Nuclear Magnetic Resonance Enantiomer Reagents. Configurational Correlations *via* Nuclear Magnetic Resonance Chemical Shifts of Diastereomeric Mandelate, *O*-Methylmandelate, and α-Methoxy-α-trifluoromethylphenylacetate (MTPA) Esters[1,2]

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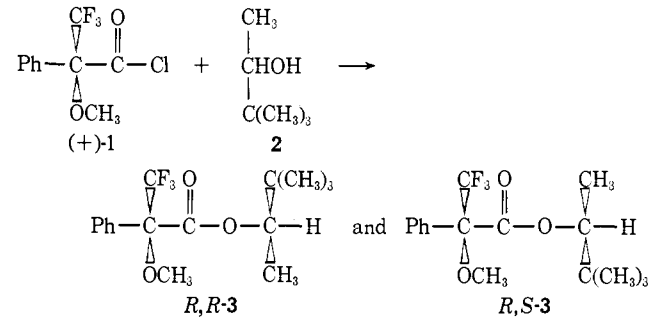
Abstract: An empirically derived correlation of configuration and nmr chemical shifts for diastereomeric mandelate, *O*-methylmandelate and α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters has been developed and rationalized in terms of useful models **4** and **5**. These models have been successfully applied to well over 40 examples as given in Table I. The correlations involve the relative chemical shifts of the proton resonances from the groups attached to the carbinyl carbon of these diastereomeric esters. This nmr-configurational correlation should prove to be widely applicable in assigning the configuration of additional secondary carbinols, as well as other chiral α-substituted carboxylic acid derivatives.

The phenomenon of nmr nonequivalence of internal or external diastereotopic groups has been thoroughly reviewed and discussed.[3-6] Such nonequivalences of the nmr spectra of diastereomeric esters and amides are being used widely to establish the composition of such mixtures and thereby the enantiomeric purity of the chiral alcohol or amine from which these stereoisomers were prepared. The derivatives of *O*-methylmandelic acid[6,7] and α-methoxy-α-trifluoromethylphenylacetic acid[8] (MTPA) have proved especially useful in this regard. In the present paper we extend these studies to include a correlation of the nmr spectral data with the configuration of these diastereomers.

Pirkle and coworkers have reported on the correlation of configuration with nmr chemical shifts for amino acid esters,[9a] alcohols,[9b] sulfoxides,[9c] α-hydroxy acids,[9d] and amines[9e] *in chiral solvents*. There have been limited studies on diastereomeric salts,[10a,b] diastereomeric sulfoxide derivatives,[10c] α-pentafluorophenylpropionamide derivatives[11a] of amphetamine and closely related compounds and hydrotropyl esters of chiral propargyl alcohols.[11b] In addition a simple discernible configurational-nmr relationship has been reported for closely related diastereoisomeric di- and trialanyl peptides.[12]

One of the most thoroughly studied systems in this regard is the diastereomeric (−)-menthyl *n*-alkylphenylphosphinate esters[13] where it has been shown that the configuration at phosphorus can be deduced from the nmr spectra of the alternate diastereomers.

The general features of the nmr spectra to be considered are exemplified by the diastereomeric mandelate, *O*-methylmandelate, atrolactate, and α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters of methyl-*tert*-butylcarbinol shown in Figure 1. The method is illustrated by the formation of the diastereomeric (*R*,*R*)- and (*R*,*S*)-methyl-*tert*-butylcarbinyl MTPA esters (*R*,*R*-**3** and *R*,*S*-**3**) *via* reaction of carbinol with an excess of the pure (+)-MTPA-Cl (**1**). Figure 1C shows



the nmr spectrum of the diastereomeric mixture resulting from the reaction with a sample of methyl-

(1) We gratefully acknowledge a grant in support of this study by the National Science Foundation (NSF GP 27448).

(2) Taken from the Ph.D. thesis of J. A. D., Stanford University, 1970.

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(8) (a) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); (b) D. L. Dull, Ph.D. Thesis, Stanford University, 1967.

(9) (a) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **91**, 5150 (1969); (b) *ibid.*, **89**, 5485 (1968); (c) *ibid.*, **90**, 6250 (1969); (d) W. H. Pirkle and S. D. Beare, *Tetrahedron Lett.*, 2579 (1968); (e) W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *ibid.*, 5849 (1968). A preliminary report of nmr nonequivalence of amine oxides, phosphine oxides, sulfinamides, sulfinates, sulfites, and thiosulfinate which did not include configurational correlations was also published: W. H. Pirkle, S. D. Beare, and R. L. Muntz, *J. Amer. Chem. Soc.*, **91**, 4575 (1969).

