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Graphical Abstract

Total Synthesis of Sch725674

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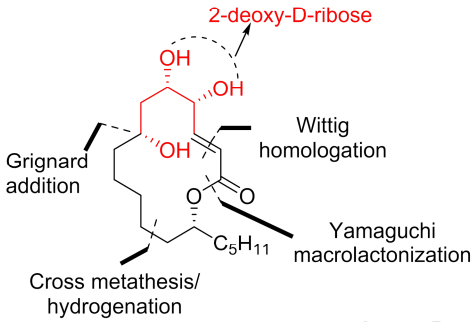

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Total Synthesis of Sch 725674

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ABSTRACT

A concise total synthesis of the macrolactone natural product Sch 725674 is accomplished starting from commercially available 2-deoxy-*D*-ribose. Pivotal reactions employed in the synthesis include the addition of 4-pentenylmagnesium bromide to the lactol derived from 2-deoxy-*D*-ribose, olefin cross metathesis and Yamaguchi macrolactonization.

1. Introduction

Sch 725674 (**1**) (Figure 1) is a 14-membered macrolactone isolated by Yang and co-workers in 2005 from the culture of *Aspergillus sp.*[1] The structure of Sch 725674 was elucidated by extensive 2D NMR spectroscopy. It contains three free hydroxy groups and a *E*- α, β-unsaturated lactone. It was shown to exhibit antifungal activity against *Saccharomyces cerevisiae* and *Candida albicans* with MICs of 8μg mL^{-1} and 32μg mL^{-1} respectively. First total synthesis of Sch 725674 (**1**) and the confirmation of the absolute configuration was disclosed by Curran's group using their trademark fluorous tagging strategy.[2]

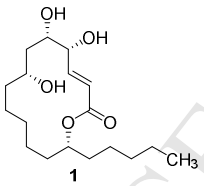

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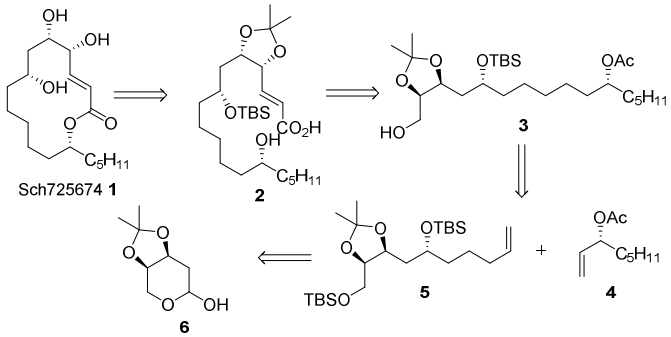
Figure 1: Sch 725674

Following Curran's synthesis our group have reported the total synthesis of Sch 725674 starting from tartaric acid using Ley's dithiaketalization as the pivotal reaction to install the trihydroxy unit.[3] Later, many groups reported the total synthesis of Sch 725674,[4a-4f] Kaliappan and Ramakrishna[4a] reported the total synthesis of Sch 725674 starting from (S)-epichlorohydrin using Smith's Linchpin coupling of silyldithianes as key step. Reddy's synthesis of **1** originated from chiral pool D-ribose and have utilized Wacker oxidation as the key step to install the required triol fragment.[4b] Hanson *et al*[4c] disclosed the synthesis of **1** based on a one pot sequential RCM/CM/hydrogenation reaction to install the triol unit. Kumar group[4d] reported the total synthesis of **1** commencing from (S)-glycidol in a multi-step sequence while Reddy and Sabitha[4e] utilised D-mannitol for the synthesis of **1**. Aggarwal's group accomplished the total synthesis of **1** using enatioselective diboration and subsequent oxidation of the chiral boronates to install the required triol.[4f] In our earlier synthesis of **1** from tartaric acid, the pivotal RCM reaction to afford the natural product suffered with a low yield. In continuation of our efforts on the use of chiral pool compounds in the total synthesis of natural products and to accomplish an improved synthesis of **1**, we undertook the total synthesis of Sch 725674 starting from commercially available 2-deoxy-D-ribose.

