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A CHEMOENZYMATIC APPROACH TO ENANTIOMERICALLY PURE (R)- AND (S)-2,3-EPOXY-2-(4-PENTENYL)-PROPANOL, A CHIRAL BUILDING BLOCK FOR THE SYNTHESIS OF (R)- AND (S)-FRONTALIN

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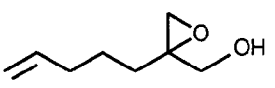
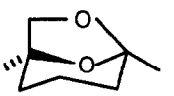
Summary. Enantiomerically pure (R)- and (S)-epoxyalcohols **1**, chiral intermediates for the synthesis of (R)- and (S)-frontalin **2**, are prepared by *Pseudomonas fluorescens* lipase-catalyzed transesterification in dichloromethane.

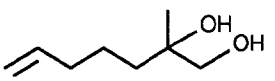
Recently, we have shown that 2-substituted oxiranemethanols are excellent substrates[1] for the enantioselective transesterification catalyzed by *Pseudomonas fluorescens* lipase (PFL) with vinyl acetate in an organic solvent.[2] In order to extend our preliminary observations and with the aim to gain additional informations on the PFL active site,[3] we have prepared another enantiomerically pure pair of isomeric epoxyalcohols, namely (R)- and (S)-2,3-epoxy-2-(4-pentenyl)-propanol **1**. These compounds could be used as chiral synthons for the preparation of both enantiomers of frontalin **2**, the aggregation pheromone of females of the southern pine bark beetle Dendroctonus frontalis and of males of western pine bark beetle, Dendroctonus brevicomis.[4] It has been shown that the biologically active species is (1S, 5R)-**2** and its antipode was found to be inactive.[5] The structure of frontalin has already attracted the attention of many researchers and, since the first synthesis of both enantiomers,[5] several other asymmetric syntheses have been reported.[6]



1



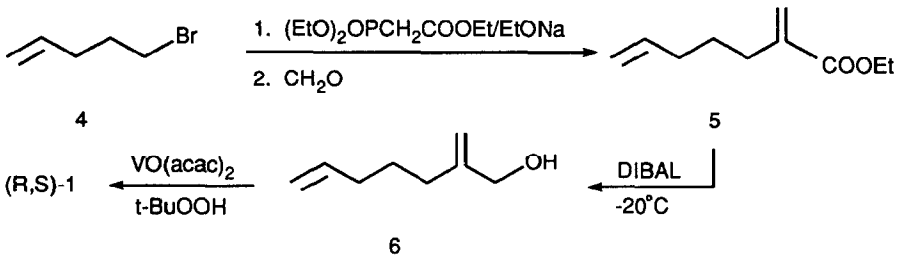
(1S,5R)-2



3

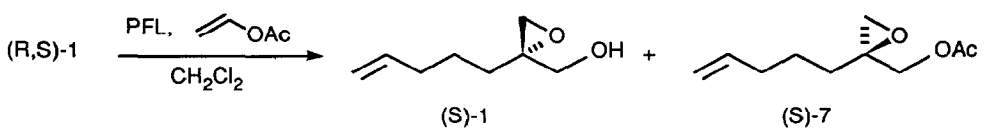
A few syntheses rely on biocatalytic approaches[7] and many chemical syntheses[8] use the Sharpless asymmetric epoxidation[9] as the crucial step, but in no case was an epoxyalcohol such as **1** the compound of choice. On the other hand, the reduction of the epoxyalcohol **1** should afford the diol **3**, which has been used as chiral intermediate for the synthesis of **2**.[7c,8c,8d] It should be remembered that only the stereochemistry of C1 has to be correctly introduced in any synthetic plan, since the

configuration of the other stereogenic center is dictated by that of C1 during the cyclization to the ketal system. (R,S)-**1** was prepared from commercially available 5-bromo-1-pentene **4**, which was converted (85% yield) into the acrylate **5** by a modification[10] of a literature method,[11] already used by us for the synthesis of similar compounds.[1] The reduction of the unsaturated **5** to the alcohol **6** was best accomplished by diisobutyl aluminum hydride at -20 °C[12] (85% yield), without formation of the corresponding saturated alcohol. Finally, the epoxidation of **6** to (R,S)-**1** was carried out (78% yield) with $VO(acac)_2$/t-BuOOH.[13] The overall sequence is depicted in Scheme 1.[14]



Scheme 1

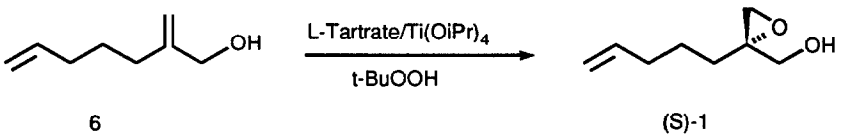
The resulting epoxyalcohol was purified and reacted with PFL and vinyl acetate[15] (Scheme 2). At 60% conversion to the acetate **7**, the unreacted (-)-alcohol **1** was obtained with 98% ee[16] (38% yield). When the transesterification was stopped at 40% formation of the acetate, nearly optically pure (+)-**7** was recovered (38% yield). The optical purity of the enzymatically formed acetate was established by comparison of the optical rotations of (+)-**7** and the acetate obtained by acetylation of the previously prepared (-)-**1**.[17]



