Total Synthesis of the Natural Goniodiol-8-monoacetate from Cinnamyl Alcohol

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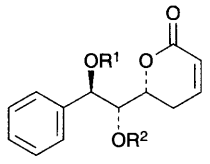
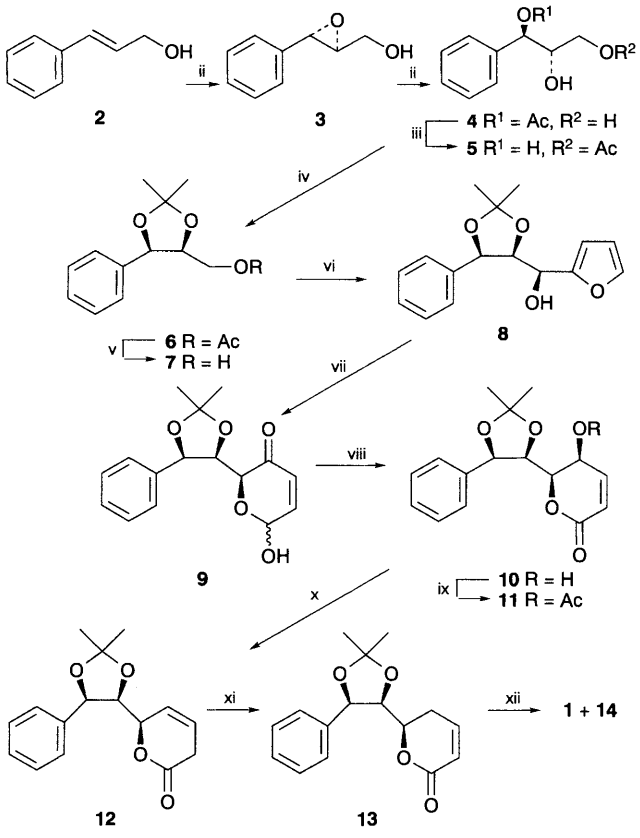
The first total synthesis of goniodiol-8-monoacetate, using the Sharpless asymmetric epoxidation starting from cinnamyl alcohol in twelve steps with an overall yield of 7%, is achieved.

In 1992, a novel bioactive styryl lactone, goniodiol-8-monoacetate **1**, was isolated from the leaves of *Goniothalamus amuyon*,[1] and shown to have significant cytotoxic activities toward several human tumour cells. The structure and relative configuration of **1** have been determined by spectroscopic studies.[1] As a part of our work on styryl lactones, we report herein the first asymmetric total synthesis of **1**.



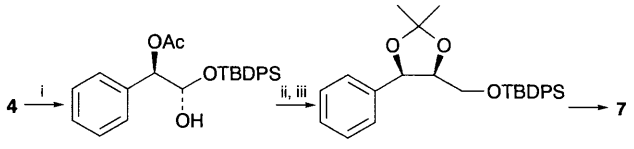
1 R^1 = Ac, R^2 = H
14 R^1 = Ac, R^2 = Ac



Scheme 1 *Reagents and conditions*: i, TBHP, $Ti(OPr^i)_4$, L-(+)-DIPT, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 86%; ii, $Ti(OAc)(OPr^i)_3$, $CHCl_3$, −20 to 0 °C, 90%; iii, 1 mol dm^{-3} HCl, silica gel, THF, room temp., 84%; iv, $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, room temp., 8 h; v, 15% NaOH, THF, H_2O, room temp., 90% from **5**; vi, Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 to −20 °C then 2-lithiofuran, THF, −78 to −30 °C, 74%; vii, TBHP, $VO(acac)_2$, CH_2Cl_2, 0 °C, 84%; viii, CrO_3, HOAc, 25–30 °C, 15 min; then $NaBH(OAc)_3$, Pr^iOH–HOAc (1 : 1), −10 °C to room temp., 60%; ix, Ac_2O, Py, DMAP, CH_2Cl_2, room temp., 4 h, 98%; x, Zn–Hg, HCl, Et_2O, room temp., 4 h, 87%; xi, DBU, C_6H_6, 80 °C, 2 h, 85%; xii, TFA, H_2O, room temp., 4 h, then Ac_2O, py, DMAP, CH_2Cl_2, 0 °C to room temp., 44%

