COMMUNICATION

Julia–Colonna asymmetric epoxidation of furyl styryl ketone as a route to intermediates to naturally-occurring styryl lactones

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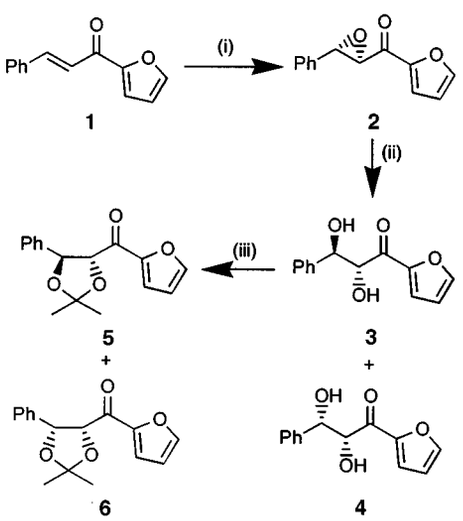
The enone 1 was oxidized stereoselectively using urea–hydrogen peroxide with polyleucine as the catalyst to give the epoxide 2 which was used to make (+)-goniotriol 7, (+)-goniofufurone 8, (+)-8-acetylgoniotriol 9 and goniopypyrone 10.

Introduction and background information

The asymmetric epoxidation of α,β-unsaturated ketones using chiral phase-transfer catalysts,[1] chiral organometallic catalysts[2] and selected polyamino acids[3] has received much attention recently. No doubt each of these methods will have a distinct advantage with particular substrates.

The asymmetric oxidation of furyl styryl ketone **1** to afford epoxide **2** (Scheme 1) is particularly well-served by the biphasic



Scheme 1 *Reagents and conditions*: i. urea–hydrogen peroxide (UHP), poly-L-leucine (PLL), diazabicycloundecene (DBU), tetrahydrofuran (THF), room temp., 20 °C, up to 2 h. For further details see Table 1; ii. I_2 (0.5–1.0 mol%), acetonitrile–water (1:1), 40 °C, 60 h; iii. $Me_2CH(OMe)_2$, toluene-*p*-sulfonic acid, CH_2Cl_2, room temp., 5 h.

polyleucine methodology[4] since the rapid rate of the transformation allows the catalyst loading to be reduced to *ca.* 2.5 mol% (Table 1). Note that the catalyst is readily recovered and may be reused at least six times, without a damaging change to the rapid rate or the exquisite stereoselectivity of the reaction.[5]

In this paper we show that the epoxide **2** serves as a useful precursor to some of the naturally-occurring styryl lactones **7**–**10** (Fig. 1), isolated from *Goniothalamus giganteus* Hook,[6] which possess significant cytotoxic activity towards human tumour cells.

Results

Thus the oxirane ring in compound **2** was hydrolysed by the method of Iranpoor[7] to furnish the *erythro*-diol **3** and *threo*-diol **4** in roughly equal quantities. Treatment of the diol mixture

Table 1 Asymmetric epoxidation of enone **1** using poly-L-leucine as catalyst[a]

Entry	DBU (equiv.)	Enone **1**/g	Reaction time/min	Yield (%) (ee of **2**)
1	1.2	0.99	20	>95 (>99)
2[b]	1.2	1.49	40	>95 (>99)
3[b]	0.3	1.49	90	>95 (97.5)
4[b]	0.15	2.97	120	>95 (96.1)
5[b]	0.3	3.96	120	>95 (95.1)
6[b]	0.3	3.96	120	>95 (96.4)

[a] Reaction of enone **1** with urea–hydrogen peroxide (1–2 equiv.) in tetrahydrofuran (20 ml) containing DBU with poly-L-leucine (1 g). [b] Recycled poly-L-leucine.

