$ = –3.1 (*c* = 1.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3508, 1462, 1036 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.24 (m, 5 H), 4.67 (AB_q, *J* = 10.6 Hz, 2 H), 3.87–3.73 (m, 2 H), 3.70–3.50 (m, 4 H), 2.07–1.97 (m, 1 H), 1.92–1.77 (m, 2 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.4, 128.7, 128.2, 127.9, 88.7, 69.2, 65.4, 37.9, 37.3, 35.5, 14.7, 13.3, 11.6 ppm. HRMS: calcd. for $C_{17}H_{28}NaO_4$ $[M + Na]^+$ 319.1885; found 319.1874.

(2*S*,3*S*,4*S*)-3-(Benzyloxy)-2-methyl-4-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-1-ol (8): To a stirred solution of triol **4** (11.0 g, 37.16 mmol) in CH_2Cl_2 (80 mL) was added 2,2-dimethoxy propane (13.7 mL, 111.48 mmol) followed by a catalytic amount of CSA (100 mg). The mixture was stirred at ambient temperature for 30 min. The reaction mixture was quenched with saturated sodium hydrogen carbonate solution (60 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (2 × 70 mL), dried with anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 9:1) to furnish pro-



Scheme 3. Accomplishment of the C31–C41 spirolactam fragment **2** of sanglifehrin A.

tected diol **8** (11.2 g, 89%) as a white solid, m.p. 96–98 °C. $[\alpha]_D^{27}$ = +26.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3453, 2962, 2928, 1457, 1382, 1199, 1098, 1064 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.22 (m, 5 H), 4.65 (AB_q, *J* = 11.3 Hz, 2 H), 3.93–3.81 (m, 2 H), 3.73–3.42 (m, 4 H), 2.95–2.49 (br. s, 1 H), 2.06–1.80 (m, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.21 (d, *J* = 7.1 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.72 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 128.4, 127.5, 126.9, 97.9, 85.5, 75.3, 73.3, 66.1, 64.1, 37.3, 36.1, 30.2, 29.7, 19.4, 16.3, 12.4, 9.8 ppm. HRMS: calcd. for $C_{20}H_{32}NaO_4$ $[M + Na]^+$ 359.2198; found 359.2185.

Ethyl (4*S*,5*S*,6*S*,*E*)-5-(Benzyloxy)-4-methyl-6-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]hept-2-enoate (9): To a solution of oxalyl chloride (7.1 g, 56.54 mmol) in CH_2Cl_2 (30 mL), was added DMSO (8.8 g, 113.09 mmol) at –78 °C. After 20 min, alcohol (9.5 g, 28.27 mmol) in CH_2Cl_2 (30 mL) was added to the reaction mixture and stirred at –78 °C for 45 min. Triethylamine (22.8 g, 226.19 mmol) was added to the reaction mixture and stirred at the same temperature for a further 45 min. Saturated aqueous NH_4Cl solution (40 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2× 75 mL). The combined organic layer was washed with water (100 mL) and brine (100 mL), dried with anhydrous Na_2SO_4 and concentrated. The crude aldehyde was used for the next reaction without further purification.

To a solution of ethyl 2-(triphenylphosphoranylidene)ethanoate (11.87 g, 34.13 mmol) in benzene (60 mL) at 70 °C, was added the crude aldehyde in benzene (40 mL). After complete addition, the reaction mixture was heated to reflux for 3 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue purified by column chromatography with silica gel (hexane/ethyl acetate = 10:1) to obtain Wittig product **9** (10.3 g, 90%) as a pale yellow liquid. $[\alpha]_D^{27}$ = –9.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2975, 2932, 1718, 1651, 1456 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.39–7.23 (m, 5 H), 7.09 (dd, *J* = 15.8, 8.5 Hz, 1 H), 5.83 (d, *J* = 15.8 Hz, 1 H), 4.64 (AB_q, *J* = 12.0 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.88 (dd, *J* = 10.4, 0.9 Hz, 1 H), 3.66 (dd, *J* = 11.5, 5.0 Hz, 1 H), 3.52–3.39 (m, 2 H), 2.74–2.62 (m, 1 H), 1.92–1.55 (m, 2 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 0.82 (d, *J* = 6.9 HZ Hz, 3 H), 0.68 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.6, 150.5, 138.8, 128.2, 127.2, 126.8, 121.4, 97.9, 83.0, 74.6, 73.2, 66.1, 60.1, 39.6, 37.5, 30.1, 29.8, 19.4, 17.6, 14.2, 12.3, 9.3 ppm. HRMS: calcd. for $C_{24}H_{36}NaO_5$ $[M + Na]^+$ 427.2455; found 427.2445.

(4*S*,5*S*,6*S*,*E*)-5-(Benzyloxy)-4-methyl-6-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]hept-2-en-1-ol (10): To a solution of compound **9** (10.0 g, 24.75 mmol) in CH_2Cl_2 (50 mL), was added DIBAL-H (20% in toluene, 35.3 mL, 49.5 mmol) dropwise down the walls of the flask at –20 °C. After completion of the reaction (monitored by TLC), it was quenched by addition of methanol (15 mL) at 0 °C followed by a saturated solution of sodium potassium tartrate (40 mL), and was stirred at room temperature for 6 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3× 60 mL). The combined organic layer was washed with brine (2× 75 mL), dried with anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by

column chromatography with silica gel (hexane/ethyl acetate = 4:1) to give allyl alcohol **10** (7.9 g, 88%) as a colorless viscous liquid. $[\alpha]_D^{27}$ = +22.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3384, 2970, 2934, 1690, 1456, 1383 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.42–7.20 (m, 5 H), 5.87–5.56 (m, 2 H), 4.62 (AB_q, *J* = 11.5 Hz, 2 H), 4.09 (d, *J* = 4.9 Hz, 2 H), 3.88 (dd, *J* = 10.6, 1.6 Hz, 1 H), 3.66 (dd, *J* = 11.5, 4.9 Hz, 1 H), 3.47 (t, *J* = 11.5 Hz, 1 H), 3.34 (dd, *J* = 9.8, 1.6 Hz, 1 H), 2.60–2.42 (m, 1 H), 1.98–1.56 (m, 2 H), 1.37 (s, 6 H), 1.17 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 7.3 Hz, 3 H), 0.68 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.0, 133.9, 129.4, 128.2, 127.2, 126.9, 97.9, 83.3, 74.7, 73.3, 66.1, 63.7, 39.3, 37.3, 30.1, 29.8, 19.5, 18.9, 12.3, 9.3 ppm. HRMS: calcd. for $C_{22}H_{34}NaO_4$ $[M + Na]^+$ 385.2349; found 385.2350.

