Stereoselective Total Synthesis of Tarchonanthuslactone and Formal Synthesis of (–)-Colletol

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Abstract: A simple and efficient stereoselective total synthesis of tarchonanthuslactone and formal synthesis of (–)-colletol is described using as the key steps Jacobsen's kinetic resolution and a Sharpless asymmetric epoxidation. The synthesis of tarchonanthuslactone and the seco acid proceeded in 14% and 13% overall yield, respectively, starting from chiral (*R*)-propylene oxide.

Keywords: hydrolytic kinetic resolution, PMB acetal formation, Sharpless asymmetric epoxidation, lactonization, one-pot oxidation/alkenation, esterification

Natural products possessing the lactone framework have attracted considerable attention in organic synthesis due to their unique structures and potent biological activity.[1] Tarchonanthuslactone (**1**), an α,β-unsaturated δ-lactone was isolated in 1979 by Bohlmann from the leaves of the tree *Tarchonanthus trilobus* (Figure 1).[2] Later, Nakata et al. established its absolute configuration by asymmetric synthesis.[3] The basic structure of tarchonanthuslactone (a dihydrocaffeic acid ester) consists of a *syn*-1,3-diol unit with one hydroxy group involved in an unsaturated lactone and the other esterified with 3,4-dihydroxyhydrocinnamic acid. A few years ago, Hsu et al. showed that **1** lowered the plasma glucose level in diabetic rats.[4] This important biological activity gave an indication that tarchonanthuslactone (**1**) or its analogues have potential to be used in human beings. Similarly, (–)-colletol (**3**), a 14-membered bis-macrolactone, was first isolated in 1973 from the fermentation broth of *Colletotrichum capsici* together with other related metabolites.[5] Moreover, these classes of compounds have shown significant activity against various pathogenic microorganisms.[6] The promising biological activity and the unique structure of these families make them attractive synthetic targets. There have been several synthetic efforts toward the synthesis of tarchonanthuslactone (**1**)[7] and (–)-colletol (**3**),[8] however, their syntheses using inexpensive and readily available raw materials with short and facile routes continue to be challenging endeavors.

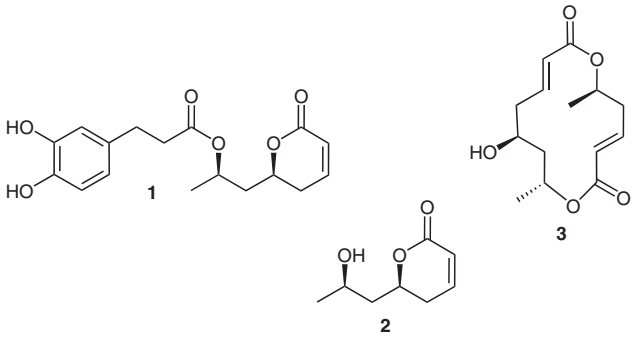
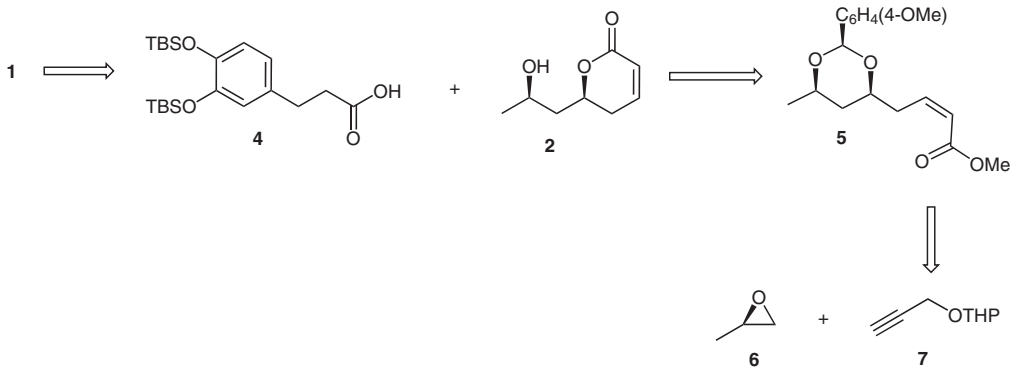


Figure 1 Tarchonanthuslactone (**1**), **2**, and (–)-colletol (**3**)

In continuation of our programme on the synthesis of bioactive lactones,[9] herein we report a facile stereoselective synthesis of tarchonanthuslactone (**1**) and formal synthesis of (–)-colletol (**3**). Our retrosynthetic strategy for **1** is outlined in Scheme 1. The first disconnection involved cleavage to give lactone **2** and acid **4**. It was envisioned



Scheme 1 Retrosynthetic analysis of **1** and **2**

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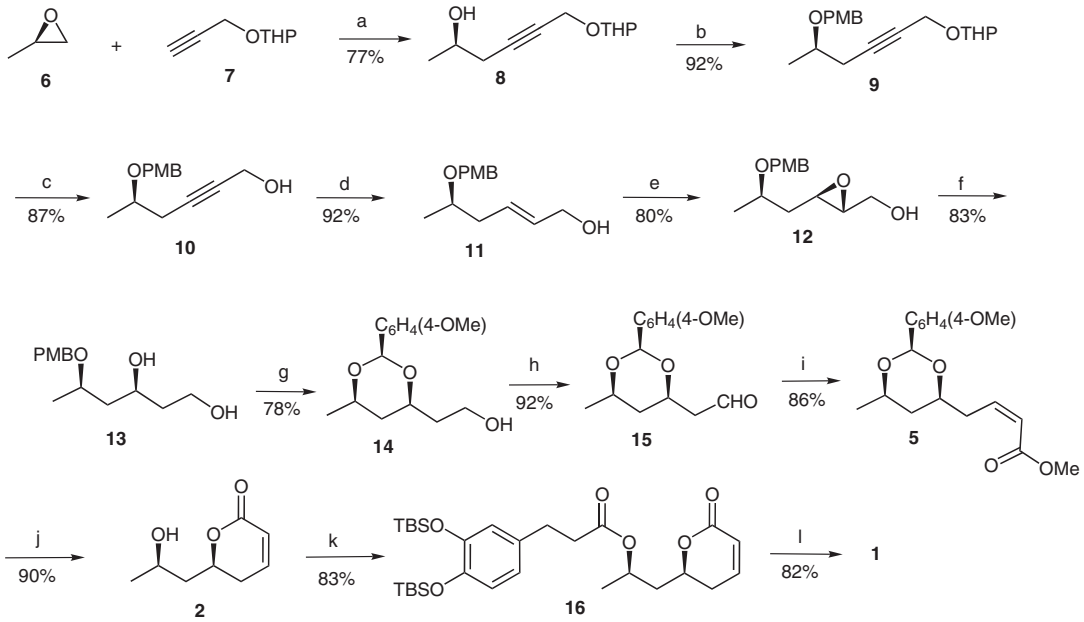
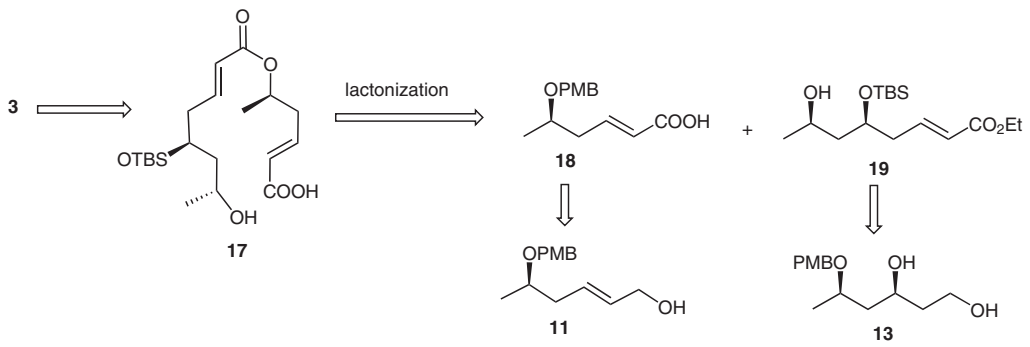


