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SYNTHESIS OF CHIRAL ADENOSINE RECEPTOR RECOGNITION UNITS VIA A SHARPLESS ASYMMETRIC EPOXIDATION PROCEDURE

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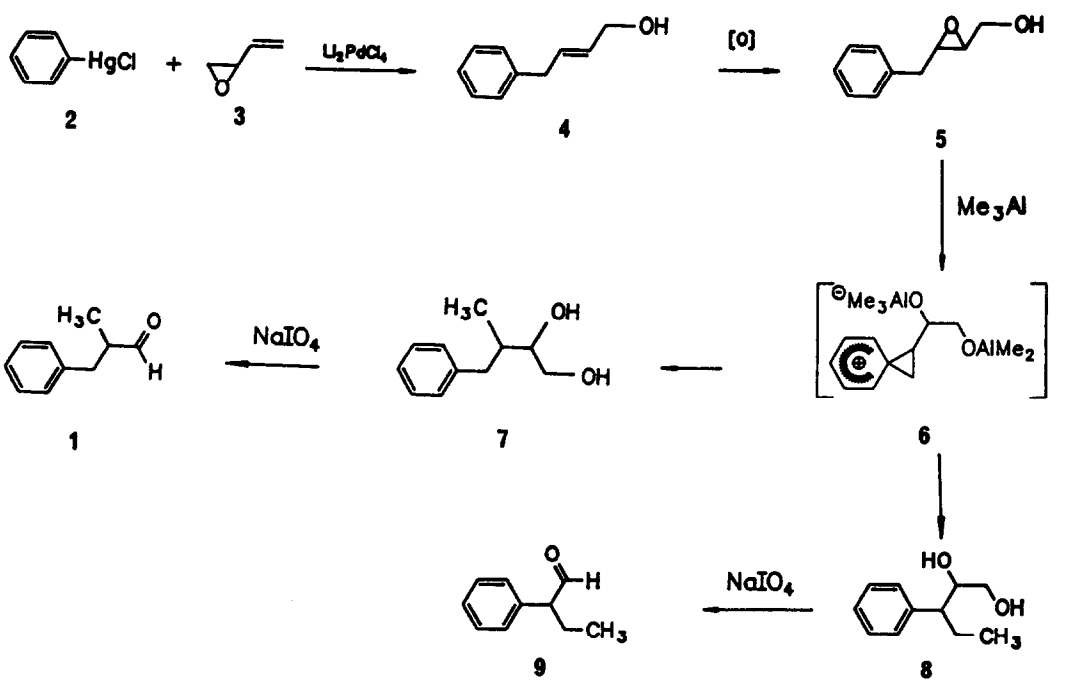
Summary: Opening of the epoxide of (E)-4-phenyl-2-buten-1-ol with trimethylaluminum gave two phenonium ion-mediated products, whose ratio was dependent on reaction conditions.

(R)-N^6-Phenylisopropyladenosine (R-PIA) is a potent, A_1-selective adenosine receptor agonist.[1] In order to incorporate the chiral phenylisopropyl recognition unit into other potential receptor agents, chiral 2-benzylpropionaldehyde (1) and/or the corresponding acid and alcohol were required. Preparation of 1, via the epoxide of (E)-4-phenyl-2-buten-1-ol (5) obtained by a Sharpless asymmetric epoxidation procedure,[2] appeared to proceed through a skeletal rearrangement which also provided chiral 2-phenylbutyraldehyde (9).

Treatment of butadiene monoxide (3) with phenylmercuric chloride (2) in the presence of a palladium catalyst gave (E)-4-phenyl-2-buten-1-ol (4).[3] Oxidation of 4 with 3-chloroperoxybenzoic acid gave epoxide 5, which was opened with trimethylaluminum[4,5] to afford diol 7. Oxidative cleavage of 7 with sodium periodate gave the desired aldehyde 1, as shown in Scheme I.



Scheme I

Coproduced with 7 during the reaction of 5 with trimethylaluminum was the rearranged diol 8. Both 7 and 8 could arise from phenonium ion[6] 6, a proposed intermediate. Oxidation of 8 with sodium periodate gave aldehyde 9. The ratio of diols 7 and 8 was dependent on reaction conditions, as shown in Table I. Thus, at -78°C, rearranged aldehyde 9 was almost exclusively produced, while at 83°C, the ratio of 1:9 was 1.1:1.

Table I. Ratios of Aldehydes 1 and 9 as a Function of Methylation Reaction Conditions.

