Stereoselective Total Synthesis of Leiocarpin C and (+)-Goniodiol

J. S. Yadav,* V. Hari Krishna, A. Srilatha, R. Somaiah, B. V. Subba Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad – 500 007, India
Fax +91(40)27160512; E-mail: yadav@iict.res.in

Received 9 April 2010; revised 28 April 2010

Abstract: Total syntheses of styryl lactones, leiocarpin C and (+)-goniodiol have been accomplished in a highly stereoselective manner. The key steps involved in these syntheses are the Chan alkyne reduction, Sharpless asymmetric dihydroxylation, Horner–Wadsworth–Emmons olefination, aryl Grignard reaction, hydroboration, stereoselective alkoxy-directed keto-reduction, stereoselective 1,3-*anti*-allylation, esterification via ozonolysis, and intramolecular lactonization.

Key words: styryl lactones, dihydroxylation, olefination, hydroboration, 1,3-*anti*-allylation, ozonolysis

Styryl lactones[1] and acetogenins[2] are two major types of bioactive compound isolated from the genus *Goniothalamus* (Annonaceae) species. Styryl lactones are natural heterocyclic compounds with potential cytotoxicity including excellent antitumor, antifungal, and antibiotic behavior.[3] Leiocarpin C was isolated from the seeds of *Goniothalamus leiocarpus* (Annonaceae), a tropical plant found in the south of the Yunnan Province in China.[4] Leiocarpins A–C (Figure 1) were found to possess cytotoxic activity against several human tumor cell lines.[5] (+)-Goniodiol was isolated from the leaves and twigs of *Goniothalamus sesquipedalis* (Annonaceae) and from the stem bark of *Goniothalamus gigantus* (Annonaceae). This is a potent and selective cytotoxic compound against human lung carcinoma A-549 (ED_{50} = 0.12 μg/mL and p-388 murine leukemia cells (IC_{50} = 4.56 mL).[6]

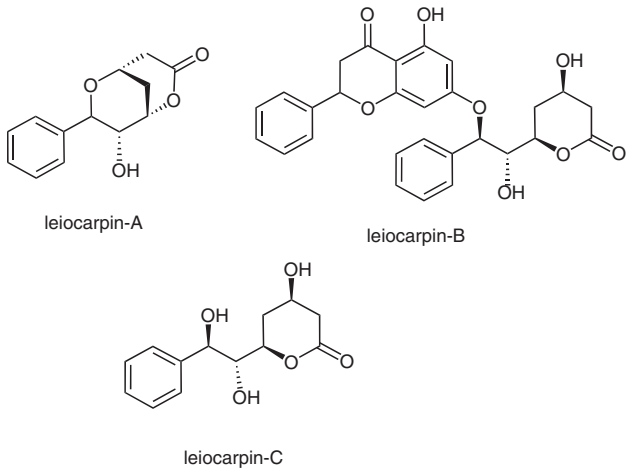
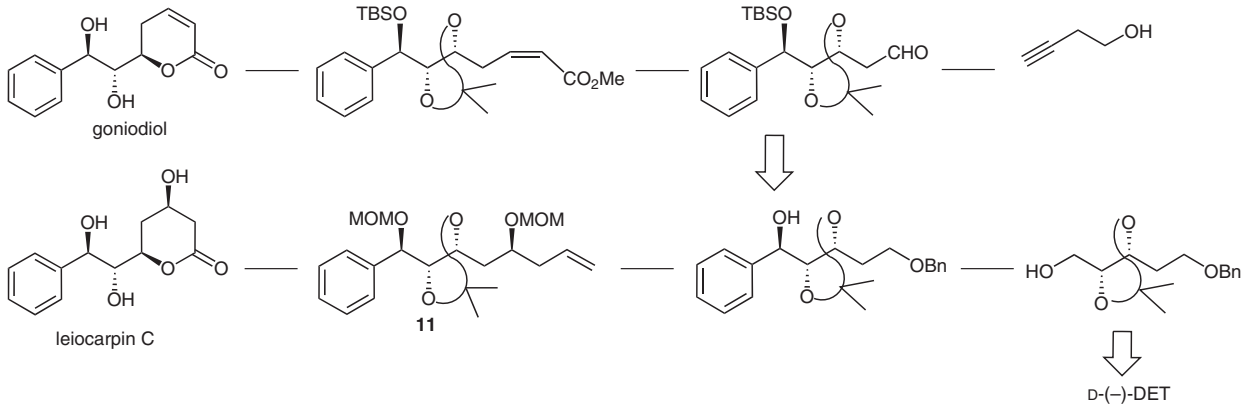


Figure 1

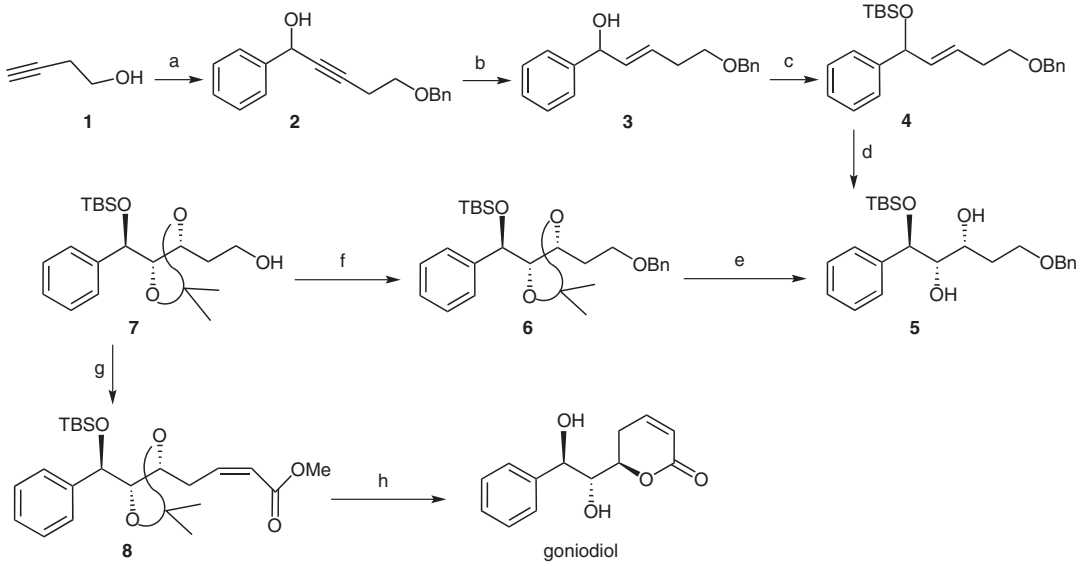
In continuation of our interest in the synthesis of lactone containing natural products,[7] we herein report a facile and modular synthetic approach towards the total synthesis of leiocarpin C and also the synthesis of (+)-goniodiol utilizing Sharpless asymmetric dihydroxylation, Horner–Wadsworth–Emmons olefination and intramolecular lactonization as key steps (Scheme 1).

