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TETRAHEDRON: *ASYMMETRY*

Enantioselective syntheses of (*S*)- and (*R*)-8,9-dihydroxydihydromagnolol

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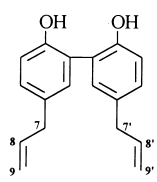
Abstract

8,9-Dihydroxydihydromagnolol **5** was synthesized in four steps in which the synthesis of magnolol **4** was improved and the absolute configuration of **5** was confirmed as (*R*). © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

8,9-Dihydroxydihydromagnolol **5** was isolated from *Magnoliae cortex* which is a Chinese crude drug used as a repressive drug for turgescence of the thorecoabdominal region, and a stomachic.[1] Magnolol **4** was known to have varied bioactivity such as: antifungal, antibacterial, antimicrobial, antiulcer and antisecretory activity.[2,3]



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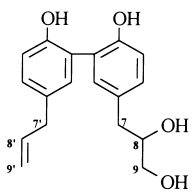

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Here we report a convenient route in which **4** was synthesized in a higher yield than before,[4] and by selective Sharpless asymmetric dihydroxylation (AD) reactions of **4**, (*S*)-**5** and (*R*)-**5** were synthesized first and the absolute configuration of the natural product **5** was confirmed as (*R*).[5]

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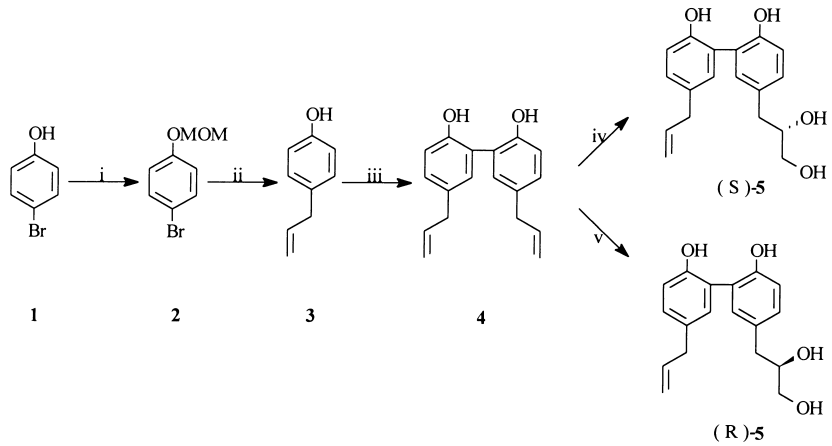
2. Results

As shown in Scheme 1, 4-bromophenol **1** was protected with chloromethyl methyl ether at room temperature to afford compound **2**, which was converted to **3** by its Grignard reaction with allyl bromide, followed by acidification. Oxidative coupling of **3** by DDQ and $AlCl_3$ in $MeNO_2$ at room temperature gave magnolol **4**,[6] and selective AD of **4** by AD-mix-α and AD-mix-β in t-BuOH–H_2O phase and $NaHCO_3$ at 0°C afforded (*S*)-**5** and (*R*)-**5**, respectively.[7,8]



Reagents and conditions : i. MOMCl, K_2CO_3, r.t. (98%); ii. Mg, THF, $BrCH_2CH{=}CH_2$, reflux, (89%); iii. DDQ, $AlCl_3$, $MeNO_2$, r.t. (77%); iv. AD-mix-α, 3eq. $NaHCO_3$, t-BuOH-H_2O, 0^0C, (88%), 90% ee; v. AD-mix-β, 3eq. $NaHCO_3$, t-BuOH-H_2O, 0^0C, (89%), 92% ee.

Scheme 1.

3. Experimental section

Melting points were measured on a Kofler apparatus and were uncorrected. AD-mix-α and AD-mix-β were purchased from Aldrich. Enantiomeric excesses were determined by HPLC analysis, using a Chiralcel OD column. The optical rotations were measured with a Jasco J-20C automatic recording spectropolarimeter. Mass spectra were recorded on a ZAB-HS spectrometer. Elemental analyses were performed on a Carlo Erba 1106 instrument. IR spectra were recorded on a Nicolet 170 SXFT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Bruker AC-80 and AM-400 instruments. Chemical shifts are referenced to TMS on the 'δ' scale. Standard flash chromatography was employed to purify the crude reaction mixture using 200–300 mesh silica gel under a positive nitrogen pressure.

