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The first stereoselective and the total synthesis of Leiocarpin C and total synthesis of (+)-Goniodiol

J. S. Yadav *, K. Premalatha, S. J. Harshavardhan, B. V. Subba Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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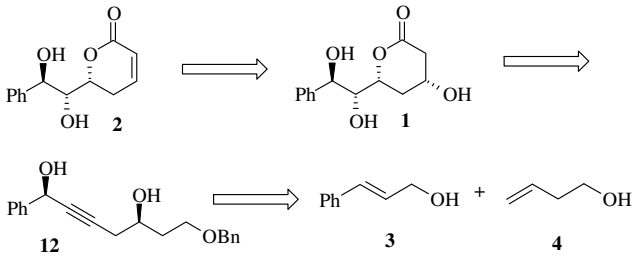
ABSTRACT

The synthesis of the styryl lactone Leiocarpin C has been achieved in a highly stereoselective manner using Jacobsen's kinetic resolution, Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation as key steps. This is the first total synthesis of Leiocarpin C, and thus establishes for the first time the absolute stereochemistry of this natural product.

The genus *Goniothalamus* (Annonaceae) consists of 115 species, spread over the entire tropics and subtropics.[1] Most of the known styryl lactones are isolated from the genus *Goniothalamus*.[2] Styryl lactones are natural heterocyclic compounds with potential cytotoxicity including antitumor, antifungal, and antibiotic properties.[3] Leiocarpin C **(1)** was isolated from the seeds of *Goniothalamus leiocarpus* (Annonaceae), a tropical plant found in the south of Yunnan Province in China.[4] Leiocarpins are found to possess cytotoxic activities against several human tumor cell lines.[5] (+)-Goniodiol **(2)** was isolated from the leaves and twigs of *Goniothalamus sesquipedalis* (Annonaceae) and from the stem bark of *Goniothalamus gigantus* (Annonaceae). It is a potent and a selective cytotoxic compound against human lung carcinoma A-549 (ED_{50} = 0.12 μg mL^{-1}) and p-388 murine leukemia cells (IC_{50} = 4.56 μg mL^{-1}).[6] Consequently, a large number of reports have appeared on the total synthesis of (+)-Goniodiol.[7–9] However, there are no reports on the total synthesis of Leiocarpin C.

In continuation of our program on the total synthesis of bioactive lactones,[10] herein, we report a flexible, stereoselective route for the first total synthesis of Leiocarpin C **(1)** and also for the synthesis of (+)-Goniodiol **(2)**. The retrosynthesis of Leiocarpin C is depicted in Scheme 1.

Sharpless asymmetric epoxidation[11] of cinnamyl alcohol **3** in the presence of D(−)-DET, TBHP, and $Ti(O^iPr)_4$ in dichloromethane gave the desired epoxyalcohol **5** in 82% yield. The epoxyalcohol **5** was converted into epoxychloride[12] **6** in 88% yield using Ph_3P and a catalytic amount of $NaHCO_3$ in refluxing CCl_4. Subsequently,



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

epoxychloride **6** was converted into chiral propargylic alcohol[13] **7** in 72% yield via base-induced ring opening with *n*-BuLi in dry THF. Protection of **7** with TBSCl in the presence of imidazole gave TBS ether **8** in 92% yield.

The commercially available homoallyl alcohol **4** was protected as its benzyl ether, and then treated with *m*-CPBA to afford the racemic epoxide **9** in 86% yield. Kinetic resolution[14] of epoxide **9** with (*S*,*S*)-Jacobsen's catalyst gave the chiral epoxide **10** in 43% yield along with the chiral diol **11** in 43% yield. Regioselective ring opening[15] of chiral epoxide **10** with alkynyl borane prepared in situ at −78 °C in dry THF by reaction of the lithium acetylide of **8** with $BF_3{\cdot}OEt_2$ followed by deprotection of the TBS group using TBAF gave propargylic alcohol **12** in 82% yield. Reduction of propargylic alcohol **12**[16] with $LiAlH_4$ in refluxing THF gave allylic alcohol **13** in 90% yield. Protection of diol **13** as its TBS ether using TBSCl and imidazole in dichloromethane followed by Sharpless asymmetric dihydroxylation[17] using AD mix-β afforded diol in only 20% yield

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J. S. Yadav).

