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Facile stereoselective syntheses of goniodiol, 8-*epi*-goniodiol and 9-deoxygoniopypyrone

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Abstract—Stereoselective syntheses of the bio-active styryllactones goniodiol and 9-deoxygoniopypyrone were accomplished from D-(−)-tartaric acid. The key step involves the elaboration of a γ-hydroxy butyramide to the styryllactones via high yielding stereoselective transformations.

Trees belonging to the genus *Goniothalamus* grown in several parts of South East Asia have been the source of a number of bio-active styryllactones.[1] Goniodiol **1**, is a styryldihydropyrone isolated from the species *Goniothalamus sesquipedalis*, a shrub growing abundantly in the hilly regions of the North Eastern Indian state of Manipur.[2] It has been shown that goniodiol **1**, exhibits potent and selective cytotoxic activity against A-549 human lung carcinoma.[3] The structurally similar lactones, 8-*epi*-goniodiol **2**, 6-*epi*-goniodiol **3** and the recently isolated 7-*epi*-goniodiol **4**,[4] serve as precursors for the synthesis of other bio-active styryllactones such as 9-deoxygoniopypyrone **5** and leiocarpin A **6** (Fig. 1).

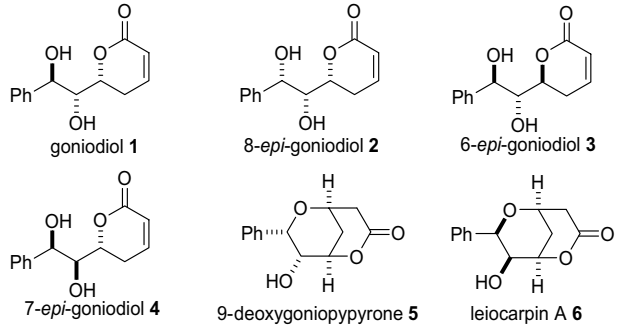

Figure 1. Bio-active styryllactones.

Consequently, **1** and its derivatives have attracted considerable interest and have been synthesized by several groups. Notable syntheses include the use of chiral glycidol, 2,3-isopropylidenedioxy glyceraldehyde, mandelic acid, chiral boron reagents, chiral chromium arene complexes, Sharpless asymmetric epoxidation as well as chemoenzymatic synthesis.[5] Our interest in the synthesis of natural products from chiral pool tartaric acid has resulted in the synthesis of a number of bio-active pheromones and styryllactones.[6] Herein, we report facile syntheses of goniodiol **1**, 8-*epi*-goniodiol **2** and 9-deoxygoniopypyrone **5** from D-(−)-tartaric acid.

Our approach for the synthesis of **1** and **2** is based on the formation of the lactone through an oxidative cyclization of triols **7** and **8** comprising an alkene tether. Synthesis of triols **7** and **8** was anticipated from **9**, the formation of which was envisaged via the deoxygenation of ketone **10**. γ-Hydroxybutyramide **11** derived from the dimethylamide **12** was identified as the precursor for the synthesis of **10** (Scheme 1).

Thus, γ-hydroxybutyramide **11** was synthesized from dimethylamide **12**, utilizing a sequence of selective Grignard addition and stereoselective reduction as previously reported by us.[6a] Protection of the free hydroxy group in **11** as the silyl ether followed by the addition of 3-butenylmagnesium bromide afforded ketone **10** in 91% yield for two steps. Reduction of **10** with $NaBH_4$ resulted in a diastereomeric mixture (dr 64:36) of alcohols **13**.[7] Since deoxygenation of alcohol **13** was planned in the next step, no effort was made to separate the diastereomers. Alcohol **13** was converted

