Use of Shift Reagent with MTPA Derivatives in ^{19}F NMR Spectroscopy

IV†—Determination of Enantiomeric Composition for a Variety of Secondary Cycloalkanols. A Survey

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Chiral secondary cycloalkanols (monocyclic alcohols) are derivatized to the corresponding (*R*)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid [(*R*)-MTPA] esters and analysed by ^{19}F NMR in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) [Eu(fod)$_3$]. Using this method the enantiomeric composition can be measured for several cyclopentanols, cyclohexanols and cycloheptanols, with a variety of substitution patterns. It is shown that a mixture of four stereoisomeric cycloalkanols, such as *cis* and *trans* disubstituted alcohols, can be analysed simultaneously.

INTRODUCTION

In the last decade, NMR spectrometry has become an increasingly important tool for determining the enantiomeric composition of chiral compounds. Two methods, both using lanthanide shift reagents, are often applied: (i) chiral lanthanide shift reagents, such as tris(3-trifluoroacetyl-*d*-camphorato)europium(III) [Eu(facam)$_3$] and tris(3-heptafluorobutyryl-*d*-camphorato)europium(III) [Eu(hfbc)$_3$], are suitable for analysing enantiomeric alcohols, especially after acylation when there is a clear methyl signal for integration;[1] and (ii) achiral lanthanide shift reagents, such as Eu(fod)$_3$, are added to diastereoisomeric derivatives of chiral alcohols. It is common practice to prepare the (*R*)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid [(*R*)-MTPA] esters with Mosher's reagent[2] and to analyse the methoxy signals or trifluoromethyl signals by ^{1}H NMR and ^{19}F NMR, respectively. The latter is more convenient because the trifluoromethyl signals are distinct and easily integrated. Table 1 lists a number of applications of the MTPA method for several alcohols.

We have previously analysed the enantiomeric composition of a number of chiral secondary cycloalkanols obtained from the enzymatic reduction of ketones.[12] Until then the enantiomeric composition of only a limited number of monocyclic cycloalkanols had been studied with NMR methods, and the results were not very promising (see also Table 1).

For this type of cycloalkanols, described in a review,[13] chiral lanthanide shift reagents give very small lanthanide-induced shifts (LIS). Also, the ^{1}H NMR LIS results with MTPA esters and Eu(fod)$_3$[3] proved to be unsatisfactory. We extended Yamaguchi's technique to ^{19}F NMR and experienced a significant improvement with 2- and 3-substituted cyclohexanols.[14] Good signal separation is obtained in almost every case, often without shift reagent; further, as can be seen from the ^{19}F NMR spectra of *cis*- and *trans*-3-isobutylcyclohexanol (Fig. 1), a mixture of four stereoisomeric cycloalkanols can be analysed.

We now report an extension of this technique to various other types of cycloalkanols. Since analogous results for a number of bicyclic carbinols have been reported elsewhere,[4] only monocyclic carbinols will be discussed. (The analysis of borneols and isoborneols with this MTPA method has been reported.[14b]) The variation of ring size, ring substituent and position of the ring substituent will illustrate the scope and limitation of the method.

An unambiguous correlation between the ^{19}F NMR LIS values and the absolute configuration or conformation of cycloalkanols cannot yet be given. Further knowledge on the exact coordination stereochemistry of the ligands is necessary before this can be achieved, and some results on these aspects will be published in the near future.[15]

RESULTS AND DISCUSSION

3-Alkylcyclohexanols

Figures 2–5 show representative examples of the ^{19}F NMR spectra for the (*R*)-MTPA esters of 3-alkylcyclohexanols. From these spectra it is clear that the signal separation between the stereoisomers improves with increasing bulkiness of the alkyl side chain. As Table 2 shows, the ^{19}F NMR chemical shifts of these products vary in a very narrow range from 811 to 831 Hz, upfield from trifluoromethylbenzene (TFB) as internal standard [20% (g/g) in $CDCl_3$, four stereoisomers simultaneously].

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† For Part III, see Ref. 14d.
‡ This work is taken in part from E. M. Merckx, PhD Thesis, UIA, Antwerpen (1982) (University Microfilms Int. Ref. 82-70,073, Abstract 15/3456).

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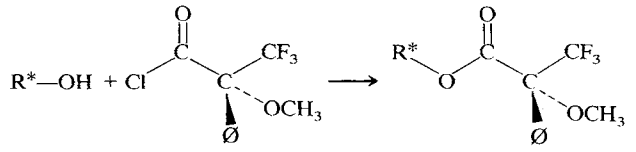
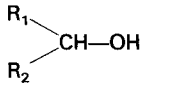
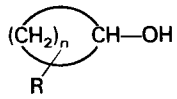
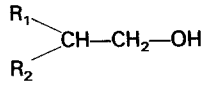
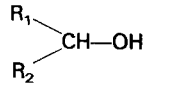
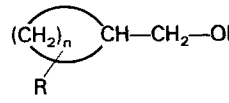
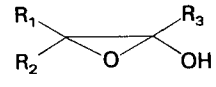
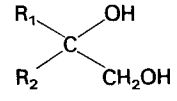
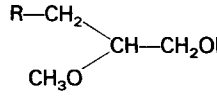
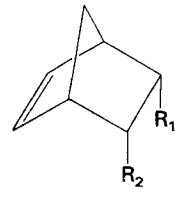
Table 1. General applications of (*R*)-MTPA esters to the determination of the enantiomeric composition of chiral alcohols