Scheme 2 *Reagents and conditions*: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, –78 °C, 3 h, 77%; (b) NaH, PMBBr, THF, 0 °C to r.t., 6 h, 92%; (c) MeOH, CSA (cat.), r.t., 4 h, 87%; (d) $LiAlH_4$, THF, r.t., 4 h, 92%; (e) (–)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, –20 °C, 6 h, 80%; (f) Red-Al, THF, –20 °C to r.t., 1 h, 83%; (g) DDQ, CH_2Cl_2, 0 °C, 2 h, 78%; (h) DMP, CH_2Cl_2, r.t., 3 h; 92%; (i) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, –78 °C, 30 min, 86%; (j) PTSA, benzene, r.t., 5 h, 90%; (k) DCC, DMAP, **4**, CH_2Cl_2, r.t., 15 h, 83%; (l) TBAF, THF, r.t., 1 h, 82%.

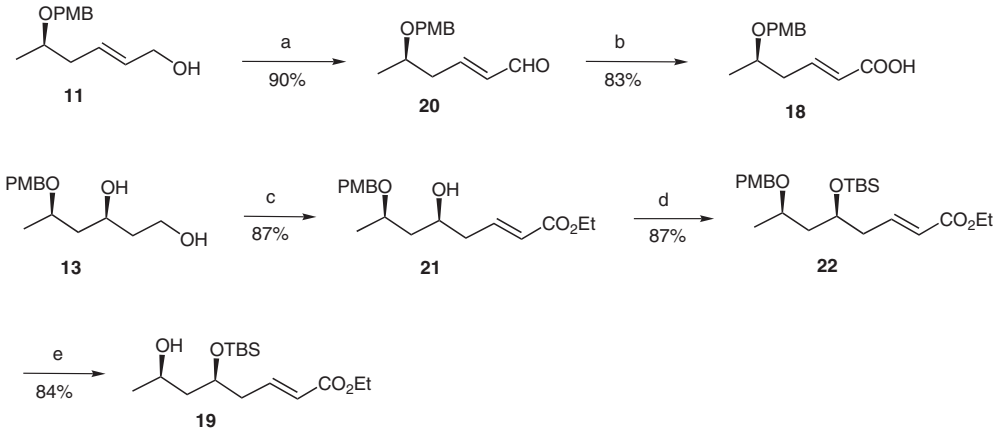
that the key fragment **2** could be obtained by lactonization of **5**, which is obtained by iterative hydrolytic kinetic resolution from propylene oxide **6**[10] followed by Sharpless asymmetric epoxidation that fixed both the stereogenic centers.

Accordingly, metalation of 3-(tetrahydro-2*H*-pyran-2-yloxy)propyne (**7**) with *n*-butyllithium at –78 °C in tetrahydrofuran[11] followed by addition of boron trifluoride–diethyl ether complex and (*R*)-propylene oxide (**6**)[12] gave the homopropargyl alcohol **8** in 77% yield (Scheme 2). The secondary alcohol was then protected as the 4-methoxybenzyl ether using sodium hydride and 4-methoxybenzyl bromide in tetrahydrofuran and followed by deprotection of the tetrahydropyranyl ether to give primary alcohol **10** in 80% yield (2 steps). The resulting primary alcohol **10** was converted into homoallylic alcohol **11** by lithium aluminum hydride reduction in tetrahydrofuran in 92% yield; **11** was subjected to Sharpless asymmetric epoxidation to afford epoxy alcohol **12** in 80% yield. Regioselectively hydride transfer of **12** with Red-Al[13] provided 1,3-diol **13** in 83% yield, treatment of which with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1 equiv) in anhydrous dichloromethane under controlled conditions resulted in the formation of 4-methoxybenzylidenedioxy acetal[14] **14** in 78% yield.

Primary alcohol **14** was oxidized with Dess–Martin periodinane to afford aldehyde **15**, which was subjected to a modified Wadsworth–Emmons olefination reaction in the presence of sodium hydride in tetrahydrofuran, to provide the key fragment **5** in 79% yield (2 steps). Treatment of **5** with 4-toluenesulfonic acid in benzene permitted simultaneous deprotection of the acetal and lactonization[15] to give the desired lactone **2** in 90% yield. Classical esterification of lactone **2** with acid **4** in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine followed by removal of the phenol protecting groups afforded tarchonanthuslactone (**1**) in 68% yield (2 steps), whose spectral data were identical with that reported.[7]