(10) (a) M. Mikolajczyk, M. Para, E. Ejchart, and J. Jurczak, *Chem. Commun.*, 654 (1970); (b) W. H. Pirkle, *ibid.*, 1525 (1970); (c) M. Nishio, *ibid.*, 51 (1969).

(11) (a) L. R. Pohl and W. F. Trager, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Abstract MEDI-60; (b) R. S. Macomber, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract ORGN-117.

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(13) R. A. Lewis, O. Korpium, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4847 (1968); **89**, 4786 (1967). Numerous applications of this method have been made: W. B. Farnham, K. Mislow, N. Mandel, and J. Donohue, *J. Chem. Soc., Chem. Commun.*, 120 (1972); N. J. Déath, K. Ellis, D. J. H. Smith, and Trippett, *ibid.*, 714 (1971); W. B. Farnham, R. K. Murray, Jr., and K. Mislow, *ibid.*, 146 (1971); W. B. Farnham, R. K. Murray, Jr., and K. Mislow, *J. Amer. Chem. Soc.*, **92**, 5809 (1970); A. W. Herriot, *ibid.*, **93**, 3304 (1971); T. L. Emmick and R. L. Letsinger, *ibid.*, **90**, 3459 (1968).

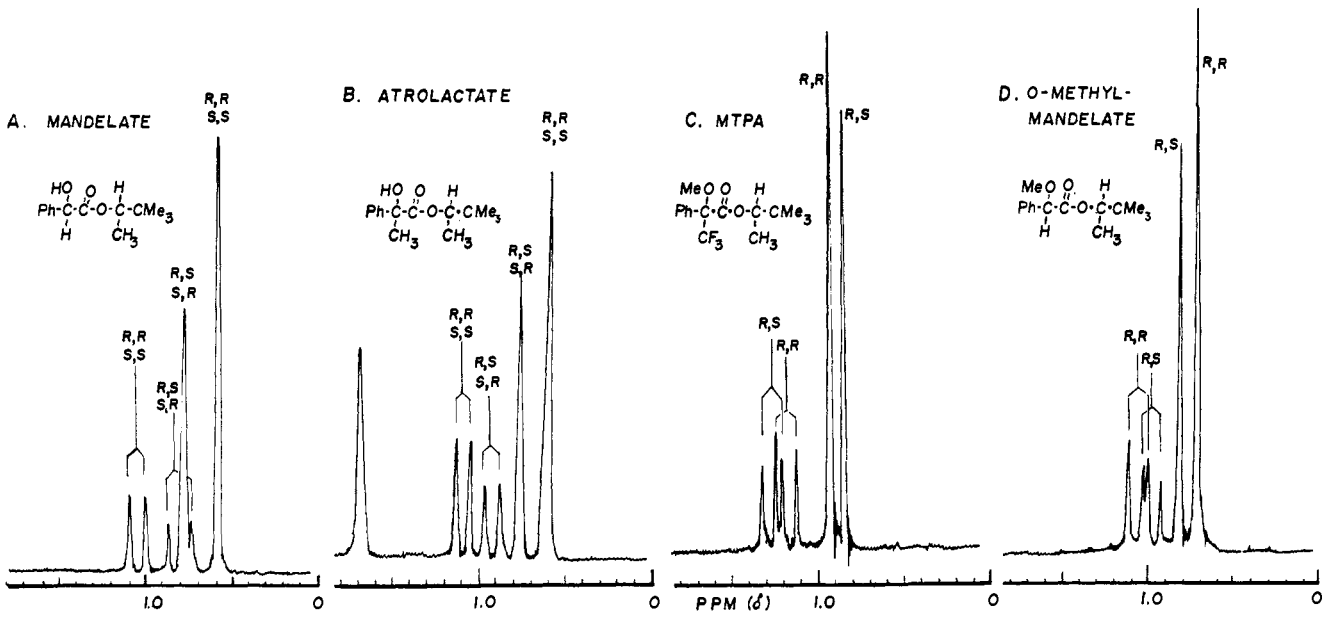


Figure 1. Nmr spectra, 60 MHz, of methyl-*tert*-butylcarbinyl esters. (A) Mandelate, prepared by reduction of (*R*,*S*)-benzoylformate ester with LiAl(O-*t*-Bu)$_3$H at 3° in THF to give a 22% excess of *R*,*R*–*S*,*S* diastereomer mixture over the *R*,*S*–*S*,*R* isomer mixture.[2,17] (B) Atrolactate, prepared by reaction of (*R*,*S*)-benzoylformate with methylmagnesium iodide in ether to give 18% excess of the *R*,*R*–*S*,*S* diastereomer mixture over the *R*,*S*–*S*,*R* isomer mixture.[19] (C) α-Methoxy-α-trifluoromethylphenyl acetate (MTPA ester), prepared from (*R*)-(+)-MTPA and methyl-*tert*-butylcarbinol 7.8% enriched in the *R*-(−) isomer[16] (analysis by rotation). Integration of this nmr gave 7.5 ± 0.5% excess of *R*,*R* diastereomer. (D) *O*-Methylmandelate, prepared from (*S*)-(+)-*O*-methylmandelyl chloride and a sample of carbinol 11.7% enriched in the *R*-(−) isomer[16] (analysis by rotation). Integration of this nmr gave 12.8 ± 0.5% excess of the *R*,*R* diastereomer.

tert-butylcarbinol (**2**) which had 7.8% excess of the *R*-(−) enantiomer, as calculated from the optical rotation. The absolute configurations of both the carbinol[13] **2** and the acid[8,14,15] from which the acid chloride **1** is prepared are known; since the reaction forming the esters was carried to completion by using an excess of the acid chloride, the signals for the major component must represent the *R*,*R* diastereomer[16] of this MTPA ester (*R*,*R*-**3**). Integration of the signals from the two diastereomers indicates a 7.5% excess of the major *R*,*R* diastereomer in excellent agreement with the value based upon the optical rotation. The determination of enantiomeric composition by this general procedure has been the subject of previous publications;[6–8] it is now our intent to analyze the relationships between configuration and differences in these nmr spectra with the purpose in mind of developing a useful correlation between configuration and nmr spectral differences for diastereomeric compounds of these types.