Enantiomeric alcohols | Enantiomerically pure (+)-MTPA chloride | Diastereoisomeric (*R*)-MTPA esters

R*—OH	Description of alcohol	Study of (R)-MTPA esters: NMR nucleus	Ref.
	R_1, R_2 = phenyl, alkyl	^{1}H	3
	R = alkyl, fused ring (steroid) or bridgehead alkyl	^{1}H	3
	R = bridgehead alkyl	^{1}H, ^{19}F	4
	R_1, R_2 = alkyl R_1 = phenyl	^{1}H	5
	R_2 = H or alkyl	^{1}H	6
	R = fused ring (steroid)	^{1}H	7
	R_1, R_2, R_3 = H, alkyl or phenyl	^{1}H	8
	R_1 = ethyl R_2 = *n*-C_3H_7	^{1}H	9
	R = phenyl	^{1}H	10
	R_1 = H and R_2 = CH_2OH R_1 = CH_2OH and R_2 = H	^{19}F	11

The pattern of the relative chemical shift sequence between the stereoisomers and the relative sequence of their ^{19}F NMR LIS values are the same and constant throughout this series. Thanks to this property, the four ^{19}F NMR resonances of the spectrum shift apart when more Eu(fod)$_3$ is added, and never re-overlap. Therefore, the ^{19}F NMR LIS values in Table 2 reveal that base line separation between the stereoisomers can be obtained in most cases (except

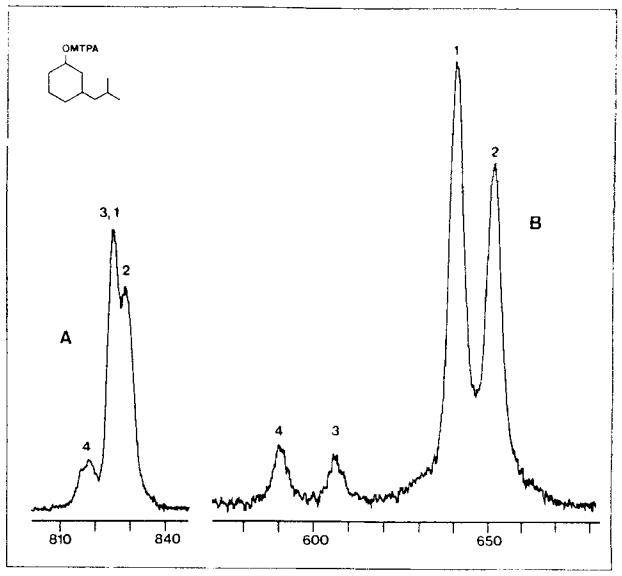


Figure 1. ^{19}F NMR spectra of the (*R*)-MTPA esters of 3-isobutylcyclohexanol [alcohols enriched in the (3*R*)-isomers]: (A) without shift reagent; (B) Eu(fod)$_3$ to ester molar ratio = 0.37. Numbering of the stereoisomers and absolute configuration: 1 = (1*S*, 3*R*)-*cis*-3-isobutylcyclohexanol; 2 = (1*R*, 3*S*)-*cis*-3-isobutylcyclohexanol; 3 = (1*S*, 3*S*)-*trans*-3-isobutylcyclohexanol; 4 = (1*R*,3*R*)-*trans*-3-isobutylcyclohexanol. Owing to the different existing NMR scale definitions for ^{19}F NMR, we prefer the use of the following convention: NMR scale in hertz, positive when upfield to the internal standard, trifluoromethylbenzene; all spectra in this paper correspond to this convention.

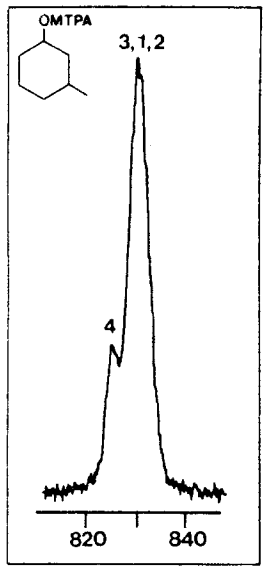


Fig. 2

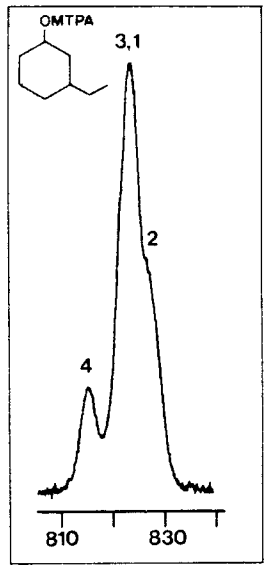


Fig. 3

Figure 2. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 3-methylcyclohexanol (racemic mixture). Numbering of the stereoisomers and spectral parameters as in Fig. 1.

