Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3305-3308, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00431-4

Easy Access to an Enantiopure Precursor of (+)-Goniodiol

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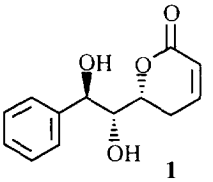
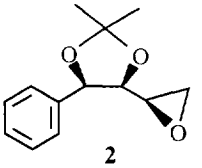
Abstract : Asymmetric synthesis of the epoxide **2** has been achieved from (*R*)-mandelic acid **3** *via* highly diastereoselective Wittig reaction and *erythro*-selective OsO_4 catalyzed *cis*-hydroxylation as key steps. Copyright © 1996 Elsevier Science Ltd

(+)-Goniodiol **1**, an oxygenated 6-dihydrostyryl-5,6-dihydro-2-pyrone, was recently isolated with other styryllactones from the stem bark of Thai *Goniothalamus giganteus* Hook. f. & Thomas[1] and from the leaves and twigs of *Goniothalamus sesquipedalis* (Annonaceae).[2] Goniodiol exhibited potent and selective cytotoxicity against human lung carcinoma (A-549) and was not significantly toxic against brine shrimp (LC_{50}> 500μg/ml).[1]

Four years ago, Honda and co-workers[3] completed the first synthesis of natural goniodiol in fifteen steps from 2,3-O-isopropylidene-D-glyceraldehyde thereby securing its absolute configuration. Very recently, we published a synthesis of enantioenriched (+)-goniodiol (92% ee) in fifteen steps starting from 3-O-allenyl diacetone-D-glucose.[4] One of the key element of our synthetic route of **1** was the elaboration of the α,β-unsaturated δ-lactone moiety from the epoxide **2** using Ghosez's methodology.[5] The epoxide **2** was thus obtained in 12 steps and 9% yield from 3-O-allenyl diacetone-D-glucose. Because we needed a practical route to (+)-goniodiol for biological testing and also because of the potentiality of **2** as a chiral building block in the synthesis of optically active natural products, we searched for an alternative and more efficient procedure enabling the preparation of **2**. We have therefore developed a process, suitable for large scale preparations, based on commercially available and cheap mandelic acid **3**.



1



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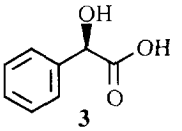


