First Total Syntheses of (+)-Garvensintriol and (+)-5-*epi*-Garvensintriol

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Abstract: A concise and efficient carbohydrate-based approach for the total syntheses of (+)-garvensintriol and (+)-5-*epi*-garvensintriol is described in nine and six steps with 20% and 37% overall yield, respectively, starting from a known intermediate. A sequence of Grignard-assisted lactol opening with terminal alkyne, stereoselective keto reduction and oxidative lactonization are the key reactions.

Keywords: garvensintriol, goniotriol, cytotoxic, oxidative lactonization, Grignard-assisted lactol opening

Lactone rings are a structural feature of simple to highly complex biologically active natural products.[1] Among them, six-membered lactone moieties are relatively common in various types of natural sources.[2] These natural and designed molecules possess cytotoxic, anti-HIV, apoptosis induction, antileukemic activity and other relevant pharmacological properties.[3] Several bioactive styryl lactones have been reported from *goniothalamus* species which are found to possess significant cytotoxic activity against several human tumor cell lines.[4] (+)-Garvensintriol (**1**) was isolated from the methanolic extract of *G. arvensis* stem bark along with (+)-altholactone (**3**), (+)-goniotriol (**4**), (+)-etharvendiol (**5**) and (+)-goniofufurone (**6**; Figure 1).[5] The structure of (+)-garvensintriol (**1**) was determined from IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

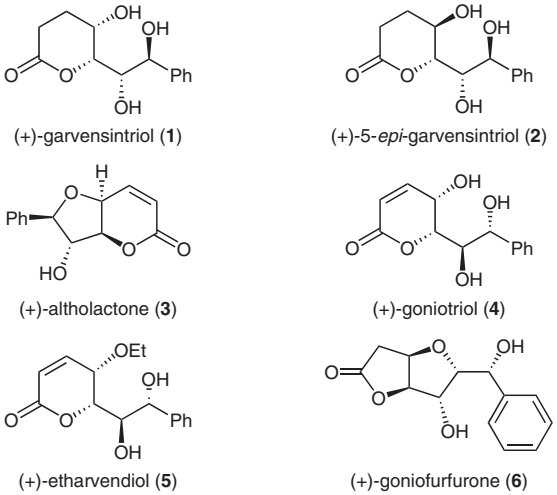
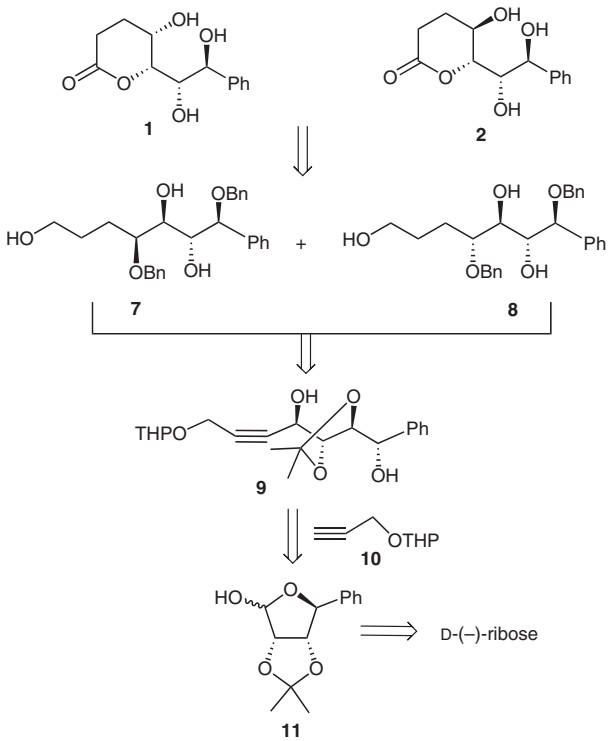


Figure 1 Structures of few novel styryl lactones

The absolute configuration was assigned as (5*S*,6*R*,7*S*,8*S*), which was different from that of (+)-goniotriol (**4**), whose absolute configuration (5*S*,6*R*,7*R*,8*R*) was previously determined by X-ray crystallographic analysis.[6] Because of the wide distribution of the styryl lactone class of natural products in nature with interesting biological activities and to confirm the structure and configuration, we have taken up the synthesis of (+)-garvensintriol (**1**) and (+)-5-*epi*-garvensintriol (**2**).