Figure 3. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 3-ethylcyclohexanol [enriched in the (3*R*)-isomers]. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

for the *cis*-3-methylcyclohexanol derivatives, where peak maxima are hardly resolved at a 1 : 1 molar ratio of shift reagent to ester). Therefore, the enantiomeric purity (and/or epimeric composition) of these alcohols can be measured. This has been done for optically

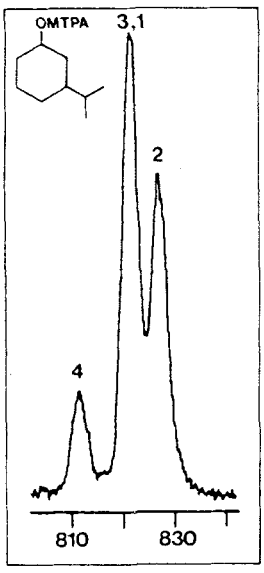


Fig. 4

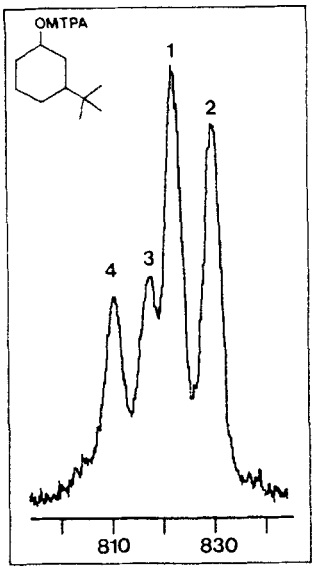


Fig. 5

Figure 4. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 3-isopropylcyclohexanol [enriched in the (3*R*)-isomers]. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

Figure 5. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 3-*tert*-butylcyclohexanol [enriched in the (3*R*) isomers]. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

active 3-alkylcyclohexanols, obtained from enzymatic *in vitro* reductions.[14c]

The sensitivity of this MTPA method in recognizing remote chiral centres is demonstrated for 3-*sec*-butyl- and 3-*sec*-pentylcyclohexanol. Some of the ^{19}F NMR resonances have a doublet structure due to the third chiral centre present in the alkyl side-chain. Figure 6 illustrates this remarkable phenomenon.

2-Alkylcyclohexanols

Both the determination of enantiomeric composition and absolute configuration for 2-alkylcyclohexanols by means of the ^{19}F NMR MTPA method have been reported previously.[14b] (These do not include those for 2-*tert*-butylcyclohexanol: the stereoisomers cannot be derivatized quantitatively to their MTPA esters by means of the classical procedure.[2] Attempts to synthesize such sterically hindered MTPA esters with the modification of Takimoto *et al.*[18] are now in progress.) Therefore, only a few examples of the ^{19}F NMR spectra will be shown here (Figs. 7–10).

Comparison of the ^{19}F NMR spectra of the (*R*)-MTPA esters of 3-alkyl- with 2-alkylcyclohexanols reveals that the latter show larger chemical shift differences between the stereoisomers. Further, the larger ^{19}F NMR LIS differences in the 2-alkylcyclohexanol series allow the use of smaller amounts of Eu(fod)$_3$ for obtaining base line separation. Again, these results confirm the advantage of analysing *cis*- and *trans*-alcohols simultaneously.

3-*n*-Alkylcyclopentanols

The enantiomeric composition of this biologically important class of products, such as cyclopentanols, can be analysed in the same way as discussed above. The ^{19}F NMR resonances of the (*R*)-MTPA esters of 3-*n*-alkylcyclopentanols (Table 3) lie between 823 and

Table 2. (*R*)-MTPA esters of 3-alkylcyclohexanols: ^{19}F NMR chemical shifts and Eu(fod)$_3$-induced shifts

Alcohol[a]	^{19}F NMR chemical shifts (Hz)[b,c] and LIS values (Hz)[c,d] of the (*R*)-MTPA esters			
	trans-Alcohols		*cis*-Alcohols	
	(1*R*, 3*R*)[e]	(1*S*, 3*S*)[e]	(1*S*, 3*R*)[e]	(1*R*, 3*S*)[e]
3-Methyl-CHL[f]	*825*	(*830*)	(*830*)	(*830*)
	321	279	267[g]	265[g]
3-Ethyl-CHL	*815*	(*823*)	*823*	*827*
	742	616	609	596
3-*n*-Propyl-CHL	*819*	(*826*)	*826*	*830*
	445	387	360	353
3-Isopropyl-CHL	*812*	(*822*)	*822*	*827*
	498	400	400	388
3-*n*-Butyl-CHL	*816*	(*824*)	*824*	*828*
	597	513	495	483
3-Isobutyl-CHL	*818*	(*826*)	*826*	*829*
	611	562	487	470
3-*sec*-Butyl-CHL	*815*	(*822*)	*822*	*828*
	649	523	487	472[h]
3-*tert*-Butyl-CHL	*811*	*818*	*823*	*830*
	708	549	532[i]	498[i]
3-*n*-Pentyl-CHL	*812*	(*820*)	*820*	*824*
	586	499	481	471
3-*sec*-Pentyl-CHL	*815*	(*825*)	*825*	*831*
	441[h]	363	347	327[h]
3-*n*-Hexyl-CHL	*815*	(*824*)	*824*	*828*
	468	409	392	383
3,3-Dimethyl-CHL			*828*	*831*
			237[j]	215[j]
trans-3,4-Dimethyl-CHL	*818*	(*827*)	*827*	*827*
	609[k]	566[k]	461[k]	454[k]