2. Results and Discussion

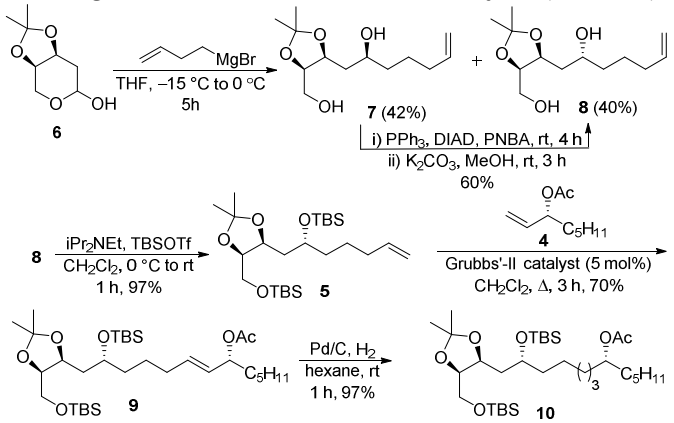
We envisaged the formation of **1** from the seco acid **2** *via* Yamaguchi macrolactonization and further deprotection of the acetonide group. Formation of the seco acid **2** was anticipated from the alcohol **3**, which in turn could be obtained by olefin cross metathesis of the alkenes **4** and the masked tetrol containing alkene **5**. Addition of 4-pentenylmagnesium bromide to **6** obtained from 2-deoxy-*D*-ribose was chosen as appropriate transformation for the synthesis of triol containing alkene **5** (Scheme 1).



Scheme 1. Retrosynthesis for Sch725674 (**1**)

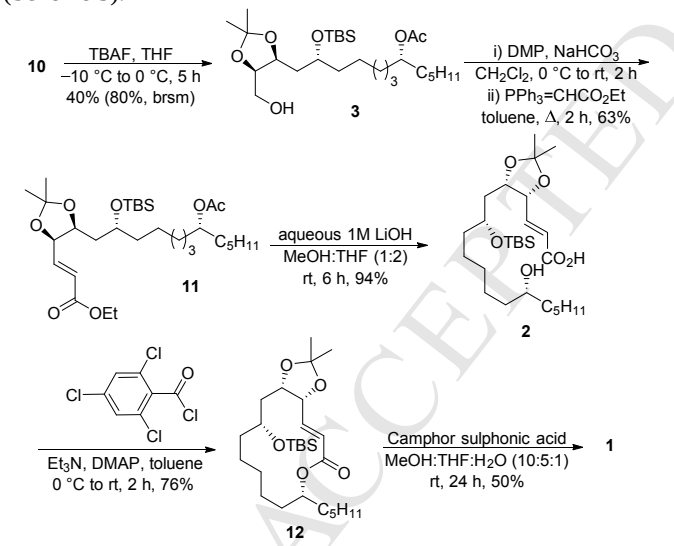
Accordingly, the synthesis commenced with the addition of 4-pentenylmagnesium bromide to the lactol **6**[5] which resulted in a seperable 1: 1 diastereomeric mixture of diols **7** and **8** in 42% and 40% yields, respectively.[6] The diastereomer **7** was transformed to the required α-isomer **8** using Mitsunobu inversion in 60% yield (65% combined yield of **8** from **6**). The diol **8** was converted to the corresponding *bis*-silyl ether **5** under standard conditions in

97% yield. Olefin cross metathesis of the alkene **5** with the allyl acetate **4**[7] in presence of Grubbs' second generation catalyst[8] furnished the product **9** in 70% yield. Hydrogenation of the olefin in **9** using Pd/C rendered the acetate **10** in 97% yield (Scheme 2).



Scheme 2. Synthesis of the key polyol unit **10**

Selective deprotection of the primary TBS group in **10** with TBAF afforded the primary alcohol **3** in 40% yield (80% based on starting material recovery). Oxidation of the primary alcohol in **3** with Dess Martin periodinane[9] followed by Wittig homologation of the resultant aldehyde furnished the conjugated ester **11** in 63% yield. Hydrolysis of both ethyl ester and acetate in **11** with 1M aqueous LiOH provided the seco acid **2** in 94% yield, which under Yamaguchi lactonization reaction conditions afforded the 14-membered macrolactone **12** in 76% yield. Deprotection of the acetonide as well as TBS group in **12** with camphorsulphonic acid furnished the natural product Sch 725674 (**1**) in 50% yield. All the physical and spectral properties of **1** were in good agreement with that reported in the literature[3b] (Scheme 3).