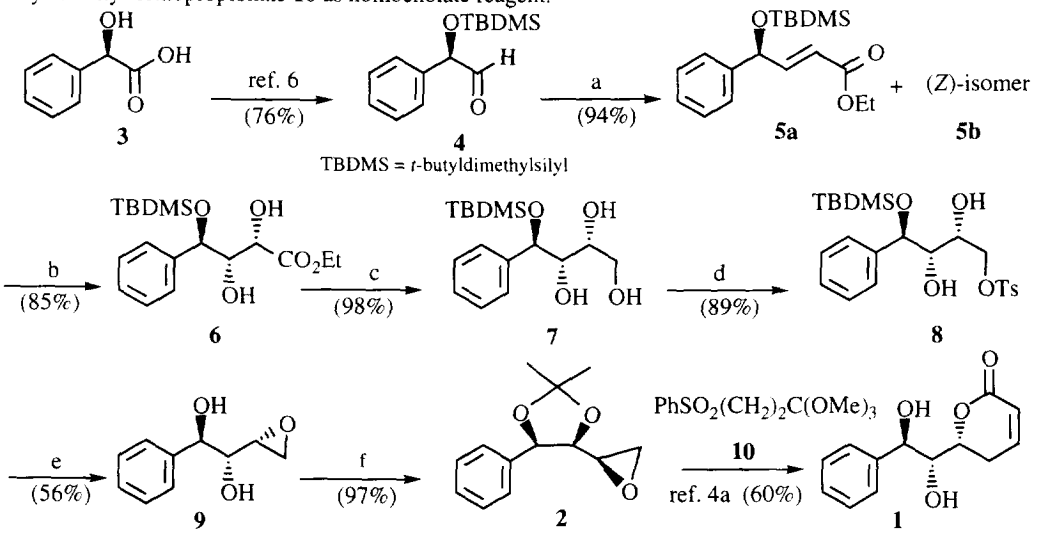
3

Results and Discussion

Firstly, (*R*)-mandelic acid **3** was converted to the protected α-hydroxy aldehyde **4** in three steps according to the literature procedure.[6] Wittig reaction between the crude **4** and ethoxycarbonylmethylenetriphenyl-phosphorane in refluxing toluene furnished the oily (*E*)-α,β-unsaturated ester **5a** in 88% yield after chromatographic separation of the 93:7 mixture of the two geometrical isomers (Scheme 1). The *E*-geometry of the double bond of the main isomer was supported by ^1H NMR spectroscopy ($J_{2,3}$= 15.5Hz). Catalytic OsO_4 *cis*-dihydroxylation of **5a** in the presence of an excess of N-methylmorpholine N-oxide in acetone-water (5:1) occurred, as expected[7], with high *anti*-selectivity (89:11 ratio) to give the α,β-dihydroxy ester **6**[8] in 85% yield after chromatographic purification. The next stage of the synthesis, the reduction of the ester function of **6** was troublesome. Indeed, initial experiments realized with $LiAlH_4$ as reducing agent were disappointing giving rise to the desired triol **7** in only 40% yield. After screening various hydride reagents in different solvents, we were delighted to find that **6** could be smoothly reduced by lithium borohydride in tetrahydrofuran in 98% yield.

The stage was now set up for the introduction of the epoxide functionality. Towards this goal, compound **7** was converted to the monotosylate **8** in 89% yield by treatment with 1.2 equiv of *p*-toluenesulfonyl chloride, at -20°C, in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP). Subsequent base-mediated epoxidation and desilylation[9] (NBu_4F in tetrahydrofuran) gave the epoxy diol **9** in 56% yield along with by-products resulting from Payne rearrangement. Finally, brief treatment of **9** with 2-methoxypropene in the presence of camphorsulfonic acid, afforded the target epoxide **2** in 97% yield $[\alpha]_D$ -94.9 (c 1.0, $CHCl_3$] [lit.[4b] $[\alpha]_D$ - 87.3(c 1.1, $CHCl_3$)] with spectroscopic properties identical to an authentic sample.

As already reported by us[4a] and according to Ghosez's protocol[5], the epoxide **2** could be efficiently transformed to enantiopure (+)-goniodiol **1** in a three steps sequence and 60% yield using methyl 3-phenylsulfonyl orthopropionate **10** as homoenolate reagent.



Scheme 1

Reagents and conditions : (a) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 30 min ; (b) cat. OsO_4, NMO, acetone-H_2O (5:1), RT, 5 h ; (c) $LiBH_4$, THF, RT, 20 min ; (d) *p*.TsCl, Et_3N, DMAP, CH_2Cl_2, -20°C, overnight ; (e) NBu_4F, THF, 0°C, 30 min ; (f) 2-methoxypropene, camphorsulfonic acid, CH_2Cl_2, RT, 10 min.

In summary, we have devised a short and highly stereocontrolled synthesis of the epoxide **2** in 9 steps and 31% yield from (*R*)-mandelic acid. This synthesis as well as our reported synthesis of (+)-goniofufurone and goniobutenolides A and B[8] highlighted the usefulness of mandelic acid, commercially available in both enantiomerically form, as a chiral building block in organic synthesis. Indeed, until now mandelic acid has been essentially used in stereochemical investigations.[10] Other applications of the epoxide **2** in the synthesis of natural products are currently underway in our laboratory.

