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Total Synthesis of (–)-Pyrenophorol

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Abstract: An efficient synthetic route has been developed for the synthesis of (–)-pyrenophorol employing Sharpless asymmetric epoxidation, olefin cross-metathesis, and intermolecular Mitsunobu cyclization.

Key words: macrodiolide, stereoselectivity, natural products, Sharpless asymmetric epoxidation, cross-metathesis

Lactone-containing natural products have attracted considerable attention due to their interesting biological properties.[1] Naturally occurring macrodiolide antibiotics (Figure 1) are divided into two groups: compounds having a C2 symmetry and a 16-membered ring derived from a head-to-tail dimerization of two identical C8 hydroxy acid subunits such as pyrenophorol (**1**),[2] pyrenophorin (**2**),[3] tetrahydropyrenophorol (**3**),[4] and vermiculin (**4**),[5] and those having an unsymmetrical 14-membered ring such as colletallol (**5**).[6]

Structurally related macrolide dilactones such as pyrenophorol (**1**) and pyrenophorin (**2**) are produced by the plant pathogenic fungi *Byssachlamys nivea*[2a] and *Pyrenophora avenae*,[7] respectively. These two macrolides have also been isolated from the culture filtrates of *Stemphylium radicinum*.[2b] They exhibit prominent antifungal antibiotic activity. Subsequently, pyrenophorol was also isolated from the imperfect fungus *Alternaria alternata* and was named as helmidiol,[8] which exhibits pronounced anthelmintic properties.[8,9] Pyrenophorol was moderately active against the fungus *Microbotryum violaceum*.[4]

The first total synthesis of the natural isomer of pyrenophorol was reported by Zwanenburg et al.[10] Later, Kibayashi et al.[11] reported its total synthesis by employing two successive esterifications. The synthesis of the (5*R*,8*S*,13*R*,16*S*)-isomer of pyrenophorol has been accomplished by Le Floc'h et al.[12] Recently, we have reported the synthesis of (–)-pyrenophorol by employing Jacobsen's hydrolytic kinetic resolution and MacMillan's α-hydroxylation to establish two stereogenic centers.[13] The use of Jacobsen's hydrolytic kinetic resolution leads to the formation of the required isomer in less than 50% yield, which limits its usage in large-scale synthesis. To address this problem, and also as part of our ongoing program on natural products synthesis,[14] we herein report a new and efficient synthetic route for the synthesis of (–)-pyrenophorol via Sharpless asymmetric epoxidation and olefin metathesis followed by an intermolecular Mitsunobu cyclization.

The retrosynthetic route adopted is outlined in Scheme 1. (–)-Pyrenophorol (**1**) was proposed to be synthesized by intermolecular Mitsunobu cyclization of seco acid **14**, which could be obtained by Sharpless asymmetric epoxidation followed by olefin metathesis of allylic alcohol **11**. The allylic alcohol **11** could be derived from a commercially available lactate ester.

The synthesis of pyrenophorol (**1**) began from lactate ester (Scheme 2), which was protected as its silyl ether using *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in anhydrous dichloromethane (CH_2Cl_2). Reduction of the TBS ether of the lactate ester with diisobutylaluminum hydride (DIBAL-H) in anhydrous CH_2Cl_2 at –78 °C gave the corresponding aldehyde, which was then subjected to Wittig olefination with $Ph_3PCHCOOEt$ in benzene under reflux conditions to give the unsaturated ester **6** in 92% yield. Reduction of the double bond using $NaBH_4$ in the presence of $NiCl_2$ gave the saturated ester **7** in 90% yield. Further reduction of ester **7** with DIBAL-H fol-

