Stereoselective Total Synthesis of (–)-Colletol by Prins Cyclisation

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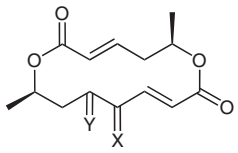
Abstract: A simple and efficient asymmetric total synthesis of the bis-macrolactone (–)-colletol was accomplished, proving the versatility of the Prins cyclisation in natural product synthesis. The synthesis mainly relies upon reductive opening of a pyran ring, Mitsunobu inversion, the Wittig reaction, and Yamaguchi macrolactonisation as the key steps.

Key words: natural products, Prins cyclization, Mitsunobu reaction, macrolactonization, lactones

(–)-Colletol (**III**), a 14-membered bis-macrolactone, was isolated from the fermentation broth of the plant pathogen *Colletotrichium capsici* along with other bis-macrolactones **I**, **II**, **IV**, and **V** (Figure 1) in 1973.[1] Although no biological activity has been reported for these macrolactones, interest in these compounds was aroused by the report of the isolation of grahamimycin A_1, which showed potent activity against bacteria, algae, and fungi.[2,3] A fascinating bis-macrolactone with a 1,3-diol system, for which we have recently established a synthetic route by Prins cyclisation, colletol[4] (**III**) has inspired us to investigate its synthesis.

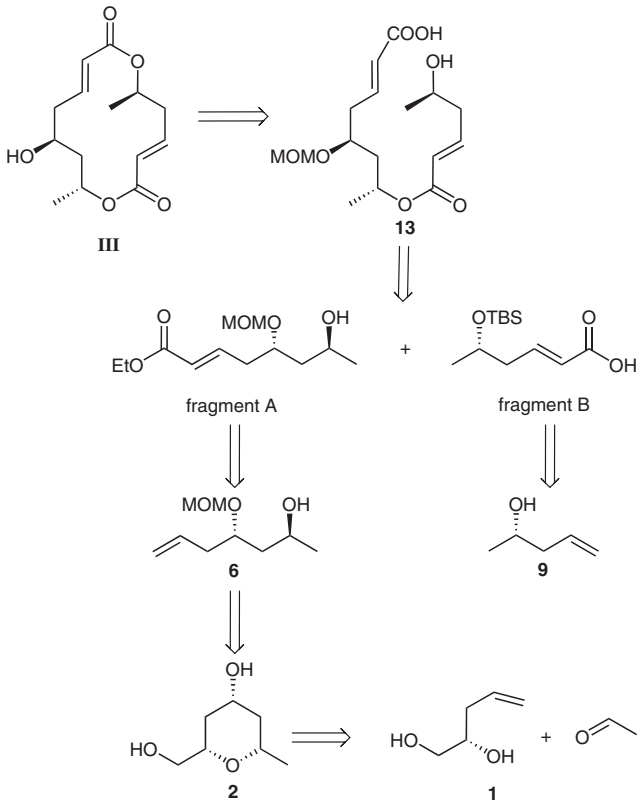


	X	Y
colletalol (**I**)	H, OH	H_2
colletoketol (**II**)	O	H, OH
colletol (**III**)	H_2	H, OH
colletodiol (**IV**)	H, OH	H, OH
grahamimycin A1 (**V**)	O	O

Figure 1

Before undertaking the synthesis, a careful retrosynthetic analysis was made (Scheme 1). We envisaged that the target molecule would be obtained by Yamaguchi macrolactonisation of **13**, which was regarded as being accessible by Mitsunobu reaction between the two fragments **A** and **B**. Fragment **A** could be obtained easily from pyran **2**, by a reductive opening followed by homologation, and in turn pyranylmethanol **2** could be obtained by Prins cyclisation of known homoallylic alcohol **1** and acetaldehyde according to our recently developed methodology.[5] Fragment **B** would be obtained from known homoallyl alcohol **9** after simple chemical modifications.

Our synthesis of fragment **A** of colletol (Scheme 2) commenced with Prins cyclisation between known homoallylic alcohol **1**[5] and acetaldehyde in the presence of trifluoroacetic acid[6] to afford the trifluoroacetate of **2**; treatment of its crude with potassium carbonate in methanol gave tetrahydropyrandiol **2** as the only isolable compound in 55% yield. The stereochemical aspects of such Prins cyclisations and structurally very close compounds of **2**were discussed in detail previously.[5f] Transformation of the primary hydroxy group of **2** into a tosylate was achieved by the use of tosyl chloride (1.1 equiv) and triethylamine, and the secondary hydroxy group was protected as a methoxymethyl ether by reaction of **3** with methoxymethyl chloride and *N*,*N*-diisopropylethylamine, to result in intermediate **4**. The tosyl group was substituted by an iodo group by use of sodium iodide in acetone; this was followed by reductive opening of the (iodomethyl)pyran to produce alcohol **6** with an *anti*-1,3-diol system. Protection of the secondary hydroxy group in **6** as a *tert*-butyldimethylsilyl ether was achieved by use of *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane, to furnish **7** in 85% yield. Ozonolytic cleavage of the olefinic bond of **7**[7] was followed by Wittig olefina-