((2*R*,3*R*)-3-{(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-2-yl}oxiran-2-yl)methanol (11): To a stirred mixture of 4 Å molecular sieves (5.0 g) in CH_2Cl_2 (40 mL), $Ti(OiPr)_4$ (0.7 mL, 2.5 mmol) and D-(–)-diethyl tartrate (0.5 mL, 3.2 mmol) were added at –20 °C. The reaction mixture was stirred vigorously for 30 min. Allyl alcohol (7.8 g, 21.54 mmol) dissolved in CH_2Cl_2 (30 mL) was added to the reaction mixture at the same temperature and stirred again for 30 min, followed by addition of *tert*-butyl hydroperoxide (4.26 g, 9.4 mL, 47.4 mmol). The reaction mixture was stirred at –20 °C for an additional 48 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite and washed with CH_2Cl_2 (3 × 40 mL). The filtrate was quenched by the addition of water (14 mL), followed by addition of 30% NaOH solution (6.0 mL) that was then saturated with NaCl. The reaction mixture was stirred at room temperature for 2 h. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (100 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 5:2) to afford epoxy alcohol **11** (7.5 g, 92%) as a colorless viscous liquid. $[\alpha]_D^{27}$ = +48.0 (*c* = 3.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3380, 2972, 1450, and 1199 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.22 (m, 5 H), 4.65 (AB_q, *J* = 11.7 Hz, 2 H), 3.99–3.82 (m, 2 H), 3.67 (dd, *J* = 11.3, 5.1 Hz, 1 H), 3.62–3.35 (m, 3 H), 3.13 (dd, *J* = 7.9, 2.0 Hz, 1 H), 2.89–2.83 (m, 1 H), 2.19–2.06 (m, 1 H), 1.98–1.62 (m, 2 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.09 (d, *J* = 7.1 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.75 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.9, 128.2, 127.2, 126.7, 97.8, 82.8, 74.7, 73.2, 66.1, 62.1, 56.3, 38.0, 37.3, 30.1, 29.8, 19.4, 15.0, 12.3, 9.6 ppm. HRMS: calcd. for $C_{22}H_{34}NaO_5$ $[M + Na]^+$ 401.2298; found 401.2296.

(3*S*,4*S*,5*S*,6*S*)-5-(Benzyloxy)-4-methyl-6-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]heptane-1,3-diol (12): To a stirred solution of epoxide **11** (7.3 g, 19.31 mmol) in THF (40 mL) was added Red-Al (70% w/w in toluene, 33.5 mL, 57.93 mmol) dropwise at –20 °C. The reaction mixture was slowly allowed to warm to room temperature and stirred for 2 h. After complete conversion (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (30 mL) at 0 °C, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (2 × 30 mL), dried with Na_2SO_4 and evaporated, and the residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 2:1) to give **12** (6.6 g, 89%) as a viscous yellow liquid. $[\alpha]_D^{27}$ = +5.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3408, 2952, 2927, 1457, 1383 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.43–7.25 (m, 5 H), 4.67 (s, 2 H), 3.98–3.64 (m, 5 H), 3.57–3.45 (m, 1 H), 3.43–3.36 (m, 1 H), 3.29–3.16 (br. s, 1 H), 2.10–1.78 (m, 4 H), 1.74–1.59 (m, 1 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 0.97 (t, *J* = 7.3 Hz, 6 H), 0.70 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 128.4, 127.6, 127.1, 97.9, 86.0, 75.4, 75.2, 73.1, 66.2, 62.1, 41.7, 39.0, 35.8, 30.2, 29.8, 19.3, 17.1, 12.4, 9.9 ppm. HRMS: calcd. for $C_{22}H_{36}NaO_5$ $[M + Na]^+$ 403.2455; found 403.2445.

(3*S*,4*S*,5*S*,6*S*)-5-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-4-methyl-6-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]heptan-3-ol (13): Imidazole (1.16 g, 17.10 mmol) and TBDPSCl (4.4 mL, 17.10 mmol) were added to a solution of diol **12** (6.5 g, 17.10 mmol) in CH_2Cl_2 (50 mL), and the reaction was stirred at room temperature for 1 h. The reaction was quenched with saturated $NaHCO_3$ solution (40 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (2 × 50 mL), dried with Na_2SO_4 and the solvents evaporated. Purification of this residue by column chromatography with silica gel (hexane/ethyl acetate = 9:1) furnished **13** (9.6 g, 90%) as a colorless liquid. $[\alpha]_D^{27}$ = –15.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3444, 2924, 2854, 1462 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.76–7.74 (m, 4 H), 7.46–7.21 (m, 11 H), 4.63 (AB_q, *J* = 11.5 Hz, 2 H), 4.10–3.99 (m, 1 H), 3.96–3.79 (m, 3 H), 3.68 (dd, *J* = 11.5, 5.0 Hz, 1 H), 3.54–3.40 (m, 2 H), 2.09–1.79 (m, 4 H), 1.75–1.56 (m, 1 H), 1.38 (s, 3 H), 1.34 (s, 3 H), 1.13–1.0 (m, 12 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.67 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.9, 135.5, 129.6, 128.2, 127.6, 127.2, 126.8, 97.9, 84.3, 74.7, 73.2, 71.6, 66.2, 62.7, 41.1, 37.9, 36.0, 30.2, 29.8, 26.7, 19.3, 19.0, 15.0, 12.3, 9.9 ppm. HRMS: calcd. for $C_{38}H_{54}NaO_5Si$ $[M + Na]^+$ 641.3632; found 641.3633.

