Total Synthesis of 8-Methoxygoniodiol via Chiron Approach

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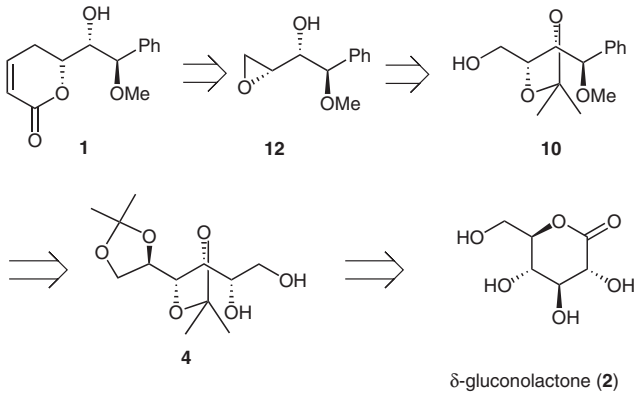
Abstract: A stereoselective synthesis of 8-methoxygoniodiol is accomplished using readily available δ-gluconolactone as a chiral source. The stereoselective addition of aryl Grignard reagent on aldehyde and regioselective opening of chiral epoxide by ethyl propiolate are the key steps involved in this synthesis.

Keywords: goniodiol, δ-gluconolactone, chiron approach, chiral epoxide

The genus *Goniothalamus* (Annonaceae) consists of 115 species, spread over entire the tropics and subtropics,[1] some of them used extensively as traditional medicines.[2] Several bioactive styryllactones have been isolated from *Goniothalamus* species.[3,4] The seeds of *G. amuyon* are reported to be useful for the treatment of edema and rheumatism.[5] In particular, 8-methoxygoniodiol was isolated from the stems and leaves of *Goniothalamus amuyon* along with seven styrylpyrones.[6] These styryllactones are found to possess significant cyctotoxicity against several human tumors.[7] The structures of some styryllactones are depicted in Figure 1.

Owing to its potent biological activity, and fascinating structural architecture, several methods have been reported for the synthesis of (+)-goniodiol and related molecules.[8] However, the reports on the synthesis of 8-methoxygoniodiol are scarce.[9]

In continuation of our interest on the total synthesis of natural products[10] and extreme scarcity of the natural material together with the novel structure prompted us to attempt the total synthesis of (+)-8-methoxygoniodiol. In this article, we describe a concise synthesis of (+)-8-methoxygoniodiol in a stereoselective manner. This approach is also useful for the synthesis of other stereoisomers and the design of analogues. Retrosynthetic analysis of (+)-8-methoxygoniodiol (**1**) is depicted in Scheme 1.



Scheme 1 Retrosynthetic analysis of (+)-8-methoxygoniodiol

Retrosynthetic analysis of (+)-8-methoxygoniodiol illustrates that optically active epoxide **12** could be prepared from δ-gluconolactone (**2**) by a sequence of reactions. Subsequently, epoxide **12** could be easily converted into target molecule **1** by means of ring opening by ethyl pro-

