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Determination of Absolute Configuration and Enantiomeric Purity of Spirocyclic Alcohols by ^{1}H NMR†

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Summary: Absolute configuration and enantiomeric purities of some hydroxy-ketones and diols of spiro[4.4]nonane and 2,2'-spirobi-indan can be simultaneously determined by use of MTPA derivatives and a lanthanoid shift reagent.

With the view of study of non-bonded homoconjugation between π-electron chromophores, the chiroptical properties of unsaturated spirocyclic compounds has been intensively studied.[1] Spiro[4.4]nonane-1,6-dione,[2]-1,6-diene[3], and 2,2'-spirobi-indan-1,1'-dione[4] are typical examples of this chiral homoconjugation. The absolute configurations of these compounds are critical bases of such studies and some of which have been empirically determined by Horeau's method and chemical correlations.[2-4] The results were confirmed later by exciton chirality method[5,6] with theoretical basis. We wish to report here the absolute configuration of spirocyclic alcohols of spiro[4.4]nonane and 2,2'-spirobi-indan including some isomers to which application of the exciton chirality method is not appropriate, can be simultaneously determined with the enantiomeric composition by use of (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters and achiral lanthanoid shift reagent.[7] The applicability of this method has been tested for the eight spirocyclic alcohols(1-8).[8] For the sake of convenience, only one of enantiomers is shown in Figure 1.

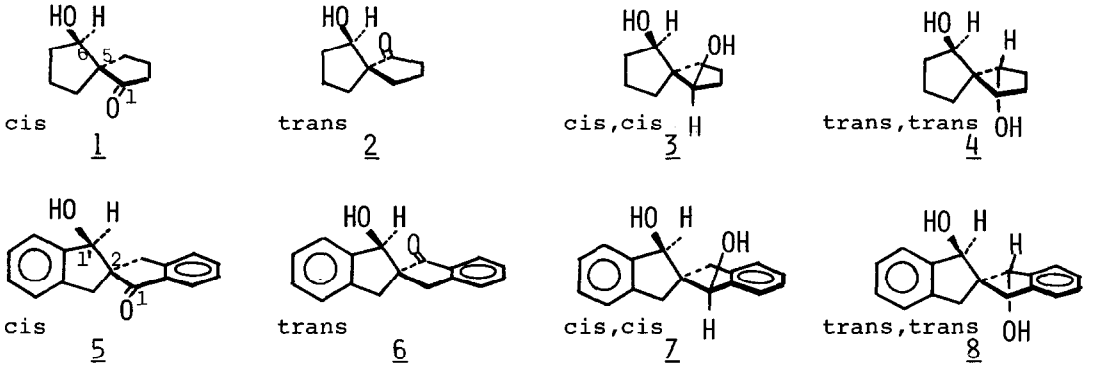


Figure 1

A partially active alcohol was completely acylated[9] with excess of acid chloride of (R)-MTPA in the presence of 4-dimethylaminopyridine and the shift study on the resulting pair of diastereomers[(R,R) and (R,S) in Table 1] was carried out using $Eu(fod)_3$. The MeO signal of MTPA acid moiety of each diastereomer was used as the probe and the correlation between the relative magnitudes of the lanthanoid induced shifts(LIS_{OMe}) and the absolute configurations of spirocyclic moieties were examined . The enantiomeric purities of the original alcohols were simultaneously determined by integration of well resolved two MeO signals. The results are summarized in Table 1.

