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Stereoselective Total Synthesis of Putaminoxin

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Abstract: The stereoselective total synthesis of a phytotoxic macrolide putaminoxin, isolated from the culture of *Phoma putaminum* fungus, has been accomplished by utilization of Sharpless asymmetric epoxidation, Birch reduction, Jacobsen's kinetic resolution of racemic epoxide, and Yamaguchi lactonization as key transformations.

Key words: macrolide, necrotic leaf disease, Sharpless asymmetric epoxidation, Birch reduction, Jacobsen's kinetic resolution, Yamaguchi lactonization

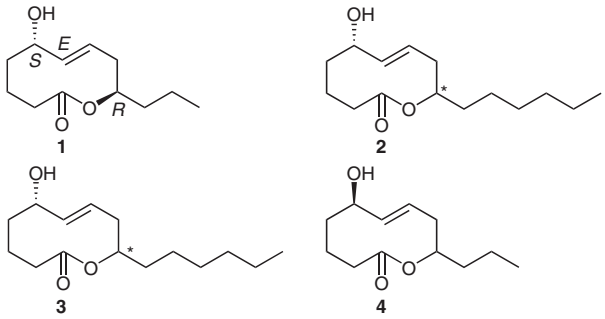
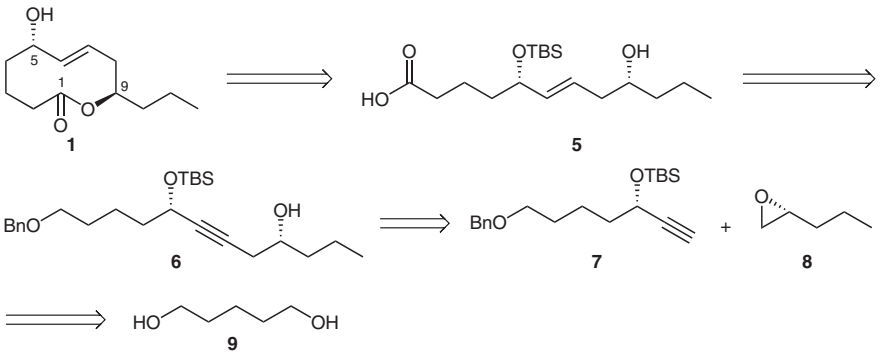


Figure 1 Putaminoxin (**1**) and putaminoxins B (**2**), D (**3**), and E (**4**)

Natural products containing ten-membered macrolide skeletons such as putaminoxin,[1] aspinolide,[2] and nonenolide[3] have been isolated from fungal sources and are known to possess potent phytotoxic properties. In particular, putaminoxin (**1**) (Figure 1), a disubstituted phytotoxic nonenolide, was isolated by Evidente et al. from the culture filtrates of *Phoma putaminum* fungus,[1] which is responsible for a necrotic leaf disease of *Erigeron annuus* (annual fleabane). Putaminoxin (**1**) is known to exhibit a range of phytotoxicities on mandarin and annual dog's mercury and also shows severe toxicity on *Erigeron annuus*. Putaminoxins B (**2**), D (**3**), and E (**4**) were also isolated by the same research group[1] from *Phoma putaminum*, and are structurally closely related to putaminoxin (**1**).[4] The absolute stereochemistry of putaminoxin (**1**) was determined by its total synthesis, and the stereochemistry of C5 and C9 were revealed as *S* and *R*, respectively.[5]

Fascinating structural features coupled with inherent phytotoxic activities of these macrolides have attracted the attention of synthetic chemists to develop elegant approaches for the synthesis of these natural products and their analogues, to develop leads for potent herbicides. Following our interest on the total synthesis of biologically active natural products, herein we wish to report an efficient synthetic approach for the total synthesis of the phytotoxic natural product putaminoxin (**1**).

In our retrosynthesis, we assumed that the target molecule **1** could be obtained from hydroxy acid **5** via Yamaguchi macrolactonization (Scheme 1). The hydroxy acid **5** would be prepared easily from a homopropargyl alcohol **6**. The intermediate alcohol **6** could be synthesized by the coupling reaction of terminal alkyne **7** with chiral oxirane **8**, which could in turn be prepared from commercially available pentane-1,5-diol (**9**) and the corresponding racemic 2-propyloxirane by using known transformations. In



Scheme 1 Retrosynthetic analysis of putaminoxin (**1**)

