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First stereoselective total synthesis of Goniothalesdiol A

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ABSTRACT

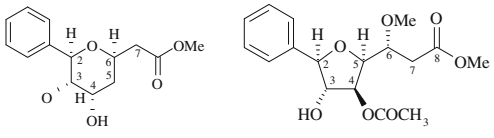
The first total synthesis of Goniothalesdiol A, isolated from the stems of *Goniothalamus amuyon* (Annonaceae) is reported. The C2 stereocentre and C3/C4 *syn* diol were created by a Sharpless kinetic resolution followed by acetonide formation. The tetrahydropyran ring was formed and the C6 stereocentre was fixed by intramolecular oxy-Michael addition.

Natural products with 2,6-disubstituted tetrahydropyran scaffolds have gained prominence recently owing to their excellent biological properties. Several natural products have the substituted pyran moiety with *cis* stereoconnectivity at the 2,6-positions.[1] Some recent examples, which fall into this class, include leucascandrolides,[2] phorboxazoles,[3] (+)-SCH 351448.[4] The synthesis of these compounds has attracted attention owing to their interesting biological properties and challenges posed by the substitution pattern.

The styryl lactones[5] and acetogenins[6] are two major types of bioactive compounds isolated from the *Goniothalamus* (Annonaceae) species. Recently, two new compounds Goniothalesdiol A **1** and Goniothalesacetate **2** (Fig. 1) were isolated from the stems of a southern Taiwan tree *Goniothalamus amuyon*. The structure and relative stereochemistry of **1** were assigned on the basis of NMR spectroscopy and the absolute configuration was predicted by biosynthesis.[7]

In continuation of our interest in synthesising natural products possessing a pyran moiety,[8] we report herein an efficient synthetic route to Goniothalesdiol A involving Chan alkyne reduction, Sharpless kinetic resolution and pyran ring formation by intramolecular oxy-Michael addition as key steps (Scheme 1).

Our synthesis began with the protection of homopropargyl alcohol **3** as its benzyl ether **4** by treating with NaH and benzyl bromide. The ether **4** was treated with *n*-BuLi in THF to generate the lithium acetylide, which was subsequently reacted with benzaldehyde to give propargyl alcohol **5**. Alcohol **5** was reduced with $LiAlH_4$ in THF to afford the allyl alcohol **6**.[9] The key intermediate



Goniothalesdiol A (**1**) Goniothalesacetate (**2**)

Figure 1. Chemical structures of Goniothalesdiol A and Goniothalesacetate.

epoxy alcohol **7** was prepared by the Sharpless kinetic resolution[10] of **6** using D(−)-DET and TBHP (80% yield, 96% ee).

Compound **7** was treated with anhydrous acetone in the presence of $BF_3{\cdot}Et_2O$ at 0 °C to furnish acetonide **8** in 90% yield.[11] This resulted in the fixing of the two hydroxyl groups on C4 and C3 with an axial–equatorial relationship in Goniothalesdiol A **1**, which was confirmed by ^1H NMR analysis (J = 3.8 Hz).

Alcohol **8** was protected as its TBDMS ether **9** by using TBDMSCl and imidazole. The oxidative cleavage of ether **9** with DDQ gave primary alcohol **10** which was subjected to Swern oxidation to give the aldehyde which was treated with phosphorous ylide in refluxing benzene to give the α,β-unsaturated ester **11** with trans-configuration. The TBDMS ether was deprotected by treating with TBAF in dry THF at room temperature to give alcohol **12**. Alcohol **12** was then treated with *p*-TSA in methanol at room temperature to cleave the acetonide followed by intramolecular oxy-Michael addition[12] of the C2 hydroxyl group to the C6, C7 double bond to accomplish the target molecule Goniothalesdiol A **1** (90%) (Scheme 2). The spectral data were identical in all respects with that of the authentic sample.[7,13] The C2, C6 *syn* stereochemistry was achieved during the pyran ring formation and was