The commercially available homopropargyl alcohol (**1**) was converted into its benzyl ether and then this treated with butyllithium in tetrahydrofuran to give the lithium acetylide which was further reacted with benzaldehyde to



Scheme 1 Retrosynthetic analysis of leiocarpin C and (+)-goniodiol

SYNTHESIS 2010, No. 17, pp 3004–3012
Advanced online publication: 30.07.2010
DOI: 10.1055/s-0030-1257858; Art ID: Z08610SS



Scheme 2 *Reagents and conditions:* (a) 1. NaH, BnBr, TBAI, THF, 0 °C to r.t., 3 h; 2. PhCHO, BuLi, THF, –78 °C, 2 h, 70%; (b) $LiAlH_4$, THF, reflux, 3 h, 95%; (c) TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 4 h, 95%; (d) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $(DHQD)_2$-PHAL, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH–H_2O (5:6), 0 °C, 38 h, 70% (>15:1 dr); (e) $Me_2CH(OMe)_2$, PTSA, CH_2Cl_2, r.t., 3 h, 94%; (f) DDQ, CH_2Cl_2–H_2O (9:1), r.t., 4 h, 80%; (g) 1. IBX, DMSO–CH_2Cl_2 (1:9), r.t., 4 h; 2. NaH, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, –78 °C, 1 h, 70%; (h) PTSA, MeOH, r.t., 2 h, 60%.

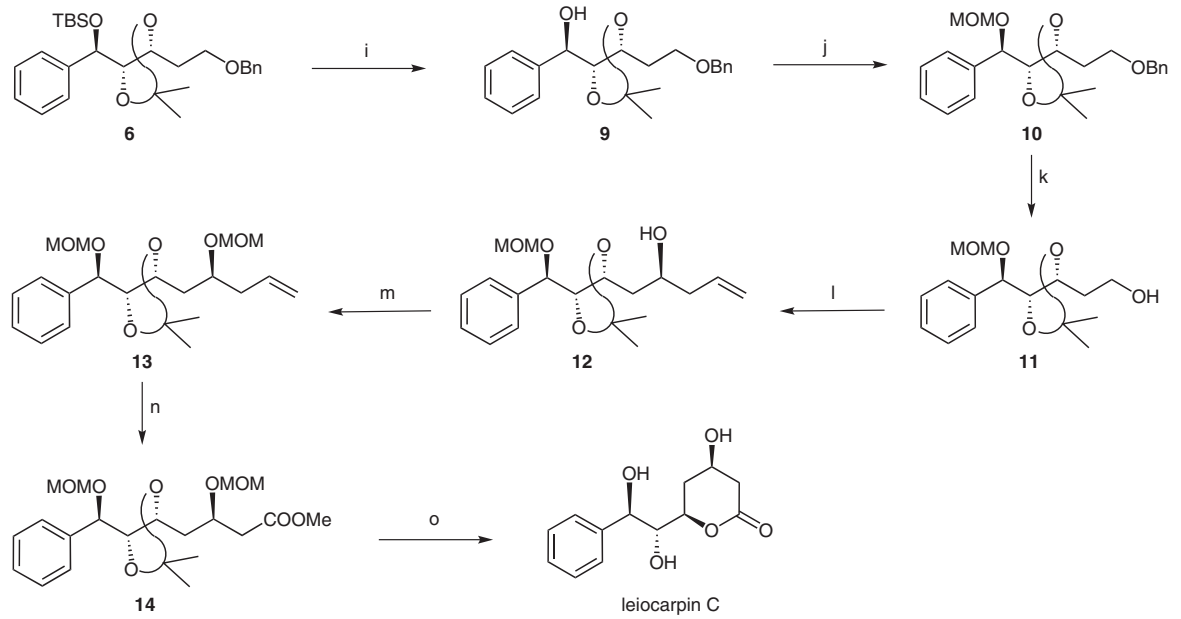
afford propargyl alcohol **2** in 70% yield (Scheme 2).[8] Reduction of propargyl alcohol **2** with lithium aluminum hydride in refluxing tetrahydrofuran gave the allylic alcohol **3** with *trans*-configuration in 95% yield.[9] Protection of **3** with *tert*-butyldimethylsilyl chloride in the presence of imidazole afforded compound **4** in 95% yield. The key intermediate, diol **5** was prepared in 70% yield by stereoselective Sharpless dihydroxylation of allylic alcohol **4** using $(DHQD)_2$-PHAL, methanesulfonamide, potassium osmate(VI) dihydrate, potassium hexacyanoferrate(III), potassium carbonate in *tert*-butyl alcohol–water (with >15:1 dr), which was confirmed by chiral HPLC analysis.[10] The diol **5** was protected as the acetonide with 2,2-dimethoxypropane using a catalytic amount of 4-toluenesulfonic acid in dry dichloromethane. Debenzylation of the acetonide **6** was achieved by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)–water[11] to give the primary alcohol **7**. The alcohol **7** was then treated with 2-iodoxybenzoic acid (IBX)/dimethyl sulfoxide in dichloromethane to furnish the corresponding aldehyde in good yield, which was further subjected to modified Horner–Wadsworth–Emmons olefination[12] using sodium hydride and bis(2,2,2-trifluoroethyl) (methoxycarbonyl)methylphosphonate in dry tetrahydrofuran at –78 °C to afford α,β-unsaturated ester **8**, predominantly as the *Z*-isomer in 70% yield (*Z*/*E*, 70:30).

The cyclization of *cis*-α,β-unsaturated ester **8** was achieved via intramolecular lactonization to afford (+)-goniodiol in 60% yield after sequential removal of silyl and acetonide protecting groups using a catalytic amount of 4-toluenesulfonic acid in methanol.[13]

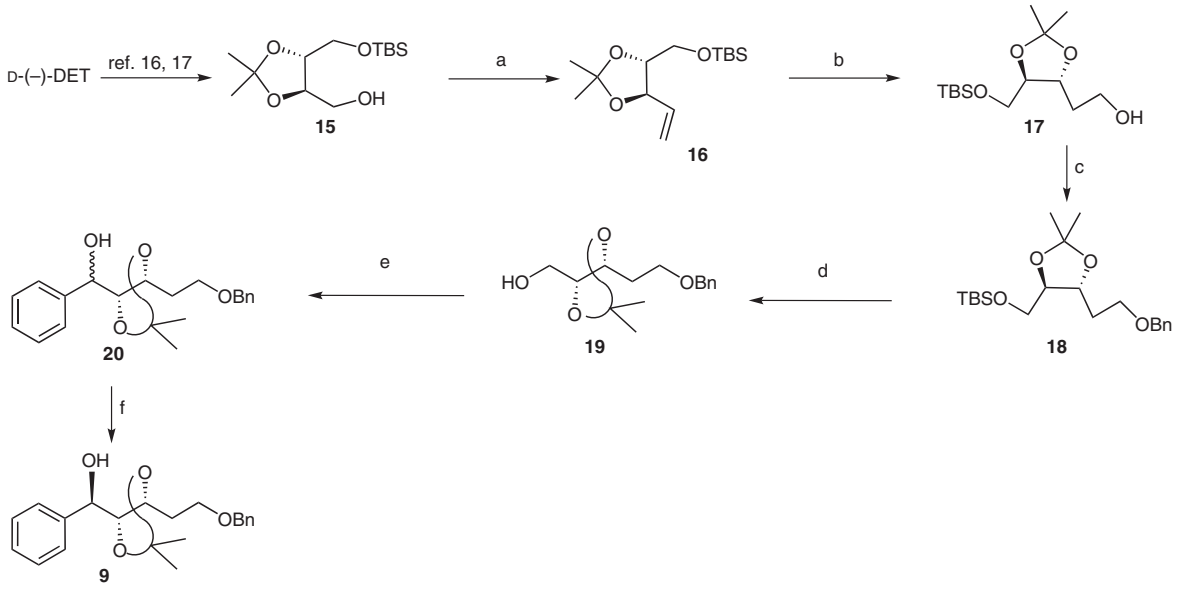
The synthesis of leiocarpin C was initiated by replacing the *tert*-butyldimethylsilyl group with methoxymethyl protection in alcohol **10** to avoid the steric hindrance generated by the TBS group (Scheme 3). After that, debenzylation of the MOM product **11** was achieved by using DDQ/H_2O,[11] which was further oxidized to afford an aldehyde using IBX/DMSO.