The resonances of individual diastereomers represented in Figure 1 (and Table I) have been identified by suitable independent means.[17] Close inspection of Figure 1 reveals an interesting pattern for the proton signals from the substituents on the carbinyl carbon.[20] In each of the four spectra the resonance for the *tert*-butyl group of one diastereomer is at higher field position while the resonance for the methyl group of the same isomer is centered at lower field position than the signals for each of the corresponding groups in the alternate diastereomer. In the mandelate, atrolactate, and *O*-methylmandelate (Figure 1, curves A, B, and D) it is the resonances of the *R*,*R* diastereomers which show the extreme upfield *tert*-butyl–downfield methyl signals with respect to the signals for each of the corresponding groups in the *R*,*S* diastereomer.[16] In the MTPA ester (Figure 1, curve C) the situation is exactly reversed. This pattern is especially clear for these methyl-*tert*-butylcarbinyl esters because the differences in chemical shifts are substantial and the spectra are relatively free of overlapping and interfering signals. Once this nmr nonequivalence pattern was recognized[2] we were able to discern uniformly this "sense of nonequivalence"[21] in the nmr spectra of a large number of such esters as well as related MTPA amides (Table I). Thus, knowing the configuration of the

(14) G. Barth, W. Voelter, H. Mosher, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **92**, 875 (1970).

(15) L. Hub and H. S. Mosher, *J. Org. Chem.*, **35**, 3691 (1970).

(16) For the sake of clarity of presentation in the discussion and tables, we will represent all reactions and spectra as though they were performed with the *R* isomers of mandelic, *O*-methylmandelic, and MTPA acids, whereas in fact, the enantiomer and/or the *dl* mixture may have been used in some experiments. The nmr spectra, in an achiral solvent, of the *R*,*R* and *S*,*S* enantiomers are of course identical, as are those of the *S*,*R* and *R*,*S* isomers. Note also ref 46 in the Experimental Section.

(17) The MTPA and *O*-methylmandelate esters were prepared from alcohol and acid chloride of known configuration and enantiomeric composition. Reduction by LiAl(O-*t*-Bu)$_3$H of the benzoylformate esters of known configuration gave the mandelate esters which were further reduced ($LiAlH_4$) to give phenylethylene glycol of known configuration.[18] Treatment of benzoylformate esters of known configuration with methylmagnesium iodide gave atrolactate esters which were hydrolyzed to atrolactic acid to determine the configuration of the acid moiety. The configuration of both the atrolactates and mandelates could also be reliably predicted on the basis of Prelog's generalization.[19]

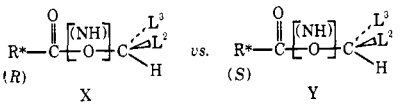
(18) J. A. Dale and H. S. Mosher, *J. Org. Chem.*, **35**, 4002 (1970).

