Goniodiol and 9-Deoxygoniopypyrone: Syntheses and Absolute Configurations

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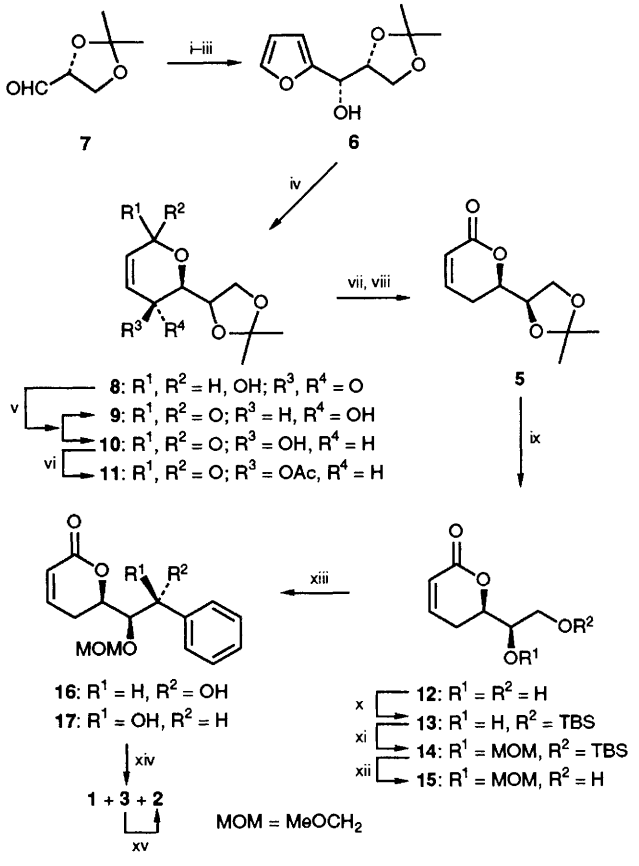
The absolute configurations of natural goniodiol and 9-deoxygoniopypyrone are confirmed as **1** and **2** respectively by enantioselective syntheses starting from (2*S*,3*R*)-1,2-*O*-isopropylidene-3-(2-furyl)glycerol **6**.

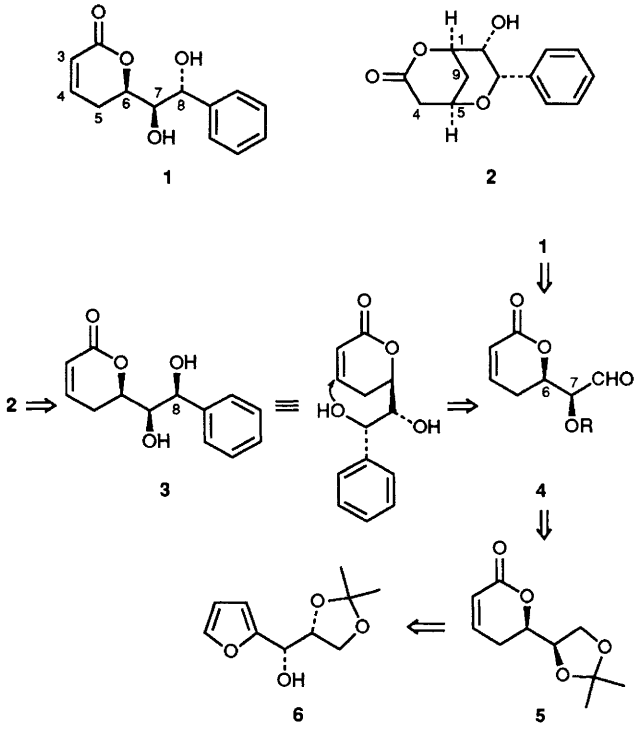
Goniodiol was isolated from the leaves and twigs of *Goniothalamus sesquipedalis*.[1] Recently, a novel styryl lactone, 9-deoxygoniopypyrone, and goniodiol have been isolated from the stem bark of *Goniothalamus giganteus* and shown to have significant cytotoxic activity.[2] The relative configurations of goniodiol and 9-deoxygoniopypyrone were determined to be **1** and **2** respectively or their enantiomers by NMR spectral studies[1,2] and X-ray crystallographic analysis.[2] As part of our continuing work on the synthesis of naturally occurring lactonic antibiotics using furylmethanols,[3] we are interested in the enantioselective syntheses of **1** and **2**, and report here their first syntheses, also confirming their absolute configurations.