(*S*)-5-{(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-2-yl}-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (14): To an ice-cooled solution of **13** (8.0 g, 12.94 mmol) in CH_2Cl_2 (60 mL), tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 4.4 mL, 19.41 mmol) and 2,6-lutidine (2.25 mL, 19.41 mmol) were added and the reaction mixture was slowly warmed to ambient temperature. After stirring for 1 h at the same temperature the reaction was quenched with saturated NH_4Cl (40 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with brine (75 mL), dried with Na_2SO_4 and the solvents evaporated. The resulting residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 20:1) to afford **14** (8.1 g, 85%) as a colorless liquid. $[\alpha]_D^{27}$ = –10.0 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2921, 2851, 1219 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.81–7.71 (m, 4 H), 7.54–7.27 (m, 11 H), 4.63 (AB_q, *J* = 10.6 Hz, 2 H), 3.99–3.68 (m, 5 H), 3.58–3.48 (m, 1 H), 3.43 (dd, *J* = 9.8, 3.0 Hz, 1 H), 2.29–2.09 (m, 1 H), 2.07–1.69 (m, 4 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 1.22–1.09 (m, 12 H), 1.03–0.85 (m, 15 H), 0.13 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.4, 135.5, 135.4, 129.5, 128.5, 127.9, 127.5, 98.6, 88.2, 77.1, 76.1, 69.4, 69.3, 61.9, 42.3, 37.2, 34.9, 30.6, 29.8, 26.8, 25.8, 19.1, 17.9, 13.3, 11.8, 11.0, –4.3, –4.7 ppm. HRMS: calcd. for $C_{44}H_{68}NaO_5Si_2$ $[M + Na]^+$ 755.4502; found 755.4508.

(2*S*,3*S*,4*R*,5*R*,6*R*,7*S*)-5-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-2,4,6-trimethylnonane-1,3-diol (15): To a stirred solution of **14** (8.0 g, 10.92 mmol) in CH_3CN (50 mL) at 0 °C, was added $CuCl_2 \cdot 2H_2O$ (2.95 g, 16.39 mmol). The reaction mixture was allowed to stir for 30 min at the same temperature. After complete conversion (monitored by TLC), the reaction was quenched by a saturated $NaHCO_3$ solution (30 mL). The organic solvent was removed under reduced pressure and the aqueous phase extracted with ethyl acetate (3 × 60 mL). The combined organic layer was washed with brine (100 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 4:1) to give **15** (6.8 g, 90%) as a colorless viscous liquid. $[\alpha]_D^{27}$ =

–35.2 (c = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3450, 2956, 2928, 1463, 1253 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.81–7.71 (m, 4 H), 7.56–7.34 (m, 9 H), 7.33–7.25 (m, 2 H), 4.62 (AB_q, J = 11.3 Hz, 2 H), 4.27–4.15 (m, 2 H), 3.99–3.87 (m, 2 H), 3.83–3.69 (m, 4 H), 3.45 (dd, J = 10.6, 1.5 Hz, 1 H), 2.28–2.13 (m, 1 H), 2.04–1.71 (m, 4 H), 1.25 (d, J = 7.5 Hz, 3 H), 1.12 (s, 9 H), 0.94 (s, 9 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.8 Hz, 3 H), 0.12 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.4, 135.6, 135.5, 133.9, 133.8, 129.5, 128.5, 127.9, 127.5, 88.2, 77.1, 76.1, 69.4, 69.2, 61.9, 42.3, 37.3, 34.9, 26.9, 25.8, 19.1, 17.9, 13.3, 11.8, 11.0, –4.3, –4.7 ppm. HRMS: calcd. for $C_{41}H_{64}NaO_5Si_2$ $[M + Na]^+$ 715.4184; found 715.4186.

(5*S*)-5-{(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]pentan-2-yl}-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (16): To a stirred solution of diol **15** (6.6 g, 9.53 mmol) in CH_2Cl_2 (60 mL), *p*-methoxyphenyl (PMP)-$CH(OMe)_2$ (1.9 mL, 11.44 mmol) was added followed by a catalytic amount of CSA (48 mg). The reaction mixture was stirred at room temperature for 1 h and then quenched by the addition of a saturated $NaHCO_3$ solution (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3× 50 mL). The combined organic layer was washed with brine (2× 20 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane/ethyl acetate = 20:1) to give **16** (7.2 g, 92%) as a colorless liquid. $[\alpha]_D^{27}$ = +10.7 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2957, 2931, 1615, 1462, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.70–7.60 (m, 4 H), 7.43–7.20 (m, 13 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.28 (s, 1 H), 4.56 (AB_q, J = 11.7 Hz, 2 H), 4.26–4.19 (m, 1 H), 4.02 (dd, J = 11.1, 4.5 Hz, 1 H), 3.83–3.71 (m, 6 H), 3.49 (dd, J = 9.8, 3.4 Hz, 1 H), 3.37 (t, J = 10.9 Hz, 1 H), 2.23–1.91 (m, 4 H), 1.69–1.53 (m, 1 H), 1.10–0.98 (m, 15 H), 0.83 (s, 9 H), 0.51 (d, J = 6.6 Hz, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.7, 139.5, 135.5, 135.4, 134.1, 131.5, 129.4, 129.3, 128.1, 127.5, 127.3, 126.9, 126.6, 113.5, 100.7, 82.9, 81.7, 75.1, 73.2, 67.8, 61.2, 55.2, 41.2, 36.7, 35.8, 30.3, 26.9, 25.8, 19.2, 18.0, 11.8, 11.4, 10.5, –4.1, –4.5 ppm. HRMS: calcd. for $C_{49}H_{70}NaO_6Si_2$ $[M + Na]^+$ 833.4603; found 833.4596.