Scheme 3 Retrosynthetic analysis of **3**



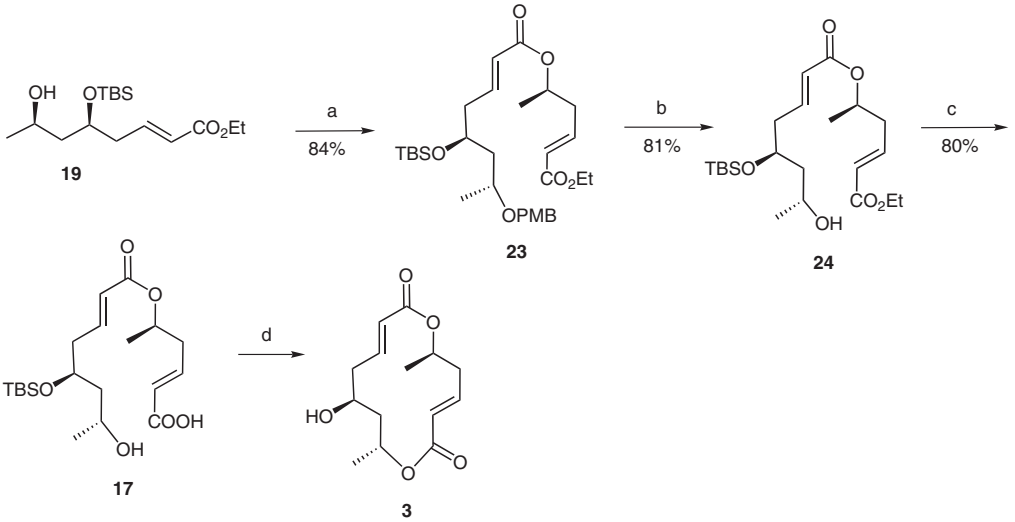
Scheme 4 *Reagents and conditions*: (a) DMP, CH_2Cl_2, r.t., 3 h; 90%; (b) NaH_2PO_4, 2-methylbut-2-ene, $NaClO_2$, *t*-BuOH–H_2O (3:1), 0 °C, 4 h, 83%; (c) (i) $PhI(OAc)_2$, TEMPO (cat.), CH_2Cl_2, r.t., 2 h. (ii) $Ph_3P{=}CHCO_2Et$ (2 equiv), r.t., 2 h, 87%; (d) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 2 h, 87%; (e) DDQ, CH_2Cl_2–H_2O (17:1), r.t., 1 h, 84%.

The disconnection approach to **17**, which could be obtained from lactonization of key fragments **18** and **19** is shown in Scheme 3. The acid **18** could be prepared from the homoallylic alcohol **11**, and **19** could be obtained from **13**.

Accordingly, homoallylic alcohol **11** was oxidized using Dess–Martin periodinane and subsequently oxidized to the acid **18** by conventional methods (Scheme 4). The primary hydroxy group of **13** was subjected to one-pot oxidation/alkenation following Vatele's protocol;[16] thus, the primary hydroxy group was oxidized with (diacetoxyiodo)benzene and catalytic TEMPO to afford the aldehyde , which was subsequently subjected to a two-carbon homologation using (ethoxycarbonylmethylene)triphenylphosphorane in dichloromethane to furnish (*E*)-α,β-unsaturated ester **21** in 87% yield. The secondary alcohol was then protected as the silyl ether using *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane followed by deprotection of the PMB ether using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane–water (17:1) to afford the fragment **19**.

Having made both the fragments **18** and **19** successfully, they were then subjected to esterification (Scheme 5) under Shiina's conditions[17] using 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(dimethylamino)pyridine in dichloromethane at room temperature to furnish **23** in 84% yield. The PMB ether of **23** was cleaved by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane–water (17:1) to afford **24** in 81% yield. Selective removal of the ethyl ester group in **23** with lithium hydroxide monohydrate in tetrahydrofuran–water (4:1) gave seco acid **17** in 80% yield.

We have described a simple and efficient route for the total synthesis of tarchonanthuslactone (**1**) and formal synthesis of (–)-colletol (**3**) starting from a chiral epoxide obtained from Jacobsen's salen reagent and later using Sharpless asymmetric epoxidation to fix both the chiral centers. This route is amenable, economic, and uses easily handled reagents to synthesize tarchonanthuslactone (**1**) and (–)-colletol (**3**).



Scheme 5 *Reagents and conditions*: (a) **18**, MNBA, DMAP, CH_2Cl_2, r.t. 2 h, 84%; (b) DDQ, CH_2Cl_2–H_2O (17:1), r.t., 1 h, 81%; (c) $LiOH{\cdot}H_2O$ (1 equiv), THF–H_2O (4:1), r.t., 6 h, 80%; (d) ref. 8b.

All solvents and reagents were purified by standard techniques. Column chromatography was performed using silica gel 60–120 mesh. All solvents were dried and distilled prior to use. IR spectra were recorded on a Perkin–Elmer Infrared spectrophotometer as KBr wafers, neat or in $CHCl_3$ as a thin film. ^1H and ^{13}C NMR were recorded on a Varian Gemini 200, Bruker Avance 300 or Varian Unity 400 instrument (^1H operating frequencies of 300 MHz and 400 MHz, respectively) using TMS as an internal standard. MS spectra were obtained on an Agilent Technologies LC/MSD Trap SL. HRMS were measured on a Varian MAT-711 and MAT-95. The optical rotations were recorded on a JASCO DIP-360 digital polarimeter at 25 °C.

(2*R*)-6-(Tetrahydro-2*H*-pyran-2-yloxy)hex-4-yn-2-ol (8)

A 1.6 M *n*-BuLi in hexane (26.7 mL, 42.8 mmol) was added slowly to a suspension of **7** (5.0 g, 35.71 mmol) in anhyd THF (60 mL) at –78 °C and the mixture was stirred for 1 h. $BF_3{\cdot}OEt_2$ (6.77 g, 42.84 mmol) followed by 2-methyloxirane (**6**, 4.14 g, 71.37 mmol) were added and the mixture was stirred at –78 °C for 1 h. On completion of the reaction (TLC, ca. 1 h), the mixture was quenched with sat. NH_4Cl (20 mL) followed by sat. $NaHCO_3$ (20 mL). After a few min, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford a residue that was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 5.4 g (77%); $[\alpha]_D^{25}$ +10.5 (*c* 2.8, $CHCl_3$).

IR (KBr): 3421, 2940, 2871, 1638, 1448, 1349, 1201, 1117, 1022, 941, 563 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.78 (t, *J* = 3.0 Hz, 1 H), 4.21 (dt, *J* = 2.2, 4.5, 6.7 Hz, 2 H), 3.89 (q, *J* = 6.0 Hz, 1 H), 3.85–3.67 (m, 1 H), 3.54–3.47 (m, 1 H), 2.63 (br s, 1 H), 2.37–2.33 (m, 2 H), 1.88–1.50 (m, 6 H), 1.25 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 22.1, 25.1, 29.2, 30.1, 54.4, 61.8, 66.1, 78.1, 82.8, 96.6.

ESI/MS: *m*/*z* = 221.1 $[M + Na]^+$, 199.1 $[M^+]$, 173.1, 102.2, 85.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}NaO_3$: 221.1153; found: 221.1152.

2-[(5*R*)-5-(4-Methoxybenzyloxy)hex-2-ynyloxy]tetrahydro-2*H*-pyran (9)

To a well-stirred suspension of freshly activated NaH (60% dispersion in mineral oil; 1.09 g, 45.45 mmol) in anhyd THF (40 mL), was added dropwise at 0 °C a soln of **8** (4.5 g, 22.75 mmol) in anhyd THF (15 mL). After 30 min, 4-methoxybenzyl bromide (5.0 g, 24.96 mmol) was added and the mixture was warmed to r.t. and stirred for 5.5 h. The reaction was quenched with crushed ice and product was extracted with Et_2O (3 × 45 mL). The combined organic layers were washed with H_2O (45 mL) and brine (2 × 15 mL) and dried (Na_2SO_4). The mixture was filtered and the volatiles removed under reduced pressure to give a crude product that was purified by column chromatography (EtOAc–hexane, 5:9.5).