[a] For the synthesis of 3-alkylcyclohexanols, see Experimental.
[b] Figures in italics; where two or more signals overlap only the peak maximum is given, with the resonance of the minor isomer in parentheses: the estimated error with this procedure is not more than ±5 Hz.
[c] Measured at 94.1 MHz, in $CDCl_3$ with 20% (g/g) trifluoromethylbenzene as internal standard: values are rounded off to 1 Hz; measurements with the four stereoisomers in the same sample.
[d] Absolute LIS values may vary considerably with absolute substrate concentration, and should be interpreted only qualitatively; however, as will be discussed elsewhere,[15] the relative order of the LIS values, defined by the LIS ratios for the different stereoisomers, is constant, independent of absolute substrate concentration, shift reagent concentration or isomeric composition.
[e] Correlation of the absolute configuration with sequence of shifts and LIS; see Experimental.
[f] CHL = cyclohexanol.
[g] The first data point with separate peak maxima for the *cis*-isomers is observed at a shift reagent to ester molar ratio of 1.1.
[h] Average value for the doublet structure of this signal, due to the third chiral centre in the alkyl side-chain (see comment in text and Fig. 6).
[i] Analogous LIS (only LIS ratios are comparable) were reported by Lightner *et al.*[16] but with *cis*- and *trans*-alcohols analysed separately. Reports of ^{19}F NMR LIS experiments with these (*R*)-MTPA esters have also been made by Van Osselaer *et al.*[14c] and Sadozai *et al.*[17]
[j] Put in these columns for conformational analogy with the *cis* derivatives.
[k] Absolute configuration of the alcohols (from left to right): (1*R*, 3*S*, 4*S*); (1*S*, 3*R*, 4*R*); (1*S*, 3*S*, 4*S*); (1*R*, 3*R*, 4*R*).

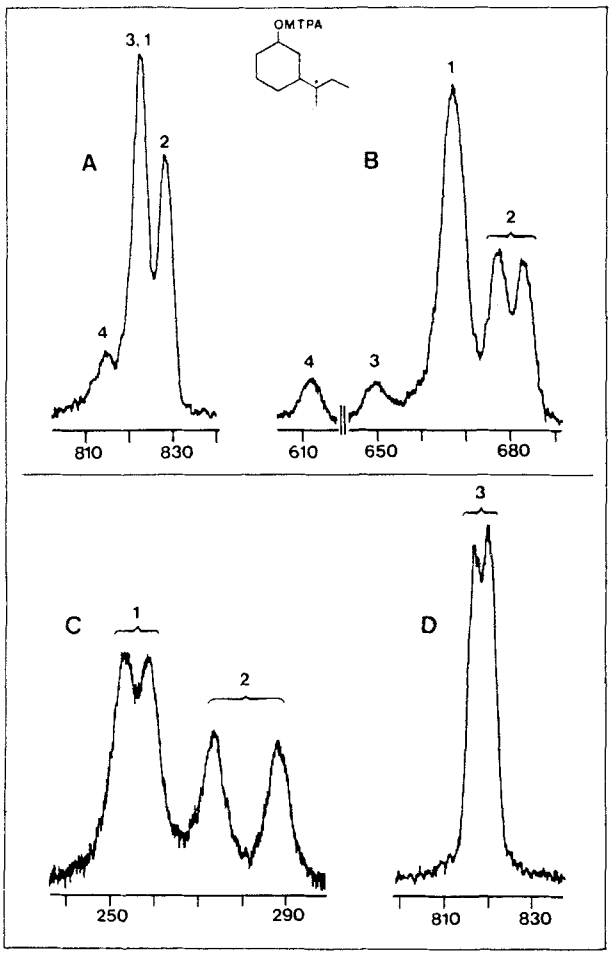


Figure 6. ^{19}F NMR spectra of the (*R*)-MTPA esters of 3-*sec*-butylcyclohexanol: (A) *cis*- and *trans*-alcohols [enriched in the (3*R*)-isomers], without shift reagent; (B) products as A, but Eu(fod)$_3$ to ester molar ratio = 0.27 [resolution of both (1*R*)-*cis*-isomers]; (C) *cis*-isomers only (racemic mixture), Eu(fod)$_3$ to ester molar ratio = 1.24 [resolution of both (1*R*)- and both (1*S*)-isomers]; (D) enantiomerically pure (1*S*,3*S*)-*trans*-isomer, without shift reagent. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

834 Hz (upfield to TFB). Table 3 also summarizes the ^{19}F NMR LIS values.

In contrast with the (*R*)-MTPA esters of 3-alkylcyclohexanols, the corresponding cyclopentanol derivatives do not follow the same stereoisomeric LIS sequence in all the homologues. Further, whereas for the former esters the LIS simply enlarges or diverges the initial chemical shift pattern, this is not true for the five-membered ring compounds. This can be ascribed to the larger conformational mobility of the cyclopentane ring compared with the more rigid cyclohexane system. The lanthanide shift reagent is therefore expected to complex in a different way, and to induce further conformational changes on complexation with cyclopentanol esters.