(2*S*,3*S*,4*R*,5*R*,6*R*,7*S*)-5-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylnonan-1-ol (17): DIBAL-H (20% in toluene, 18.5 mL, 25.92 mmol) was added to a stirred solution of PMP-acetal **15** (7.0 g, 8.64 mmol) in CH_2Cl_2 (70 mL) at –20 °C under an argon atmosphere. The reaction mixture was allowed to stir for 30 min at the same temperature. After complete conversion (monitored by TLC) the reaction was quenched by the addition of methanol (10 mL), followed by a saturated solution of sodium potassium tartrate (40 mL) and stirred for 5 h. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3× 50 mL). The combined organic layer was washed with brine (100 mL), dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane/ethyl acetate = 7:1) to obtain alcohol **16** (6.6 g, 94%) as a colorless liquid. $[\alpha]_D^{27}$ = +3.5 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3485, 2957, 2926, 1464, 1249 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.75–7.66 (m, 4 H), 7.49–7.34 (m, 6 H), 7.33–7.28 (m, 5 H), 7.12 (d, J = 8.3 Hz, 2 H), 6.83 (d, J = 8.3 Hz, 2 H), 4.59 (AB_q, J = 11.3 Hz, 2 H), 4.50 (AB_q, J = 10.6 Hz, 2 H), 4.30–4.22 (m, 1 H), 3.90–3.79 (m, 4 H), 3.78–3.57 (m, 3 H), 3.33–3.26 (dd, J = 7.5, 5.3 Hz, 1 H), 2.99–2.91 (m, 1 H), 2.17–1.81 (m, 4 H), 1.80–1.65 (m, 1 H), 1.20 (d, J = 6.8 Hz, 3 H),1.07 (s, 9 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 138.6, 135.5, 135.4, 133.9, 130.7, 129.4, 129.3, 128.2, 127.5, 127.4, 127.3, 113.6, 85.3, 83.2, 75.0, 73.8, 68.8, 66.1, 61.7, 55.1, 42.2, 39.4, 38.9, 35.0, 26.8, 25.8, 19.1, 18.0, 15.2, 13.0, 11.2, –4.1, –4.6 ppm. HRMS: calcd. for $C_{49}H_{72}NaO_6Si_2$ $[M + Na]^+$ 835.4759; found 835.4749.

(2*S*,3*R*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-7-(benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-3-hydroxy-5-(4-methoxybenzyloxy)-4,6,8-trimethylundecan-1-one (18): To a stirred solution of alcohol **16** (6.5 g, 8.0 mmol) in CH_2Cl_2 (60 mL), Dess–Martin periodinane (5.09 g, 12.0 mmol) was added at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at room temperature. After complete conversion of the starting material (monitored by TLC) the reaction was quenched with a saturated $NaHCO_3$ solution (30 mL) and diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2× 50 mL). The combined organic layer was washed with brine (2× 75 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to get a crude product that was quickly purified by column chromatography with silica gel (hexane/ethyl acetate = 10:1) to obtain aldehyde **18** (6.4 g) as a colorless liquid that was immediately used for the next reaction.

$TiCl_4$ (0.83 mL, 7.65 mmol) was added slowly to a solution of (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl) propan-1-one (1.94 g, 6.953 mmol) in CH_2Cl_2 (15 mL) at 0 °C and stirred for 5 min. To this yellow suspension, (–)-sparteine (4.0 mL, 17.38 mmol) was added. After stirring for 20 min, to the dark red enolate, freshly prepared aldehyde (6.4 g) dissolved in CH_2Cl_2 (20 mL) was added slowly at 0 °C. After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated NH_4Cl (25 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3× 60 mL). The combined organic layer was washed with brine (100 mL), dried with Na_2SO_4, evaporated under reduced pressure, and purified by column chromatography over silica gel (hexane/ethyl acetate = 9:1) to afford **18** (7.4 g, 85%) as a pale yellow liquid. $[\alpha]_D^{27}$ = +32.2 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3456, 2924, 2853, 1702, 1513, 1462 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.78–7.68 (m, 4 H), 7.54–7.28 (m, 16 H), 7.09 (d, J = 8.3 Hz, 2 H), 6.85 (d, J = 8.3 Hz, 2 H), 4.94–4.81 (m, 1 H), 4.73–4.52 (m, 4 H), 4.39 (d, J = 9.0 Hz, 1 H), 4.28 (d, J = 10.5 Hz, 2 H), 3.96–3.82 (m, 5 H), 3.80–3.67 (m, 2 H), 3.32–3.20 (m, 2 H), 3.16–3.05 (m, 1 H), 2.88 (d, J = 11.3 Hz, 1 H), 2.33–2.19 (m, 1 H), 2.17–1.72 (m, 6 H), 1.29 (d, J = 6.8 Hz, 3 H), 1.18–1.05 (m, 12 H), 1.02 (d, J = 7.5 Hz, 3 H), 0.91 (t, J = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 201.0, 175.9, 158.9, 138.6, 136.6, 135.5, 135.4, 133.9, 130.3, 129.4, 128.7, 128.2, 127.5, 127.3, 127.0, 113.6, 85.1, 83.4, 74.7, 73.9, 73.8, 70.2, 68.6, 61.3, 55.1, 49.0, 41.9, 40.9, 39.5, 36.6, 35.3, 26.8, 25.8, 19.1, 18.0, 16.6, 14.7, 12.5, 12.4, 11.3, –4.1, –4.5 ppm. HRMS: calcd. for $C_{63}H_{87}NNaO_7S_2Si_2$ $[M + Na]^+$ 1112.5360; found 1112.5357.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-7-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-5-(4-methoxybenzyloxy)-4,6,8-trimethylundecane-1,3-diol (19): To a stirred solution of aldol adduct **18** (7.0 g, 6.42 mmol) in MeOH (40 mL) at 0 °C $NaBH_4$ (475 mg, 12.85 mmol) was added portion wise. The reaction mixture was allowed to stir for 1 h at room temperature and then quenched with saturated aqueous NH_4Cl (20 mL). The solvent was removed under reduced pressure and the resulting residue was diluted with water (20 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3× 60 mL). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography with silica

gel (hexane/ethyl acetate = 4:1) to afford **19** (5.1 g, 89%) as a viscous colorless liquid. $[\alpha]_D^{27}$ = +5.2 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3442, 2956, 2930, 1513, 1463, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.72–7.64 (m, 4 H), 7.47–7.23 (m, 11 H), 7.11 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 4.71–4.62 (m, 2 H), 4.55–4.37 (m, 4 H), 4.30–4.21 (m, 1 H), 3.86–3.69 (m, 5 H), 3.65 (d, *J* = 7.5 Hz, 1 H), 3.42–3.15 (m, 2 H), 2.17–1.61 (m, 6 H), 1.43–1.25 (m, 2 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 1.05 (s, 9 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.94 (t, *J* = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.68 (d, *J* = 6.0 Hz, 3 H), 0.07 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.9, 135.5, 133.9, 129.5, 129.2, 128.8, 128.5, 127.5, 113.6, 84.2, 74.6, 74.4, 68.8, 66.0, 55.2, 41.9, 38.9, 38.0, 33.3, 31.9, 26.8, 26.0, 19.2, 18.3, 17.4, 13.9, 13.3, 12.2, –3.3, –4.0 ppm. HRMS: calcd. for $C_{53}H_{80}NaO_7Si_2$ $[M + Na]^+$ 907.5340; found 907.5335.