Table 1 Lanthanoid Induced Shifts of Methoxyl Group in the Acid Moiety for Diastereomeric (R)-MTPA esters of Spirocyclic Alcohols[a]

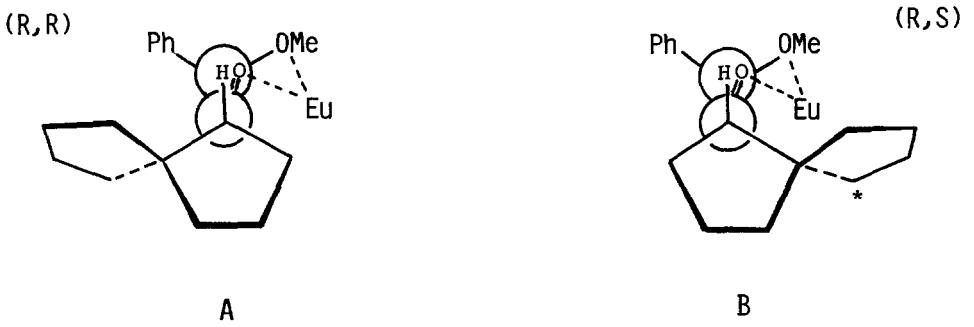
Entry	Alcohol	$[\alpha]_D^{20}$ (c,solvent) % ee (config.)	LIS_{OMe} (R^b,R^c)	LIS_{OMe} (R^b,S^c)	Config. with larger LIS_{OMe}
1	1	+17.7°(1.09,$CHCl_3$) 37%(5R,6R)	8.6	4.2	(+)-(5R,6R)
2	2	+55.2°(0.91,$CHCl_3$) 40%(5R,6S)	4.7	4.0	(-)-(5S,6R)
3	1(5S,6S)+2(5S,6R)	43% de for 1	9.6	6.1	(-)-(5S,6R)
4	3	-25.9°(1.21,EtOH) 26%(1R,5R,6R)	6.8	4.3	(-)-(1R,5R,6R)
5	4	+27.6°(0.33,EtOH) 49%(1S,5R,6S)	11.2	7.0	(-)-(1R,5S,6R)
6	5	-39.9°(1.36,EtOH) 40%[d](1'R,2R)	8.9	6.8	(-)-(1'R,2R)
7	6	+24.3°(0.60,EtOH) 38%[d](1'S,2R)	4.3	3.1	(-)-(1'R,2S)
8	7	-8.6°(0.42,acetone) 21%(1R,1'R,2R)	8.2	6.5	(-)-(1R,1'R,2R)
9	8	+3.5°(1.00,MeOH) 67%(1S,1'S,2R)	8.7	5.1	(-)-(1R,1'R,2S)

[a] Spectra determined at 90 MHz on CCl_4 solutions. [b] the configuration of MTPA moiety. [c] the configuration of carbinyl carbon atom. [d] determined by the relative intensities of $C_{1'}$-H signals.

In all the cases except entry 3, the alcohols employed were enantiomeric mixtures. Entry 3 shows the case of diastereomeric mixture of cis- and trans-hydroxyketones with the same configuration at spiro-carbon atoms(5S). As is seen from the Table, a regularity was observed between the relative magnitudes of LIS_{OMe} values and the absolute configuration of carbinyl carbon atoms; LIS_{OMe} due to (R,R) isomers consistently larger than those of (R,S) isomers,[7] irrespective of the configuration of spiro center. This regularity means that the present

method can be used for the determination of absolute configuration of the spiro carbon atoms of these alcohols, provided the relative configuration between the hydroxyl group in question and the carbonyl or the hydroxyl group on the other ring is known.

The above configurational correlation scheme can be explained by the following empirical model(Figure 2), where the ester carbonyl locates between Ph and OMe groups of MTPA acid moiety and in the eclipsed conformation with the carbinyl hydrogen.[10] The MTPA esters work as a bidentate ligand with ester carbonyl and



A B

Figure 2

MTPA-MeO groups as the coordination sites.[7b] The coordination with $Eu(fod)_3$ would be easier in the (R,R) isomer than in the alternate (R,S) isomer, since the other spiro five membered ring hinders the approach of Eu to the coordination sites. Easier formation of the complex A should make LIS_{OMe} of the (R,R) isomer larger than that of the (R,S) isomer. In the cases of entries 1, 3, 4, 6, and 8, the additional oxygen functionalities(carbonyl or hydroxyl group) in (R,S) isomers locate in the vicinity(on the carbon atoms with asterisk) of Eu ion as is indicated in Figure 2. If these groups work as the additional coordinating sites and the coordination effect is the dominant factor, the relative magnitude of LIS_{OMe} would be reversed. Experimental results indicate this coordination effect is only secondary effect in the present case.