Because of this discrepancy between the initial shift sequence and the LIS sequence, the ^{19}F NMR resonances of the stereoisomeric cyclopentanol esters exhibit several peak overlaps as increasing lanthanide shift reagent is added. For this reason, the method of analysing *cis*- and *trans*-isomers simultaneously in one NMR tube is not suitable for this type of MTPA ester.

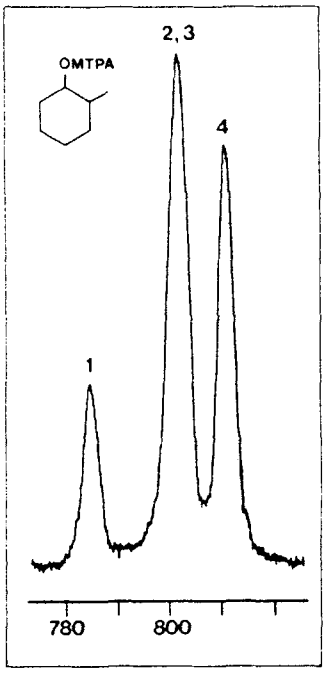


Figure 7. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 2-methylcyclohexanol. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

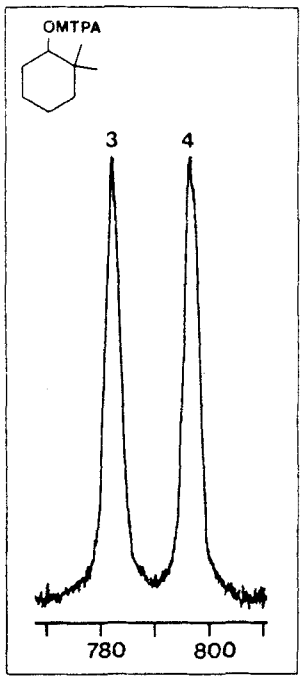


Figure 8. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 2,2-dimethylcyclohexanol. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

However, it is still possible to make a semi-quantitative estimation of the enantiomeric composition for this class of carbinols and, as far as we know, no other method capable of determining the enantiomeric composition for these cyclopentanols has been previously reported.

The ^{19}F NMR spectra for one of these compounds are shown in Fig. 11.

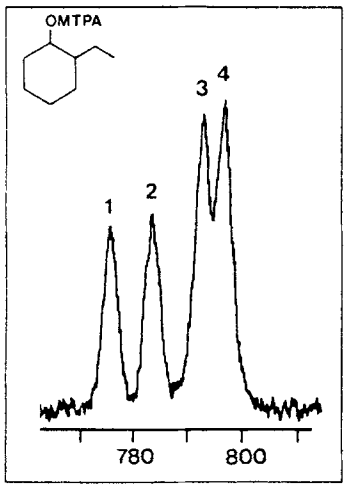


Figure 9. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 2-ethylcyclohexanol. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

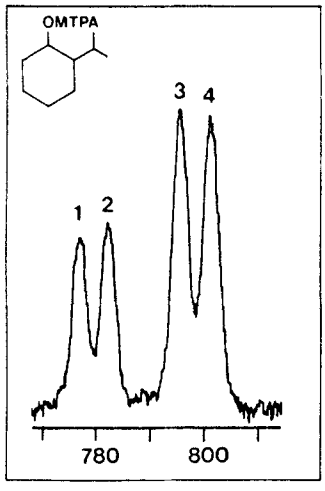


Figure 10. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 2-isopropylcyclohexanol. Numbering of the stereoisomers and spectral parameters as in Fig. 1.

Various cycloalkanols

Table 4 gives the ^{19}F NMR chemical shifts and LIS values for several cycloalkanols containing halogen substituents, another functional group or a hetero ring atom. The ^{19}F NMR spectral data for the (*R*)-MTPA esters of 2-chlorocyclopentanols and 2-chlorocycloheptanols complete the short series of 2-chlorocycloalkanols, of which the cyclohexanol homologue was previously discussed.[19]

The ^{19}F NMR spectrum of the (*R*)-MTPA esters of 2-chlorocycloheptanol (Fig. 12) and the corresponding LIS sequence is closely related to the results for 2-chlorocyclohexanol. 2-Chlorocyclopentanol, on the other hand, has less pronounced LIS differences and gives rise to substantial peak overlap, at least in the mixture of four stereoisomers. However, *cis*- and *trans*-isomers can be successfully analysed separately.

The same parallel is observed in the LIS behaviour of 2-methylcycloheptanol and 2-methylcyclopentanol derivatives. In the latter case, only the *cis*-isomers can be resolved (Fig. 13). The results for 2-methylcycloheptanol are analogous to those for the corresponding cyclohexanol derivative,[14a] so that the *cis*/*trans*-alcohols can be analysed simultaneously.