The retrosynthetic analysis of our approach is shown in Scheme 1. It was envisioned that (+)-garvensintriol (**1**) and (+)-5-*epi*-garvensintriol (**2**) could be obtained from D-(–)-ribose. The six-membered lactone could be constructed by oxidative lactonization of triol **8**. The triol **8** could be obtained from keto derivative **13**. The crucial intermediate **9** could be obtained from a Grignard-assisted opening of a known lactol **11** with a terminal alkyne **10**.



Scheme 1 Retrosynthetic analysis of (+)-garvensintriol (**1**) and (+)-5-*epi*-garvensintriol (**2**)

The synthesis of the key intermediate **11** was obtained from D-(–)-ribose following a known protocol.[7] The lactol ring opening with in situ metalated alkyne (obtained by treating **10** with ethyl magnesium bromide) afforded the

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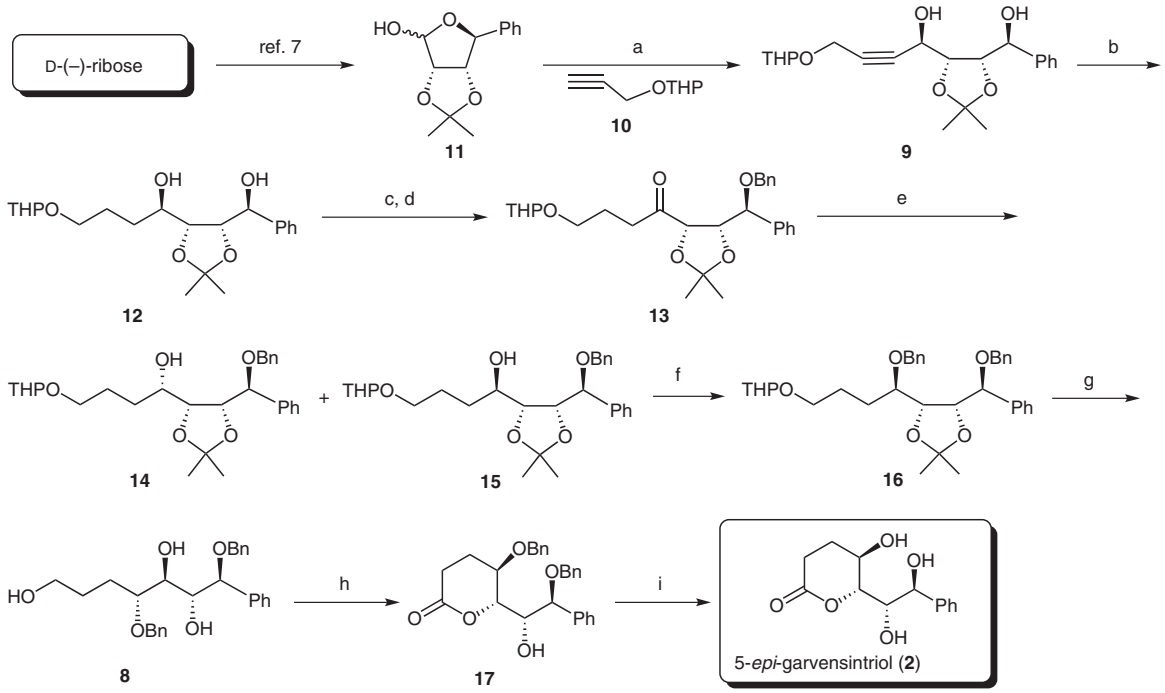