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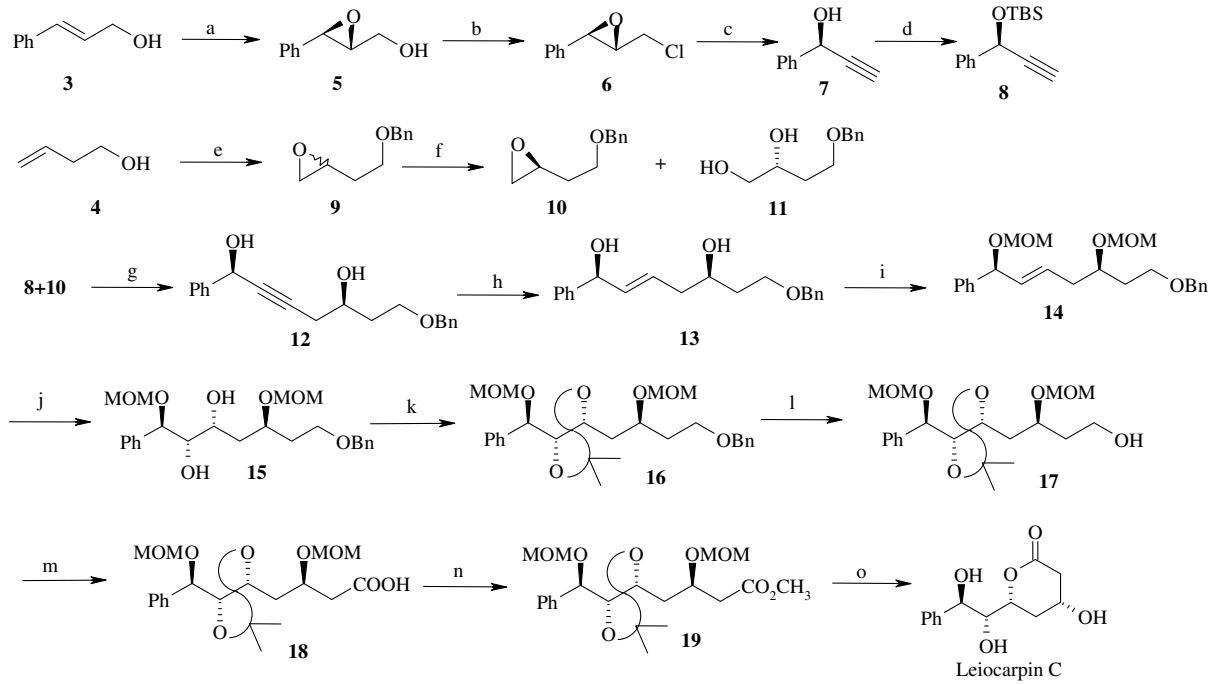
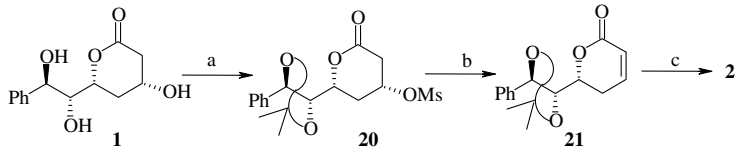


Scheme 2. Reagents and conditions: (a) D(−)-DET, Ti(O^{i}Pr)4, TBHP, CH_2Cl_2, −30 °C, 82%; (b) Ph_3P, CCl_4, $NaHCO_3$ reflux, 88%; (c) *n*-BuLi, THF, 72% (d) TBSCl, Imidazole, CH_2Cl_2, 0 °C to rt 92%; (e) (i) NaH/BnBr, TBAI, THF, 0 °C to rt 92%; (ii) *m*-CPBA, CH_2Cl_2, 0 °C, 86%; (f) (*S*,*S*)-Jacobsen's catalyst, H_2O, rt 43%; (g) (i) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF; (ii) TBAF, THF, 0 °C to rt 82%; (h) $LiAlH_4$, THF, reflux, 90%; (i) MOMCl, Hunig's base, CH_2Cl_2, 0 °C to rt 92%; (j) AD mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C; (k) 2,2-DMP, *p*-TSA, CH_2Cl_2, 90%; (l) DDQ:H2O (9:1), 85%; (m) (i) IBX/DMSO, CH_2Cl_2, 0 °C to rt 70%; (ii) NaH_2PO_4, $NaClO_2$, DMSO, H_2O, 0 °C to rt 85%; (n) CH_2N_2 in ether, 0 °C, 85%; (o) MeOH/*p*-TSA, reflux, 78%.



