Stereoselective Total Synthesis of (–)-9-Deoxygoniopypyrone

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Abstract: Stereoselective synthesis of (–)-9-deoxygoniopypyrone was achieved from the naturally occurring L-(+)-tartaric acid. Key step involves the elaboration of a γ-hydroxybutyramide to the title compound involving high-yielding stereoselective transformations.

Key words: styryllactone, (–)-9-deoxygoniopypyrone, stereoselective reduction, tartaric acid

Trees of genus *Goniothalamus* of the plant family *Annonaceae* have been known for a long time as a source of potent biologically active styryllactones.[1] The extracts and leaves from these plants have traditionally been used in folk medicine to treat various ailments. The research group of McLaughlin isolated a series of styryllactones, possessing marginal to significant cytotoxic, antitumour, pesticidal, ratogenic and embryotoxic activities. These styryllactones can be mainly classified into two groups, on the basis of the size of the lactone ring. Amongst the group comprising the six-membered lactones, 9-deoxygoniopypyrone (**1**), goniopypyrone (**2**), and goniodiol (**3**) (Figure 1), isolated from the ethanol extract of the stem bark of *Goniothalamus* giganteus showed considerable antitumor activity.[2] The unique structural feature and the associated bioactivity made lactone **1** an interesting synthetic target.

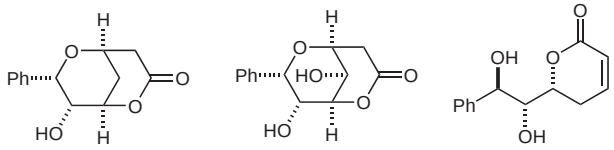
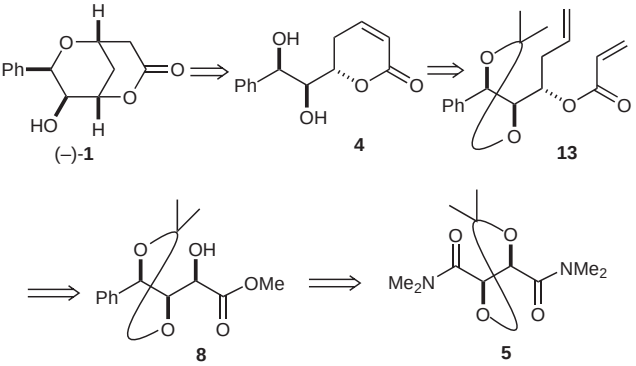


Figure 1 Cytotoxic styryllactones isolated from *Goniothalamus* giganteus

Asymmetric hetero-Diels–Alder reaction,[3a] asymmetric allylation[3b] and asymmetric dihydroxylation[3c] were employed as key reactions in the recent syntheses of 9-deoxygoniopypyrone. Syntheses starting from abundant chiral compounds such as, glyceraldehyde and mandelic acid have also been reported.[3d,e] As part of our program involving the asymmetric synthesis of styryllactones, we recently accomplished the total synthesis of 7-*epi*-goniofufurone and goniothalesdiol from tartaric acid.[4] In continuation of our efforts, herein we report a facile and high-yielding total synthesis of *ent*-9-deoxygoniopypyrone.

Our approach for the synthesis of (–)-9-deoxygoniopypyrone is based on the cyclization of diol **4**, which can be obtained from the acryloyl ester **13** by a ring-closing metathesis reaction. Synthesis of the ester **13** was anticipated from the elaboration of the α-hydroxy ester **8**. Bis-dimethylamide **5** derived from L-(+)-tartaric acid was envisaged as the starting point for the synthesis of **8** (Scheme 1).



Scheme 1 Retrosynthesis for (–)-9-deoxygoniopypyrone

The synthetic sequence commenced with the known γ-hydroxybutyramide **6**, readily obtained from the bis-dimethylamide **5**, derived from tartaric acid employing a combination of selective Grignard addition and a stereoselective reduction.[4a]

Deprotection of acetonide with concomitant hydrolysis of the amide to the methyl ester within **6** was achieved in refluxing MeOH–benzene with *p*-toluenesulfonic acid to afford the trihydroxy ester **7** in 88% yield.[5] Treatment of the trihydroxy ester **7** with 2,2-dimethoxypropane resulted in the α-hydroxy ester **8** in 96% yield (Scheme 2).