*3.1. 4-Bromophenol methoxy methyl ether **2***

To a stirred solution of 4-bromophenol **1** (2.00 g, 9.26 mmol) in 25 mL acetone was added K_2CO_3 (1.28 g). The mixture was stirred at room temperature for 15 mins and MOMCl (1.06 g, 1 mL) was added dropwise over 5 mins. The mixture was stirred and refluxed for 2 h. The solvent was evaporated in vacuo. Crude products were dissolved in water and then extracted with Et_2O (3×50 mL). The combined extracts were dried (Na_2SO_4), the Et_2O was distilled off, the residue was flash chromatographed using petroleum ether and ethyl acetate (16:1, v/v) as eluent. The colorless oil **2** (1.22 g) was obtained in 98%

yield. IR (cm^{-1}): 2825, 1277, 1078, 922, 825, 590; EI-MS: m/z 216 (M^+, 40), 186 (16), 155 (16), 76 (25), 45 (100); ^{1}H-NMR (80 MHz, $CDCl_3$): δ 3.47 (s, 3H, –OC**H**$_3$), 5.15 (s, 2H, –OC**H**$_2$), 6.93, 7.39 (dd, J=8.9, 8.7 Hz, 4H, Ar–**H**).

3.2. 4-Allylphenol **3**

To a stirred Grignard reagent of **2**, which was prepared with **2** (1 g, 4.6 mmol) and magnesium turnings (0.12 g) in dry THF (20 mL), was added allyl bromide (0.6 g) at r.t. for 30 mins dropwise. The reaction mixture was refluxed for 3 h, then cooled to r.t. 3 N HCl (30 mL) was added in portions, refluxed for 3 h, then cooled to r.t. The THF phase was separated and the water phase was extracted with Et_2O (3×50 mL). The THF and the ether layers were combined, washed with brine and dried (Na_2SO_4). The residue was flash chromatographed using petroleum ether and ethyl acetate (12:1, v/v) as eluent. The colorless oil **3** (0.53 g) was obtained in 86% yield. IR (cm^{-1}): 3240, 1639, 1440, 1365, 1108, 1058, 999, 914, 823; EI-MS: m/z 134 (M^+, 100), 119 (36), 105 (20), 91 (44), 77 (37), 65 (8), 63 (10), 51 (17), 39 (16); ^{1}H-NMR (80 MHz, $CDCl_3$): δ 3.38 (d, J=6.4 Hz, 2H, –C**H**$_2$CH=CH_2), 5.16 (d, J=13.8 Hz, 2H, –CH_2CH=C**H**$_2$), 5.93 (m, 1H, –CH_2C**H**=CH_2), 6.73–7.14 (dd, J=8.35, 8.36 Hz, 4H, Ar–**H**).

3.3. Magnolol **4**

To a solution of **3** (0.3 g) in dry nitromethane (10 mL) was added $AlCl_3$ (0.45 g) under nitrogen. After stirring the mixture for 0.5 h, DDQ (0.38 g) in dry nitromethane (5 mL) was added dropwise and the solution was stirred at r.t. for 1 h. A solution of 2 N HCl was added with stirring. The resulting mixture was extracted with CH_2Cl_2 (3×25 mL). The combined extracts were dried (Na_2SO_4), the CH_2Cl_2 was distilled off, and the residue was flash chromatographed using petroleum ether and ethyl acetate (6:1, v/v) as eluent. A white powder **4** (0.23 g) was obtained in 77% yield; mp 101–103°C (lit:[9] 103°C). IR (cm^{-1}): 3167, 1639, 1610, 1498, 1411, 1373, 1230, 991, 908, 819; EI-MS: m/z 266 (M^+, 100), 247 (18), 237 (23), 224 (10), 207 (15), 197 (26), 184 (22), 165 (12), 152 (11), 133 (9), 115 (15), 91 (8), 77 (12), 55 (5), 43 (8); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.31 (br d, 4H, J=6.5 Hz, H-7, H-7′), 4.98 (br d, 2H, J=10.1 Hz, H-9, H-9′), 5.09 (br d, 2H, J=18.5 Hz, H-9, H-9′), 5.92 (ddt, 2H, J=16.7, 10.8 Hz, H-8, H-8′), 6.87 (d, 2H, J=8.1 Hz, Ar–**H**), 7.04 (dd, 2H, J=8.5 Hz, Ar–**H**), 7.11 (d, 2H, J=2.1 Hz, Ar–**H**). Found: C, 81.09; H, 6.79. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%. The above data were consistent with the literature.[1,10]