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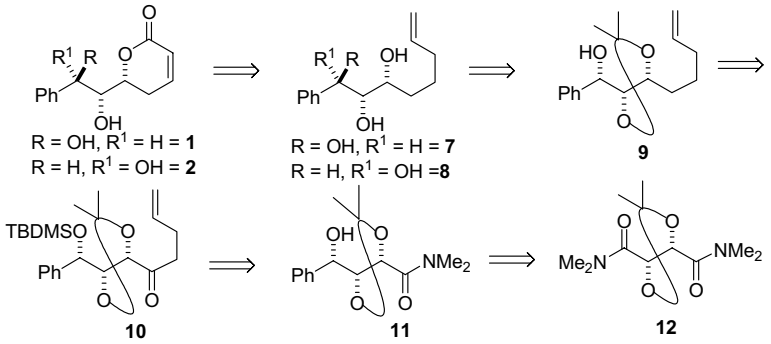
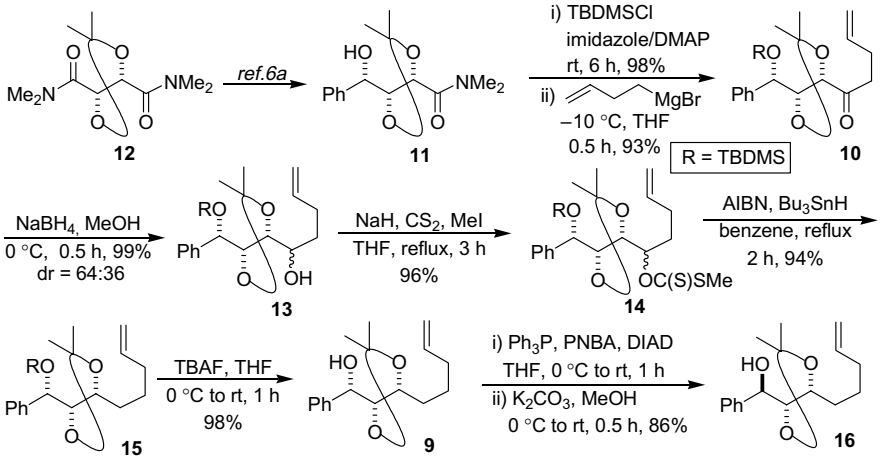


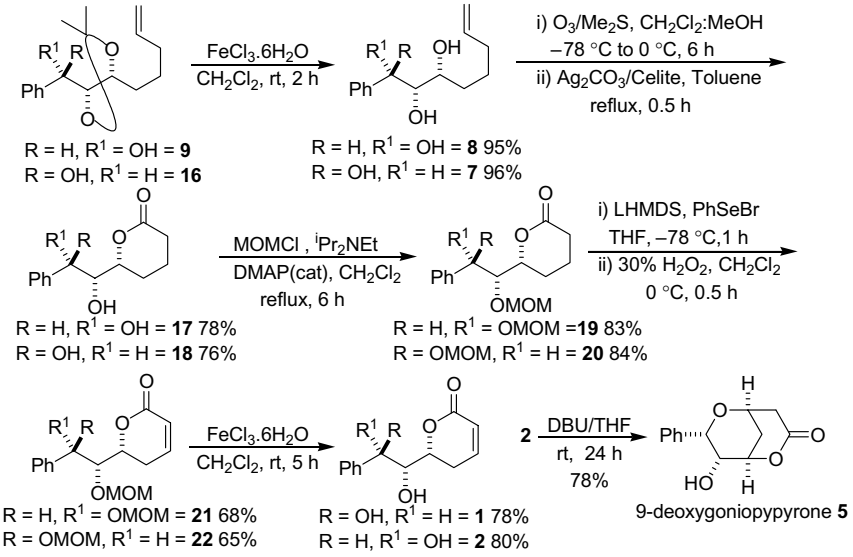
Scheme 1. Retrosynthesis of goniodiol **1** and 8-*epi*-goniodiol **2**.

to the corresponding xanthate **14**, which on subsequent reaction with Bu_3SnH furnished the deoxygenated product **15** in 94% yield. Reaction of **15** with tetrabutylammonium fluoride (TBAF) produced the free alcohol **9** and Mitsunobu inversion of the free alcohol in **9** gave **16** in 86% yield (Scheme 2).

