Stereoselective Total Synthesis of Macrolide Sch-725674 and C-7-*epi*-Sch-725674

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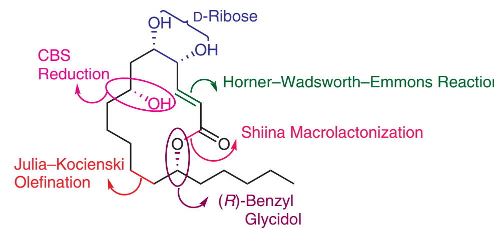

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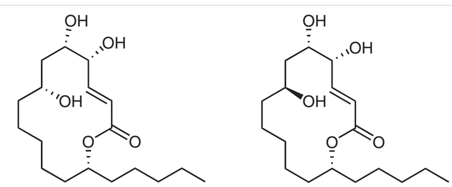
Abstract The stereoselective total synthesis of Sch-725674 in 14 linear synthetic steps with 10.3% overall yield is described. The synthesis started from commercially available starting materials, D-ribose and (*R*)-benzyl glycidol. The key reactions involved CBS reduction, Julia–Kocienski olefination, Horner–Wadsworth–Emmons reaction, and Shiina macrolactonization.

Keywords natural product synthesis, macrolides, Sch-725674, C-7-*epi*-Sch-725674, antifungal agents

Macrolactones are privileged core units in many bioactive molecules obtained from natural resources. Among them, 14-membered macrolides have received much attention because of their prominent biological activities such as antifungal and cytocidal properties. A novel 14-membered macrolide, Sch-725674, was isolated from a culture of *Aspergillus sp* (Figure 1). Its structural identification by NMR studies and biological screening against *Saccharomyces cervisiae* and *Candida abicans* (MICs 8 and 32 μg mL^{-1}, respectively) were reported in 2005 by Yang et al.[1] Sch-725674 is a macrolactone having three free hydroxyl groups, four stereogenic centers, an (*E*)-α,β-unsaturated ester and an unusual *n*-pentyl chain. The absolute stereochemistry of Sch-725674 was reported by Curran et al. to be (4*R*,5*S*,7*R*,13*R*) by synthesizing all of its 16 isomers using a fluorous tagging protocol.[2] The structural complexity and biological importance of Sch-725674 has made it the target of synthetic chemists globally and led to its synthesis by various groups.[3]



Sch-725674 **C-7-*epi*-Sch-725674**

1 **2**

Figure 1

As part of our ongoing research program on the synthesis of biologically active natural and synthetic compounds,[4] we herein report the stereoselective total synthesis of Sch-725674 (**1**) and C-7-*epi*-Sch-725674 (**2**) (Figure 1). Our synthetic strategy consisted of Julia–Kocienski olefination, CBS reduction, HWE reaction and Shiina macrolactonization.

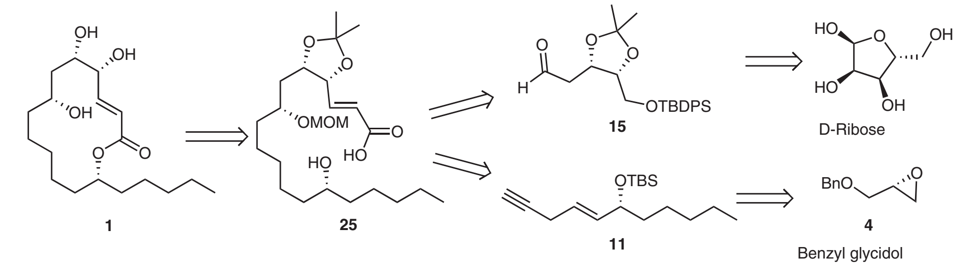
As shown in the retrosynthetic analysis (Scheme 1), compound **1**, could be obtained from compound **25** via Shiina macrolactonization and global deprotection of both protecting groups. Compound **25** (*seco*-acid) could be obtained from alkyne **11** and aldehyde **15** by a nucleophilic addition. The key precursor, alkyne fragment **11**, could be obtained from (*R*)-benzyl glycidol and the aldehyde fragment **15** could be obtained from D-ribose.

The synthesis started from commercially available (*R*)-benzyl glycidol **4**, which, on regioselective ring opening with butyl magnesium bromide,[5] gave the corresponding secondary alcohol **5** in 86% yield, followed by silylation[6] with TBSCl and imidazole in CH_2Cl_2 to furnish compound **6** in excellent yield (Scheme 2). Reductive debenzylation[7] of compound **6** in the presence of Pd/C (10%) in EtOAc at room temperature resulted in the formation of primary alcohol **7** in quantitative yield. The hydroxyl group was oxidized under Swern[8] conditions to furnish the aldehyde **8**, which was directly subjected to Julia–Kocienski olefination[9] with sulfone **9**, in the presence of KHMDS, to afford *trans* olefin **10** in 87% yield. The TMS deprotection of compound **10** was smoothly carried out using K_2CO_3 in MeOH to give compound **11** in 88% yield,[10] as shown in the Scheme 2.

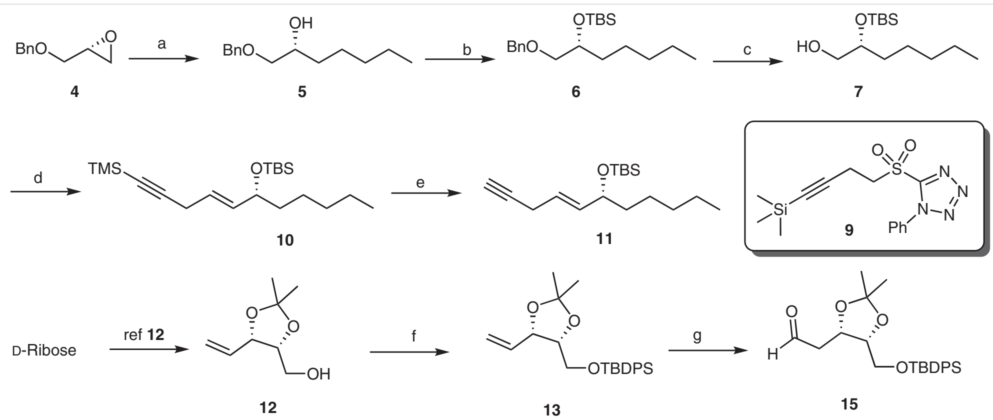
Synthesis of the aldehyde fragment started from commercially available D-ribose, which, by the sequential application of reported reactions led to [(4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxo lan-4-yl]methanol (**12**).[11] The hydroxyl group was silylated[12] with TBDPSCl / imidazole in CH_2Cl_2 to afford **13** in 86% yield. Hydroboration[13] of **13** with $BH_3{\cdot}Me_2S$ and subsequent oxidation in the presence of NaOH / H_2O_2 afforded primary alcohol **14** in 89% yield. This was oxidized under Swern conditions to afford the corresponding aldehyde **15**, which was used without purification. At this stage, we coupled the two fragments alkyne **11** and aldehyde **15**, in the presence of *n*-BuLi[14] at –78 °C, to achieve the racemic propargylic alcohol **16** and, on subsequent oxidation with 2-iodoxybenzoic acid (IBX)[15] in DMSO, to the ynone **17** in 81% yield over two steps.

The asymmetric reduction of ynone **17** was carried out using the CBS reagent[16] [(*S*)-(–)-2-Me-CBS-oxazaborolidine] and $BH_3{\cdot}Me_2S$ to give the desired chiral propargylic alcohol **18** in 86% yield, with excellent stereoselectivity (96:4, *dr*, confirmed by HPLC). The secondary alcohol was converted into its MOM ether **19** by treating with methoxymethyl chloride[17] and DIPEA in CH_2Cl_2. Compound **19** was subjected to hydrogenation[18] in the presence of Pd/C (10%) to afford completely saturated compound **20** in 89% yield; selective desilylation[19] was then achieved by using NH_4F in anhydrous MeOH at 40 °C to afford primary alcohol **21** in 84% yield. The resulting alcohol **21** was oxidized with Dess–Martin periodinane[20] in the presence of $NaHCO_3$ in CH_2Cl_2 to give the corresponding aldehyde **22**, which was directly subjected to Horner–Wadsworth–Emmons reaction[21] with triethyl phosphonoacetate and NaH in THF to give exclusively *trans*-(*E*)-α,β-unsaturated ester **23** in 85% yield over two steps (Scheme 3).