Scheme 3. Reagents and conditions: (a) (i) 2,2-DMP, *p*-TSA, 85%; (ii) MsCl, Et_3N, CH_2Cl_2, 79%; (b) DBU, CH_2Cl_2, 80%; (c) MeOH/*p*-TSA, rt 75%.

even at 0 °C for 4 days. This maybe due to the steric hindrance of the TBS groups. Therefore, the diol **13** was protected as its MOM ether **14** in 92% yield using Hunig's base and MOMCl in dry dichloromethane, which was then subjected to Sharpless asymmetric dihydroxylation to afford diol **15** in 80% yield (see Scheme 2).

The diol **15** was protected as the corresponding acetonide using 2,2-DMP and a catalytic amount of *p*-TSA to afford **16**. Debenzylation of **16** using DDQ:H_2O[18] gave the primary alcohol **17,** which was oxidized to the corresponding acid **18** by a two-step process.

In the first step, the alcohol was oxidized to an aldehyde using IBX and in the second step, the aldehyde was oxidized to acid[19] **18** using $NaClO_2/NaH_2PO_4$. The resulting acid **18** was converted into ester **19** in 85% yield using diazomethane in ether. Cyclization of **19** was achieved using *p*-TSA in refluxing methanol to afford the target lactone, Leiocarpin C **(1)** in 78% yield. Thus, obtained Leiocarpin C **(1)** was treated with 2,2-DMP in the presence of a catalytic amount of *p*-TSA followed by mesylation of the secondary hydroxyl group using mesyl chloride and triethylamine to afford product **20**. The compound **20** was treated with DBU to furnish **21**. Deprotection of the acetonide in compound **21** using *p*-TSA in MeOH gave (+)-Goniodiol **2** (Scheme 3).

Leiocarpin C **(1)** exist as colorless needles, optical rotation $[\alpha]_D^{20}$ −63.2 (*c* 0.5, CH_3OH). (+)-Goniodiol **2** is a colorless liquid, optical rotation $[\alpha]_D^{20}$ +72.2 (*c* 0.68, $CHCl_3$). The spectroscopic analyses and optical rotation values were in accordance with the data reported in the literature.[20]

In conclusion, the first total synthesis of Leiocarpin C has been achieved in a highly stereoselective manner involving Jacobsen's kinetic resolution, Sharpless asymmetric epoxidation, regioselective ring opening of a chiral epoxide by an alkynyl borane and Sharpless asymmetric dihydroxylation. This synthetic sequence provides an easy access to the preparation of styryl lactones of biological importance.

