SHORT PAPER

J. Chem. Research (S), 2003, 358–359

First enantioselective synthesis of Rhaphidecursinol A†

Xinfeng Ren, Xuegong She, Kun Peng, Ying Su, Xingang Xie and Xinfu Pan*

Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

The enantioselective synthesis of Rhaphidecursinol A was reported for the first time and the absolute configuration of Rhaphidecursinol A was confirmed.

Keywords: enantioselective, synthesis, neolignan, Rhaphidecursinol A

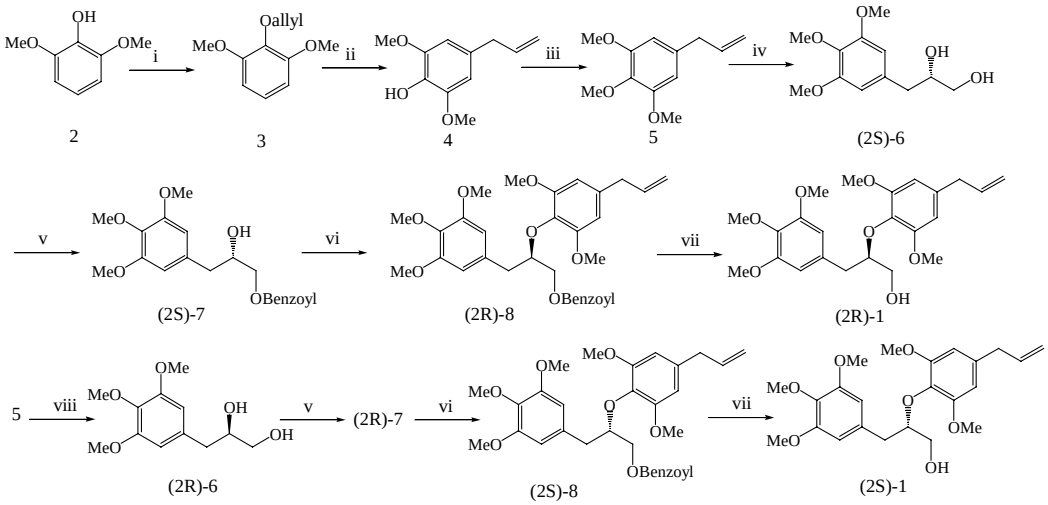
The 8-O-4' neolignans are a class of naturally occurring neolignans. Many of them showed strong activity against the penetration of cercaria of *Schistosoma mansoni*, inhibition of the growth of silkworm larvae, and antileukemic activity in rats[1]. Rhaphidecursinol A **1**, an optically active substance with varying degrees of antimalarial activity, was isolated from *Rhaphidophora decursiva*[2]. It was shown to be an 8-O-4' neolignan. Neither its absolute configurations nor its asymmetric syntheses have yet been reported. Herein, we wish to report the first asymmetric synthesis of Rhaphidecursinol A, and establish the absolute configuration of Rhaphidecursinol A by its optical rotation.

As shown in Scheme 1, phenol **2**, protected by allyl bromide, was easily converted to compound **3**, which underwent the Claisen rearrangement gave the phenol **4**. Methylation of the phenolic hydroxy group afforded **5**. Compound (2*S*)-**6** was obtained by asymmetric dihydroxylation[3] of compound **5**. Treatment of (2*S*)-**6** with benzoyl chloride provided the primary ester (2*S*)-**7**. Using the Mitsunobu reaction[4] with compound **4,** the characterised ether (2*R*)-**8** was obtained, in which the absolute configuration at the C-8 stereogenic centre was inverted completely by the S_N2-type nucleophilic displacement by phenol **4**. The benzoyl group of (2*R*)-**8** was removed and (2*R*)-**1** was obtained. Similarly, after asymmetric dihydroxylation of **5** by AD-mix-β, (2*S*)-**1** was obtained in the same three steps in good yield. All spectroscopic data of Rhaphidecursinol A were in agreement with those found in the literature[2]. The optical rotation of Rhaphidecursinol A in the literature[2] is +2.61, and the optical rotation value of (2*R*)-**1** we obtained is +3.5. Hence we can confirm that the absolute configuration of Rhaphidecursinol A is *R*.

Experimental

The ^{1}H NMR and ^{13}C NMR data were recorded with Avance-200 MHz and Avance-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS. Mass spectra were recorded on a ZAB-HS spectrometer. Optical rotations were determined on a Perkin Elmer 341 polarimeter. IR spectra were recorded on a Nicolet FT-170 SX spectrometer. Flash column chromatography was generally performed on silica gel (200–300 mesh) eluting with petroleum ether: ethyl acetate and TLC inspections on silica gel GF_{254} plates with petroleum ether: ethyl acetate.