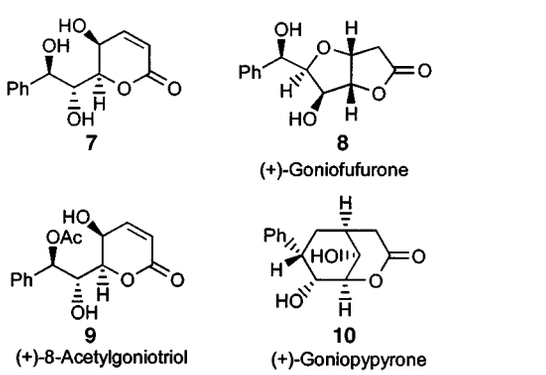
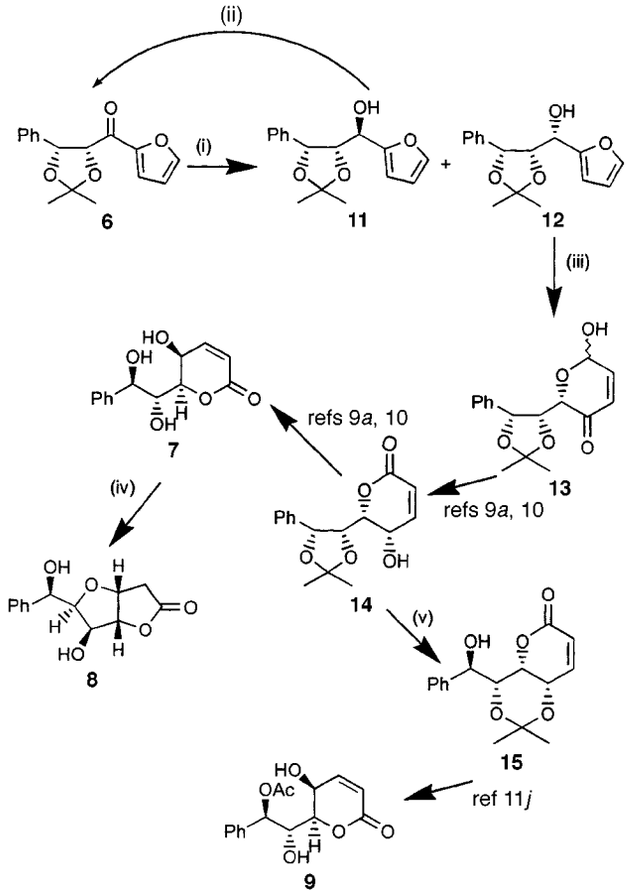


Fig. 1

with 2,2-dimethoxypropane and acid afforded the acetonides **5** and **6** which were readily separated by chromatography over silica in 46% and 38% yield (respectively) from the epoxide **2**. With multigram quantities of the protected diols available, syntheses of the naturally-occurring styryllactones were undertaken.

Reduction of the ketone **6** with zinc borohydride in ether at 0 °C gave a mixture of the alcohols **11** and **12** (ratio 5.5:1) in quantitative yield. Similarly methanolic borohydride reduced **6** to afford alcohols **11** and **12** in the ratio 8:1, again in high yield. The stereoselectivity of the reduction was altered to a small but useful extent by using Luche's reagent which afforded the alcohol **11** (60%) and the more useful alcohol **12** (38%). The former compound could be recycled by oxidation to the ketone **6** using manganese dioxide (93%) (Scheme 2).

Treatment of the alcohol **12** with *N*-bromosuccinimide (NBS) in aqueous tetrahydrofuran as described by Geogiadis[8] and used by others[9a] afforded the lactol **13** in near quantitative yield. One-pot treatment of the lactol **13** with chromium trioxide in acetic acid, then sodium borohydride in propan-2-ol–acetic acid gave the lactone **14**[9a,10] which, when exposed to aqueous acetic acid, produced (+)-goniotriol {$[\alpha]_D^{20}$ +121 (*c* 0.8, MeOH); lit.,[11j] $[\alpha]_D$ +121 (MeOH)} (78% overall yield from compound **13**). Isomerization of goniotriol **7** using DBU in THF gave (+)-goniofufurone {$[\alpha]_D^{20}$ +8.9 (*c* 2.0, EtOH); lit.,[11j] $[\alpha]_D$ +8.9 (*c* 0.4, EtOH)}. Isomerization of the acetonide **14**



Scheme 2 *Reagents and conditions*: i. $NaBH_4$–$CeCl_3$, MeOH, −78 °C; ii. MnO_2, CH_2Cl_2, Δ, 3 days; iii. NBS, THF–H_2O (8:2), 0 °C, 30 min; iv. DBU (cat), THF, room temp., 2 days (67%); v. Acetone, *p*-TsOH (cat), room temp., 4 days.

