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Asymmetric Synthesis of (*R*)-(−)-Rhododendrol, the Aglycone of the Hepatoprotective Agent Rhododendrin

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Abstract: Starting from 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) as chiral material, (*R*)-(−)-rhododendrol **2**, the aglycone of the naturally occurring rhododendrin **1** was synthesized.

Keywords: aglycone, melanin inhibitor, natural product, rhododendrin, rhododendrol

INTRODUCTION

The glycoside rhododendron, along with its aglycone rhododendrol, was isolated for the first time from leaves of *Rhododendron chrysanthum* Linn. in 1901.[1] Later Khan et al.[2] isolated rhododendrin as the major component of the aqueous extract of the leaves of *Taxus baccata* L., which possessed good tranquilizing activity.[3] This glycoside was also isolated from the bark of the white birch, *Betula alba* L.,[4] and from *Rhododendron fauriae* var. *rufescens*.[5] More recently, rhododendrin was found in *Bergenia*,[6] *Abies webbiana* Lindl.,[7] *Rhodiola*,[8] *Alnus glutinosa* Gaertn,[9] and *Cotyledon wallichii*.[10] Recently, rhododendrol and its glycoside have been used as a melanin inhibitor and in skin-lightening cosmetics.[11] Rhododendrin exhibited hepatoprotective activity against two hepatotoxins in rats. The aglycone (−)-rhododendrol is

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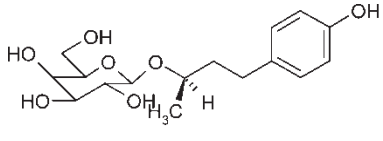
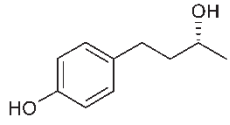
found to co-occur in many species. It has been unequivocally established that the carbohydrate moiety is attached via the aliphatic hydroxyl group.[12]

From X-ray diffraction studies, the absolute configuration at the chiral center in the aglycone portion has been found to be *R*.[13] Syntheses of (*R*)-(−)-rhododendrol by enantioselective addition of diallyl zinc to an aldehyde using chiral tricarbonyl chromium (0) catalyst[14a] and resolution of racemic rhododendrol by lipase-catalyzed enatioselective acetylation[14b] were reported. In continuation of our studies on the synthesis of biologically active molecules,[15] we herein report a simple and practical synthesis of (*R*)-(−)-rhododendrol from a chiral pool material.