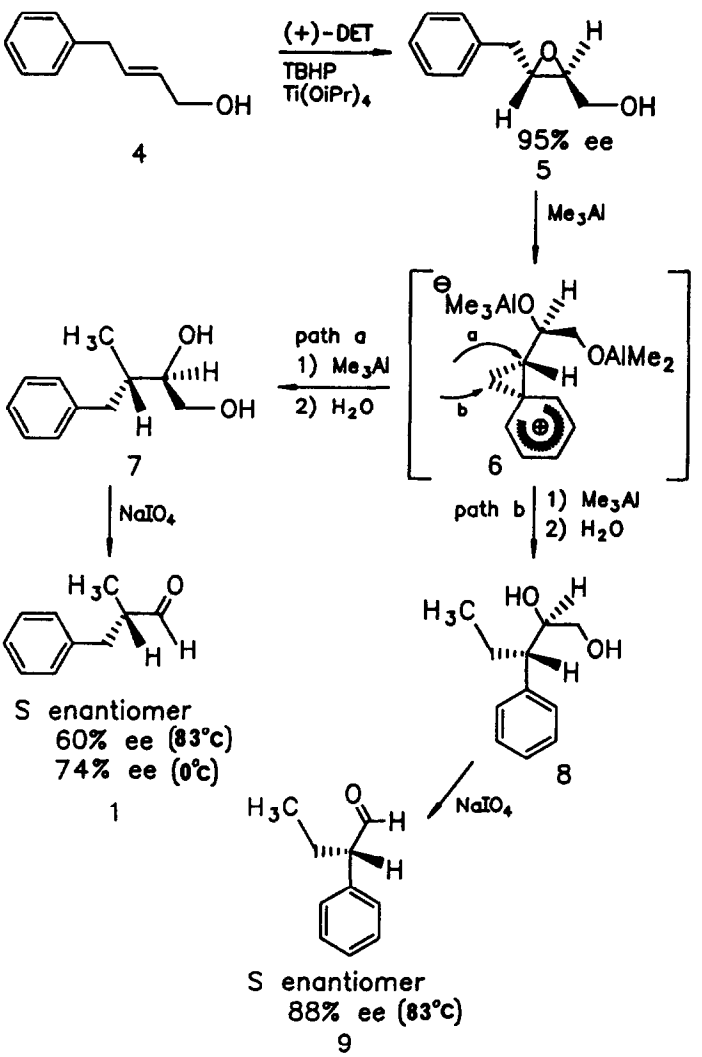
Reaction	Temp °C	Solvent[a]	% Yield[b] 1 + 9	Ratio[c] 1:9
i	-78	CH_2Cl_2	86	1:18
ii	0	CH_2Cl_2	96	1:2.4
iii	24	CH_2Cl_2	83	1:1.8
iv	83	$ClCH_2CH_2Cl$	90	1.1:1

[a]Three equivalents of Me_3Al were added to a solution of 5 with the solvent and temperature specified. For reactions i-iii, 2 M Me_3Al in hexane was used; for reaction iv, 2 M Me_3Al in toluene was used.

[b]Yields are from mixtures of diols 7 and 8 which were purified but not separated by radial chromatography.

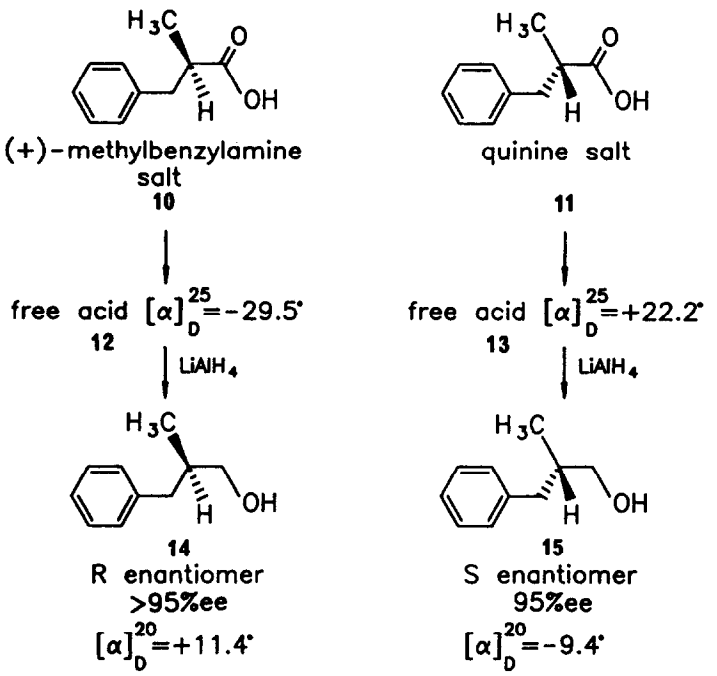
[c]Ratios were determined by gas chromatography. In all cases, ratios of 7:8 were greater than those of 1:9, reflecting the instability of 1.

Allylic alcohol 4 was subjected to Sharpless epoxidation conditions, which allowed the preparation of the enantiomers of aldehydes 1 and 9. Thus, when diethyl L-tartrate[2] was used, as shown in Scheme II, (2S-trans)-3-(phenylmethyl)oxiranemethanol (5) was produced in 95% ee, as determined from its Mosher's ester.[7] Treatment of 5 with trimethylaluminum gave a mixture of chiral diols 7 and 8, which were oxidized with $NaIO_4$ to give (S)-1 and (S)-9. It is felt that (S)-9, which represents a net inversion of configuration at the 3-position of 5, can only arise from phenonium ion 6 via path b. Aldehyde 1, whose absolute configuration arises from double inversion at the 3-position of 5, derives mainly from 6. However, it is felt that a portion of 1 comes directly from 5 by simple epoxide opening, since enantiomeric excess of 1 was greater at 0°C, where rearrangement and presumably phenonium ion participation is favored, than at 83°C. Enantiomeric excesses of 1 and 9 were determined using Mosher's esters[7] of the corresponding alcohols, which were prepared by $LiAlH_4$ reduction.



Scheme II

Authentic samples of (R)-2-benzylpropanol (14) and the S enantiomer (15) were made as shown in Scheme III. 2-Benzylpropanoic acid[8] was resolved by repeated recrystallization of the (+)-methylbenzylamine salt (10) to give, after treatment with sulfuric acid, free acid 12.[9] Reduction with $LiAlH_4$ afforded (R)-14[10] in >95% ee, as determined from its Mosher's ester.[7] Similarly, (S)-15[10] was prepared via quinine salt 11[9] in 95% ee. Thus, the chemical resolution method was preferred over the asymmetric epoxidation procedure for the preparation of chiral 2-benzylpropanols.



Scheme III

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