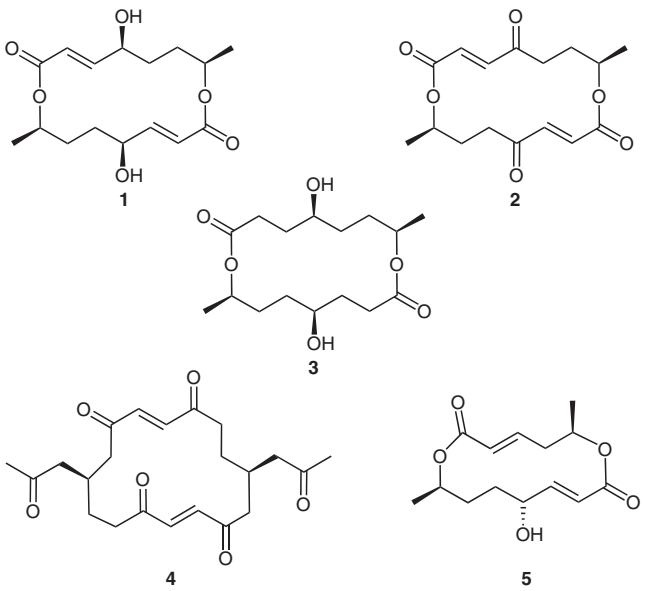

Figure 1 Naturally occurring macrodiolide antibiotics

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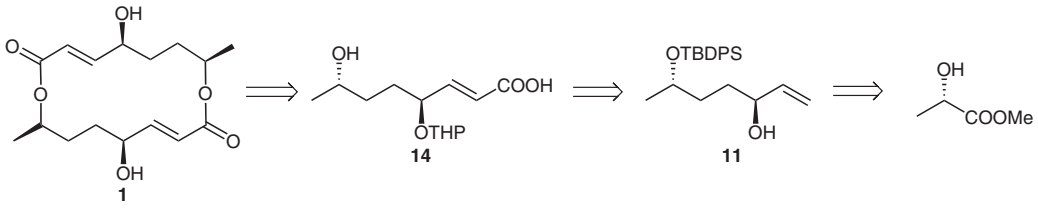
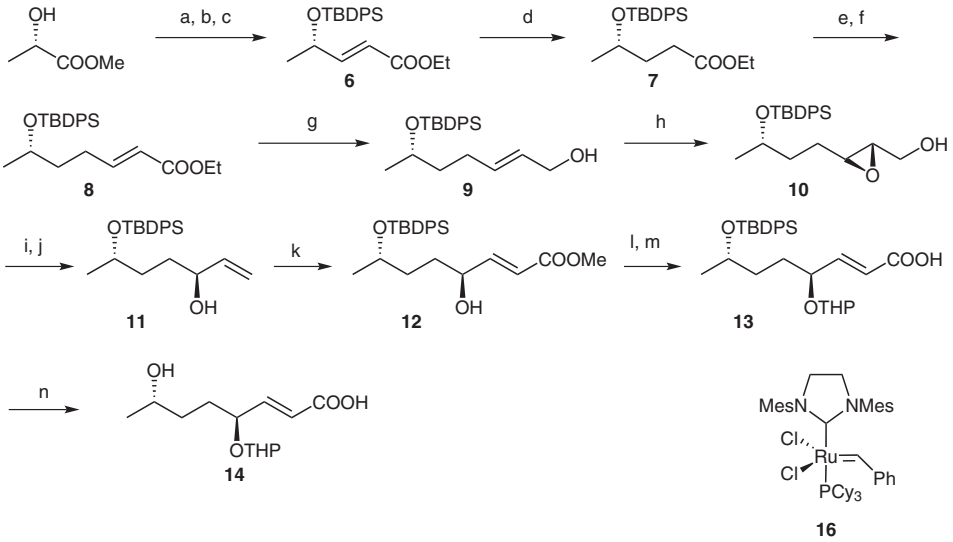
lowed by Wittig olefination gave ester **8** in 94% yield. Reduction of ester **8** using DIBAL-H in anhydrous CH_2Cl_2 gave the allylic alcohol **9** in 92% yield, which was then subjected to Sharpless asymmetric epoxidation to give the epoxy alcohol **10** in 78% yield. Iodination of **10** followed by epoxide opening with metallic zinc powder in refluxing MeOH[15] afforded the allylic alcohol **11** in 82% yield. Olefin cross metathesis of **11** with methyl acrylate gave the enoate **12** in 78% yield. Protection of the hydroxy group of enoate **12** as its tetrahydropyranyl ether (THP), followed by hydrolysis of the ester moiety under basic conditions gave the carboxylic acid **13** in 85% yield. Desilylation of **13** gave the key intermediate **14**, which was then subjected to an intermolecular Mitsunobu cyclization.

