An Expeditious Enantiospecific Total Synthesis of (+)-7-*epi*-Goniofufurone

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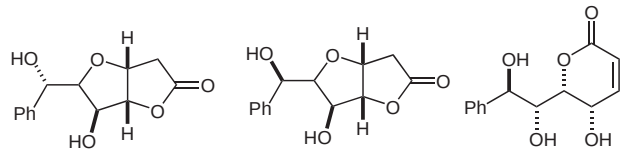
Abstract: Stereoselective synthesis of styryl lactone, (+)-7-*epi*-goniofufurone was achieved in high yield via simple transformations from tartaric acid. The key step involves the successive stereoselective reduction of ketones with borohydride and selectride.

Key words: styryl lactones, (+)-goniofufurone, stereoselective reduction

Trees of genus *Goniothalamus* of the plant family *Annonaceae* have been known for a long time as a source of potent biologically active styryl lactones.[1] Due to their proven use in folk medicine in Taiwan, Malaysia, and India to treat rheumatism, edema, as an abortifacient, and as a mosquito repellant, there has been an interest in the active ingredients as potential therapeutic targets. This resulted in the isolation by McLaughlin et al. of a series of styryl lactones which were reported to show cytotoxic, antitumor, pesticidal, ratogenic, and embryotoxic activities.[2] The styryl lactones isolated can be mainly classified into two groups related to the size of the lactone ring. The first group consists of the five-membered lactone moiety for e.g. 7-*epi*-(+)-goniofufurone (**1**) and goniofufurone (**2**). The second group consists of the six-membered lactones such as, goniotriol (**3**), etharvendiol (**4**), altholactone (**5**), and goniopyrone (**6**). Amongst these, goniofufurones containing a furanofurone bicyclic structure has exhibited significant cytotoxic activities against several human tumor cell lines.[3] Coupled with their unique and intriguing structures as well as their broad spectrum of activity, these compounds have attracted the attention of several synthetic groups.[4]

Of the several syntheses reported for 7-*epi*-goniofufurone and its derivatives, most of them utilized carbohydrates such as D-glucose and D-mannose, as well as other chiral pool sources. For example Shing et al. reported the first synthesis of the title compound from D-glycero-D-gulo-heptano-γ-lactone.[5] An elegant strategy involving a Wittig reaction of a lactol derived from glucose was described by Prakash and Rao.[6] Mukai et al.[7] utilized a chiral arene chromium(0) complex, while unstable chiral lactonic aldehydes as the key intermediates were employed by Tsubuki et al[8] in their synthesis. Mereyala et al.[9] described the synthesis of 7-*epi*-goniofufurone and its analogues involving a Pd(0)-mediated cyclization. Recently Su et al.



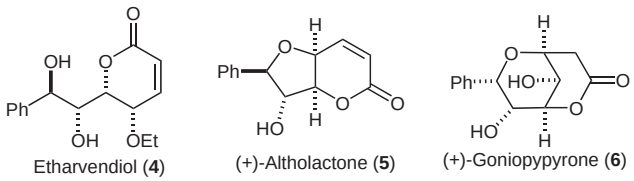
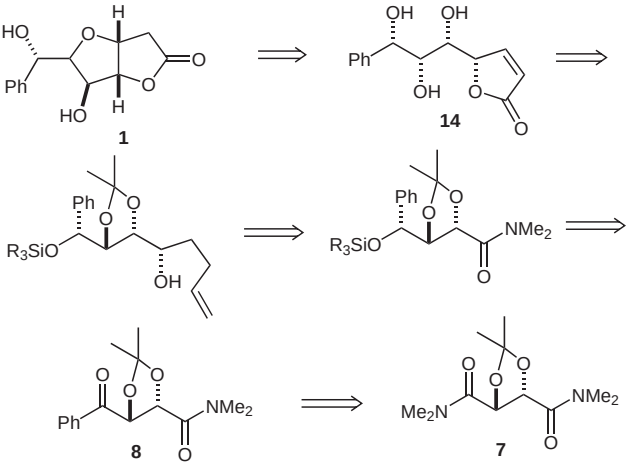


Figure 1 Bioactive styryllactones

recently disclosed a multi-step synthesis starting from a chiral aldehyde derived from D- and L-tartaric acid.[10]

During the course of the synthesis of symmetrical 1,4-diaryl diones from **7**, we observed that careful addition of Grignard reagent furnished the mono-addition product, keto amide **8**, which can be further elaborated. Thus, we envisaged that the known intermediate **14** for the synthesis of 7-*epi*-gonifufurone can easily be accessed via the reduction of the keto amide, as depicted in the retrosynthesis (Scheme 1).