In accordance with a possible extension of the method to alcohols with other functional groups (as

Table 3. (*R*)-MTPA esters of 3-*n*-alkylcyclopentanols: ^{19}F NMR chemical shifts and ^{19}F NMR Eu(fod)$_3$-induced shifts

Alcohol[a]	^{19}F NMR chemical shifts (Hz)[b] and LIS values (Hz)[b] of the (*R*)-MTPA esters			
	cis-Alcohols		*trans*-Alcohols	
	(1*R*, 3*S*)[c]	(1*S*, 3*R*)[c]	(1*R*, 3*R*)[c]	(1*S*, 3*S*)[c]
3-Methyl-CPL[d]	*825*	*825*	*832*	*832*
	750	724	707[e]	701[e]
3-Ethyl-CPL	*825*	*825*	*831*	*834*
	725	685	677	629
3-*n*-Butyl-CPL	*823*	*823*	*829*	*832*
	591	561	568	521
3-*n*-Pentyl-CPL	*824*	*824*	*829*	*832*
	474	432	445	406
3-*n*-Hexyl-CPL	*824*	*824*	*829*	*832*
	402	381	384	355

[a] Synthesis of 3-*n*-alkylcyclopentanols: see Experimental.
[b] See footnotes [b], [c] and [d] in Table 2.
[c] Correlation of absolute configuration with ^{19}F NMR chemical shifts and LIS values: see Experimental.
[d] CPL = cyclopentanol.
[e] First data point with separate peak maxima is obtained at a shift reagent to ester molar ratio of 0.93.

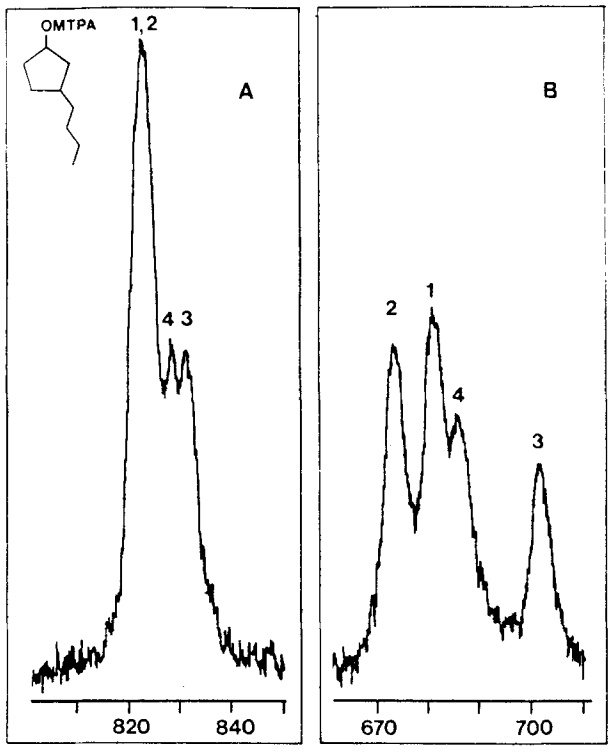


Figure 11. ^{19}F NMR spectra of the (*R*)-MTPA esters of 3-*n*-butylcyclopentanol (racemic mixture): (A) without shift reagent; (B) Eu(fod)$_3$ to ester molar ratio = 0.45. Numbering of the stereoisomers (see also experimental section concerning the stereochemistry of the cyclopentanols) and spectral parameters as in Fig. 1.

Table 4. (*R*)-MTPA esters of various secondary cycloalkanols: ^{19}F NMR chemical shifts and ^{19}F NMR Eu(fod)$_3$-induced shifts

Alcohol[a]	^{19}F NMR chemical shifts (Hz)[b] and LIS values (Hz)[b] of the (*R*)-MTPA esters			
	cis-Alcohols[c]		trans-Alcohols[c]	
2-Chloro-cyclopentanol	*866*	*845*	*840*	*845*
	582	568	518	500
2-Chloro-cycloheptanol	*835*	*815*	*839*	*807*
	668	454	512	444
2-Methyl-cyclopentanol	*820*	*803*	*830*	*830*
	455	373	321	321
2-Methyl-cycloheptanol	*796*	*783*	*807*	*796*
	343	312	344	250
3-Cyano-cyclohexanol[d]	*835*	*835*	*818*	*820*
	626	626	632	586
N-Methyl-3-hydroxy-piperidine	*842*	*835*		
	232	257		

[a] Synthesis of the alcohols: see Experimental.
[b] See footnotes [b], [c] and [d] in Table 2.
[c] Correlation of absolute configuration with chemical shift and/or LIS is not yet established.
[d] A complete chemical correlation of the absolute configuration of all stereoisomers, and their relationship to the ^{19}F NMR spectra, has been submitted by J. J. Willaert, G. L. Lemière, E. M. Merckx, J. A. Lepoivre and F. C. Alderweireldt to *J. Org. Chem.*

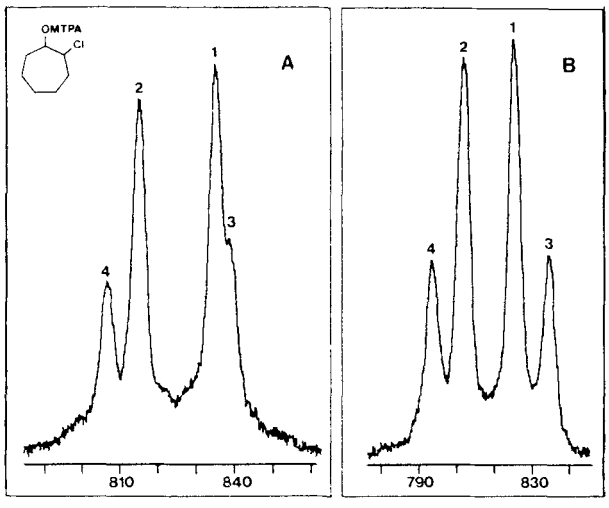


Figure 12. ^{19}F NMR spectra of the (*R*)-MTPA esters of 2-chlorocycloheptanol (racemic mixture): (A) without shift reagent; (B) Eu(fod)$_3$ to ester molar ratio = 0.06. 1 and 2 = *cis*-isomers (absolute configuration unknown); 3 and 4 = *trans*-isomers (absolute configuration unknown). Spectral parameters as in Fig. 1.