Mitsunobu cyclization of **14** was carried out by using Gerlach's procedure[16] to achieve the macrolactonization with complete inversion of configuration at C4 to give compound **15** (Scheme 3). Finally, cleavage of the THP ether furnished the target macrolide (**1**) in 96% yield as a white solid. The analytical and spectral data of the macrolide (**1**) were in good agreement with those of an authentic sample.[13]

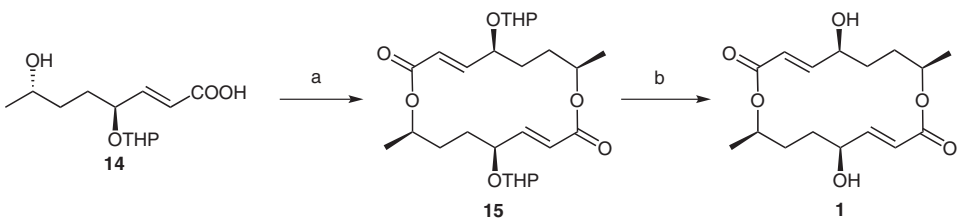
In summary, we have developed an efficient approach for the total synthesis of (–)-pyrenophorol involving



Scheme 1 Retrosynthetic analysis of **1**



Scheme 2 *Reagents and conditions*: (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C→r.t., 30 min, 98%; (b) DIBAL-H, CH_2Cl_2, –78 °C, 20 min, 80%; (c) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 92%; (d) $NiCl_2·6H_2O$, $NaBH_4$, MeOH, 0 °C, 1 h, 90%; (e) DIBAL-H, CH_2Cl_2, –78 °C, 15 min, 82%; (f) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 94%; (g) DIBAL-H, CH_2Cl_2, –78→0 °C, 1 h, 92%; (h) L-(+)-DIPT, $Ti(O\textit{i}\text{-}Pr)_4$, TBHP, CH_2Cl_2, –20 °C, 7 h, 78%; (i) I_2, imidazole, Ph_3P, THF–MeCN (4:1), 0 °C→r.t., 30 min, 92%; (j) Zn, MeOH, reflux, 12 h, 82%; (k) methyl acrylate, **16**, CH_2Cl_2, reflux, 24 h, 78%; (l) 3,4-dihydropyran, CSA, CH_2Cl_2, r.t., 1 h, 88%; (m) 20% aq NaOH, MeOH, r.t., 30 min, 85%; (n) TBAF, THF, 60 °C, 2 h, 90%.



Scheme 3 *Reagents and conditions*: (a) Ph_3P, DEAD, toluene–THF (10:1), –25 °C, 24 h, 60%; (b) PTSA, MeOH, r.t., 30 min, 96%.

Sharpless asymmetric epoxidation, olefin cross metathesis and intermolecular Mitsunobu cyclization starting from a readily available lactate ester. This approach may find application in generating new derivatives of (–)-pyrenophorol.

Melting points were recorded with a Büchi R-535 apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer FTIR 240-c spectrophotometer using KBr optics. ^{1}H and ^{13}C NMR spectra were recorded with a Gemini-200 spectrometer (200 MHz) or a Bruker-300 spectrometer (300 MHz) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded with a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60–120, mesh silica gel. Optical rotations were measured with a JASCO DIP-370 polarimeter operating at 25 °C.

Compound 6

To a stirred solution of (2*S*)-2-*tert*-butyldimethylsilyloxypropanal (3.25 g, 10.41 mmol) in benzene (50 mL), was added $Ph_3PCHCOOEt$ (4.35 g, 12.5 mmol) and the resulting mixture was heated to reflux for 1 h. The reaction was then quenched with H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (EtOAc–*n*-hexane, 1%) to give **6**.

Yield: 3.66 g (92%); colorless oil; $[\alpha]_D^{25}$ –39.6 (*c* 2.0, $CHCl_3$).