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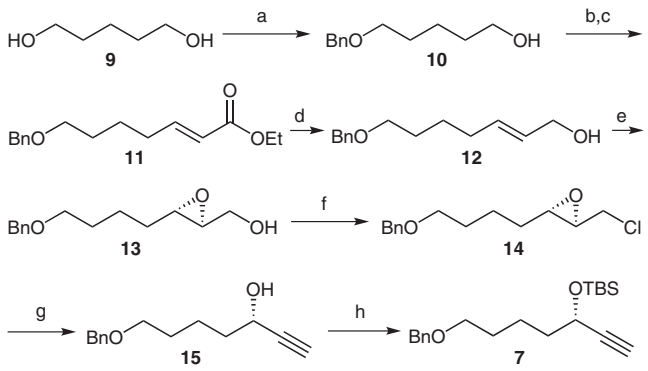
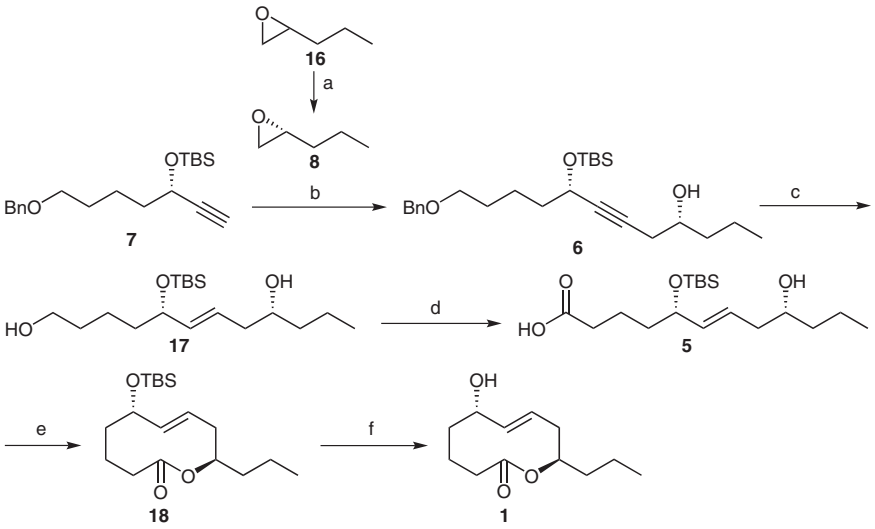


Scheme 2 *Reagents and conditions*: (a) NaH, TBAI, BnBr, THF, 0 °C to r.t., 75%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to r.t., 86%; (c) $Ph_3P{=}CHCO_2Et$, benzene, r.t., 82%; (d) LAH, $AlCl_3$, Et_2O, –78 °C, 80%; (e) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –20 °C, 92%; (f) Ph_3P, CCl_4, $NaHCO_3$, reflux, 3 h, 90%; (g) Li, liquid NH_3, THF, –33 °C, 1 h, 95%; (h) TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 1 h, 95%.

this synthetic route, we planned to install stereocenters at C5 and C9 using Sharpless asymmetric epoxidation and Jacobsen's kinetic resolution, respectively.

Accordingly, the synthesis of putaminoxin (**1**) began from commercially available pentane-1,5-diol (**9**), which was protected as its monobenzyl ether **10** (75% yield) by reaction with benzyl bromide in the presence of sodium hydride and tetrabutylammonium iodide (Scheme 2).[6] Oxidation of alcohol **10** by using Swern reaction conditions[7] [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2] gave the corresponding aldehyde (86% yield), which was subsequently homologated with a Wittig ylide[8] ($Ph_3P{=}CHCO_2Et$) to afford the α,β-unsaturated ester **11** in 82% yield. The selective reduction of ester **11** (LAH, $AlCl_3$, Et_2O, –78 °C)[9] gave allyl alcohol **12** in good yield (80%). Sharpless asymmetric epoxidation[9a,10] [L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2] of allyl alcohol **12** afforded epoxy alcohol **13** in 92% yield. Treatment of **13** with triphenylphosphine in anhydrous carbon tetrachloride afforded the corresponding α-chlorooxirane **14** in 90% yield.[9a] Compound **14** was then converted into propargyl alcohol **15** under Birch reaction conditions[11] (Li, liquid NH_3, THF, –33 °C) in 95% yield. Propargyl alcohol **15** was converted into its *tert*-butyldimethylsilyl ether **7** in 95% yield by reaction with *tert*-butylchlorodimethylsilane and imidazole in dichloromethane.[9a]