(6*R*,7*S*,8*S*,9*S*,10*R*,11*R*,12*R*,13*S*)-11-(Benzyloxy)-13-(*tert*-butyldimethylsilyloxy)-3,3,6-triethyl-9-(4-methoxybenzyloxy)-8,10,12,18,18-pentamethyl-17,17-diphenyl-4,16-dioxa-3,17-disilanonadecan-7-ol (20): TES-Cl (0.9 mL, 5.42 mmol) and imidazole (615 mg, 9.04 mmol) were added to a solution of diol **19** (4.0 g, 4.52 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h, the reaction was quenched with saturated $NaHCO_3$ solution (25 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2× 40 mL). The combined organic layer was washed with brine (2× 50 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 9:1) to afford **20** (3.9 g, 86%) as a pale yellow liquid. $[\alpha]_D^{27}$ = –6.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3499, 2956, 2928, 1463, 1219 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.77–7.69 (m, 4 H), 7.51–7.36 (m, 7 H), 7.34–7.27 (m, 4 H), 7.20 (d, *J* = 9.0 Hz, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 4.63 (AB_q, *J* = 11.3 Hz, 2 H), 4.55 (AB_q, *J* = 10.6 Hz, 2 H), 4.32–4.23 (m, 1 H), 3.94–3.80 (m, 7 H), 3.78–3.67 (m, 2 H), 3.33 (dd, *J* = 7.5, 5.3 Hz, 1 H), 2.20–1.89 (m, 4 H), 1.81–1.68 (m, 2 H), 1.60–1.33 (m, 2 H), 1.21 (d, *J* = 6.8 Hz, 3 H), 1.10 (s, 9 H), 1.07–0.96 (m, 15 H), 0.89 (s, 9 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.68 (q, *J* = 7.5 Hz, 6 H), 0.09 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.8, 139.1, 135.5, 135.4, 134.0, 131.1, 129.4, 128.8, 128.0, 127.5, 127.1, 127.0, 113.5, 85.9, 81.7, 74.4, 74.3, 72.6, 68.9, 64.1, 61.9, 55.2, 43.8, 41.8, 39.5, 38.1, 35.0, 26.8, 25.8, 19.1, 18.0, 16.3, 13.8, 13.1, 12.6, 10.9, 6.7, 4.3, –4.1, –4.7 ppm. HRMS: calcd. for $C_{59}H_{94}NaO_7Si_3$ $[M + Na]^+$ 1021.6199; found 1021.6197.

(6*R*,7*S*,8*R*,9*R*,10*R*,11*R*,12*R*,13*S*)-11-(Benzyloxy)-13-(*tert*-butyldimethylsilyloxy)-3,3,6-triethyl-9-(4-methoxybenzyloxy)-8,10,12,18,18-pentamethyl-17,17-diphenyl-4,16-dioxa-3,17-disilanonadecan-7-yl *S*-Methyl Carbonodithioate (21): Alcohol **20** (3.5 g, 3.50 mmol) in THF (25 mL) was added to a suspension of NaH (252 mg, 10.52 mmol) in THF (10 mL) under a nitrogen atmosphere at 0 °C. Carbon disulfide (5 mL) was added to the reaction mixture and heated to 60 °C and stirring continued at the same temperature for 5 h. After cooling the reaction mixture to room temperature, MeI (1.7 mL, 28.05 mmol) was added dropwise to the reaction mixture and stirred at same temperature for 1 h. After completion of the reaction (monitored by TLC), it was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution (30 mL). The reaction mixture was diluted with ethyl acetate (40 mL) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3× 40 mL) and the combined organic layer washed with brine (2× 75 mL), dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 10:1) to furnish xanthate **21** (3.6 g, 94%) as a brown liquid. $[\alpha]_D^{27}$ = –6.5 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2955, 1710, 1513, and 1219 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.82–7.73 (m, 4 H), 7.55–7.34 (m, 11 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 6.93 (d, *J* = 8.3 Hz, 2 H), 4.74–4.54 (m, 4 H), 4.29–4.20 (m, 1 H), 3.96–3.77 (m, 7 H), 3.70 (dd, *J* = 10.5, 3.7 Hz, 1 H), 3.61 (dd, *J* = 9.8, 5.2 Hz, 1 H), 3.41 (t, *J* = 6.8 Hz, 1 H), 2.65 (s, 3 H), 2.30–2.01 (m, 3 H), 1.94–1.67 (m, 3 H), 1.63–1.36 (m, 2 H), 1.21 (d, *J* = 6.8 Hz, 3 H), 1.15 (s, 9 H), 1.11 (d, *J* = 7.5 Hz, 3 H), 1.09–1.0 (m, 12 H), 0.95–0.87 (m, 12 H), 0.66 (q, *J* = 7.5 Hz, 6 H), 0.15–0.10 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.3, 158.6, 139.1, 135.5, 134.1, 133.9, 129.4, 128.6, 128.0, 127.5, 127.2, 127.0, 113.4, 87.5, 85.2, 78.5, 74.7, 71.6, 68.9, 62.2, 61.7, 55.2, 44.7, 42.0, 38.5, 37.9, 35.1, 26.8, 25.8, 19.8, 19.1, 14.8, 12.3, 12.1, 11.0, 6.8, 4.3, –4.1, –4.7 ppm. HRMS: calcd. for $C_{61}H_{96}NaO_7S_2Si_3$ $[M + Na]^+$ 1111.5802; found 1111.5805.