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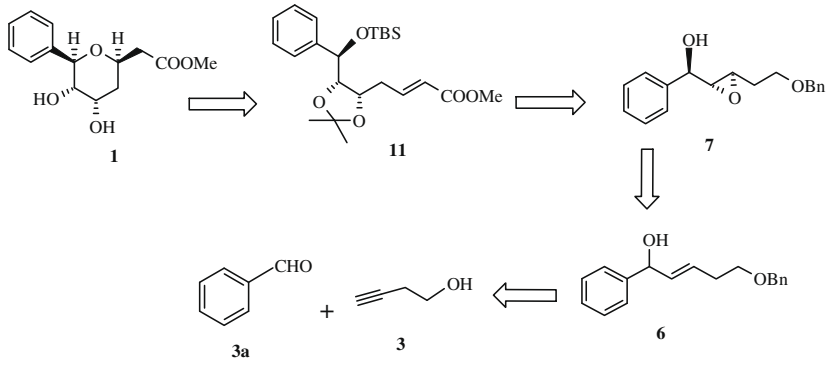
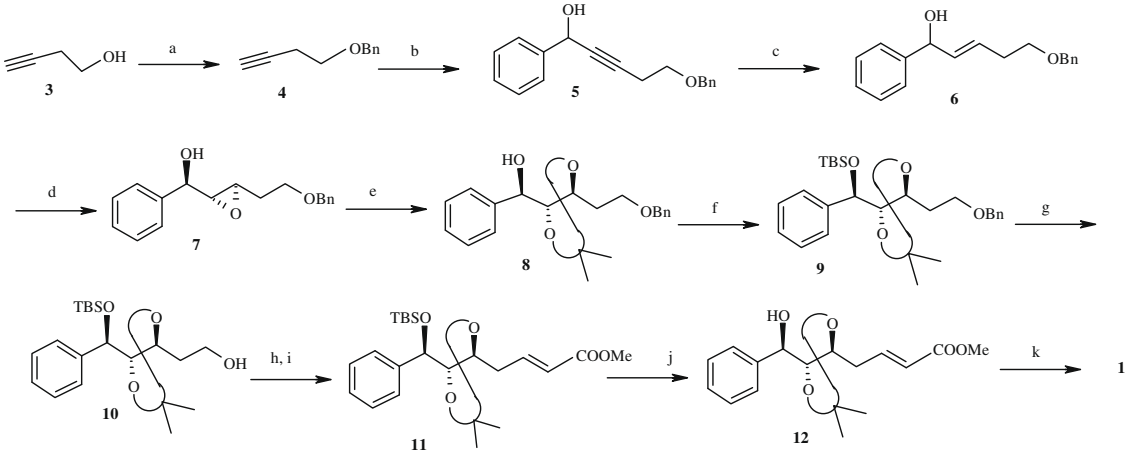


Scheme 1. Retrosynthetic analysis of Goniothalesdiol A.



Scheme 2. *Reagents and conditions*: (a) (i) NaH, DMF, 0–25 °C, 1 h, BnBr, 0–25 °C, 3 h 85%; (b) *n*-BuLi, dry THF, −78 °C, PhCHO, 4 h , 90%; (c) $LiAlH_4$, dry THF, reflux, 3 h, 95%; (d) (−)Diisopropyl-D-tartrate, TBHP, Ti $(O^iPr)_4$, dry DCM, −20 °C, 12 h, 80%; (e) $BF_3{\cdot}Et_2O$, dry acetone, 0 °C, 4 h, 88%; (f) TBDMSOTf, 2,6-lutidine, DCM, 0–25 °C, 1 h, 95%; (g) DDQ, DCM, 25 °C, 2 h , 95%; (h) Oxalyl chloride, dry DMSO, dry DCM, −78 °C, Et_3 N, quant.; (i) $Ph_3P{=}CHCOOMe$, benzene, reflux, 1 h, 80%; (j) TBAF, dry THF, 25 °C, 2 h, quant.; (k) PTSA, methanol, 25 °C, 2 h, 95%.

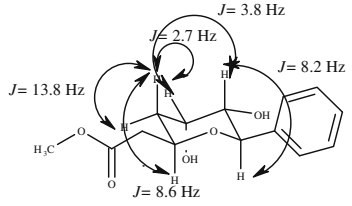


Figure 2. Coupling correlations in ^1H NMR spectroscopy.

confirmed by measuring the coupling constants in ^1H NMR spectroscopy of the final molecule Goniothalesdiol A **1**.

The stereochemistry of Goniothalesdiol A was assigned by analysis of ^1H NMR coupling constants. The *J* 2/3 value 8.2 Hz indicated the axial-axial position of H2 and H3. The observed *J* 5/6 value 8.6 Hz determined the confirmation of H6 as axial and *J* 3/4 Hz value 3.8 Hz indicated the axial–equatorial relationship between H3 and H4 (Fig. 2).