(19) (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 50–78; (b) V. Prelog, *Bull. Soc. Chim. Fr.*, 987 (1956).

(20) We shall refer to the carbon atom of the alcohol or amine moiety of the esters or amides to which the two groups L^2 and L^3 are attached as the "carbinyl carbon" atom.

(21) The term sense of nonequivalence was introduced by Pirkle and Beare[9a] who used it for the sake of brevity in the following way. "Sense of nonequivalence refers to the relative field positions of a resonance of one isomer relative to the corresponding resonance of its enantiomer (in a given chiral solvent)." The term is equally applicable to the relationship of resonances in alternate diastereomers of the type discussed here, in an achiral solvent.

Table I. Nmr Chemical Shift Differences for Diastereomeric Mandelic, *O*-Methylmandelic, and α-Methoxy-α-trifluoromethylphenylacetic Acid (MTPA) Derivatives[a,16]



Substituent of alcohol (or amine)[b] moiety[c] L³	L²	Ref configuration	Substituent chemical shift difference, (X − Y) in ppm: Mandelic acid deriv,[d] δ (X − Y) L³	L²	*O*-Methylmandelic acid deriv,[e] δ (X − Y) L³	L²	MTPA deriv,[b] δ (X − Y) L³	L²
Et[c]	Me	*h*					(+0.07)	(−0.07)[b]
Et[c]	Me	*h*	−0.30	+0.18	−0.08	+0.15	+0.10	−0.13
n-Hex	Me	*h*	---	+0.13		+0.05[g]	+0.08	−0.08
i-Pr[c]	Me	*h*	−0.15	+0.20	−0.12	+0.12	+0.08	−0.08
c-Hex	Me	*h*			---	+0.08		
t-Bu	Me	*i*	−0.15	+0.24	−0.10	+0.10	+0.07	−0.07
t-Bu	Et[c]	*i*	−0.22	+0.37	−0.13	+0.10		
t-Bu	*n*-Bu	*i*	−0.32				+0.06	---
t-Bu	*i*-Bu	*i*					+0.02	---
CF_3	Me	*j*	−0.17	+0.21	---	+0.12	+0.12	−0.41
Ph	CF_3	*j*	---	+0.06			---	−0.33
Ph	Me	*k*	---	+0.15	---	+0.08	---	−0.06
Ph	Me	*k*					---	(−0.07)[b]
Ph	Et[c]	*k*	---	+0.28	---	+0.12	---	−0.08
Ph	*i*-Pr[c]	*k*	---	+0.25	---	+0.08		
Ph	*t*-Bu	*k*	---	+0.22	---	+0.08	---	−0.05
α-Naph	Me	*l*					(+0.04)	(−0.11)[b]
$PhCH_2$	Me	*h*						(−0.08)[b]
COOEt	Me	*h*						−0.09
COOMe	Me	*h*						(−0.08)[b]
Ph	$SiMe_3$	*m*					+0.15	−0.06
$CMe_2(CH_2)_4CH_2$		*n*					+0.09	
Menthyl		*o*					+0.10	---
CH_2NMe_2	CH_3	*p*					+0.05	−0.11

[a] Values are differences in δ (Δδ), ppm, obtained by subtracting the chemical shift of the designated group (either L^2 or L^3) of diastereomer Y from that of the same group in X. A positive number means that the signal from the specified group in X is downfield from that of the corresponding groups in Y; a negative number means that the signal for the group in question is upfield from that of the corresponding group in Y. Numerical values are found in references 6 and 8 and Table III. A dashed entry (---) signifies that the resonance was not clearly identifiable because of interfering signals or that it was not possible to discern any significant chemical shift difference for the signal in question. [b] Values are normally for esters; those in parentheses are for the MTPA amides. [c] In ethyl, isopropyl, and isobutyl the value given is that for the terminal methyl. [d] Data from J. A. Dale, Ph.D. Thesis, Stanford University, 1970, pp 35–39. [e] Data adapted from J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968). [f] Data adapted from J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2545 (1969). [g] The resonances reported for (*R,S*)- and (*R,R*)-methyl-*n*-hexylcarbinyl *O*-methyl mandelate in footnote *e* were reversed. [h] J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 177 (1954). [i] W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **81**, 2779 (1959). [j] H. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968). [k] R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960). [l] (*R*)-(+)-α-1-Naphthylethylamine, M. G. B. Drew, *Acta Crystallogr.*, **1325**, 1320 (1969). [m] M. Biernbaum and H. S. Mosher, *J. Amer. Chem. Soc.*, **93**, 6221 (1971). [n] E. M. La Combe, R. Mertz, unpublished results, Stanford University. The *gem*-dimethyl is L^3. [o] (−)-Menthyl in which the α-isopropyl substituent is designated L^3 and the α-methylene as L^2. This example is of course complicated by that of other chiral centers. [p] (*R*)-(−)-1-Dimethylamino-2-propanol: A. H. Beckett, N. J. Harper, and J. W. Cletherow, *J. Pharm. Pharmacol.*, **15**, 8577g (1963).

