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The first total synthesis of goniothalesdiol

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Abstract—The first total synthesis of goniothalesdiol, a dihydroxylated tetrahydrofuran isolated from *Goniothalamus borneensis* (Annonaceae), and its 7-epimer is described starting with D-mannitol. The key step of these syntheses is palladium(II)-catalyzed oxycarbonylation of unsaturated triols with D-*lyxo* and D-*xylo* configuration, respectively, which allowed efficient construction of the tetrahydrofuran ring with excellent *threo*-selectivity at the newly formed stereogenic centre.

The genus *Goniothalamus* (Annonaceae) is well known as an interesting source of various bioactive compounds; acetogenins,[1] alkaloids,[2] styryl-lactones[3] and flavanoids.[4] Recently a new natural compound, goniothalesdiol **1** (Fig. 1), was isolated from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae), and has been revealed to have significant cytotoxicity against P388 mouse leukemia cells, and insecticidal activities.[5] The structure and relative stereochemistry of **1** was assigned on the basis of ^{1}H, ^{13}C NMR spectroscopy and the absolute configuration was confirmed by semi-synthesis from natural (+)-goniothalenol.

In the course of our program directed towards the application of palladium(II)-catalyzed oxycarbonylation of unsaturated polyols[6] to natural product synthesis, we have developed the syntheses of goniofufurone,[7a,b] 7-*epi*-goniofufurone,[7a,b] and erythroskyrine.[7c] Herein, we report on the first total synthesis of goniothalesdiol **1** and 7-*epi*-goniothalesdiol **2**.

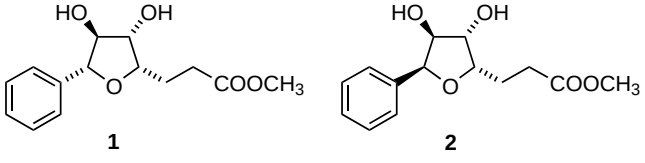

Figure 1. Goniothalesdiol **1** and 7-*epi*-goniothalesdiol **2**.

Keywords: palladium(II) catalysis; stereoselective oxycarbonylation; natural products; goniothalesdiol.

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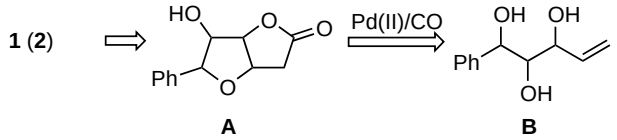
To the best of our knowledge, there is only one paper in the literature which deals with the synthesis of 7-*epi*-goniothalesdiol from D-tartaric acid based on Lewis acid-promoted hydrogenation.[8] Our synthetic plan relies on a successful $PdCl_2$-catalyzed oxycarbonylation of C_5- and C_6-enitols, leading to corresponding 3,6-anhydro-2-deoxy-1,4-glyconolactones with high regiopreference and excellent *threo*-selectivity concerning the newly formed stereogenic centre.[6]

Thus, the targets could be accessible from hexonolactones **A** of D-*gluco* and L-*ido* configuration, respectively, which can be obtained by oxycarbonylating bicyclization of the unsaturated triols **B** of the required configuration (Scheme 1).

The intermediates for oxycarbonylation, the 1-phenyl-4-pentenitols **6** and **7** with D-*lyxo* and D-*xylo* configuration were obtained from D-mannitol via the route using standard carbohydrate chemistry (Scheme 2). Following the reaction sequence, acetonization of D-mannitol,[9] selective hydrolysis of the terminal acetonide,[9] *O*-mesylation of both unprotected hydroxyl groups, reductive elimination with sodium iodide[10] and subsequent selective hydrolysis of the next terminal acetonide with HCl in ethanol, the tetraol **3** was readily prepared. Treatment of **3** with sodium periodate in water furnished the



Scheme 1. Retrosynthetic analysis of **1** and **2**.

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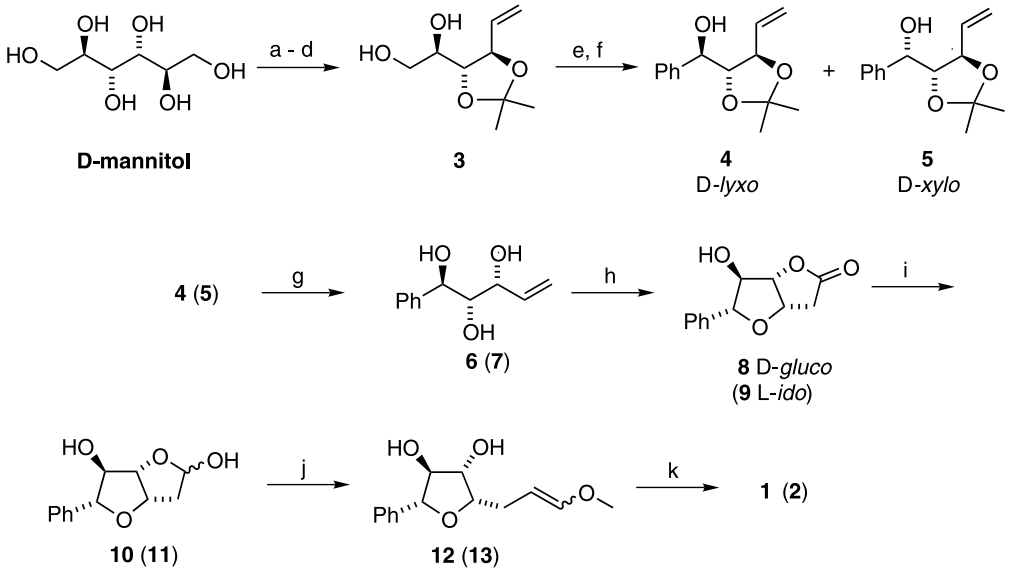