IR (neat): 3071, 2965, 2931, 2860, 1736, 1473, 1427, 1376, 1267, 1177, 1135, 1110, 1029, 997, 822, 742, 701 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.66–7.73 (m, 4 H), 7.33–7.44 (m, 6 H), 6.92 (dd, *J* = 15.1, 4.7 Hz, 1 H), 6.08 (d, *J* = 15.1 Hz, 1 H), 4.40–4.44 (m, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.04–1.08 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.4, 151.0, 135.6, 134.1, 129.8, 129.4, 127.5, 127.4, 119.1, 68.6, 60.2, 26.9, 23.2, 19.2, 14.2.

MS (ESI): *m*/*z* = 383 [M + H].

Compound 7

To a solution of **6** (3.542 g, 9.27 mmol) in anhydrous MeOH (30 mL) at 0 °C, was added $NiCl_2 \cdot 6\,H_2O$ (0.66 g, 2.78 mmol) and $NaBH_4$ (0.70 g, 18.54 mmol) portion-wise. The resulting mixture was stirred at the same temperature for 1 h. Upon completion, the reaction mixture was filtered through Celite, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography (EtOAc–hexane, 1%) to give **7**.

Yield: 3.20 g (90%); colorless oil; $[\alpha]_D^{25}$ –6.2 (*c* 2.0, $CHCl_3$).

IR (neat): 3071, 2959, 2931, 2856, 1722, 1656, 1472, 1428, 1367, 1272, 1152, 1110, 1051, 980, 822, 740, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.66–7.73 (m, 4 H), 7.33–7.44 (m, 6 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 3.92–3.94 (m, 1 H), 2.38 (t, *J* = 7.5 Hz, 1 H), 2.37 (t, *J* = 7.5 Hz, 1 H), 1.78 (m, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.03–1.08 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.6, 136.2, 134.0, 129.6, 129.4, 127.5, 127.4, 68.4, 60.0, 34.5, 30.0, 27.2, 23.0, 19.2, 14.1.

MS (ESI): *m*/*z* = 385 [M + H].

Compound 8

A solution of DIBAL-H (1.0 M in toluene, 9.5 mL, 9.5 mmol) was added dropwise to a solution of ester **7** (3.08 g, 8.03 mmol) in CH_2Cl_2 (35 mL) at –78 °C and stirred for 15 min at the same temperature. The reaction mixture was then quenched with sat. aq potassium sodium tartrate (20 mL) and then allowed to stir vigorously for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. The crude aldehyde was dissolved in benzene (30 mL) and then $Ph_3PCHCOOEt$ (3.43 g, 9.87 mmol) was added. The resulting mixture was heated to reflux for 1 h. Upon completion, the reaction was quenched with H_2O (15 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by silica gel flash chromatography (EtOAc–*n*-hexane, 1%) to give **8**.

Yield: 2.53 g (94%); colorless oil; $[\alpha]_D^{25}$ –19.4 (*c* 2.75, $CHCl_3$).

IR (neat): 2953, 2859, 1721, 1269, 1172, 1109, 1045, 738, 703, 618 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64–7.69 (m, 4 H), 7.33–7.46 (m, 6 H), 6.81–6.92 (m, 1 H), 5.73 (d, *J* = 15.6 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.82–3.91 (m, 1 H), 2.16–2.26 (m, 2 H), 1.50–1.66 (m, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.03–1.08 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.1, 149.0, 135.8, 129.6, 129.4, 127.5, 127.4, 121.1, 68.7, 60.3, 37.4, 27.8, 27.0, 23.1, 14.2.

MS (ESI): *m*/*z* = 411 [M + H].

Compound 9

A solution of **8** (2.30 g, 5.61 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and then DIBAL-H (1 M in toluene, 14.0 mL, 14.0 mmol) was slowly added over 10 min under a N_2 atmosphere. After addition was complete, stirring was continued for 1 h at 0 °C. Upon completion, the mixture was carefully quenched with sat. aq potassium sodium tartrate (25 mL) and then allowed to stir vigorously for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was subjected to silica gel flash chromatography (EtOAc–*n*-hexane, 10%) to give **9**.