Scheme 1 Retrosynthesis of colletol (**III**)

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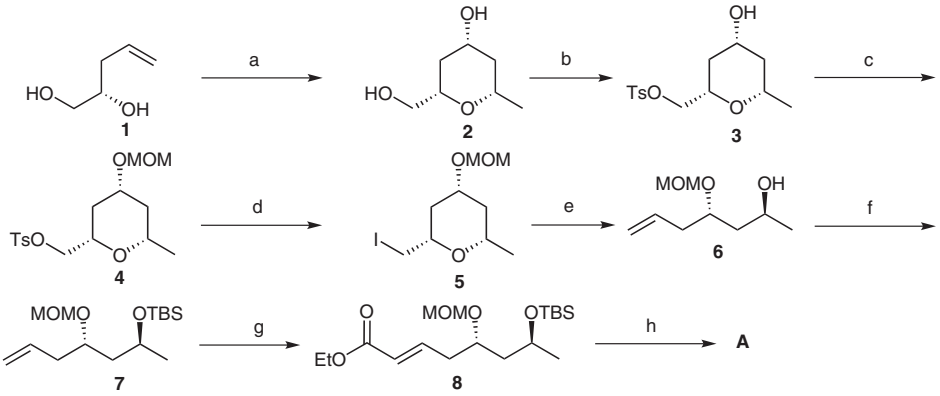
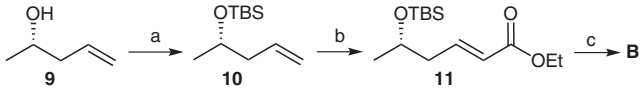


Scheme 2 Synthesis of fragment **A**. *Reagents and conditions*: (a) MeCHO, TFA, CH_2Cl_2, 3 h, then K_2CO_3, MeOH, r.t., 0.5 h, 52%; (b) Et_3N, TsCl, CH_2Cl_2, 0 °C to r.t., 3 h, 95%; (c) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 3 h, 90%; (d) NaI, acetone, reflux, 24 h, 95%; (e) Zn, EtOH, $NaHCO_3$, reflux, 2 h, 92%; (f) DMAP, TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 4 h, 85%; (g) O_3, Ph_3P, CH_2Cl_2, then $Ph_3P{=}CHCO_2Et$, benzene, r.t., 74%; (h) NH_4F, MeOH, reflux, 12 h, 86%.

tion with the stable ylide (ethoxycarbonylmethylene)triphenylphosphorane in benzene, to give α,β-unsaturated ester **8**.[6] Deprotection of the *tert*-butyldimethylsilyl ether was carried out by using ammonium fluoride and methanol,[4f] to give fragment **A** in 86% yield.

Synthesis of fragment **B** (Scheme 3) commenced from commercially available optically active homoallylic alcohol **9**.[8] Compound **11** was obtained from **9** in a two-step sequence, consisting of the same reagents and conditions as those described in Scheme 2 (for the synthesis of **8** from **6**). In the final step, ester **11** was hydrolysed in the presence of sodium hydroxide and methanol–water to afford the requisite acid **B** in 90% yield.

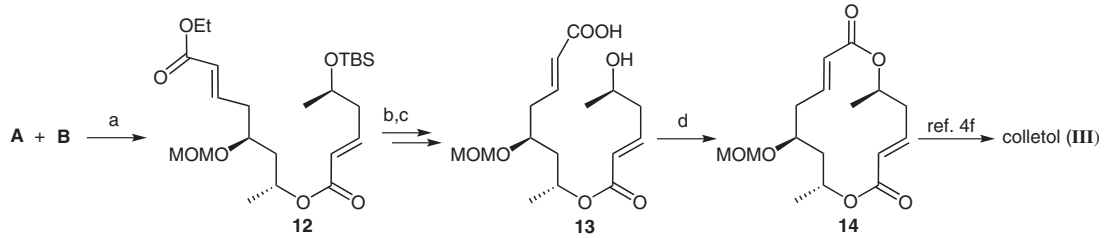


Scheme 3 Synthesis of fragment **B**. *Reagents and conditions*: (a) DMAP, TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 85%; (b) O_3, Ph_3P, CH_2Cl_2, then $Ph_3P{=}CHCO_2Et$, benzene, r.t., 98%; (c) 2 N aq NaOH, MeOH–H_2O (2:1), 6 h, 90%.