3.4. (S)-8,9-Dihydroxydihydromagnolol (S)-**5**

To a stirred solution of t-BuOH (2.5 mL) and H_2O (2.5 mL) was added AD-mix-α (0.7 g) and $NaHCO_3$ (0.13 g). The mixture was stirred at r.t. until both phases were clear, and then cooled to 0°C, **4** (0.13 g) was added at once and the mixture was stirred vigorously at 0°C until TLC revealed the absence of **4**. The reaction was quenched at 0°C by addition of Na_2SO_3 (0.75 g), then warmed to r.t. and stirred for 0.5 h. The reaction mixture was extracted with CH_2Cl_2 (3×25 mL) and dried (Na_2SO_4), the CH_2Cl_2 was distilled off. The residue was flash chromatographed using petroleum ether and ethyl acetate (4:1, v/v) as eluent. A white powder (*S*)-**5** (0.12 g, 90% ee) was obtained in 88% yield, and 59% overall yield from **1**. (*S*)-**5**: mp 126–128°C. $[\alpha]_D^{20}$ 0.75 (c=1.50, $CHCl_3$); IR (cm^{-1}): 3346, 1638, 1605, 1415, 1222, 1076, 993, 911, 822; FAB: 301 (M+1), 239 ($M^+ - C_2H_5O_2$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.58 (dd, 1H, J=13.8 Hz, H-7), 2.78 (dd, 1H, J=14.0 Hz, H-7), 3.30 (br d, 2H, J=6.4 Hz, H-7′), 3.42 (m, 2H, H-9), 3.90 (m, 1H, H-8), 4.99 (br d, 1H, J=9.8 Hz, H-9′), 5.05 (br d, 1H, J=18.5 Hz, H-9′), 5.96 (ddt, 1H, J=16.9,

10.8 Hz, H-8′), 6.85–7.19 (m, 6H, Ar–**H**). Found: C, 71.79; H, 6.69. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%.

*3.5. (*R*)-8,9-Dihydroxydihydromagnolol (*R*)-**5***

By a procedure similar to the preparation of (*S*)-**5**, the reaction of **4** (0.13 g, 0.05 mmol), AD-mix-β (0.7 g), t-BuOH (2.5 mL) and H_2O (2.5 mL), gave (*R*)-**5** as a white powder (0.13 g, 92% ee) in 89% yield, and 60% overall yield: mp 143–145°C; $[\alpha]_D^{20}$ −0.76 (c=1.50, $CHCl_3$); IR (cm^{-1}): 3346, 1638, 1605, 1415, 1222, 1076, 993, 911, 822; FAB: 301 (M+1), 239 ($M^+ - C_2H_5O_2$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.58 (dd, 1H, J=13.8 Hz, H-7), 2.78 (dd, 1H, J=14.0 Hz, H-7), 3.30 (br d, 2H, J=6.4 Hz, H-7′), 3.42 (m, 2H, H-9), 3.90 (m, 1H, H-8), 4.99 (br d, 1H, J=9.8 Hz, H-9′), 5.05 (br d, 1H, J=18.5 Hz, H-9′), 5.96 (ddt, 1H, J=16.9, 10.8 Hz, H-8′), 6.85–7.19 (m, 6H, Ar–**H**). Found: C, 71.82; H, 6.72. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%.

Lit:[1] $[\alpha]_D^{20}$ −0.8 (c=1.50, MeOH); EI-MS: m/z 300.134 (M^+, $C_{18}H_{20}O_4$, requires: 300.136), 282, 269, 239; ^{1}H-NMR (acetone-d_6): δ 2.64 (dd, 1H, J=14.7 Hz, H-7), 2.80 (dd, 1H, J=14.5 Hz, H-7), 3.35 (br d, 2H, J=7 Hz, H-7′), 3.50 (m, 2H, H-9), 3.82 (m, 1H, H-8), 5.01 (br d, 1H, J=11 Hz, H-9′), 5.06 (br d, 1H, J=18 Hz, H-9′), 6.00 (ddt, 1H, J=18, 11.7 Hz, H-8′), 6.80–7.35 (m, 6H, Ar–**H**).

Acknowledgements

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