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CHIRAL 1-DEUTERIO ALCOHOLS. SYNTHESIS AND DETERMINATION OF ENANTIOMERIC PURITY BY CHIRAL LANTHANIDE NMR SHIFT REAGENTS.[1]

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Primary 1-deuterio alcohols, RCHDOH, which are chiral by virtue of deuterium substitution, have great value in the study of mechanisms of chemical and biochemical reactions.[2,3] Enantiomerically pure alcohols of this type have been obtained invariably by enzymic processes, but various chemical asymmetric reactions have been used to prepare partially active alcohols.[4]

The chiral reducing agent made by mixing one mole of lithium aluminum hydride with two moles of (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (R*OH)[5], gives a chiral reagent, $LiAlH_2(OR^*)_2$, which is effective in the asymmetric reduction of carbonyl compounds.[6] We have now made use of the corresponding deuterio reagent, $LiAlD_2(OR^*)_2$, to reduce various aldehydes to 1-deuterio alcohols. We have also investigated the efficacy of the chiral lanthanide shift reagent, tris-[(3-heptafluoropropylhydroxymethylene)-d-camphorato]europium III[7], $Eu(HFC)_3$, for the determination of enantiomeric purity and have also investigated the correlation of configuration with the extent of lanthanide induced shifts, LIS, for RCHDOH enantiomers.

Asymmetric Reduction of Aldehydes by $LiAlD_2(OR^*)_2$ It is apparent from Table I that this chiral reducing reagent [$LiAlD_2(OR^*)_2$] constitutes a convenient, general, and rapid method for the synthesis of primary 1-deuterio alcohols with enantiomeric purities of 20-66%. The chiral inducing amino alcohol (R*OH) was recovered and reused repeatedly.

Enantiomeric Purity of RCHDOH Compounds. Chiral lanthanide shift reagents cause nonequivalent nmr chemical shifts of certain signals of enantiomeric alcohols and amines.[7,8,9,10] This property has been used to determine the enantiomeric purity of secondary alcohols, R-CHOHR', and comparable primary amines, $R\text{-}CHNH_2R'$. The enantiotopic methylene protons of benzyl alcohols also demonstrate nmr nonequivalence in the presence of a chiral shift reagent.[11] Our data (Table I) show that the chiral lanthanide shift reagent $Eu(HFC)_3$ also can be used to determine the enantiomeric purity of 1-deuterio primary alcohols, RCHDOH.

In the case of 2,2,2-triphenylethanol-1-d there was no significant lanthanide induced shift (LIS) difference between the enantiomers However, the diastereomeric MTPA esters[12] of this alcohol show a chemical shift difference sufficient for satisfactory nmr analysis. This difference is enhanced by $Eu(fod)_3$, as in the case of the benzyl-1-d MTPA ester.[6, 12b] H. Gerlach finds good $Eu(dpm)_3$ induced nmr shift differences for diastereotopic protons of RCHDOH camphanic acid esters.[13]

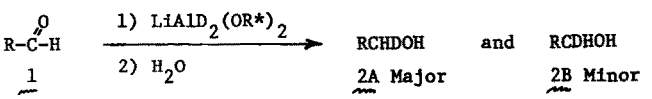
Stereochemistry of Asymmetric Reductions of RCHO by $LiAlD_2(OR^*)_2$. Compounds 1, 2, 3, 4 and 5 in Table I have known configurations. The stereochemistries of these reductions were determined to be S as given in the footnotes. Therefore, this reagent preferentially attacks the si face of the carbonyl group in these compounds. It seems altogether reasonable to assume that this will be generally so and that nos. 6 and 7 also possess the S configuration.[14] Thus this procedure is valuable for producing partially active 1-deuterio primary alcohols and offers a method for deducing their relative configurations.

Correlation of Configuration of RCHDOH Alcohols with Differences in $Eu(HFC)_3$ Induced NMR Shifts. We have shown that five of the seven RCHDOH carbinols in Table I have the S enantiomer in excess. We have concluded that this may well be generally so for aldehyde reductions by this reagent. In each of the six cases reported in this table where an LIS difference in enantiomers in the presence of $Eu(HFC)_3$ was observed, there was a larger shift for the carbinyl proton of the minor R enantiomer than for the major S enantiomer. We therefore tentatively conclude that the enantiomer of RCHDOH which undergoes the more extensive shift in the presence of the chiral $Eu(HFC)_3$ reagent (from d-camphor) has the R configuration.