After construction of the two fragments **A** and **B**, they were coupled under Mitsunobu conditions (Scheme 4). Thus, acid **B**, upon treatment with alcohol **A** under standard Mitsunobu conditions[9] (Ph_3P, DEAD, THF), smoothly formed ester **12**. The *tert*-butyldimethylsilyl group was deprotected, followed by hydrolysis of the ester group, to form conjugated hydroxy acid **13** in 80% yield. Acid **13** was macrolactonised under Yamaguchi's conditions[10] to afford the macrolactone **14**, which, after treatment with hydrochloric acid, afforded (–)-colletol (**III**) in 70% yield. The spectral and analytical data (^1H and ^{13}C NMR, IR, R_f, and $[\alpha]_D$) for the synthetic compound were in accordance with the data reported in the literature.[4]

In summary, we have described a stereoselective approach to colletol from polyketide precursors, prepared by Prins cyclisation according to our recently developed synthetic sequence. The approach can provide a means for probing the structure–activity relationships of these and other related bioactive macrolides.[1]

All reactions were carried out under an inert atmosphere unless mentioned otherwise, and standard syringe–septa techniques were followed. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC, using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) and neutral alumina, and Et_2O, EtOAc, and hexane were used as eluents. Optical rotation values were measured on a Perkin-Elmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 25 °C, and IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometer; TMS was used as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070 H (EI) and VG Autospec M (MS–FAB) spectrometers.



Scheme 4 Coupling of fragments **A** and **B**. *Reagents and conditions*: (a) Ph_3P, DEAD, then **B**, THF, 0 °C to r.t., 30 min, then r.t., 4 h, 75%; (b) NH_4F, MeOH, reflux, 6 h, 86%; (c) LiOH, THF–H_2O (1:1), 6 h, 80%; (d) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, toluene, r.t., then DMAP, toluene, 110 °C, 60%.

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(2*S*,4*R*,6*S*)-2-(Hydroxymethyl)-6-methyltetrahydro-2*H*-pyran-4-ol (2)

TFA (21.50 mL) was added slowly to a soln of homoallylic alcohol **1** (1.5 g, 14.70 mmol) and acetaldehyde (3.8 g, 44.11 mmol) in CH_2Cl_2 (50 mL) at 25 °C under a N_2 atmosphere. The reaction mixture was stirred for 3.0 h and then sat. aq $NaHCO_3$ (150 mL) was added and the pH was adjusted to >7 by the addition of Et_3N. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The organic layers were combined and the solvent was removed under reduced pressure. The trifluoroacetate obtained in this reaction was directly used in the next reaction without purification. The residue was dissolved in MeOH (40 mL) and stirred with K_2CO_3 (4.05 g) for 0.5 h. The MeOH was then removed under reduced pressure and H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the crude by column chromatography (silica gel, EtOAc–hexane, 6:4) yielded **2**.

Yield: 1.32 g (52%); colourless liquid; R_f = 0.3 (silica gel, EtOAc–hexane, 6:4); $[\alpha]_D^{20}$ +9.7 (*c* 1.0, $CHCl_3$).

IR (neat): 3398, 2925, 2856, 1452, 1363, 1178, 1030, 976 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.09–1.20 (m, 2 H), 1.22 (d, *J* = 6.04 Hz, 3 H), 1.78–1.99 (m, 2 H), 3.38–3.62 (m, 4 H), 3.75–3.86 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 36.5, 42.3, 65.8, 67.3, 67.8, 72.1.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_7H_{14}O_3Na$: 169.0840; found: 169.0839.

[(2*S*,4*R*,6*S*)-4-Hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]methyl 4-Toluenesulfonate (3)

Et_3N (1.38 mL, 13.6 mmol), followed by TsCl (1.56 g, 8.2 mmol) were added over 2 h to a soln of diol **2** (1.0 g, 6.8 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 3 h. The reaction mixture was treated with 1 M aq HCl (7 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was washed with sat. aq $NaHCO_3$ (15 mL) and H_2O (15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (silica gel, EtOAc–hexane, 3:7) of the crude afforded tosylate **3**.

Yield: 1.95 g (95%); gummy liquid; R_f = 0.6 (silica gel, EtOAc–hexane, 6:4); $[\alpha]_D^{20}$ +3.6 (*c* 1.25, $CHCl_3$).

IR (neat): 3410, 2926, 2855, 1741, 1597, 1451, 1358, 1176, 974 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 5.8 Hz, 3 H), 1.37–1.41 (m, 2 H), 1.83–1.96 (m, 2 H), 2.46 (m, 3 H), 3.32–3.45 (m, 1 H), 3.48–3.61 (m, 1 H), 3.67–3.83 (m, 1 H), 3.90–4.02 (m, 2 H), 7.32 (d, *J* = 8.08 Hz, 2 H), 7.79 (m, *J* = 8.08 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.32, 21.51, 36.45, 42.26, 67.30, 71.78, 72.02, 72.71, 127.84, 129.70, 132.73, 144.75.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{21}O_5S$: 301.1104; found: 301.1097.

[(2*S*,4*R*,6*S*)-4-(Methoxymethoxy)-6-methyltetrahydro-2*H*-pyran-2-yl]methyl 4-Toluenesulfonate (4)

DIPEA (6.30 mL, 36.0 mmol), DMAP (cat.), and MOMCl (1.44 g, 18.0 mmol) were added successively to alcohol **3** (1.8 g, 9.13 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C, and the resulting mixture was stirred for 3 h at r.t. and then quenched by the addition of H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to remove the solvent. Purification of the crude by column chromatography (silica gel, EtOAc–hexane, 5:95) afforded pure product **4**.