Scheme 3. Total synthesis of Sch 725674 (**1**)

3. Conclusions

In conclusion, a consise total synthesis of Sch 725674 was accomplished starting from known lactol derived from commeriallyl available 2-deoxy-*D*-ribose in ~4% overall yield in 10 steps. Key reaction in the synthesis include cross metathesis and Yamaguchi lactonization to effect the macrolactonization. The reaction sequence is amenable for the synthesis of number of analogues of Sch 725674.

4. Experimental section

General Procedures: Column chromatography was performed on silica gel, Acme grade 100-200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz machine in $CDCl_3$ as solvent with TMS or residual solvent $CDCl_3$ or CD_3OD peak as reference. Unless stated otherwise, all the reactions were performed under inert atmosphere. All the specific rotations were determined at 24 °C.

Preparation of (*S*)-1-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-6-en-2-ol (7)

In an oven dried two neck 100 mL round-bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed 4-pentenylmagnesium bromide (9.2 mmol, 18.4 mL of 0.5M solution in THF). It was cooled to –15 °C and a solution of the lactol **6** (0.7 g, 3.6 mmol) in THF (10 mL) was added dropwise, at the same temperature. The reaction mixture was stirred for 30 min at the same temperature, slowly warmed to 0 °C and stirred for 5 h at the same temperature. After the reaction was complete (TLC), it was cautiously quenched by addition of saturated solution of aqueous NH_4Cl (20 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude residue (as 1:1 mixture of diastereomers), which were separated by silica gel column chromatography to afford the less polar 3,5-*syn* diastereomer **7** (2:3 ethylacetate/hexane) (0.38 g, 42%), and the more polar 3,5-*anti* diastereomer **8** (1:1 ethylacetate/hexane) (0.36 g, 40%). **Data for diastereomer (7)**:$[\alpha]_D^{24}$: +9.9 (*c* 1.2, $CHCl_3$). IR (neat): 3415, 2984, 2933, 2362, 1640, 1376 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.05 – 4.91 (m, 2H), 4.42 – 4.33 (m, 1H), 4.23 – 4.16 (m, 1H), 3.85 – 3.75 (m, 1H), 3.62 (t, *J* = 5.6 Hz, 2H), 3.17 (bs, 1H), 2.13 – 2.00 (m, 3H), 1.69 – 1.61 (m, 2H), 1.57 – 1.43 (m, 7H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 114.6, 108.7, 78.0, 77.0, 71.4, 61.5, 36.7, 35.7, 33.6, 28.0, 25.4, 24.7. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{24}O_4Na$: 267.1572; found: 267.1570.

Data for diastereomer (8): $[\alpha]_D^{24}$: +4.8 (*c* 1.35, $CHCl_3$). IR (neat): 3392, 2984, 2932, 2359, 1640, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (ddt, *J* = 16.4, 10.4, 6.8 Hz, 1H), 5.05 – 4.90 (m, 2H), 4.42 (dt, *J* = 8.0, 5.6 Hz, 1H), 4.19 (q, *J* = 5.6 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.61 (m, 2H), 2.62 (brs, 1H), 2.51 (brs, 1H), 2.12 – 2.00 (m, 2H), 1.79 (ddd, *J* = 14.4, 8.4, 2.8 Hz, 1H), 1.65 – 1.40 (m, 8H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 114.7, 107.7, 77.8, 74.5, 69.2, 61.4, 37.4, 35.7, 33.5, 28.1, 25.4, 24.8. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{24}O_4Na$: 267.1572; found: 267.1572.