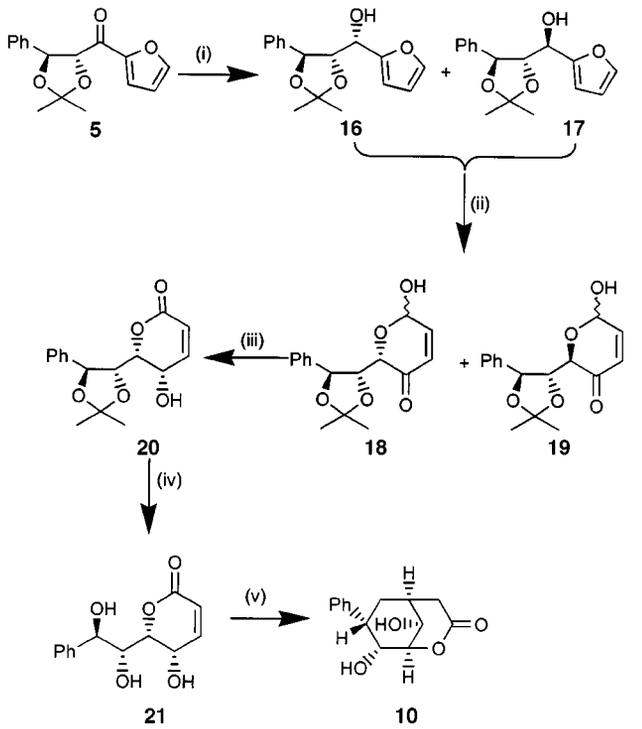
using acidic acetone gave the alcohol **15** {$[a]_D^{20}$ +44.7 (*c* 1.0, MeOH); lit.,[11j] $[a]_D$ +45 (*c* 0.3, MeOH)}, an established precursor to (+)-8-acetylgoniotriol **9**.[11j]

Reduction of the ketone **5** using sodium borohydride in methanol at 0 °C gave the diastereoisomeric alcohols **16** and **17** in the ratio 1:2.6 (Scheme 3). However employment of L-Selectride® as the reducing agent reversed the stereoselectivity of the reaction, affording the required diastereomer **16** as the major product (ratio *ca.* 2:1). Treatment of this mixture of compounds **16** and **17** with NBS in aqueous acetone gave the desired lactol **18** (61%) which was separated from the epimer **19** (30%) by chromatography.

Oxidation of the lactol **18** using chromium(VI) oxide gave the ketolactone **20** (88% yield) with an optical rotation {$[a]_D^{20}$ +3.8 (*c* 3.0, EtOH)} which did not correspond to the documented literature value.[12d] However subsequent conversion of the ketolactone **20** into 8-*epi*-goniotriol **21** {$[a]_D$ +104.9 (*c* 0.8 EtOH); lit.,[11j] $[a]_D$ +88 (*c* 0.8, EtOH)} and into (+)-goniopypyrone **10** {$[a]_D^{20}$ +55 (*c* 1.2, EtOH); lit.,[11j] $[a]_D$ +54 (*c* 0.5, EtOH)} confirmed our stereochemical assignments.

Discussion

The above route to goniotriol and related compounds complements previously described methods of synthesis using starting materials from the chiral pool,[9,11,13–17] and those employing Sharpless asymmetric epoxidation[10] and hydroxylation[12] in the key step. Asymmetric aldol reactions have also been featured.[18] The employment of a furan moiety to provide the lactone fragment is also precedented but in these other routes the furan unit is introduced at a late stage in the synthesis. Our route is unique in that the furan unit is already present at the very start of the preparative route.



Scheme 3 *Reagents and conditions*: i. L-Selectride®, THF, −78 °C, quantitative; ii. NBS, THF–H_2O (8:2), 0 °C, 30 min; iii. CrO_3, AcOH, room temp., 10 min; then $NaBH_4$ (4.0 equiv.), AcOH–HOPr-i (1:1), −20 °C to −10 °C, 1.5 (88%); iv. AcOH–H_2O (4:1), 65 °C, 4.5 h (90%); v. DBU (cat), THF, room temp., 24 h (76%).

Experimental

(2*R*,3*R*)-2,3-Dihydroxy-1-(2-furyl)-3-phenylpropan-1-one 3 and (2*R*,3*S*)-2,3-dihydroxy-1-(2-furyl)-3-phenylpropan-1-one 4

