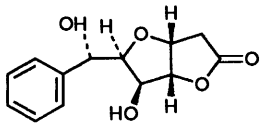
A Convenient Enantioselective Synthesis of (+)-8-*epi*-Goniofufurone

Zhi-Cai Yang and Wei-shan Zhou *
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

A convenient synthesis of (+)-8-*epi*-goniofufurone from methyl cinnamate has been completed. A key step is the intramolecular double cyclisation reaction.

Recently, one of the styryl lactones, (+)-8-*epi*-goniofufurone **1**, was isolated from the stem bark of *Goniothalamus giganteus* (Annonaceae)[1] and shown to have cytotoxic activity. The structure of this goniofufurone **1** has been established by both spectroscopy and X-ray crystallography,[1] and its absolute configuration has been determined to be that shown, based on the synthesis of its enantiomer, (−)-8-*epi*-goniofufurone, starting from sugars.[2,3] As part of our work on styryl lactones, we recently described the asymmetric total synthesis of (+)-goniopypyrone from methyl cinnamate.[4] Herein, we present a convenient synthesis from the same starting material of (+)-8-*epi*-goniofufurone **1** employing an intramolecular double cyclisation as the key step.



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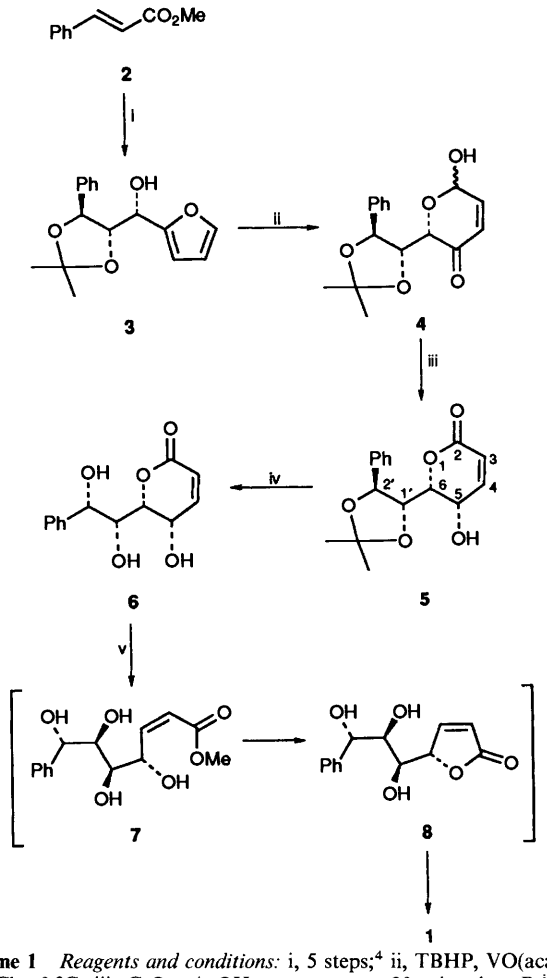
Our previous work has indicated that methyl cinnamate **2** could be converted into the highly *syn*-selective adduct **3** in five steps with an overall yield of 46%.[4] Oxidation of the furyl methanol **3** with *tert*-butyl hydroperoxide (TBHP), in the presence of vanadyl acetylacetonate, smoothly afforded the hydropyranone **4** as a mixture of the α- and β-anomers. Subsequent oxidation of the anomeric mixture of **4** with chromium(VI) oxide in acetic acid followed by immediate reduction with sodium triacetoxyborohydride in a 1:1 mixture of isopropyl alcohol and acetic acid furnished the allyl alcohol **5** (56% yield from the furan **3**),[4,5] $[\alpha]_D^{20}$ −37.0 (*c* 1.2, in EtOH). The configuration of the 5-OH in compound **5** was confirmed after deprotection with trifluoroacetic acid (THF–water) provided the known triol **6** in 90% yield (Scheme 1).[6]

In order to transform the six-membered ring lactone **6** into the five-membered ring lactone **8**, we first tried acidic hydrolysis of **6** with HCl in THF, but no reaction occurred. Basic hydrolysis of compound **6** with 0.5 mol dm^{-3} NaOH followed by acidification of the resulting carboxylate with 1 mol dm^{-3} HCl unfortunately afforded the recovered lactone **6** as the major component. Finally, hydrolysis of the lactone **6** with 0.5 mol dm^{-3} NaOH followed by treatment with 1 mol dm^{-3} HCl and CH_2N_2 gave neither the expected ester **7** nor the lactone **8**, but instead the (+)-8-*epi*-goniofufurone **1** directly, m.p. 194–195 °C, $[\alpha]_D^{20}$ 103 (*c* 0.3, in EtOH) {lit.[1] m.p. 190–192 °C, $[\alpha]_D^{20}$ 108 (*c* 0.2, in EtOH)}. On a six-membered α,β-unsaturated lactone, the intramolecular Michael reaction (forming the second six-membered ring) have to be initiated by a catalytic amount of DBU in THF.[4,5] However, this double cyclisation (lactonisation and intramolecular Michael addition) that could be performed in one pot, may be due to the easy formation of the five-membered ring.