The terminal chiral oxirane **8** (prepared from the corresponding racemic oxirane **16** by using Jacobsen's kinetic resolution)[12,17] was opened[13] regioselectively with terminal alkyne **7** by using *n*-butyllithium and boron trifluoride–diethyl ether complex in tetrahydrofuran to afford the homopropargyl alcohol **6** in 70% yield (Scheme 3). Debenzylation of compound **6** with sodium in liquid ammonia with concomitant partial reduction[14] of the homopropargyl alcohol gave the corresponding homoallyl alcohol **17** with *E* stereochemistry in 90% yield. Selective oxidation of the primary hydroxy[15a] group of diol **17** by using 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and (diacetoxyiodo)benzene in anhydrous dichloromethane, and a subsequent oxidation[15b,c,17] with sodium chlorite and sodium dihydrogen phosphate afforded the hydroxy acid **5** in 80% yield (over two steps). Hydroxy acid **5** was then subjected to Yamaguchi macrolactonization[16] by using 2,4,6-trichlorobenzoyl chloride, triethylamine, and 4-(*N*,*N*-dimethylamino)pyridine in toluene to afford the macrolide **18** in good yield (70%). Removal of the *tert*-butyldimethylsilyl group in macrolide **18** by using tetrabutylammonium fluoride in tetrahydrofuran gave the target molecule putaminoxin (**1**) in 90% yield. The ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data of the synthetic putaminoxin (**1**) were in good agreement with those of the natural product reported in the literature.[1,5]



Scheme 3 *Reagents and conditions*: (a) (*R*,*R*)-(+)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II), AcOH, toluene, r.t., 42%; (b) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, –78 °C to r.t., 70%; (c) Na, liquid NH_3, THF, –33 °C, 90%; (d) (i) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20 min; (ii) $NaClO_2$, NaH_2PO_4, DMSO–H_2O, 80% (over two steps); (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 70%; (f) 1.0 M TBAF in THF, THF, 6 h, 90%.

In conclusion, we have demonstrated an efficient linear synthetic approach to the total synthesis of the phytotoxic macrolide putaminoxin (**1**). This approach utilizes readily available precursors and follows simple and high yielding protocols such as Sharpless asymmetric epoxidation, Birch reduction, Jacobsen's kinetic resolution of a racemic epoxide, and Yamaguchi lactonization as key steps; this makes it attractive for the generation of new derivatives of the natural product.

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on a Gemini-200 spectrometer (200 MHz) and a Bruker-300 spectrometer (300 MHz); $CDCl_3$ was used as solvent and TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed on Merck silica gel (60–120 mesh). Optical rotations were measured on a JASCO DIP-370 polarimeter at 25 °C.

5-(Benzyloxy)pentan-1-ol (10)

A soln of **9** (2.0 g, 19.2 mmol) in anhyd THF (25 mL) was added dropwise to a stirred suspension of a 55% dispersion of NaH in mineral oil (0.92 g, 38.4 mmol) in anhyd THF (20 mL) for 15 min at 0 °C. The mixture was then allowed to stir at r.t. for 45 min. To this soln, BnBr (2.32 mL, 19.2 mmol) was added at 0 °C over 10 min and then TBAI (40 mg, 1.92 mmol) was added. The resulting mixture was stirred at r.t. for 10 h and then quenched with cold H_2O (20 mL) at 0 °C. The crude mixture was extracted with EtOAc (3 × 20 mL) and the organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexanes–EtOAc, 70:30).

Yield: 2.78 g (75%); colorless liquid.

IR (neat): 3387, 3030, 2928, 2858, 1454, 1362, 1206, 1097, 737, 697, 610 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.17–7.34 (m, 5 H), 4.17 (s, 2 H), 3.61 (t, *J* = 5.1 Hz, 2 H), 3.45 (t, *J* = 6.6 Hz, 2 H), 1.37–1.71 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.1, 127.5, 127.3, 72.7, 70.1, 62.2, 32.3, 29.3, 22.3.

ESI-MS: *m*/*z* = 194 [M + H$^+$].

Ethyl (*E*)-7-(Benzyloxy)hept-2-enoate (11)

DMSO (1.58 mL, 22.3 mmol) was added dropwise over 10 min to a soln of oxalyl chloride (1.64 mL, 18.6 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C under a N_2 atmosphere. The mixture was stirred for an additional 10 min and then a soln of alcohol **10** (2.4 g, 12.4 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The resulting mixture was stirred for 30 min and then Et_3N (10.3 mL, 74.4 mmol) was added dropwise at –78 °C; stirring was continued at r.t. for 30 min. After completion of the reaction, the mixture was quenched with ice-cold H_2O (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent gave the crude product 5-(benzyloxy)pentanal as a colorless liquid; yield: 2.04 g (86%). A soln of this aldehyde in benzene was added dropwise to a soln of $Ph_3P{=}CHCO_2Et$ (3.2 g, 9.4 mmol) in benzene (15 mL) at 80 °C. After 1 h, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 90:10).