Scheme 2 *Reagents and conditions*: (a) EtMgBr, THF, **6**, 0 °C to r.t., 6 h, 80%; (b) Pd/C, H_2, EtOAc, 4 h, 91%; (c) NaH, BnBr, DMF, 0 °C to r.t., 2 h, 90%; (d) PDC, CH_2Cl_2, r.t., 85%; (e) (*S*)-CBS, $BH_3{\cdot}Me_2S$, THF, –100 °C, 4 h, 82%; (f) NaH, BnBr, DMF, 0 °C to r.t., 2 h, 84%; (g) *p*-TSA, MeOH, r.t., 6 h, 89%; (h) TEMPO, BAIB, CH_2Cl_2, 0 °C to r.t., 4 h, 87%; (i) $TiCl_4$, CH_2Cl_2, r.t., 2 h, 76%

anti isomer as the only product in 80% yield.[8] The initial attempt for inversion of secondary hydroxyl center following Mitsunobu protocol[9] was not successful. At this juncture, proceeding further with compound **9** led to the (+)-5-*epi*-garvensintriol (**2**) in five steps. To obtain both (+)-garvensintriol (**1**) and (+)-5-*epi*-garvensintriol (**2**), compound **9** was treated with Pd/C under hydrogen atmosphere to obtain the saturated product **12** in 91% yield. The selective protection of the benzyl alcohol with NaH and benzyl bromide followed by oxidation with pyridinium dichromate (PDC)[10] reagent in CH_2Cl_2 resulted in keto derivative **13** in 77% yield over two steps. The selective reduction under different reaction conditions (Table 1) was studied at this stage to obtain the required *syn* isomer.

Table 1 Results of Selective Reduction

Entry	Reducing agents	Conditions	**14/15**	Yield (%)[a]
1	$NaBH_4$	MeOH, 0 °C, 30 min	1:9	89
2	L-Selectride	THF, –78 °C, 4 h	1:4	85
3	$NaB(OAc)_3H$	THF, –78 °C, 2 h	1:4	90
4	$NaBH_4$–$CeCl_3$	MeOH, –100 °C, 4 h	2:3	84
5	(*R*)-CBS	THF, –78 °C, 4 h	1:9	85
6	(*S*)-CBS	THF, –78 °C, 4 h	9:1	82
7	$ZnBH_4$	THF, –78 °C, 3 h	1:9	80

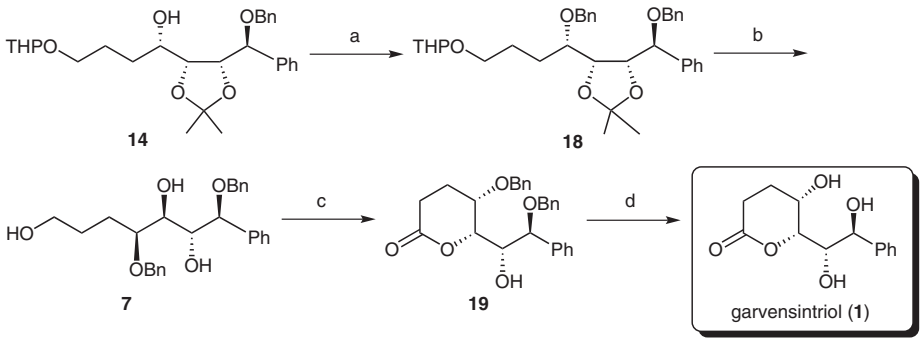
[a] Isolated yield.

Out of all the reagents tried, reduction using (*S*)-2-methyl-CBS-oxazaborolidine[11] afforded the required hydroxyl compound **14** and its epimer **15** in a ratio of 9:1 (Scheme 2). Both the isomers were separated by silica gel column chromatography and characterized separately.