(2R)-1-benzoyloxy-2-(4-allyl-2,6-dimethoxyphenoxy)-3-(3,4,5-trimethoxyphenyl)propane **8**: A solution of PPh_3 (191 mg, 0.73 mmol) and (2*S*)-**7** (210 mg, 0.6 mmol) in dry THF (10 ml) was added dropwise to a solution of **4** (141 mg, 0.73 mmol) and DIAD (147 mg, 0.73 mmol) in dry THF at room temperature under nitrogen. After stirring of the mixture overnight at room temperature, the mixture was evaporated in *vacuo*. The residue was flash chromatographed using petroleum ether and ethyl acetate (7:1, v/v) as eluent. A colourless oil (2*R*)-**8** (164 mg) was obtained in 52% yield. $[\alpha]_D^{25}$ +5.2 (*c* 3.2, $CHCl_3$). MS (EI): 522(M^+), 417, 329, 207, 193, 176, 105, 77. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.07 (dd, 1H, *J*=13.8, 7.2 Hz),



Scheme 1 Reagents: (i) allyl bromide, K_2CO_3, acetone; (ii) 200 °C, 2 h; (iii) MeI, K_2CO_3; (iv) AD-mix-α; (v) Et_3N, benzoyl chloride; (vi) DIAD, Ph_3P, THF, 5; (vii) K_2CO_3, methanol and H_2O (9:1); (viii) AD-mix-β, *t*-BuOH, H_2O.

* To receive any correspondence. E-mail: panxf@lzu.edu.cn

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

3.26 (dd, 1H, *J*=14.0, 6.0 Hz), 3.33 (d, 2H, *J*=6.4 Hz), 3.69 (s, 6H), 3.82 (s, 9H), 4.40 (dd, 1H, *J*=12.2, 3.6 Hz), 4.43 (dd, 1H, *J*=12.2, 2.6 Hz), 4.64 (m, 1H), 5.09 (dd, 1H, *J*=10.6, 1.2 Hz), 5.11 (dd, 1H, *J*=17.6, 1.6 Hz), 5.97 (m, 1H), 6.37 (s, 2H), 6.56 (s, 2 H), 7.37-7.96 (m, 5H).

(2R)-2-(4-allyl-2,6-dimethoxypheny)-3-(3,4,5-trimethoxyphenyl)propanol **1**: (2*R*)-**8** (104 mg, 0.2 mmol) was dissolved in a mixture of methanol (9 ml) and water (1 ml), and then potassium carbonate (82 mg, 0.6 mmol) was added. The suspension was stirred for 6 h at room temperature. The solvent was evaporated and water (15 ml) was added. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was distilled off and the residue was flash chromatographed using petroleum ether and ethyl acetate (4:1, v/v) as eluent. A colourless oil (2*R*)-**1** (60 mg, 72%) was obtained. [α] +3.5 (*c* 1.5, $CHCl_3$). MS (EI): 418(M^+), 326, 224, 207, 194, 181, 91, 77. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (dd, 1H, *J*=13.6, 8.3 Hz), 3.24 (dd, 1H, *J*=13.6, 5.4 Hz), 3.35 (d, 2H, *J*=6.6 Hz), 3.45 (dd, 1H, *J*=12.4, 3.8 Hz), 3.59 (dd, 1H, *J*=12.4, 2.3 Hz), 3.83 (s, 6H), 3.86 (s, 9H), 4.22 (m, 1H), 5.11 (dd, 1H, *J*=10.6, 1.2 Hz), 5.13 (dd, 1H, *J*=17.6, 1.6 Hz), 5.98 (m, 1H), 6.44 (s, 2H), 6.54 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1, 40.5, 56.1, 60.8, 62.4, 84.1, 105.6, 106.5, 116.1, 134.2, 136.2, 137.0, 152.9, 153.2. IR (KBr/cm^{-1}): 3508, 2936, 2838, 1590, 1504, 1460, 1422, 1331, 1239, 1127, 1015. HRFABMS m/z 436.2337 (calcd for $C_{23}H_{34}O_7N$, 436.2330).

Support from the National Natural Science Foundation of China (No. 29972015; 20172023) is gratefully acknowledged.

Received 20 January 2003; accpeted 21 February 2003
Paper 03/1754

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