Highly diastereoselective allylation of the aldehyde was achieved with allyltributyltin using magnesium bromide–diethyl ether complex in dichloromethane at –78 °C to give the β-hydroxyallyl derivative **12** in 80% yield and 90% ee (*anti*/*syn*, 95:5).[14] The β-hydroxy group was protected to give MOM ether **13**, which was then subjected to ozonolysis followed by treatment with potassium hydroxide in methanol to furnish methyl ester **14**.[15] The resulted methyl ester **14** was cyclized through an intramolecular lactonization in a single step using a catalytic amount of 4-toluenesulfonic acid in methanol to afford leiocarpin C in 70% yield.[13]

The fragment **9** was prepared from a chiral C_2-asymmetrical diol which in turn was derived from readily available (–)-diethyl D-tartarate (Scheme 4).[16] Monoprotection of the diol was achieved with *tert*-butyldimethylsilyl chloride in the presence of sodium hydride to give the TBS ether **15** in 95% yield. Swern oxidation of **15** gave the unstable aldehyde in 95% yield,[17] which was immediately subjected to one-carbon Wittig olefination with triphenylphosphonium iodide using butyllithium in tetrahydrofuran at 0 °C to room temperature to afford olefin **16** in 80% yield.[18] The olefin derivative **16** was converted into the corresponding primary alcohol **17** in 70% yield by hydroboration with 9-BBN dimer in dry tetrahydrofuran followed by oxidation with hydrogen peroxide in the presence of sodium hydroxide.[19] The protection of primary alcohol **17** with benzyl bromide in the presence of sodium hydride afforded benzyl ether **18** in 90% yield. Deprotection of the TBS ether **18** using tetrabutylammo-



Scheme 3 *Reagents and conditions:* (i) 1.0 M TBAF, THF, 0 °C to r.t., 2 h, 95%; (j) MOMCl, DIPEA, CH_2Cl_2, 0 °C to r.t., 15 h, 80%; (k) DDQ, CH_2Cl_2–H_2O (9:1), r.t., 4 h, 80%; (l) 1. IBX, DMSO–CH_2Cl_2 (1:9), r.t., 4 h; 2. $MgBr_2$·OEt_2, CH_2Cl_2, allyltributyltin, –78 °C, 2 h then –20 °C, 0.5 h, 80% (90% ee); (m) MOMCl, DIPEA, CH_2Cl_2, r.t., 15 h, 90%; (n) O_3, NaOH, MeOH, –78 °C, 60%; (o) PTSA, MeOH, reflux, 2 h, 70%.



Scheme 4 *Reagents and conditions:* (a) 1. $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, 95%; 2. BuLi, Ph_3PCH_2I, THF, –78 °C, 3 h, 80%; (b) 1. 9-BBN, THF, r.t., overnight; 2. NaOH, 30% H_2O_2, 12 h, 70%; (c) NaH, BnBr, TBAI, THF, r.t., 2 h, 90%; (d) 1.0 M TBAF, THF, 0 °C, 1 h, 94%; (e) 1. $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; 2. PhMgBr, THF, –78 °C, 2h then r.t., 12 h, 70% (inseparable mixture of diastereoisomers); (f) 1. IBX, CH_2Cl_2–DMSO (3:1), 180–200 °C, 12 h, 67%; 2. $Zn(BH_4)_2$, THF, –20 °C, 12 h, 85% (90% de).

nium fluoride gave the primary alcohol **19** in 94% yield.[20] Swern oxidation of the resulting primary alcohol **19** with oxalyl chloride, dimethyl sulfoxide in dichloromethane at –78 °C gave the aldehyde, which was subsequently treated with phenylmagnesium bromide to afford the secondary alcohol **20** in 70% yield as an inseparable mixture of diastereoisomers.[21] To obtain the required diastereomer as the major product, the racemic mixture of alcohol **20** was oxidized with IBX (DMSO–CH_2Cl_2, 1:3) under reflux conditions to give the ketone, which was subsequently subjected to stereoselective alkoxy-directed 1,2-*anti*-keto-reduction with zinc borohydride in tetrahydrofuran at –20 °C to afford the secondary alcohol **9** as the major isomer in 85% yield in two steps.[22]

In conclusion, a concise and efficient synthesis of leiocarpin C has been achieved in a highly stereoselective manner. The synthesis involves Chan alkyne reduction,[9] Sharpless asymmetric dihydroxylation, Horner–

Wadsworth–Emmons olefination, aryl Grignard reaction, hydroboration, stereoselective alkoxy-directed keto reduction, and intra molecular lactonization. This synthetic sequence provides an easy access to the preparation of styryl lactones of biological importance.

All commercial reagents were used without further purification and all the solvents were purified by standard techniques. The crude products were purified by column chromatography on silica gel (60–120 mesh) using EtOAc–hexane as the eluent. IR spectra were recorded on Perkin-Elmer 683 spectrophotometer. Optical rotations were obtained on Perkin Elmer Model 343 polarimeter preparing the samples in $CHCl_3$. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS) on Varian Gemini 200, Bruker 300 NMR spectrometers. ESI and HRMS were recorded on High Resolution QSTAR XL hybrid MS/MS system, Applied Biosystems by preparing the sample solutions in MeOH.

5-(Benzyloxy)-1-phenylpent-2-yn-1-ol (2)

To a stirred soln of 4-(benzyloxy)prop-1-yne (90.0 g, 0.562 mol) in anhyd THF (750 mL) was added 1.6 M BuLi (300 mL, 0.505 mol) dropwise slowly at –78 °C. The resulting mixture was stirred at this temperature for 1 h. PhCHO (74.5 g, 0.702 mol) was added very slowly and stirring was continued at –78 °C for a further 2 h. The mixture was quenched with NH_4Cl soln (50 mL) at 0 °C and extracted with EtOAc (500 mL). The combined organic layers were washed with H_2O (500 mL) and brine, dried (Na_2SO_4) and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 1:9) furnished **2** (104 g, 70%) as a colorless liquid.

IR (neat): 3420, 2922, 2854, 1453, 1096, 970, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.22 (m, 10 H), 5.38 (d, *J* = 6.4 Hz, 1 H), 4.54 (s, 2 H), 3.62 (t, *J* = 6.9 Hz, 2 H), 2.58 (t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 137.8, 128.5, 128.4, 128.3, 128.0, 127.6, 126.8, 84.1, 80.8, 76.2, 69.0, 61.6, 20.1.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{18}H_{18}NaO_2$: 289.3282; found: 289.3278.

(*E*)-5-(Benzyloxy)-1-phenylpent-2-en-1-ol (3)

To a stirred soln of $LiAlH_4$ (57.0 g, 1.51 mol) was added **2** (100.0 g, 0.377 mol) dropwise in anhyd THF (800 mL) at 0 °C. The mixture was allowed to warm to r.t. and stirred for 10 min. Then the mixture was refluxed for 3 h and quenched with sat. aq Na_2SO_4 (200 mL) at 0 °C and filtered through a sintered funnel. The collected filtrate was extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with H_2O (100 mL) and brine, dried (Na_2SO_4), and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 1:9) gave **3** (95.71 g, 95%) as a colorless liquid.