Pale yellow liquid; yield: 6.6 g (92%); $[\alpha]_D^{25}$ –2.8 (*c* 1.0, $CHCl_3$).

IR (KBr): 2941, 2869, 1724, 1629, 1444, 1129, 1076, 1030, 972, 813 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 9.0 Hz, 2 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 4.77 (t, *J* = 3.0 Hz, 1 H), 4.45 (s, 2 H), 4.18 (td, *J* = 2.2, 4.5, 6.7 Hz, 1 H), 3.83–3.78 (m, 1 H), 3.78 (s, 3 H), 3.67–3.45 (m, 2 H), 2.55–2.46 (m, 1 H), 2.32 (ddt, *J* = 2.2, 4.5, 7.5 Hz, 1 H), 1.88–1.48 (m, 7 H), 1.25 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.5, 25.3, 26.3, 30.2, 54.4, 55.1, 61.8, 70.2, 72.9, 83.2, 96.5, 113.6, 129.0, 130.5, 159.0.

MS (ESI): *m*/*z* = 341.1 $[M + Na]^+$, 245.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{26}NaO_4$: 341.1728; found: 341.1724.

(5*R*)-5-(4-Methoxybenzyloxy)hex-2-yn-1-ol (10)

MeOH (20 mL) and CSA (cat.) were added to **9** (4.0 g, 12.57 mmol) at r.t. After 4 h the solvent was removed in vacuo, and crude residue was diluted with CH_2Cl_2 (20 mL) and sat. aq $NaHCO_3$ (15 mL). The organic layer was separated, washed with brine (2 × 15 mL) and H_2O (20 mL) and then dried (Na_2SO_4). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 2.56 g (87%); $[\alpha]_D^{25}$ +7.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3412, 2931, 2868, 1612, 1513, 1247, 1030, 821, 575 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.0 Hz, 2 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 4.44 (s, 2 H), 4.12 (s, 2 H), 3.76 (s, 3 H), 3.59 (q, *J* = 6.0 Hz, 1 H), 2.74 (br s, 1 H), 2.48–2.28 (m, 2 H), 1.25 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 26.0, 50.9, 55.1, 70.1, 72.7, 80.1, 82.4, 113.6, 129.1, 130.3, 159.0.

MS (ESI): *m*/*z* = 257.1 $[M + Na]^+$, 217.2, 173.1, 121.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_3$: 257.1153; found: 257.1150.

(5*R*,*E*)-5-(4-Methoxybenzyloxy)hex-2-en-1-ol (11)

$LiAlH_4$ (0.467 g, 12.30 mmol) was added portionwise to **10** (2.4 g, 10.25 mmol) dissolved in anhyd THF (30 mL) at 0 °C. The mixture was warmed to r.t. and stirred for 4 h. On completion of the reaction (TLC) it was quenched by slow addition of sat. aq Na_2SO_4 (10 mL) at 0 °C. After a few min, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to afford a residue that was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 2.2 g (92%); $[\alpha]_D^{25}$ –3.6 (*c* 1.0, $CHCl_3$).

IR (KBr): 3450, 2929, 2865, 1612, 1513, 1247, 1032, 821, 517 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.1 Hz, 2 H), 6.82 (d, *J* = 9.1 Hz, 2 H), 5.63–5.59 (m, 2 H), 4.40 (d, *J* = 6.6 Hz, 2 H), 3.98 (br d, *J* = 2.2 Hz, 2 H), 3.76 (s, 3 H), 3.49 (q, *J* = 6.6 Hz, 1 H), 2.32 (br s, 1 H), 2.26–2.14 (m, 2 H), 1.16 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 38.8, 55.0, 63.1, 69.7, 73.9, 113.5, 128.3, 128.9, 130.7, 131.4, 158.8.

MS (ESI): *m*/*z* = 259.1 $[M + Na]^+$, 219.1, 159.1, 121.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}NaO_3$: 259.1310; found: 259.1302.

{(2*R*,3*R*)-3-[(2*R*)-2-(4-Methoxybenzyloxy)propyl]oxiran-2-yl}methanol (12)

Anhyd CH_2Cl_2 (20 mL) was cooled to –20 °C under N_2, $Ti(O\textit{i}\text{-}Pr)_4$ (0.31 g, 1.10 mmol) and (–)-DIPT (0.30 g, 1.27 mmol) were sequentially added and stirred for 5–10 min. A soln of alcohol **11** (2.0 g, 8.47 mmol) in CH_2Cl_2 (5 mL) followed by *t*-BuOOH (1.52 g, 16.94 mmol) were added to the mixture, which was stirred at –20 °C for 6 h. The mixture was allowed to warm to 0 °C, quenched with 10% aq NaOH soln saturated with NaCl (10 mL), and stirred vigorously for 1 h. The mixture was filtered through Celite and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified by column chromatography (EtOAc–hexane, 2.5:7.5).

Colorless liquid; yield: 1.7 g (80%); $[\alpha]_D^{25}$ –7.3 (*c* 1.0, $CHCl_3$).

IR (KBr): 3423, 2969, 2927, 2863, 1612, 1513, 1247, 1033, 821, 516 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 9.1 Hz, 2 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.35 (d, *J* = 11.3 Hz, 1 H), 3.80–3.76 (m, 1 H), 3.78 (s, 3 H), 3.64 (q, *J* = 6.0 Hz, 1 H), 3.58–3.51 (m, 1 H), 3.01 (dt, *J* = 2.2, 6.0, 8.0 Hz, 1 H), 2.84–2.81 (m, 1 H), 1.87–1.62 (m, 2 H), 1.25 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 38.2, 53.1, 55.1, 58.1, 61.6, 69.7, 71.8, 113.6, 129.1, 130.5, 158.9.

MS (ESI): *m*/*z* = 275.1 $[M + Na]^+$, 231.1, 121.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}NaO_4$: 275.1259; found: 275.1257.

(3*S*,5*R*)-5-(4-Methoxybenzyloxy)hexane-1,3-diol (13)

Red-Al (65% in toluene; 10.0 mL) was added dropwise to **12** (1.5 g, 5.95 mmol) dissolved in anhyd THF (20 mL) at –20 °C. Vigorous gas evolution was observed. After 1 h, the reaction was quenched with sat. aq potassium sodium tartrate soln and stirred for 3 h. Two clear layers were obtained which were separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the solvent was removed by rotary evaporation to afford a residue that was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 1.25 g (83%); $[\alpha]_D^{25}$ –44.6 (*c* 1.0, $CHCl_3$).

