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The stereoselective total synthesis of (+)-garvensintriol

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ABSTRACT

A simple and highly efficient stereoselective total synthesis of (+)-garvensintriol, isolated from the stem bark of *Goniothalamus arvensis*, is described using Sharpless kinetic resolution, MacMillan α-hydroxylation, and Horner–Wadsworth–Emmons olefination as the key steps.

The trees of genus *Goniothalamus* of the plant family *Annonaceae* have attracted considerable interest as a source of potent biologically active styryllactones.[1,2] Due to their proven use in folk medicine in Taiwan, Malaysia, and India to treat rheumatism, edema, and as abortifacients and mosquito repellents, there has been interest in the active ingredients as potential therapeutic targets.[3] Styryl lactones are natural heterocyclic compounds with potential cytotoxicity including antitumor, antifungal, and antibiotic properties.[4] The novel styryl-pyrones, (+)-garvensintriol **1**, (+)-etharvendiol **3**, were isolated from the stem bark of *Goniothulamus arvensis*.[5] Especially, isolated lactones can mainly be classified into two groups related to the size of the lactone ring. The first group consists of the six-membered lactones such as (+)-garvensintriol **1**, (+)-goniotriol **2,** and (+)-etharvendiol **3**; the second group consists of the five-membered lactone moiety, for example, (+)-cardiobutanolide **4** and goniofufurone **5** as shown in Figure 1. Their unique and intriguing structures coupled with diverse and useful characteristics as well as their broad spectrum of activity have made them attractive targets for total synthesis.[6] Consequently, we have recently reported the total synthesis of (+)-garvensintriol.[7a] Due to the unusual structure and biological significance of this class of compounds, we were encouraged to continue our program on the total synthesis of bioactive lactones.[7b–h]

Herein, we report a concise and flexible stereoselective synthetic route for the total synthesis of (+)-garvensintriol **1** starting from the readily available homopropargyl alcohol by employing Sharpless kinetic resolution, MacMillan α-hydroxylation, Horner–Wadsworth–Emmons olefination, and finally, the acid-catalyzed cyclization.

Retrosynthetic analysis of **1** revealed that a key intermediate **14** can be synthesized through MacMillan α-hydroxylation followed by Horner–Wadsworth–Emmons olefination of the aldehyde derived from the Swern oxidation of **12**. The alcohol **12** could in turn be obtained by opening of epoxy alcohol **9** with dry acetone. This epoxy alcohol can be prepared from homopropargylic alcohol by means of Chan alkyne reduction and Sharpless kinetic resolution (Scheme 1).

Our synthetic approach began with the protection of homopropargyl alcohol as its benzyl ether **6** by treating with NaH and benzyl bromide. It was then treated with *n*-BuLi in THF to generate the lithium acetylide, which was subsequently reacted with benzaldehyde to give the propargyl alcohol **7**. Compound **7** was reduced with $LiAlH_4$ in THF to afford the allyl alcohol **8**.[8] The key epoxy alcohol **9** was obtained in 45% yield with 96% ee by the Sharpless kinetic resolution[9] of **8** using L(+)-DET and TBHP. Then compound **9** was treated with dry acetone in the presence of $BF_3{\cdot}Et_2O$ at 0 °C to furnish acetonide **10** in 90% yield. This resulted in fixing of the two hydroxyl groups as we reported earlier.[10] Thereafter, alcohol **10** was protected as its MOM ether **11** in 92% yield using Hunig's base and MOMCl in dry dichloromethane. Debenzylation of ether **11** with 10% Pd–C/H_2 gave primary alcohol **12,** which was then subjected to Swern oxidation to give aldehyde **13**. Treatment of aldehyde **13** with L-proline and nitrosobenzene gave an intermediate α-oxyamino aldehyde with high levels of enantioselectivity[11,12] by means of α-oxidation. Olefination of aminoxy aldehyde under Horner–Wadsworth–Emmons conditions followed by cleavage of the aminoxy bond gave the γ-hydroxy-α,β-unsaturated ester **14**.[13] The resulting free hydroxyl group of compound **14** was treated with MOMCl in the presence

