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A total synthesis of (+)-Goniodiol using an anomeric oxygen-to-carbon rearrangement

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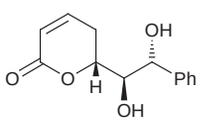
A new route to (+)-Goniodiol 1, a potent and selective cytotoxin, is described, using a diastereoselective oxygen-to-carbon rearrangement of an anomerically linked silyl enol ether as the key step.

Studies on natural products isolated from Asian trees of the genus *Goniothalamus* have led to the discovery of several classes of compounds with interesting biological properties, including acetogenins, alkaloids and styrylactones. For example, (+)-Goniodiol † **1** was isolated from petroleum ether extracts of the



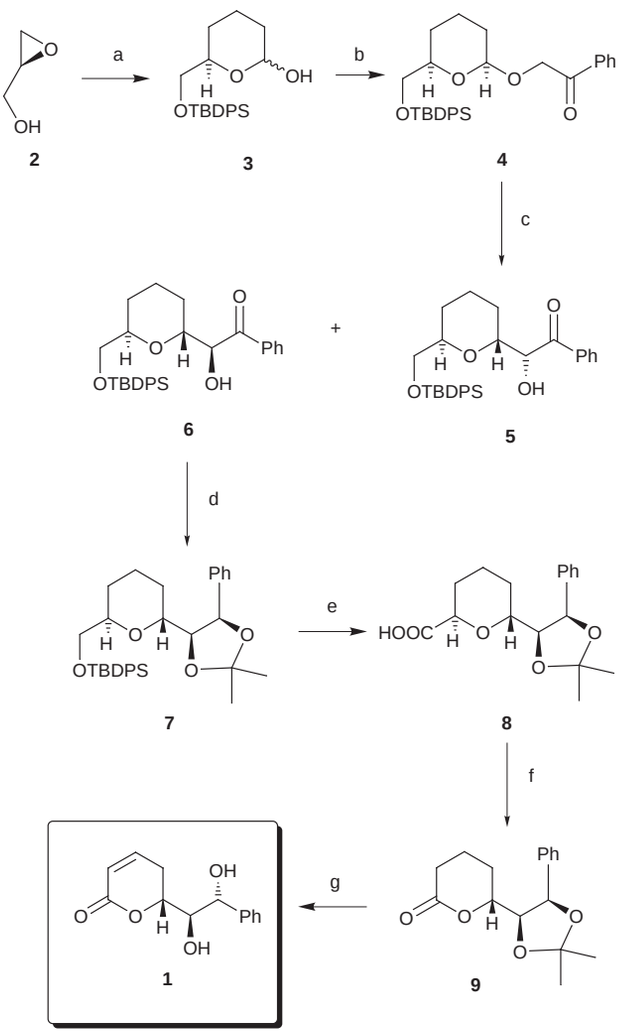
Goniodiol **1**

leaves and twigs of *Goniothalamus sesquipedalis*,[1] and shown to have potent and selective cytotoxic activity against A-549 human lung carcinoma.[2] Closely related derivatives have since been found in a number of other *Goniothalamus* species.[3]

We have recently communicated a general method for the introduction of carbon linked substituents adjacent to the heteroatom in pyran ring systems *via* Lewis acid mediated oxygen-to-carbon rearrangements of a variety of different anomerically linked carbon centred nucleophiles.[4a–c] For the total synthesis of (+)-Goniodiol[5] reported here we anticipated that an anomeric rearrangement of this type, using a silyl enol ether as the nucleophile, could be used to introduce important elements of the functionality present in the target molecule. We envisaged using a protected hydroxymethyl group opposite to the anomeric position to control the stereochemistry at C-5 in the rearrangement step and we hoped for some degree of concurrent diastereocontrol at C-6, similar to that seen in previous examples.[4c] Furthermore, we expected that the protected hydroxymethyl group could be efficiently converted to the lactone present at C-1 of (+)-Goniodiol in the final stages of the synthesis.

The synthesis begins from commercially available *S*-(−)-glycidol **2** (Scheme 1). Treatment with *tert*-butyldiphenylsilyl chloride in the presence of Et_3N gave the protected alcohol in 86% yield. Subsequent addition of 1.2 equivalents of but-3-enylmagnesium bromide in the presence of 0.1 equivalents of dilithium copper(II) chloride[6] proceeded with exclusive attack at the less substituted end of the epoxide to afford the corresponding alkenol in 99% yield. Reductive ozonolysis of this material afforded lactol **3** in 99% yield. Alkylation of **3** with α-bromo-*N*-methyl-*N*-methoxyacetamide in the presence of KHMDS afforded 81% yield, at 84% conversion, of the *cis* anomerically-linked amide. Subsequent treatment with phenylmagnesium bromide in THF at −30 °C led directly to the phenyl ketone **4** in 95% yield.[7,8]

With gram quantities of **4** in hand, we were in a position to examine the key oxygen-to-carbon rearrangement step. Treatment of **4** with 1.4 equivalents of Et_3N followed by 1.2 equivalents of trimethylsilyl triflate at 0 °C afforded the TMS enol ether exclusively as the *Z*-isomer.[9] On exposure to 0.1 equivalents of TMSOTf at −30 °C this was smoothly converted to the exclusively *trans* α-hydroxy ketones **5** and **6** (**5**:**6**, dr 1:1), as a separable mixture, in 88% overall combined yield from **4**.[10] Somewhat surprisingly, unlike our previous study,[4c] no control is observed at the position adjacent to the ring.