(7*S*,8*R*,9*R*,10*R*,11*S*,12*S*,14*S*)-9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-14,17,17-triethyl-11-(4-methoxybenzyloxy)-2,2,8,10,12-pentamethyl-3,3-diphenyl-4,16-dioxa-3,17-disilanonadecane (22): Bu_3SnH (0.9 mL, 3.44 mmol) followed by a catalytic amount of AIBN (20 mg) were added to a stirred solution of xanthate **21** (2.5 g, 2.29 mmol) in toluene (30 mL) and the reaction mixture was heated to reflux under an incandescent lamp for 8 h. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 11:1) to obtain **22** (2.0 g, 87%) as a pale yellow liquid. $[\alpha]_D^{27}$ = –11.5 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2956, 2930, 1513, 1462, 1248 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.80–7.69 (m, 4 H), 7.53–7.37 (m, 8 H), 7.36–7.28 (m, 3 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 4.61 (AB_q, *J* = 11.3 Hz, 2 H), 4.51 (AB_q, *J* = 10.6 Hz, 2 H), 4.32–4.24 (m, 1 H), 3.95–3.82 (m, 4 H), 3.79–3.60 (m, 2 H), 3.49–3.38 (m, 2 H), 3.26 (dd, *J* = 7.5, 3.7 Hz, 1 H), 2.15–1.64 (m, 5 H), 1.57–1.34 (m, 5 H), 1.21 (d, *J* = 7.5 Hz, 3 H), 1.12 (s, 9 H), 1.08–0.94 (m, 15 H), 0.93–0.88 (m, 12 H), 0.66 (q, *J* = 7.5 Hz, 6 H), 0.10 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.6, 139.0, 135.5, 134.1, 134.0, 131.8, 129.4, 128.7, 128.0, 127.5, 127.2, 127.0, 113.4, 85.9, 82.1, 74.6, 72.4, 68.9, 64.7, 62.1, 55.2, 42.2, 39.7, 37.8, 35.1, 34.8, 33.2, 31.4, 26.9, 25.8, 19.1, 17.9, 16.7, 13.7, 11.2, 11.1, 6.8, 4.4, –4.2, –4.6 ppm. HRMS: calcd. for $C_{59}H_{94}NaO_6Si_3$ $[M + Na]^+$ 1005.6250; found 1005.6255.

(2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-7-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-5-(4-methoxybenzyloxy)-4,6,8-trimethylundecan-1-ol (23): To a stirred solution of **22** (1.5 g, 1.52 mmol) in CH_2Cl_2 (30 mL) at 0 °C, was added a catalytic amount of *p*-TSA (30 mg) and the reaction was allowed to stir for 30 min at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layer was washed with brine (2× 40 mL), dried with Na_2SO_4, and then evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane/ethyl acetate = 9:1) to give TES-deprotected **23** as viscous colorless liquid (1.1 g, 84%). $[\alpha]_D^{27}$ = –23.3 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3453, 2950, 2928, 1461, 1382, 1251 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.78–7.72 (m, 4 H), 7.51–7.40 (m, 6 H), 7.38–7.30 (m, 5 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 6.90 (d, *J* = 7.9 Hz, 2 H), 4.66–4.44 (m, 4 H), 4.31–4.26 (m, 1 H), 3.93–3.87 (m, 4 H), 3.80–3.73 (m, 1 H), 3.62 (dd, *J* = 10.9, 4.9 Hz, 1 H), 3.55–3.48 (m, 2 H), 3.31 (dd, *J* = 7.9, 4.9 Hz, 1 H), 2.15–2.06 (m, 2 H), 2.04–195 (m, 1 H), 1.90–1.74 (m, 2 H), 1.69–1.56 (m, 2 H), 1.56–1.44 (m, 1 H), 1.39–1.29 (m, 2 H), 1.22 (d, *J* = 7.9 Hz, 3 H), 1.13 (s, 9 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 6.9 Hz, 3 H), 0.92 (s, 9 H), 0.11 (s. 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.6, 138.7, 135.2, 133.8, 133.7, 131.2, 129.2, 128.8,

127.9, 127.3, 127.0, 126.9, 113.3, 85.1, 82.2, 74.3, 72.7, 68.8, 64.2, 61.9, 54.9, 41.9, 39.3, 37.3, 34.7, 34.4, 33.2, 26.6, 25.6, 24.7, 18.9, 17.7, 16.8, 12.9, 11.0, 10.7, –4.4, –4.9 ppm. HRMS: calcd. for $C_{53}H_{80}NaO_6Si_2$ [M + Na]$^+$ 891.5391; found 891.5396.

(2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-7-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-5-(4-methoxybenzyloxy)-4,6,8-trimethylundecanoic Acid (24): A solution of alcohol **19** (0.8 g, 0.92 mmol) in CH_2Cl_2 (20 mL) was added to a suspension of Dess–Martin periodinane (0.59 g, 1.38 mmol) in CH_2Cl_2 (10 mL) at 0 °C and stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (2× 25 mL). The organic layer was dried with Na_2SO_4, evaporated under reduced pressure. The crude aldehyde (0.81 g) was immediately used for the next reaction. To a solution of aldehyde in a mixture of *tert*-butanol and water (3:1, 16 mL) at 0 °C was added NaH_2PO_4 (221 mg, 1.84 mmol) followed by 2-methyl-2-butene (0.2 mL, 1.84 mmol) and stirred for 5 min. $NaClO_2$ (166 mg, 1.84 mmol) was added and the reaction mixture was stirred at 0 °C. After completion of the reaction, the organic solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3× 20 mL). The combined organic layer was washed with brine (50 mL) and dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 4:1) to afford **24** (700 mg, 85% yield) as a colorless viscous liquid. $[\alpha]_D^{27}$ = –7.1 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3250, 2924, 2854, 1709, 1462, 1219 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.89–7.78 (m, 4 H), 7.62–7.37 (m, 1 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 6.99 (d, *J* = 8.5 Hz, 2 H), 4.76–4.54 (m, 4 H), 4.28–4.19 (m, 1 H), 4.01–3.83 (m, 5 H), 3.58–3.52 (m, 1 H), 3.41 (dd, *J* = 7.7, 3.6 Hz, 1 H), 2.65–2.47 (m, 1 H), 2.35–2.22 (m, 1 H), 2.14–1.98 (m, 3 H), 1.93–1.76 (m, 2 H), 1.73–1.61 (m, 1 H), 1.56–1.43 (m, 2 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 1.23 (s, 9 H), 1.17 (d, *J* = 6.7 Hz, 3 H), 1.12 (t, *J* = 7.3 Hz, 3 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.7, 158.8, 139.0, 135.5, 133.4, 133.3, 129.6, 129.0, 128.0, 127.6, 127.3, 127.0, 113.5, 83.7, 77.1, 74.0, 73.5, 69.1, 63.0, 55.2, 44.8, 42.3, 38.5, 34.7, 33.5, 26.8, 26.7, 25.7, 22.6, 17.8, 17.2, 12.9, 11.9, 10.3, –4.3, –4.8 ppm. HRMS: calcd. for $C_{53}H_{79}O_7Si_2$ [M + H]$^+$ 883.5364; found 883.5359.