In summary, we have stereoselectively synthesized (+)-8-*epi*-goniofufurone **1** from methyl cinnamate **2** in nine steps with an overall yield of 14%.



Scheme 1 *Reagents and conditions:* i, 5 steps;[4] ii, TBHP, $VO(acac)_2$, CH_2Cl_2, 0 °C; iii, CrO_3, AcOH, room temp., 20 min; then Pr^iOH, $NaBH(OAc)_3$, −10 °C; iv, CF_3CO_2H, THF, H_2O, room temp.; v, 0.5 mol dm^{-3} NaOH, room temp. 20 min; then 1 mol dm^{-3} HCl, CH_2N_2

Experimental

All m.p.s were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM300 instrument with TMS as the internal standard; chemical shift values as given in δ and *J* values are given in Hz. Mass spectra were obtained on HP5890A spectrometer. IR Spectra were taken for solid samples as KBr pellets and for liquid samples as thin films, using a Shimadzu-440 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter and $[\alpha]_D$ values are given in values of 10^{-1} deg cm^2 g^{-1}.

(2S)-6-*Hydroxy*-2-[(1R,2S)-1,2-*isopropylidenedioxy*-2-*phenylethyl*]-2,6-*dihydropyran*-3-*one* **4**.—To a stirred solution of the furan **3** (1.129 g, 4.1 mmol) and $VO(acac)_2$ (10 mg, 0.037 mmol) in CH_2Cl_2 (20 cm^3) was added TBHP (*tert*-butyl hydroperoxide) (0.924 cm^3, 6.18 mmol; 6.69 mol dm^{-3} in CH_2Cl_2) at 0 °C. The solution was stirred for 10 h at 0 °C, and then Me_2S (0.5 cm^3, 6.8 mmol) was added at 0 °C. After stirring for a further 30 min at 0 °C, water (20 cm^3) was added. The organic layer was separated, and the aq. layer was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated to give crude oil, which was purified by flash chromatography [ethyl acetate–hexane (1 : 5)] to afford the pyranone **4** as an inseparable mixture (1 : 3) of the α- and β-anomers (1.04 g, 87%) (Found: C, 66.05; H, 6.6. $C_{16}H_{18}O_5$ requires C, 66.19; H, 6.24%); ν_{max}/cm^{-1} 3340, 2950, 2890, 1700, 1620, 1590, 1440, 1380, 1360, 1200, 1160, 1040, 890, 760 and 690; $\delta_H(CDCl_3)$ 1.51 (3 H, s, Me), 1.55 (3 H, s, Me), 2.30 (1 H, br, OH), 4.39 (1 H, dd, *J* 8.8 and 1.7, 1′-H), 4.49 (1 H, d, *J* 1.7, 2-H), 5.15 (1 H, d, *J* 8.8, 2′-H), 5.92 (1 H, d, *J* 3.0, 6-H), 6.19 (1 H, d, *J* 10.3, 4-H), 6.94 (1 H, dd, *J* 3.0 and 10.3, 5-H) and 7.32–7.45 (5 H, m, Ph); *m/z* (EI) 251 (M^+ − Me), 272 (M^+ − H_2O), 233, 215, 197, 184, 176, 148, 131, 126, 119, 105, 97, 77 and 43 (100%).

(5S,6R)-5-*Hydroxy*-6-[(1R,2S)-1,2-*isopropylidenedioxy*-2-*phenylethyl*]-5,6-*dihydropyran*-2-*one* **5**.—To a stirred solution of compound **4** (413 mg, 1.42 mmol) in acetic acid (5 cm^3) was added chromium(VI) oxide (170 mg, 1.7 mmol) in acetic acid (3 cm^3). After 15 min stirring at room temp., isopropyl alcohol (10 cm^3) was added and the reaction mixture was stirred at constant temp. for a further 5 min. The resulting mixture was then cooled to −10 °C, and freshly prepared sodium triacetoxyborohydride [prepared from $NaBH_4$ (270 mg) and acetic acid (8 cm^3) below 10 °C] was added. The reaction mixture was stirred for 1 h at the same temp. and then poured into water (50 cm^3) and diethyl ether (20 cm^3). The organic layer was separated and the aq. layer was extracted with diethyl ether (2 × 20 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [ethyl acetate–hexane (1 : 4)] to give compound **5** (267 mg, 65%) as a colourless oil, $[\alpha]_D^{20}$ −37.0 (*c* 1.2, in EtOH) (Found: C, 66.1; H, 6.4. $C_{16}H_{18}O_5$ requires C, 66.19; H, 6.24%); ν_{max}/cm^{-1} 3350, 2910, 2830, 1700, 1610, 1440, 1360, 1350, 1260, 1120, 1060, 890, 860, 810, 740 and 690; $\delta_H(CDCl_3)$ 3.61 (1 H, br, OH), 4.12 (1 H, dd, *J* 8.7 and 1.4, 1′-H), 4.28 (1 H, dd, *J* 2.8 and 1.4, 6-H), 4.30 (1 H, dd, *J* 5.2 and 2.8, 5-H), 5.31 (1 H, d, *J* 8.7, 2′-H), 6.14 (1 H, d, *J* 9.6, 3-H), 6.94 (1 H, dd, *J* 9.6 and 5.2, 4-H) and 7.35–7.48 (5 H, m, Ph); *m/z* (EI) 291 (M^+ + 1), 275 (M^+ − Me), 233, 215, 197, 184, 176, 166, 148, 133, 126, 119, 97 (100%), 97 and 77.