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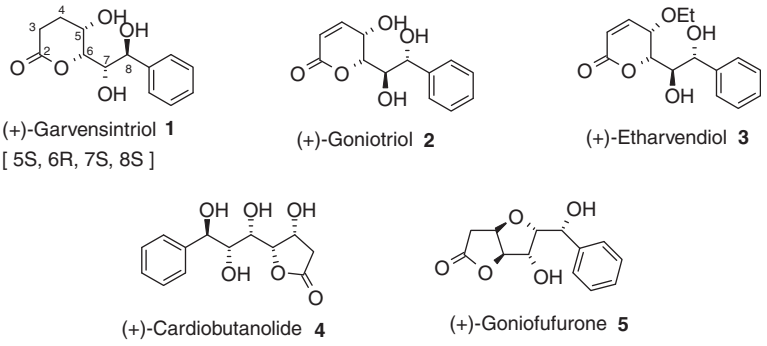
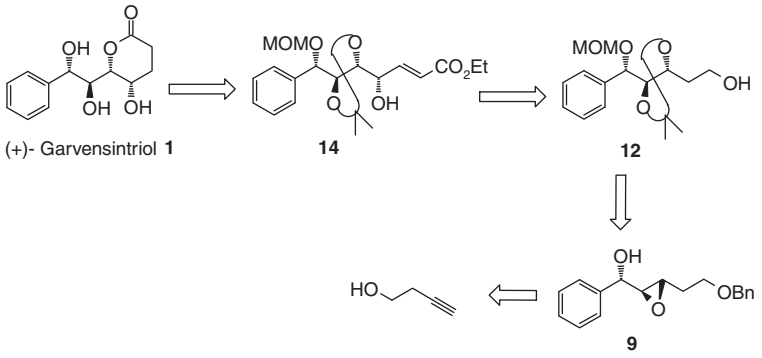
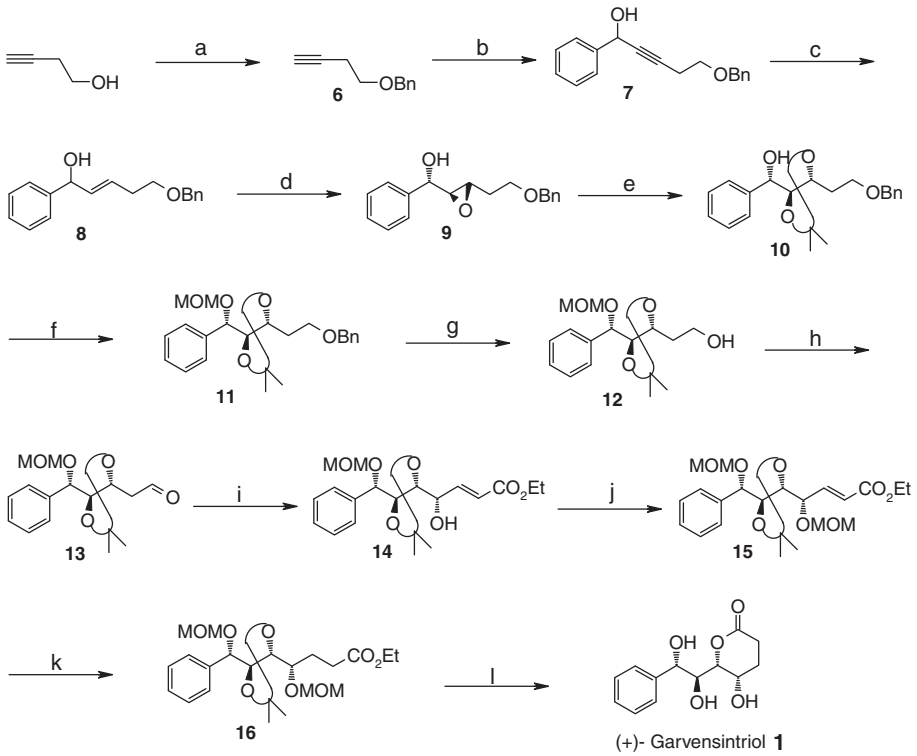


Figure 1. Examples of some lactone-containing natural products.



Scheme 1. Retrosynthetic analysis of (+)-garvensintriol **1**.



Scheme 2. Reagents and conditions: (a) (i) NaH, THF, 0–25 °C, 0.5 h; (ii) BnBr, 0–25 °C, 3 h, 90%; (b) *n*-BuLi, dry THF, −78 °C, PhCHO, 4 h , 85%; (c) $LiAlH_4$, dry THF, reflux, 3 h, 95%; (d) (+)-diisopropyl-L-tartrate, TBHP, $Ti(O^iPr)_4$, dry DCM, −20 °C, 12 h, 45%; (e) $BF_3{\cdot}OEt_2$, dry acetone, 0 °C, 4 h, 90%; (f) MOMCl, DIPEA, dry DCM, 0 °C to rt, 6 h; 92%; (g) 10% Pd/C, H_2, EtOAc, rt, 10 h, 92%; (h) Oxalyl chloride, dry DMSO, dry DCM, −78 °C, Et_3N, 1 h 85%; (i) nitrosobenzene (1.0 equiv), L-proline (0.4 equiv), DMSO, 20 °C, 25 min, then triethylphosphonoacetate, DBU, LiCl, 0 °C, 15 min, then MeOH, NH_4Cl, $Cu(OAc)_2$, rt, 24 h, 45% (one-pot); (j) MOMCl, DIPEA, dry DCM, 0 °C to rt, 6 h; 90%; (k) 10% Pd/C, H_2, EtOAc, rt, 10 h, 95%; (l) PTSA, MeOH, reflux, 1 h, 75%.

