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SYNTHESIS OF THE ENANTIOMERIC FORMS OF CIS AND TRANS 1-BENZYLOXY-2,3-EPOXY BUTANE AND OF (3S,4S) 4-METHYL-3-HEPTANOL

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Abstract- The C_4 *erythro* and *threo* diols (7) and (8) are converted either into the chiral epoxides (13) and (15) or into the enantiomers (14) and (16); the epoxide (13) is used as chiral synthon for the preparation of (3S,4S) 4-methyl-3-heptanol (21).

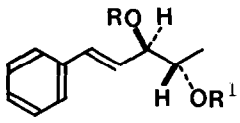
There is a current interest in the synthesis from readily available, optically active natural products of relatively small, highly functionalized chiral synthons which can be used as starting materials in the preparation of enantiomerically pure forms of natural products and drugs.[1] We present now the synthesis of the four epoxides (13), (14), (15) and (16) from the C_4 chiral *erythro* and *threo* diols (7) and (8), respectively, through a route allowing the preparation, by means of the same reagent set, either of (13) and (15) or of the enantiomers (14) and (16) exclusively, and, furthermore, the synthesis from the epoxide (13) of (3S,4S) 4-methyl-3-heptanol (21), the pheromone of *Scolytus multistriatus*.[2]

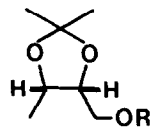
The epoxides (13) and (15) have been recently prepared from natural tartaric acid, and,formally the enantiomers (14) and (16) are available from the much costly unnatural enantiomer[3], whereas the present procedures allow the obtainement of the two enantiomeric forms of each epoxide at the same cost.

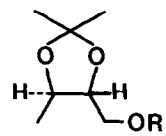
As chiral material for the synthesis of (13) and (14) we used the (2S,3R) diol (1), obtained in fermenting baker's yeast from cinnamaldehyde.[4] Compound (1) was protected to (2), which,on ozonolysis in MeOH and $NaBH_4$ reduction,yielded the C_4 alcohol (3), $[\alpha]_D^{\#}$ +52°(80% overall). The latter material was O-benzylated (NaH, DMF, C_6H_5Cl) (95%) to (4), $[\alpha]_D$ +1.7°;hydrolysed,in turn with 20% aqueous acetic acid (82)% to the (2R,3S) diol (7), $[\alpha]_D$ +17°. The diol (7)[5], when treated with 1 mol. eq. of benzoyl chloride in CH_2Cl_2- pyridine at r.t. overnight, gave the 3- and 2-O-benzoates (9) and (10), $[\alpha]$ +37.8° and -2.3°, respectively, separated by SiO_2 column chromatography, in ca 1:1 ratio and 48% yield, with 30% unreacted material.The structure of the isomeric benzoates (9) and (10) is based on ^{1}H-n.m.r. studies. In compound (7) the C-2 and C-3

we refer to $[\alpha]$ values at 20°C and,if not otherwise stated c=1 in $CHCl_3$

protons appear at 3.8 δ and 3.6 δ, respectively. In compound (9) the C-3 proton signal is at 5.2 δ, whereas in (10) the C-2 proton signal appears at 5.15 δ. The 3-monobenzoate (9) was converted into the 2-tosylate (TsCl, pyridine, 0°C,overnight) (90%), $[\alpha]_D$ +12°, giving rise, upon treatment with K_2CO_3 in MeOH 3 h at 80°, to the epoxide (13), $[\alpha]_D$ -14°,in 80% yield, the optical rotation of which agreed well with the lit.[3] value. The isomeric 2-benzoate (10) can also be converted into the epoxide (13). This was achieved by protecting the free hydroxyl group at position 3 as the tetrahydropyranyl ether and removing with 2N NaOH the benzoate ester at position 2. The resulting material was converted into the 2-tosylate, which, on sequential tretment with 2N HCl and with methanolic K_2CO_3, gave rise, in ca 60% yield overall, to optically pure (13).