rhododendrin 1



rhododendrol 2

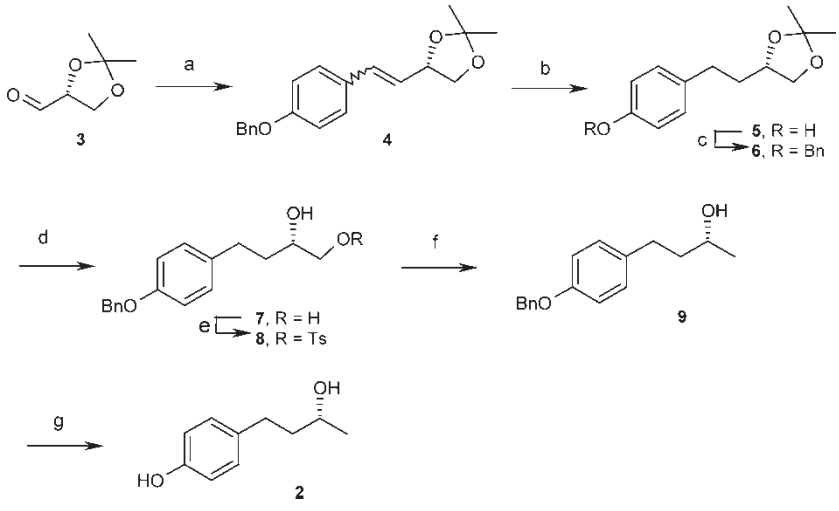
RESULTS AND DISCUSSION

The chiral center in the molecule can be elaborated from (*R*)-isopropylidene glyceraldehyde (**3**), which can easily be synthesized from oxidative cleavage of readily available 1,2:5,6-di-*O*-isopropylidene-D-mannitol.[16] The (*R*)-acetonide **3** thus synthesized from D-mannitol on a large scale, was subjected to the Wittig reaction[17] with 4-benzyloxybenzylphosphonium bromide to give a mixture of *Z* and *E* olefin (6 4) **4** in an overall yield of 80%. Hydrogenation of compound **4** (mixture of *Z* and *E* olefin) over 10% Pd/C gave a saturated compound **5** in 78% yield in which simultaneously debenzylation also occured. Thus, the protection of phenolic -OH was carried out using benzyl bromide to afford benzyl ether **6**. Hydrolysis of the acetonide afforded diol **7** in 92% yield. Selective tosylation of the primary hydroxyl group of **7** with TsCl in dry pyridine produced tosylate **8** in 80% yield, and further reduction with lithium aluminium hydride (LAH) in THF afforded mono hydroxy compound **9**. Finally, the synthesis of target molecule **2** was achieved in 85% yield by debenzylation using Pd/C. The physical (mp), optical rotation [α_D −17.4 (c 0.5, MeOH) lit.[13] α_D −17 (c 0.5, MeOH)], and spectral data (^{1}H NMR, ^{13}C NMR, and mass) are identical to those of the natural product (Scheme 1).

In conclusion, we have developed a synthetic route for the synthesis of (*R*)-(−)-rhododendrol from a chiral source.

EXPERIMENTAL

All solvents were distilled before use. Dry solvents were prepared according to the standard procedures. All reactions were carried out under an N_2



Scheme 1. Reagents and conditions: a) $[BnOC_6H_4CH_2Ph_3P]^+Br^-$ (1.0 eq), *n*-BuLi (1.0 eq), THF, 0°C, 2 h, 80%; b) H_2, 10% Pd-C, MeOH, rt, on, 78%; c) $PhCH_2Br$, acetone, K_2CO_3, TBAI, rt, 6 h, 88%; d) PTSA, MeOH, 3 h, rt, 92%; e) TsCl (1.1 eq), dry DCM, DMAP, 0°C, 4 h, 80%; f) LAH, THF, 0°C to rt, 6 h, 78%; g) H_2, 10% Pd-C, MeOH, rt, on, 85%.

atmosphere and monitored by thin-layer chromatography (TLC) on silica gel (60–120 mesh, Merck). NMR spectra were recorded on Bruker (300 MHz ^1H; 75 MHz ^{13}C) and Varian (200 MHz ^1H; 50 MHz ^{13}C) NMR spectrometers using $CDCl_3$ as solvent. ESI-mass spectra were recorded with LC-MSD-Trap-SL (Agilent Technologies). IR spectra were recorded with FTIR (Thermo Nicolet Nexus 670 spectrometer). Optical rotations were measured with Jasco DIP-370 polarimeter at 20°C.

(4*S*)-4-{(*E*)-2-[4-(Benzyloxy)phenyl]-1-ethenyl}-2,2-dimethyl-1,3-dioxolane (4)

To a solution of Wittig salt, 4-benzyloxybenzylphosphonium bromide (9.17 g, 1.2 eq, 19.99 mmol) in dry THF (20 ml) under N_2 at 0°C, *n*-butyl lithium (12.5 ml, 1.6 M) was added dropwise at 0°C. Immediately the solution became red. After 30 min, the solution of aldehyde **3** (3 g, 16.66 mmol) in dry THF was added at 0°C and allowed to stir for 3–4 h. Then, the reaction mixture was filtered and extracted with ethyl acetate, dried over Na_2SO_4, concentrated on vacuum, and purified by silica-gel column chromatography to get a mixture of *Z* and *E* olefin **4** (6:4) (4.6 g, 80%). Data for *Z*-olefin: IR (KBr): 3025, 2986, 1607, 1511, 1379, 1245, 1062, 844 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.48 (s, 3H) 3.64 (t, $J = 7.8$ Hz, 1H), 4.12 (dd, $J = 6.2$, 7.8 Hz,

1H), 4.81–4.93 (m, 1H), 5.10 (s, 2H), 5.60 (dd, $J = 9.3$, 11.7 Hz, 1H), 6.62 (d, $J = 11.7$ Hz, 1H), 6.95 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 7.26–7.48 (m, 5H). FAB mass: 310 (M^+).