IR (KBr): 3396, 2927, 1612, 1513, 1247, 1033, 819, 567, 418 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 4.31 (d, *J* = 11.0 Hz, 1 H), 4.41–3.65 (m, 4 H), 3.78 (s, 3 H), 1.83–1.45 (m, 4 H), 1.22 (d, *J* = 5.8 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.8, 38.6, 43.7, 55.2, 61.0, 69.6, 71.8, 75.6, 113.8, 129.3, 129.9, 159.3.

MS (ESI): *m*/*z* = 277.0 $[M + Na]^+$, 121.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{22}NaO_4$: 277.1415; found: 277.1414.

(3*S*,5*R*)-3,5-(4-Methoxybenzylidenedioxy)hexan-1-ol (14)

Compound **13** (1.1 g, 4.33 mmol) was added slowly to a suspension of DDQ (1.0 g, 4.33 mmol) and anhyd CH_2Cl_2 (15 mL) at 0 °C and the mixture was stirred for 2 h. On completion of the reaction (TLC), it was quenched by slow addition of sat. aq $NaHCO_3$ (10 mL) at 0 °C. After a few min, the layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford a residue, which was purified by column chromatography (EtOAc–hexane, 1:9).

Colorless liquid, yield: 0.85 g (78%); $[\alpha]_D^{25}$ –27.2 (*c* 0.72, $CHCl_3$).

IR (KBr): 3421, 2924, 2854, 1614, 1516, 1248, 1030, 827, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.45 (s, 1 H), 4.07–3.86 (m, 2 H), 3.81–3.76 (m, 2 H), 3.78 (s, 3 H), 1.86–1.71 (m, 2 H), 1.59–1.41 (m, 2 H), 1.30 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 37.9, 38.4, 55.1, 60.0, 72.8, 75.7, 100.6, 113.5, 127.3, 131.1, 159.8.

MS (ESI): *m*/*z* = 275.1 $[M + Na]^+$, 24.2, 172.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}NaO_4$: 275.1259; found: 275.1265.

(3*R*,5*R*)-3,5-(4-Methoxybenzylidenedioxy)hexanal (15)

A soln **14** (0.7 g, 2.77 mmol) in anhyd CH_2Cl_2 (10 mL) was added by cannula to a soln of DMP (1.7 g, 4.16 mmol) in anhyd CH_2Cl_2 (2.5 mL) at r.t. After 3 h, the pale pink mixture was transferred to an Erlenmeyer flask containing sat. aq $NaHCO_3$ (25 mL). The separated organic layer was washed with brine (2 × 10 mL) and H_2O (10 mL), dried (Na_2SO_4), and filtered and the solvent was removed in vacuo. Crude **15** was utilized in the next step without further purification. Yellow oil; yield 0.64 g (92%).

Methyl (*Z*,5*S*,7*R*)-5,7-(4-Methoxybenzylidenedioxy)oct-2-enoate (5)

To soln of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (0.70 g, 2.2 mmol) in anhyd THF (10 mL) was added NaH (60% dispersion in mineral oil, 96 mg, 4.0 mmol) at 0 °C; vigorous gas evolution was observed. After 45 min, to the resulting clear soln was added aldehyde **15** (0.5 g, 2.0 mmol) in anhyd THF (5 mL) dropwise at –78 °C. After 30 min, the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and brine (2 × 20 mL) and dried (Na_2SO_4). Solvent was removed and the residue was purified by column chromatography (EtOAc–hexane, 3:7).

Colorless liquid, yield: 0.53 g (86%); $[\alpha]_D^{25}$ –18.6 (*c* 0.5, $CHCl_3$).

IR (KBr): 2925, 2854, 1721, 1615, 1518, 1249, 1175, 1034, 827, 674, 591 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 6.46 (dt, *J* = 7.4, 11.6, 14.1 Hz, 1 H), 5.83 (dt, *J* = 1.6, 3.3, 11.6 Hz, 1 H), 5.41 (s, 1 H), 3.97–3.81 (m, 2 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.14–2.99 (m, 1 H), 2.91–2.75 (m, 1 H), 1.65–1.40 (m, 2 H), 1.27 (d, *J* = 5.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 35.5, 38.1, 51.0, 55.2, 72.8, 75.8, 100.7, 113.5, 120.7, 127.4, 131.3, 145.8, 159.8, 166.7.

MS (ESI): *m*/*z* = 329.1 $[M + Na]^+$, 211.0, 186.1, 171.0, 12.0, 93.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_5$: 329.1364; found: 329.1375.

(*S*)-6-[(*R*)-2-Hydroxypropyl]-5,6-dihydro-2*H*-pyran-2-one (2)

A soln of **5** (0.2 g, 0.65 mmol) in benzene (2 mL) was added PTSA (cat.) was stirred at r.t. for 5 h. The solvent was removed and residue was diluted with EtOAc (10 mL), and quenched with sat. $NaHCO_3$ (2 mL); the layers were separated and aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with brine (2 × 6 mL) and H_2O (6 mL), dried (Na_2SO_4), and concentrated to give a residue that was purified by column chromatography (EtOAc–hexane, 3:7).

Colorless liquid; yield: 91 mg (90%); $[\alpha]_D^{25}$ –110 (*c* 0.8, $CHCl_3$).

IR (KBr): 3420, 2925, 2853, 1715, 1386, 1251, 1117, 1046 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.89 (ddd, *J* = 3.0, 6.0, 9.8 Hz, 1 H), 6.08 (dt, *J* = 3.0, 9.8 Hz, 1 H), 4.62–4.59 (m, 1 H), 4.12–4.09 (m, 1 H), 2.47–2.36 (m, 2 H), 2.00–1.75 (m, 2 H), 1.26 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 29.7, 43.5, 65.2, 75.6, 121.3, 145.4, 164.1.

MS (ESI): *m*/*z* = 179.0 $[M + Na]^+$, 157.0 $[M]^+$, 130.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{12}NaO_3$: 179.0684; found: 179.0692.

(*R*)-1-Methyl-2-[(*S*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl 3-[3,4-Bis(*tert*-butyldimethylsiloxy)phenyl]propanoate (16)

To the soln of acid **4** (0.23 g, 0.54 mmol) and DCC (0.11 g, 0.54 mmol) in CH_2Cl_2 (8 mL), was added to a soln of **2** (70 mg, 0.45 mmol) in CH_2Cl_2 (2 mL). After 10 min, DMAP (65 mg, 0.54 mmol) was added and the mixture was stirred for 15 h at r.t. The solid residue was filtered and solvent was evaporated. The crude product was purified by column chromatography (EtOAc–hexane, 1:9).

Colorless liquid; yield: 0.2 g (83%); $[\alpha]_D^{25}$ –42.8 (*c* 0.8, $CHCl_3$).