Yield: 1.85 g (90%); liquid; R_f = 0.5 (silica gel, EtOAc–hexane, 5:95); $[\alpha]_D^{28}$ +7.60 (*c* 0.70, $CHCl_3$).

IR (neat): 2924, 2852, 1598, 1451, 1361, 1178, 1039, 977, 817, 668, 555 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.23 Hz, 3 H), 1.16–1.26 (m, 2 H), 1.87–1.96 (dd, 2 H), 2.43 (s, 3 H), 3.33 (s, 3 H), 3.35–3.43 (m, 2 H), 3.51–3.74 (m, 2 H), 3.93–4.04 (m, 2 H), 4.64 (s, 2 H), 7.32 (d, *J* = 7.93 Hz, 2 H), 7.77 (d, *J* = 8.49 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.44, 21.56, 34.15, 39.86, 55.24, 71.90, 72.02 72.31, 72.86, 94.40, 127.95, 129.71, 132.98, 144.70.

ESI-MS: *m*/*z* = 345 $[M + H]^+$, 362 $[M + NH_4]^+$.

(2*S*,4*R*,6*S*)-2-(Iodomethyl)-4-(methoxymethoxy)-6-methyltetrahydro-2*H*-pyran (5)

NaI (6.97 g, 46 mmol) was added to a soln of **4** (1.6 g, 4.6 mmol) in acetone (40 mL) and the mixture was heated to reflux for 24 h. The acetone was removed under reduced pressure. H_2O (40 mL) and CH_2Cl_2 (3 × 40 mL) were added to the residue, the organic layer was separated, dried (Na_2SO_4), and concentrated, and the crude was chromatographed (silica gel, EtOAc–hexane, 1:32) to afford **5**.

Yield: 1.32 g (95%); colourless liquid; R_f = 0.7 (silica gel, EtOAc–hexane, 1:9); $[\alpha]_D^{28}$ +15.30 (*c* 1.09, $CHCl_3$).

IR (neat): 2939, 2885, 1379, 1144, 1099, 914 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.04 Hz, 3 H), 1.88–1.97 (m, 2 H), 2.16–2.25 (m, 2 H), 3.16–3.21 (dd, *J* = 2.45, 5.85 Hz, 2 H), 3.31–3.34 (m, 1 H), 3.36 (s, 3 H), 3.45–3.56 (m, 1 H), 3.63–3.80 (m, 1 H), 4.69 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.84, 21.57, 37.92, 39.83, 55.32, 72.10, 72.51, 75.02, 94.48.

ESI-MS: *m*/*z* = 318 $[M + NH_4]^+$.

(2*S*,4*S*)-4-(Methoxymethoxy)hept-6-en-2-ol (6)

Commercially obtained Zn dust (5.04 g, 80 mmol) was added to a soln of iodide **5** (1.2 g, 4.0 mmol) in EtOH (60 mL). The mixture was refluxed for 2 h and then cooled to 25 °C. Addition of solid NH_4Cl (6.5 g) and Et_2O (100 mL) followed by stirring for 5 min gave a grey suspension. The suspension was filtered through a pad of Celite and the filtrate was concentrated in vacuo. Purification by flash chromatography (silica gel, EtOAc–hexane, 1:9) gave **6**.

Yield: 0.64 g (92%); colourless liquid; R_f = 0.6 (silica gel, EtOAc–hexane, 3:7); $[\alpha]_D^{20}$ +69.50 (*c* 1.30, $CHCl_3$).

IR (neat): 3443, 3076, 2934, 1641, 1442, 1373, 1099, 1039 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.61 Hz, 3 H), 1.49–1.55 (m, 2 H), 2.20–2.37 (m, 2 H), 2.55 (br, OH), 3.38 (s, 3 H), 3.73–3.88 (m, 1 H), 3.92–4.09 (m, 1 H), 4.57–4.67 (m, 2 H), 5.01–5.10 (m, 2 H), 5.64–5.85 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.35, 39.34, 42.86, 55.85, 64.04, 75.26, 96.26, 117.59, 134.26.

ESI-MS: *m*/*z* = 175 $[M + H]^+$, 192 $[M + NH_4]^+$.

(*tert*-Butyl){[(2*S*,4*S*)-4-(methoxymethoxy)hept-6-en-2-yl]oxy}dimethylsilane (7)

DMAP (10 mg), imidazole (0.78 g, 11.4 mmol), in one portion, and TBSCl (0.86 g, 5.73 mmol), in two portions, were sequentially added to a soln of **6** (0.5 g, 2.8 mmol) in anhyd CH_2Cl_2 (12 mL) at 0 °C. The reaction mixture was stirred for 4 h while slowly warming to r.t. It was quenched with sat. aq NH_4Cl (10 mL), diluted with CH_2Cl_2 (20 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude by column chromatography (silica gel, EtOAc–hexane, 1:32) afforded TBS ether **7**.