of base to afford MOM ether **15**. Then compound **15** was subjected to hydrogenation with Pd–C/H_2 to provide compound **16** in good yield. Deprotection of acetonide and MOM groups with concomitant cyclization was achieved using *p*-TSA in refluxing methanol[7c] to afford the target lactone, (+)-garvensintriol **1** in 75% yield from compound **16** as a yellowish oil (Scheme 2). The analytical and spectral properties of compound **1** were in good agreement with the data reported in the literature.[14]

In conclusion, we have developed a stereoselective synthetic route for the total synthesis of garvensintriol from readily available homopropargyl alcohol. The salient features of this synthesis include the use of Sharpless kinetic resolution to yield epoxy alcohol, MacMillan α-hydroxylation and HWE reaction for the construction of key intermediate, that is, γ-hydroxy-α,β-unsaturated ester in a single step, which allows the preparation of target molecule in a short and efficient route.

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14. Spectral data for compound **14**: Pale yellow oily liquid, $[\alpha]_D^{25}$ +11.5 (*c* 0.5, $CHCl_3$), IR (neat): ν_{max} 3451, 2924, 2854, 1714, 1660, 1158, 1032, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.28 (m, 5H), 6.95 (dd, *J* = 15.8, 3.7 Hz, 1H), 6.13 (dd, *J* = 15.8, 2.2 Hz, 1H), 4.60 (d, *J* = 9.8 Hz, 1H), 4.23–4.13 (m, 4H), 3.86 (dd, *J* = 9.0, 2.2 Hz, 1H), 3.81 (d, *J* = 6.0 Hz, 1H), 3.58 (t, *J* = 9.0 Hz, 1H), 3.10 (s, 3H), 1.58 (s, 3H), 1.47 (s, 3H), 1.32 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 147.7, 138.9, 129.6, 128.4, 127.7, 121.8, 99.4, 97.7, 75.8, 74.9, 74.7, 68.7, 60.2, 56.0, 29.2, 19.4, 14.3; ESI- MS: *m*/*z*: 381 $(M+H)^+$, 398 $(M+NH_4)^+$, 403 $(M+Na)^+$; HRMS (ESI) calcd for $C_{20}H_{28}O_7Na$: 403.1732, found: 403.1735. Compound **16**: colorless liquid, $[\alpha]_D^{25}$ +9.0 (*c* 0.5, $CHCl_3$), IR (neat): ν_{max} 2927, 1733, 1453, 1377, 1161, 1036, 760, 537 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40–7.37 (m, 2H), 7.31–7.22 (m, 3H), 4.70 (dd, *J* = 2.4, 6.7 Hz, 2H), 4.55 (d, *J* = 4.5 Hz, 1H), 4.15–4.04 (m, 3H), 3.91 (d, *J* = 5.7 Hz, 1H), 3.81 (m, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.60 (dd, *J* = 1.9, 9.6 Hz, 1H), 3.35 (s, 3H), 2.98 (s, 3H), 2.44–2.32 (m, 2H), 2.06–1.91 (m, 2H), 1.51 (s, 3H), 1.45 (s, 3H), 1.20 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.4, 139.5, 129.3, 128.5, 127.9, 99.0, 97.3, 97.2, 76.4, 75.6, 74.5, 74.0, 60.3, 55.9, 55.8, 30.5, 29.4, 26.7, 19.0, 14.2; ESI- MS: *m*/*z*: 449 $(M+Na)^+$; HRMS (ESI) calcd for $C_{22}H_{34}O_8Na$: 449.2151, found: 449.2141. Compound **1**: yellow oil liquid, $[\alpha]_D^{25}$ +8.2 (*c* 0.3, EtOH), IR (neat): ν_{max} 3410, 2924, 2854, 1753, 1649, 1455, 1194, 1080, 1024, 765, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.46–7.35 (m, 5H), 4.94 (td, *J* = 7.5, 6.0, 2.2 Hz, 1H), 4.83 (d, *J* = 6.7 Hz, 1H), 3.91 (dd, *J* = 8.3, 7.5 Hz, 1H), 3.60 (dd, *J* = 8.3, 2.2 Hz, 1H), 2.54–2.21 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.7, 136.8, 128.8, 128.7, 127.1, 79.4, 77.1, 75.0, 73.4, 29.7, 23.5; ESI-MS: *m*/*z*: 270 $(M+NH_4)^+$, 275 $(M+Na)^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_5Na$: 275.0895, found: 275.0898.