Based on retrosynthetic analysis of **1** and **2**, the lactonic aldehyde **4** having a *syn*-diol system at C-6 and C-7 was chosen as a common intermediate (Scheme 1). We thought that introduction of a phenyl function to **4** could afford both **1** and its 8-epimer **3**, and the latter could be transformed into **2** by an intramolecular Michael addition reaction. The stereochemical course of the cyclisation should be controlled in the intermediate *cis*-fused [3.3.1]bicyclic ring system owing to the preexisting stereocentre at C-6. Aldehyde **4** with the correct absolute stereochemistries should be available from the known chiral furylmethanol **6**[4] *via* the α,β-unsaturated lactone **5** on the basis of our previous work.[3d,e]

The synthesis of **1** and **2**, which we have developed, are shown in Scheme 2. Homochiral alcohol **6** was prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde **7**[5] according to Jurczak's protocol.[6] A mixture of diastereoisomeric furylmethanols,[4] obtained from 2-lithiofuran and **7**, was oxidised with chemical manganese dioxide to afford the ketone, which on treatment with L-Selectride furnished **6**,† m.p. 62–62.5 °C; $[\alpha]_D^{24}$ −10.2(*c* 1.1, $CHCl_3$). Treatment of **6** with *N*-bromosuccinimide (NBS)[7] in aqueous tetrahydrofuran (THF) brought about ring transformation to afford the lactol **8** quantitatively. Oxidation of **8** with chromium(VI) oxide[8] in acetic acid (AcOH) gave the unstable lactone, which without isolation was reduced with sodium triacetoxyborohydride in the same pot to provide the allyl alcohols **9** and **10** in a ratio of 1 : 7. Deoxygenation[3d,e] of **10** was carried out by sequential acetylation of **10**, reductive deacetoxylation of the allyl acetate



Scheme 2 *Reagents and conditions*: i, 2-lithiofuran, THF, −78 °C (92%); ii, MnO_2, MeCN, room temp., 3 days; iii, L-Selectride, THF, −78 °C [84% (2 steps)]; iv, NBS, 80% aq. THF, 0 °C (97%); v, CrO_3, AcOH, room temp., 0.5 h; then Pr^iOH, $NaBH(OAc)_3$, −20 °C (41% from **6**), **9** : **10** = 1 : 7; vi, Ac_2O, pyridine, cat. 4-*N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp. (99%); vii, Zn, $CuSO_4 \cdot 5H_2O$, AcONa, 50% aq. AcOH, THF, 0 °C to room temp., 1 h (92%); viii, cat. DBU, THF, room temp., 16 h (99%); ix, 75% aq. AcOH, THF, 40 ° C, 2 h (99%); x, Bu^tMe_2SiCl, Et_3N, cat. DMAP, CH_2Cl_2, room temp. (99%); xi, $MeOCH_2Cl$, Pr^i_2NEt, cat. DMAP, CH_2Cl_2, room temp. (99%); xii, 75% aq. AcOH, 50 °C, 5 h (89%); xiii, $(COCl)_2$, Me_2SO, CH_2Cl_2, −65 °C, Et_3N, then *ca.* 0.4 mol dm^{-3} $PhTi(OPr^i)_3$ in Et_2O, 0 °C, 1 h (94% from **15**), **16** : **17** ≈ 1 : 1; xiv, 75% aq. AcOH, 65 °C, 4 h (97%), **1** : **3** : **2** = 10.7 : 9.4 : 1, xv, cat. DBU, THF, room temp. 15 h (82%)



Scheme 1

† Satisfactory analytical and spectral data were obtained for all new compounds.

11 and isomerisation of the β,γ-unsaturated lactone to furnish the lactone **5**, $[\alpha]_D^{28}$ + 134.3 (*c* 1.5, $CHCl_3$), in 90% overall yield from **10**. Acid removal of the acetonide group in **5** afforded the diol **12**, m.p. 84–84.5 °C; $[\alpha]_D^{28}$ + 101.3 (*c* 1.5, MeOH), which was further converted into the alcohol **15**, $[\alpha]_D^{25}$ + 148.6 (*c* 0.9, $CHCl_3$), by sequential selective silylation of the primary alcohol in **12**, methoxymethylation of the secondary alcohol in **13** and desilylation of the ether **14** in 86% overall yield from **5**. Swern oxidation[9] of **15** followed by chemoselective phenylation of the aldehyde **4** (R = MOM)‡ with triisopropoxyphenyltitanium[10] in one pot afforded an inseparable mixture of diastereoisomers **16** and **17** (*ca.* 1 : 1). Deprotection of the methoxymethyl group in **16** and **17** with aqueous AcOH provided goniodiol **1** (49.4%) as a colourless oil, $[\alpha]_D^{25}$ + 74.8 (*c* 0.7, $CHCl_3$) { lit. $[\alpha]_D^{30}$ + 75.76 ($CHCl_3$)[1] and $[\alpha]_D^{22}$ + 74.4 (*c* 0.3, $CDCl_3$)[2]}, and 8-epigoniodiol **3** (43.2%) as a colourless oil, $[\alpha]_D^{25}$ −13.7 (*c* 0.7, $CHCl_3$), together with 9-deoxygoniopypyrone **2** (4.6%). Treatment of **3** with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF brought about the intramolecular Michael addition reaction to furnish the desired compound **2** as colourless needles, m.p. 203–204 °C (lit.[2] 203–204 °C); $[\alpha]_D^{26}$ + 11.1 (*c* 0.3, EtOH) [lit.[2] + 12 (*c* 0.1, EtOH)]. Since the spectroscopic data including the optical rotations of both synthetic goniodiol **1** and 9-deoxygoniopypyrone **2** are identical with those of natural products,[1,2] the absolute configurations of goniodiol and 9-deoxygoniopypyrone are unambiguously determined to be **1** and **2**, respectively.

‡ Since the aldehyde **4** could not be isolated owing to its instability, **4** was prepared *in situ* by Swern oxidation of **15**.

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