Scheme 1 Retrosynthesis for (+)-*epi*-goniofufurone

Our synthesis of **1** began with the D-(–)-isopropylene-dioxy tartaric amide **7**,[11] which on reaction with two equivalents of PhMgBr cleanly produced the mono-addition product keto amide **8** in 92% yield along with traces of the diketone. Stereoslective reduction of ketone **8** with

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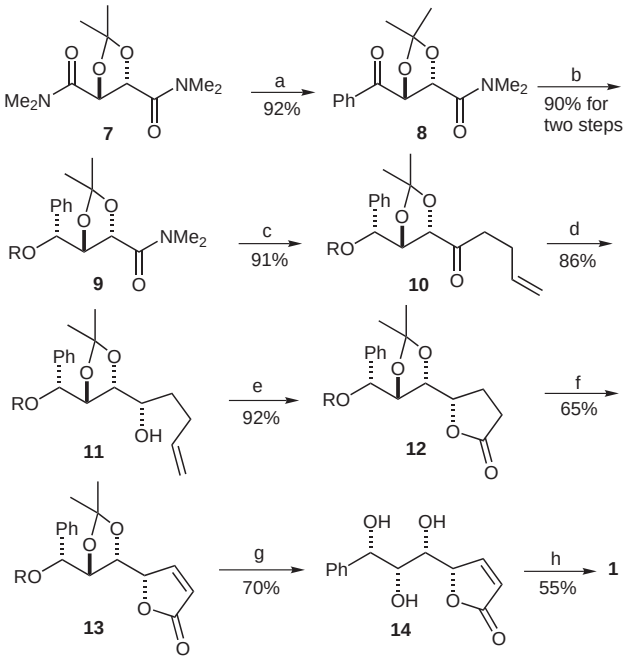
$NaBH_4/CeCl_3$ resulted in the alcohols forming in a 94:6 ratio, with **9** being the major isomer.[12] Protection of the benzylic alcohol **9** as the corresponding TBDMS ether was realized in almost quantitative yield. Addition of 4-butenylmagnesium bromide[13] proceeded smoothly to give the ketone **10** in 91% yield. Stereoselective reduction of ketone **10** was accomplished with L-selectride to furnish the alcohol **11** in 86% yield after flash chromatography. Ozonolysis of alcohol **11** produced the corresponding lactol, which was oxidized to lactone **12** in 92% combined yield. Phenylselenation of the lactone followed by elimination of the phenylselenyl moeity furnished α,β-unsaturated ketone **13** in 65% isolated yield. On treatment with HCl/AcOH in THF the known triol **14** {$[\alpha]_D$ –83 (*c* 0.3, MeOH) [lit.[5] –85 (*c* 0.3, MeOH)]}, was obtained in 70% yield, which upon treatment with DBU in THF produced 7-*epi*-(+)-goniofufurone (Scheme 2). All the physical constants and spectral data[14] are in complete agreement with those reported in the literature. Similarly, starting from L-(+)-isopropylenedioxy tartaric amide (**7**), we synthesized the corresponding (–)-enantiomer in 19% overall yield.

In summary, we have shown that the rapid assembly of the pivotal intermediate containing four contiguous stereogenic centers en route to (+)-7-*epi*-goniofufurone is achieved in a short synthetic sequence. The strategy is general and is quite suitable for creating a pool of analogues in addition to the synthesis of other bioactive styryllactones. Further work in this direction is currently in progress.



Scheme 2 Stereoselective synthesis of (+)-7-*epi*-goniofufurone a) PhMgBr (2 equiv), THF, –10 °C, 0.5 h; b) (i) $NaBH_4$ (1.2 equiv)/$CeCl_3$ (1.2 equiv), –78 °C, 2 h; (ii) TBDMSCl (1.5 equiv), imidazole (3 equiv), DMAP (20 mol%), DMF, r.t., 6 h; c) butenylMgBr (2 equiv), THF, –10 °C, 0.5 h; d) L-Selectride (1.2 equiv), THF, –78 °C, 1 h; e) (i) O_3/Me_2S, MeOH–CH_2Cl_2, –78 °C to 0 °C, 4 h; (ii) PCC (2 equiv)/NaOAc/Celite/CH_2Cl_2, 1 h; f) (i) LiHMDS (2.5 equiv)/THF, –78 °C to –50 °C; PhSeCl (1.5 equiv) or PhSeSePh (1.5 equiv); (ii) 30% H_2O_2, CH_2Cl_2, 0 °C, 0.5 h; g) HCl–THF–AcOH (1:1:1), r.t., 6 h); cat. DBU/THF, r.t., 24 h.