Scheme 2. *Reagents and conditions*: (a) (1) lit.[9] H_2SO_4, acetone; (2) H_2O, HCl, 43%; (b) lit.[10] MsCl, pyridine; 90%; (c) lit.[10] NaI, acetone, 80%; (d) HCl, EtOH, 38%; (e) (1) $NaIO_4$, H_2O, 90%; (2) PhMgBr, THF, 55% (**4**:**5**, d.r. 50:50); (f) flash chromatography; (g) HCl, EtOH, 90% of **6** (90% of **7**); (h) $PdCl_2$, $CuCl_2$, AcONa, AcOH, CO, 70% of **8** (85% of **9**); (i) DIBAL-H, CH_2Cl_2, 90% of **10** (90% of **11**); (j) $Ph_3PCH_2OCH_3Cl$, ^{t}BuOK, ^{t}BuOH–THF, 55% of **12** (58% of **13**); (k) (1) H_2SO_4, dioxane; (2) Ag_2O, NaOH, H_2O; (3) H_2SO_4, MeOH, 50% of **1** (45% of **2**).

corresponding aldehyde in 90% yield, which was subjected without further purification to Grignard addition with phenylmagnesium bromide in THF. A diastereomeric mixture of D-*lyxo* (**4**) and D-*xylo* (**5**) partially protected pentitols in the ratio 50:50 and 55% yield was obtained. After flash chromatography on silica (EtOAc–hexane 1:20), the following syntheses were run in parallel with the pure diastereomers.

Firstly, the protecting group was removed by acidic hydrolysis in ethanol (90%) and the unprotected pentitols **6** and **7** were exposed to oxycarbonylation. The reaction was carried out under standard conditions with palladium(II) chloride as catalyst (0.1 equiv.), copper(II) chloride as oxidant (3 equiv.), sodium acetate (3 equiv.) in acetic acid as buffer under a carbon monoxide atmosphere (balloon) at room temperature. Only required lactones **8** and **9**, respectively, with high regio- and *threo*-selectivity were formed as expected.[6,7] After flash chromatography and recrystallization the key intermediates **8** in 70% ($[\alpha]_D^{25}=-75$ (*c* 0.38, CH_2Cl_2) and **9** in 85% yield (mp 177–179°C, $[\alpha]_D^{25}=+38$ (*c* 0.31, CH_3OH) were isolated. The configuration of both lactones, D-*gluco* for **8** (intermediate with correct stereochemistry for the natural product) and L-*ido* for **9** (precursor of **2**) was established by comparison of ^{1}H NMR data and coupling constants ($J_{5,6}=0$ Hz for **8**, indicated a *trans* relationship versus $J_{5,6}=3.6$ Hz for **9**, corresponding to a *cis* arrangement)[11] with the literature data of 3,6-anhydro-2-deoxy-1,4-heptonolactones of the same configurations.[6a] The final confirmation of the absolute stereochemistry came from single crystal X-ray analysis of **9**.[12]

The syntheses continued with partial reduction of the lactones using diisobutylaluminium hydride in CH_2Cl_2 at −78°C affording a mixture of anomeric lactols **10** and **11** (*exo*:*endo*, 9:1 and 90% yields in both cases), which were transformed to tetrahydrofuran derivatives **12** and **13** by Wittig reaction with (methoxymethylene)-triphenylphosphonium chloride and potassium *tert*-butoxide in ^{t}BuOH–THF (55 and 58%).

Finally, the *E*/*Z*-isomeric mixtures (*E*:*Z*, 2:1) of **12** and **13** were subjected to a three-step sequence in one-pot to convert the vinyl ether to the methyl carboxylate. Ether cleavage with sulfuric acid in dioxane, followed by Ag_2O oxidation of the aldehyde and an acidic esterification with methanol afforded the target goniothalesdiol **1** and its 7-epimer **2** in 55 and 45% yields, respectively, over three steps.

The physical and spectroscopic data of **1** and **2** were in good agreement[13] with the reported data for the natural product[2] and its 7-epimer.[8]

In conclusion, (+)-goniothalesdiol and (+)-7-*epi*-goniothalesdiol have been synthesized in a short sequence from commercially available and cheap D-mannitol using palladium(II)-catalyzed oxycarbonylation methodology for construction of the tetrahydrofuran ring.