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Yield: 0.70 g (85%); colourless oil; R_f = 0.7 (silica gel, EtOAc–hexane, 1:9); $[\alpha]_D^{20}$ +19.31 (*c* 4.32, $CHCl_3$).

IR (neat): 2932, 2892, 2858, 1466, 1374, 1253, 1148, 1097, 1043, 916, 833, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88 (s, 9 H), 1.14 (d, *J* = 6.04 Hz, 3 H), 1.48–1.54 (m, 2 H), 2.27–2.32 (m, 2 H), 3.34 (s, 3 H), 3.64–3.75 (m, 1 H), 3.88–4.01 (m, 1 H), 4.63 (s, 2 H), 5.02–5.07 (m, 2 H), 5.70–5.84 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.76, –3.92, 17.97, 24.49, 25.84, 39.79, 44.98, 55.46, 65.60, 75.15, 96.10, 117.07, 134.50.

ESI-MS: *m*/*z* = 289 $[M + H]^+$, 311 $[M + Na]^+$.

Ethyl (2*E*,5*S*,7*S*)-7-(*tert*-Butyldimethylsiloxy)-5-(methoxymethoxy)oct-2-enoate (8)

O_3 was bubbled through a soln of **7** (0.6 g, 2.08 mmol) in CH_2Cl_2 (8 mL) at –78 °C until no unreacted starting material was observed. The reaction mixture was purged with N_2 to remove the excess O_3 and cooled to 0 °C; Ph_3P (1.09 g, 4.16 mmol) was added and the mixture was stirred for 2 h. The mixture was concentrated in vacuo. After the addition of hexane (30 mL), the mixture was filtered through a pad of Celite. The residue was washed with hexane. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude aldehyde obtained was subjected to the next reaction without further purification.

$Ph_3P{=}CHCO_2Et$ (1.44 g, 4.14 mmol) was added in one portion to a soln of the crude aldehyde in anhyd benzene (12 mL) at r.t. The mixture was stirred for 2 h at the same temperature. The benzene was removed under reduced pressure, EtOAc (15 mL) was added, and the mixture was washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (silica gel, EtOAc–hexane, 1:24) afforded **8**.

Yield: 0.56 g (74%, 2 steps); colourless oil; R_f = 0.7 (silica gel, EtOAc–hexane, 1:9); $[\alpha]_D^{28}$ +12.50 (*c* 1.96, $CHCl_3$).

IR (neat): 2933, 2857, 1722, 1655, 1097, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88 (s, 9 H), 1.14 (d, *J* = 6.04 Hz, 2 H), 1.29 (t, *J* = 7.55, 14.35 Hz, 3 H), 1.48–1.55 (ddd, *J* = 3.75, 8.30 Hz, 2 H), 2.35–2.55 (m, 2 H), 3.34 (s, 3 H), 3.75–3.84 (m, 1 H), 3.90–3.98 (m, 1 H), 4.13–4.20 (q, *J* = 7.50, 14.35 Hz, 2 H), 4.63 (d, *J* = 4.53 Hz, 2 H), 5.82 (d, *J* = 15.86 Hz, 1 H), 6.86–6.97 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.75, –3.91, 14.20, 23.70, 24.46, 25.83, 38.25, 45.18, 55.61, 60.11, 65.49, 74.57, 96.30, 123.57, 144.93, 166.22.

ESI-MS: *m*/*z* = 388 $[M + Na]^+$, 361 $[M + H]^+$.

Ethyl (2*E*,5*S*,7*S*)-7-Hydroxy-5-(methoxymethoxy)oct-2-enoate (A)

NH_4F (0.41 g, 11.08 mmol) was added to a soln of compound **8** (0.40 g, 1.1 mmol) in anhyd MeOH (12 mL). The reaction mixture was refluxed for 12 h. After completion of the reaction, the mixture was washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (silica gel, EtOAc–hexane, 1:2.5) afforded **A**.

Yield: 235 mg (86%); colourless oil; R_f = 0.35 (silica gel, EtOAc–hexane, 6:4); $[\alpha]_D^{28}$ +28.5 (*c* 1.24, $CHCl_3$).

IR (neat): 3475, 2936, 1717, 1653, 1371, 1270, 1154, 1098, 1037, 916 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.23 Hz, 3 H), 1.24–1.30 (t, *J* = 7.17, 15.10 Hz, 3 H), 1.50–1.64 (m, 2 H), 2.43–2.48 (m, 2 H), 3.39 (s, 3 H), 3.91–3.98 (m, 1 H), 3.99–4.07 (m, 1 H), 4.14–4.21 (q, *J* = 6.98, 13.07 Hz, 2 H), 4.66 (s, 2 H), 5.86 (d, *J* = 15.68 Hz, 1 H), 6.86–6.97 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.20, 23.48, 37.80, 43.31, 55.87, 60.26, 63.87, 74.44, 96.35, 123.92, 144.42, 166.28.