IR (KBr): 2960, 2860, 1740, 1690, 1600, 1575, 1500, 1450 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.82–6.62 (m, 4 H), 5.99 (d, *J* = 9.8 Hz, 1 H), 5.13–5.04 (m, 1 H), 4.44–4.40 (m, 1 H), 2.83 (t, *J* = 7.0 Hz, 2 H), 2.53 (t, *J* = 7.0 Hz, 2 H), 2.40–2.37 (m, 2 H), 2.23–1.72 (m, 2 H), 1.25 (d, *J* = 7.0 Hz, 3 H), 0.96 (s, 9 H), 0.95 (s, 9 H), 0.19 (s, 6 H), 0.17 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.2, 18.3, 20.2, 25.8, 29.0, 30.1, 36.1, 40.7, 67.0, 74.8, 120.76, 120.97, 121.02, 121.17, 133.3, 144.7, 145.1, 146.5, 163.8, 172.3.

MS (ESI): *m*/*z* = 571.1 $[M + Na]^+$.

Anal. Calcd for $C_{29}H_{48}O_6Si_2$ (548.86); C, 63.46; H, 8.81. Found: C, 62.51; H, 8.57.

(*R*)-1-Methyl-2-[(*S*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl 3-(3,4-Dihydroxyphenyl)propanoate (1)

Compound **16** (100 mg, 0.18 mmol) was added to a suspension of TBAF (142 mg, 0.54 mmol) in anhyd THF (8 mL) at r.t. The mixture was stirred for 1 h at r.t., diluted with EtOAc (10 mL) and aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 6 mL). The combined organic layers were washed with brine (2 × 6 mL) and H_2O (6 mL), dried (Na_2SO_4), and concentrated to give a residue that was purified by column chromatography (EtOAc–hexane, 3:7).

White solid; yield: 48 mg (82%); mp 89–90 °C; $[\alpha]_D^{25}$ –80 (*c* 0.4, $CHCl_3$).

IR (KBr): 3341, 2925, 2853, 1715, 1606, 1522, 1415 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.84 (ddd, *J* = 3.0, 6.0, 9.8 Hz, 1 H), 6.77 (d, *J* = 10.5 Hz, 1 H), 6.74 (d, *J* = 2.2 Hz, 1 H), 6.58 (dd, *J* = 2.2, 8.3 Hz, 1 H), 5.99 (ddd, *J* = 3.0, 9.8, 12.0 Hz, 1 H), 5.12–5.02 (m, 1 H), 4.17 (dddd, *J* = 3.7, 6.0, 10.5, 12.8 Hz, 1 H), 2.85 (t, *J* = 6.7 Hz, 2 H), 2.62 (t, *J* = 6.7 Hz, 2 H), 2.42–2.00 (m, 3 H), 1.77 (ddd, *J* = 3.7, 6.7, 11.3, 14.3 Hz, 1 H), 1.25 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 28.8, 30.1, 36.0, 40.5, 67.2, 75.2, 115.2, 120.1, 120.5, 132.4, 142.4, 144.0, 146.0, 165.3, 173.0.

MS (ESI): *m*/*z* = 343.1 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{20}O_6$ (320.336); C, 63.74; H, 6.29; Found: C, 63.37; H, 6.08.

(5*R*,*E*)-5-(4-Methoxybenzyloxy)hex-2-enal (20)

A soln of **11** (0.2 g, 0.85 mmol) in anhyd CH_2Cl_2 (10 mL) was added by cannula to a soln of DMP (0.4 g, 0.94 mmol) in anhyd CH_2Cl_2 (2.5 mL) at r.t. After 3 h, the pale pink mixture was transferred into an Erlenmeyer flask containing sat. aq $NaHCO_3$ (25 mL) The separated organic layer was washed with brine (2 × 10 mL) and H_2O (10 mL), dried (Na_2SO_4), and filtered and the solvent was removed in vacuo. Crude **20** was utilized in the next step without further purification. Yellow liquid; yield: 0.18 g (90%).

(5*R*,*E*)-5-(4-Methoxybenzyloxy)hex-2-enoic Acid (18)

NaH_2PO_4 (152 mg, 1.27 mmol) and 2-methylbut-2-ene (89 mg, 1.27 mmol) were added to a soln of **20** (200 mg, 0.85 mmol) in a mixture of *t*-BuOH (6 mL) and H_2O (2 mL) at 0 °C. The mixture was stirred for 5 min and then $NaClO_2$ (114 mg, 1.27 mmol) was added at this temperature. After completion of the reaction (ca. 4 h), the solvent was removed in vacuo. The residue was diluted with EtOAc (10 mL) and H_2O (10 mL). After 5 min, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and H_2O (10 mL) and dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane, 3:7).

Colorless liquid; yield: 177 mg (83%); $[\alpha]_D^{25}$ –4.3 (*c* 1.1, $CHCl_3$).

IR (KBr): 2970, 2932, 1696, 1513, 1248, 1175, 1034, 821, 749, 518 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.6 Hz, 2 H), 7.04 (dt, *J* = 7.5, 14.9, 15.6 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 5.83 (dt, *J* = 1.3, 2.8, 15.6 Hz, 1 H), 4.44 (q, *J* = 11.5 Hz, 2 H), 3.78 (s, 3 H), 3.62 (q, *J* = 6.0 Hz, 1 H), 2.52–2.31 (m, 2 H), 1.20 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 39.4, 55.2, 70.2, 73.0, 113.8, 122.7, 129.2, 130.4, 148.4, 159.1, 171.6.

MS (ESI): *m*/*z* = 273.12 $[M + Na]^+$, 121.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_4$: 273.1102; found: 273.1101.

Ethyl (5*S*,7*R*,*E*)-5-Hydroxy-7-(4-methoxybenzyloxy)oct-2-enoate (21)

To a suspension of $PhI(OAc)_2$ (126 mg, 0.40 mmol) and **13** (100 mg, 0.40 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C was added TEMPO (cat.), and the mixture was stirred at r.t. for 2 h. On completion of the reaction (TLC), (ethoxycarbonylmethylene)triphenylphosphorane (274 mg, 0.79 mmol) was added and the mixture was stirred at r.t. for 2 h. On completion of the reaction (TLC), the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL), and stirred for 5 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 6 mL) and H_2O (6 mL), dried (Na_2SO_4), and concentrated; this gave a residue that was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 110 mg (87%); $[\alpha]_D^{25}$ –34.8 (*c* 0.3, $CHCl_3$).