potential binding sites to the lanthanide shift reagent), some preliminary results are given for 3-cyanocyclohexanol and *N*-methyl-3-hydroxypiperidine (Table 4). The ^{19}F NMR LIS data of the former resemble those for 3-methylcyclohexanol: the *trans*-enantiomers are easily resolved, while this does not apply to the *cis*-isomers. The (*R*)-MTPA esters of the two enantiomeric *N*-methylpiperidinols were successfully analysed with base line separation. Experiments with a series of other *N*-alkyl-3-hydroxypiperidines are in progress.

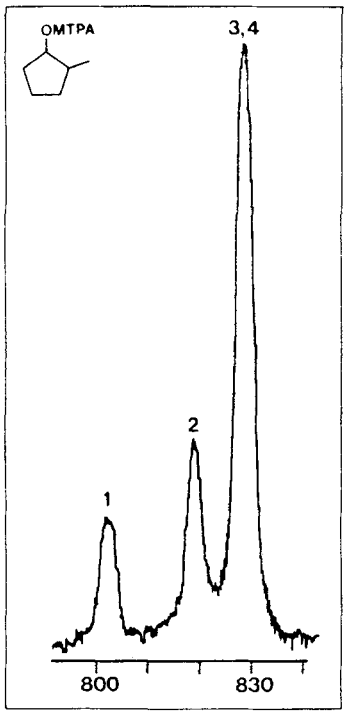


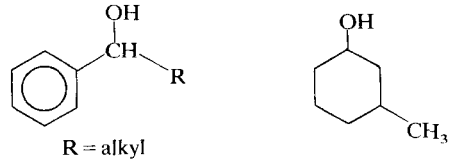
Figure 13. ^{19}F NMR spectrum of the (*R*)-MTPA esters of 2-methylcyclopentanol; racemic mixture, without shift reagent. 1 and 2 = *cis*-isomers (absolute configuration unknown); 3 and 4 = *trans*-isomers (absolute configuration unknown). Spectral parameters as in Fig. 1.

CONCLUSIONS

Several substituted cycloalkanols have been analysed with the modified ^{19}F NMR MTPA method. In spite of the complexity of the analysis for secondary carbinols with two chiral centres, i.e. a mixture of four stereoisomers, it is often possible to resolve the four corresponding resonances. If this cannot be done with a single molar ratio of shift reagent to substrate, a series of progressive additions of Eu(fod)$_3$, with resolution of the isomers one by one (in the worst case), usually gives satisfactory results.

The method is very suitable for the 2- and 3-alkyl (and 2-chloro-)cyclohexanols and -cycloheptanols. The corresponding cyclopentanols are less suitable for this purpose. An approximate estimate of the enantiomeric composition for the *cis*/*trans* alcohol mixture can always be made, but LIS experiments on the separate *cis*- and/or *trans*-isomers for these alcohols are more convenient and accurate. The method is also suitable for extension to a variety of alcohols with other functional groups. Consequently, greater applicability can be created for the MTPA method.

The most striking feature of the MTPA method, as presented here, is its ability to resolve enantiomers with only small differences in the stereochemical environment around the carbinol chiral centre:



I 1

This is illustrated by the fact that conventional methods for the determination of enantiomeric composition are based on a large difference in the substitution pattern of the carbinol moiety; 1-phenylalkanols (I), for example, are commonly used to test the resolving power of such a method.

By comparison with products I, the chirality of the carbinol moiety in 3-methylcyclohexanol (**1**), caused by the small and remote methyl group, is much less obvious. Nevertheless, the ^{19}F NMR MTPA technique detects this small 'enantiomeric' difference, so that the enantiomeric composition can be measured.

EXPERIMENTAL

Synthesis of alcohols and stereochemistry

All commercially available starting materials were bought from Aldrich Europe.

3-Alkylcyclohexanols. Commercially available 3-methylcyclohexanol was used as a reference mixture and enriched with (1*S*, 3*R*)- and (1*R*, 3*R*)-3-methylcyclohexanol, obtained by $NaBH_4$ reduction of (3*R*)-3-methylcyclohexanone; the stereoisomeric composition of this alcohol mixture was known from this procedure.

3-Alkylcyclohexanones were synthesized as described previously[12,20] and enzymatically reduced.[12] The alcohol mixture, enriched in the (3*R*)-isomers and used for esterification and NMR analysis, was obtained and analysed as illustrated in the following idealized example.