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11. 3,6-Anhydro-2-deoxy-6-phenyl-D-*gluco*-1,4-hexonolactone {(1*S*,5*S*,7*R*,8*R*)-8-hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.0]octan-3-one} **8**: ^{1}H NMR (300 MHz, DMSO-d_6, TMS, numbered according to carbohydrate name): 2.64 (d, 1H, $J_{2A,2B}=18$ Hz, H-2), 2.97 (dd, 1H, $J_{2A,2B}=18$ Hz, $J_{2,3}=2.7$ Hz, H-2), 4.06 (dd, 1H, $J_{5,OH}=5.1$ Hz, $J_{4,5}=5.4$ Hz, H-5), 4.66 (d, 1H, $J_{4,5}=5.7$ Hz, H-4), 4.87 (bs, 2H, H-3, H-6), 5.97 (d, 1H, $J_{5,OH}=5.1$ Hz, OH), 7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): 35.7 (t, C-2), 77.4 (d, C-5), 81.8 (d, C-3), 86.8 (d, C-4), 90.1 (d, C-6), 125.8 (d, C-2′), 127.7 (d, C-4′), 128.3 (d, C-3′), 139.4 (s, C-1′), 175.5 (s, C-1).
3,6-Anhydro-2-deoxy-6-phenyl-L-*ido*-1,4-hexonolactone {(1*S*,5*S*,7*S*,8*R*)-8-hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.0]octan-3-one} **9**: ^{1}H NMR (300 MHz, DMSO-d_6, TMS, numbered according to carbohydrate name): 2.47 (d, 1H, $J_{2A,2B}=18.3$ Hz, H-2), 2.86 (dd, 1H, $J_{2A,2B}=18.3$ Hz, $J_{2,3}=6.6$ Hz, H-2), 4.20 (dd, 1H, $J_{5,OH}=5.1$ Hz, $J_{5,6}=3.6$ Hz, H-5), 4.88 (2×d, 2H, $J_{3,4}=3.5$ Hz, $J_{5,6}=3.6$ Hz, H-4, H-6), 4.94 (dd, 1H, $J_{2,3}=6.0$ Hz, $J_{3,4}=3.8$ Hz, H-3), 5.19 (d, 1H, $J_{5,OH}=5.4$ Hz, OH), 7.20 (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): 35.7 (t, C-2), 74.4 (d, C-5), 76.4 (d, C-3), 82.2 (d, C-4), 88.1 (d, C-6), 127.1 (d, C-4′), 127.3 (d, C-2′), 127.4 (d, C-3′), 136.7 (s, C-1′), 176.0 (s, C-1).
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13. Goniothalesdiol **1**: $[\alpha]_D^{25}=+6.5$ (*c* 0.6, EtOH) {lit.[5] $[\alpha]_D^{25}=+7.5$ (*c* 0.23, EtOH)}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS, numbered according to carbohydrate nomenclature): 2.09 (m, 2H, H-3), 2.55 (m, 2H, H-2), 3.68 (s, 3H, OMe), 4.03–4.07 (m, 3H, H-4, H-5, H-6), 4.59 (d, 1H, $J_{6,7}=4.5$ Hz, H-7), 7.25 (d, 1H, $J=7.0$ Hz, H-4′), 7.33 (t, 2H, $J=7.0$ Hz, H-3′, H-5′), 7.41 (d, 2H, $J=7.0$ Hz, H-2′, H-6′); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): 23.7 (t, C-3), 30.6 (t, C-2), 51.9 (q, OMe), 79.0 (d, C-5), 80.7 (d, C-4), 85.3 (d, C-6), 86.1 (d, C-7), 126.1 (d, C-3′, C-5′), 127.9 (d, C-4′), 128.7 (d, C-2′, C-6′), 139.9 (s, C-1′), 174.7 (s, C-1).
7-*epi*-Goniothalesdiol **2**: $[\alpha]_D^{20}=+70.3$ (*c* 0.23, EtOH) {lit.[8] $[\alpha]_D^{29}=+66.6$ (*c* 0.74, EtOH)}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS, numbered according to carbohydrate nomenclature): 2.07 (dd, 2H, $J_{2,3}=J_{3,4}=7.2$ Hz, H-3), 2.40–2.65 (m, 2H, H-2), 3.70 (s, 3H, OMe), 4.16 (d, 1H, $J_{6,7}=3.0$ Hz, H-6), 4.21 (d, 1H, $J_{4,5}=2.7$ Hz, H-5), 4.31 (dt, 1H, $J_{3,4}=7.2$ Hz, $J_{4,5}=3.0$ Hz, H-4), 5.32 (d, 1H, $J_{6,7}=3.0$ Hz, H-7), 7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): 23.5 (t, C-3), 30.6 (t, C-2), 52.0 (q, OMe), 76.9 (d, C-5), 79.1 (d, C-4), 81.4 (d, C-6), 82.3 (d, C-7), 126.7 (d, C-3′, C-5′), 127.9 (d, C-4′), 128.6 (d, C-2′, C-6′), 136.8 (s, C-1′), 175.1 (s, C-1).