Experimental Section

General. ^1H NMR spectra were recorded in $CDCl_3$ (δH = 7.25) at ambient probe temperatures on a Bruker AC 200 (200MHz) spectrometer. Data are presented as follows : chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant and interpretation. ^{13}C NMR spectra were recorded at ambient probe temperatures on Bruker AC 200 (50.3 MHz) in $CDCl_3$ used as reference (δ_c 77.0). IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer using 5mm sodium chloride plates. Wavelengths of maximum absorbance ($\sqrt{}$max) are quoted in cm^{-1}. Mass spectra were carried out on a Nermag R10-10 H quadrupole mass spectrometer. Optical

rotations were measured on a Perkin-Elmer 141 polarimeter at the sodium D line (589 mm). Combustion analyses were performed by the Service Central de Microanalyse, CNRS, Solaize.

Reagents and solvents were purified by standard means. Diethyl ether and tetrahydrofuran were distilled from sodium wire / benzophenone and stored under a nitrogen atmosphere. Dichloromethane , toluene and triethylamine were distilled from calcium hydride. All other chemicals were used as received. Unless otherwise stated, all experiments were performed under anhydrous conditions in an atmosphere of nitrogen.

Ethyl (Z or E, 4S)-4-(t-butyldimethylsilyloxy)-4-phenylbutan-2-enoate 5a and 5b . To a solution of ethyl (*R*)-2-(*t*-butyldimethylsilyloxy)-2-phenylacetate **4**[6] (5 g, 18 mmol) in Et_2O (22 ml), cooled to -78°C, was added dropwise DIBAL-H (1M in hexanes, 18 ml, 1 equiv). After stirring for 20 min at -78°C, the reaction mixture was quenched with water (2 ml), filtered on a pad of Celite and concentrated *in vacuo*. The crude aldehyde was taken up in toluene (50 ml) and carboethoxymethylenetriphenylphosphorane (6.45 g, 18 mmol) was added. The reaction mixture was refluxed for 30 min, cooled down to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:19) to give first the (*Z*)-isomer **5b** as an oil (0.34 g, 8% yield) : $[\alpha]_D$ +188 (c 2.5, $CHCl_3$) ; IR (neat) 3420, 1725, 1665 ; ^1H NMR : 0.046 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.9 (s, 9H, $SiC(CH_3)_3$), 1.33 (t, 3H, J= 7.1Hz, $OCH_2C\underline{H}_3$), 4.24 (q, 2H, J= 7.1Hz, $OC\underline{H}_2CH_3$), 5.72 (d, 1H, J=11.4Hz; $PhC\underline{H}OSi$), 6.21 (dd, 1H, J=8.9 and 11.4 Hz), $CH{=}C\underline{H}{-}CO$), 6.57 (d, 1H, J= 8.9Hz, $C\underline{H}{=}CH{-}CO$), 7.2-7.5 (m, 5H, Ph) ; ^{13}C NMR : -4.89, -4.76, 14.2, 18.2, 25.8 (3C), 60.2, 69.2, 117.0, 125.8 (2C), 127.2, 128.2 (2C), 142.9, 151.3, 166.1 ; MS m/z (relative intensity) : 305 (2, M^+-15), 264 (21), 263 (100). The second fraction was constituted of pure (*E*)-isomer **5a** obtained as a viscous oil (4.74 g, 86% yield) : $[\alpha]_D$ -71 (c 2.5, $CHCl_3$) ; IR (neat) 3420, 1730, 1660 ; ^1H NMR : -0.06 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.9 (s, 9H, $SiC(CH_3)_3$), 1.27 (t, 3H, J= 7.1Hz, $OCH_2C\underline{H}_3$), 4.17 (q, 2H, J= 7.1Hz, $OC\underline{H}_2CH_3$), 5.3 (dd, 1H, J=1.5 and 4.5Hz; $PhC\underline{H}OSi$), 6.1 (dd, 1H, J= 1.5 and 15.3 Hz), $CH{=}C\underline{H}{-}CO$), 6.96 (dd, 1H, J= 4.5 and 15.3Hz, $C\underline{H}{=}CH{-}CO$), 7.25-7.3 (m, 5H, Ph) ; ^{13}C NMR : -4.85, -4.81, 14.3, 18.3, 25.8 (3C), 60.4, 74.5, 118.9, 126.3 (2C), 127.8, 128.6 (2C), 141.7, 150.3, 166.7 ; Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.80. Found : C, 67.86 ; H, 8.99.