Scheme 1 *Reagents and conditions*:‡ (a) i. TBDPSCl, Et_3N, CH_2Cl_2 (86%); ii. 1.2 eq. but-3-enylmagnesium bromide, 0.1 eq. $CuLi_2Cl_2$, THF, −30 °C, 5 min (99%); iii. O_3, CH_2Cl_2, −78 °C, 10 min, then PPh_3, rt, 12 h (99%); (b) i. 0.5 M KHMDS in toluene, $BrCH_2CON(OMe)Me$, THF, −78 °C, 2 h (81% + 16% returned **3**); ii. PhMgBr, THF, −30 °C, 2 min (95%); (c) i. 1.4 eq. Et_3N then 1.2 eq. TMSOTf, CH_2Cl_2, 0 °C, 30 min; ii. 0.1 eq. TMSOTf, CH_2Cl_2, −30 °C, 5 min (88% combined yield over two steps from **4**); (d) i. 2 eq. $NaBH_4$, MeOH, 0 °C, 5 min; ii. $CH_3C(OMe)_2CH_3$, acetone, cat. CSA, rt, 30 min (95% over two steps from **6**); (e) i. 1 M TBAF in THF, rt, 4 h (96%); ii. DMSO, $(ClCO)_2$, −78 °C, 30 min then Et_3N, rt, 1 h (93%); iii. NaO_2Cl, ^tBuOH, H_2O, $KHPO_4$, 2-methylbut-2-ene, rt, 10 min; (f) i. $Pb(OAc)_4$, py, THF, rt, 1 h (68% over two steps); ii. 0.5 eq. NaOMe, MeOH, rt, 30 min; iii. TPAP, NMO, CH_2Cl_2, 4 Å sieves, rt, 10 min (97% over two steps); (g) i. 3 eq. LDA, THF then 3 eq. PhSeCl, −78 °C, 1 h; ii. 30% H_2O_2, CH_2Cl_2, 0 °C (82% over two steps from **9**); iii. 50% aq. AcOH, 80 °C, 30 min (97%).

The stereochemistry present at C-7 of (+)-Goniodiol was

introduced *via* a highly diastereoselective reduction of the ketone moiety of **6** (>95% de) using 2 equivalents of $NaBH_4$ in MeOH at 0 °C. Subsequent reaction with 2,2-dimethoxypropane in acetone with catalytic camphorsulfonic acid gave the protected diol **7** in 95% yield from **6**. The sequence to convert the *tert*-butyldiphenylsilyl protected alcohol of **7** into the α,β-unsaturated lactone of the natural product was initiated by treatment with TBAF to release the free alcohol in 96% yield. Oxidation to the aldehyde using Swern's protocol[11] in 93% yield, was followed by exposure to NaO_2Cl, $KHPO_4$ and 2-methylbut-2-ene in 1:2 water–^{t}BuOH[12] to give acid **8**, which was used without further purification.

Exposure of acid **8** to lead tetraacetate[13] in the presence of pyridine in THF at room temperature afforded the anomeric acetate in 68% yield, as a 2:1 mixture of anomers. Deacetylation using 0.5 equivalents of NaOMe in MeOH was followed by oxidation with tetra *n*-propylammonium perruthenate[14] (TPAP) to give the lactone **9** in 97% overall yield. Introduction of the α,β-unsaturation was achieved *via* α-selenation followed by oxidative elimination with H_2O_2 (82% from **9**). Final deprotection of the C-6, C-7 diol with 50% aqueous AcOH at 80 °C for 30 minutes gave the natural product (+)-Goniodiol in 97% yield. The ^{1}H NMR, ^{13}C NMR, IR and mass spectra of this synthetic sample were all in excellent agreement with previously published data.[1,3] The specific rotation, $[\alpha]_D^{30} = +71.4°$ (*c* 0.74, $CHCl_3$), was also in good agreement with that reported for the natural product, $[\alpha]_D^{22} = +74.4°$ (*c* 0.3, $CHCl_3$).[3]

The route to (+)-Goniodiol described above illustrates the utility of the anomeric oxygen-to-carbon rearrangement in natural product synthesis. It provides rapid and diastereoselective access to a densely functionalised molecule, starting from a commercially available starting material, which was subsequently converted to the desired product *via* a short reaction sequence.

Acknowledgements

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Notes and References

† IUPAC name: 6-(1,2-dihydroxyphenethyl)-5,6-dihydro-2-pyrone.
‡ Satisfactory acurate mass and/or microanalysis data was obtained for all new compounds.

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