IR (neat): 3419, 2923, 2854, 1453, 1363, 1095, 969, 754, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 10 H), 5.82–5.62 (m, 2 H), 5.12 (d, *J* = 3.0 Hz, 1 H), 4.47 (s, 2 H), 3.50 (t, *J* = 6.7 Hz, 2 H), 2.39–2.32 (m, 2 H), 1.77 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 138.3, 134.2, 131.9, 129.7, 128.4, 128.3, 127.6, 126.4, 125.0, 75.0, 72.8, 69.5, 29.6.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{18}H_{20}NaO_2$: 291.1360; found: 291.1348.

(*E*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsiloxy)-1-phenylpent-2-ene (4)

To a stirred soln of **3** (90.0 g, 0.34 mol) and imidazole (27.5 g, 0.40 mol) was added TBSCl (55.7 g, 0.37 mol) dropwise in anhyd CH_2Cl_2 (800 mL) at 0 °C and stirring was continued at r.t. for 4 h. The mixture was quenched with ice flakes and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 1:9) furnished **4** (122.0 g, 95%) as a colorless liquid.

IR (neat): 3028, 2922, 2854, 1647, 1493, 1453, 1363, 1212, 1093, 1021, 969, 755, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 10 H), 7.24–7.17 (m, 1 H), 5.76–5.54 (m, 1 H), 5.12 (d, *J* = 6.0 Hz, 1 H), 4.49 (s, 2 H), 3.50 (t, *J* = 6.8 Hz, 2 H), 2.39–2.31 (m, 2 H), 0.90 (s, 9 H), 0.05 (s, 3 H), –0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.6, 133.1, 129.6, 128.5, 128.3, 127.7, 127.6, 127.4, 73.0, 70.6, 66.7, 38.4, 29.7, 25.9, 18.2, –4.8.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{24}H_{34}NaO_2Si$: 404.6115; found: 404.6119.

(1*R*,2*S*,3*R*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsiloxy)-1-phenylpentane-2,3-diol (5)

To a mixture of $K_3Fe(CN)_6$ (77.6 g, 0.235 mol), K_2CO_3 (32.8 g, 0.235 mol), $MeSO_2NH_2$ (7.45 g, 78.6 mmol), $(DHQD)_2$-PHAL (0.61 g, 0.78 mmol), and $K_2OsO_4 \cdot 2\ H_2O$ (0.22 g, 0.59 mmol) was added H_2O (400 mL) and *t*-BuOH (350 mL); the resulting mixture was stirred at r.t. for 15 min to afford a homogeneous soln. The mixture was then cooled to 0 °C and a suspension of allyl alcohol **4** (30 g, 78.6 mmol) in *t*-BuOH (50 mL) was added slowly. The mixture was vigorously stirred at 0 °C for 38 h and the mixture was quenched with Na_2SO_3 (70 g) at 0 °C. The resulting layers were separated and the aqueous portion was extracted with EtOAc (3 × 500 mL). The combined organic layers were then washed with aq 2 M NaOH (2 × 500 mL), H_2O (2 × 200 mL), and brine (2 × 250 mL), dried (Na_2SO_4), filtered, and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 6:4) afforded **5** (22.8 g, 70%) as a colorless liquid; 15:1 de.

$[\alpha]_D^{29}$ –39 (*c* 1, $CHCl_3$).

IR (neat): 3449, 3063, 3030, 2953, 2929, 2857, 1720, 1639, 1455, 1389, 1363, 1254, 1094, 1027, 836, 777, 740, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.28 (m, 10 H), 4.95 (d, *J* = 5.3 Hz, 1 H), 4.57 (s, 2 H), 4.22–4.12 (m, 1 H), 3.68 (t, *J* = 6.0 Hz, 2 H), 3.51 (m, 1 H), 3.20 (br, 1 H), 2.68 (br, 1 H), 2.1–1.89 (m, 1 H), 1.87–1.69 (m, 1 H), 1.20 (s, 9 H), 0.22 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7, 137.9, 128.3, 127.3, 127.1, 127.0, 126.5, 126.3, 76.7, 76.3, 73.0, 67.5, 65.8, 34.5, 25.8, 15.3, –4.7.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{24}H_{36}NaO_4Si$: 439.6197; found: 439.6194.

(1*R*,2*S*,3*R*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)-1-phenylpentane (6)

To a stirred soln of diol **5** (22.0 g, 52.0 mmol) in anhyd CH_2Cl_2 (250 mL) was added PTSA (0.5 g, 2.0 mmol) and 2,2-dimethoxypropane (17.7 g, 169.0 mmol) dropwise at 0 °C and stirring was continued at r.t. for 3 h. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layer were washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4) and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 1:9) furnished **6** (22.7 g, 94%) as a colorless liquid.

$[\alpha]_D^{29.7}$ +11.2 (*c* 2.0, $CHCl_3$).

IR (neat): 3031, 2925, 2854, 1718, 1603, 1453, 1376, 1206, 1170, 1075, 890, 755, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.32 (m, 10 H), 4.89 (d, *J* = 5.1 Hz, 1 H), 4.60 (s, 2 H), 4.41–4.28 (m, 1 H), 3.93–3.83 (m, 1 H), 3.66 (t, *J* = 7.3 Hz, 2 H), 1.86–1.61 (m, 2 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.05 (s, 9 H), 0.22 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7, 140.5, 128.4, 127.9, 127.5, 126.8, 85.4, 77.4, 75.8, 75.4, 61.2, 37.0, 27.7, 27.4, 26.2, 18.5, –4.4.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{27}H_{40}NaO_4Si$: 479.2596; found: 479.2593.

Methyl (*Z*)-(5*R*,6*S*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5,6-(isopropylidenedioxy)-7-phenylhept-2-enoate (8)

To a stirred soln of **6** (5.0 g, 10.9 mmol) in CH_2Cl_2–H_2O (9:1, 100 mL:11 mL) was added DDQ (19.4 g, 43.8 mmol) at 0 °C; the mixture was stirred at r.t. for 4 h. The reaction was quenched with $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layer were washed with brine and dried (Na_2SO_4). Removal of solvent followed by purification by column chromatography (silica gel, EtOAc–hexane, 1:9) afforded pure **7** (3.2 g, 80%) as a colorless liquid.

To a stirred soln of IBX (4.6 g, 16.4 mmol) in DMSO (2 mL, 32.8 mmol) at r.t. was added dropwise a soln of alcohol **7** (3.0 g, 8.22 mmol) in anhyd CH_2Cl_2 (50 mL) and the mixture was stirred at r.t. for 4 h. When the reaction was complete, the mixture was diluted with Et_2O (90 mL) and filtered through a Celite pad. The filtrate was washed with sat. aq $NaHCO_3$ and brine, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The resulted crude aldehyde was used directly in next reaction.

A soln of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (2.58 g, 8.12 mmol) in anhyd THF (70 mL) was treated with 60% NaH in paraffin oil (0.35 g, 14.0 mmol) at –78 °C for 15 min. Aldehyde (2.68 g, 7.38 mmol) was then added and the mixture was stirred at –78 °C for 1 h. The mixture was quenched with sat. NH_4Cl (5 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The mixture was subjected to column chromatography (silica gel, EtOAc–hexane, 1:9) to give **8** (2.1 g, 70%) as a colorless liquid.

$[\alpha]_D^{29}$ +24 (*c* 0.2, $CHCl_3$).

IR (neat): 2925, 2854, 1727, 1657, 1463, 1437, 1381, 1261, 1165, 1095, 864, 836, 778 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 6.31–6.15 (m, 1 H), 5.75 (d, *J* = 11.7 Hz, 1 H), 4.74 (d, *J* = 5.1 Hz, 1 H), 4.20–4.03 (m, 1 H), 3.81–3.67 (m, 1 H), 3.65 (s, 3 H), 2.84–2.52 (m, 2 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), –0.15 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 145.5, 140.5, 128.2, 128.0, 127.8, 120.9, 109.0, 78.0, 77.1, 76.8, 51.1, 34.2, 32.3, 27.5, 27.4, 25.9, 18.4, –4.6.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{23}H_{36}NaO_5Si$: 443.6074; found: 443.6078.