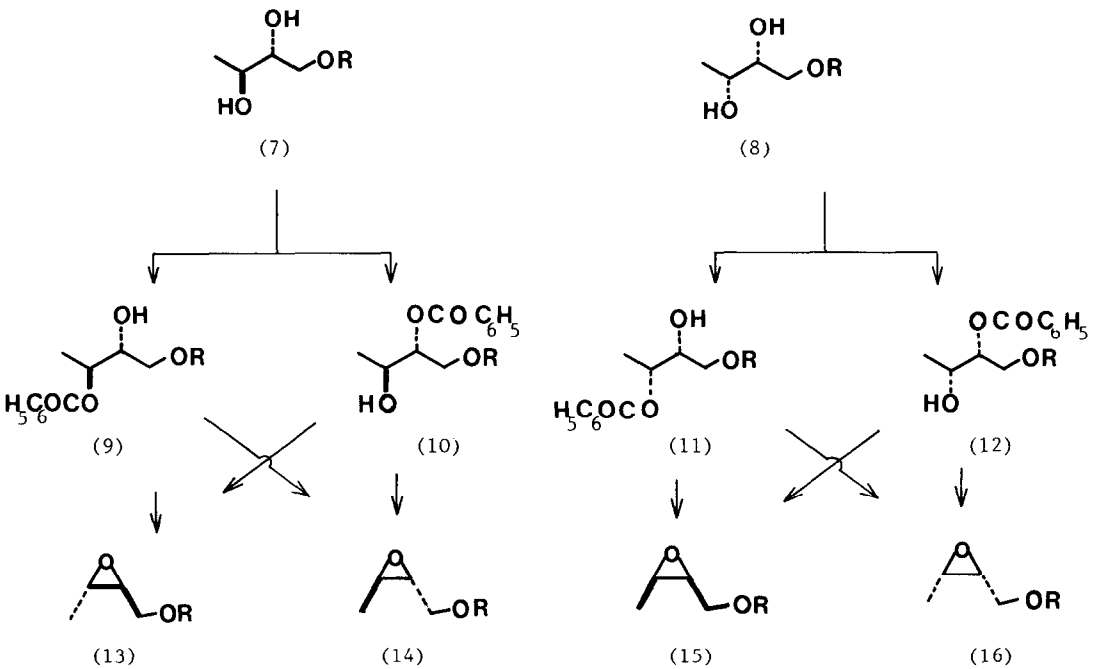


(1) R = R^1 = H (3) R = H (5) R = H

(2) R,R^1 = CMe_2 (4) R = $CH_2C_6H_5$ (6) R = $CH_2C_6H_5$

The enantiomeric epoxide (14) was obtained directly from the 2-benzoate (10), *via* the 3-tosylate $[\alpha]_D$ -19°, which, on K_2CO_3 treatment, yielded the expected epoxide with $[\alpha]_D$ +13.8°,in 70% overall yield. Again, by applying to the 3-benzoate (9) the reaction sequence used for the conversion of (10) into (13), the epoxide (14) was prepared in ca.55% yield. In this way, as indicated in the Scheme, it is possible to direct the conversion of the diol (7) either into (13) or (14),exclusively.

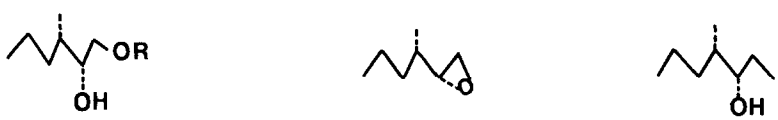
As a synthetic application of the above chiral synthons we chose the preparation of (3S,4S)-4-methyl-3-heptanol (21), the pheromone of *Scolytus multistriatus*, recently obtained in enantiomerically pure form from D-glucose.[6] Thus , the epoxide (13) was reacted with $(n\text{-}C_3H_7)_2CuLi$ in Et_2O to give the adduct (17), in ca. 8:2 ratio with the product of α-opening, in ca. 60% overall yield. Compound (17), $[\alpha]_D$ -17°, purified by SiO_2 column chromatography, was quantitatively debenzylated (H_2, 10% Pd/C) to (18), $[\alpha]_D$ -26°, and converted (0.9 mol. eq. TsCl,CH_2Cl_2-pyridine,r.t. 24 h) (56%) into the 1-tosylate (19), $[\alpha]_D$ - 22.4°. The latter material gave the epoxide (20), $[\alpha]_D$ +3.2° on treatment with KOH in aqueous ethylene glycol (50%).[7] Addition of $(Me)_2CuLi$ in Et_2O onto (20) gave (21), $[\alpha]_D$ -23.3° (c 1, hexane)[7,8] in 80% yield. Compound (21) was purified by SiO_2 column chromatography (light petroleum ether /Et_2O) and bulb-to-bulb distillation. It was 97% pure by



R= $CH_2C_6H_5$

-Scheme-

g.l.c. and devoid of the *erythro* isomer.[8] Furthermore, ^{1}H-n.m.r. studies on (21) with $Eu(hfc)_3$ indicated it to be enantiomerically pure.[8]



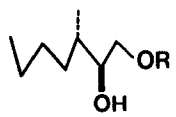
(17) R = $CH_2C_6H_5$
(18) R = H
(19) R = Ts

(20)

(21)

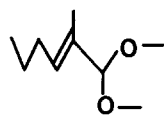
The synthesis of the *cis* enantiomeric epoxides (15) and (16) was achieved starting from the (2R,3R) diol (8), $[\alpha]_D$ +7.6°, prepared in turn, from the amino acid L-threonine, *via* the C_4 alcohol (5)[9] and the O-benzyl derivative (6), $[\alpha]_D$ -3.7°. As above, monobenzylation of (8)[5] gave in *ca.* 4:6 ratio, the 3-benzoate (11), $[\alpha]_D$ -23.2° and the 2-isomer (12), $[\alpha]_D$ -8.4°. Compound (11), *via* the 2-

-tosylate, $[\alpha]_D$ -43,1°, gives rise, on basic treatment, to (15), $[\alpha]_D$+17.6°,whereas the isomer (12) *via* the 3-tosylate, $[\alpha]_D$ -21°,yields (16), $[\alpha]_D$-17.6°,in good agreement with the lit.[3] value. The overall yields of the conversion of (11) and (12) into (15) and (16), respectively, are in the range of 70-75%. Again, the 2-benzoate (12) can be converted into the epoxide (15) and, similarly, the 3-benzoate (11) into (16), by applying the reaction sequence mentioned above, as outlined in the Scheme. Treatment of the epoxide (16) with $(n\text{-}C_4H_9)_2CuLi$ yields the product of β-attack (22),with ca. 10% of the isomer derived by α-opening of (16). Compound (22), was debenzylated to (23), which yielded, on HIO_4 oxidation in dry THF and $NaBH_4$ reduction, (2S) 2-methyl hexanol (25), $[\alpha]_D$-10.7°, in good agreement with the lit.[10] value reported for the enantiomerically pure isomer. This latter material was used as comparison in a study on the baker's yeast mediated reduction of the acetal (24). Indeed, the acetal (24) gives rise in ca. 35% yield to 2-methylhexanol, containing ca. 90% of the



(22) R = $CH_2C_6H_5$

(23) R = H



(24)

(25)

(2S)-isomer (25).The preparation of the epoxides (13) and (14) and of the pheromone (21) from the diol (1), lends further support to the synthetic significance of this class of chiral products obtained by biotransformations of non-conventional substrates.

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