acid moiety, there seems to be a fundamental correlation between configuration and diastereomer sense of nonequivalence which can be used for predicting the configuration of the alcohols from which the esters were prepared. We shall approach this configuration-nmr correlation in two different ways: first, we shall consider the data in a factual manner, thereby developing a strictly empirical relationship concerning diastereomeric chemical shifts and configuration; second, we shall rationalize the empirically correlated data in terms of a proposed configurational correlation model.

In Table I we have summarized the relative positions of the signals from the carbinyl substituents (L^2 and L^3) of a large series of mandelate, *O*-methylmandelate and α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters (and some MTPA amides). The data for the mandelates were largely obtained from mechanistic studies[2] dealing with stereochemistry or reduction of chiral benzoylformate esters.[2,18] The data for the *O*-methylmandelates[6] and MTPA[8] derivatives were collected during studies aimed at developing an analytically useful nmr method for determining enantiomeric composition.[6,8]

Table I represents the nmr chemical shift differences observed between alternate diastereomers represented as X and Y at the head of the table. The configuration of the carbinyl portion of both X and Y is the same but that of the acid moiety is *R* in X and *S* in Y. The absolute configurations for all of the compounds in this table are known. Thus in these examples the designation of one specific group on the carbinyl carbon as L^3 and the other as L^2 is dictated by the known configuration. It is seen from the more than forty entries in Table I that the pattern observed in the examples of Figure 1 is symmetrically repeated here; namely: when resonances from both ligands L^2 and L^3 have been clearly identified in both diastereomers no exception was found to the upfield–downfield pattern for the sense of nonequivalence of the signals

from one diastereomer *vs.* those from the alternate diastereomer. It should be noted, however, that the sense of nonequivalence observed for the MTPA esters is opposite to that found for the mandelates and *O*-methylmandelates.[22]

The uniformity of these correlations is remarkable since the examples encompass mandelate, *O*-methylmandelate, and MTPA esters of carbinols containing such diverse substituents as alkyl, aryl, trifluoromethyl, trimethylsilyl, and carbomethoxy groups. Such a correspondence must reflect some fundamental conformational pattern of these diastereomers and the key role exercised by steric interactions in establishing this conformational pattern.[23]

The correlations, based on compounds of known configuration, as revealed by the data in Table I, can be used for assigning the configuration to an alcohol of unknown configuration as follows. A chiral[24] secondary carbinol is converted into the two diastereomeric MTPA derivatives. The nmr spectra of these diastereomers with known configuration at the acid moiety but unknown configuration at the carbinyl center are studied to determine in which diastereomer is the resonance for one of the groups (L^3 or L^2) further upfield and the resonance for the other group (L^2 or L^3) further downfield than in the alternate diastereomer. Then the data for this new compound are fitted into the appropriate columns in Table I. The specifications of groups L^3 and L^2 follow from the column in which the data must be entered in order to accommodate to the established pattern.[25,26] The configurations of X and Y are therefore defined. The nomenclatural designation of the diastereomer as *R,R vs. S,R* follows from application of the Cahn–Ingold–Prelog nomenclature rules.[27]

We now turn to a consideration of the factors responsible for the observed nmr nonequivalence for diastereotopic groups in the esters of the type under discussion here and to the configuration correlation model which we have devised[2] to rationalize the data. The following points must be considered in any attempt to reconcile these data on chemical shifts with configuration.

(1) As previously discussed,[6] significant chemical shift differences occur most consistently for the groups L^2 and L^3 attached to the carbinyl carbon atom of the alcohol moiety of these diastereomeric esters.