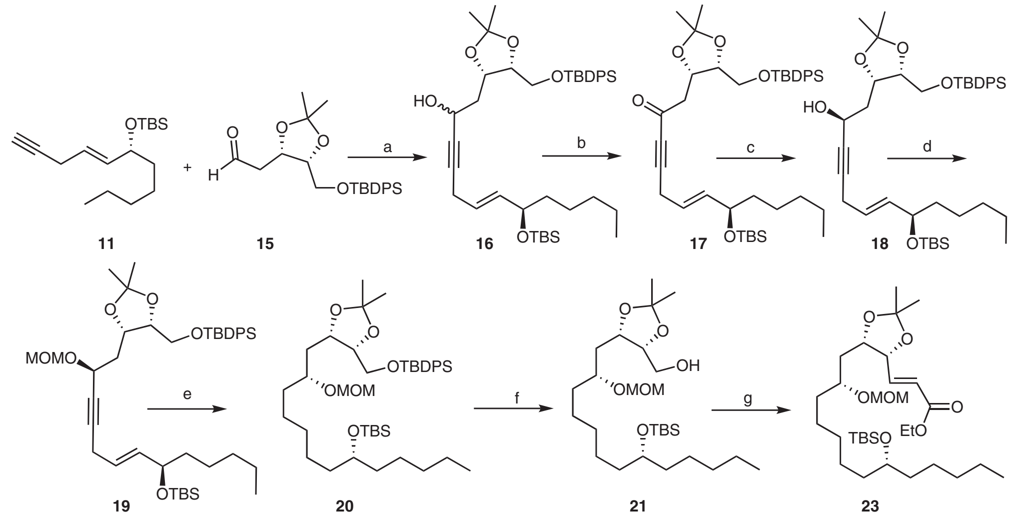
Compound **23** was desilylated with HF·Py[22] in THF to afford secondary alcohol **24** in 90% yield, followed by base-induced ester hydrolysis with LiOH to yield *seco*-acid **25**. *Seco*-acid **25** cyclized into macrolide **26** under Shiina macro-



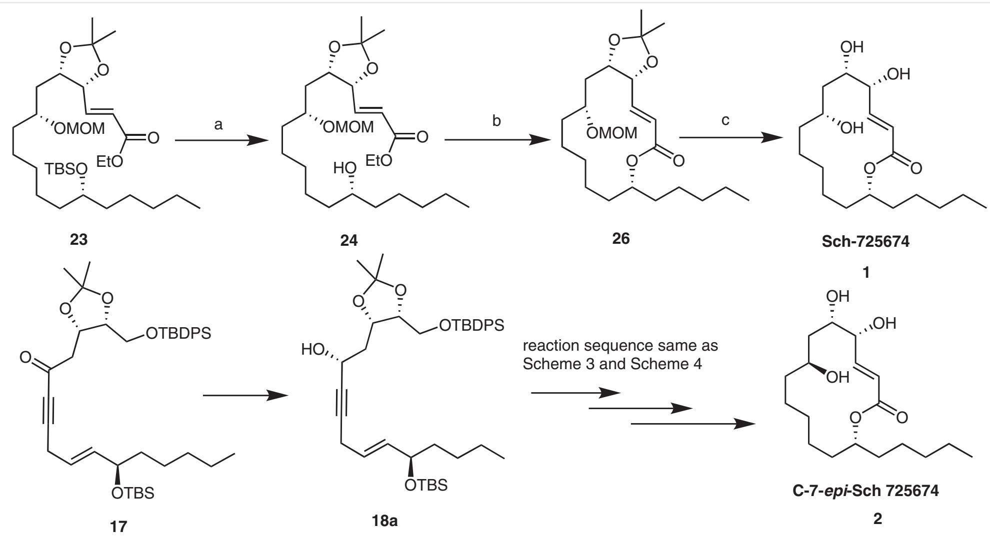
Scheme 1 Retrosynthetic analysis



Scheme 2 Synthesis of alkyne fragment **11** and aldehyde fragment **15**. *Reagents and conditions*: (a) Butyl magnesium bromide (1.2 equiv), CuI (0.1 equiv), anhydrous THF, –78 °C to r.t., 1 h, 86%; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 1.5 h, 88%; (c) H_2-Pd/C, EtOAc, 8 h, 96%; (d) (i) $(COCl)_2$, DMSO, CH_2C_2, –78 °C, 2 h; (ii) **9**, KHMDS, anhydrous THF, –78 °C, 1 h, 80% (over two steps); (e) K_2CO_3, anhydrous MeOH, r.t., 30 min, 88%; (f) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 8 h, 86%; (g) (i) $BH_3{\cdot}SMe_2$, THF, 0 °C to r.t., 1 h; NaOH, H_2O_2, 0 °C to r.t., 2 h, 89% (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2 h, 87%.



Scheme 3 Coupling of alkyne fragment **11** and aldehyde fragment **15**. *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C, 30 min; (b) IBX, DMSO, THF (1:1), 0 °C to r.t., 2 h, 81% (over two steps); (c) (*S*)-(–)-2-Me-CBS-oxazaborolidine (1.0 equiv), $BH_3{\cdot}Me_2S$ (1.5 equiv), THF, –40 °C, 1 h, 86%; (d) MOM-Cl, DIPEA, CH_2Cl_2, 0 °C to r.t., 4 h, 87%; (e) H_2, Pd/C, EtOAc, 1 h, 89%; (f) NH_4F, MeOH, 40 °C, 1 h, 84%; (g) (i) DMP, CH_2Cl_2, $NaHCO_3$, 0 °C to r.t., 1 h; (ii) NaH, $(OEt)_2P(O)CH_2CO_2Et$, THF, 0 °C to r.t., 30 min, 85% (over two steps).

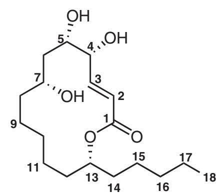


Scheme 4 Synthesis of target molecules Sch-725674 and C-7-*epi*-Sch725674. *Reagents and conditions*: (a) HF·Py, THF, 0 °C to r.t., 8 h, 90%; (b) (i) LiOH, THF/MeOH/H_2O (1:1:2), 0 °C to r.t., 3 h; (ii) MNBA, DMAP, toluene, r.t., 8 h, 80% (over two steps); (c) TFA, THF/MeOH/H_2O (2:4:1), 0 °C to r.t., 2 h, 73%.

lactonization[23] conditions in 80% yield over two steps. Removal of both acetonide and MOM ether protecting groups was achieved using trifluoroacetic acid (TFA)[24] in THF/ MeOH/ H_2O (1:2:1) mixture to afford natural product Sch-725674 (**1**) in 73% yield, as shown in Scheme 4.

C-7-*Epi*-Sch-725674 (**2**) was achieved by asymmetric reduction of common intermediate ynone **17**, using the CBS reagent [(*R*)-(+)-2-Me-CBS-oxaza-borolidine] and $BH_3{\cdot}Me_2S$ in THF to give the desired chiral propargyl alcohol **18a** in 83% yield, with excellent stereoselectivity (98:2, *dr*), the structure of which was confirmed by ^1H NMR analysis. The same reaction sequence was used (Scheme 3 and Scheme 4) for the synthesis of the C-7-epi-Sch-725674. Global removal of the acetonide and MOM ether in macrolides **26** and **26a** was carried out using TFA to afford both target compounds Sch-725674 (**1**) and C-7-*epi*-Sch-725674 (**2**) in good yields. The spectroscopic data and specific rotations of **1** and **2** are identical with the reported values (Table 1).