Deprotection of acetonides in **9** and **16**, with $FeCl_3 \cdot 6H_2O$ resulted in triols **8** and **7**. Ozonolysis of **8** and **7**, and subsequent oxidation of the resulting lactols with silver carbonate,[8] gave lactones **17** and **18** in 78% and 76% yields, respectively, for the two steps. The free hydroxyl groups in **17** and **18** were protected as the



Scheme 2. Stereoselective synthesis of masked triols **9** and **16**.



Scheme 3. Synthesis of goniodiol **1**, and 8-*epi*-goniodiol **2**, and 9-deoxygoniopypyrone **5**.

corresponding methoxymethyl (MOM) ethers **19** and **20** using standard conditions. Selenation and deselenation of lactones **19** and **20** resulted in α,β-unsaturated lactones **21** and **22**. Deprotection of the MOM ethers in **22** and **21** with $FeCl_3{\cdot}6H_2O$ afforded goniodiol **1** and 8-*epi*-goniodiol **2**, respectively, in 78% and 80% yields, the spectral and physical data of which were consistent with that reported in the literature.[9] Treatment of **2** with DBU furnished 9-deoxygoniopypyrone in 78% yield[5j] (Scheme 3).

In summary, a facile synthesis of the cytotoxic styryllactones goniodiol and 9-deoxygoniopypyrone was accomplished starting from D-(−)-tartaric acid. The synthetic sequence en route to the title compound is highly diastereoselective with good overall yields (20% for 8-*epi*-goniodiol and 17% for goniodiol from the dimethylamide **12**) and is amenable for the synthesis of similar natural products and their analogues.