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(12) The minor isomer was removed by simple crystallization from hexane–EtOAc.

(13) We anticipated that the addition of vinyl magnesiumbromide to **9** followed by a stereoselective reduction of the ketone and RCM would yield the intermediate **14**. However, addition of vinyl magnesium bromide to **9** proceeded with low yield. Full details of this strategy will be discussed in a future article.

(14) All new compounds exhibited satisfactory spectral data. **8**: $[\alpha]_D$ +23 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.50 (s, 3 H), 3.00 (s, 3 H), 3.17 (s, 3 H), 5.16 (d, *J* = 5.7 Hz, 1 H), 5.934 (d, *J* = 5.4 Hz, 1 H), 7.40–7.65 (m,

3 H), 8.05–8.15 (m, 2 H). ^{13}C NMR (75 MHz): δ = 26.40, 35.97, 37.13, 75.04, 76.59, 77.43, 79.45, 112.56, 128.55, 129.41, 133.69, 134.94, 168.25, 196.38. Anal. calcd for $C_{21}H_{34}NO_4Si$: C, 64.97; H, 6.91. Found: C, 65.28; H, 7.02. **9**: $[\alpha]_D$ +67.5 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.14 (s, 3 H), –0.04 (s, 3 H), 0.84 (s, 9 H), 1.26 (s, 3 H), 1.34 (s, 3 H), 2.84 (s, 3 H), 2.99 (s, 3 H), 4.44 (d, *J* = 6.6 Hz, 1 H), 4.72–4.88 (m, 2 H), 7.15–7.40 (m, 5 H). ^{13}C NMR (75 MHz): δ = –5.15, –4.85, 18.21, 25.71, 26.43, 26.71, 35.78, 36.96, 73.23, 74.14, 82.03, 110.97, 127.29, 127.52, 127.71, 140.59, 169.04. Anal. calcd for $C_{21}H_{35}NO_4Si$: C, 64.08; H, 8.96. Found: C, 64.10; H, 9.21. **11**: $[\alpha]_D$ +38.9 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.12 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 1.10 (s, 3 H), 1.32 (s, 3 H), 1.33–1.50 (m, 1 H), 1.85–2.15 (m, 3 H), 3.09 (br s, 1 H), 3.64 (dd, *J* = 8.1 Hz, 2.4 Hz 1 H), 4.10 (dd, *J* = 8.1 Hz, 5.4 Hz 1 H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.80–5.00 (m, 2 H), 5.67 (ddt, *J* = 16.8 Hz, 10.2 Hz, 6.9 Hz, 1 H), 7.15–7.30 (m, 5 H). ^{13}C NMR (75 MHz): δ = –4.99, –4.85, 18.26, 25.79, 27.04, 27.39, 29.87, 33.87, 69.33, 75.54, 79.25, 80.57, 109.13, 114.79, 127.40, 127.78, 127.88, 138.14, 139.97. **13**: $[\alpha]_D$ +11.7 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.17 (s, 3 H), 1.34 (s, 3 H), 3.87 (dd, *J* = 8.1, 2.4 Hz, 1 H), 4.46 (dd, *J* = 8.1, 5.7 Hz, 1 H), 4.52 (q, *J* = 2.0 Hz, 1 H), 4.94 (d, *J* = 5.7 Hz, 1 H), 6.07 (dd, *J* = 5.7 Hz, 1.8 Hz, 1 H), 7.26 (dd, *J* = 5.7, 1.8 Hz, 1 H), 7.25–7.45 (m, 5 H). ^{13}C NMR (75 MHz): δ = –4.97, –4.94, 18.27, 25.79, 26.27, 26.99, 75.08, 75.11, 80.03, 81.47, 110.23, 122.14, 127.27, 128.03, 139.38, 153.10, 172.82. Anal. calcd for $C_{22}H_{33}O_5Si$: C, 65.31; H, 7.97. Found: C, 65.26; H, 7.80.