Table 1 NMR Data for Synthetic and Natural **1**


Sch-725674 (1)

Position	Natural product [δ, ppm,in CD_3OD]		Synthetic product [δ, ppm,in CD_3OD]	
	^{13}C	^1H (*J* Hz)	^{13}C	^1H (*J* Hz)
1	168.4		168.4	
2	123.1	6.07 (dd, 15.8, 1.6)	123.1	6.08 (dd, 15.7, 1.1)
3	149.3	6.86 (dd, 15.8, 6.0)	149.3	6.87 (dd, 15.7, 5.9)
4	76.0	4.48 (ddd, 6.0, 3.0, 1.6)	76.0	4.51–4.46 (m)
5	72.9	3.84 (ddd, 6.0, 4.7, 3.0)	72.9	3.88–3.83 (m)
6	38.3	1.82 (ddd, 14.7, 6.5, 6.0), 1.65 (m)	38.3	1.83 (dt, 14.5, 5.9), 1.66 (m)
7	69.5	3.98 (q, 6.5)	69.5	4.03–3.95 (m)
8	36.8	1.36 (m)	36.8	1.36 (m)
9	25.8	1.19 (m), 1.37 (m)	25.8	1.19 (m), 1.37 (m)
10	29.5	1.15 (m), 1.40 (m)	29.5	1.15(m), 1.40 (m)
11	27.0	1.19 (m), 1.45 (m)	27.0	1.19 (m), 1.45 (m)
12	34.1	1.54 (m), 1.70 (m)	34.1	1.54 (m), 1.70 (m)
13	77.6	4.94 (dddd, 9.8, 7.5, 5.0, 2.2)	77.6	4.99–4.91 (m)
14	36.5	1.57 (m), 1.61 (m)	36.5	1.57 (m), 1.61 (m)
15	26.4	1.32 (m)	26.4	1.32 (m)
16	32.9	1.30 (m)	32.9	1.30 (m)
17	23.8	1.31 (m)	23.8	1.31 (m)
18	14.5	0.89 (t, 6.8)	14.5	0.90 (t, 6.6)

In summary, we have completed the stereoselective total synthesis of Sch-725674 (**1**) and C-7-*epi*-Sch-725674 (**2**) in 14 steps from commercially available D-ribose and (*R*)-benzyl glycidol, with an overall yield of 10.3%. The main features of the synthesis are construction of the alkyne fragment by using Julia Kocienski reaction, generation of a stereogenic center using CBS reduction, and 14-membered lactone formation using Shiina macrolactonization.

All reagents were purchased from commercial sources and were used without further purification. All reactions were performed under an inert atmosphere unless otherwise noted. THF was freshly distilled from Na/benzophenone ketyl. Petroleum ether refers to the fraction boiling in the 60–80 °C range. Column chromatography was performed on silica gel (Acme grade 60–120 mesh). All reactions were monitored by TLC to completion (Merck precoated silica gel 60 F 254 plates), visualizing with UV light, in an I_2 chamber or with phosphomolybdic acid spray. Melting points were recorded with a Büchi M-560 melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer FT-IR 240-c spectrometer. ^1H NMR spectra were recorded with a Bruker-400 MHz spectrometer in $CDCl_3$ and CD_3OD using TMS as internal standard, ^{13}C NMR spectra were recorded on the same instrument operating at 100 MHz. Mass spectra were recorded with a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Specific rotations were measured with a Rudolph Autopol IV polarimeter at 25 °C.

(*R*)-1-(Benzyloxy)heptan-2-ol (5)

To a stirred solution of CuI (0.34 g, 1.82 mmol) in anhydrous THF was added freshly prepared butyl-MgBr solution (2 M, 10.9 mL, 21.96 mmol) at –78 °C. The mixture was stirred for 30 min, (*R*)-(–)-benzyl glycidol (3 g, 18.3 mmol) was added and the mixture was stirred for 1 h. On completion, as monitored by TLC, the reaction was quenched with saturated NH_4Cl solution and the mixture was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using silica, eluting with EtOAc–hexane (1:9), to give compound **5** as a colorless liquid.

Yield: 3.5 g (86%); $[\alpha]_D^{25}$ –13.5 (*c* 1, $CHCl_3$).

IR (neat): 3396, 2926, 2856, 1454, 1219, 1102, 772, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 4.55 (s, 2 H), 3.85–3.77 (m, 1 H), 3.50 (dd, *J* = 9.4, 3.0 Hz, 1 H), 3.32 (dd, *J* = 9.3, 7.7 Hz, 1 H), 2.48–2.35 (brs, 1 H), 1.50–1.23 (m, 8 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.3, 127.6, 74.6, 73.2, 70.4, 33.0, 31.8, 25.1, 22.5, 13.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{23}O_2$: 223.1693; found: 223.1689.

(*R*)-{[1-(Benzyloxy)heptan-2-yl]oxy}*tert*-butyldimethylsilane (6)

To a stirred solution of alcohol **5** (3.0 g, 13.5 mmol) in anhydrous CH_2Cl_2 (30 mL) were added imidazole (1.37 g, 20.3 mmol) and TBDMS-Cl (2.44 g, 16.2 mmol) at 0 °C and the mixture was stirred at r.t. for 2 h. After completion (monitored by TLC), the mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (10 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using silica, eluting with EtOAc–hexane (0.5:9.5), to afford compound **6** as a pale-yellow oil.

Yield: 4.0 g (88%); $[\alpha]_D^{25}$ +10.5 (*c* 1.8, $CHCl_3$).

IR (neat): 3031, 2954, 2927, 2855, 1463, 1252, 1114, 835, 774, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 4 H), 7.30–7.24 (m, 1 H), 4.52 (s, 2 H), 3.85–3.77 (m, 1 H), 3.42–3.33 (m, 2 H), 1.59–1.22 (m, 8 H), 0.88 (s, 12 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 128.2, 127.5, 127.4, 74.8, 73.2, 71.5, 34.6, 31.9, 25.8, 24.8, 22.6, 18.1, 14.0, –4.3, –4.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{37}O_2Si$: 337.2528; found: 337.2530.

(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]heptan-1-ol (7)

To a stirred solution of compound **6** (3.78 g, 11.3 mmol) in EtOAc (30 mL) was added Pd/C (10%, 250 mg) and the reaction mixture was stirred under hydrogen at r.t. for 12 h. After completion of the reaction (monitored by TLC), the mixture was filtered through Celite®, and the pad was washed with EtOAc (50 mL). The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica, eluting with EtOAc–hexane (1:9), to give **7** as a colorless oil.

Yield: 2.65 g (96%); $[\alpha]_D^{25}$ –33.3 (*c* 1.2, $CHCl_3$).

IR (neat): 3394, 2954, 2927, 2856, 1464, 1253, 1098, 1046, 834, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76–3.70 (m, 1 H), 3.56 (dd, *J* = 10.9, 3.5 Hz, 1 H), 3.44 (dd, *J* = 10.9, 5.4 Hz, 1 H), 1.52–1.45 (m, 2 H), 1.35–1.24 (m, 6 H), 0.91 (s, 9 H), 0.89 (t, *J* = 7.0 Hz, 3 H), 0.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.9, 66.2, 33.9, 31.9, 25.8, 24.9, 22.5, 18.0, 13.9, –4.4, –4.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{31}O_2Si$: 247.2089; found: 247.2080.