Ethyl (2S,3S,4R)-4-(t-butyldimethylsilyloxy)-2,3-dihydroxy-4-phenylbutanoate 6. To a solution of **5a** (8.52 g, 27 mmol) in acetone-H_2O (80 ml, 5:1) were added N-methyl morpholine N-oxide hydrate (7.16 g, 53 mmol, 2 equiv) followed by OsO_4 solution (2.5%wt. in *t*-BuOH, 3.4 ml, 0.27 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by flash chromatography (Et_2O-petroleum ether, 3:1) to give **6** as an oil (7.97 g, 85% yield) : $[\alpha]_D$ -33.7 (c 2.52, $CHCl_3$) ; IR (neat) 3500, 3080, 3060, 3030, 1740 ; ^1H NMR : -0.2 (s, 3H, $SiCH_3$), 0.1 (s, 3H, $SiCH_3$), 0.9 (s, 9H, $SiC(CH_3)_3$), 1.27 (t, 3H, J= 7.1Hz, $OCH_2C\underline{H}_3$), 2.0 (d, 1H, J= 7.8Hz, OH), 3.3 (d, 1H, J= 5.5Hz, OH), 4.0 (td, 1H, J= 1.3 and 7.8Hz, $C\underline{H}OH{-}CHOSi$), 4.3 (q, 2H, J= 7.1Hz, $OC\underline{H}_2CH_3$), 4.6 (dd, 1H, J=1.2 and 5.5Hz, $C\underline{H}OHCO_2Et$), 4.80 (d, 1H, J= 7.96Hz, $PhC\underline{H}OSi$), 7.34-7.48 (m, 5H, Ph) ; ^{13}C NMR : -5.0, -4.5, 14.2, 18.1, 25.8 (3C), 61.9, 70.2, 76.0, 76.6, 128.0 (2C), 128.2, 128.4 (2C), 141.7, 173.8 ; Anal. Calcd for $C_{18}H_{30}O_5Si$: C, 60.71; H, 8.75. Found : C, 60.98 ; H, 8.53.

(1R,2S,3R)-1-(t-Butyldimethylsilyloxy)-1-phenylbutan-2,3,4-triol 7. To a cooled (0°C) solution of **6** (3.1 g, 8.7 mmol) in THF (43 ml) was added lithium borohydride (0.76 g, 35 mmol). The reaction mixture was warmed up to room temperature and stirred for 20 min. Water (40 ml) and 2N HCl (10 ml) were successively added to the reaction mixture and stirred for 30 min. The mixture was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (Et_2O then CH_2Cl_2-MeOH, 93:7) to afford **7** (2.67 g, 98% yield) : $[\alpha]_D$ -69.5 (c 1.04, $CHCl_3$) ; IR (neat) 3400, 3060,3030 ; ^1H NMR (CD_3OD) : -0.22 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 3.3-3.62 (m, 3H, $C\underline{H}OH{-}CHOH{-}C\underline{H}_2OH$), 4.03 (td, 1H, J=1 and 5.9Hz, $C\underline{H}OH{-}CH_2OH$), 4.73 (d, 1H, J= 8.1Hz, $PhC\underline{H}OSi$), 7.23-7.4 (m, 5H, Ph) ; ^{13}C NMR (CD_3OD): -4.5, -4.0, 19.2, 26.6 (3C), 65.3, 71.4, 76.1, 76.8, 128.7, 128.9 (2C), 129.4 (2C), 144.6 ; Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.03. Found : C, 61.78 ; H, 9.07.