Yield: 1.89 g (92%); colorless liquid; $[\alpha]_D^{25}$ –11.4 (*c* 2.5, $CHCl_3$).

IR (neat): 3380, 3069, 2930, 2857, 1665, 1464, 1427, 1375, 1188, 1107, 1050, 1003, 972, 821, 739, 703, 611, 507 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63–7.70 (m, 4 H), 7.34–7.45 (m, 6 H), 5.50–5.56 (m, 2 H), 3.98–4.03 (m, 2 H), 3.79–3.89 (m, 1 H), 1.99–2.09 (m, 2 H), 1.40–1.63 (m, 2 H), 1.00–1.11 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 135.9, 133.1, 129.4, 128.8, 127.5, 127.4, 68.9, 63.7, 38.7, 27.9, 27.0, 23.1, 19.2.

MS (ESI): *m*/*z* = 369 [M + H].

Compound 10

To a stirred suspension of 4 Å molecular sieves (10 g) in anhydrous CH_2Cl_2 (250 mL) under N_2 was added L-(+)-diisopropyl tartrate (0.127 mL, 0.606 mmol, 0.12 equiv) in one portion. The mixture was then cooled to –20 °C and $Ti(O\textit{i}Pr)_4$ (0.148 mL, 0.50 mmol, 0.1 equiv) was added. After 10 min, *t*-BuOOH (8.69 M in CH_2Cl_2, 1.16 mL, 10.04 mmol, 2 equiv) was added dropwise over 5 min. The mixture was stirred at –20 °C for 30 min and then a solution of allylic alcohol **9** (1.85 g, 5.05 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise over 30 min. The mixture was stirred at –20 °C for 7 h and then quenched with H_2O (10 mL), diluted with EtOAc (100 mL) and the resulting mixture was allowed to warm to r.t. The organic layer was separated, washed with H_2O (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo, followed by purification by silica gel chromatography (EtOAc–*n*-hexane, 15%) gave **10**.

Yield: 1.51 g (78%); colorless oil; $[\alpha]_D^{25}$ –6.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3424, 3069, 2927, 2856, 1740, 1463, 1427, 1376, 1262, 1107, 1047, 1002, 877, 821, 739, 703, 611, 507 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64–7.71 (m, 4 H), 7.32–7.47 (m, 6 H), 3.80–3.95 (m, 2 H), 3.51–3.59 (m, 1 H), 2.79–2.87 (m, 2 H), 1.49–1.66 (m, 2 H), 1.30–1.33 (m, 2 H), 1.01–1.10 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 135.8, 129.6, 129.5, 127.5, 127.4, 69.0, 68.7, 61.6, 58.4, 35.2, 29.7, 27.0, 23.1, 19.2.

MS (ESI): *m*/*z* = 407 [M + Na].

Compound 11

To a vigorously stirred solution of epoxy alcohol **10** (1.5 g, 3.90 mmol) in anhydrous THF–MeCN (4:1, 30 mL) was successively added imidazole (1.59 g, 23.4 mmol), Ph_3P (2.93 g, 11.2 mmol) and I_2 (2.84 g, 11.2 mmol). Stirring was continued at r.t. for 30 min, then Et_2O (20 mL) was added to precipitate out the Ph_3P=O. The solids were filtered through a short pad of silica gel and the filtrate was concentrated in vacuo to obtain the crude iodo epoxide. To a vigorously stirred solution of iodo epoxide in MeOH (25 mL) was added Zn dust (2.61 g, 40 mmol) and the mixture was heated under reflux for 12 h. After cooling to r.t., the mixture was filtered through a short pad of Celite, washed thoroughly with MeOH, and the filtrate was concentrated in vacuo. Purification of the residue by silica gel flash chromatography (EtOAc–hexane, 10%) gave allylic alcohol **11**.

Yield: 1.08 g (82%); colorless oil; $[\alpha]_D^{25}$ –5.8 (*c* 1.0, $CHCl_3$).

