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THE STEREOSPECIFIC SYNTHESIS OF (S)-2-[$^2H_3$]METHYL-2-METHYLBUTANOL. CHARACTERISATION OF THE (R) AND (S) ENANTIOMERS OF THE RACEMIC [$^2H_3$]ALCOHOL BY ^{2}H-NMR IN THE PRESENCE OF A CHIRAL SHIFT REAGENT.

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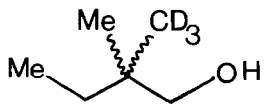
SUMMARY. The synthesis of the title compound is described. Assignments have been made in the ^{2}H-nmr spectrum for the [$^2H_3$]methyl resonances of racemic 2-[$^2H_3$]methyl-2-methylbutanol which were rendered anisochronous by the presence of tris(3-heptafluorobutyryl-d-camphorato)europium(III).

In connection with a biosynthetic problem[1] we have devised a procedure, which is reported below, to identify the (R) or (S) enantiomers of 2-[$^2H_3$]-methyl-2-methylbutanol[2] 1 in the presence of 2,2-dimethylbutanol 2a. For calibration purposes we required one enantiomer of 1 with defined absolute configuration. Several compounds are known which are chiral solely by virtue of the replacement of one member of a pair of enantiotopic methyl groups by a [$^2H_3$]-methyl group.[3] We now report the stereospecific synthesis of (S)-2-[$^2H_3$]methyl-2-methylbutanol 2b by a route which utilises a Claisen rearrangement to generate the chiral centre.



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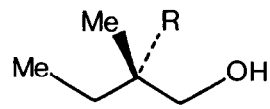


2 a; R = Me
b; R = CD_3

Synthetic Studies. Ethyl (S)-2-hydroxypropanoate 3 provided a convenient starting point for the synthesis of (S)-2-[$^2H_3$]methyl-2-methylbutanol by the sequence of reactions which is outlined in Scheme 1. Protection of the hydroxyl function of 3 by reaction with benzyl chloromethyl ether, followed by partial reduction of the ester moiety with diisobutyl aluminium hydride, gave the propanal derivative[4] 4. The latter was condensed with the stable phosphorane $Ph_3P{=}C(Me)CO_2Et$ to yield the conjugated ester 5; the (E) stereochemistry depicted for the olefinic bond of 5 was assigned on the basis of published precedent[5] and confirmed as described below. The ester function of 5 was reduced with lithium aluminium deuteride to give the [$^2H_2$]-allylic alcohol 6 (R=CD_2OH) which was treated with triphenylphosphine in carbon tetrachloride[6] to yield the [$^2H_2$]-allylic chloride 6 (R=CD_2Cl). This compound did not react satisfactorily with lithium aluminium deuteride, despite successful reduction of 6 (R=CH_2Cl) with