To obtain (+)-5-*epi*-garvensintriol (**2**), compound **12** was benzylated with NaH and benzyl bromide to afford the dibenzyl derivative **16** in 86% yield. Dibenzyl derivative **16** was also obtained by treating compound **15** with NaH and benzyl bromide in 84% yield. Both acetonide and THP group deprotection with *p*-TSA in methanol afforded the triol **8**[12] in 89% yield. The oxidation of the triol **8** in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) produced the six-membered lactone **17**[13] in 87% yield.[14] Finally, deprotection of the benzyl groups with excess $TiCl_4$ in CH_2Cl_2 at room temperature afforded the (+)-5-*epi*-garvensintriol (**2**)[15] in 76% yield.[16]

The assigned structure of (+)-5-*epi*-garvensintriol (**2**) was confirmed by IR, ^1H NMR, ^{13}C NMR and mass spectral analysis. The product after purification and recrystallization produced single crystals whose X-ray analysis further confirmed its structure and absolute configuration to be (5*S*,6*R*,7*S*,8*S*).[17]

After the synthesis of (+)-5-*epi*-garvensintriol (**2**) and confirmation of its absolute configuration by X-ray crystallographic analysis, the synthesis of the natural product **1** was initiated. Starting from intermediate **14** and following the same sequence of reactions[18,19] as followed for compound **15** to (+)-5-*epi*-garvensintriol (**2**), the total



Scheme 3 *Reagents and conditions*: (a) NaH, BnBr, DMF, 0 °C to r.t., 4 h, 80%; (b) *p*-TSA, MeOH, r.t., 6 h, 87%; (c) TEMPO, BAIB, CH_2Cl_2, 0 °C to r.t., 4 h, 85%; (d) $TiCl_4$, CH_2Cl_2, r.t., 2 h, 74%.

synthesis of (+)-garvensintriol (**1**)[20] was achieved in four steps (Scheme 3).

The spectral data were in good agreement with those of the natural product but the analytical value showed a difference {$[\alpha]_D^{25}$ +70.3 (*c* = 1.5, EtOH); lit.[5] $[\alpha]_D^{25}$ +7.8 (*c* = 3.3, EtOH)} which might be due to typographical error.

In conclusion, we have succeeded in the concise stereoselective syntheses of (+)-garvensintriol (**1**) and (+)-5-*epi*-garvensintriol (**2**) from a known lactol **11** in nine and six steps with 20% and 37% overall yield, respectively. The absolute configurations of (+)-garvensintriol (**1**) and (+)-5-*epi*-garvensintriol (**2**) have been elucidated. Following the same protocol, other related natural products syntheses are in progress and will reported in due course.

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(12) **Analytical and Spectral Data of 8**: white solid; mp 67 °C; $[\alpha]_D^{25}$ +48.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.62 (m, 15 H), 4.60 (d, *J* = 6.0 Hz, 1 H), 4.46 (d, *J* = 13.6 Hz, 3 H), 4.29 (d, *J* = 11.3 Hz, 1 H), 3.96 (dd, *J* = 7.6, 2.7 Hz, 1 H), 3.48–3.72 (m, 4 H), 3.23 (br s, 1 H), 2.96 (br s, 1 H), 1.89 (br s, 1 H), 1.50–1.81 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 137.5, 137.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 83.2, 80.3, 74.3, 71.7, 71.5, 70.7, 62.6, 28.2, 24.9. MS (ESI): *m*/*z* = 437 $[M + H]^+$.

(13) **Analytical and Spectral Data of 17**: white solid; mp 139 °C; $[\alpha]_D^{25}$ = –22.2 (*c* = 1.5, $CHCl_3$). IR (neat): 3395, 3029, 2960, 2911, 2859, 1746, 1453, 1396, 1259, 1086, 1028, 761, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.51 (m, 15 H), 4.31–4.59 (m, 5 H), 4.19 (d, *J* = 11.3 Hz, 1 H), 3.99–4.12 (m, 2 H), 2.56–2.79 (m, 1 H), 2.19–2.55 (m, 2 H), 1.93–2.16 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 137.7, 137.2, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.7, 81.8, 81.0, 74.4, 70.7, 70.5, 69.7, 26.0, 22.7. MS (ESI): *m*/*z* = 455 $[M + Na]^+$.