IR (neat): 3420, 3067, 2926, 2859, 1108, 871, 844, 819, 737, 704, 665, 610 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63–7.72 (m, 4 H), 7.34–7.45 (m, 6 H), 5.72–5.87 (m, 1 H), 5.04–5.21 (m, 2 H), 4.16–4.23 (m, 1 H), 3.46–3.56 (m, 1 H), 1.46–1.81 (m, 7 H), 1.05 (s, 9 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.1, 135.6, 129.4, 127.5, 127.3, 115.7, 73.5, 71.2, 33.1, 31.4, 28.6, 26.9, 21.2.

MS (ESI): *m*/*z* = 369 [M + H].

Compound 12

To a solution of **11** (0.50 g, 1.37 mmol) in CH_2Cl_2 (50 mL), Grubbs II catalyst (0.058 g, 0.067 mmol) was added and the mixture was heated to reflux for 24 h in a N_2 atmosphere. The solvent was partially distilled off and the resulting solution was stirred at r.t. for 2 h under open air in order to decompose the catalyst. The mixture was evaporated to dryness to give a brown residue, which was purified by silica gel flash chromatography (EtOAc–hexane, 15%) to give **12**.

Yield: 0.45 g (78%); colorless syrup; $[\alpha]_D^{25}$ –15.5 (*c* 0.35, $CHCl_3$).

IR (neat): 3447, 2925, 2855, 1724, 1657, 1461, 1432, 1376, 1272, 1168, 1108, 1045, 820, 738, 703, 611, 506 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.65–7.70 (m, 4 H), 7.34–7.44 (m, 6 H), 6.90 (dd, *J* = 1.5, 15.8 Hz, 1 H), 6.02 (dt, *J* = 1.5, 15.8 Hz, 1 H), 4.18–4.26 (m, 1 H), 3.91 (q, *J* = 12.0, 6.0 Hz, 1 H), 3.75 (s, 3 H), 1.52–1.64 (m, 4 H), 1.20 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.4, 150.3, 135.8, 129.6, 127.6, 127.4, 119.7, 71.1, 69.1, 51.6, 34.2, 31.6, 29.7, 27.0, 22.3.

MS (ESI): *m*/*z* = 427 [M + H].

Compound 13

3,4-Dihydropyran (0.41 g, 4.93 mmol) was added to a solution of **12** (0.42 g, 0.98 mmol) in CH_2Cl_2 (10 mL) and then a catalytic amount of 10-camphorsulfonic acid (CSA; 0.023 g, 0.1 mmol) was added. The resulting mixture was stirred at r.t. for 1 h. The solvent and excess dihydropyran were removed in vacuo and the crude product was purified by silica gel flash chromatography (EtOAc–hexane, 5%) to give the protected alcohol as a colorless syrup. The syrup was then dissolved in MeOH (10 mL) and treated with 20% aq NaOH (2 mL) for 30 min. The reaction mixture was neutralized with aq HCl and the solvent was evaporated in vacuo. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was then subjected to silica gel flash chromatography (EtOAc–hexane, 40%) to give **13**.

Yield: 0.36 g (85%); colorless liquid; $[\alpha]_D^{25}$ –10 (*c* 0.65, $CHCl_3$).

IR (neat): 3424, 2923, 2854, 1703, 1655, 1460, 1376, 1265, 1122, 1108, 1072, 1044, 1026, 980, 811, 771, 738, 705, 609, 509 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60–7.67 (m, 4 H), 7.29–7.41 (m, 6 H), 6.75–6.83 (m, 1 H), 5.85 (d, *J* = 15.8 Hz, 1 H), 4.49–4.61 (m, 1 H), 4.14–4.2 (m, 1 H), 3.69–3.89 (m, 2 H), 3.36–3.47 (m, 1 H), 1.38–1.86 (m, 10 H), 1.07 (d, *J* = 6.1 Hz, 3 H), 1.04 (s, 9 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.5, 150.4, 135.8, 129.5, 129.4, 129.3, 127.3, 127.2, 121.6, 95.9, 74.6, 74.3, 74.1, 69.1, 62.2, 62.1, 34.6, 30.9, 30.7, 30.5, 30.4, 29.6, 29.0, 27.0, 25.4, 25.3, 23.0, 19.2.