(2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-7-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-5-(4-methoxybenzyloxy)-4,6,8-trimethylundecanamide (25): To a solution of acid **24** (400 mg, 0.453 mmol) in CH_2Cl_2 (10 mL), Et_3N (91 μL, 0.906 mmol) was added at 0 °C and stirred for 20 min, followed by addition of ethyl chloroformate (64 μL, 0.680 mmol), followed by further stirring for 30 min at the same temperature. To this reaction mixture aqueous ammonia (30%, 2.0 mL) was added slowly at 0 °C and slowly warmed to room temperature. After complete conversion of the reaction (monitored by TLC), it was quenched with saturated NH_4Cl solution (10 mL) and was extracted with CH_2Cl_2 (3× 10 mL). The combined organic layer was washed with brine (2× 30 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane/ethyl acetate = 1:1) to give amide **25** (350 mg, 88%) as a colorless viscous liquid. $[\alpha]_D^{27}$ = –15.2 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3410, 2923, 2853, 1692, 1461, 1219 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.81–7.72 (m, 4 H), 7.53–7.39 (m, 6 H), 7.38–7.32 (m, 5 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.90 (d, *J* = 8.3 Hz, 2 H), 5.61–5.55 (br. s, 1 H), 5.37–5.28 (br. s, 1 H), 4.65 (AB_q, *J* = 10.6 Hz, 2 H), 4.49 (AB_q, *J* = 11.3 Hz, 2 H), 4.30–4.22 (m, 1 H), 3.96–3.85 (m, 4 H), 3.84–3.73 (m, 1 H), 3.48 (dd, *J* = 5.3, 3.0 Hz, 1 H), 3.33 (dd, *J* = 7.5, 4.5 Hz, 1 H), 2.31–2.18 (m, 1 H), 2.16–1.96 (m, 2 H), 1.92–1.49 (m, 6 H), 1.44–1.28 (m, 1 H), 1.20 (d, *J* = 7.5 Hz, 3 H), 1.16–1.11 (m, 12 H), 1.06–0.95 (m, 6 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.1, 158.8, 138.8, 135.4, 134.7, 133.9, 131.2, 129.4, 129.1, 128.1, 128.0, 127.5, 127.4, 127.2, 113.5, 84.9, 82.0, 74.6, 73.0, 68.9, 62.0, 55.2, 46.2, 42.2, 37.6, 35.2, 34.9, 34.6, 26.9, 25.8, 24.8, 22.6, 19.1, 17.1, 13.0, 11.8, 10.9, –4.2, –4.6 ppm. HRMS: calcd. for $C_{53}H_{80}NO_6Si_2$ [M + H]$^+$ 882.5518; found 882.5512.

(2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*)-7-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-5-hydroxy-4,6,8-trimethylundecanamide (26): To a ice-cold mixture of amide **25** (250 mg, 0.283 mmol) in CH_2Cl_2/H_2O (9:1; 15 mL), DDQ (128 mg, 0.567 mmol) was added in one portion. The resulting mixture was stirred at the same temperature for 30 min. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3× 10 mL). The combined organic layer was washed with brine (3× 15 mL), dried with Na_2SO_4, and concentrated to afford a residue that was purified by column chromatography with silica gel (hexane/ethyl acetate = 1:4) to furnish alcohol **26** (205 mg, 96%) as a pale yellow liquid. $[\alpha]_D^{27}$ = +5.1 (*c* = 0.9, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3450, 2923, 2853, 1690, 1219 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.77–7.70 (m, 4 H), 7.54–7.33 (m, 9 H), 7.31–7.25 (m, 2 H), 6.53 (br. s, 1 H), 5.37 (br. s, 1 H), 4.61 (s, 2 H), 4.22–4.13 (m, 2 H), 3.96–3.85 (m, 1 H), 3.79–3.68 (m, 1 H), 3.62 (d, *J* = 9.0 Hz, 1 H), 3.42 (dd, *J* = 10.5, 1.5 Hz, 1 H), 2.45–2.31 (m, 1 H), 2.24–2.08 (m, 2 H), 2.04–1.94 (m, 1 H), 1.86–1.60 (m, 4 H), 1.46–1.29 (m, 2 H), 1.16 (d, *J* = 7.5 Hz, 3 H), 1.10 (s, 9 H), 1.04 (t, *J* = 7.5 Hz, 3 H), 0.94–0.87 (m, 15 H), 0.10 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.6, 137.5, 135.5, 135.4, 129.5, 128.4, 128.1, 127.7, 127.5, 127.3, 127.0, 126.9, 88.1, 76.0, 74.8, 69.2, 61.9, 46.6, 42.3, 35.3, 34.8, 34.4, 26.8, 25.8, 24.7, 22.6, 19.0, 16.1, 11.6, 11.4, 10.9, –4.3, –4.7 ppm. HRMS: calcd. for $C_{45}H_{71}NNaO_5Si_2$ [M + Na]$^+$ 784.4768; found 784.4775.