Yield: 1.67 g (82%); colorless liquid.

IR (neat): 2927, 2856, 1720, 1654, 1455, 1366, 1266, 1197, 1165, 1105, 1024, 982, 737, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20–7.35 (m, 5 H), 6.83–6.99 (m, 1 H), 5.77 (d, *J* = 5.6 Hz, 1 H), 4.46 (s, 2 H), 4.15 (q, *J* = 7.0, 14.0 Hz, 2 H), 3.44 (t, *J* = 5.4, 11.7 Hz, 2 H), 2.22 (q, *J* = 7.3, 14.0 Hz, 2 H), 1.54–1.68 (m, 4 H), 1.29 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 148.6, 138.3, 127.3, 127.2, 127.1, 121.2, 72.7, 69.5, 60.0, 31.6, 28.9, 24.5, 14.0.

ESI-MS: *m*/*z* = 285 [M + Na$^+$].

(*E*)-7-(Benzyloxy)hept-2-en-1-ol (12)

A soln of $AlCl_3$ (392 mg, 2.9 mmol) in Et_2O (7 mL) was added over 5 min to a suspension of LAH (326 mg, 8.6 mmol) in anhyd Et_2O (10 mL) at –78 °C under N_2. After complete addition, the mixture was allowed to stir at r.t. for 30 min. To this stirred suspension was added a soln of ester **11** (1.5 g, 5.73 mmol) in anhyd Et_2O (10 mL) over 10 min. After stirring at 0 °C for 30 min, the mixture was quenched with sat. aq Na_2SO_4 (10 mL) and filtered through Celite. The residue was washed with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes–EtOAc, 8:2).

Yield: 1.0 g (80%); colorless viscous liquid.

IR (neat): 3399, 3029, 2929, 2857, 1454, 1364, 1206, 1096, 1006, 971, 737, 697, 610 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.33 (m, 5 H), 5.54–5.70 (m, 2 H), 4.46 (s, 2 H), 4.03 (d, *J* = 3.7 Hz, 2 H), 3.43 (t, *J* = 6.0 Hz, 2 H), 2.05 (q, *J* = 6.7, 12.8 Hz, 2 H), 1.41–1.66, (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 132.4, 129.2, 128.6, 127.5, 127.3, 72.7, 70.2, 63.2, 31.7, 29.0, 25.5.

ESI-MS: *m*/*z* = 243 [M + Na$^+$].

{(2*S*,3*S*)-3-[4-(Benzyloxy)butyl]oxiran-2-yl}methanol (13)

L-(+)-DET (0.2 mL, 1.0 mmol) and Ti(O*i*-Pr)$_4$ (0.308 mL, 1.0 mmol) were added to a stirred suspension of activated 4 Å MS (1.0 g) in anhyd CH_2Cl_2 (10 mL), and the mixture was stirred for 30 min at –20 °C. To this mixture, a soln of allyl alcohol **12** (0.9 g, 4.0 mmol) in anhyd CH_2Cl_2 (15 mL) was added dropwise and the mixture was stirred for another 30 min at –20 °C. Then a 4.0 M soln of *t*-BuOOH in toluene (4.3 mL, 9.0 mmol) was added and the resulting mixture was stirred at the same temperature for 8 h. It was then warmed to 0 °C and quenched with H_2O (5 mL) and a 20% aq soln of NaOH (3 mL). The resulting mixture was vigorously stirred for 3 h at r.t. and then filtered through Celite. The residue was washed well with CH_2Cl_2 (3 × 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 888 mg (92%); colorless viscous liquid; $[\alpha]_D^{25}$ –19.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3422, 2928, 2859, 1727, 1455, 1365, 1276, 1099, 1026, 877, 740, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.32 (m, 5 H), 4.43 (s, 2 H), 3.74–3.82 (m, 1 H), 3.47–3.57 (m, 1 H), 3.41 (t, *J* = 6.0 Hz, 2 H), 2.83–2.89 (m, 1 H), 2.76–2.80 (m, 1 H), 1.44–1.70 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.5, 127.4, 72.7, 69.9, 61.6, 58.4, 55.8, 31.2, 29.3, 22.5.