(5S,6R)-5-*Hydroxy*-6-[(1R,2S)-1,2-*dihydroxyethyl*-2-*phenylethyl*]-5,6-*dihydropyran*-2-*one* **6**.—To a stirred solution of compound **5** (146 mg, 0.5 mmol) in THF–H_2O (1 : 1, 6 cm^3) was added trifluoroacetic acid (0.5 cm^3). After stirring at room temp. overnight, water (10 cm^3) was added. The organic layer was separated and the aq. layer was extracted with ethyl acetate (3 × 20 cm^3). The combined organic layers were washed with brine, dried ($NaSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [ethyl acetate–hexane (3 : 1)] to give the title compound **6** (225 mg, 90%) as a white solid, m.p. 133–134 °C; $[\alpha]_D^{20}$ 53 (*c* 0.5, EtOH) (Found: C, 62.1; H, 5.3. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.63%); ν_{max}/cm^{-1} 3350, 1710, 1620, 1490, 1440, 1380, 1260, 1150, 1020, 910, 820, 760 and 700; $\delta_H([^2H_6]acetone)$ 4.18 (1 H, dd, *J* 3.6 and 2.8, 1-H), 4.33 (1 H, dd, *J* 2.7 and 2.8, 6-H), 4.51 (1 H, dd, *J* 5.8 and 2.7, 5-H), 4.57 (1 H, 1-OH), 4.83 (1 H, 2′-OH), 5.04 (1 H, d, *J* 3.6, 2′-H), 5.41 (1 H, 5-OH), 6.04 (1 H, d, *J* 9.7, 3-H), 7.07 (1 H, dd, *J* 9.7 and 5.8, 4-H) and 7.20–7.49 (5 H, m, Ph); *m/z* (EI) 250 (M^+), 232 (M^+ − H_2O), 215, 188, 173, 162, 149, 144, 126, 107 (100%), 97 and 91.

(+)-8-epi-*Goniofufurone* **1**.—To a stirred solution of the triol **6** (50 mg, 0.2 mmol) in THF (5 cm^3) was added 0.5 mol dm^{-3} NaOH (0.5 cm^3, 0.25 mmol). After stirring for 20 min at room temp., 1 mol dm^{-3} HCl (1 cm^3, 1 mmol) and CH_2N_2 (in diethyl ether) were added and the reaction mixture was stirred at room temp. for a further 10 min. The resulting mixture was treated with sat. aq. $NaHCO_3$ (3 cm^3) and organic layer was separated. The aq. layer was extracted with diethyl ether (2 × 10 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [ethyl acetate–hexane (2 : 1)] to give the title compound **1** (30 mg, 60%) as colourless needles, m.p. 194–195 °C; $[\alpha]_D^{20}$ 103 (*c* 0.3, EtOH) (Found: C, 62.0; H, 5.5. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.63%); ν_{max}/cm^{-1} 3430, 1650, 1320, 1000, 820 and 695; $\delta_H(CDCl_3)$ 2.71–2.79 (3 H, m, 3-H and -OH), 3.5 (1 H, br, -OH), 4.24 (1 H, dd, *J* 3.5 and 4.0, 7-H), 4.43 (1 H, dd, *J* 3.5 and 0.5, 6-H), 4.90 (1 H, dd, *J* 4.0 and 0.5, 5-H), 5.09 (1 H, d, *J* 4.0, 8-H), 5.12 (1 H, m, *J* 6.0 and 4.0, 4-H) and 7.34–7.45 (5 H, m, Ph); *m/z* (EI) 232 (M^+ − H_2O), 213, 199, 173, 149, 143, 126 (57), 107 (100), 105 (64), 97, 91, 82, 79, 77 and 55.

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