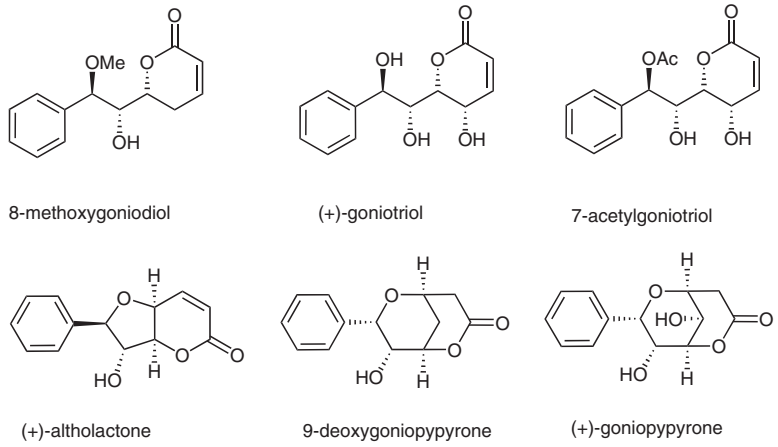


Figure 1

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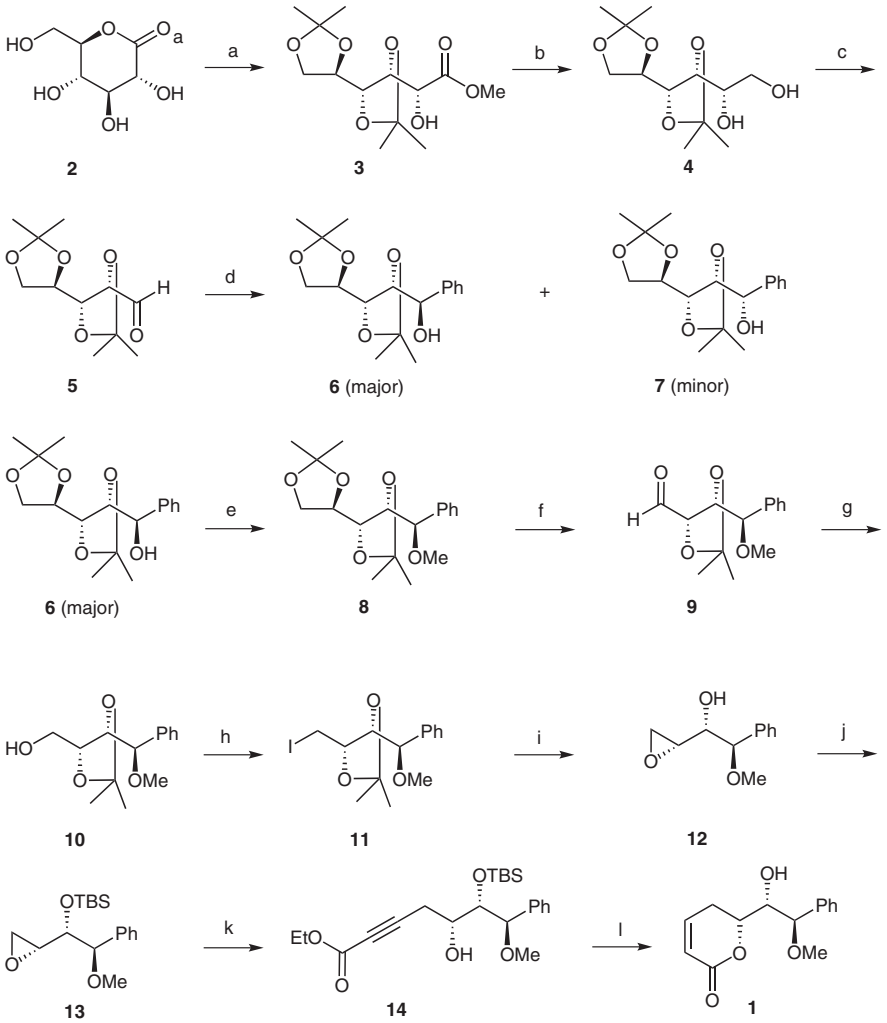
piolate followed by partial hydrogenation using Lindlar's catalyst.

The synthesis of 8-methoxygoniodiol (**1**) began with δ-gluconolactone (**2**) which could be easily obtained from commercial source. Accordingly, δ-gluconolactone (**2**) was treated with methanol in the presence of PTSA followed by 2,2-dimethoxypropane to give compound **3** in 86% yield.[11] Reduction of ester **3** with LAH gave the diol **4** in 96% yield, which upon treatment with $NaIO_4$ furnished the aldehyde **5** in 90% yield. Addition of phenylmagnesium bromide to an aldehyde **5** gave predominantly compound **6** along with a minor amount of compound **7**. The diastereomeric ratio of **6** to **7** was 95:5, which could be easily separated by column chromatography. The configuration of a newly formed hydroxyl group was assigned by converting the compound **6** into a known product.[12] The hydroxyl group of major isomer **6** was protected as its methyl ether **8** using methyl iodide and NaH in THF. Hydrolysis of primary acetonide and the cleavage of resulting diol occurred simultaneously with H_5IO_6 at room temperature resulted in aldehyde **9** in 95% yield.[13] Reduction of **9** with $NaBH_4$ in methanol gave the alcohol **10** in 90% yield which was then converted into the corresponding iodide **11** by using I_2, TPP, and imidazole. Upon treatment of **11** with 1 N HCl in ethanol for 3 days followed by addition of excess K_2CO_3 gave the hydroxy epoxide **12** in 70% yield.[14] The hydroxyl group was then protected as its TBS ether **13** using TBSCl and imidazole. Treatment of **13** with ethyl propiolate in the presence of *n*-BuLi and $BF_3{\cdot}OEt_2$ afforded ring-opened product **14** in 80% yield. Partial hydrogenation of **14** under Lindlar's conditions followed by treatment with 1 N HCl gave the target molecule **1** in 60% yield (Scheme 2).[15]