MS (ESI): *m*/*z* = 495 [M – H].

Compound 14

To a solution of **13** (0.35 g, 0.70 mmol) in anhydrous THF (40 mL) was added TBAF (1.0 M in THF, 0.85 mL, 0.85 mmol) at 0 °C, and the resulting mixture was stirred for 2 h at r.t. Upon completion, the reaction was quenched with sat. aq NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc–hexane, 70%) to afford **14**.

Yield: 0.164 g (90%); yellow liquid; $[\alpha]_D^{25}$ +4.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3421, 2923, 2852, 1702, 1656, 1459, 1378, 1266, 1122, 1072, 1026, 982, 810, 771 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.79–7.07 (m, 1 H), 5.94–6.13 (m, 1 H), 4.73–4.77 (m, 1 H), 4.55–4.59 (m, 1 H), 4.33–4.44 (m, 1 H), 3.39 (t, *J* = 7.3 Hz, 2 H), 1.97–2.11 (m, 2 H), 1.46–1.88 (m, 8 H), 1.20 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.5, 150.8, 120.1, 97.3, 74.8, 67.9, 60.3, 33.9, 30.6, 29.9, 25.2, 23.4, 19.2.

MS (ESI): *m*/*z* = 281 [M + Na].

Compound 15

To a solution of **14** (0.13 g, 0.50 mmol) in anhydrous toluene–THF (20:1, 80 mL), was added Ph_3P (0.66 g, 2.51 mmol) at –40 °C under an argon atmosphere. DEAD (0.437 g, 2.51 mmol) was added at the same temperature and the mixture was stirred at –25 °C for 24 h. The solvent was removed in vacuo and the residue was subjected to silica gel flash chromatography (EtOAc–hexane, 25%) to afford **15**.

Yield: 0.072 g (60%); yellow liquid; $[\alpha]_D^{25}$ +7.5 (*c* 0.75, $CHCl_3$).

IR (neat): 3446, 2924, 2854, 1749, 1718, 1647, 1459, 1373, 1271, 1073, 1271, 1073, 1026, 987, 868, 764 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.54–6.81 (m, 2 H), 5.78–5.88 (m, 2 H), 4.99–5.09 (m, 2 H), 4.65–4.70 (m, 1 H), 4.45–4.49 (m, 1 H), 3.99–4.18 (m, 4 H), 3.69–3.85 (m, 1 H), 3.36–3.47 (m, 1 H), 1.72–1.84 (m, 4 H), 1.41–1.56 (m, 4 H), 1.12–1.32 (m, 18 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.0, 146.3, 122.8, 96.5, 73.9, 69.5, 64.0, 30.7, 29.7, 28.8, 25.3, 19.2, 18.4, 14.3, 14.1.

MS (ESI): *m*/*z* = 503 [M + Na].

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{40}O_8Na$: 503.2620; found: 503.2601.

Compound 1

To a stirred suspension of **15** (0.026 g, 0.054 mmol) in MeOH (1.5 mL) was added a catalytic amount of PTSA (0.001 g, 0.005 mmol)

and the resulting mixture was stirred at r.t. for 30 min. The solvent was evaporated in vacuo and the crude product was purified by silica gel flash chromatography (EtOAc–hexane, 40%) to afford **1**.

Yield: 0.015 g (96%); white solid; mp 136–138 °C; $[\alpha]_D^{25}$ –3.2 (*c* 0.25, acetone).

IR (KBr): 3382, 2924, 2854, 1713, 1647, 1274, 1173, 1119 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.83 (dd, *J* = 15.6 Hz, 2 H), 5.89 (m, 2 H), 5.10–5.01 (m, 2 H), 4.24–4.16 (m, 2 H), 2.69–2.48 (m, 2 H), 2.01–1.53 (m, 8 H), 1.20 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.0, 149.3, 122.0, 70.3, 69.7, 30.4, 28.8, 18.2.

MS (ESI): *m/z* = 335 [M + Na].

HRMS (ESI): *m/z* calcd for $C_{16}H_{24}O_6$: 313.1651; found: 313.1656.

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