The free hydroxyl group in **8** was protected as the corresponding *tert*-butyldimethylsilyl ether **9** using the standard conditions. Reduction of the ester **9** with DIBAL-H furnished the alcohol **10** in almost quantitative yield. Conversion of the alcohol **10** to the corresponding tosylate, followed by deprotection of the silyl group with TBAF produced the epoxide **11** in 95% yield. Reaction of the epoxide **11** with vinylmagnesium bromide in the presence of CuI afforded the homoallylic alcohol **12**, which on reaction with acryloyl chloride resulted in the ester **13** in 75% yield. Ring-closing metathesis (RCM) of **13** with Grubbs' first-generation catalyst yielded the lactone **14** in 52%

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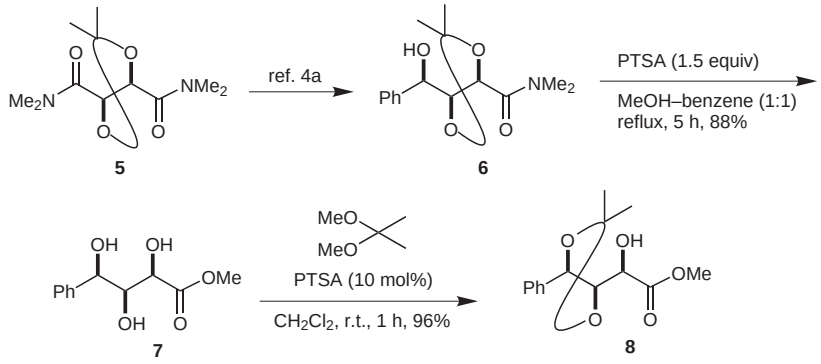
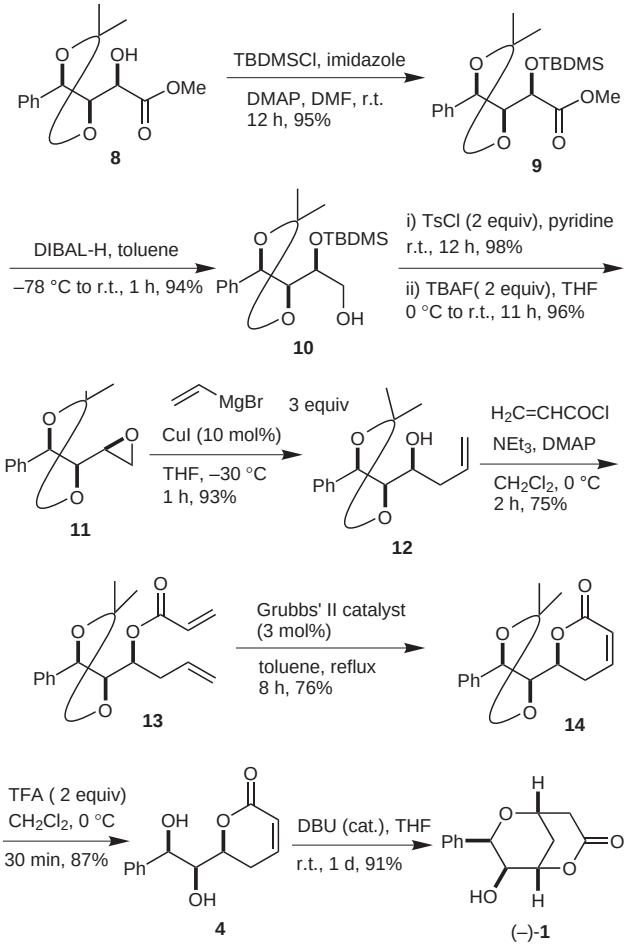


Scheme 2 Synthesis of methyl-α,β,γ-trihydroxy-γ-phenylbutyrate

yield, while employing Grubbs' second-generation catalyst afforded the lactone in 76% yield.[6] Deprotection of the acetonide group in **14** afforded the diol **4**, {$[\alpha]_D^{25}$ +12.9 (*c* = 0.7, $CHCl_3$); lit.[2] $[\alpha]_D^{25}$ –13.7 (*c* = 0.7, $CHCl_3$)}, which on treatment with DBU furnished *ent*-9-deoxygoniopypyrone (**1**), {$[\alpha]_D^{25}$ –12 (*c* = 0.5, EtOH); lit[3d] $[\alpha]_D^{25}$ +12 (*c* = 0.1, EtOH for the enantiomer)} in 91% yield (Scheme 3).[7]



Scheme 3 Synthesis of (–)-9-deoxygoniopypyrone

In summary, (–)-9-deoxygoniopypyrone was prepared in 30% overall yield from γ-hydroxybutyramide **6**, readily obtained from tartaric acid dimethylamide. Further application of this strategy in the synthesis of other styryllactones is underway.