(2*S*,4*S*,6*S*,7*S*,8*R*,9*S*)-7-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-2-ethyl-4,6,8-trimethyl-5-oxoundecanamide (3): To a stirred solution of alcohol **17** (90 mg, 0.118 mmol) in CH_2Cl_2 (10 mL), Dess–Martin periodinane (75 mg, 0.177 mmol) was added at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at room temperature. After complete conversion of the starting material (monitored by TLC), the reaction was quenched with saturated $NaHCO_3$ solution (10 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2× 20 mL). The combined organic layer was washed with brine (2× 30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was rapidly purified by flash column chromatography with silica gel (hexane/ethyl acetate = 3:2) to obtain keto **3** (75 mg, 83%) as a colorless liquid. $[\alpha]_D^{27}$ = +11.1 (*c* = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3361, 2923, 2853, 1659, 1463, 1219 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.72–7.64 (m, 4 H), 7.46–7.22 (m, 11 H), 5.45 (br. s, 2 H), 4.47 (AB_q, *J* = 11.3 Hz, 2 H), 4.22–4.13 (m, 1 H), 3.83–3.76 (m, 2 H), 3.71 (dd, *J* = 8.3, 4.5 Hz, 1 H), 3.12 (dd, *J* = 8.3, 6.8 Hz, 1 H), 2.62–2.52 (m, 1 H), 2.40–2.30 (m, 1 H), 2.19–1.88 (m, 2 H), 1.75–1.54 (m, 3 H), 1.47–1.23 (m, 2 H), 1.11–1.05 (m, 12 H), 1.01 (d, *J* = 7.5 Hz, 3 H), 0.95–0.87 (m, 6 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 216.2, 177.5, 138.8, 135.4, 134.0, 133.9, 129.5, 128.1, 127.6, 127.5, 127.1, 83.4, 74.5, 68.3, 61.4, 47.1, 46.0, 44.2, 41.3, 35.6, 35.0, 26.9, 25.8, 24.7, 22.6, 19.2, 15.6, 13.7, 12.0, 10.9, –4.1, –4.5 ppm. HRMS: calcd. for $C_{45}H_{69}NNaO_5Si_2$ [M + Na]$^+$ 782.4606; found 782.4605.

(2*S*,3*S*,4*S*,5*S*,6*R*,9*R*,11*S*)-4-(Benzyloxy)-9-ethyl-2-(2-hydroxyethyl)-3,5,11-trimethyl-1-oxa-7-azaspiro[5.5]undecan-8-one (27): To a stirred solution of **3** (50 mg, 0.065 mmol) in acetonitrile (6 mL) and water (0.6 mL), HF (0.2 mL, 40% in water) was added at 0 °C. The reaction mixture was allowed to stir at room temperature for overnight. After complete conversion of the starting material (monitored by TLC), the reaction was quenched by saturated aqueous solution of $NaHCO_3$ (10 mL). The organic solvent was removed under reduced pressure and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to get a residue, which on purification by column chromatography over silica gel (hexane/ethyl acetate = 1:1), furnished spirolactam **27** (20 mg, 80%) as a viscous pale yellow liquid. $[\alpha]_D^{27}$ = –45.0 (*c* = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3460, 2972, 1645, 1455 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.96 (br. s, 1 H), 7.41–7.33 (m, 4 H), 7.32–7.28 (m, 1 H), 4.67 (AB_q, *J* = 11.0 Hz, 2 H), 3.98–3.92 (m, 1 H), 3.73 (t, *J* = 5.5 Hz, 2 H), 3.60 (t, *J* = 3.3 Hz, 1 H), 2.37–2.30 (m, 1 H), 2.27–2.18 (m, 1 H), 2.05–1.80 (m, 4 H), 1.73–1.49 (m, 4 H), 1.03 (d, *J* = 7.7 Hz, 3 H), 0.97–0.89 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.2, 137.5, 128.6, 128.0, 127.7, 87.7, 83.8, 70.3, 60.8, 42.0, 40.8, 38.4, 34.5, 33.9, 33.4, 24.3, 14.7, 13.9, 13.4, 10.6 ppm. HRMS: calcd. for $C_{23}H_{35}NNaO_4$ $[M + Na]^+$ 412.2458; found 412.2452.

(2*S*,3*R*,4*S*,5*S*,6*R*,9*R*,11*S*)-9-Ethyl-4-hydroxy-2-(2-hydroxyethyl)-3,5,11-trimethyl-1-oxa-7-azaspiro[5.5]undecan-8-one (2): To a stirred solution of **27** (15.0 mg, 0.038 mmol) in MeOH/THF (2.0 mL, 5:1) was added $Pd(OH)_2$ (20%, 10.0 mg) under an argon atmosphere. The reaction mixture was stirred under H_2 overnight at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a short pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography with silica gel (ethyl acetate) to afford **2** (10.0 mg, 86%) as a white solid, m.p. 137–139 °C. $[\alpha]_D^{27}$ = –57.4 (*c* = 0.45, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3395, 2949, 2873, 1691, 1456, 1219 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.28 (br. s, 1 H), 3.98 (t, *J* = 8.7 Hz, 1 H), 3.82–3.72 (m, 3 H), 2.39–2.19 (m, 1 H), 2.08–1.95 (m, 1 H), 1.94–1.81 (m, 3 H), 1.75–1.50 (m, 5 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 0.98 (t, *J* = 6.7 Hz, 3 H), 0.95–0.85 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.1, 88.1, 74.5, 70.0, 61.0, 41.8, 40.3, 37.7, 34.6, 29.6, 28.0, 25.6, 14.7, 13.7, 13.0, 12.2 ppm. HRMS: calcd. for $C_{16}H_{29}NNaO_4$ $[M + Na]^+$ 322.1944; found 322.1962.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge through the internet at http://www.eurjoc.org or from the author.

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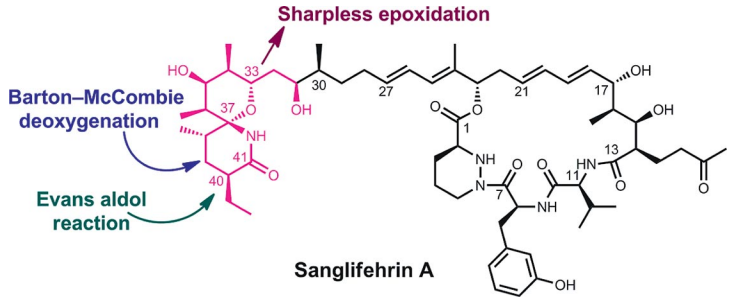

An efficient and highly-stereoselective synthesis for the spirolactam segment of the extremely potent immunosuppressant sanglifehrin A was successfully accomplished by following our own desymmetrization strategy, followed by Sharpless asymmetric epoxidation, Crimmins *syn* aldol reaction, Barton–McCombie deoxygenation, and spirolactamization as key reactions.

Keywords: Synthetic methods / Asymmetric synthesis / Medicinal chemistry / Natural products / Spiro compounds / Lactams