(1R,2R,3S)-3,4-Epoxy-1-phenylbutane-1,2-diol 9 . To a solution of the triol **7** (2.06 g, 6.6 mmol) in CH_2Cl_2 (43 ml) cooled to -50°C were successively added triethylamine (1.44 ml, 11 mmol), 4-dimethylaminopyridine (0.16 g, 1.3 mmol) and finally *p*-toluenesulfonyl chloride (1.5 g, 8 mmol). The reaction

mixture was then warmed up to -20°C and let overnight at this temperature in a freezer. The mixture was then quenched at -20°C with 1N HCl solution (5 ml) and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:1) to give the tosylate **8** (7.97 g, 85% yield) : ^1H NMR : -0.24 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.8 (s, 9H, $SiC(CH_3)_3$), 2.35 (s, 3H, SO_2PhCH_3), 3.45 (dd, 1H, J= 1 and 5.5Hz, CHOH-CHOSi), 3.8-4.1 (m, 3H), 4.77 (d, 1H, J= 55 Hz, PhCHOSi), 7.28-7.8 (m, 9H, Ph). To a cooled (0°C) solution of **8** (2.75 g, 6 mmol) in THF (20 ml) was added dropwise NBu_4F (1M in THF, 24 ml, 4 equiv). After stirring for 30 min at 0°C, water (30 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:2) to afford **9** as an oil (0.59 g, 56% yield) : $[\alpha]_D$ -56.4 (c 1.03, $CHCl_3$) ; IR (film) 3400, 1605, 1495, 1450 ; ^1H NMR (CD_3OD): 2.43 (dd, 1H, J=2.8 and 5Hz, CH_2(epoxide)), 2.65 (dd, 1H, J=4.3 and 5Hz, CH_2(epoxide)), 3.15 (ddd, 1H, J=2.8, 4.3 and 6Hz, CH(epoxide)), 3.4 (br t, 1H, J=6.2Hz, CHOHCHOHPh), 4.65 (d, 1H, J=6.3Hz, CHOHPh), 7.2-7.5 (m, 5H, Ph) ; ^{13}C NMR (CD_3OD) : 45.7, 53.3, 76.5, 76.8, 128.0 (2C), 128.5, 129.1 (2C), 143.3 ; Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; O, 26.6. Found : C, 66.67; H, 6.68; O, 26.46.

(1R,2S,3R)-3,4-Epoxy-1,2-isopropylidenedioxy-1-phenylbutane ***2***. To a solution of diol epoxide **9** (1.44 g, 8 mmol) in CH_2Cl_2 (35 ml) was added at room temperature camphorsulfonic acid (0.18 g, 0.8 mmol) followed by 2-methoxypropene (1.25 ml, 16 mmol). The reaction was stirred for 10 min and then filtered on a pad of silica gel. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (Et_2O-petroleum ether, 1:4) to give **2** as an oil (1.71 g, 97% yield): $[\alpha]_D$ -94.7 (c 1.1 $CHCl_3$) ; ^1H NMR : 1.46 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.35 (dd, 1H, J=4 and 5Hz, CH_2(epoxide)), 2.37 (dd, 1H, J=3 and 5Hz, CH_2(epoxide)), 2.5 (ddd, 1H, J=3, 4 and 6.8Hz, CH(epoxide)), 3.98 (dd, 1H, J=6.8 and 7.1Hz, CHOR-CHORPh), 5.3 (d, 1H, J=7.1Hz, PhCH), 7.2-7.4 (m, 5H, Ph) ; ^{13}C NMR : 24.9, 26.8, 43.5, 51.5, 78.8, 80.3, 109.5, 126.3 (2C), 127.9, 128.4 (2C), 136.6 ; Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found : C, 70.75; H, 7.30.

Acknowledgments : One of us (JPS) thanks the Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship. We thank Professor J. Goré for helpful and stimulating discussions and Matthias Herdemann for skillful technical assistance.

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(*Received in UK* 6 *September* 1996)