The structure of the (+)-8-methoxygoniodiol was confirmed by comparing its spectral and physical data with the natural product isolated by Wu et al,[6] and also with previous synthetic report.[9] The spectroscopic analysis and optical rotation value, $[\alpha]_D^{25}$ +24.9 (*c* 0.35, $CHCl_3$) were in agreement with the data reported in literature $[\alpha]_D^{25}$ +24.2 (*c* 0.68, $CDCl_3$).[6,9]



Scheme 2 *Reagents and conditions*: (a) 2,2-DMP, PTSA, acetone, MeOH, 12 h, r.t., 86%; (b) $LiAlH_4$, THF, 0 °C to r.t., 4 h, 96%; (c) $NaIO_4$, CH_2Cl_2, aq sat. $NaHCO_3$, 5 h, 90%; (d) PhMgBr, THF, –5 °C to 0 °C to r.t. (**6**/**7** = 95:5), 30 min, 95%; (e) NaH, MeI, THF, 0 °C to r.t., 2 h, 96%; (f) H_5IO_6, EtOAc, 0 °C to r.t., 1 h, 95%; (g) $NaBH_4$, MeOH, 0 °C to r.t., 2 h, 90%; (h) TPP, I_2, imidazole, MeCN–Et_2O (1:3) 0 °C to r.t., 2 h, 90%; (i) 1 N HCl, EtOH, 0 °C to r.t., 3 d then K_2CO_3, 70%; (j) imidazole, TBSCl, CH_2Cl_2, 0 °C to r.t., 2 h, 90%; (k) ethyl propiolate, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, –78 °C, 2 h, 80%; (l) (i) Lindlar, EtOAc; (ii) 1 N HCl, 60%.

In summary, we have described a concise and highly stereoselective synthetic route for the synthesis of (+)-8-methoxygoniodiol using a readily available δ-gluconolactone as a chiral precursor. The synthesis involves direct and straightforward reactions such as the aryl Grignard addition, epoxide formation from iodohydrin, and stereoselective ring opening of epoxide by an alkyne, which makes it quite simple and more convenient for up-scaling the products.