Preparation of (*S*)-1-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-6-en-2-ol (8) from 7: To a pre-cooled (0 °C) solution of diol **7** (0.14 g, 0.57 mmol) in THF (10 mL) were added triphenylphosphine (0.9 g, 3.44 mmol) and DIAD (0.68 mL, 3.44 mmol) and was stirred for 10 min at the same temperature. *p*-Nitrobenzoic acid (0.57 g, 3.44 mmol) was added at once to the reaction mixture and stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), most of the solvent was evaporated under vacuum and the residue thus obtained was purified by silica gel column chromatography using petroleum ether: EtOAc (9:1) as eluent furnish the corresponding *p*-nitro benzoate (80 mg) as colourless

oil, which was used in the next step without further characterization.

To a stirred solution of the *p*-nitrobenzoate (obtained above) in ethanol was added K_2CO_3 (0.48 g, 3.44 mmol) and was stirred for 3h at room temperature. After completion of the reaction (monitored by TLC), the solvent was evaporated off under vacuum and the residue thus obtained was diluted with water (10 mL) and was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether: EtOAc (6:4) as eluent to furnish **8** (0.084 g, 60%) as a colourless oil.

Preparation of tert-butyl(((4*R*,5*S*)-5-((*R*)-2-((tert-butyldimethylsilyl)oxy)hept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (5)

To a pre-cooled solution of diol **8** (0.16 g, 0.66 mmol) in dry CH_2Cl_2 (8 mL) at 0 °C, under argon atmosphere, diisopropylethyl amine (0.46 mL, 2.6 mmol), TBSOTf (0.32 mL, 1.4 mmol) were added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 1 h. After completion of the reaction (TLC), water (15 mL) was added and was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent using petroleum ether:EtOAc (20:1) as eluent gave the *bis*-silylether **5** (0.3 g, 97%) as a colorless oil; $[\alpha]_D^{24}$: −26.7 (*c* 0.9, $CHCl_3$). IR (neat): 2936, 2860, 2358, 1466, 1373 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.79 (ddt, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.03 – 4.96 (m, 1H), 4.94 (d, *J* = 10.0 Hz, 1H), 4.33 (ddd, *J* = 10.0, 6.0, 2.4 Hz, 1H), 4.07 – 3.99 (m, 1H), 3.95 – 3.85 (m, 1H), 3.62 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.55 (dd, *J* = 10.4, 4.8 Hz, 1H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.73 – 1.36 (m, 9H), 1.32 (s, 3H), 0.88 (s, 18H), 0.08 – 0.02 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 114.4, 107.6, 77.9, 73.8, 69.0, 62.1, 37.9, 36.1, 33.9, 28.3, 25.9 (3C), 25.86 (3C), 25.6, 23.7, 18.2, 18.1, −4.2, −4.6, −5.4, −5.5. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{25}H_{52}O_4Si_2Na$: 495.3302; found: 495.3300.

Preparation of (6*R*,12*R*,*E*)-12-((tert-butyldimethylsilyl)oxy)-13-((4*S*,5*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)tridec-7-en-6-yl acetate (9)

To a solution of the *bis*-silyl ether **5** (135 mg, 0.3 mmol) in CH_2Cl_2 (6 mL) was added **4** (73 mg, 0.43 mmol) followed by Grubbs' 2nd generation catalyst (10.0 mg, 0.011 mmol) under argon atmosphere and the resulting solution was stirred under reflux for 3 h. After completion of the reaction (TLC), the solvent was evaporated off and the crude residue thus obtained was purified through silica gel column chromatography to afford the compound **9** (123 mg, 70%) as colourless oil; $[\alpha]_D^{24}$: −12.6 (*c* 1.0, $CHCl_3$). IR (neat): 2933, 2859, 2359, 1739, 1465 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.67 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.37 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.18 (q, *J* = 6.8 Hz, 1H), 4.32 (ddd, *J* = 10.0, 6.0, 2.4 Hz, 1H), 4.08 – 3.99 (m, 1H), 3.93 – 3.85 (m, 1H), 3.62 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.55 (dd, *J* = 10.4, 4.8 Hz, 1H), 2.07 – 1.97 (m, 5H), 1.72 – 1.42 (m, 8H), 1.39 (s, 3H), 1.32 (s, 3H), 1.31 – 1.24 (m, 6H), 0.91 – 0.85 (m, 21H), 0.07 – 0.03 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 134.0, 128.6, 107.6, 77.9, 75.0, 73.8, 69.0, 62.1, 38.0, 36.1, 34.5, 32.4, 31.5, 28.3, 25.9 (3C), 25.86 (3C), 25.6, 24.8, 23.7, 22.5, 21.4, 18.2, 18.1, 14.0, −4.2, −4.6, −5.4, −5.5. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{33}H_{66}O_6Si_2Na$: 637.4296; found: 637.4298.