A 3-alkylcyclohexanone was reduced with the horse liver alcohol dehydrogenase (HLAD)/NADH/ethanol recycling system on a preparative scale until 30% ketone was reduced (GLC analysis).[12] Only *trans* alcohol was formed (GLC comparison with reference alcohols). After preparative separation of ketone from alcohol by HPLC,[14c] the alcohol was derivatized to the (*R*)-MTPA ester.[14c] ^{19}F NMR analysis in the presence of $Eu(fod)_3$ proved that this alcohol was enantiomerically pure.[14c] Measurement of the Cotton effect of the residual ketone indicated that it was enriched in the (3*R*)-isomer. Since only the 100% enantiomerically pure *trans* alcohol was found, this alcohol had the (1*S*, 3*S*) configuration. In addition, the reacting ketone (30%) was 100% (3*S*)-ketone. The residual ketone then had an isomeric composition 50:70 (3*R*)-ketone and 20:70 (3*S*)-ketone, or an enantiomeric ratio of (3*R*):(3*S*) = 71:29. This ketone was then reduced with $NaBH_4$ in isopropanol to an alcohol mixture with a *cis*/*trans* ratio of 85:15 (GLC). Accordingly, the stereoisomeric composition of all the alcohols could be calculated as 25% (1*R*, 3*S*), 60% (1*S*, 3*R*), 11% (1*R*, 3*R*) and 4% (1*S*, 3*S*). If necessary, this ratio could be changed by addition of racemic alcohol and/or (1*S*, 3*S*)-alcohol.

3-*n*-Alkylcyclopentanols. 3-Methylcyclopentanol, enriched in the (3*R*)-isomers, was obtained in the same manner as described for 3-methylcyclohexanol, starting from commercially available (3*R*)-methylcyclopentanone.

3-*n*-Alkylcyclopentanones were prepared analogously to the 3-alkylcyclohexanones. The ketones were reduced with $NaBH_4$ in isopropanol for reference purposes. Enzymatic reduction of these ketones, according to the usual procedure,[12] led to one enantiomerically pure *cis*- and one enantiomerically pure *trans*-alcohol, as determined with the MTPA method by comparison with the reference mixture. Since this enzymatic reduction had previously exclusively resulted in alcohols with (3*S*) configuration, it was assumed that the same was true for the 3-*n*-alkylcyclopentanols; however, this has not been proved with a reliable, independent method, as was done for the 3-alkylcyclohexanols. Therefore, the alcohols from enzymatic reduction were assumed to have the (1*S*, 3*S*) and (1*R*, 3*S*) configurations. In this way, the absolute configuration of the four stereoisomeric alcohols in the reference mixture was correlated with the ^{19}F NMR chemical shifts and LIS values of the (*R*)-MTPA esters (Table 3).

Other substrates. 2-Methylcyclopentanol, 2-methylcycloheptanol, 2-chlorocyclopentanol and 2-chlorocycloheptanol were prepared as described earlier.[21] The diastereoisomeric composition was analysed by GLC.

3-Cyanocyclohexanol was prepared by adding to 1 equivalent of 2-cyclohexenone a mixture of 1.2 equivalents of KCN and 1.4 equivalents of triethylammonium chloride. This is a modification of the procedure published by Mertes and Ramsey.[22] The ketone was reduced with $NaBH_4$ in isopropanol (*cis*/*trans* ratio = 90:10, by GLC).

N-Methyl-3-hydroxypiperidine is commercially available.

GLC of ketones and alcohols

Analytical GLC of ketones and alcohols was performed on FFAP columns (7.5% on Chromosorb W, 1.5 m × 1/8 in. i.d.) or Carbowax columns (5.5% on Chromosorb P, 1.5 m × 1/8 in. i.d.).

Base line separation was obtained for the ketone and *cis*- and *trans*-alcohols simultaneously. The analyses were performed with a Varian 1840-41 or a Varian 3700 gas chromatograph, equipped with a Varian CDS 111 integrator. The products were dissolved in CS_2 or diethyl ether.

Synthesis of (*R*)-MTPA esters

The (*R*)-MTPA esters were prepared according to the usual procedure,[2] but worked up with microdistillation (minimum amount *ca* 30 mg, boiling points 100–200 °C at 0.01 mmHg, colourless oils).

^{19}F NMR spectra and LIS studies

^{19}F NMR spectra were recorded on a JEOL PS 100 NMR spectrometer (CW spectra) at 94.1 MHz,

with the frequency sweep method and internal lock on trifluoromethylbenzene as internal standard; spectra were recorded at 30 °C and with a sweep rate of 250 Hz s^{-1} for a sweep width of 270 Hz. The chemical shifts were electronically measured in hertz (accuracy ±0.5 Hz).

Products were dissolved in dried $CDCl_3$ (Aldrich 15, 183-1) containing 20% (g/g) of distilled trifluoromethylbenzene (Aldrich T6,370-3). This NMR solvent was stored over molecular sieves 3 Å. Concentrations varied in the range 0.3–0.6 M.

LIS studies were performed as described previously[14a,b] with $Eu(fod)_3$ (Aldrich 16,093-8) [without special precautions to keep the shift reagent dry; in our experience, the hydrated $Eu(fod)_3$ gives very reproducible LIS results, which is not the case with the rigorously dried, but very hygroscopic reagent]. LIS values were calculated on the total substrate concentration (sum of all isomers).[14a,b]

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