The catalytic Sharpless asymmetric epoxidation[2] of cinnamyl alcohol **2** using L-(+)-diisopropyl tartrate [0.1 equiv.; 0.05 equiv. $Ti(OPr)_4$, 4 Å molecular sieves] as chiral ligand yielded 2α,3α-epoxyalcohol **3** in 86% yield, mp 50–51 °C, $[\alpha]_D^{20}$ −50.9 (*c* 1.3, $CHCl_3$), {lit.[3] mp 51–52 °C, $[\alpha]_D^{20}$ −51.7 (*c* 1.2, $CHCl_3$)}. Highly regioselective cleavage of the oxirane ring of **3** with triisopropoxytitanium acetate[4] successfully afforded acetate **4** in 90% yield, $[\alpha]_D^{20}$ −77.2 (*c* 1.9, $CHCl_3$). Acid treatment of **4** with silica gel and HCl in THF caused the migration of the acetoxy group from the secondary to the primary hydroxy group to provide acetate **5** in 84% yield,† $[\alpha]_D^{20}$ −83.1 (*c* 1.1, $CHCl_3$). Protection of the diol **5** with 2,2-dimethoxypropane followed by deacetoxylation with 15% aq. NaOH in THF afforded the alcohol **7** in 90% overall yield from **5**, mp 57–58 °C, $[\alpha]_D^{20}$ −112 (*c* 1.2, $CHCl_3$), 98% ee.‡ The conversion of **4** into **7** by the route in Scheme 2 gave a product with an identical $[\alpha]_D^{20}$. The optical purity of **7** was determined by GC (98% enantiomeric excess) on a chiral column (Cydex-B). Swern oxidation afforded a unstable aldehyde, which was immediately treated with 2-furyllithium[5] to give the *syn*-adduct **8** as colourless prisms§ in 74% yield, together with the *anti*-adduct as an oil in 2.4% yield. The *syn*-configuration in compound **8** was confirmed by X-ray diffraction analysis (Fig. 1).¶

Oxidation of furylmethanol **8** with *tert*-butylhydroperoxide in the presence of $VO(acac)_2$ gave compound **9** as a mixture of α- and β-anomers. Oxidation of **9** with chromium(VI) oxide in acetic acid followed by immediate reduction with sodium triacetoxyborohydride[6] in one pot furnished the allyl alcohol **10** in 60% yield. Acetylation of **10** with acetic anhydride furnished the acetate **11** in 98% yield. Reductive deacetoxylation of acetate **11** with zinc amalgam in ethereal hydrogen chloride[7]



Scheme 2 *Reagents and conditions*: i, TBDPSCl, imidazole, THF, room temp.; ii, 15% NaOH, THF, H_2O, room temp.; iii, $Me_2C(OMe)_2$, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2, room temp.; iv, Bu^n_4NF, THF, 0 °C