A brown solution of epoxy ketone **2** (6.43 g, 30 mmol) and iodine (571 mg, 2.25 mmol) in acetonitrile–water (1:1) (180 mL) was stirred for 60 h at 40 °C. Most of acetonitrile was removed under reduced pressure. Dichloromethane (50 mL) and 10% aqueous $Na_2S_2O_3$ (50 mL) were added and the mixture was shaken. The organic layer was separated; the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: EtOAc–petroleum ether = 1:2) to give a pale yellow oil (6.41 g, 92%) as an inseparable mixture of *erythro*-isomer **3** and *threo*-isomer **4**. The ratio of *erythro*-isomer **3** and *threo*-isomer **4** was determined by ^1H NMR to be 1:1.3. ^1H NMR ($CDCl_3$ + D_2O) of *erythro*-isomer **3**: 5.14 (1H, d, J = 4.2), 5.18 (1H, d, J = 4.2), 6.54 (1H, dd, J = 3.6 and 1.8), 7.15 (1H, d, J = 3.6), 7.23–7.45 (5H, m), 7.57 (1H, d, J = 1.8). ^1H NMR ($CDCl_3$ + D_2O) of *threo*-isomer **4**: 4.99 (1H, d, J = 3.0), 5.10 (1H, d, J = 3.0), 6.55 (1H, dd, J = 3.6 and 1.8), 7.18 (1H, d, J = 3.6), 7.23–7.45 (5H, m), 7.59 (1H, d, J = 1.8); MS (EI): 232 (M^+, 0.04%), 126 (58.76%), 106 (46.33%), 105 (58.19%), 95 (100%) (HRMS: Calc. for $C_{13}H_{12}O_4$ + NH_4^+: 250.10793. Found: 250.10820).

(4*R*,5*R*)-2,2-Dimethyl-4-(2-furoyl)-5-phenyl-1,3-dioxolane 6 and (4*R*,5*S*)-2,2-dimethyl-4-(2-furoyl)-5-phenyl-1,3-dioxolane 5

The mixture of α,β-dihydroxy ketones **3** and **4** (**3**:**4** = 1:1.3) (6.039 g, 26 mmol) was dissolved in dichloromethane (60 mL). 2,2-Dimethoxypropane (10.832 g, 104 mmol) and toluene-*p*-sulfonic acid (40 mg) were added. The reaction solution was stirred for 5 h at room temperature, then washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: EtOAc–petroleum ether = 1:8). The first fraction gave *threo*-acetal **5** (3.561 g,

50.3%) as pale yellow prisms. Mp 65–66 °C; $[a]_D = -80.2$ (*c* 1.3, CH_2Cl_2); IR (Nujol): ν_{max}/cm^{-1} 1677; ^1H NMR ($CDCl_3$): 1.56 (3H, s), 1.66 (3H, s), 4.82 (1H, d, *J* = 7.5), 5.34 (1H, d, *J* = 7.5), 6.48 (1H, dd, *J* = 3.6 and 1.8), 7.22 (1H, d, *J* = 3.6), 7.31–7.43 (5H, m), 7.57 (1H, d, *J* = 1.8); ^{13}C NMR ($CDCl_3$): 26.16, 27.01, 80.16, 84.36, 111.55, 112.28, 120.64, 126.69, 128.45, 128.63, 137.99, 147.56, 151.18, 184.86; MS (EI): 257 (0.38%), 215 (7.31%), 214 (34.15%), 197 (1.83%), 177 (7.39%), 1.66 (7.66%), 151 (7.57%), 119 (29.58%), 105 (36.62%), 95 (100%) (HRMS: Calc. for $C_{16}H_{16}O_4 + H^+$: 273.11268. Found: 273.11257). Chiral HPLC analysis showed the ee is over 98% (AD column, 254 nm, 10% EtOH in hexane, 2*R*,3*S*-isomer: t_R 9.47 min; 2*S*,3*R*-isomer: t_R 6.36 min). The second fraction afforded *erythro*-acetal **6** (2.891 g, 40.8%) as colourless needles. Mp 83–84 °C; $[a]_D = -17.6$ (*c* 1.6, CH_2Cl_2); IR (Nujol): ν_{max}/cm^{-1} 1682; ^1H NMR ($CDCl_3$): 1.57 (3H, s), 1.86 (3H, s), 5.59 (2H, s), 6.31 (1H, dd, *J* = 3.6 and 1.5), 6.90 (1H, d, *J* = 3.6), 7.09–7.21 (5H, m), 7.38 (1H, d, *J* = 1.5); ^{13}C NMR ($CDCl_3$): 24.90, 26.48, 80.41, 81.45, 110.80, 112.27, 117.57, 127.05, 127.97, 128.30, 135.78, 145.84, 151.68, 184.84; MS (EI): 215 (5.32%), 214 (17.52%), 177 (9.70%), 166 (15.19%), 151 (7.48%), 120 (4.99%), 119 (30.84%), 95 (100%) (HRMS: Calc. for $C_{16}H_{16}O_4 + H^+$: 273.11268. Found: 273.11257). Chiral HPLC analysis showed the ee is over 98% (AD column, 254 nm, 10% EtOH in hexane, 2*R*,3*R*-isomer: t_R 22.07 min; 2*S*,3*S*-isomer: t_R 10.15 min).

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