1-Phenyl-5-{[4-(trimethylsilyl)but-3-yn-1-yl]sulfonyl}-1*H*-tetrazole (9)

To a stirred solution of 4-(trimethylsilyl)-but-3-yn-1-ol (2 g, 14 mmol), in anhydrous THF (30 mL) were added 5-mercapto-1-phenyl tetrazole (2.5 g, 14 mmol), PPh_3 (3.67 g, 14 mmol) and diisopropylazodicaboxylate (2.75 mL, 14 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at the same temperature and, after completion of the reaction as monitored by TLC, the reaction was quenched with saturated aq. $NaHCO_3$. The reaction mixture was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude tetrazole (3.5 g). To a stirred solution of this tetrazole (3.5 g, 11.57 mmol) in EtOH (30 mL) were added $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.42 g, 1.15 mmol) and H_2O_2 (13.1 mL, 30%) at 0 °C. The reaction mixture was warmed slowly to r.t. and stirred for a further 1.5 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The reaction was quenched with saturated aq. $NaHCO_3$ and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using silica, eluting with EtOAc–hexane (1:9) mixture, to afford compound **9** as a white solid.

Yield: 3.6 g (78% over two steps).

IR (neat): 2960, 2180, 1498, 1353, 1147, 842, 769, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.57 (m, 5 H), 3.90 (t, *J* = 7.5 Hz, 2 H), 2.93 (t, *J* = 7.5 Hz, 2 H), 0.14 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 132.8, 131.5, 129.6, 125.1, 99.7, 88.4, 54.6, 14.5, –0.2.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}N_4O_2SSi$: 335.09926; found: 335.09925.

(*R*,*E*)-*tert*-Butyldimethyl-{[1-(trimethylsilyl)undec-4-en-1-yn-6-yl]oxy}silane (10)

To a stirred solution of oxalyl chloride (1.35 mL, 15.8 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DMSO (2.41 mL, 33.8 mmol) slowly at –78 °C and the mixture was stirred for 30 min. Then a solution of alcohol **6** (2.6 g, 10.6 mmol) in anhydrous CH_2Cl_2 (10 mL) was added at –78 °C and the mixture was stirred for another 3 h at the same temperature. Et_3N (5.8 mL, 42.2 mmol) was added at 0 °C, the mixture was stirred for a further 45 minutes, the reaction was quenched with water (20 mL) and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give crude aldehyde **8** as a pale-yellow syrup (2.2 g). To a stirred solution of sulfone **9** (3.6 g, 10.8 mmol) in anhydrous THF (40 mL) under argon was added KHMDS (9.9 mL 1 M, 9.9 mmol) at –78 °C and the mixture was stirred for 10 minutes. Then aldehyde **8** (2.2 g, 9.0 mmol) dissolved in anhydrous THF (10 mL) was added and the mixture was stirred for 30 min at the same temperature. The reaction mixture was warmed slowly to r.t. and stirring was continued for 1 h. The reaction was quenched with saturated aq. NH_4Cl (10 mL) and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using silica, eluting with EtOAc–hexane (0.3:9.7), to give **10** as a colorless liquid.

Yield: 2.98 g (80% over two steps); $[\alpha]_D^{25}$ –9.0 (*c* 1.0, $CHCl_3$).

IR (neat): 2956, 2929, 2856, 2177, 1467, 1250, 1076, 836, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (ddt, *J* = 15.2, 6.3, 1.5 Hz, 1 H), 5.51 (dtd, *J* = 15.2, 5.3, 0.9 Hz, 1 H), 4.12–4.04 (m, 1 H), 2.99–2.93 (m, 2 H), 1.51–1.23 (m, 8 H), 0.89 (s, 9 H), 0.88 (t, *J* = 5.0 Hz, 3 H), 0.16 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 123.2, 104.1, 86.4, 73.0, 38.1, 31.7, 25.9, 24.9, 22.7, 22.6, 14.0, 0.06, –4.2, –4.7.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{40}OSi_2Na$: 375.2690; found: 375.2694.

(*R*,*E*)-*tert*-Butyldimethyl(undec-4-en-1-yn-6-yloxy)silane (11)

To a stirred solution of compound **10** (2.85 g, 8.1 mmol) in anhydrous MeOH was added K_2CO_3 (3.35 g, 24.3 mmol) at 0 °C and the mixture allowed to stir at r.t. for 20 min. After completion of the reaction, as monitored by TLC, the reaction was quenched with saturated NH_4Cl solution and the solvent was evaporated under vacuum. The reaction mixture was extracted with EtOAc (2 × 25 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum to furnish the crude product. The crude product was purified by column chromatography using silica, eluting with EtOAc–hexane (0.5:9.5), to afford pure product **11** as a colorless liquid.

Yield: 2 g (88%); $[\alpha]_D^{25}$ –23.7 (*c* 0.8, $CHCl_3$).

IR (neat): 3313, 2955, 2928, 2856, 2178, 1464, 1252, 1075, 968, 833, 773, 630 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (ddt, *J* = 15.2, 6.2, 1.6 Hz, 1 H), 5.53 (dtd, *J* = 15.2, 5.4, 1.0 Hz, 1 H), 4.11–4.06 (m, 1 H), 2.96–2.92 (m, 2 H), 2.09 (t, *J* = 2.7 Hz, 1 H), 1.52–1.40 (m, 2 H), 1.34–1.23 (m, 6 H), 0.89 (s, 9 H), 0.88 (t, *J* = 5.6 Hz, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 122.9, 81.5, 72.9, 70.0, 38.2, 31.7, 25.9, 24.9, 22.6, 21.2, 14.0, –4.2, –4.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{33}OSi$: 281.2959; found: 281.2962.

***tert*-Butyl{[(4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methoxy}diphenylsilane (13)**

To a stirred solution of alcohol **12** (1.2 g, 7.6 mmol), in anhydrous CH_2Cl_2 (15 mL) were added imidazole (0.77 g, 11.4 mmol) and TBDPSCl (2.4 mL, 9.1 mmol) at 0 °C, followed by a catalytic amount of DMAP and the mixture was stirred at r.t. for 6 h. After completion of the reaction (monitored by TLC), the mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using silica, eluting with EtOAc–hexane (0.5:9.5), to give **10** as a colorless liquid.

Yield: 2.6 g (86%); $[\alpha]_D^{25}$ –3.9 (*c* 1.1, $CHCl_3$).

IR (neat): 3071, 2931, 2858, 1428, 1216, 1109, 1084, 772, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 4 H), 7.44–7.35 (m, 6 H), 5.97–5.89 (m, 1 H), 5.36 (dt, *J* = 17.2, 1.0 Hz, 1 H), 5.21 (dt, *J* = 10.3, 0.9 Hz, 1 H), 4.68–4.63 (m, 1 H), 4.30–4.26 (m, 1 H), 3.72–3.63 (m, 2 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 133.6, 133.4, 133.3, 129.6, 127.6, 117.9, 108.5, 78.7, 78.4, 62.8, 27.7, 26.7, 25.3, 19.1.

HRMS: *m*/*z* $[M + NH_4]^+$ calcd for $C_{24}H_{36}O_3SiN$: 414.2194; found: 414.2199.

2-{(4*S*,5*R*)-5-[((*tert*-Butyldiphenylsilyl)oxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl} ethan-1-ol (14)

To a stirred solution of compound **13** (2.3 g, 5.8 mmol) in anhydrous THF (30 mL) was added $BH_3{\cdot}SMe_2$ (5.8 mL, 11.6 mmol, 2 M, THF) at 0 °C. The reaction mixture was then allowed to warm r.t. and stirred for 2 h. After consumption of starting material (monitored by TLC), the reaction mixture was cooled to 0 °C, then 3 M aq. NaOH (8 mL) was added, followed by hydrogen peroxide (2.5 mL, 33% w/w aq. solution) and the mixture was stirred for 2 h at r.t. The solvent was removed under vacuum, and the residue was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography using silica gel, eluting with EtOAc–hexane (3:7), to afford alcohol **14**, as a colorless liquid.

Yield: 2.15 g (89%); $[\alpha]_D^{25}$ –29.9 (*c* 0.6, $CHCl_3$).

