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STEREOSPECIFIC SYNTHESIS OF EXO- AND ENDO-1,3-DIMETHYL-2,9-DIOXABICYCLO-[3.3.1]-NONANE

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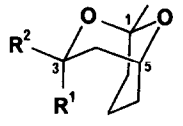
Summary : The title compounds may be synthesised in an enantioselective and diastereospecific manner from (±)-4-hydroxynona-2,8-diene using the Sharpless asymmetric epoxidation as the key step in the reaction sequence.

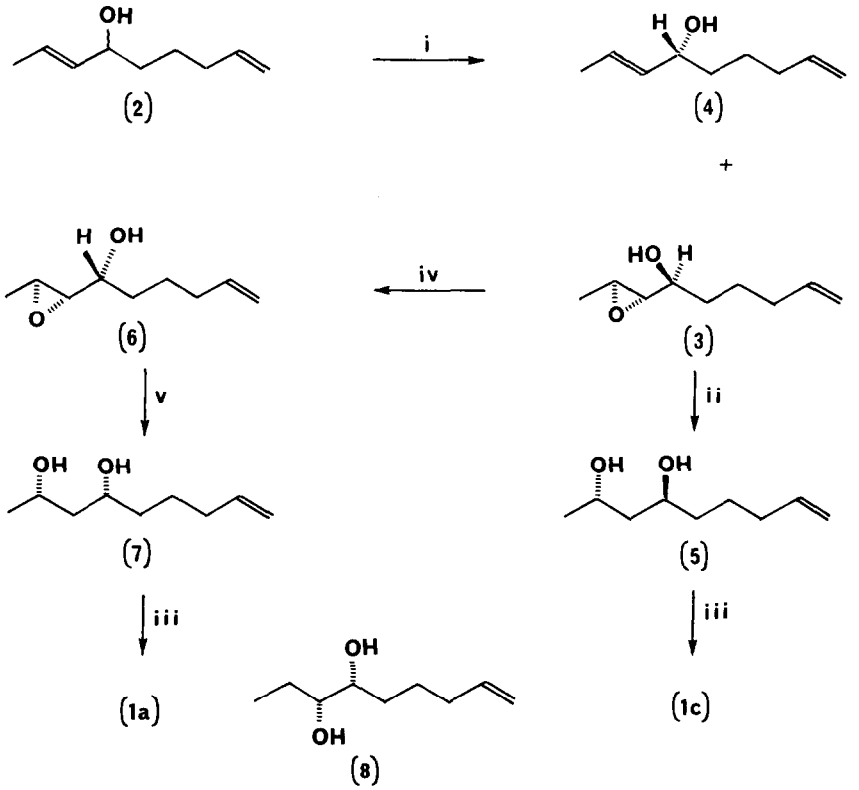
Endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (1a,b)[+] is a host specific substance isolated from the Norway Spruce infested by the ambrosia beetle (Trypodendron lineatum Oliv.)[1]. Several syntheses of both the racemic and optically active forms have been published but the syntheses either lack stereoselectivity or involve a large number of steps.[2] We report short, diastereospecific, and enantioselective syntheses of both endo (1a,b) and exo (1c,d) stereoisomers from a common achiral precursor using the Sharpless asymmetric epoxidation[3] to control the absolute and relative configurations of the three chiral centres.



1 a) R^1 = Me, R^2 = H (1S, 3S, 5R)
b) R^1 = Me, R^2 = H (1R, 3R, 5S)
c) R^1 = H, R^2 = Me (1R, 3S, 5S)
d) R^1 = H, R^2 = Me (1S, 3R, 5R)

[+] The absolute configuration of natural endo- (1) is unknown and its specific rotation has not been reported.

The (±)-allylic alcohol (2) (E/Z ratio 96:4 by capillary G.C.) was prepared (92% yield) by the reaction of E-but-2-enal with pent-4-enyl magnesium bromide. Catalytic enantioselective epoxidation of the (±) alcohol (2) using L-(+)-diisopropyl tartrate as the chiral auxiliary was allowed to proceed to 40% reaction. This procedure gave a mixture of epoxyalcohol (3) (2S, 3S, 4S)



Reagents.

(i) 0.10 eq. $Ti(O^iPr)_4$, 0.12 eq. L-(+)-DIPT, 0.40 eq. ^tBuOOH, CH_2Cl_2, -20^0C, 3 days.

(ii) 2.0 eq. Red-Al, THF, 0^0C RT, 12 hrs.

(iii) $PdCl_2$ (cat). $CuCl_2.2H_2O$ (1.1 eq), THF, RT.

(iv) PPh_3, $EtO_2CN{=}NCO_2Et$, p-Nitrobenzoic acid, THF, RT, 18 hrs; MeOH/MeONa (cat).

(v) 2.0 eq. Red-Al, 1.0 eq. MeOH, THF, 0^0C RT, 12 hrs.

and partially resolved allylic alcohol (4) which were separated by silica gel chromatography (ether/hexane/triethylamine, 50:50:1, Merck 9385) in 38% and 50% yields respectively. Alternatively the mixture could be isolated and treated with Red-Al in tetrahydrofuran[4] to give a mixture of the (2S, 4S) diol (5) (35% yield) and allylic alcohol (4) (55% recovery) which proved readily separable by chromatography on alumina. Wacker type cyclisation of the diol (5) by the reported procedure[2b,5] provided the exo ketal (1c) in 56% yield ($[\alpha]_D^{24} = -4.0^0 \pm 1.0^0$, c = 2.5 (pentane)†, >95% purity by ^{13}C n.m.r. analysis). The diastereoisomeric purity of the epoxy alcohol (3) was established as >95% de and the optical purity as >96% ee.‡ Synthesis of the antipode of the exo ketal, (1d) could be accomplished using D-(-)-diisopropyl tartrate as the chiral auxiliary in the epoxidation reaction.

Synthesis of the natural endo stereoisomers by a similar scheme requires an inversion at C4 of epoxy alcohol (3) and its enantiomer. Hence pure (3) (2S, 3S, 4S; >96% ee; >95% de) was reacted under the conditions of Mitsonobu[6]; hydrolysis of the resulting p-nitrobenzoate ester gave epoxy alcohol (6) (2S, 3S, 4R; >96% ee; >93% de‡) in 55% overall yield. Reductive cleavage of the epoxide moiety of (6) using Red-Al in tetrahydrofuran gave a mixture of products containing up to 50% of the 3,4-diol (8). However, reaction of (6) with Red-Al (2.0 equivalents) in tetrahydrofuran containing one equivalent of methanol gave the desired 2,4-diol (7) in 93% yield with no detectable contamination by regioisomers or diastereoisomers (capillary G.C.). Wacker type cyclisation as before gave the endo ketal (1a) (1S, 3S, 5R) in 52% yield ($[\alpha]_D^{28} = +36.0^0$, c = 0.77 (pentane) , > 95% by ^{13}C n.m.r. analysis). The antipode (1b) could be similarly prepared using D-(-)-diisopropyl tartrate as the chiral auxiliary in the epoxidation reaction.

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† literature values [2d]: (1a): $[\alpha]_D^{22} = +37.5^0$ (pentane)

(1c): $[\alpha]_D^{22} = -4.4^0$ (pentane)

‡ Calculated on the basis of the ^{19}F n.m.r. and capillary G.C. analysis of the ester with (-)-α-methoxy-α-trifluoromethylphenylacetic acid[7].

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