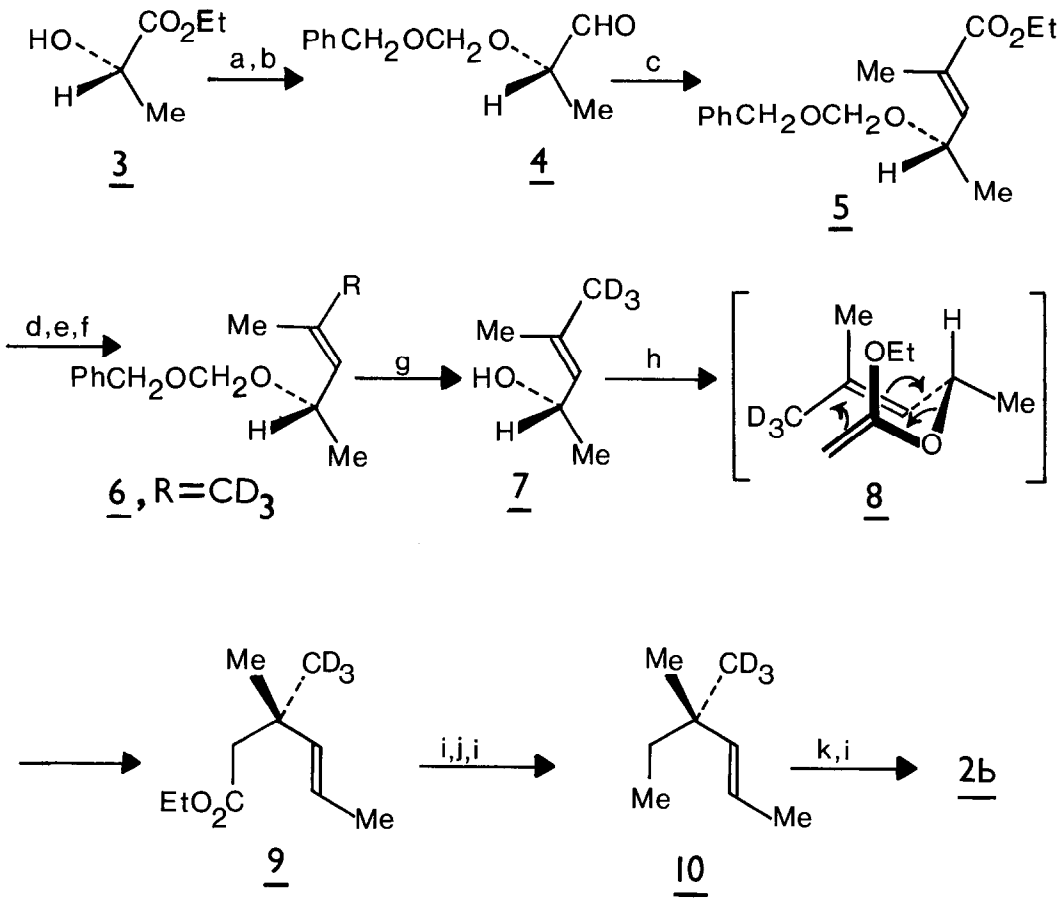
lithium aluminium hydride, but was reduced smoothly with lithium triethylborodeuteride[7] to give the required product 6 (R=CD_3). The (E) stereochemistry of the latter was confirmed by the ^{13}C-nmr spectrum[8] which showed only two methyl resonances, at 18.1 and 21.5 ppm. For comparison, the ^{13}C-nmr spectrum of the unlabelled compound 6 (R=Me) showed three methyl carbon resonances at 18.1 and 25.8 ppm, assigned to the (Z) and (E) vinyl methyl groups respectively,[9] and at 21.5 ppm.

Deprotection of 6 (R=CD_3) with lithium in liquid ammonia gave the trideuterioallylic alcohol 7. The stereochemical integrity of 7 at the chiral centre was demonstrated by ^1H-nmr in the presence of Eu(hfbc)$_3$.[10] Thus the ^1H-nmr of the racemic unlabelled alcohol 7 (D=H, racemic) showed two doublets, separated by 0.3 ppm, for the C-1 protons of the two enantiomers when examined in the presence of the chiral shift reagent ([Eu(hfbc)$_3$]/[alcohol] = 0.7); under the same conditions the chiral deuteriated alcohol 7 showed only one methyl doublet whose chemical shift was coincident with that doublet of higher frequency which was observed for the racemic alcohol. We estimate that the chiral alcohol contained less than 5% of the undesired (R) enantiomer.

The key step in the synthetic sequence (Scheme 1) was the acid-catalysed reaction of the chiral allylic alcohol 7 with ethyl orthoacetate. The intermediate mixed acetal was predicted to undergo Claisen rearrangement predominantly (~ 95%) *via* that chair-like conformation 8 in which the methyl group which was attached to the chiral centre would attain an equatorial configuration in the transition state.[11] Thus the unsaturated ester product was assigned the (3S) stereochemistry shown 9. Stepwise reduction of the ester moiety in 9 led to the chiral alkene 10 which was diluted three-fold with unlabelled 4,4-dimethylhex-2-ene prior to purification. Finally ozonolysis and reduction of the ozonide with lithium aluminium hydride gave 2,2-dimethylbutanol, enriched (~ 25%) with the required chiral [$^2H_3$]-alcohol 2b.