IR (neat): 3394, 2932, 2858, 1427, 1217, 1109, 1081, 822, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4 H), 7.45–7.36 (m, 6 H), 4.41–4.36 (m, 1 H), 4.26–4.20 (m, 1 H), 3.87–3.78 (m, 2 H), 3.76–3.69 (m, 1 H), 3.68–3.63 (m, 1 H), 2.41–2.36 (m, 1 H), 1.94–1.87 (m, 2 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.5, 133.0, 132.9, 129.7, 127.7, 108.1, 77.6, 77.2, 62.4, 61.4, 31.4, 28.0, 26.7, 25.4, 19.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{35}O_4Si$: 415.2290; found: 415.2294.

(*R*,*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-1-{(4*S*,5*R*)-5-[((*tert*-butyldiphenylsilyl)oxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}dodec-6-en-3-yn-2-one (17)

To a stirred solution of oxalyl chloride (0.46 mL, 5.43 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DMSO (0.83 mL, 11.6 mmol) slowly at –78 °C and the mixture was stirred for 30 min. Then a solution of alcohol **14** (1.5 g, 3.62 mmol) in anhydrous CH_2Cl_2 (10 mL) was added and the mixture was stirred for another 3 h at the same temperature. Then, Et_3N (2.5 mL, 18.1 mmol) was added at 0 °C and the mixture was stirred for a further 45 minutes. The reaction mixture was diluted with water (15 mL), extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give crude aldehyde compound **15** as a pale-yellow syrup (1.3 g). To a stirred solution of alkyne **11** (1.5 g, 5.35 mmol) in anhydrous THF (15 mL) was added *n*-BuLi (3.3 mL, 5.3 mmol, 1.6 M, hexane) at –78 °C and the mixture was stirred for 20 min. Aldehyde **15** (1.3 g, 3.15 mmol) in anhydrous THF (10 mL) was added and the reaction mixture was stirred at the same temperature for a further 1 h. The reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using silica, eluting with EtOAc–hexane (1:9), to afford **16** as an inseparable mixture of diastereoisomers as a yellow oil (yield: 1.98 g, 91%).

To a stirred solution of IBX (1.21 g, 4.32 mmol) in DMSO (10 mL) was added alcohol **16** (1.5 g, 2.16 mmol) in THF (10 mL) at 0 °C and the reaction mixture was then stirred at r.t. for 1 h. After completion of reaction (monitored by TLC), the reaction was quenched with saturated aq. $Na_2S_2O_3$ (6 mL) and the mixture was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with cold water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel, eluting EtOAc–hexane (0.5:9.5), to afford **17** as a yellow oil.

Yield: 1.35 g (81% for two steps); $[\alpha]_D^{25}$ –15.6 (*c* 1.0, $CHCl_3$).

IR (neat): 2924, 2854, 2217, 1679, 1465, 1219, 1075, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4 H), 7.45–7.36 (m, 6 H), 5.70 (ddt, *J* = 15.2, 5.8, 1.4 Hz, 1 H), 5.51 (dtd, *J* = 15.4, 5.6, 1.1 Hz, 1 H), 4.82–4.76 (m, 1 H), 4.28–4.22 (m, 1 H), 4.11–4.06 (m, 1 H), 3.68–3.63 (m, 2 H), 3.13–3.09 (m, 2 H), 3.07–3.01 (m, 1 H), 2.97–2.89 (m, 1 H), 1.48–1.23 (m, 14 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8, 137.0, 135.5, 133.0, 132.9, 129.8, 127.7, 120.7, 108.3, 91.7, 82.0, 77.1, 76.8, 72.8, 62.3, 45.7, 38.0, 31.7, 27.8, 26.8, 25.8, 25.3, 24.8, 22.5, 21.8, 14.0, –4.2, –4.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{41}H_{63}O_5Si$: 691.42080; found: 691.42085.

(2*S*,8*R*,*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-1-{(4*S*,5*R*)-5-[((*tert*-butyldiphenylsilyl)oxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}dodec-6-en-3-yn-2-ol (18)

To a stirred solution of (*S*)-CBS (0.86 mL, 0.86 mmol, 1 M, toluene) in anhydrous THF was added a solution of ynone **17** (0.6 g, 0.86 mmol) in anhydrous THF (5 mL) at –40 °C, followed by addition of $BH_3.SMe_2$ (1.29 mL, 1.29 mmol, 1 M, THF) dropwise over 5 min, and the mixture was then stirred for 1.5 h at –40 °C. After completion of reaction (monitored by TLC), the reaction was quenched with MeOH (2 mL), the mixture was stirred for another 10 min and then concentrated under vacuum. The residue was purified by column chromatography using silica, eluting with EtOAc–hexane (1:9), to give alcohol **18** as a colorless oil.

Yield: 0.52 g (86%); $[\alpha]_D^{25}$ –9.9 (*c* 1, $CHCl_3$).

IR (neat): 3395, 2955, 2928, 2856, 2318, 1466, 1219, 1110, 1077, 834, 773, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.45–7.36 (m, 6 H), 5.67 (ddt, *J* = 15.2, 6.2, 1.5 Hz, 1 H), 5.52 (dtd, *J* = 15.2, 5.3, 0.9 Hz, 1 H), 4.72–4.61 (m, 2 H), 4.27–4.22 (m, 1 H), 4.11–4.04 (m, 1 H), 3.73–3.63 (m, 2 H), 3.11 (d, *J* = 8.5 Hz, 1 H), 3.01–2.96 (m, 2 H), 2.11–1.96 (m, 2 H), 1.50–1.21 (m, 14 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.87 (t, *J* = 6.9 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.55, 133.50, 133.0, 132.9, 129.8, 127.7, 123.4, 108.3, 82.8, 82.3, 77.5, 74.7, 73.0, 62.3, 60.9, 38.2, 36.1, 31.7, 28.0, 26.8, 25.9, 25.5, 24.9, 22.6, 21.6, 14.0, –4.1, –4.7.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{64}O_5Si_2Na$: 715.4364; found: 715.4369.

(5*S*,11*R*,*E*)-11-Butyl-5-{[(4*S*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-13,13,14,14-tetramethyl-2,4,12-trioxa-13-silapentadec-9-en-6-yne (19)

To a stirred solution of **18** (0.4 g, 0.6 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C under nitrogen, was added iPr_2NEt (0.4 mL, 2.3 mmol) dropwise. After 5 min, methoxymethyl chloride (0.09 mL, 1.14 mmol) was added dropwise and the mixture was stirred for 8 h at r.t. After completion (monitored by TLC), the reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by flash column chromatography using silica, eluting with EtOAc–hexane (0.5:9.5), to afford **19** as a colorless oil.

Yield: 0.37 g (87%); $[\alpha]_D^{25}$ –18.8 (*c* 0.9, $CHCl_3$).

IR (neat): 2955, 2927, 2855, 2312, 1219, 1079, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 4 H), 7.44–7.35 (m, 6 H), 5.65 (ddt, *J* = 15.2, 6.2, 1.5 Hz, 1 H), 5.51 (dtd, *J* = 15.2, 5.3, 0.9 Hz, 1 H), 4.98 (d, *J* = 6.6 Hz, 1 H), 4.60 (d, *J* = 6.6 Hz, 1 H), 4.58–4.55 (m, 1 H), 4.49–4.42 (m, 1 H), 4.21–4.14 (m, 1 H), 4.10–4.03 (m, 1 H), 3.74–3.61

(m, 2 H), 3.38 (s, 3 H), 2.99–2.93 (m, 2 H), 2.18–2.09 (m, 1 H), 2.04–1.95 (m, 1 H), 1.48–1.20 (m, 14 H), 1.05 (s, 9 H), 0.88 (s, 9 H), 0.87 (t, *J* = 5.8 Hz, 3 H), 0.03 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 135.4, 133.3, 133.2, 129.6, 127.6, 123.3, 107.9, 93.8, 82.9, 80.5, 77.5, 72.9, 62.5, 62.4, 55.5, 38.2, 36.4, 31.7, 28.1, 26.8, 25.9, 25.5, 24.9, 22.6, 21.5, 14, –4.2, –4.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{43}H_{68}O_6Si_2Na$: 759.4623; found: 759.4626.