Preparation of (6*R*,12*R*)-12-((tert-butyldimethylsilyl)oxy)-13-((4*S*,5*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)tridecan-6-yl acetate (10)

To a solution of **9** (0.122 g, 0.2 mmol) in hexane (5 mL) was added 10% Pd/C (20 mg) under argon atmosphere. The mixture was stirred for 1 h under H_2 atmosphere. After the reaction was complete, the reaction mixture was filtered through a short pad of celite and the celite pad was washed with EtOAc (10 mL). Evaporation of solvent followed by column chromatography (silica gel, PE–EtOAc, 9:1) yielded **10** (0.2 g, 97%) as a colourless oil; $[\alpha]_D^{24}$: −19.8 (*c* 1.35, $CHCl_3$). IR (neat): 2930, 2858, 2360, 1730, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (*quint*, 1H), 4.32 (ddd, *J* = 10.0, 6.0, 2.4 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.94 – 3.82 (m, 1H), 3.62 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.55 (dd, *J* = 10.0, 4.8 Hz, 1H), 2.03 (s, 3H), 1.68 – 1.43 (m, 8H), 1.39 (s, 3H), 1.34 – 1.22 (m, 15H), 0.96 – 0.83 (m, 21H), 0.08 – 0.02 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 107.6, 77.9, 74.4, 73.9, 69.2, 62.1, 38.4, 36.1, 34.1 (2C), 31.7, 29.8, 28.3, 25.92 (3C), 25.87 (3C), 25.6, 25.3, 24.9, 24.3, 22.5, 21.3, 18.2, 18.1, 14.0, −4.2, −4.6, −5.4, −5.5. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{33}H_{68}O_6Si_2Na$: 639.4452; found: 639.4452.

Preparation of (6*R*,12*R*)-12-((tert-butyldimethylsilyl)oxy)-13-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)tridecan-6-yl acetate (3)

To pre-cooled solution of **10** (80 mg, 0.13 mmol) in THF (5 mL) at −10 °C was added TBAF (0.16 mmol, 0.16 mL of 1M in THF) under argon atmosphere, and the resulting solution allowed to stir at 0 °C for 5 h. After the reaction was complete (TLC), it was diluted with cold water and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue using petroleum ether/EtOAc (3:2) as eluent furnished **3** (26 mg, 40%), (80% brsm) as pale yellow oil; $[\alpha]_D^{24}$ –8.9 (*c* 2.5, $CHCl_3$). IR (neat): 3486, 2986, 2930, 1733, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (*quint*, *J* = 6.2 Hz, 1H), 4.36 – 4.25 (m, 1H), 4.11 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.85 (d, *J* = 3.6 Hz, 1H), 3.64 – 3.48 (m, 2H), 2.20 (s, 1H), 2.02 (s, 3H), 1.70 – 1.59 (m, 1H), 1.58 – 1.39 (m, 10H), 1.33 (s, 3H), 1.25 (s, 12H), 0.85 (d, *J* = 10.9 Hz, 12H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 107.7, 77.8, 74.3, 73.6, 69.4, 61.9, 38.2, 35.6, 34.04, 34.0, 31.6, 29.7, 28.1, 25.8 (3C), 25.4, 25.2, 24.9, 24.2, 22.3, 21.2, 18.0, 14.0, −4.3, −4.6. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{54}O_6SiNa$: 525.3587; found: 525.3592.

Preparation of ethyl (*E*)-3-((4*R*,5*S*)-5-((2*R*,8*R*)-8-acetoxy-2-((tert-butyldimethylsilyl)oxy)tridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (11)

To a stirred solution of the alcohol **3** (24 mg, 0.05 mmol) in dry CH_2Cl_2 (2 mL) under nitrogen atmosphere, were added $NaHCO_3$ (20 mg, 0.24 mmol) and Dess-Martin periodinane (30 mg, 0.07 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction it was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated. The crude aldehyde thus obtained was used as such in the next step without further purification.