4-{2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]ethyl}phenol (5)

Compound **4** (5 g, 16.12 mmol) was dissolved in MeOH (40 mL), then cat. 10% Pd/C was added and hydrogenated overnight. Then the reaction mixture was filtered, and MeOH was removed in vacuo. The residue was purified by column chromatography using silica gel to afford the saturated compound **5** (2.8 g, 78%). $[\alpha]_D^{25}$: +4.4 ($c = 0.015$, MeOH). IR (KBr): 3391, 3012, 2986, 1515, 1375, 1217, 1064 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H) 1.39 (s, 3H), 1.69–2.02 (m, 2H), 2.47–2.86 (m, 2H), 3.42–3.61 (m, 1H), 3.80–4.05 (m, 2H), 6.65 (d, $J = 8.4$ Hz, 2H), 7.00 (d, $J = 8.4$ Hz, 2H), 8.45 (s, -OH). ^{13}C NMR (75 MHz, $CDCl_3$): 27.8, 28, 30, 34, 75, 79, 108, 115, 129, 133, 155. LCMS: 221 (M-1). Anal. calcd. for $C_{13}H_{18}O_3$ (222.28): C, 70.25; H, 8.16. Found: C, 68.58; H, 7.70.

(4*S*)-4-[4-(Benzyloxy)phenethyl]-2,2-dimethyl-1,3-dioxolane (6)

To a stirred solution of compound **5** (10 g, 81.96 mmol) in dry acetone (80 ml), K_2CO_3 (4 eq, 45.2 g) was added at room temperature under N_2. After 30 min, benzyl bromide (1 eq, 9.74 ml) was added slowly, followed by the addition of a catalytic amount of TBAI, and the reaction mixture was allowed to stir for 6 h at room temperature. Acetone was removed under vacuum, and the residue was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The crude product was purified by silica-gel column chromatography to afford compound **6** (15.2 g, 88%). $[\alpha]_D^{25}$: +7.3 ($c = 0.015$, MeOH). IR (KBr): 3031, 2985, 1610, 1510, 1239, 1065, 847 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.38 (s, 3H), 1.67–2.01 (m, 2H), 2.51–2.82 (m, 2H), 3.83–4.13 (m, 3H), 5.01 (s, 2H), 6.84 (d, $J = 8.3$ Hz, 2H), 7.06 (d, $J = 8.3$ Hz, 2H), 7.24–7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 29, 36, 69,70, 75, 106, 114, 128–132 (8C), 156. LCMS: 313 (M + 1). Anal. calcd. for $C_{20}H_{24}O_3$ (312.40): C, 76.89; H, 7.74. Found: C, 74.17; H, 7.31.

(2*S*)-4-[4-(Benzyloxy)phenyl]butane-1,2-diol (7)

To a solution of compound **6** (4 g, 12.82 mmol) in MeOH, a catalytic amount of PTSA was added and allowed to stir for 3 h at room temperature. MeOH was removed under vaccum, then the residue was extracted with ethyl acetate and dried over Na_2SO_4. The crude product was purified by column chromatography to get compound 7 (3.2 g, 92%). $[\alpha]_D^{25}$: −16.0 ($c = 0.015$, MeOH). IR (KBr): 3371, 3037, 2925, 1611, 1511, 1102, 1015, 813, 736,

695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ +DMSO): δ 1.56–1.67 (m, 2H), 2.49–2.79 (m, 2H), 3.25–3.59 (m, 3H), 3.90–3.97 (d, $J = 5.4$ Hz, 2H), 5.02 (s, 2H), 6.82 (d, $J = 8.5$ Hz, 2H), 7.09 (d, $J = 8.5$ Hz, 2H), 7.26–7.42 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): 29, 34, 65, 68, 72, 113, 128–133 (8C), 155. LCMS: 295 (M + Na). Anal. calcd. for $C_{17}H_{20}O_3$ (272.34): C, 74.97; H, 7.40. Found: C, 73.52; H, 6.71.