IR (KBr): 3474, 2971, 2934, 1716, 1514, 1249, 1036 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.4 Hz, 2 H), 6.93 (dt, *J* = 7.5, 12.4, 15.6 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 5.83 (dt, *J* = 1.3, 2.8, 15.6 Hz, 1 H), 4.59 (d, *J* = 11.1 Hz, 1 H), 4.32 (d, *J* = 11.1 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.90–3.81 (m, 2 H), 3.78 (s, 3 H), 2.38–2.29 (m, 2 H), 1.68–1.49 (m, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.23 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 19.6, 40.2, 43.2, 55.2, 60.2, 69.9, 70.6, 75.7, 114.0, 123.5, 129.4, 129.8, 145.3, 159.3, 166.4.

MS (ESI): *m*/*z* = 345.1 $[M + Na]^+$, 74.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{26}NaO_5$: 345.1677; found: 345.1680.

Ethyl (5*S*,7*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-7-(4-methoxybenzyloxy)oct-2-enoate (22)

TBDMSCl (84 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred soln of **21** (90 mg, 0.28 mmol) in anhyd CH_2Cl_2 (10 mL) and imidazole (50 mg, 0.73 mmol) at 0 °C. The mixture was stirred at r.t. for 2 h and then diluted with H_2O (10 mL) and stirred for a few min, the layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and H_2O (10 mL), and dried (Na_2SO_4). The solvent was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 1:9).

Colorless liquid; yield: 106 mg (87%); $[\alpha]_D^{25}$ –6.7 (*c* 0.6, $CHCl_3$).

IR (KBr): 2931, 2856, 1719, 1512, 1250, 1170, 1043, 833, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.8 Hz, 2 H), 6.96 (dt, *J* = 6.6, 9.3, 15.4 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 5.75 (d, *J* = 15.4 Hz, 1 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.32 (d, *J* = 11.7 Hz, 1 H), 4.18 (q, *J* = 6.6 Hz, 2 H), 3.89 (quint, *J* = 8.0, 13.9 Hz, 1 H), 3.80 (s, 3 H), 3.54 (q, *J* = 5.8 Hz, 1 H), 2.39–2.22 (m, 1 H), 1.92–

1.39 (m, 3 H), 1.28 (t, *J* = 6.6 Hz, 3 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, 14.2, 17.9, 19.6, 25.6, 25.7, 39.9, 44.5, 60.0, 68.5, 69.9, 70.9, 113.7, 123.3, 123.4, 128.9, 129.1, 130.8, 145.4, 145.8, 159.1, 166.3.

MS (ESI): *m*/*z* = 459.3 $[M + Na]^+$, 345.1, 301.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{40}NaO_5Si$: 459.2542; found: 459.2555.

Ethyl (5*S*,7*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-7-hydroxyoct-2-enoate (19)

Compound **22** (80 mg, 0.18 mmol) was added slowly to a suspension of DDQ (41.6 mg, 0.18 mmol) and CH_2Cl_2–H_2O (17:1, 10 mL) at r.t. and the mixture was stirred for 1 h. On completion of the reaction (TLC), it was quenched by slow addition of sat. aq $NaHCO_3$ (10 mL) at 0 °C. After a few min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford a residue that was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 48 mg (84%); $[\alpha]_D^{25}$ +8.3 (*c* 0.8, $CHCl_3$).

IR (KBr): 3445, 2956, 2928, 2855, 1720, 1257, 1048, 853, 775, 664 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66 (dd, *J* = 1.4, 5.9, 14.0 Hz, 1 H), 5.78 (d, *J* = 14.0 Hz, 1 H), 4.15 (q, *J* = 7.4 Hz, 2 H), 4.01 (quint, *J* = 5.9, 12.5 Hz, 1 H), 3.89 (quint, *J* = 6.6, 16.9 Hz, 1 H), 2.54 (br s, 1 H), 2.40 (tt, *J* = 1.4, 3.7, 7.4, 8.8 Hz, 2 H), 1.56 (d, *J* = 6.6 Hz, 2 H), 1.29 (t, *J* = 6.6 Hz, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7, –4.2, 14.2, 23.6, 25.6, 25.7, 40.6, 45.1, 60.2, 66.5, 71.2, 123.9, 144.4, 166.2.

MS (ESI): *m*/*z* = 339.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{32}NaO_4Si$: 339.1967; found: 339.1969.

(1*R*,*E*)-5-Ethoxy-1-methyl-5-oxopent-3-enyl (5*S*,7*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-7-(4-methoxybenzyloxy)oct-2-enoate (23)

To a soln of **19** (30 mg, 0.094 mmol), MNBA (39 mg, 0.11 mmol), and DMAP (28 mg, 0.22 mmol) in CH_2Cl_2 (8 mL) at r.t. was slowly added a soln of **18** (24 mg, 0.096 mmol) in CH_2Cl_2 (2 mL) with a mechanically driven syringe over 1 h period. After addition of the soln, the mixture was additionally stirred for 1 h. On completion of the reaction (TLC), sat. aq $NaHCO_3$ (5 mL) was added and aqueous layer was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were washed with brine (2 × 6 mL) and H_2O (6 mL), dried (Na_2SO_4), and concentrated; this gave a residue that was purified by column chromatography (EtOAc–hexane, 3:7).

Colorless liquid; yield: 43.7 mg (84%); $[\alpha]_D^{25}$ +3.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 9.0 Hz, 2 H), 7.0–6.90 (m, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 5.86 (dt, *J* = 3.7, 6.7, 15.8 Hz, 2 H), 5.12–4.93 (m, 1 H), 4.48 (q, *J* = 11.3 Hz, 2 H), 4.19 (q, *J* = 6.7 Hz, 2 H), 3.81 (s, 3 H), 3.64 (q, *J* = 6.0 Hz, 1 H), 2.65–2.35 (m, 4 H), 1.95–1.61 (m, 3 H), 1.32–1.20 (m, 9 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

MS (ESI): *m*/*z* = 571.1 $[M + Na]^+$, 393.1, 287.1, 189.19, 60.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{48}NaO_7Si$: 571.3067; found: 571.3071.

(1*R*,*E*)-5-Ethoxy-1-methyl-5-oxopent-3-enyl (5*S*,7*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-7-hydroxyoct-2-enoate (24)

Compound **23** (25 mg, 0.045 mmol) was added slowly to a suspension of DDQ (13 mg, 0.06 mmol) and CH_2Cl_2–H_2O (17:1, 6 mL) at r.t. and the mixture was stirred for 1 h. On completion of the reaction (TLC) it was quenched by slow addition of sat. aq $NaHCO_3$ (5 mL) at 0 °C. After a few min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with aq $NaHCO_3$ (3 × 5 mL), dried (Na_2SO_4), and concentrated to afford a residue that was purified by column chromatography (EtOAc–hexane, 2:8).

Colorless liquid; yield: 16 mg (81%); $[\alpha]_D^{25}$ –7.4 (*c* 0.7, $CHCl_3$).