(2) The chemical shifts for the resonances of the L^2 and L^3 groups of one diastereomer show the characteristic upfield–downfield pattern relative to the resonance of the corresponding groups in the alternate diastereomer as indicated in Table I; this pattern is the same for (*R*)-mandelates and (*R*)-*O*-methyl mandelates but reversed for (*R*)-MTPA derivatives (*i.e.*, Table I, columns 1 and 2 *vs.* 3).

(3) The proton nmr chemical-shift differences in diastereomers recorded for these L^2 and L^3 groups are not significant unless the acid moiety possesses an α-aromatic substituent; *cf.* Table II.

(4) The resonance of one of the groups, either L^2 or L^3, in each diastereomer appears at abnormally high field compared to standard derivatives such as acetates, pivalates, benzoates, benzoylformates, or simple phenylacetates; *cf.* Table III. Furthermore, an nmr temperature study of methyl-*tert*-butylcarbinyl, methyltrifluoromethylcarbinyl, and methylisopropylcarbinyl mandelates has shown that as the temperature is increased, the chemical-shift differences between diastereotopic groups decrease; specifically, as the temperature was increased it was only the upfield resonance (shielded group) which was displaced significantly, and then towards the more normally positioned downfield signal.

(5) The nmr chemical shift differences for externally diastereotopic L^2 and L^3 groups are substantially larger in those phenylacetic acid derivatives which

(22) As represented in Table I, the L^3 group in any one example can be considered to be larger than the L^2 group in the same example. This is a consequence of our arbitrary choice in arranging the data and has no fundamental significance. In any one entry in Tabe I the groups designated L^3 and L^2 in columns 1 and 2 can be interchanged. This will require inverting the configuration at the carbinyl carbon (column 3) as well as interchanging the values for the observed chemical shift differences and the sign of these differences in the subsequent columns.

(23) Table I, last column, also contains data for five examples of MTPA amides of chiral primary amines. The nmr of these MTPA amides follows the same sense of nonequivalence as the corresponding MTPA esters. Although the MTPA amide examples are limited, this same generalization should hold for a wide variety of comparable derivatives of primary amines in which the nitrogen is attached to a chiral center. Some additional MTPA amides which follow this same pattern have been described: J.-P. Charles, H. Cristol, and G. Solladié, *Bull. Soc. Chim. Fr.*, 4439 (1970). However, the situation for chiral amides of secondary amines may be very different. This is evident from the complex temperature dependence of the nmr spectra of the (*S*)-*O*-methylmandelate of (*S*)- and (*R,S*)-deoxyephedrin: J. Jacobus and T. B. Jones, *J. Amer. Chem. Soc.*, **92**, 4583 (1970). We have been informed that mandelamides or *O*-methylmandelamides which have the possibility of hydrogen bonding between the α-OH or α-OCH_3 and amide NH group constitute a much more complex system and that a publication on nmr configurational correlation of amides of these and related types is in preparation [private communication, Professor V. Prelog, Eidg. Techn. Hochschule, Zürich, and G. Helmchen, Universität, Stuttgart, Germany; communication of this work has now been published: *Tetrahedron Lett.*, 3873 (1972)].

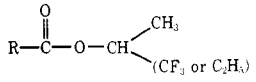
(24) This example assumes that one pure isomer is available, such as is often the case with a natural product. Diastereomeric derivatives of this isomer are then generated for both the *R* and *S* forms of the acid moiety in order to establish the sense of nonequivalence. Table I is set up in this fashion. If both enantiomers of a substrate are available the alternate diastereomers may be generated from a single form of the acid moiety. If a partially active substrate sample is converted to a mixture of diastereomers using one known form of the acid moiety so that signals representing the major and minor stereoisomers are clearly identifiable, then a single reaction will give a sample from which the necessary nmr data can be obtained. Since *R,S* and *S,R* or *R,R* and *S,S* enantiomers give identical nmr spectra, these data can be accommodated to Table I.

(25) In case the relative chemical shift of only one ligand is readily identifiable, as in the phenylalkylcarbinol series, the nmr pattern revealed in Table I for the single ligand is very often quite clear; configurational assignments can then be made reliably, based only on the relative diastereomer chemical-shift difference for the one group (either L^2 or L^3).