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(15) **Analytical and Spectral Data of 2**: white solid; mp 163 °C; $[\alpha]_D^{25}$ –10.1 (*c* = 0.5, EtOH). IR (neat): 3533, 3346, 2923, 1773, 1200, 1083, 1026, 897, 850, 705, 673 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 7.07–7.51 (m, 5 H), 4.77 (m, 2 H), 4.60 (br s, 3 H), 3.65–3.78 (m, 2 H), 2.09–2.62 (m, 4 H). ^1H NMR (300 MHz, DMSO-d_6): δ = 7.12–7.53 (m, 5 H), 5.35

(dd, *J* = 13.8, 3.8 Hz, 2 H), 4.84 (d, *J* = 4.9 Hz, 1 H), 4.71 (s, 2 H), 3.44–3.66 (m, 2 H), 1.95–2.48 (m, 4 H). ^{13}C NMR (75 MHz, CD_3OD): δ = 180.8, 142.2, 129.9, 128.9, 128.6, 83.1, 76.4, 75.3, 73.4, 29.8, 21.8. MS (ESI): *m*/*z* = 275 $[M + Na]^+$.

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(17) Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 755246 for **17**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

(18) **Analytical and Spectral Data of 7**: white solid; mp 93 °C; $[\alpha]_D^{25}$ +26.4 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.50 (m, 15 H), 4.40–4.64 (m, 4 H), 4.24 (d, *J* = 11.5 Hz, 1 H), 3.99 (t, *J* = 5.7 Hz, 1 H), 3.75 (t, *J* = 5.5 Hz, 1 H), 3.48 (t, *J* = 6.0 Hz, 2 H), 3.38 (d, *J* = 7.6 Hz, 1 H), 2.90 (br s, 3 H), 1.61–1.74 (m, 2 H), 1.38–1.52 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 137.6, 137.5, 128.4, 128.3, 128.2, 128.0, 127.8, 82.6, 78.3, 74.3, 72.3, 72.0, 70.6, 62.5, 28.5, 26.5. MS (ESI): *m*/*z* = 437 $[M + H]^+$.

(19) **Analytical and Spectral Data of 19**: white solid; mp 127 °C; $[\alpha]_D^{25}$ = +3.2 (*c* = 0.5, $CHCl_3$). IR (neat): 3464, 3030, 2923, 1736, 1494, 1452, 1354, 1239, 1201, 1090, 1055, 741, 700, 579 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.54 (m, 15 H), 4.75 (d, *J* = 3.6 Hz, 1 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.41–4.55 (m, 3 H), 4.31 (d, *J* = 11.3 Hz, 1 H), 3.95 (br s, 1 H), 3.74 (dd, *J* = 8.7, 1.5 Hz, 1 H), 2.58–2.76 (m, 1 H), 2.88 (br s, 1 H), 2.35–2.56 (m, 1 H), 2.78–2.15 (m, 1 H), 1.57–1.78 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 137.7, 137.5, 136.3, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 80.7, 80.5, 71.3, 71.1, 71.0, 68.2, 25.4, 23.0. MS (ESI): *m*/*z* = 455 $[M + Na]^+$.

(20) **Analytical and Spectral Data of 1**: $[\alpha]_D^{25}$ +70.3 (*c* = 1.5, MeOH). IR (neat): 3396, 2921, 1756, 1453, 1371, 1270, 1195, 1079, 1043, 917, 815, 705, 578 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.51 (m, 5 H), 4.95 (t, *J* = 6.2 Hz, 1 H), 4.85 (d, *J* = 6.6 Hz, 1 H), 3.93 (t, *J* = 7.6 Hz, 1 H), 3.59 (dd, *J* = 7.9, 1.3 Hz, 1 H), 2.58–2.75 (m, 1 H), 2.39–2.56 (m, 1 H), 2.14–2.38 (m, 2 H), 1.71 (br s, 2 H). ^{13}C NMR (75 MHz, CD_3OD): δ = 180.9, 142.2, 128.6, 128.9, 129.1, 81.3, 76.6, 75.6, 74.4, 29.5, 24.4. MS (ESI): *m*/*z* = 253 $[M + H]^+$.