NMR Studies. Addition of Eu(hfbc)$_3$ to a solution of 2,2-dimethylbutanol 2a in carbon tetrachloride caused typical downfield shifts of all resonances in the ^1H-nmr of the alcohol. The 2-pro-R and 2-pro-S methyl groups of 2a displayed chemical shift non-equivalence ($\Delta\Delta\delta$) which increased linearly with [Eu(hfbc)$_3$] reaching a value of 0.05 ppm for [Eu(hfbc)$_3$]/[2a] = 0.3; on further addition of the shift reagent $\Delta\Delta\delta$ increased less rapidly, reaching a value of 0.07 ppm for molar ratios greater than 1.0. The ^1H-nmr of the racemic [$^2H_3$]-alcohol 1 behaved in an identical manner; when mixtures of 1 and 2a were examined, resonances due to corresponding groups in the labelled and unlabelled alcohols were shifted by identical amounts on addition of the chiral shift reagent.

In the ^2H-nmr spectrum of 1 the resonances due to the [$^2H_3$]methyl groups of



Reagents: a, $PhCH_2OCH_2Cl/{}^{i}Pr_2NEt$; b, $^{i}Bu_2AlH/PhMe$; c, $Ph_3P{=}C(Me)CO_2Et$; d, $LiAlD_4$; e, Ph_3P/CCl_4; f, $LiBDEt_3$; g, $Li/NH_{3(l)}$; h, $MeC(OEt)_3/H^+$; i, $LiAlH_4$; j, TsCl/pyridine; k, O_3.

SCHEME 1

the two enantiomers were also non-equivalent in the presence of Eu(hfbc)$_3$ (fig. 1a). As expected the ^{2}H-nmr of the chiral [$^2H_3$]-alcohol 2b, in the presence of the shift reagent, showed only one resonance for the [$^2H_3$]methyl group (fig. 1b). This resonance was coincident with the less-shifted resonance of the racemic alcohol when the ^{2}H-nmr of a mixture of chiral and racemic alcohols was examined in the presence of Eu(hfbc)$_3$ (fig. 1c). Thus the following critical assignment[12] has been made for the ^{2}H-nmr: on addition of Eu(hfbc)$_3$ to 2-[$^2H_3$]methyl-2-methylbutanol the [$^2H_3$]methyl resonance due to the (R)-alcohol is shifted further (to higher frequency) than is the [$^2H_3$]methyl resonance due to the (S) enantiomer.

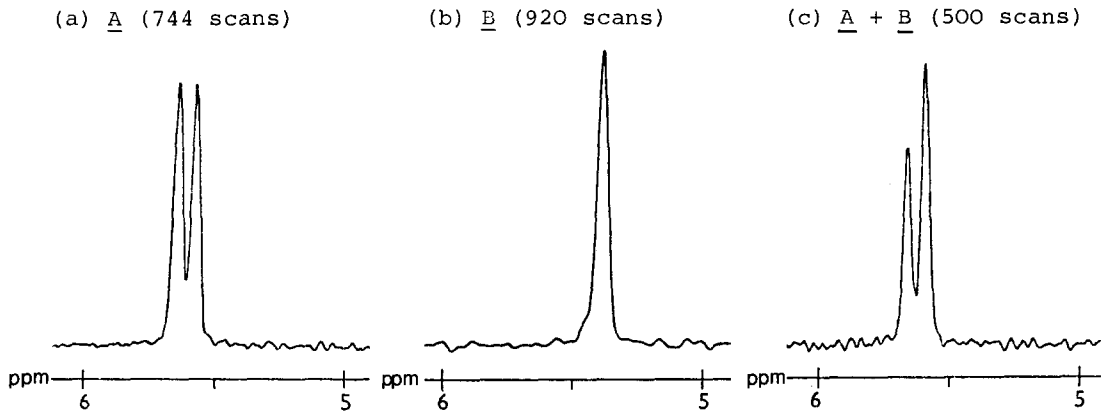


FIGURE 1. 55.3 MHz ^{2}H-NMR SPECTRA Spectra are calibrated with internal $CDCl_3$ reference at 7.25 ppm and are computer-line-narrowed.
Sample A: 0.103 mmol. of 2a enriched (~ 25%) in 1, plus 0.053 mmol. of $Eu(hfbc)_3$, plus ~ 5 mg. $CDCl_3$ in CCl_4 (0.8 ml).
Sample B: 0.103 mmol. of 2a enriched (~ 25%) in 2b, plus 0.051 mmol. of $Eu(hfbc)_3$, plus ~ 5 mg. $CDCl_3$ in CCl_4 (0.8 ml).

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