ESI-MS: *m*/*z* = 259 [M + Na$^+$].

(2*S*,3*R*)-2-[4-(Benzyloxy)butyl]-3-(chloromethyl)oxirane (14)

A soln of epoxy alcohol **13** (0.7 g, 3.0 mmol) in CCl_4 (10 mL) followed by $NaHCO_3$ (25 mg, 0.3 mmol) were added to a stirred soln of Ph_3P (0.95 g, 3.6 mmol) in anhyd CCl_4 (10 mL). The reaction

mixture was stirred at reflux temperature for 3 h. After completion of the reaction, the mixture was cooled to r.t. and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 9.5:0.5).

Yield: 0.678 g (90%); colorless liquid; $[\alpha]_D^{25}$ +18.7 (*c* 1.0, $CHCl_3$).

IR (neat): 3030, 2935, 2860, 1493, 1454, 1362, 1258, 1207, 1102, 1026, 739, 710, 649 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.35 (m, 5 H), 4.47 (s, 2 H), 4.35–4.42 (m, 1 H), 4.07–4.14 (m, 1 H), 3.86–4.00 (m, 1 H), 3.70–3.77 (m, 1 H), 3.46 (t, *J* = 5.8 Hz, 2 H), 1.49–2.02 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.4, 127.3, 72.7, 69.7, 58.7, 56.9, 44.6, 31.0, 29.2, 22.4.

ESI-MS: *m*/*z* = 255 [M + H^+].

(*S*)-7-(Benzyloxy)hept-1-yn-3-ol (15)

$Fe(NO_3)_3$ (20 mg, cat.) was added to a freshly condensed soln of anhyd NH_3 (20 mL) in a two-necked round-bottomed flask at –33 °C fitted with a cold condenser; cautious addition of Li metal pieces (100 mg, 14.16 mmol) followed. The resulting gray suspension was stirred for 1 h at the same temperature. A soln of epoxy chloride **14** (0.6 g, 2.36 mmol) in anhyd THF (10 mL) was added dropwise and then stirring was continued for another 2 h at –33 °C. To this mixture, solid NH_4Cl (10 g) was added and then NH_3 was allowed to evaporate slowly. The residue was dissolved in Et_2O (15 mL) and then filtered though small pad of Celite. The filtrate was dried (Na_2SO_4) and the crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 8:2).

Yield: 4.9 g (95%); colorless liquid; $[\alpha]_D^{25}$ –7.3 (*c* 1.0, $CHCl_3$).

IR (neat) 3416, 2927, 2858, 1697, 1456, 1385, 1259, 1214, 1175, 1096, 759, 697, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.34 (m, 5 H), 4.48 (s, 2 H), 4.32 (t, *J* = 5.2 Hz, 1 H), 3.46 (t, *J* = 6.0 Hz, 2 H), 2.28 (d, *J* = 2.2 Hz, 1 H), 1.40–1.76 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.5, 127.4, 84.9, 72.8, 72.7, 70.0, 61.9, 37.26, 29.2, 21.7.

ESI-MS: *m*/*z* = 241 [M + Na^+].

[(*S*)-7-(Benzyloxy)hept-1-yn-3-yloxy](*tert*-butyl)dimethylsilane (7)

Imidazole (20 mg, 2.76 mmol) followed by TBSCl (0.331 g, 2.20 mmol) were added to a soln of propargyl alcohol **15** (0.4 g,1.84 mmol) in anhyd CH_2Cl_2 (10 mL) under a N_2 atmosphere at 0 °C, and the stirring was continued for 1 h at r.t. The mixture was then quenched with sat. aq NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with H_2O (1 × 20 mL) and brine (1 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 9.8:0.2).

Yield: 0.578 g (95%); colorless liquid; $[\alpha]_D^{25}$ –9.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3308, 2930, 2857, 1461, 1361, 1254, 1104, 936, 837, 776, 736, 696, 665 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ = 7.21–7.36 (m, 5 H), 4.47 (s, 2 H), 4.27–4.36 (m, 1 H), 3.45 (t, *J* = 6.2 Hz, 2 H), 2.31 (d, *J* = 2.3 Hz, 1 H), 1.43–1.77 (m, 6 H), 0.90 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7, 128.4, 127.5, 127.4, 85.5, 72.8, 72.0, 70.2, 62.6, 38.3, 29.3, 25.8, 21.8, 18.2, –5.17.

ESI-MS: *m*/*z* = 333 [M + Na^+].