MS (ESI): 247 $[M + 1]^+$, 269 $[M + Na]^+$.

***tert*-Butyldimethyl[(*S*)-pent-4-en-2-yloxy]silane (10)**

Compound **10** was prepared from **9** according to the same procedure used for the synthesis of **7** from **6**.

Yield: 0.98 g (85%); colourless oil; R_f = 0.8 (silica gel, EtOAc–hexane, 1:9); $[\alpha]_D^{28}$ –3.0 (*c* 0.87, $CHCl_3$).

IR (neat): 2955, 2931, 1467, 1254, 1051 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.05 (s, 3 H), 0.87 (d, 9 H), 1.13 (d, *J* = 6.04 Hz, 3 H), 2.10–2.24 (m, 2 H), 3.79–3.89 (m, 1 H), 4.98–5.06 (m, 2 H), 5.74–5.88 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.70, –4.52, 23.41, 25.70, 25.87, 44.28, 68.42, 116.51, 135.63.

Ethyl (2*E*,5*S*)-5-(*tert*-Butyldimethylsiloxy)hex-2-enoate (11)

Compound **11** was prepared from **10** according to the same procedure used for the synthesis of **8** from **7**.

Yield: 603 mg (98%); colourless oil; R_f = 0.7 (silica gel, EtOAc–hexane, 1:9); $[\alpha]_D^{20}$ –10.4 (*c* 2.22, $CHCl_3$).

IR (neat): 2958, 2932, 1722, 1655, 1259, 1175, 1034 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.16, (d, *J* = 6.04 Hz, 3 H), 1.28 (t, *J* = 7.55, 14.35 Hz, 3 H), 2.25–2.33 (m, 2 H), 3.84–3.95 (m, 1 H), 4.13–4.20 (q, *J* = 7.55, 14.35 Hz, 2 H), 5.79 (d, *J* = 15.10 Hz, 1 H), 6.83–6.95 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.89, –4.58, 14.22, 18.03, 23.75, 25.75, 42.39, 60.06, 67.60, 123.14, 145.98, 166.37.

ESI-MS: *m*/*z* = 295 $[M + Na]^+$, 273 $[M + H]^+$.

(2*E*,5*S*)-5-(*tert*-Butyldimethylsiloxy)hex-2-enoic Acid (B)

To a soln of ester **11** (0.5 gm) in MeOH (30 mL), 2 N aq NaOH (13 mL) was added. The reaction mixture was stirred for 6 h at r.t., acidified to pH 4 by the addition of 1 M aq HCl, and extracted with EtOAc (2 × 15 mL). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, EtOAc–hexane, 1:9) afforded **B**.

Yield: 403 mg (90%); colourless liquid; R_f = 0.35 (silica gel, EtOAc–hexane, 4:6); $[\alpha]_D^{28}$ –7.6 (*c* 0.81, $CHCl_3$).

IR (neat): 3442, 2931, 2858, 1701, 1653, 1255, 1255, 835, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88 (s, 9 H), 1.16 (d, *J* = 6.04 Hz, 3 H), 2.32–2.37 (m, 2 H), 3.91–3.97 (m, 1 H), 5.84 (d, *J* = 15.64 Hz, 1 H), 7.03–7.12 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.84, –4.56, 18.04, 23.78, 25.77, 42.48, 67.47, 122.49, 149.03, 171.52.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{24}NaO_3Si$: 267.1392; found: 267.1383.

Ethyl (2*E*,5*S*,7*R*)-7-[(2*E*,5*R*)-5-(*tert*-butyldimethylsiloxy)hex-2-enoyloxy]-5-(methoxymethoxy)oct-2-enoate (12)

DEAD (0.63 g, 3.65 mmol) was added by syringe to a stirred mixture of **A** (0.3 g, 1.20 mmol), Ph_3P (0.96 g, 3.6 mmol), and **B** (0.36 g, 1.46 mmol) in anhyd THF (10 mL) at 0 °C. The reaction mixture was then stirred for 4 h at r.t., diluted with H_2O (10 mL), and extracted with EtOAc (2 × 15 mL). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, EtOAc–hexane, 1:20) afforded **12**.

Yield: 0.43g (75%); colourless liquid; R_f = 0.65 (silica gel, EtOAc–hexane, 3:7); $[\alpha]_D^{28}$ –1.8 (*c* 0.66, $CHCl_3$).

IR (neat): 2927, 2855, 1721, 1655, 1462, 1261, 1371, 1261, 1174, 1097, 1038, 836, 776 cm^{-1}.