To a solution of the crude aldehyde (obtained above), in toluene (2 mL) were added the ylide (carbethoxymethylene) triphenylphosphorane (25 mg, 0.07 mmol) under argon atmosphere, and the reaction mixture was refluxed for 2 h. After the reaction was complete (TLC), most of the solvent was evaporated off and the residue thus obtained was purified by column chromatography using petroleum ether/EtOAc (20:1) as eluent to obtain the unsaturated ester **11** (17 mg, 63% over 2 steps) as yellow oil; $[\alpha]_D^{24}$ −12.1 (*c* 0.85, $CHCl_3$).IR (neat): 2936, 2857, 2361, 1729, 1651, 1373 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (dd, *J* = 15.2, 6.0 Hz, 1H), 6.04 (dd, *J* = 15.2, 1.2 Hz, 1H), 4.90 – 4.79 (m, 1H), 4.63 (t, *J* = 6.0 Hz, 1H), 4.41 (ddd, *J* = 9.6,

6.4, 3.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.89 – 3.78 (m, 1H), 2.03 (s, 3H), 1.55 – 1.39 (m, 11H), 1.36 (s, 3H), 1.34 – 1.16 (m, 15H), 0.91 – 0.83 (m, 12H), 0.053 (s, 3H), 0.049 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 166.1, 144.3, 122.8, 108.7, 77.3, 74.4, 74.3, 69.0, 60.4, 38.2, 37.5, 34.1, 34.0, 31.7, 29.8, 28.0, 25.9 (3C), 25.5, 25.3, 24.9, 24.3, 22.5, 21.3, 18.0, 14.2, 14.0, –4.3, –4.6. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{31}H_{58}O_7SiNa$: 593.3850; found: 593.3848.

Preparation of (*E*)-3-((4*R*,5*S*)-5-((2*R*,8*R*)-2-((tert-butyldimethylsilyl)oxy)-8-hydroxytridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid (2): To a stirred solution of **11** (17 mg, 0.02 mmol) in MeOH:THF (1:1, 1.0 mL) was added 1 M aqueous LiOH (0.5 mL, 0.5 mmol) and was stirred at room temperature for 7 h. After completion of the reaction (TLC), the solvent was evaporated off to give the residue, which was diluted with water (5 mL), neutralized with a saturated solution of citric acid (pH 4), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure and the resulting seco-acid **2** (14 mg, 94%), which was subjected to the next reaction without further purification; $[\alpha]_D^{24}$ –15.7 (*c* 1.1, $CHCl_3$). IR (neat): 3401, 2929, 2857, 2685, 2359, 1704, 1653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (dd, *J* = 15.6, 6.0 Hz, 1H), 6.07 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.10 (bs, 2H), 4.75 – 4.59 (m, 1H), 4.51 – 4.38 (m, 1H), 3.96 – 3.77 (m, 1H), 3.68 – 3.52 (m, 1H), 1.54 – 1.20 (m, 26H), 0.96 – 0.81 (m, 12H), 0.063 (s, 3H), 0.060 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 147.0, 122.0, 108.8, 77.2, 74.9, 72.1, 69.1, 38.2, 37.5, 37.3, 31.9, 29.9, 29.7, 27.9, 25.9 (3C), 25.5, 25.5, 25.3, 24.3, 22.6, 18.1, 14.0, –4.2, –4.6. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{52}O_6SiNa$: 523.3431; found: 523.3431.