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(15) Compound **6**: $[\alpha]_D^{25}$ +15.8 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41, 1.37, 1.34, 1.32 (4 s, 12 H), 3.90–4.20 (m, 5 H), 4.25 (d, *J* = 4.6 Hz, 1 H), 7.3 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 26.3, 26.6, 27.1, 72.6, 75.4, 76.7, 82.6, 83.6, 109.0, 110.0, 126.8, 127.74, 128.5, 140.0. IR (KBr): ν_{max} = 3438, 2990, 2874, 1376, 1153, 1070, 843, 702 cm^{-1}. HRMS: *m/z* calcd for $C_{17}H_{24}O_5$ $[M + Na]^+$: 331.1521; found: 331.1512.
Compound **8**: $[\alpha]_D^{25}$ +67.6 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41, 1.37, 1.34, 1.32 (4 s, 12 H), 3.23 (s, 3 H), 3.94–4.15 (m, 5 H), 4.25 (d, *J* = 4.5 Hz, 1 H), 7.13 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 26.3, 26.5, 27.2, 56.4, 72.3, 75.4, 76.6, 82.5, 83.4, 109.0, 110.0, 126.0, 127.7, 128.5, 138.5. IR (KBr): ν_{max} = 2987, 1456, 1372, 1214, 1076, 848, 706 cm^{-1}. HRMS: *m/z* calcd for $C_{18}H_{26}O_5$ $[M + Na]^+$: 345.1676; found: 345.1669.
Compound **10**: $[\alpha]_D^{25}$ +37.2 (*c* 1.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.39 (s, 3 H), 2.85 (m, 1 H), 3.12 (dd, *J* = 3.0, 3.7 Hz, 1 H), 3.30 (s, 3 H), 3.70 (m, 1 H), 4.05 (dd, *J* = 6.7, 8.3 Hz, 1 H), 4.25 (d, *J* = 6.7 Hz, 1 H), 7.25–7.36 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.0, 29.0, 56.0, 62.0, 78.0, 79.0, 85.0, 109.0, 127.0, 128.0, 136.0. IR (KBr): ν_{max} = 3462, 2987, 1455, 1375, 1097, 860, 705 cm^{-1}. HRMS: *m/z* calcd for $C_{14}H_{20}O_4$ $[M + Na]^+$: 275.1259; found: 175.1250.
Compound **12**: $[\alpha]_D^{25}$ +37.9 (c 2.9, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$): δ = 2.48–2.54 (m, 2 H), 2.70 (dd, *J* = 3.0, 3.7 Hz 1 H), 3.27 (s, 3 H), 3.65 (dd, *J* = 2.2, 7.5 Hz, 1 H), 4.17 (d, *J* = 7.5 Hz, 1 H), 7.30 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.0, 52.0, 57.0, 75.0, 86.0, 127.0, 128.0, 129.0, 138.0. IR (KBr): ν_{max} = 3424, 2927, 1724, 1453, 1102, 760, 701 cm^{-1}. HRMS: *m/z* calcd for $C_{11}H_{14}O_3$ $[M + Na]^+$: 217.0840; found: *m/z* 217.0843.
Compound **14**: $[\alpha]_D^{25}$ +61.0 (*c* 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.16 (s, 3 H), 0.18 (s, 3 H), 0.93 (s, 9 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 2.40 (dd, *J* = 3.1, 6.2 Hz, 2 H), 3.12 (s, 3 H), 3.25 (m, 1 H), 3.89 (d, *J* = 7.8 Hz, 1 H), 4.11 (d, *J* = 7.8 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 7.30 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –3.7, 14.0, 25.1, 26.2, 29.7, 56.3, 61.8, 68.7, 76.6, 85.3, 85.8, 127.8, 128.3, 128.6, 138.1, 150.4. IR (KBr): ν_{max} = 3423, 3300, 2927, 1742, 1458, 1105, 760 cm^{-1}. LC-MS: *m/z* = 429 $[M + Na]^+$.
Compound **1**: $[\alpha]_D^{25}$ +24.9 (*c* 0.35, $CHCl_3$); lit.: +24.2 (*c* 0.68, $CDCl_3$. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (ddd, *J* = 4.0, 6.2, 18.5 Hz, 1 H), 2.94 (ddd, *J* = 2.4, 13.0, 18.5 Hz, 1 H), 3.27 (s, 3 H), 3.56 (d, *J* = 8.5 Hz, 1 H), 3.92 (ddd, *J* = 3.9, 12.5, 17.9 Hz, 1 H), 4.55 (d, *J* = 8.5 Hz, 1 H), 5.93 (dd, *J* = 3.1, 10.2 Hz, 1 H), 6.82 (ddd, *J* = 2.3, 6.2, 9.4 Hz, 1 H), 7.30–7.39 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 56.8, 61.8, 75.7, 75.8, 83.4, 120.7, 127.7, 128.6, 128.7, 137.3, 145.7, 163.8. IR (KBr): ν_{max} = 3445, 2909, 1719, 1380, 1109, 1057, 757 cm^{-1}. HRMS: *m/z* calcd for $C_{14}H_{16}O_4$ $[M + Na]^+$: 271.0946; found: 271.0945.