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.16 (d, *J* = 6.04 Hz, 3 H), 1.24–1.31 (m, 6 H), 1.56–1.73 (m, 1 H), 2.28–2.34 (m, 2 H), 2.38–2.53 (m, 2 H), 3.36 (s, 3 H), 3.70–3.78 (m, 1 H), 3.95–3.89 (m, 1 H), 4.14–4.21 (q, *J* = 6.97, 13.97 Hz, 2 H), 4.62 (s, 2 H), 5.04–5.12 (m, 2 H), 5.83 (dd, *J* = 15.8 Hz, 2 H), 6.86–6.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.26, –4.42, 14.35, 18.14, 20.35, 23.93, 25.90, 29.76, 37.22, 40.76, 42.53, 55.72, 67.63, 73.42, 96.20, 123.44, 124.02, 144.50, 146.10, 165.56, 166.02.

ESI-MS: *m*/*z* = 495 $[M + Na]^+$.

Ethyl (2*E*,5*S*,7*R*)-7-[(2*E*,5*R*)-5-Hydroxyhex-2-enoyloxy]-5-(methoxymethoxy)oct-2-enoate (12a)

NH_4F (0.31 g, 8.46 mmol) was added to a soln of **12** (0.4 g, 0.84 mmol) in anhyd MeOH (6 mL). The reaction mixture was refluxed for 12 h, washed with H_2O (15 mL), and extracted with EtOAc (2 × 15 mL). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, EtOAc–hexane, 1:3) afforded **12a**.

Yield: 0.27 g (86%); colourless liquid; R_f = 0.35 (silica gel, EtOAc–hexane, 4:6); $[\alpha]_D^{28}$ –8.4 (*c* 0.91, $CHCl_3$).

IR (neat): 3480, 2975, 2934, 1716, 1653, 1450, 1268, 1174, 1099, 984 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.29 (m, 9 H), 1.58–1.76 (m, 1 H), 1.90–2.01 (m, 1 H), 2.33–2.38 (m, 2 H), 3.36 (s, 3 H), 3.72–3.80 (m, 1 H), 3.93–4.0 (m, 1 H), 4.10–4.21 (m, 2 H), 4.63 (s, 2 H), 5.03–5.13 (m, 1 H), 5.88 (d, *J* = 15.674 Hz, 2 H), 6.87–7.00 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.22, 20.23, 23.26, 37.18, 40.61, 41.85, 60.25, 66.68, 67.93, 72.23, 95.41, 123.94, 144.52, 165.63, 166.24.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{30}O_7Na$: 381.1889; found: 381.1890.

(2*E*,5*S*,7*R*)-7-[(2*E*,5*R*)-5-Hydroxyhex-2-enoyloxy]-5-(methoxymethoxy)oct-2-enoic Acid (13)

LiOH (16 mg, 0.66 mmol) was added to a soln of **12a** (0.25 g, 0.69 mmol) in THF–H_2O (1:1), and the reaction mixture was stirred for 6 h. The mixture was acidified to pH 4 by the addition of 1 M aq HCl, and diluted with EtOAc (20 mL). The layers were separated and the organic layer was washed with brine (2 × 10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, EtOAc–hexane, 2:1) afforded **13a**.

Yield: 0.184 g (80%); colourless liquid; R_f = 0.3 (silica gel, EtOAc–hexane, 7:3); $[\alpha]_D^{28}$ –7.5 (*c* 0.49, $CHCl_3$).

IR (neat): 3427, 2925, 2853, 1709, 1653, 1264, 1174, 1100, 1033, 983 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.23 Hz, 2 H), 1.28 (d, *J* = 6.23 Hz, 2 H), 1.62–1.74 (m, 1 H), 1.86–2.02 (m, 1 H), 2.31–2.42 (m, 2 H), 2.44–2.58 (m, 2 H), 3.36 (s, 3 H), 3.74–3.82 (m, 1 H), 3.92–4.03 (m, 1 H), 4.64 (d, *J* = 2.64 Hz, 2 H), 5.03–5.14 (m, 1 H), 5.88 (dd, *J* = 1.70, 15.67 Hz, 2 H), 6.90–7.11 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.24, 20.75, 23.18, 37.28, 40.62, 41.77, 55.75, 66.79, 67.92, 73.16, 95.40, 123.17, 123.96, 145.30, 147.61, 165.74, 171.03, 277.67.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{26}NaO_7$: 353.1576; found: 353.1580.

(3*E*,6*R*,9*E*,12*S*,14*R*)-12-(Methoxymethoxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (14)

Et_3N (0.09 g, 0.90 mmol), followed by 2,4,6-$Cl_3C_6H_2COCl$ (0.22 g, 0.90 mmol) in THF were added to a soln of **13** (0.15 g, 0.45 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h under an argon atmosphere. Then a soln of DMAP (0.33 g, 2.72 mmol) in toluene (15 mL) was heated at 100 °C for 1 h, and the above-prepared soln of acid **13** in toluene (75 mL) was added to the DMAP–toluene soln. The whole reaction mixture was stirred for 12 h at 100 °C. After completion of the reaction, the mixture was washed with 7% aq $NaHCO_3$ (20 mL), 2 M aq HCl (20 mL), and brine (2 × 30 mL), and extracted with EtOAc (2 × 50 mL). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, EtOAc–hexane, 1:3) afforded **14**.