In conclusion, we have described a concise stereoselective synthesis of Goniothalesdiol A in 11 steps from homopropargyl alcohol in a highly stereoselective manner using Sharpless kinetic resolution and intramolecular oxy-Michael addition as key steps.

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13. *Spectroscopic data for compound* (−)-**7**: $[\alpha]_D^{25}$ −3.6 (*c* 1.5, $CHCl_3$); IR (neat): *v* 3425, 2923, 2855, 1491, 1452, 1361, 1098, 897, 739, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.18 (m, 10H), 4.83 (s, 1H), 4.43 (s, 2H), 3.58–3.45 (m, 2H), 3.35–3.25 (m, 1H), 3.0–2.96 (m, 1H), 1.81 (dd, *J* = 5.4, 6.2 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.6, 138, 128.2, 127.5, 126.4, 72.9, 71.0, 66.8, 61.0, 60.2, 53, 31.8. ESI-MS: *m/z* 307 ($M+Na^+$); HRMS for $C_{18}H_{20}O_3Na$: found: 307.1313, calcd: 307.1310. *Spectroscopic data for compound* (−)-**8**: Colourless liquid; $[\alpha]_D^{25}$ −51.7 (*c* 0.65, $CHCl_3$); IR (neat): *v* 3434, 2924, 2855, 1718, 1603, 1492, 1455, 1377, 1205, 1074, 889, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.23 (m, 10H), 4.58–4.55 (d, *J* = 3.0 Hz, 1H), 4.53 (s, 2H), 3.92–3.8 (m, 1H), 3.69–3.56 (m, 2H), 3.3–3.2 (t, *J* = 9.0 Hz, 1H), 2.95 (d, *J* = 2.2 Hz, 1H), 2.0–1.90 (m, 1H), 1.90–1.77 (m, 1H), 1.60 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 137.5, 128.3, 127.7, 127.4, 127.1, 98.8, 73.0, 72.5, 66.6, 34.1, 29.6. ESI-MS: *m/z* 365 ($M+Na^+$). HRMS for $C_{21}H_{26}O_4Na$: found: 365.1726, calcd: 365.1728. *Spectroscopic data for compound* (-)−**11**: Colourless liquid; $[\alpha]_D^{25}$ −53.4 (*c* 0.3, $CHCl_3$). IR (neat): *v* 2925, 2854, 1727, 1657, 1463, 1437, 1381, 1261, 1165, 1095, 864, 836, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.37–8.20 (m, 5H), 8.0–7.87 (m, 1H), 6.83 (d, *J* = 15.8 Hz, 1H), 5.43 (d, *J* = 9.0 Hz, 1H), 4.80–4.65 (m, 1H), 4.70 (s, 1H), 4.31 (t, *J* = 9.0 Hz, 1H), 3.70–3.60 (m, 1H), 3.28–3.15 (m, 1H), 2.54 (s, 3H), 2.34 (s, 3H), 1.73 (s, 9H), 0.84 (s, 3H), 0.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 128.7, 128.3, 122.7, 78.1 73.8, 73.1, 34.8, 29.4, 25.8, 19.4, −4.1, −5.7. ESI-MS: *m/z* 443 ($M+Na^+$); HRMS for $C_{23}H_{36}O_5NaSi$: found: 443.2228, calcd: 443.2229. *Spectroscopic data for Goniothalesdiol* ***A***: White solid, mp 92 °C; $[\alpha]_D^{25}$ −27.2 (*c* 0.3, $CHCl_3$). IR (neat): *v* 3406, 2918, 2849, 2373, 1733, 1435, 1200, 1170, 1068 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.28 (m, 5H), 4.54 (d, *J* = 9.8 Hz, 1H), 4.45–4.35 (m, 1H), 4.24–4.19 (m, 1H), 3.68 (s, 3H), 3.49 (dd, *J* = 9.8, 3.0 Hz, 1H), 2.61 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.45 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.11 (ddd, *J* = 13.5, 3.0, 2.2 Hz, 3H), 1.76 (ddd, *J* = 12.0, 3.0, 2.2 Hz, 3H), 1.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 139.2, 128.4, 128.2, 127.3, 77.7, 72.6, 68.4, 67.0, 51.6, 40.3, 37.1; ESI-MS: *m/z* 267 ($M+H^+$); HRMS for $C_{14}H_{19}O_5$: found: 267.1227, calcd: 267. 1232.