(5*R*,10*R*)-5{[(4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-12,12,13,13-tetramethyl-10-pentyl-2,4,11-trioxa-12-silatetradecane (20)

To a stirred solution of **19** (0.3 g, 0.4 mmol) in EtOAc (8 mL) was added Pd/C (10%, 50 mg) and the reaction mixture was stirred under a hydrogen atmosphere at r.t. for 2 h. After completion (monitored by TLC), the mixture was filtered through Celite® and the filter pad was washed with EtOAc (2 × 10 mL). The filtrate was evaporated in vacuo, and the residue was purified by flash column chromatography using silica, eluting with EtOAc–hexane (0.5:9.5), to give **20** as a colorless oil.

Yield: 0.27 g (89%); $[\alpha]_D^{25}$ –6.9 (*c* 0.8, $CHCl_3$).

IR (neat): 2928, 2856, 1467, 1429, 1252, 1218, 1108, 1043, 834, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.63 (m, 4 H), 7.45–7.34 (m, 6 H), 4.69 (q, *J* = 8.8, 6.7 Hz, 2 H), 4.45–4.39 (m, 1 H), 4.18–4.12 (m, 1 H), 3.83–3.74 (m, 1 H), 3.70 (dd, *J* = 10.5, 7.5 Hz, 1 H), 3.65–3.57 (m, 2 H), 3.39 (s, 3 H), 1.88–1.79 (m, 1 H), 1.77–1.68 (m,1 H), 1.59–1.50 (m, 2 H), 1.44–1.23 (m, 20 H), 1.05 (s, 9 H), 0.88 (s, 12 H), 0.03 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 133.3, 133.2, 129.6, 127.6, 107.7, 95.9, 77.7, 75.0, 73.8, 72.3, 62.6, 55.5, 37.1, 35.4, 34.5, 32.0, 30.2, 28.1, 26.8, 25.9, 25.5, 25.4, 24.99, 24.90, 22.6, 19.1, 14.0, –4.3, –4.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{42}H_{73}O_6Si_2$: 743.5110; found: 743.5113.

{(4*R*,5*S*)-5-[(2*R*,8*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxymethoxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (21)

To a stirred solution of **20** (0.21 g, 0.28 mmol) in anhydrous MeOH (5 mL) was added ammonium fluoride (0.2 g, 5.6 mmol) at r.t. The reaction mixture was warmed to 40 °C and stirred for 1 h. After completion (monitored by TLC), the reaction was quenched with saturated NH_4Cl (5 mL), solvent was removed under vacuum and the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 filtered and concentrated under vacuum. The crude product was purified by flash column chromatography using silica, eluting with EtOAc–hexane (4:6), to obtain pure **21** as a yellow oil.

Yield: 120 mg (84%); $[\alpha]_D^{25}$ –51.1 (*c* 0.8, $CHCl_3$).

IR (neat): 3395, 2925, 2854, 1463, 1375, 1218, 1038, 834, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (q, *J* = 14.8, 6.8 Hz, 2 H), 4.42–4.32 (m, 1 H), 4.21–4.12 (m, 1 H), 3.83–3.69 (m, 1 H), 3.69–3.53 (m, 3 H), 3.39 (s, 3 H), 2.22–2.12 (m, 1 H), 1.81–1.22 (m, 25 H), 0.89 (s, 12 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.7, 95.8, 77.8, 75.2, 73.9, 72.3, 61.7, 55.7, 37.0, 35.0, 34.1, 32.0, 30.1, 28.1, 25.9, 25.4, 25.2, 24.9, 24.8, 22.6, 14.0, –4.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{56}O_6SiNa$: 527.3919; found: 527.3925.

Ethyl (*E*)-3-{(4*R*,5*S*)-5-[(2*R*,8*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-(methoxymethoxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (23)

To a stirred solution of alcohol **21** (105 mg, 0.208 mmol) in anhydrous CH_2Cl_2 (3 mL) were added Dess–Martin periodinane (114 mg, 0.27 mmol) and $NaHCO_3$ (34 mg, 0.42 mmol) at 0 °C and the mixture was stirred at r.t. for 1 h. After completion (monitored by TLC), the reaction was quenched with saturated aq. $Na_2S_2O_3$ (10 mL) and saturated aq. $NaHCO_3$ (10 mL) and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were washed sequentially with water, brine, dried over Na_2SO_4, filtered and concentrated under vacuum to give the corresponding aldehyde **22**, which was used in the next step without further purification. Triethyl phosponoacetate (87 mg, 0.39 mmol) was added to a stirred suspension of NaH (14 mg, 0.35 mmol) in anhydrous THF (3 mL) at 0 °C. The resulting solution was stirred for 45 min at 0 °C, then aldehyde **22** (100 mg, 0.195 mmol) in anhydrous THF (3 mL) was added and the resulting mixture was stirred at r.t. for 1 h. After completion (monitored by TLC), the reaction was quenched by adding saturated aq. NH_4Cl (10 mL), and the mixture was extracted with EtOAc (2 × 20 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography using silica, eluting with EtOAc–hexane (1:9), to give **23** as a colorless liquid.

Yield: 101 mg (85% over two steps); $[\alpha]_D^{25}$ +63.3 (*c* 0.5, $CHCl_3$).

IR (neat): 2927, 2854, 1726, 1467, 1375, 1219, 1040, 835, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (dd, *J* = 15.5, 5.8 Hz, 1 H), 6.07 (dd, *J* = 15.5, 1.4 Hz, 1 H), 4.71–4.62 (m, 2 H), 4.50–4.43 (m, 1 H), 4.21 (q, *J* = 14.3, 7.2 Hz, 2 H), 3.78–3.69 (m, 1 H), 3.65–3.57 (m, 1 H), 3.39 (s, 3 H), 1.61–1.20 (m, 30 H), 0.88 (s, 12 H), 0.03 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 143.7, 123.0, 108.7, 95.9, 77.3, 74.9, 72.3, 60.4, 55.6, 37.0, 35.8, 35.1, 32.0, 30.0, 29.6, 28.0, 25.9, 25.5, 25.3, 24.99, 24.92, 22.6, 14.2, 14.0, –4.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{61}O_7Si$: 573.4193; found: 573.4187.

Ethyl (*E*)-3-{(4*R*,5*S*)-5-[(2*R*,8*R*)-8-Hydroxy-2-(methoxymethoxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (24)

To a stirred solution of compound **23** (95 mg) in anhydrous THF was added HF·Py (0.05 mL) at 0 °C and the reaction mixture was stirred at r.t. for 8 h. After completion of the reaction (monitored by TLC), the mixture was cooled to 0 °C and the reaction was quenched with saturated aq. $NaHCO_3$ (5 mL), followed by 0.05 M HCl (5 mL) and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using silica, eluting with EtOAc–hexane (3:7), to afford pure **22** as a colorless liquid.

Yield: 65 mg (90%); $[\alpha]_D^{25}$ +53.3 (*c* 0.2 $CHCl_3$).

IR (neat): 3325, 2924, 2854, 1724, 1464, 1373, 1218, 1160, 1035, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (ddd, *J* = 15.5, 5.9, 1.06 Hz, 1 H), 6.07 (dd, *J* = 15.5, 1.2 Hz, 1 H), 4.71–4.64 (m, 2 H), 4.51–4.43 (m, 1 H), 4.21 (q, *J* = 14.3, 7.1 Hz, 2 H), 3.77–3.70 (m, 1 H), 3.63–3.55 (m, 1 H), 3.39 (s, 3 H), 1.63–1.25 (m, 30 H), 0.89 (t, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 143.8, 122.9, 108.7, 95.9, 77.2, 74.8, 74.8, 71.8, 60.4, 55.6, 37.4, 37.3, 35.8, 35.0, 31.8, 29.7, 28.0, 25.5, 25.4, 25.3, 24.8, 22.6, 14.2, 14.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{47}O_7$: 459.3324; found: 459.3322.