Acknowledgment

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References and Notes

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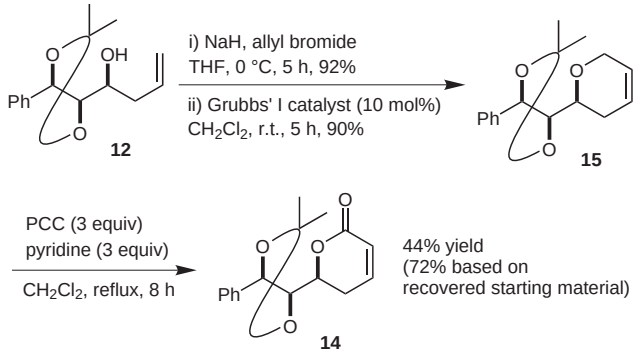
(5) For the synthesis of α,β-dihydroxy-γ-alkyl(aryl)-γ-butyrolactones from γ-hydroxybutyramides, see: Prasad, K. R.; Chandrakumar, A. *Tetrahedron* **2007**, *63*, 1798.

(6) To circumvent the use of expensive Grubbs' second-generation catalyst in the synthesis of lactone **14**, an alternate route for **14** from alcohol **12** was examined. As shown below (Scheme 4), homoallylic alcohol **12** was protected as its allyl ether, which underwent smooth RCM reaction with Grubbs' first generation catalyst to yield the dihydropyran **15** in 90% yield. PCC oxidation of the dihydropyran **15** resulted in the lactone **14** in 44% yield (72% based on recovered starting material).



Scheme 4

(7) All new compounds exhibited satisfactory spectral data. Compound **8**: $[\alpha]_D^{25}$ –44.0 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.48 (m, 5 H), 5.12 (d, *J* = 8.4 Hz, 1 H), 4.11 (d, *J* = 8.4 Hz, 1 H), 4.04 (dd, *J* = 0.9, 8.4 Hz, 1 H), 3.74 (s, 3 H), 3.25 (dd, *J* = 1.8, 9.0 Hz, 1 H, OH, exchangeable with D_2O), 1.55 (s, 3 H), 1.50 (s, 3 H). ^{13}C NMR (75 MHz): δ = 172.7, 136.9, 128.6, 128.4, 126.6, 109.8, 83.6, 78.4, 67.6, 52.6, 27.1, 26.5. HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{18}O_5$: 289.1054; found: 289.1052. Compound **12**: $[\alpha]_D^{25}$ –18.9 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.44 (m, 5 H), 5.68–5.84 (m, 1 H), 4.94–5.07 (m, 3 H), 3.76 (ddd, *J* = 1.2, 2.4, 8.4 Hz, 1 H), 3.58–3.68 (m, 1 H), 2.13–2.35 (m, 3 H), 1.58 (s, 3 H), 1.53 (s, 3 H). ^{13}C NMR (75 MHz): δ = 137.6, 134.2, 128.6, 128.3, 126.9, 117.8, 109.2, 84.9, 79.3, 68.0, 39.6, 27.2, 27.0. HRMS: *m*/*z* [M + Na] calcd for $C_{15}H_{20}O_3$: 271.1312; found: 271.1310. Compound **14**: $[\alpha]_D^{25}$ –5.0 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.46 (m, 5 H), 6.87 (ddd, *J* = 2.5, 5.9, 9.6 Hz, 1 H), 6.04 (dd, *J* = 2.5, 9.6 Hz, 1 H), 5.24 (d, *J* = 8.6 Hz, 1 H), 4.42 (ddd, *J* = 2.5, 4.2, 11.7 Hz, 1 H), 3.82 (dd, *J* = 2.0, 8.6 Hz, 1 H), 2.63–2.75 (m, 1 H), 2.20–2.30 (m, 1 H), 1.59 (s, 3 H), 1.55 (s, 3 H). ^{13}C NMR (100 MHz): δ = 163.6, 144.8, 137.1, 128.8, 128.6, 126.8, 121.2, 110.0, 83.9, 77.5, 73.5, 27.3, 26.7, 26.6. HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{18}O_4$: 297.1105; found: 297.1103.