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20. *Spectral data of selected compounds*: *(1S,5R)-7-(benzyloxy)-1-phenylhept-2-yne-1,5-diol* **(12)**: $[\alpha]_D^{20}$ +2.9 (*c* 0.90, $CHCl_3$); IR (neat): *v* 3421, 2923, 2180, 1453, 1079, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.48 (m, 2H) 7.38–7.25 (m, 8H), 5.39 (s, 1H), 4.50 (s, 2H), 4.01–3.94 (m, 1H), 3.71–3.60 (m, 2H), 2.46 (d, *J* = 2.5 Hz, 2H), 1.89–1.80 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.5, 137.8, 129.0, 128.5, 127.5, 127.2, 84.2, 82.6, 74.2, 70.5, 68.9, 64.5, 35.8, 28.2. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}O_3Na$: 333.1466, Found: 333.1469. *(1S,2E,5R)-7-(benzyloxy)-1,5-bis (methoxymethyl)-1-phenylhept-2-ene*[12] (**14**): $[\alpha]_D^{20}$ −4.5 (*c* 1.02, $CHCl_3$); IR (neat): *v* 3095, 2850, 1630, 1250, 1100, 896 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.21 (m, 10H), 5.83–5.52 (m, 2H), 5.01 (d, *J* = 7.0 Hz, 1H), 4.57–4.51 (m, 4H), 4.50 (s, 2H), 3.80–3.72 (m, 1H), 3.56–3.45 (m, 2H), 3.27 (d, *J* = 6.2 Hz, 6H) 2.22–2.19 (m, 2H), 1.89–1.80 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.9, 138.2, 132.9, 129.0, 128.5, 127.5, 127.0, 95.2, 93.2, 78.1, 74.3, 73.0, 66.8, 55.5, 38.2, 34.6. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{32}O_5Na$: 423.2147, Found: 423.2150. *(4R,5R)-4-[(2S)-4-(benzyloxy)-2-methoxymethyl)butyl]-5-[(R)methoxymethyl)-1-(phenyl)methyl]-2,2-dimethyl-1,3-dioxalane* (**16**): $[\alpha]_D^{20}$ −49.6 (*c* 0.75, $CHCl_3$); IR (neat): *v* 2925, 2885, 1170, 1050, 915, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.25 (m, 10H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.57 (s, 2H), 4.51 (s, 2H), 4.45 (s, 2H), 4.12 (t, *J* = 7.3 Hz, 1H), 3.89–3.83 (m, 1H), 3.77–3.72 (m, 1H), 3.51–3.44 (m, 2H), 3.34 (s, 3H), 3.30 (s, 3H), 1.83–1.76 (m, 2H), 1.69–1.49 (m, 2H), 1.32 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.5, 138.2, 129.0, 128.5, 128.2, 127.5, 126.2, 109.2, 95.2, 93.0, 82.1, 74.5, 73.2, 71.5, 66.8, 62.8, 55.6, 38.2, 34.5, 30.5. HRMS (ESI-MS): calcd for $C_{27}H_{38}O_7Na$: 497.2515. Found: 497.2526. *(4S,6R)-6-[(1R,2R)-1,2-dihydroxy-2-phenylethyl]-4-hydroxy-tetrahydro-2H-2-pyranone (Leiocarpin C)* (**1**): $[\alpha]_D^{20}$ −63.2 (*c* 0.5, CH_3OH); IR (KBr): *v* 3450, 3180, 2885, 1720, 1460, 1150, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.38–7.21 (m, 5H), 5.42 (d, *J* = 5.8 Hz, 1H), 4.77 (dd, *J* = 5.8, 2.4 Hz, 1H), 4.45–4.40 (m, 1H), 4.35 (dt, *J* = 7.0, 3.2 Hz, 1H), 3.35 (dd, *J* = 14.8, 7.2 Hz, 2H), 2.38 (t, *J* = 4.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 141.2, 129.2, 128.4, 127.3, 74.5 70.05, 68.8, 67.9, 41.5, 38.1. HRMS (ESI): calcd for $C_{13}H_{16}O_5Na$: 275.0895, Found: 275.0895. *(6R)-6-[(1R,2R)-1,2-dihydroxy-2-phenylethyl]-5,6-dihydro-2H-pyran-2-one; [(+)-Goniodiol]* (**2**): $[\alpha]_D^{20}$ +72.2 (*c* 0.68, $CHCl_3$). IR (neat): *v* 3451, 2986, 1730, 1645, 1440, 1375, 1210, 1058 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.75 (m, 5H), 6.82 (ddd, *J* = 9.5, 5.9, 2.9 Hz, 1H), 5.86 (dd, *J* = 9.6, 2.7 Hz, 1H), 5.32 (d, *J* = 3.7 Hz, 1H), 4.70 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.30 (dt, *J* = 12.5, 3.8 Hz, 1H), 2.18–2.60 (m, 2H). ^{13}C NMR (75 MHz $CDCl_3$): δ 29.6, 75.1, 78.4, 120.8, 126.4, 128.1, 129.3, 140.3, 145.8, 164.0. HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{14}O_4$: 235.0970. Found: 235.0968.