(+)-Goniodiol [(6*R*)-6-[(1*R*,2*R*)-1,2-Dihydroxy-2-phenylethyl]-5,6-dihydro-2*H*-pyran-2-one]

To a stirred soln of **8** (0.5 g, 1.23 mmol) in MeOH (10 mL) was added PTSA·H_2O (13 mg, 0.12 mmol) at 0 °C and stirring was continued at r.t. for 2 h and then the solvent was removed under reduced pressure. The crude residue was subjected to column chromatography (silica gel, EtOAc–hexane, 2:8) to afford pure product (0.17 g, 60%) as a colorless liquid.

$[\alpha]_D^{29}$ +72.4 (*c* 0.68, $CHCl_3$).

IR (neat): 3451, 2986, 1730, 1645, 1440, 1375, 1210, 1058 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 5 H), 6.93 (ddd, *J* = 2.3, 6.4, 9.8 Hz, 1 H), 5.99 (dd, *J* = 2.7, 9.8 Hz, 1 H), 4.94 (dd, *J* = 3.4, 7.1 Hz, 1 H), 4.80 (ddd, *J* = 2.3, 3.8, 12.9 Hz, 1 H), 3.72 (td, *J* = 2.2, 8.1 Hz, 1 H), 2.79 (ddt, *J* = 2.7, 12.9, 18.5 Hz, 1 H), 2.63 (d, *J* = 5.6 Hz, 1 H), 2.18 (ddd, *J* = 3.8, 6.4, 18.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 145.9, 139.6, 128.7, 128.5, 126.8, 120.8, 78.0, 74.8, 73.9, 24.5.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{13}H_{15}O_4$: 235.0970; found: 235.0969.

(1*R*,2*R*,3*R*)-5-(Benzyloxy)-2,3-(isopropylidenedioxy)-1-phenylpentan-1-ol (9)

To a well-stirred soln of **6** (15 g, 32.9 mmol) in anhyd THF (150 mL) was added 1 M TBAF (39.5 mL, 39.5 mmol) at 0 °C. Then the reaction was quenched with ice flakes and concentrated under reduced pressure. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O and brine and dried (Na_2SO_4). After removing the volatiles under reduced pressure, the crude product was purified by column chromatography (silica gel, EtOAc–hexane, 4:6) to afford pure **9** (10.7 g, 95%) as a colorless liquid.

$[\alpha]_D^{25}$ –32.4 (*c* 1, $CHCl_3$).

IR (neat): 3451, 2985, 2926, 1605, 1454, 1250, 919, 878, 837 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (m, 10 H), 4.18 (d, *J* = 4.5 Hz, 1 H), 4.37 (s, 2 H), 4.15–4.08 (m, 1 H), 3.89–3.84 (m, 1 H), 3.46–3.39 (m, 2 H), 2.64 (s 1 H), 1.51–1.41 (m, 1 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.32–1.23 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3, 138.3, 128.3, 127.8, 127.5, 126.1, 108.6, 83.9, 74.2, 72.6, 67.0, 57.3, 34.0, 28.0.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{21}H_{26}NaO_4$: 365.1728; found: 365.1732.

(1*R*,2*S*,3*R*)-5-(Benzyloxy)-2,3-(isopropylidenedioxy)-1-(methoxymethoxy)-1-phenylpentane (10)

To a well-stirred soln of **9** (8 g, 23.4 mmol) in anhyd CH_2Cl_2 (150 mL) was added DIPEA (6.03 g, 46.8 mmol) dropwise at 0 °C and the stirring was continued for 1 h. Then MOMCl (2.8 mL, 35.1 mmol) was added slowly at 0 °C and the mixture was again stirred at r.t. for 15 h. The reaction was quenched with ice flakes and the product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 2:8) afforded pure **10** (7.24 g, 80%) as a colorless liquid.

$[\alpha]_D^{25}$ +16.0 (*c* 0.2, $CHCl_3$).

IR (neat): 3450, 2986, 2927, 1607, 1493, 1453, 1372, 1249, 1213, 1154, 1097, 1030, 919, 877, 837, 740, 701, 631 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 10 H), 4.64 (d, *J* = 4.5 Hz, 1 H), 4.50 (s, 2 H), 4.49 (s, 2 H), 4.15–4.05 (m, 1 H), 3.88–3.82 (m, 1 H), 3.60–3.50 (m, 2 H), 3.30 (s, 3 H), 1.94–1.80 (m, 1 H), 1.76–1.63 (m, 1 H), 1.32 (s, 3 H), 1.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 137.8, 128.2, 128.1, 128.0, 127.5, 109.1, 94.1, 83.4, 77.7, 75.7, 72.8, 67.2, 55.7, 34.3, 27.4, 26.8.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{23}H_{30}NaO_5$: 409.1990; found: 409.1989.

(3*R*,4*S*,5*R*)-3,4-(Isopropylidenedioxy)-5-(methoxymethoxy)-5-phenylpentan-1-ol (11)

To a stirred soln of **10** (7 g, 18.1 mmol) in CH_2Cl_2 and H_2O (90 mL:9 mL) was added DDQ (31.98 g, 72.3 mmol) and the mixture was stirred at r.t. for 4 h. The mixture was quenched with sat. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with H_2O (200 mL) and brine (100 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford **11** (4.29 g, 80%) as a colorless syrupy liquid.

$[\alpha]_D^{26}$ –73.5 (*c* 1, $CHCl_3$).

IR (neat): 3448, 2925, 2855, 1455, 1374, 1249, 1214, 1153, 1072, 1027, 918, 895, 762, 703, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 5 H), 4.64 (d, *J* = 3.5 Hz, 1 H), 4.51 (s, 2 H), 4.15–4.05 (m, 1 H), 3.88–3.82 (m, 1 H), 3.6–3.5 (m, 2 H), 3.36 (s, 3 H), 1.94–1.80 (m, 1 H), 1.76–1.63 (m, 1 H), 1.32 (s, 3 H), 1.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 128.3, 128.1, 127.6, 109.2, 94.3, 85.5, 77.9, 60.8, 55.9, 36.5, 26.8.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{16}H_{24}NaO_5$: 319.1521; found: 319.1519.

(4*S*,6*R*,7*S*,8*R*)-6,7-(Isopropylidenedioxy)-8-(methoxymethoxy)-8-phenyloct-1-en-4-ol (12)

To a stirred soln of IBX (11.3 g, 40.2 mmol) in DMSO (5.7 mL, 80.5 mmol) at r.t. was added alcohol **11** (6 g, 20.1 mmol) dropwise in anhyd CH_2Cl_2 (100 mL) and stirring was continued at r.t. for 4 h. When the reaction was complete it was extracted with Et_2O (3 × 100 mL) and filtered through a Celite pad. The filtrate was washed with sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulted crude aldehyde was directly used for next reaction.