IR (KBr): 3482, 2980, 2934, 2412, 1692, 1655 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 10.2 Hz, 2 H), 5.86 (dt, *J* = 2.9, 7.3, 15.4 Hz, 2 H), 5.18–4.94 (m, 1 H), 4.18 (q, *J* = 6.6 Hz, 2 H), 3.85 (q, *J* = 6.6 Hz, 1 H), 2.44–2.24 (m, 4 H), 1.95–1.60 (m, 4 H), 1.33–1.22 (m, 9 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, 14.1, 20.2, 23.5, 26.1, 39.4, 42.1, 43.4, 60.3, 67.0, 68.2, 68.6, 123.4, 123.8, 144.9, 145.2, 165.4, 166.2.

MS (ESI): *m*/*z* = 451.2 $[M + Na]^+$, 395.2, 353.2, 337.2, 332.2, 315.2, 297.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{40}NaO_6Si$: 451.2491; found: 451.2495.

(1*R*,*E*)-5-[(5*S*,7*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-7-hydroxyoct-2-enoyloxy]-1-methylpent-2-enoic Acid (17)

Ester **24** (13 mg, 0.03 mmol) was dissolved in THF–H_2O (4:1, 5 mL), followed by slow addition of $LiOH·H_2O$ (1.4 mg, 0.036 mmol). The mixture was stirred at r.t. for 6 h.; the reaction progress was monitored by TLC. On completion of the reaction, EtOAc (8 mL) was added and the mixture was extracted with H_2O (4 mL). The aqueous layer was neutralized (pH ~6.0) with $NaHSO_4$ and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (2 × 4 mL) and H_2O (4 mL), dried (Na_2SO_4), and concentrated under vacuum. The crude acid was washed with hexane (3 × 4 mL) to remove the nonpolar impurities.

Colorless liquid; yield: 10 mg (80%); $[\alpha]_D^{25}$ –10.8 (*c* 0.4, $CHCl_3$).

IR (KBr): 3484, 2978, 3934, 1716, 1655, 1450, 1430, 1381, 1370, 1300, 1268, 1219, 1170 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (dt, *J* = 7.3, 14.6 Hz, 1 H), 6.94 (dt, *J* = 7.3, 14.6 Hz, 1 H), 5.86–5.84 (m, 2 H), 5.18–4.94 (m, 1 H), 4.01–3.96 (m, 1 H), 3.85–3.82 (m, 1 H), 2.42–2.25 (m, 4 H), 1.85–1.62 (m, 2 H), 1.22 (d, *J* = 4.8 Hz, 3 H), 1.18 (d, *J* = 4.8 Hz, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, –4.4, 17.8, 20.4, 22.9, 25.6, 39.5, 41.4, 43.2, 66.6, 67.8, 68.0, 123.0, 123.7. 145.0, 147.9, 165.4, 170.6.

MS (ESI): *m*/*z* = 423.5 $[M + Na]^+$.

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References

(1) (a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, *28*, 641. (b) Hartmann, T.; Witte, L. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, **1995**, Chap. 4, 155. (c) Yadav, J. S.; Gupta, M. K.; Pratahp, I. *Synthesis* **2007**, 1343; and references cited therein. (d) Smith, A. B. III; Freeze, B. S.; LaMarche, M. J.; Hirose, T.; Brouard, I.;

Rucker, P. V.; Xian, M.; Sundermann, K. F.; Shaw, S. J.; Burlingame, M. A.; Horwitz, S. B.; Myles, D. C. *Org. Lett.* **2005**, *7*, 311; and references cited therein.
(2) Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677.
(3) Akata, T.; Hata, N.; Iida, K.; Oishi, T. *Tetrahedron Lett.* **1987**, *28*, 5661.
(4) Hsu, F. L.; Chen, Y. C.; Cheng, J. T. *Planta Med.* **2000**, *66*, 228.
(5) (a) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, *9*, 5497. (b) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1487.
(6) Ronald, R. C.; Curusiddaih, S. *Tetrahedron Lett.* **1980**, *21*, 681.
(7) (a) Yadav, J. S.; Kumar, N. N.; Reddy, M. S.; Prasad, A. R. *Tetrahedron* **2007**, *63*, 2689. (b) Scott, M. S.; Luckhurst, C. A.; Dixon, D. J. *Org. Lett.* **2005**, *7*, 5813. (c) Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, N.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567. (d) Baktharaman, S.; Selvakumar, S.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 7527. (e) Gupta, P.; Naidu, V.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6571. (f) Enders, D.; Steinbusch, D. *Eur. J. Org. Chem.* **2003**, 4450. (g) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682. (h) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512. (i) Solladie, G.; Gressot-Kempf, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2371. (j) Mori, Y.; Kageyama, H.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2574. (k) Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809. (l) Nakata, T.; Hata, N.; Iida, K.; Oishi, T. *Tetrahedron Lett.* **1987**, *28*, 5661.
(8) (a) BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2006**, *47*, 901. (b) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606. (c) Shimizu, I.; Omura, T. *Chem. Lett.* **1993**, 1759. (d) Sharma, G. V. M.; Raja Rao, A. V. S.; Murthy, V. S. *Tetrahedron Lett.* **1995**, *36*, 4117. (e) Solladie, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem.* **2000**, 357. (f) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447.
(9) (a) Yadav, J. S.; Reddy, P. M. K.; Reddy, P. V. *Tetrahedron Lett.* **2007**, *48*, 1037. (b) Yadav, J. S.; Prathap, I.; Tadi, B. P. *Tetrahedron Lett.* **2006**, *47*, 3773. (c) Yadav, J. S.; Rao, K. V.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4393. (d) Yadav, J. S.; Srinivas, R.; Sathaih, K. *Tetrahedron Lett.* **2006**, *47*, 1603. (e) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133. (f) Yadav, J. S.; Reddy, K. B.; Sabitha, G. *Tetrahedron Lett.* **2004**, *45*, 6475.
(10) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(11) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(12) (*R*)-Propylene oxide(**6**) was obtained by a literature procedure [Co(OAc)(*R*,*R*-Salen) (0.003 equiv), distd H_2O (0.55 equiv.), 0 °C, 12 h, yield: 47% of **6**, 48% of (*S*)-propane-1,3-diol][10] and is easily isolated from the more polar diol (*S*)-propane-1,3-diol by distillation. Compound **6**: $[\alpha]_{25}^{D}$ +11.6 (neat) {Lit.[10] (*S*)-propylene oxide $[\alpha]_{25}^{D}$ –11.7 (neat)}.
(13) Honda, H.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857.
(14) Yadav, J. S.; Chander, M. C.; Joshi, B. V. *Tetrahedron Lett.* **1988**, *29*, 2732.
(15) Radha Krishna, P.; Srinivas, R. *Tetrahedron Lett.* **2007**, *48*, 2013.
(16) Vatele, J. M. *Tetrahedron Lett.* **2006**, *47*, 715.
(17) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.