

## Note

### Enantioselective synthesis of (*R*)-(+)-safrole oxide<sup>††</sup>

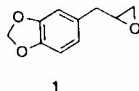
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Received 26 March 1997; accepted 20 June 1997

The first synthesis of (*R*)-(+)-safrole oxide **4**, starting from safrole **2** employing Sharpless asymmetric dihydroxylation as the key step, has been reported.

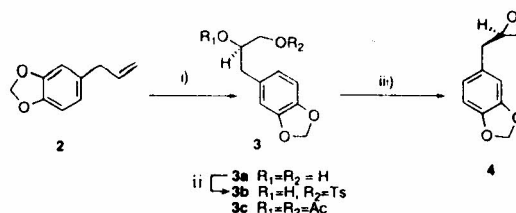
Safrole oxide **1** is used for estimating epoxide hydratase and for the synthesis of some lignan lactones<sup>1</sup>. Though the racemic epoxide **1** has been synthesised<sup>1,2</sup>, there are no reports on the synthesis of pure enantiomers of **1**. We now report the synthesis of (*R*)-(+)-safrole oxide **4** according to Scheme I.



Usually asymmetric hydroxylations of terminal alkenes proceed with moderate enantioselectivity. However, we have now observed that asymmetric hydroxylation of the terminal alkene in safrole **2** with the reagent AD-mix- $\beta$ <sup>3</sup> furnished the diol **3a** having 88% ee; the hydroxylation product has been assigned (*R*) configuration based on observations made with related compounds such as 1-decene<sup>4</sup>. For further identification **3a** was converted to diacetate **3c** by reaction with Ac<sub>2</sub>O. Tosylation of the diol **3a** proceeded with high regioselectivity to furnish the primary tosylate **3b**, which on treatment with K<sub>2</sub>CO<sub>3</sub> in absolute methanol furnished the (*R*)-(+)-epoxide **4**.

#### Experimental Section

**General.** The AD-mix- $\beta$  and safrole employed for this study were purchased from Aldrich and Fluka respectively. Silica gel (60-120 mesh) was



Reagents: i) AD-mix- $\beta$ , CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, aq tert. BuOH ii) tosyl chloride, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, DMAP iii) K<sub>2</sub>CO<sub>3</sub>, absolute methanol

Scheme I

used for column chromatography. <sup>1</sup>H NMR spectra were recorded on a Varian FT-200 spectrometer (200 MHz) using TMS as internal standard. Optical rotations were measured on a JASCO DIP 370 digital polarimeter at 25°C.

#### (*R*)-(+)-5-(2,3-Dihydroxypropyl)-1,3-benzodioxole

**3a.** A mixture of **2** (0.162 g, 1.0 mmole), AD-mix- $\beta$  (1.4 g) and methanesulfonamide (95 mg) in 50% aqueous tert. BuOH (10 mL) was stirred at 0°C for 30 hr. To the mixture was added Na<sub>2</sub>SO<sub>3</sub> (1.5 g) and after 1 hr at room temperature the reaction mixture was extracted with ethyl acetate (5 mL×3). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to afford **3a** as a white solid (0.170 g, 87%). <sup>1</sup>H NMR spectrum of the Mosher ester prepared according to known procedure<sup>5</sup> from the crude diol **3a** showed 88% ee. Sample recrystallized from EtOAc gave colourless crystals, m.p. 93°; [ $\alpha$ ]<sub>D</sub>+32° (*c*, 1.65, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.6-2.8 (m, 2H), 3.4-3.7 (octet, 2H), 3.75-3.95 (m, 1H), 5.9 (s, 2H), 6.62 (d, *J*=8 Hz, 1H), 6.70 (s, 1H), 6.73 (d, *J*=8 Hz, 1H); Anal. Found: C, 61.27; H, 6.04. Calcd for C<sub>10</sub>H<sub>12</sub>O<sub>4</sub>: C, 61.21; H, 6.17%.

#### (*R*)-(-)-5-(2,3-Diacetoxypropyl)-1,3-benzodioxole

**3c.** A mixture of **3a** (0.020 g, 0.102 mmole), acetic anhydride (0.041 g, 0.408 mmole) and pyridine (0.032 g, 0.408 mmole) was stirred at 25°C for 12 hr. Work-up afforded the diacetate which was purified by column chromatography with hexane as eluent to furnish **3c** (0.027 g, 96%); [ $\alpha$ ]<sub>D</sub>-1.0° (*c*, 2.75, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.04 (s, 3H), 2.06 (s, 3H), 2.8 (octet, 2H), 3.9-4.3 (octet, 2H), 5.2 (m, 1H), 5.9 (s, 2H), 6.62 (d, *J*=8 Hz, 1H), 6.70

<sup>†</sup>IICT Communication No. 3411

<sup>††</sup>Taken in part from Ph.D thesis of H Rama Mohan submitted to Osmania University, Hyderabad, 1995.

(s, 1H), 6.72 (d,  $J=8$  Hz, 1H); Anal. Found: C, 59.74; H, 5.64. Calcd for  $C_{14}H_{16}O_6$ : C, 59.99; H, 5.75%.

**(R)-5-(2-Hydroxy-3-tosyloxypropyl)-1,3-benzodioxole 3b.** Tosylation of **3a** (0.140 g, 0.714 mmole) with tosyl chloride (0.149 g, 0.785 mmole), triethylamine (0.18 g, 1.78 mmole) and 4-dimethylaminopyridine (0.010 g) in dry  $CH_2Cl_2$  (5 mL) was carried out at  $0^\circ C$  for 36 hr. The resulting tosylate after work-up was column chromatographed using 1:9 mixture of ethyl acetate-hexane as eluent to furnish **3b** (0.231 g, 92%);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.48 (s, 3H), 2.75-2.9 (m, 2H), 3.9-4.1 (m, 3H), 5.9 (s, 2H), 6.6-6.9 (m, 3H), 7.38 (d,  $J=8$  Hz, 2H), 7.81 (d,  $J=8$  Hz, 2H); Anal. Found: C, 58.14; H, 5.12. Calcd for  $C_{17}H_{18}O_6S$ : C, 58.28; H, 5.18%.

**(R)-(+)-5-Oxiranylmethyl-1,3-benzodioxole 4.** To a stirred mixture of tosylate **3b** (0.125 g, 0.357 mmole) in absolute methanol (20 mL),  $K_2CO_3$  (0.493 g, 3.57 mmole) was added and stirred the suspension vigorously for 30 min. Methanol was removed under reduced pressure on a rotavapor. The residue was diluted with water (5 mL) and extracted into ethyl acetate (5 mL $\times$ 2). The organic

layer was dried over  $Na_2SO_4$  and after removal of solvent the residue was purified using 5% EtOAc-hexane as eluent to afford **4** (0.051 g, 79%);  $[\alpha]_D^{+13}$  ( $c$ , 1.04;  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.50 (dd,  $J=5.5$  and 2.5 Hz, 1H), 2.7-2.9 (m, 3H), 3.02-3.10 (m, 1H), 5.92 (s, 2H), 6.65 (d,  $J=8$  Hz, 1H), 6.72 (s, 1H), 6.74 (d,  $J=8$  Hz, 1H); Anal. Found: C, 67.38; H, 5.70. Calcd for  $C_{10}H_{10}O_3$ : C, 67.40; H, 5.66%.

#### Acknowledgement

We thank Dr A V Rama Rao for his keen interest in our work and the CSIR, New Delhi for awarding Emeritus Scientistship to one of us (A S R).

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