To a stirred soln of $MgBr_2{\cdot}OEt_2$ (8.72 g, 33.8 mmol) in anhyd CH_2Cl_2 (100 mL) was added the aldehyde (5 g, 16.9 mmol) in anhyd CH_2Cl_2 (80 mL) at 0 °C and stirring was continued at this temperature for 15 min. To the mixture was added allyltributyltin (7.8 mL, 25.3 mmol) dropwise at –78 °C and under inert atmosphere. The resulted mixture was stirred at this temperature for a further 2 h. The mixture was warmed to –20 °C and stirring was continued for 30 min. The mixture was quenched with sat. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Column chromatography (silica gel, EtOAc–hexane, 2:8) furnished the allylated product (4.58 g, 80%) as a colorless liquid as a diastereomeric mixture. The pure diastereomers were separated by column chromatography to obtained purified 1,3-*anti*-allylated product **12** (4.31 g); 90% de.

$[\alpha]_D^{26}$ –34.4 (*c* 1, $CHCl_3$).

IR (neat): 3453, 2926, 1638, 1454, 1377, 1250, 1214, 1154, 1074, 1029, 917, 764, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 5.82–5.65 (m, 1 H), 5.12–4.98 (m, 2 H), 4.68 (d, *J* = 6.0 Hz, 1 H), 4.54 (s, 2 H), 4.27 (td, *J* = 3.8, 7.5 Hz, 1 H), 4.16–4.05 (m, 1 H), 3.90–3.82 (m, 1 H), 3.83–3.74 (br s, 1 H), 3.36 (s, 3 H), 2.24–2.10 (m, 2 H), 1.67 – 1.49 (m, 2 H), 1.35 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 134.1, 127.8, 127.3, 127.1, 117.3, 108.9, 93.9, 82.8, 77.4, 77.3, 67.8, 55.5, 41.5, 39.9, 27.0, 26.4.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{19}H_{28}NaO_5$: 359.1834; found: 359.1834.

(4*S*,6*R*,7*S*,8*R*)-6,7-(Isopropylidenedioxy)-4,8-bis(methoxymethoxy)-8-phenyloct-1-ene (13)

To a well-stirred soln of **12** (3.48 g, 10.35 mmol) in anhyd CH_2Cl_2 (50 mL) was added DIPEA (4 mL, 20.7 mmol) dropwise at 0 °C and stirring was continued for 30 min. MOMCl (1.06 mL, 13.3 mmol) was then added and the mixture was stirred at r.t. for 15 h. The reaction was quenched with ice flakes and the product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 4:6) afforded pure **13** (3.542 g, 90%) as a colorless liquid.

$[\alpha]_D^{26}$ –37.6 (*c* 1, $CHCl_3$).

IR (neat): 3453, 2928, 1640, 1452, 1214, 1152, 1034, 917, 764, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H), 5.84–5.68 (m, 1 H), 5.12–4.98 (m, 2 H), 4.71–4.49 (m, 5 H), 4.17–4.07 (m, 1 H), 3.88–3.70 (m, 2 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 2.30–2.22 (m, 2 H), 1.70–1.40 (m, 2 H), 1.33 (s, 3 H), 1.20 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 134.4, 128.1, 128.0, 127.8, 117.3, 108.9, 95.7, 94.2, 83.5, 77.9, 77.1, 73.9, 55.8, 39.7, 39.2, 27.5, 26.7.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{21}H_{32}O_6Na$: 403.2085; found: 403.2096.

Methyl (3*R*,5*R*,6*S*,7*R*)-5,6-(Isopropylidenedioxy)-3,7-bis(methoxymethoxy)-7-phenylheptanoate (14)

The soln of **13** (2.5 g, 6.52 mmol) in anhyd CH_2Cl_2 (15 mL) and 2.5 M NaOH in MeOH (13 mL) was stirred at –78 °C and ozone was passed through the soln at the same temperature till the mixture acquired the blue characteristic color of ozone and a yellow precipitate had formed. The mixture was diluted with Et_2O (100 mL) and H_2O (20 mL). The resulting mixture was allowed to warm to r.t. and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 2:8) afforded **14** (1.6 g, 60%) as a colorless product.

$[\alpha]_D^{25}$ –25.8 (*c* 1.55, $CHCl_3$).

IR (neat): 2895, 1745, 1230, 1050, 736 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H), 4.65 (d, *J* = 6.2 Hz, 1 H), 4.61–4.55 (m, 4 H), 4.12 (m, 1 H), 3.98–3.85 (m, 2 H), 3.84 (s, 3 H), 3.39–3.35 (d, *J* = 7.5 Hz, 6 H), 2.68–2.35 (m, 2 H), 1.82–1.47 (m, 2 H), 1.32 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 128.1, 128.0, 127.8, 117.3, 108.9, 95.7, 94.2, 83.5, 77.9, 77.1, 73.9, 55.8, 39.7, 39.2, 27.5, 26.7.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{21}H_{32}NaO_8$: 435.1994; found: 435.1995.

Leiocarpin C [(4*R*,6*R*)-6-[(1*R*,2*R*)-1,2-Dihydroxy-2-phenylethyl]-4-hydroxytetrahydro-2*H*-pyran-2-one]

To a stirred soln of ester **14** (0.5 g, 1.20 mmol) in MeOH (2 mL) was added PTSA (23 mg, 0.12 mmol) at r.t. The mixture was heated under reflux for 2 h. The mixture was then cooled to r.t. and solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, EtOAc–hexane, 2:8) to afford leiocarpin C (0.21 g, 70%) as needles.

$[\alpha]_D^{29}$ –63.2 (*c* 0.5, MeOH).

IR (neat): 3450, 3180, 2885, 1720, 1460, 1150, 890 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H), 5.42 (d, *J* = 5.8 Hz, 1 H), 4.77 (dd, *J* = 2.4, 5.8 Hz, 1 H), 4.45–4.40 (m, 1 H), 4.35 (dt, *J* = 3.2, 7.0 Hz, 1 H), 3.35 (dd, *J* = 7.2, 14.8 Hz, 2 H), 2.38 (t, *J* = 4.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 141.2, 129.2, 128.4, 127.3, 74.5, 70.0, 68.8, 67.9, 41.5, 38.1.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{13}H_{16}NaO_5$: 275.0895; found: 275.0895.

(2*R*,3*R*)-4-(*tert*-Butyldimethylsiloxy)-2,3-(isopropylidenedioxy)butan-1-ol (15)

To a stirred soln of [(4*R*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (11.7 g, 72 mmol) and NaH (3.4 g, 144 mmol) in anhyd THF (400 mL) was added TBSCl (10.8 g, 72 mmol) in anhyd THF (200 mL) dropwise through a dropping funnel at 0 °C over 60 min under an inert atmosphere. The mixture was stirred for 2 h and then it was allowed to warm up to r.t. The reaction was

quenched with ice flakes and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Column chromatography (silica gel, EtOAc–hexane, 1:9) gave pure **15** (16.00 g, 80%) as a colorless liquid.

$[\alpha]_D^{20}$ –18 (*c* 1.02, $CHCl_3$).

IR (neat): 3468, 2932, 2860, 1375, 1253, 1083, 839, 778 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.10–3.90 (m, 1 H), 3.90–3.85 (m, 2 H), 3.85–3.60 (m, 3 H), 2.44 (dd, *J* = 4.5, 8.0 Hz, 1 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 0.91 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.1, 80.1, 78.1, 63.7, 62.7, 27.0, 26.9, 25.8, 18.3, –5.5.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{13}H_{29}O_4Si$: 277.1835; found: 277.1838.