Scheme 2

In order to assign the configuration of the products (-)-**1** and (+)-**7**, an authentic sample of (S)-epoxyalcohol **1** was prepared from **6** using L-tartrate as the chiral auxiliary in a Sharpless

asymmetric epoxidation (Scheme 3).[18] The (S)-**1** obtained by this route (35% yield and 90% ee) exhibited $[\alpha]_D$ -14.4[15] and this result allowed us to assign the (S)-configuration to the enzymatically prepared alcohol (-)-**1** and acetate (+)-**7**.[19]



6 (S)-1

Scheme 3

Finally, the lithium aluminum hydride reduction of the enzymatically prepared (S)-(-)-**1** afforded the 98% ee (S)-(-)-diol **3** with $[\alpha]_D$ -2.6,[20] an excellent building block for the synthesis of (1S,5R)-frontalin **2**.[7c, 8c, 8d]

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Synthesis **1986**, 89.

(10) We used sodium ethylate as base for the preparation of the intermediate phosphonoalkanoate. The reaction, carried out in ethanol (8 h) considerably lowered the time of the original procedure (12 days, Ref. 11).

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(14) Compound **5**: b.p. 98-100°C (10 mm Hg); ^{1}H-NMR δ 1.3 (t, 3H, CH_3); 1.5-1.9 (m, 2H, CH_2); 1.9-2.6 (m, 4H, CH_2); 4.3 (q, 2H, CH_2O); 4.9-6.6 (m, 3H, CH_2=CH), 5.65 (s, 1H, CH=); 6.3 (s, 1H, CH=). Compound **6**: b.p. 102-105°C (7 mm Hg); ^{1}H-NMR δ 1.35-1.85 (m, 2H, CH_2); 1.85-2.4 (m, 4H, $2CH_2$), 3.7-4.0 (m, 1H, exchangeable with ^2H_2O), 4.2 (s, 2H, CH_2O), 4.9-6.6 (m, 3H, CH_2=CH); 4.95 (s, 1H, CH=); 5.15 (s, 1H, CH=). Compound **1**: b.p. 124-125°C (14 mm Hg); ^{1}H-NMR δ 1.2-1.9 (m, 4H, CH_2); 1.9-2.5 (m, 3H, CH_2 and H exchangeable with ^2H_2O), 2.8 (d, 1H, CH_2O); 2.9 (d, 1H, CH_2O); 3.5-4.1 (m, 2H, CH_2OH); 4.9-6.4 (m, 3H, CH_2=CH).

(15) Experimental conditions for the enzymatic reaction were as in Ref. 1. To a solution of the epoxyalcohol **1** (0.5 g, 3.5 mmol) in dichloromethane (6.7 ml), vinyl acetate (1.29 ml, 14 mmoles) and PFL (49 mg, 31.5 U/mg) were added. The mixture was kept at 30°C under stirring for a time depending on the required alcohol/acetate ratio (0.5-1h). The progress of the reaction was monitored by GC analysis on capillary column HP5 (oven temperature 170°C). The enzyme was filtered off and the products were purified by a silica gel chromatography (hexane-diethylether as eluants). At *c* 2.5 in $CHCl_3$ the optical rotations were -15.9 for (S)-**1** and +9.32 for (S)-**7**. The chemicophysical properties of (S)-**1** were in agreement with those of racemic **1**. Compound (S)-**7**: b.p. 108-110 °C (10 mm Hg). ^{1}H-NMR: δ 1.2-1.9 (m, 4H, CH_2); 1.9-2.4 (m, 5H, CH_3CO and CH_2); 2.7-2.95 (m, 2H, CH_2O); 4.1 (d, 1H, CH_2O); 4.3 (d, 1H, CH_2O); 4.9-6.4 (m, 3H, CH_2=CH).

(16) The ee of (-)-**1** was established by the 500 MHz ^{1}H-NMR spectra of the MTPA ester (Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512), prepared by reaction with (S)-(-)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (JPS, Switzerland), by the integrations of signals at 4.16-4.51 ppm for the CH_2OCOR.

(17) From 98% ee (-)-**1**, the (-)-acetate **7** chemically prepared exhibited $[\alpha]_D$ -9.30.

(18) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure & Appl. Chem.* **1983**, *55*, 1823.

(19) Due to the change of priorities of the groups bound to the chirality center, the (S)-acetate **7** is the ester of the (R)-alcohol **1**.

(20) Reported value for the optically pure (S)-diol **3**, $[\alpha]_D$-2.6 (Ref. 7c).