(*R*)-2-Propyloxirane (8)

A mixture of (*R*,*R*)-(+)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (42 mg, 0.069 mmol) in toluene (0.2 mL) and AcOH (84 mg, 0.140 mmol) was stirred under open air for 1 h at r.t. The resulting mixture was concentrated under reduced pressure and the brown residue was dried under reduced pressure. Then racemic 2-propyloxirane (**16**; 3.0 g, 34.8 mmol) was added in one portion at 0 °C and dropwise addition of H_2O (0.35 mL, 19.2 mmol) over 10 min followed. The mixture was then allowed to warm to r.t. and was allowed to stir for 20 h. The desired (*R*)-2-propyloxirane (**8**) was isolated after distillation from the reaction mixture at atmospheric pressure.

Yield: 1.26 g (42%); colorless liquid; $[\alpha]_D^{25}$ +11.0 (*c* 1.0, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.81–2.88 (m, 1 H), 2.69 (dd, *J* = 3.7, 5.2 Hz, 1 H), 2.40 (dd, *J* = 2.6, 5.2 Hz, 1 H), 1.44–1.55 (m, 4 H), 0.98 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.3, 41.0, 31.2, 23.4, 15.8.

(4*R*,8*S*)-12-(Benzyloxy)-8-(*tert*-butyldimethylsiloxy)dodec-6-yn-4-ol (6)

A soln of 1.6 M *n*-BuLi in hexane (1.04 mL, 1.65 mmol) was added to a stirred soln of alkyne **7** (0.5 g, 1.5 mmol) in anhyd THF (10 mL) under an N_2 atmosphere at –78 °C. The mixture was allowed to stir for 30 min at the same temperature. $BF_3{\cdot}OEt_2$ (0.2 mL, 1.65 mmol) was then added slowly. After 10 min, a soln of (*R*)-2-propyloxirane (**8**; 0.5 g, 5.81mmol) in anhyd THF (10 mL) was added and the mixture was stirred for a further 3 h at –78 °C. The mixture was then quenched with sat. aq $NaHCO_3$ (10 mL) and sat. aq NH_4Cl (10 mL) at –78 °C. The mixture was allowed to warm to r.t. and then extracted with EtOAc (3 × 20 mL) and dried (Na_2SO_4). Removal of the solvent was followed by purification by column chromatography (silica gel, hexanes–EtOAc, 70:30).

Yield: 0.44 g (70%); colorless viscous liquid; $[\alpha]_D^{25}$ –10.7 (*c* 1.0, $CHCl_3$).

IR (neat): 3415, 2925, 2855, 1630, 1383, 1272, 1106, 840, 703 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.21–7.35 (m, 5 H), 4.47 (s, 2 H), 4.26–4.36 (m, 1 H), 3.69 (m, 1 H), 3.44 (t, *J* = 6.2 Hz, 2 H), 2.21–2.47 (m, 2 H), 1.24–1.81 (m, 10 H), 0.80–1.06 (m, 12 H), 0.09 (d, *J* = 4.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 128.2, 127.5, 127.4, 84.5, 80.5, 72.8, 70.2, 69.7, 63.0, 38.6, 38.3, 29.3, 27.7, 25.7, 22.0, 18.7, 18.2, 13.9, –4.5, –5.0.

ESI-MS: *m*/*z* = 441 [M + Na^+].

(5*S*,9*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)dodec-6-ene-1,9-diol (17)

Freshly cut Na (230 mg, 10 mmol) was cautiously and portionwise added to a freshly condensed soln of anhyd NH_3 (25 ml) in a two-necked round-bottomed flask at –78 °C and fitted with a cold condenser. The resulting deep blue suspension was stirred for 30 min at the same temperature. A soln of homopropargylic alcohol **6** (0.4 g, 1.0 mmol) in anhyd THF (10 mL) was added dropwise and then the mixture was stirred for another 2 h at –78 °C. After completion of the reaction, the mixture was quenched with solid NH_4Cl (10 g) and then NH_3 was allowed to evaporate slowly. The residue was dissolved in Et_2O and then filtered though small pad of Celite. The filtrate was dried (Na_2SO_4) and the crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 0.284 g (90%); colorless liquid; $[\alpha]_D^{25}$ +7.7 (*c* 2.0, $CHCl_3$).