(26) One must be circumspect in applying this correlation to examples which differ significantly in chemical nature from those represented in Table I; *e.g.*, examples where the groups L^2 and L^3 contain additional chiral centers, possess heteroatoms, or show unusual conformational restraints. This does not imply that the correlation will not hold with other more complex esters but that extension to such types is not warranted without suitable further supporting evidence gathered on compounds of known configuration.

(27) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966). In the usual case where the group order of a nomenclatural preference at the carbinyl carbon is O > L^3 > L^2 > H, then that diastereomer prepared from a chiral alcohol and (*R*)-(+)-MTPA (Table I, last two columns) showing the downfield chemical shift for the L^3 group and upfield shift for the L^2 group relative to the same groups in the alternate diastereomer prepared from (*S*)-(−)-MTPA will have the *R,R* configuration. It is crucial to point out that this correlation for MTPA derivatives is reversed for the mandelates and *O*-methylmandelates; *i.e.*, in the usual case where the nomenclature sequence rule orders O > L^3 > L^2 > H, the configuration of the diastereomer prepared from (*R*)-(−)-mandelic acid or (*R*)-(−)-*O*-methylmandelic acid showing the relative upfield chemical shift for the L^3 group, will have the *R,R* configuration. The nomenclature sequence rules are arbitrary and the configuration correlation model cannot be enunciated solely in terms of the *R,R vs. R,S* configurational designation.

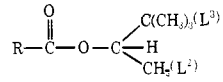
Table II. Nmr Diastereomer Chemical-Shift Differences for α-Substituted Esters of Methyltrifluoromethylcarbinol and Methylethylcarbinol[2,6,8]



Acid moiety R	Chemical shift Δδ, ppm[a] CH_3–CH(O)–CF_3		CH_3–CH(O)– CH_2–CH_3	
MeCHCl-	0.00			
MeCH(NHTFA)-[b]	0.00			
i-Bu(NHTFA)-	0.03			
MeCH(OPh)-	0.00			
MeCH(ONaph)-	0.00			
Menthyl-*O*-CH_2-	0.00	0.05		
PhCH(CF_3)OCH_2-	0.00			
PhCHCl-	0.10	0.16		
PhCH(CH_3)-	0.12	0.08		
PhCH(CF_3)-	0.12	0.10		
PhCH(*t*-Bu)-	9.15	0.24	0.13	0.12
PhCH(OMe)	0.12	0.14	0.08	0.15
o-ClPhCH(OMe)-	0.11	0.18		
PhCH(OH)-	0.21	0.17	0.18	0.30
PhCCN(OH)-	0.15		0.18	0.28
PhCCF$_3$(OMe)-	0.12	0.28	0.10	0.13
p-BiPhCCF$_3$(OMe)-			0.10	0.13
MeCH(NTFSI)-[c]			0.02	
PhCH(CF_3)CH_2			0.07	0.09
Me_3CCCF_3(OMe)-			0.00	0.00
1-Indanyl-	0.00	0.16		
o-CH_3PhCCF$_3$(OMe)-			0.00	0.13

[a] Data taken on Varian A-60. Differences less than 0.02 ppm are uncertain and are given as zero. [b] NTFA refers to trifluoroacetamido. [c] NTFSI refers to tetrafluorosuccinimido.

Table III. Nmr Resonance Positions for Methyl-*tert*-butylcarbinyl Esters[a,16]



Acid moiety R–	Chemical shifts, δ (ppm, downfield TMS) $L^2 = CH_3$ *R,R*	*R,S*	H	$L^3 = C(CH_3)_3$ *R,S*	*R,R*
CH_3- (acetate)	1.11		4.65	0.92	
$(CH_3)_3C$- (pivalate)	1.11		4.64	0.92	
$PhCH_2$- (phenylacetate)	1.08		4.67	0.82	
Ph-	1.32		4.98	0.96	
PhCO- (benzoylformate)	1.32		4.98	0.96	
PhCH(OCH_3)-	1.08	0.98	4.62	0.83	0.72
PhCH(OH)-	1.12	0.88	4.72	0.85	0.60
PhCH(OAc)-	1.17	0.98	4.70	0.92	0.70
PhCCH$_3$(OH)-	1.03	0.97		0.76	0.59
PhCCN(OH)-[b,c]	1.19	0.95		0.89	0.66
PhC(*p*-CH_3Ph)(OH)-[c]	1.15	1.12	4.70	0.92	0.70
PhCCF$_3$(OCH_3)-	1.19	1.25	4.90	0.85	0.90
o-CH_3PhCCF$_3$(OCH_3)-[c]	1.18	1.18	4.75	0.73	0.82