Yield: 0.085 g (85%); colourless liquid; R_f = 0.62 (silica gel, EtOAc–hexane, 4:6); $[\alpha]_D^{20}$ –5.6 (*c* 0.7, $CHCl_3$).

IR (neat): 2927, 1723, 1653, 1265, 1172, 1035 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (d, *J* = 6.79 Hz, 3 H), 1.36 (d, *J* = 6.79 Hz, 3 H), 1.66 (qd, *J* = 3.77, 15.86 Hz, 1 H), 1.91 (td, *J* = 3.70 Hz, 15.80, 1 H), 2.15–2.36 (m, 2 H), 2.51 (td, *J* = 3.02 Hz, 11.33, 1 H), 2.66–2.76 (m, 1 H), 3.39 (s, 3 H), 3.81–3.89 (m, 1 H), 4.72 (d, *J* = 3.77 Hz, 2 H), 5.10–5.29 (m, 2 H), 5.72–5.83 (dt, *J* = 4.5, 15.86 Hz, 2 H), 6.62–6.74 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): 18.21, 20.48, 36.94, 38.69, 40.81, 55.82, 68.0, 68.33, 74.24, 95.77, 125.06, 126.11, 143.7, 144.0, 165.20, 166.12.

ESI-HRMS: *m*/*z* $[M + NH_4]^+$ calcd for $C_{16}H_{28}NO_6$: 330.1911; found: 330.1913.

Colletol (III)

To a soln of **14** (0.06 g, 0.19 mmol) in THF (5 mL), 2 M aq HCl (1 mL) was added. The reaction mixture was stirred for 12 h, neutralised with $NaHCO_3$ soln and extracted with EtOAc (2 × 10 mL). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, EtOAc–hexane, 1:2) afforded **III**.

Yield: 0.036 g (70%); white solid; R_f = 0.32 (silica gel, EtOAc–hexane, 4:6); $[\alpha]_D^{28}$ –28.7 (*c* 0.44, $CHCl_3$).

IR (KBr): 3436, 2925, 2853, 1717, 1653, 1318, 1263, 1227, 1177, 1108, 1056, 983, 756 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 5.28 Hz, 3 H), 1.35 (d, *J* = 6.04 Hz, 3 H), 1.51 (qd, *J* = 3.0, 15.86 Hz, 1 H), 1.67 (br, OH, 1 H), 1.89–1.97 (m, 1 H), 2.15–2.35 (m, 2 H), 2.43–2.54 (m, 2 H), 3.97–4.06 (m, 1 H), 5.17–5.28 (m, 2 H), 5.68–5.82 (dt, *J* = 8.30, 15.86 Hz, 2 H), 6.70 (ddd, *J* = 6.04, 10.53, 15.86 Hz, 1 H), 6.70 (ddd, *J* = 4.5, 9.06, 15.86 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.15, 20.56, 29.70, 40.05, 40.30, 40.07, 68.14, 68.40, 125.06, 126.10, 143.74, 144.03, 165.24, 165.93.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}NaO_5$: 291.1208; found: 291.1194.

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References

(1) (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.
(2) Gurusiddaiah, S.; Ronald, R. C. *Antimicrob. Agents Chemother.* **1981**, *19*, 153.
(3) (a) O'Neill, J. A.; Simpson, T. J.; Willis, C. L. *J. Chem. Soc., Chem. Commun.* **1993**, 738. (b) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896.

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(4) For the previous synthesis of colletol, see: (a) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606. (b) Shimizu, I.; Omura, T. *Chem. Lett.* **1993**, 1759. (c) Sharma, G. V. M.; Raja Rao, A. V. S.; Murthy, V. S. *Tetrahedron Lett.* **1995**, *36*, 4117. (d) Solladié, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem.* **2000**, 357. (e) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447. (f) BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2006**, *47*, 901. (g) Yadav, J. S.; Reddy, M. K.; Gupta, M. K.; Chary, Ch. J. *Synthesis* **2007**, *23*, 3639.

(5) (a) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397. (b) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4937. (c) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133. (d) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995. (e) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Synlett* **2007**, 2049. (f) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469. (g) Yadav, J. S.; Kumar, N. N.; Reddy, M. S.; Prasad, A. R. *Tetrahedron* **2006**, *63*, 2689. (h) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 5427.

(6) For the Prins cyclisation, see for example: (a) St. J. Barry, C.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (b) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739. (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3485. (d) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. S. *Org. Lett.* **2005**, *7*, 2683. (e) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216. (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407. (g) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (h) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (i) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. (j) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (k) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (l) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (m) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (n) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, 885. (o) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem.* **2004**, *210*, 99. (p) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem.* **2003**, 1779.

(7) Kadota, I.; Park, C.-H.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6195.

(8) (*R*)-Pent-4-en-2-ol(**9**) is commercially available, e.g. from Aldrich.

(9) Mitsunobu, O. *Synthesis* **1981**, 1.

(10) Inagawa, J.; Hirata, K.; Katsuki, H.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

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