IR (neat): 3351, 2931, 2860, 1463, 1362, 1242, 1065, 973, 836, 775, 670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.41–5.60 (m, 2 H), 4.03–4.15 (m, 1 H), 3.69–3.76 (m, 1 H), 3.61 (t, *J* = 6.7 Hz, 2 H), 2.00–2.29 (m, 2 H), 1.21–1.62 (m, 10 H), 0.94 (t, *J* = 7.5 Hz, 3 H), 0.89 (s, 9 H), 0.03 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.1, 125.8, 73.2, 70.7 62.7, 40.2, 38.8, 37.9, 32.5, 25.8, 21.3, 18.8, 18.1, 14.0, –4.3, –4.7.

ESI-MS: *m*/*z* = 353 [M + Na^+].

(5*S*,9*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-9-hydroxydodec-6-enoic acid (5)

$PhI(OAc)_2$ (0.3 g, 0.935 mmol) was added to a soln of **17** (0.28 g, 0.85 mmol) and TEMPO (0.014 g, 0.085 mmol) in anhyd CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 20 min at r.t. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (20 mL), washed with sat. aq $Na_2S_2O_3$ (10 mL), and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL) followed by brine soln (10 mL), and then dried (Na_2SO_4) and concentrated in vacuo. The crude aldehyde was immediately used for the next reaction. A soln of $NaClO_2$ (0.12 g, 1.275 mmol) in H_2O (2 mL) was added dropwise within 5 min at r.t. To a stirred soln of the above aldehyde in DMSO (3 mL) was added NaH_2PO_4 (0.27 g, 1.7 mmol) in H_2O (3 mL). The mixture was left overnight at r.t., and then 5% aq $NaHCO_3$ (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 70:30).

Yield: 0.233 g (80%; two steps); yellow oil; $[\alpha]_D^{25}$ –18.1 (*c* 0.33, $CHCl_3$).

IR (neat): 2956, 2927, 2855, 1712, 1463, 1253, 1084, 973, 835, 776, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.44–5.59 (m, 2 H), 4.06–4.16 (m, 1 H), 3.56–3.66 (m, 1 H), 2.35 (t, *J* = 6.79 Hz, 2 H), 2.03–2.28 (m, 2 H), 1.19–1.74 (m, 8 H), 0.94 (t, *J* = 7.5 Hz, 3 H), 0.89 (s, 9 H), 0.03 (d, *J* = 7.5 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.8, 136.7, 126.0, 72.8, 70.7, 40.11, 38.8, 37.4, 31.8, 25.8, 22.5, 20.4, 18.7, 14.0, –4.7, –4.8.

ESI-MS: *m*/*z* = 367 [M + Na^+].

(6*S*,10*R*,*E*)-6-(*tert*-Butyldimethylsiloxy)-10-propyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (18)

2,4,6-Trichlorobenzoyl chloride (0.13 ml, 0.71 mmol) was added to a stirred soln of **5** (0.15 g, 0.47 mmol) and Et_3N (100 mg, 0.71 mmol) in anhyd THF (3 ml) at r.t. The resulting mixture was stirred at r.t. for 3 h, and then a soln of DMAP (0.29 g, 2.35 mmol) in anhyd toluene (20 mL) was added. The mixture was refluxed for 10 h and then cooled to r.t. After completion of the reaction, the mixture was quenched with a sat. aq $NaHCO_3$ and then the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 8.0:2.0).

Yield: 0.099 g (70%); colorless oil; $[\alpha]_D^{25}$ –8.7 (*c* 0.30, $CHCl_3$).

IR (neat): 3433, 2962, 2935, 2890, 1730, 1670, 1450, 1366, 1183, 1007 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.43 (ddd, *J* = 4.3, 10.0, 15.0 Hz, 1 H), 5.27 (dd, *J* = 9.0, 15.0 Hz, 1 H), 4.90–5.05 (m, 1 H), 4.00 (dt, *J* = 3.0, 10.0, 19.0 Hz, 1 H), 2.37–2.57 (m, 2 H), 1.80–2.0 (m, 4 H), 1.22–1.75 (m, 6 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.87 (s, 9 H), 0.03 (d, *J* = 7.4 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 138.3, 129.5, 75.6, 72.3, 40.3, 39.6, 36.7, 35.8, 22.2, 18.9, 18.2, 14.0, 13.8, –4.3, –4.7.

ESI-MS: *m*/*z* = 249 [M + Na^+].

(6*R*,10*R*,*E*)-6-Hydroxy-10-propyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (Putaminoxin; 1)

A 1.0 M soln of TBAF in THF (0.34 ml, 0.34 mmol) was added to a stirred soln of **18** (0.07 g, 0.215 mmol) in anhyd THF (7 mL) at 0 °C. The mixture was stirred for 6 h and then diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The solvent was removed and the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 70:30).