Preparation of (3a*R*,8*R*,14*R*,15a*S*,*E*)-14-((tert-butyldimethylsilyl)oxy)-2,2-dimethyl-8-pentyl-3a,8,9,10,11,12,13,14,15,15a-decahydro-6H-[1,3]dioxolo[4,5-e][1]oxacyclotetradecin-6-one (12): To a solution of the acid **2** (14 mg, 0.028 mmol) and Et_3N (0.02 mL, 0.17 mmol) in anhydrous toluene (2.0 mL) was added 2,4,6-trichlorobenzoyl chloride (24 µL, 0.17 mmol) dropwise under argon atmosphere at 0 °C. The mixture was stirred at room temperature for 1 h and diluted with anhydrous toluene (6 mL). It was added dropwise to a solution of DMAP (51 mg, 0.42 mmol) in anhydrous toluene (3 mL) at room temperature. On completion of the addition, the mixture was stirred for 1 h at room temperature. After completion of the reaction (TLC), it was quenched by addition of $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue using petroleum ether/EtOAc (1:9) as eluent furnished the macrolactone **12** (10 mg, 76%) as yellow oil; $[\alpha]_D^{24}$: –9.1 (*c* 0.5, $CHCl_3$). IR (neat): 2931, 2859, 2363, 1720, 1640, 1461 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.97 (d, *J* = 15.6 Hz, 1H), 5.00–4.88 (m, 1H), 4.69–4.61 (m, 1H), 4.48 (q, *J* = 6.0 Hz, 1H), 3.91–3.81 (m, 1H), 1.76–1.53 (m, 5H), 1.52-1.48 (m, 4H), 1.46–1.39 (m, 3H), 1.38–1.24 (m, 14H), 0.91–0.85 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 144.2, 124.3, 108.7, 77.5, 76.0, 75.1, 69.1, 37.24, 37.17, 34.6, 31.7, 31.6, 29.7, 27.9, 25.9 (3C), 25.3, 25.2, 25.1, 23.7, 22.5, 18.1, 14.0, –4.6, –4.7. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{50}O_5SiNa$: : 507.3325; found: : 507.3325.

Preparation of (5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (1): To a solution of macrolactone **12** (9 mg, 0.02 mmol) in 2.2 mL of MeOH-THF-H_2O (10:5:1) was added camphorsulphonic acid (15 mg, 0.06 mmol) in one portion at room temperature and stirred for 24 h. The reaction mixture was diluted with EtOAc (5 mL) and washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to get the crude product, which on purification using silica gel column chromatography with 50% EtOAc in petroleum ether as an eluent afforded Sch 725674 (**1**) (3 mg) as an amorphous white solid in 50% yield. R_f = 0.10 (50% EtOAc in petroleum ether), M.P.: 181-184 °C**,** [Lit.[3b] M.P.: 180-184 °C]; $[\alpha]_D^{24}$: +4.7 (*c* 0.15, CH_3OH), [Lit.[3b] $[\alpha]_D^{24}$: +5.0 (*c* 0.1, CH_3OH)]. IR (KBr): 3441, 3268, 2926, 2855, 2363, 1705, 1590 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.88 (dd, *J* = 15.6, 5.6 Hz, 1H), 6.09 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.99-4.92 (m, 1H), 4.53 – 4.45 (m, 1H), 3.99 (quint, *J* = 6.4 Hz, 1H), 3.89 – 3.80 (m, 1H), 1.84 (dt, *J* = 14.8, 6.0 Hz, 1H), 1.76 – 1.52 (m, 5H), 1.49 – 1.28 (m, 11H), 1.24 – 1.11 (m, 3H), 0.91 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3OD): δ = 168.3, 149.4, 123.1, 77.7, 76.1, 72.9, 69.5, 38.3, 36.8, 36.5, 34.1, 33.0, 29.5, 27.0, 26.4, 25.8, 23.8, 14.5. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{32}O_5Na$: 351.2147; found: 351.2147.

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Supplementary Material

Copies of ^{1}H NMR and ^{13}C NMR spectra for all the new compounds synthesized are provided.

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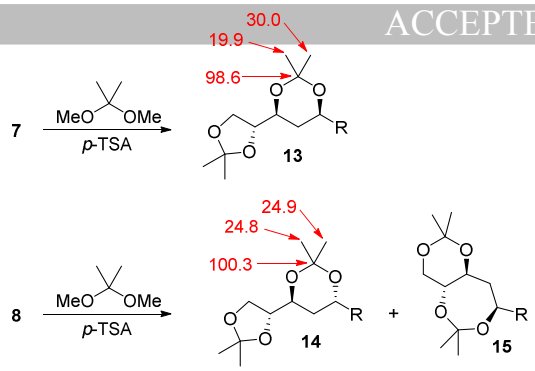

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