(3a*R*,8*R*,14*R*,15a*S*,*E*)-14-(Methoxymethoxy)-2,2-dimethyl-8-pentyl-3a,8,9,10,11,12,13,14,15,15a-decahydro-6*H*-[1,3]dioxolo[4,5-e][1]oxacyclotetradecin-6-one (26)

To a stirred solution of ester **24** (45 mg, 0.098 mmol) in a mixture of THF-MeOH-H_2O (4 mL, 1:1:2) was added LiOH (11 mg, 0.5 mmol) at 0°C and the mixture was stirred at r.t. for 1.5 h. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum, the residue was extracted with Et_2O (5 mL) and the aqueous layer was acidified with 10% aqueous citric acid solution (5 mL) at 0 °C and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude *seco*-acid **25** (35 mg). To a stirred solution of 2-methyl-6-nitro benzoic anhydride (MNBA) (33 mg, 0.097 mmol) in anhydrous toluene (50 mL) was added DMAP (59 mg, 0.5 mmol), then *seco*-acid **25** (35 mg, 0.081 mmol) in anhydrous toluene (10 mL) was slowly added by syringe pump at r.t. over 12 h. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography using silica to afford macrolide **26** as pale-yellow oil.

Yield: 28 mg (80% over two steps); $[\alpha]_D^{25}$ +1.9 (*c* 1.1 $CHCl_3$).

IR (neat): 2922, 2852, 1725, 1465, 1219, 1038, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 15.7, 8.3 Hz, 1 H), 6.01 (dd, *J* = 15.7, 0.8 Hz, 1 H), 5.02–4.94 (m, 1 H), 4.71–4.65 (m, 2 H), 4.64–4.59 (d, *J* = 6.7 Hz, 1 H), 4.53–4.47 (m, 1 H), 3.78–3.70 (m, 1 H), 3.37 (s, 3 H), 1.99–1.90 (m, 1 H), 1.77–1.69 (m, 1 H), 1.69–1.21 (m, 24 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 143.6, 124.8, 108.7, 95.1, 77.8, 77.1, 76.0, 75.4, 73.7, 55.6, 35.3, 34.7, 33.7, 31.6, 31.5, 29.6, 29.2, 27.6, 25.0, 25.07, 25.02, 23.9, 22.5, 13.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{40}O_6Na$: 435.901; found: 435.2903.

(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one

[Sch-725674 (1)]

To a stirred solution of compound **24** (20 mg, 0.05 mmol) in THF-MeOH-H_2O (2 mL, 1:2:1) mixture was added TFA (0.05 mL) in anhydrous CH_2Cl_2 (1 mL) dropwise at 0 °C. The reaction mixture was slowly warmed to r.t. and stirred for a further 2 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aq. $NaHCO_3$ (5 mL) and the mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with brine, and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using silica, eluting with EtOAc–hexane (3:7), to afford target molecule Sch-725674 (**1**) as a white solid.

Yield: 11 mg (73%); mp 171–172 °C; $[\alpha]_D^{25}$ +6.2 (*c* 1.1, $CHCl_3$) {Lit.[2] +5.15 (*c* 0.27, MeOH)}.

IR (neat): 3395, 2921, 2857, 1704, 1463, 1276, 1219, 1079, 1004 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 6.87 (dd, *J* = 15.7, 5.9 Hz, 1 H), 6.08 (dd, *J* = 15.7, 1.1 Hz, 1 H), 4.99–4.91 (m, 1 H), 4.51–4.46 (m, 1 H), 4.03–3.95 (m, 1 H), 3.88–3.83 (m, 1 H), 1.83 (dt, *J* = 14.5, 5.9 Hz, 1 H), 1.76–1.49 (m, 5 H), 1.45–1.26 (m, 11 H), 1.25–1.10 (m, 3 H), 0.90 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 168.4, 149.3, 123.1, 77.6, 76.0, 72.9, 69.5, 38.3, 36.8, 36.5, 34.1, 32.9, 29.5, 27.0, 26.4, 25.8, 23.8, 14.5.

HRMS: *m*/*z* [M + H]$^+$ cald for $C_{18}H_{33}O_5$: 329.2330; found: 329.2328.

(2*R*,8*R*,*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-1-{(4*S*,5*R*)-5-[((*tert*-butyldiphenylsilyl)oxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}dodec-6-en-3-yn-2-ol (18a)

This was prepared by following the procedure used for **18** (0.3 g, 0.44 mmol).

Yield: 0.25 g (83%); $[\alpha]_D^{25}$ –2.9 (*c* 1, $CHCl_3$).

IR (neat): 3395, 2955, 2926, 2855, 1466, 1219, 1110, 1076, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4 H), 7.46–7.35 (m, 6 H), 5.66 (ddt, *J* = 15.2, 6.2, 1.5 Hz, 1 H), 5.52 (dtd, *J* = 15.2, 5.3, 0.9 Hz, 1 H), 4.69–4.62 (m, 1 H), 4.46–4.40 (m, 1 H), 4.27–4.21 (m, 1 H), 4.10–4.03 (m, 1 H), 3.73–3.63 (m, 2 H), 3.01–2.96 (m, 2 H), 2.82–2.77 (m, 1 H), 2.09–2.02 (m, 2 H), 1.49–1.22 (m, 14 H), 1.06 (s, 9 H), 0.88 (s, 9 H), 0.87 (t, *J* = 6.8 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.54, 135.50, 133.0, 132.9, 129.7, 127.7, 123.3, 108.4, 82.7, 82.1, 77.5, 77.1, 75.8, 73.0, 62.3, 61.7, 38.2, 37.6, 31.7, 28.0, 26.8, 25.9, 25.5, 24.9, 22.6, 21.6, 19.1, 14.0, –4.1, –4.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{41}H_{64}O_5Si_2Na$: 715.4360; found: 715.4369.

(5*R*,11*R*,*E*)-11-Butyl-5-{[(4*S*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-13,13,14,14-tetramethyl-2,4,12-trioxa-13-silapentadec-9-en-6-yne (19a)

This was prepared by following the procedure used for **19** from alcohol **18a** (0.2 g, 0.3 mmol).

Yield: 0.2 g (95%); $[\alpha]_D^{25}$ +5.3 (*c* 1.5, $CHCl_3$).

IR (neat): 2955, 2928, 2856, 2230, 1466, 1428, 1219, 1109 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 5.66 (ddt, *J* = 15.2, 6.2, 1.5 Hz, 1 H), 5.52 (dtd, *J* = 15.2, 5.3, 0.9 Hz, 1 H), 4.94 (d, *J* = 6.7 Hz, 1 H), 4.62–4.56 (m, 2 H), 4.47–4.42 (m, 1 H), 4.24–4.19 (m, 1 H), 4.09–4.04 (m, 1 H), 3.76–3.71 (m, 1 H), 3.70–3.65 (m, 1 H), 3.35 (s, 3 H), 3.01–2.96 (m, 2 H), 2.10–1.99 (m, 2 H), 1.49–1.22 (m, 14 H), 1.05 (s, 9 H), 0.88 (s, 9 H), 0.87 (t, *J* = 5.9 Hz, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 135.6, 133.3, 133.2, 129.6, 127.6, 123.3, 108.1, 93.9, 84.1, 79.7, 77.5, 74.3, 73.0, 64.4, 62.5, 55.5, 38.2, 35.8, 31.7, 28.1, 26.8, 25.9, 25.6, 24.9, 22.6, 21.6, 19.1, 14.0, –4.2, –4.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{43}H_{68}O_6Si_2Na$: 759.4620; found: 759.4626.

(5*S*,10*R*)-5-{[(4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-12,12,13,13-tetramethyl-10-pentyl-2,4,11-trioxa-12-silatetradecane (20a)

This was prepared by following the procedure used for **20** from **19a** (192 mg, 0.26 mmol).

Yield: 183 mg (95%); $[\alpha]_D^{25}$ –27.9 (*c* 1, $CHCl_3$).