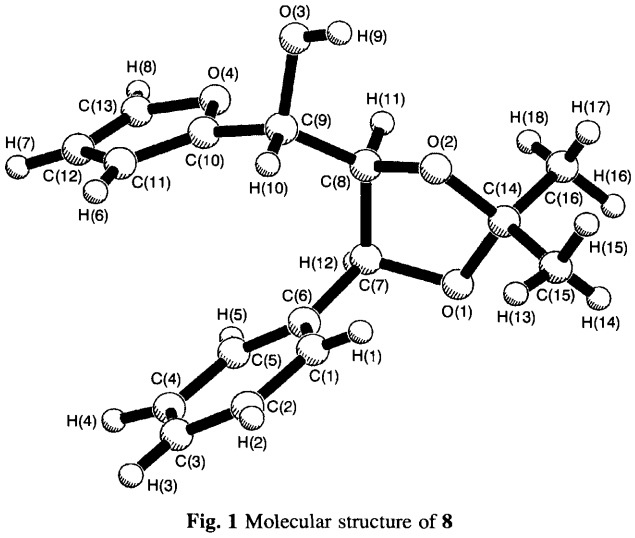


Fig. 1 Molecular structure of **8**

gave the olefin **12** in 87% yield.§ Reconjugation of **12** with DBU produced the lactone **13** in 85% yield (reconjugation of **12** with triethylamine only gave poor yield),[8] mp 133–134 °C, $[\alpha]_D^{20}$ −100 (*c* 0.9, EtOH). Hydrolysis of ketal **13** with trifluoroacetic acid and water (3 : 1) followed by acetylation of **13** with acetic anhydride afforded **1** in 44% overall yield in two steps, mp 110–111 °C, $[\alpha]_D^{20}$ + 44 (*c* 0.3, $CHCl_3$), {lit.[1] mp 111–113 °C, $[\alpha]_D^{20}$ +43 (*c* 0.1, $CHCl_3$)}, and another natural styryl lactone, goniodiol diacetate **14**,[9] in 38% overall yield, mp 150–151 °C, $[\alpha]_D^{20}$ +82 (*c* 0.5, $CHCl_3$) {lit.[11] mp 150 °C, $[\alpha]_D^{20}$ + 84.5 ($CHCl_3$)}.

Since the spectroscopic data of the synthetic **1** are in accord with the data for natural **1**[1] and the X-ray diffraction analysis of **8** is determined, the absolute configuration of the goniodiol-8-monoacetate is confirmed as **1**.

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Footnotes

† It has been reported[4] that the acetoxy groups on polyols have a proclivity to migrate from secondary to primary hydroxy groups with minimal loss of optical purity in mild alkaline medium.

‡ The ee value was determined by GLC analysis on a chiral column (CYDEX-b).

§ *Selected analytical data* for **8**: mp 90–91 °C, $[\alpha]_D^{20}$ +14.3 (*c* 1.0, $CHCl_3$). IR ν/cm^{-1} 3400 (OH); ^{1}H NMR (300 MHz, CD_3COCD_3): δ 1.50 (3H, s, Me), 1.65 (3H, s, Me), 4.17 (1H, d, *J* = 8.0 Hz, 1-H), 4.85 (1H, dd, *J* = 7.0, 8.0 Hz, 2-H), 5.22 (1H, d, *J* = 7.0 Hz, 3-H), 5.89 (1H, d, *J* = 3.3 Hz, furyl), 6.19 (1H, dd, *J* = 1.8, 3.3 Hz, furyl), 7.08–7.29 (6H, m, Ph, furyl); MS(EI) *m/z*: 274 (M^+), 216 ($M^+ - Me_2CO$), 199 ($M^+ - Me_2CO - OH$) (Calc. for $C_{16}H_{18}O_4$: C, 70.06, H, 6.61. Found: C, 70.26, H, 6.61%); for **12**: mp 131–132 °C, $[\alpha]_D^{20}$ −152.6 (*c* 0.6, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (3H, s, Me), 1.63 (3H, s, Me), 2.85–3.05 (2H, m, 3-H), 4.39 (1H, dd, *J* = 7.4, 2.6 Hz, 7-H), 4.55 (1H, dd, *J* = 4.7, 2.6 Hz, 6-H), 5.39 (1H, d, *J* = 7.4 Hz, 8-H), 5.54 (1H, m, *J* = 9.9 Hz, 5-H), 5.78 (1H, m, *J* = 9.9 Hz, 4-H), 7.31–7.51 (5H, m, Ph); MS(EI) *m/z*: 274 (M^+), 259 (M^+ −Me), 217 ($M^+ + 1 - Me_2CO$); HRMS: Calc. for $C_{16}H_{18}O_4$ *m/z* 274.1205. Found 274.1190.

¶ The crystal of **8** was in the monoclinic system with space group $P2_1$ (no. 4) and the lattice parameters were precisely determined as *a* = 8.844(3), *b* = 9.883(1), *c* = 8.936(2) Å, β = 111.24(2)°, *U* = 728.0(3) Å^3, *Z* = 2, D_c = 1.251 g cm^{-3}. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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