Acknowledgements

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9. Selected spectral data: Compound **9**: $[\alpha]_D$ +40.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 5.65 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 4.96–4.84 (m, 2H), 4.58 (d, $J = 5.7$ Hz, 1H), 3.93–3.68 (m, 2H), 2.83 (br s, 1H), 1.94–1.81 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H) 1.40–1.12 (m, 2H), 1.04–0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.3, 128.6, 128.4, 126.9, 114.6, 109.0, 84.3, 77.8, 75.4, 33.3, 32.5, 27.5, 27.2, 24.9; HRMS for $C_{17}H_{24}O_3$+Na calcd 299.1625; found 299.1623. Compound **17**: $[\alpha]_D$ −82.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.21 (m, 5H), 4.91 (d, $J = 7.5$ Hz, 1H), 4.04 (d, $J = 11.1$ Hz, 1H), 3.96 (br s, 1H), 3.82 (br s, 1H), 3.59 (d, $J = 6.9$ Hz, 1H), 2.63–2.28 (m, 2H), 2.05–1.79 (m, 2H) 1.77–1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 140.3, 128.5, 128.0, 127.0, 79.4, 77.2, 74.1, 29.6, 24.2, 18.2; HRMS for $C_{13}H_{16}O_4$+Na calcd 259.0948; found 259.0946. Compound **18**: $[\alpha]_D$ −93.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.22 (m, 5H), 4.87 (d, $J = 7.2$ Hz, 1H), 4.67–4.60 (m, 1H), 3.65 (d, $J = 6.9$ Hz, 1H), 3.14 (br s, 1H), 2.66–2.33 (m, 3H), 2.08–1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 141.1, 128.5, 127.9, 126.7, 79.1, 75.7, 73.6, 29.5, 24.2, 18.3; HRMS for $C_{13}H_{16}O_4$+Na calcd 259.0948; found 259.0946. Compound **21**: $[\alpha]_D$ +42.9 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.24 (m, 5H), 6.86 (ddd, $J = 9.6$, 6.3, 2.4 Hz, 1H), 5.94 (ddd, $J = 9.6$, 3.0, 0.9 Hz, 1H), 5.07 (d, $J = 7.2$ Hz, 1H), 4.96 (d, $J = 6.9$ Hz, 1H), 4.79 (d, $J = 6.9$ Hz, 1H), 4.58 (d, $J = 6.6$ Hz, 1H), 4.52 (d, $J = 6.6$ Hz, 1H), 4.14 (dt, $J = 6.9$, 3.3 Hz, 1H), 3.80 (dd, $J = 7.2$, 3.3 Hz, 1H) 3.37 (s, 3H), 3.32 (s, 3H), 2.83 (ddt, $J = 18.3$, 12.0, 2.7 Hz, 1H), 2.22 (dddd, $J = 18.3$, 6.6, 3.9, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 145.4, 138.0, 128.7, 128.3, 127.7, 120.9, 98.8, 94.5, 80.9, 78.4, 76.9, 56.5, 55.8, 26.0; HRMS for $C_{17}H_{22}O_6$+Na calcd 345.1316; found 345.1314. Compound **22**: $[\alpha]_D$ −45.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.21 (m, 5H), 6.95 (ddd, $J = 9.6$, 6.3, 2.4 Hz, 1H), 6.03 (ddd, $J = 9.6$, 2.7, 0.9 Hz, 1H), 4.98 (ddd, $J = 12.6$, 3.6, 2.4 Hz, 1H), 4.94 (d, $J = 8.4$ Hz, 1H), 4.62–4.51 (m, 2H), 4.17 (d, $J = 6.9$ Hz, 1H), 3.82 (d, $J = 6.9$ Hz, 1H), 3.72 (dd, $J = 8.4$, 2.1 Hz, 1H), 3.33 (s, 3H), 3.16 (s, 3H), 2.75 (ddt, $J = 18.6$, 12.6, 2.7 Hz, 1H), 2.28 (dddd, $J = 18.6$, 6.0, 3.9, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 145.6, 138.7, 128.4, 128.3, 128.2, 121.1, 97.9, 94.2, 81.5, 76.3, 75.3, 56.3, 56.0, 26.2; HRMS for $C_{17}H_{22}O_6$+Na calcd 345.1316; found 345.1314. Goniodiol **1**: $[\alpha]_D$ +74.1 (*c* 0.5, $CHCl_3$) [lit.[3] $[\alpha]_D$ +74.4 (*c* 0.3, $CDCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.24 (m, 5H), 6.93 (ddd, $J = 9.3$, 6.0, 2.1 Hz, 1H), 6.00 (dd, $J = 9.9$, 3.0 Hz, 1H), 4.95 (dd, $J = 7.5$, 5.7 Hz, 1H), 4.80 (ddd, $J = 12.9$, 3.9, 2.4 Hz, 1H), 3.73 (td, $J = 8.1$, 2.1 Hz, 1H), 2.80 (ddt, $J = 18.3$, 12.9, 2.1 Hz, 1H), 2.63 (d, $J = 5.4$ Hz,

1H), 2.30 (d, $J = 8.4$ Hz, 1H), 2.18 (ddd, $J = 19.2$, 6.3, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 146.1, 140.7, 128.8, 128.4, 126.5, 120.6, 76.8, 75.0, 73.8, 20.1; HRMS for $C_{13}H_{14}O_4$+Na calcd 257.0792; found 257.0790. 8-*epi*-Goniodiol **2**: $[\alpha]_D$ −13.3 (*c* 0.6, $CHCl_3$) [lit.[5m] $[\alpha]_D$ −13.7 (*c* 0.8, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.24 (m, 5H), 6.87 (ddd, $J = 9.9$, 6.3, 2.1 Hz, 1H), 5.96 (dd, $J = 9.9$, 3.0 Hz, 1H), 4.98 (d, $J = 7.5$ Hz, 1H), 4.22 (ddd, $J = 12.9$, 4.2, 2.4 Hz, 1H), 3.65 (t, $J = 5.4$ Hz, 1H), 3.34 (br s, 1H), 3.23 (br s, 1H), 2.84 (ddt, $J = 18.6$, 12.9, 2.7 Hz, 1H), 2.14 (ddd, $J = 18.6$, 6.3, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 145.9, 139.9, 128.7, 128.3, 126.9, 120.6, 77.0, 76.5, 74.1, 26.0; HRMS for $C_{13}H_{14}O_4$+Na calcd 257.0792; found 257.0790.