It is important to note that application of this method to diols is essentially limited to ones which have two equivalent hydroxyl groups. Of three possible diols(cis,cis-, cis,trans-, and trans,trans-isomers), cis,cis- and trans,trans-isomers have C_2 symmetry and satisfy this requirement. Exciton chirality method can not be applied for these isomers[6] because the angle between two electric transition moments is 0° for cis,cis- and 180° for trans,trans-isomer, respectively.

Acknowledgement: We thank Dr. N. Harada, Tohoku University, for kind gift of optically active spiro[4.4]nonane-1,6-dione and racemic 2,2'-spirobi-indan-1,1'-dione.

References and Notes

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8) These optically active alcohols were prepared as follows. Optical rotation and enantiomeric excess are shown in Table 1. (+)-1 and (+)-2; (i)LAH reduction (ether, r.t., 2h) of (+)-(5R)-spiro[4.4]nonane-1,6-dione[5] ($[\alpha]_D^{20}$+59°,c 0.61, cyclohexane) to a mixture of diols. (ii) partial oxidation with MnO_2(CH_3CN, r.t.,7h) and chromatographic separation(silica gel, 4% EtOH in benzene) (+)-1: 28% , (+)-2: 8% . (+)-4; reduction of the dione(+64.4°) with dicyclohexyl borane(THF, 0°C, 8h) and chromatographic separation(SiO_2, 5% EtOH in benzene). 18%. (-)-3; (i) esterification of (+)-1(+10.4°,c 1.20,$CHCl_3$) with $(CH_3)_3CCOCl$ (1.4 eq., CCl_4-Py, r.t., 24h) (ii) LAH (ether, r.t.) then HPLC(μ-Bondapak C_{18}, 50% MeOH) 55%. The structrures of 1-4 were confirmed by comparison of spectral data with those of authentic racemic alcohols.[11] (-)-5 and (+)-6; (i) LAH reduction of partially resolved ω-camphanate[6,12](+31.2°,c 1.99,$CHCl_3$) of 6 to diol mixture. Jones oxidation of this mixture gave (-)-(2R)-2,2'-spirobi-indan-1,1'-dione(-70.3°,c 1.37,$CHCl_3$) (ii) partial oxidation with MnO_2 (acetone, r.t., 15 min), then chromatographic separation(SiO_2, 10% AcOEt in benzene (-)-5, 16%, (+)-6, 7%. (-)-7; (i) esterification of[2](-)-5(-27.3°, c 1.33, EtOH) with $(CH_3)_3CCOCl$(1.6 eq., CCl_4-Py, r.t., 12h). (ii) LAH(ether, r.t., 12h) then HPLC(μ-Bondapak C_{18}, 70% MeOH) Yield 40%. (+)-8 ; LAH reduction of ω-camphanate of 6 (+31.2°)[8]then HPLC (μ-Bondapak C_{18}, 60% MeOH) 13%. (±)-5 and (±)-7 were also newly prepared by similar method.[9] (±)-5; mp. 122-123 °C, Found C, 81.63; H, 5.68%. Calcd for $C_{17}H_{14}O_2$; C, 81.58; H, 5.64%. ^{1}H NMR($CDCl_3$)δ 2.82-3.74(two AB patterns, J=16 and 18 Hz, CH_2), 5.04 (CH-OH). (±)-7; mp. 241-242°C, Found: C, 80.94; H, 6.37%. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39%. ^{1}H NMR (DMSO-d_6+D_2O)δ 2.31-3.13(CH_2, J=16 Hz), 4.94(s, CH-OH).
9) Preparation of di-MTPA ester of cis,cis-diols(3 and 7) was difficult even in the presence of 4-dimethylaminopyridine. Use of 1.1 equivalent of the acid chloride gave quantitatively mono-MTPA esters, to which the shift studies were conducted.
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