Yield: 0.035 g (90%); colorless oil; $[\alpha]_D^{25}$ –25.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3433, 2959, 2930, 2871, 1729, 1641, 1442, 1365, 1182, 1007 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.54 (ddd, *J* = 4.7, 10.4, 15.3 Hz, 1 H), 5.32 (dd, *J* = 9.3, 15.5 Hz, 1 H), 4.97–5.10 (m, 1 H), 4.01 (dt, *J* = 3.4, 10.2, 19.8 Hz, 1 H), 2.31–2.50 (m, 2 H), 1.83–2.09 (m, 4 H), 1.20–1.75 (m, 6 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 137.2, 131.7, 75.4, 74.2, 40.3, 38.7, 36.4, 35.7, 22.3, 19.2, 13.9.

ESI-MS: *m*/*z* = 235 [M + Na^+].

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References

(1) Evidente, A.; Lanzetta, R.; Capasso, R.; Andolfi, A.; Bottalico, A.; Vurro, M.; Zonno, M. C. *Phytochemistry* **1995**, *40*, 1637.
(2) Fuschser, J.; Zeeck, A. *Liebigs Ann./Recl.* **1997**, 87.
(3) Sabitha, G.; Padmaja, P.; Reddy, P. N.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 6166.
(4) Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Zonno, M. C. *Nat. Toxins* **1998**, *6*, 183.
(5) (a) Sabitha, G.; Yadagiri, K.; Swapna, R.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 5417. (b) Kamal, A.; Reddy, P. V.; Balakrishna, M.; Prabhakar, S. *Lett. Org. Chem.* **2011**, *8*, 143.
(6) Smith, A. B. III.; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Boldi, A. M.; Murase, N.; Moser, W. H.; Brook, C. S.; Bennett, C. S.; Nakayama, K.; Sobukawa, M.; Lee Trout, R. E. *Tetrahedron* **2009**, *65*, 6470.
(7) (a) Osterkamp, F.; Ziemer, B.; Koert, U.; Wiesner, M.; Raddatz, P.; Goodman, S. L. *Chem. Eur. J.* **2000**, *6*, 666. (b) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849.
(8) Liu, J.; Yang, J. H.; Ko, C.; Hsung, R. P. *Tetrahedron Lett.* **2006**, *47*, 6121.
(9) (a) Yadav, J. S.; Sreenivas, M.; Reddy, A. S.; Reddy, B. V. S. *J. Org. Chem.* **2010**, *75*, 8307. (b) Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. J. *Bioorg. Chem.* **2009**, *37*, 46.
(10) (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*, Vol. 5; Morrison, J. D., Ed.; Acadamic Press: New York, **1985**, Chap. 8, 247. (b) Pfenninger, A. *Synthesis* **1986**, 89. (c) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (d) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (e) Yadav, J. S.; Reddy, Ch. S. *Org. Lett.* **2009**, *11*, 1705.
(11) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033.
(12) (a) Braun, M. G.; Vincent, A.; Boumediene, M.; Prunet, J. *J. Org. Chem.* **2011**, *76*, 4921. (b) Florence, G. J.; Cadou, R. F. *Tetrahedron Lett.* **2010**, *51*, 5761. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (d) Kretschmer, M.; Menche, D. *Synlett* **2010**,

2989.
(13) (a) Van de Weghe, P.; Bourg, S.; Eustache, S. *Tetrahedron* **2003**, *59*, 7365. (b) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (c) Yadav, J. S.; Sipak, J.; Dutta, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2007**, *48*, 5335.
(14) Naidu, V. S.; Gupta, P.; Kumar, P. *Tetrahedron* **2007**, *63*, 7624.
(15) (a) Hansen, M. T.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. C.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. Jr. *Tetrahedron* **1981**, *37*, 2091. (c) Yadav, J. S.; Thrimurthulu, N.; Venkatesh, M.; Rao, K. V. R.; Prasad, A. R.; Reddy, B. V. S. *Synthesis* **2010**, 73.
(16) (a) Shiina, I.; Fujisawa, H.; Ishii, T.; Fukuda, Y. *Heterocycles* **2000**, *52*, 1105. (b) Sabitha, G.; Reddy, R. T.; Ramesh, M.; Srinivas, C.; Yadav, J. S. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 229. (c) Kaliappan, K. P.; Si, D. *Synlett* **2009**, 2441.
(17) Srihari, P.; Kumaraswamy, B.; Somaiah, K.; Yadav, J. S. *Synthesis* **2010**, 1039.