(2*S*)-4-[4-(Benzyloxy)phenyl]-2-hydroxybutyl 4-methyl-1-benzene Sulfonate (8)

p-Toluene sulphonyl choride (1 eq) and a catalytic amount of DMAP were added to a stirred solution of compound **7** (2 g, 7.35 mmol) in dry DCM at 0°C and left stirring for 4 h. Then the reaction mixture was extracted with DCM, concentrated under vacuum, dried over Na_2SO_4, and purified by column chromatography to give compound **8** (2.3 g, 80%). $[\alpha]_D^{25}$: +6.6 ($c = 0.0075$, MeOH). IR (KBr): 3568, 3034, 2924, 1608, 1512, 1351, 1174, 1090, 949 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.58–1.76 (m, 2H), 2.45 (s, 3H), 2.54–2.74 (m, 2H), 3.72–3.81 (m, 1H), 3.86 (t, $J = 9.8$ Hz, 1H), 3.98 (dd, $J = 3.0$, 9.8 Hz, 1H), 5.02 (s, 2H), 6.82 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.3$ Hz, 2H), 7.26–7.40 (m, 7H), 7.76 (d, $J = 8.3$ Hz, 2H). LCMS: 449 (M + Na). Anal. calcd. for $C_{24}H_{26}O_5S$ (426.52): C, 67.58; H, 6.14. Found: C, 67.45; H, 6.63.

(2*R*)-4-[4-(Benzyloxy)phenyl]butan-2-ol (9)

To a suspension of lithium aluminium hydride (0.3 g, 2 eq) in dry THF, compound **8** (2 g, 4.69 mmol) was added, and the reaction mixture was allowed to stir at 0°C, then brought to room temperature, and stirred for 6 h. The reaction mixture was filtered and extracted with ethyl acetate, dried over Na_2SO_4, and concentrated, and the residue was purified by column chromatography to furnish compound **9** (0.84 g, 78%). IR (KBr): 3310, 3035, 1512, 1245, 1175, 1012, 738, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.24 (d, $J = 6.0$ Hz, 3H), 1.70–1.78 (m, 2H), 2.57–2.76 (m, 2H), 3.75–3.86 (m, 1H), 5.05 (s, 2H), 6.86 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.3$ Hz, 2H), 7.30–7.44 (m, 5H); LCMS: 279 (M + Na).

4-(3-Hydroxy-butyl)-phenol [(R)-(−)-rhododendrol] (2)

To a solution of compound **9** (1.5 g, 5.8 mmol) in MeOH, cat. 10% Pd/C was added and hydrogenated overnight. Then the reaction mixture was filtered, and filtrate was concentrated in vacuo. The residue was purified by silica-gel column chromatography to afford the target molecule **2** as a colorless solid (0.826 g, 85%), mp 80°C, lit.[13] 79–80°C. [α_D −17.4 (c 0.5, MeOH)

lit.[13] α_D −17 (c 0.5, MeOH)]. IR (KBr): 3367, 3067, 2931, 1614, 1515, 1240, 1071, 819 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ + DMSO): δ 1.16 (d, J = 5.8 Hz, 3H), 1.58–1.75 (m, 2H), 2.44–2.71 (m, 2H), 3.46 (bs, 1H), 3.62–3.76 (m, 1H), 6.67 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 8.46 (s, 1H). ^{13}C NMR: (50 MHz, $CDCl_3$ + DMSO): 30, 39, 40.5, 65.9, 114, 128, 133, 154. EI-MASS: 166 (M^+), 148, 133, 107 (100%).

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