(3*R*,4*R*)-5-(*tert*-Butyldimethylsiloxy)-3,4-(isopropylidenedioxy)pent-1-ene (16)

To a stirred soln of oxalyl chloride (6.07 mL, 70.5 mmol) in anhyd CH_2Cl_2 (150 mL) was added dropwise DMSO (6.52 mL, 92.1 mmol) in anhyd CH_2Cl_2 (50 mL) at –78 °C. The mixture was stirred at this temperature for 15 min. To this mixture was added dropwise a soln of **15** (15 g, 54.2 mmol) in anhyd CH_2Cl_2 (100 mL) and stirring was continued at –78 °C for a further 1 h. The reaction mixture was quenched by addition of Et_3N (45.2 mL, 325.0) at –78 °C, then was allowed to warm to r.t. and stirring was continued for 40 min. After addition of H_2O (100 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Rapid chromatography of the resulting residue (silica gel, 60–100 mesh, 20% EtOAc–hexane) furnished unstable aldehyde (14.12 g, 95%) as a colorless liquid.

To the soln of methyltriphenylphosphonium iodide (82.8 g, 204 mmol) was added 1.6 M BuLi (63.8 mL, 102 mmol) in anhyd THF (400 mL) and the mixture was allowed to stir at r.t. under N_2 for 3 h. Stirring was stopped and the solid was allowed to settle. The clear supernatant orange-yellow liquid was cannulated into the soln of aldehyde (14 g, 51 mmol) in anhyd THF (200 mL) at –78 °C. The mixture was stirred at –78 °C for a further 3 h and then slowly allowed to warm to r.t. The mixture was then quenched with crushed ice and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 1:9) gave **16** (11.09 g, 80%) as a pale yellow syrup.

$[\alpha]_D^{25}$ –4.5 (*c* 1, $CHCl_3$).

IR (neat): 2987, 2932, 2860, 1466, 1374, 1251, 1142, 1251, 1087, 991, 926, 835 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.69 (m, 1 H), 5.27 (d, *J* = 17.4 Hz, 1 H), 5.13 (d, *J* = 9.8 Hz, 1 H), 4.21 (t, *J* = 6.8 Hz, 2 H), 3.68–3.63 (m 2 H), 1.33 (s, 6 H), 0.83 (s, 9 H), 0.01 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.7, 118.0, 109.2, 81.2, 79.3, 62.2, 27.0, 26.0, 19.0, 18.5, –5.4.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{14}H_{28}NaO_3Si$ 298.4476; found: 298.4473.

(3*R*,4*R*)-5-(*tert*-Butyldimethylsiloxy)-3,4-(isopropylidenedioxy)pentan-1-ol (17)

Solid 9-BBN dimer (8.95 g, 36.7 mmol) in anhyd THF (100 mL) was stirred at 0 °C for 1 h. Then a soln of **16** (10 g, 36.7 mmol) in anhyd THF (50 mL) was added to the mixture slowly at 0 °C and was stirred for 1 h. The mixture was warmed to r.t. and stirred overnight. The mixture was cooled to 0 °C and 20% NaOH soln (36 mL), followed by aq 30% H_2O_2 soln (36 mL) were added and the mixture was stirred at r.t. for a further 12 h. When the reaction was complete, the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were dried (anhyd Na_2SO_4) and the solvent was evaporated. Purification of the crude product by column chromatography (silica gel, EtOAc–hexane, 2:8) afforded **17** (7.45 g, 70%) as a colorless liquid.

$[\alpha]_D^{25}$ –3.2 (c 0.71, CH_2Cl_2).

IR (neat): 3450, 2930, 2859, 1728, 1250, 1072, 830 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.75 (d, *J* = 1.5 Hz, 1 H), 4.04–3.96 (m, 1 H), 3.80–3.72 (m, 2 H), 3.67–3.53 (m, 3 H), 2.01–1.90 (m, 1 H), 1.85–1.72 (m, 1 H), 1.45 (s, 3 H), 1.40 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.8, 80.7, 78.6, 63.6, 60.8, 35.5, 27.2, 26.8, 25.8, 18.3, –5.5.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{14}H_{30}NaO_4Si$: 313.4623; found: 313.4632.

(2*R*,3*R*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)pentane (18)

To a soln of 60% NaH in mineral oil (1.15 g, 48 mmol) in anhyd THF (100 mL) was added alcohol **17** (7 g, 24.1 mmol) dissolved in anhyd THF (100 mL) at 0 °C and stirring was continued for 20 min. BnBr (2.88 mL, 24.1 mmol) was added very slowly and stirring was continued at r.t. for a further 2 h. The reaction was quenched with sat. NH_4Cl (40 mL) and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification of the crude product by column chromatography (silica gel, 40% EtOAc–hexane) afforded **18** (8.24 g, 90%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +12.0 (*c* 1, $CHCl_3$).

IR (neat): 3447, 2930, 2859, 1633, 1461, 1370, 1251, 1091, 838, 777, 737, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 4 H), 7.24–7.18 (m, 1 H), 4.49 (s, 2 H), 4.01–3.93 (m, 1 H), 3.75–3.52 (m, 5 H), 2.15 (s, 6 H), 2.01–1.89 (m, 1 H), 1.85–1.71 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 128.4, 127.6, 108.7, 81.2, 75.8, 72.9, 67.2, 63.5, 33.63, 27.3, 27.0, 25.9.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{21}H_{36}O_4SiNa$: 403.2280; found: 403.2294.

(2*R*,3*R*)-5-(Benzyloxy)-2,3-(isopropylidenedioxy)pentan-1-ol (19)

To a well-stirred soln of **18** (8 g, 21.5 mmol) in anhyd THF (100 mL) was added 1 M TBAF (25.8 mL, 25.8 mmol) dropwise at 0 °C and stirring was continued for 1 h. The reaction was quenched with ice flakes, allowed to warm to r.t. and concentrated under reduced pressure. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Purification by column chromatography (silica gel, 60–120 mesh, 15% EtOAc–hexane) afforded pure **19** (5.37 g, 94%) as a colorless liquid.

$[\alpha]_D^{25}$ +17.6 (*c* 1, $CHCl_3$).

IR (neat): 3441, 2930, 1634, 1465, 1374, 1252, 1084, 838, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 4.50 (s, 2 H), 4.03–3.94 (m, 1 H), 3.78–3.70 (m, 2 H), 3.65–3.51 (m, 3 H), 1.92–1.84 (m, 2 H), 1.37 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 128.4, 127.6, 108.6, 81.3, 74.8, 73.1, 67.0, 61.9, 33.2, 27.2, 27.0.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{15}H_{22}NaO_4Si$: 289.1415; found: 289.1420.

(2*R*,3*R*)-5-(Benzyloxy)-2,3-(isopropylidenedioxy)-1-phenylpentan-1-ol (20)

To a stirred soln of oxalyl chloride (2.1 mL, 24.5 mmol) in anhyd CH_2Cl_2 (40 mL) was added dropwise DMSO (2.3 mL, 32.1 mmol) in anhyd CH_2Cl_2 (20 mL) at –78 °C. The mixture was stirred at this temperature for 15 min. To this mixture was added dropwise a soln of alcohol **19** (5 g, 18.9 mmol) in anhyd CH_2Cl_2 (30 mL) and stirring was continued at –78 °C for a further 1 h. The reaction mixture was quenched by addition of Et_3N (15.7 mL, 113.4 mmol) at –78 °C, then was allowed to warm to r.t. and stirring was continued for 40 min. After addition of H_2O (100 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulted crude aldehyde was directly used for next reaction.

The suspension of PhMgBr was generated in situ using Mg turnings (0.95 g, 39 mmol) with PhBr (2.78 mL, 26 mmol) in anhyd THF at r.t. under N_2. The soln of aldehyde (4.0 g, 13.0 mmol) in THF (15 mL) was then added slowly at –78 °C under an inert atmosphere and stirring was continued for 2 h. The mixture was warmed to r.t. and stirring was continued a further 12 h. The reaction was quenched with sat. NH_4Cl (25 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Purification by column chromatography (silica gel, EtOAc–hexane, 2:8) gave **20** (4.49 g, 70%) as a brown colorless oil.