Experimental. All spectra were run on a Varian XL-100 nmr spectrometer[1]; the signal used in all analyses was that of the proton attached to the chiral carbinyl carbon. The substrate concentrations were 0.18 to 0.22 molar in $CDCl_3$. The optimum molar ratio of $Eu(HFC)_3$ to substrate as reported in Table I was 0.5 to 0.6. Results are reported in δ, ppm downfield from TMS. The starting aldehydes were commercially available except for adamantyl carboxaldehyde[15] and triphenylacetaldehyde. These latter two were made by a Collins oxidation (CrO_3Py_2) of the corresponding carbinols which were obtained by reduction of the corresponding carboxylic acids.[14] The asymmetric reductions were performed according to the previous procedure.[6] An ether solution of 2 molar equivalents of the chiral alcohol (+)-2S,3R-$Me_2NCH_2CHMeCOH(Ph)CH_2Ph$ (R*OH,[5] Aldrich Chemical Co.) was added to 1 molar equivalent of $LiAlD_4$ in anhydrous ether at 0°. Hydrogen was immediately liberated and a precipitate formed. Within three minutes after mixing these reactants, the aldehyde was added. After stirring (0°, 1/2 hr), the mixture was allowed to warm to room temperature, acidified, extracted with ether, dried ($MgSO_4$) and concentrated to give crude RCHDOH. In each case less than 2% aldehyde was detected in the product. The reductions were therefore near quantitiative although isolation yields of the more volatile products (examples 2, 3 and 4) fell short of this. The crude material was either used directly for the nmr studies, purified by distillation and/or converted to the MTPA ester derivative[12] as appropriate. The dilute acid solution was neutralized and the chiral inducing alcohl, R*OH, recovered in near quantitative yield.

TABLE I

Synthesis[a] and Chiral Analysis[b] of 1-Deuterio Alcohols



No.	R	Stereoselectivity[b] % e.e.	Configuration of 2A	LIS of 2A and 2B in presence of Eu(HFC)$_3$[c] δ_{H_A}	δ_{H_B}	$[\delta_{H_B} - \delta_{H_A}]$	$[\alpha]^{20}_D$ observed[d] °
1	Adamantyl	34±5[e] 28±3[g]	S[f]	15.15	15.43	0.28	+0.21±.1 (c 2.33)
2	Me_3C-	39±5[e] 44±5[g]	S[h]	14.93	15.04	0.11	---
3	Me_2CH-	23±3[i] 29±10[j]	S[j]	14.12	14.23	0.11	+0.23±.04 (neat, ℓ=1)
4	$CH_3CH_2CH_2$-	15±5[i] 19±3[k]	S[k]	14.60	14.67	0.07	+0.085±.008 (neat, ℓ=1)
5	Ph-	39±3[e] 40±3[i] 42±3[m]	S[m]	15.09	15.26	0.15	+0.68±.02 (c 6.7)
6	CPh_3-	66±5[n]	o	13.80	13.80	0.00	-0.95±.1 (c 1.9)
7	Cl_3C-	27±3[i]	o	11.08	11.22	0.14	0.00 (c 14)

NOTES FOR TABLE

(a) See text for general experimental procedure.

(b) The enantiomeric composition of the asymmetric reduction product was determined as outlined in notes e, g, i, j, k, l, m and n; % e.e. refers to % enantiomer excess.

(c) Lanthanide induced shift (LIS) using Eu(HFC)$_3$/RCHDOH molar ratios from 0.5 to 0.6.

(d) Observed optical rotations in cyclopentane solvent at the specified concentration unless otherwise noted.

(e) Based on the integrals of carbinyl proton signals in the presence of Eu(HFC)$_3$.

(f) S. H. Liggero, R. Sustman, and P. von R. Schleyer, J Amer. Chem. Soc., 91, 4571 (1969); no rotation was given but the nmr spectrum of the (R)-O-methylmandelate for the S enantiomer obtained by fermentation was identical to that of the major isomer obtained here.

(g) Based on the integrals of carbinyl proton signals in the presence of Eu(HFC)$_3$.

(h) Based on correlation of the nmr spectrum of the MTPA ester of authentic S-neopentyl-1-d alcohol obtained by fermentation.[13]

(i) Based on the area of carbinyl proton signals in the presence of Eu(HFC)$_3$ as determined by weighing appropriately adjusted tracings of the individual peaks.

(j) Based on optical rotation; configuration established as S-(+)-isobutyl-1-d alcohol, α_D +0.61°, $[\alpha]_D$ +0.77° (neat, ℓ=1), by K. R. Varma and E. Caspi, Tetrahedron, 24, 6365 (1968).

(k) Based on optical rotation, configuration established as S-(+)-n-butyl-1-d alcohol, $[\alpha]^{27.5}_D$ max. +0.47° (neat) by V. E. Althouse, D. M. Feigl, M. A Sanderson and H. S. Mosher J. Amer. Chem. Soc., 88, 3595 (1966).

(l) Based on integrals of nmr signal of carbinyl proton of MTPA derivative in the presence of $Eu(fod)_3$.

(m) Based on optical rotation. The configuration has been established as S-(+)-benzyl-1-d alcohol $[\alpha]^{20}_D$ max. +1.58° (c 7, cyclohexane), α^{20}_D max. +1.66° (neat, ℓ=1).[k]

(n) Based on integrals of nmr signals of carbinyl protons of MTPA derivatives in the presence of $Eu(fod)_3$ as determined by weighing properly adjusted tracings of the individual peaks.

(o) Configuration presumably S from these studies but this has not been verified independently.

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