IR (neat): 2929, 2856, 1466, 1377, 1219, 1252, 1109, 1042, 834, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.63 (m, 4 H), 7.43–7.34 (m, 6 H), 4.64 (q, *J* = 11.6, 6.8 Hz, 2 H), 4.31–4.25 (m, 1 H), 4.20–4.14 (m, 1 H), 3.79–3.69 (m, 2 H), 3.68–3.57 (m, 2 H), 3.36 (s, 3 H), 1.95–1.80 (m, 2 H), 1.45–1.22 (m, 22 H), 1.05 (s, 9 H), 0.88 (s, 12 H), 0.03 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.56, 135.53, 133.2, 133.1, 129.7, 127.6, 107.9, 95.4, 77.7, 75.4, 74.4, 72.3, 62.6, 55.4, 37.1, 37.0, 34.1, 33.8, 32.0, 28.1, 26.8, 25.9, 25.6, 25.3, 25.0, 24.9, 22.6, 19.1, 14.0, –4.40, –4.41.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{42}H_{73}O_6Si_2$: 743.5116; found: 743.5113.

{(4*R*,5*S*)-5-[(2*S*,8*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxymethoxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (21a)

This was prepared by following the procedure used for **21** from **20a** (173 mg, 0.233 mmol).

Yield: 100 mg (86%); $[\alpha]_D^{25}$ +54.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3375, 2927, 2855, 1464, 1377, 1219, 1252, 1041, 835, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.73–4.64 (m, 2 H), 4.41–4.26 (m, 1 H), 4.20–4.13 (m, 1 H), 3.79–3.57 (m, 4 H), 3.41–3.36 (m, 2 H), 1.93–1.83 (m, 1 H), 1.79–1.63 (m, 2 H), 1.49–1.22 (m, 24 H), 0.88 (s, 12 H), 0.03 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 108.0, 95.4, 77.8, 75.2, 73.6, 72.3, 61.6, 55.5, 37.0, 34.0, 33.4, 32.0, 30.0, 28.2, 25.9, 25.5, 25.2, 25.1, 24.9, 22.6, 14.0, –4.4.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{27}H_{56}O_6SiNa$: 527.3922; found: 527.3925.

Ethyl (*E*)-3-{(4*R*,5*S*)-5-[(2*S*,8*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxy methoxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (23a)

This was prepared by following the procedure used for **23** from **22a** (90 mg, 0.178 mmol).

Yield: 70 mg (84%); $[\alpha]_D^{25}$ –62.4 (*c* 0.5, $CHCl_3$).

IR (neat): 2924, 2853, 1724, 1464, 1372, 1218, 1160, 1036, 984, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.83 (dd, *J* = 15.5, 6.3 Hz, 1 H), 6.06 (dd, *J* = 15.6, 1.3 Hz, 1 H), 4.66 (td, *J* = 6.2, 1.3 Hz, 1 H), 4.63 (s, 2 H), 4.43–4.33 (m, 1 H), 4.20 (q, *J* = 14.3, 7.2 Hz, 2 H), 3.70–3.57 (m, 2 H), 3.41–3.36 (m, 3 H), 1.84–1.72 (m, 1 H), 1.63–1.54 (m, 1 H), 1.51 (s, 3 H), 1.44–1.22 (m, 24 H), 0.92–0.85 (m, 12 H), 0.03 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 143.3, 123.3, 108.9, 95.4, 77.3, 75.0, 74.8, 72.3, 60.4, 55.5, 37.0, 34.9, 34.0, 32.0, 30.0, 28.0, 25.9, 25.5, 25.2, 25.1, 24.9, 22.6, 14.2, 14.0, –4.4.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{31}H_{61}O_7Si$: 573.4190; found: 573.4187.

Ethyl (*E*)-3-{(4*R*,5*S*)-5-[(2*S*,8*R*)-8-Hydroxy-2-(methoxymethoxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (24a)

This was prepared by following the procedure used for **24** from ester **23a** (55 mg, 0.096 mmol).

Yield: 35 mg (79%); $[\alpha]_D^{25}$ –33.2 (*c* 0.5, $CHCl_3$).

IR (neat): 3385, 2923, 2853, 1723, 1463, 1373, 1218, 1034, 882, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.83 (dd, *J* = 15.4, 6.3 Hz, 1 H), 6.07 (dd, *J* = 15.6, 1.3 Hz, 1 H), 4.73–4.59 (m, 3 H), 4.47–4.33 (m, 1 H), 4.21 (q, *J* = 14.3, 7.1 Hz, 2 H), 3.73–3.51 (m, 2 H), 3.44–32 (m, 3 H), 1.86–1.69 (m, 1 H), 1.63–1.49 (m, 4 H), 1.49–1.22 (m, 24 H), 0.89 (t, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 143.4, 123.3, 108.9, 95.4, 77.2, 75.0, 74.8, 71.8, 60.5, 55.6, 37.4, 37.3, 34.9, 34.0, 31.9, 29.6, 28.0, 25.5, 25.3, 25.0, 22.6, 14.2, 14.0.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{47}O_7$: 459.3320; found: 459.3322.

(3a*R*,8*R*,14*S*,15a*S*,*E*)-14-(Methoxymethoxy)-2,2-dimethyl-8-pentyl-3a,8,9,10,11,12,13,14,15,15a-decahydro-6*H*-[1,3]dioxolo[4,5-e][1]oxacyclotetradecin-6-one (26a)

This was prepared by following the procedure used for **26** from *seco*-acid **25a** (20 mg, 0.046 mmol).

Yield: 16 mg (84%); $[\alpha]_D^{25}$ +33 (*c* 1.3, $CHCl_3$).

IR (neat): 2923, 2853, 1721, 1460, 1379, 1219, 1041, 989, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.80 (dd, *J* = 15.6, 8.9 Hz, 1 H), 6.08 (dd, *J* = 15.7, 0.7 Hz, 1 H), 5.05–4.97 (m, 1 H), 4.68 (dd, *J* = 8.4, 6.2 Hz, 1 H), 4.63–4.58 (m, 1 H), 4.57–4.46 (m, 2 H), 3.41–3.28 (m, 4 H), 1.91 (ddd, *J* = 14.4, 11.4, 1.4 Hz, 1 H), 1.77–1.21 (m, 25 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 142.1, 125.9, 108.7, 95.3, 76.8, 75.9, 75.4, 73.5, 55.6, 36.2, 34.9, 34.2, 31.6, 30.4, 28.2, 27.9, 25.28, 25.23, 25.20, 25.1, 22.5, 13.9.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{23}H_{40}O_6Na$: 435.906; found: 435.2903.

(5*R*,6*S*,8*S*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one [C-7-*epi*-Sch-725674 (2)]

This was prepared by following the procedure used for natural product Sch-725674 (**1**) from lactone **26a** (14 mg, 0.031 mmol).

Yield: 8.5 mg (77%); $[\alpha]_D^{25}$ –39.5 (*c* 0.5, $CHCl_3$) {Lit.[2] –38.6 (*c* 0.24, MeOH)}.

IR (neat): 3395, 2921, 2852, 1714, 1696, 1271, 1219 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (dd, *J* = 15.7, 4.2 Hz, 1 H), 6.13 (dd, *J* = 15.6, 1.8 Hz, 1 H), 4.99–4.89 (m, 1 H), 4.57–4.52 (m, 1 H), 3.89 (dt, *J* = 8.8, 2.0 Hz, 1 H), 3.44–3.34 (m, 1 H), 2.02 (ddd, *J* = 14.6, 8.9, 2.4 Hz, 1 H), 1.70–1.16 (m, 19 H), 0.91 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 121.8, 75.5, 74.9, 72.1, 68.8, 40.4, 36.1, 35.9, 33.8, 32.9, 27.2, 26.4, 24.7, 24.5, 23.7, 14.48.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{18}H_{33}O_5$: 329.2331; found: 329.2328.

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Supporting Information

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