IR (neat): 3434, 2924, 2855, 1718, 1603, 1492, 1455, 1377, 1205, 1074, 889, 755 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.22 (m, 10 H), 4.58–4.53 (m, 1 H), 4.53 (s, 2 H), 3.93–3.70 (m, 1 H), 3.68–3.55 (m, 2 H), 3.30–3.20 (m, 1 H), 2.85 (d, *J* = 9.0 Hz, 1 H), 2.20–1.92 (m, 1 H), 1.90–1.76 (m, 1 H), 1.56 (s, 3 H), 1.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3, 137.5, 128.3, 127.7, 127.4, 127.1, 98.8, 73.0, 72.5, 66.6, 34.1, 29.6.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{21}H_{26}NaO_4$: 365.1728; found: 365.1731.

(1*R*,2*R*,3*R*)-5-(Benzyloxy)-2,3-(isopropylidenedioxy)-1-phenylpentan-1-ol (9)

To a stirred soln of IBX (4.6 g, 16.4 mmol) in DMSO (2.33 mL, 32.8 mmol) at r.t. was added dropwise alcohol **20** (3.0 g, 8.21 mmol) in anhyd CH_2Cl_2 (50 mL). The mixture was kept at reflux at 180–200 °C for 12 h. The mixture was cooled to r.t. and extract with Et_2O (3 × 100 mL) and filtered through a Celite pad. The filtrate was washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Purification of the crude product by flash column chromatography (silica gel, EtOAc–hexane, 4:6) yielded the pure ketone (2 g, 67%) as colorless oil that was used directly for next reaction.

A soln of ketone (2.0 g, 7.25 mmol) in THF (20 mL) under N_2 was cooled to –20 °C and 2 M $Zn(BH_4)_2$ in THF (2.8 mL, 5.45 mmol) was added slowly over a 10-min period. The mixture was stirred at this temperature for 12 h and then the reaction was quenched by addition of sat. aq NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and the solvent removed. Purification of the crude product by column chromatography (silica gel, EtOAc–hexane, 1:9) gave **9** (1.71 g, 85%) as a colorless oil.

Acknowledgment

V.H.K, A.S.L., and R.S. thank to CSIR, New Delhi for the award of fellowships.

References

(1) (a) El-Zayat, A. A. E.; Ferringi, N. R.; McCloud, T. G.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M.; Chang, C.-J.; McLaughlin, J. L. *Tetrahedron Lett.* **1987**, *26*, 955. (b) Sam, T. W.; Chew, S. Y.; Matsjeh, S.; Gan, E. K.; Razak, D.; Mohamed, A. L. *Tetrahedron Lett.* **1987**, *28*, 2541. (c) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1655. (d) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; Fanwick, P. E.; McLaughlin, J. L. *Tetrahedron* **1991**, *47*, 9751. (e) Fang, X.-P.; Anderson, J. E.; Qiu, X.-X.; Kozlowski, J. F.; Chang, C.-J.; McLaughlin, J. L. *Tetrahedron* **1993**, *49*, 1563.

(2) (a) Gu, Z.-M.; Fang, X.-P.; Zeng, L.; McLaughlin, J. L. *Tetrahedron Lett.* **1994**, *35*, 5367. (b) Fang, X.-P.; Anderson, J. E.; Smith, D. L.; Wood, K. V.; McLaughlin, J. L. *J. Nat. Prod.* **1992**, *55*, 1655.

(3) (a) Mu, Q.; Tang, W. D.; Liu, R. Y.; Li, C. M.; Lou, L. G.; Sun, H. D. *Planta Med.* **2003**, *69*, 826. (b) Pihie, A. H.; Stanslas, J.; Din, L. B. *Anticancer Res.* **1998**, *18*, 1739.

(4) Mu, Q.; Tang, W.; Li, C.; Lu, Y.; Sun, H.; Zheng, H.; Hoa, X.; Zheng, Q.; Wu, N.; Lou, L.; Xu, B. *Heterocycles* **1999**, *51*, 2969.

(5) Mu, Q.; Li, C. M.; He, Y. N.; Sun, H. D.; Zheng, H. L.; Lu, Y.; Zheng, Q. T.; Jiang, R. W. *Chin. Chem. Lett.* **1999**, *10*, 135.

(6) (a) Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Prog. Chem. Org. Nat. Prod.* **1997**, 181. (b) Talapatra, S. K.; Basu, D.; Deb, T.; Goswami, S.; Talapatra, B. *Indian J. Chem., Sect. B* **1985**, *24*, 29. (c) Alkofahi, A.; Ma, W. W.; Mckenzie, A. T.; Byrn, S. R.; Mclaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 1371. (d) Tsubuki, M.; Kanai, K.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1640. (e) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493.

(7) (a) Yadav, J. S.; Rao, B. M.; Rao, K. S.; Reddy, B. V. S. *Synlett* **2008**, 1039. (b) Yadav, J. S.; Reddy, P. M. K.; Reddy, P. V. *Tetrahedron Lett.* **2007**, *46*, 1037. (c) Yadav, J. S.; Rao, K. V.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 3773. (d) Yadav, J. S.; Srinivas, R.; Sathaiah, K. *Tetrahedron Lett.* **2006**, *47*, 1603. (e) Yadav, J. S.; Raju, A. K.; Rao, P. P.; Rajaiah, G. *Tetrahedron: Asymmetry* **2005**, *16*, 3283.

(8) Yadav, J. S.; Ramreddy, N.; Harikrishna, V.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 1318.

(9) (a) Bates, E. B.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1854. (b) Eguchi, T.; Koudate, T.; Kakinuma, K. *Tetrahedron* **1993**, *49*, 4527.

(10) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420.

(11) (a) Yadav, J. S.; Ramreddy, N.; Harikrishna, V.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 1318. (b) Yadav, J. S.; Chandrasekhar, S.; Sumitra, G.; Rajashekar, K. *Tetrahedron Lett.* **1996**, *37*, 6603.

(12) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934. (c) Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599.

(13) Suemune, H.; Oda, K.; Saeki, S.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 172.

(14) (a) De Brabander, J.; Vandewalle, M. *Synthesis* **1994**, 855. (b) Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040.

(15) (a) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496. (b) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643. (c) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.
(16) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039.
(17) Henry, N.; Robertson, M. N.; Marquez, R. *Tetrahedron Lett.* **2007**, *48*, 6088.
(18) (a) Yadav, J. S.; Rami Reddy, N.; Harikrishna, V.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 1318. (b) Yadav, J. S.; Chander, M. C. *Tetrahedron Lett.* **1990**, *31*, 4349. (c) Jin, Y.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. *J. Org. Chem.* **2003**, *68*, 9012.
(19) (a) Dubost, C.; Marko, I. E.; Ryckmans, T. *Org. Lett.* **2006**, *8*, 5137. (b) Rajesh, K.; Suresh, V.; Paul selvam, J. J.; Chantibabu, D.; Venkateswarlu, Y. *Helv. Chim. Acta* **2010**, *93*, 147.
(20) Gallos, J. K.; Damianous, K. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 5769.
(21) Popsavin, V.; Benedekovic, G.; Sreco, B.; Popsavin, M.; Francuz, J.; Kojic, V.; Bogdanovic, G. *Org. Lett.* **2007**, *9*, 4235.
(22) (a) Ghosh, S.; Nageshwerrao, C.; Dutta, S. *Synlett* **2007**, 1464. (b) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139.