[a] Resonance values in δ, ppm downfield from TMS; $CDCl_3$ solvent taken on Varian A-60. [b] HCN solvent. [c] Configuration unknown, designation as *R,S* or *R,R* is arbitrary since the rule developed in this paper cannot be applied to these examples.

also carry an α-hydroxy group such as the mandelates (CH_3 range Δδ 0.12–0.37 ppm) and α-hydroxy-α-cyanophenylacetates (CH_3 range Δδ 0.12–0.58 ppm) as compared to the *O*-methylmandelates (CH_3 range Δδ 0.07–0.13 ppm) and MTPA esters (CH_3 range Δδ 0.06–0.12 ppm).

(6) The chemical shift differences for internally diastereotopic groups ($L^2 = L^3$) attached to an achiral carbinyl carbon are of the same magnitude as for externally diastereotopic groups (L^2 in *R,R* diastereomer *vs.* L^2 in *R,S* diastereomer). For instance, the chemical-shift difference between methyls in isopropyl α-methoxy-α-trifluoromethylphenylacetate is 0.08 ppm comparable to the difference of 0.08 ppm for the resonances of the methyls in the diastereomeric MTPA derivatives of methylisopropylcarbinol.

(7) The proton directly attached to the carbinyl carbon typically shows, under the usual conditions, a chemical-shift difference of less than 0.02 ppm between diastereomers of the type shown in Tables I, II, and III.[28]

(8) The diastereomeric chemical shift differences observed for α-substituents at the acid moiety were generally too small to be useful, except for those of the trifluoromethyl group.[29]

These observations taken together, but especially points 1 and 3, implicate a crucial differential interaction of the anisotropic α-phenyl substituent on the chiral acid moiety with the alkyl substituents (L^2 and L^3) on the carbinol carbon. Furthermore, the chemical-shift pattern and the position of the resonances (points 2 and 4) indicate that this interaction produces a selective shielding by the phenyl ring upon the L^2–L^3 substituents, while the minimum chemical shift differences noted with respect to other substituents (points 7 and 8) indicate that these other groups are not uniformly shielded or deshielded in a generally consistent manner. Also, the typically greater chemical-shift differences of the mandelate diastereomers (point 5) are consistent with a more rigid structure, presumably brought about by hydrogen bonding of the α-hydroxyl group, with the carbonyl of the ester.

Although diastereotopic groups need not exhibit identical properties, even when there is free rotation within a molecule,[30] contributions from the "intrinsic asymmetry" factor should be minor in comparison with conformational effects arising from more rigid structures. We therefore conclude that the observed differences in chemical shifts for the resonances of the L^2 and L^3 groups attached to the carbinyl carbon of diastereomeric mandelates, atrolactates, and MTPA esters and amides result from a time weighted average preferential shielding[31] of these groups by the π cloud of the α-phenyl substituent in the acid moiety.

(28) However, the shift differences are large enough for the diastereotopic hydrogens in primary alcohols to permit the determination of enantiomeric purity of compounds such as benzyl-*1-d* and neopentyl-*1-d* alcohols and amines. In addition, we find dramatic and useful nmr chemical-shift differences for the proton attached to the carbinyl carbon upon the addition of the lanthanide-shift reagents.

(29) The nmr nonequivalence of the α-trifluoromethyl group in diastereomeric MTPA derivatives is significant probably because of the inherently large chemical shifts associated with fluorine nuclei and because of the differential deshielding of the α-CF_3 by the carbonyl group when the molecule is more or less skewed out of the coplanar conformation shown in **5**. The lanthanide chemical-shift reagents cause a dramatic separation of proton signals for the α-methyl, α-hydrogen, and α-methoxy groups of diastereomeric atrolactate, mandelate, *O*-methylmandelate esters, and MTPA esters. The correlation of configuration and ^{19}F chemical shift differences of MTPA derivatives will be the subject of a subsequent paper.

(30) H. Gutowsky, *J. Chem. Phys.*, 37, 2196 (1962).

(31) Both shielding and deshielding effects are theoretically possible, depending upon the precise orientation of the phenyl ring relative to groups L^2 and L^3. However, in the many compounds studied, resonances for L^2 and L^3 are more or less upfield, *i.e.*, shielded, in comparison to standard chemical shift positions for each type of group (Table III). We therefore view the observed chemical shift differences of the externally diastereotopic L^2 and L^3 groups in terms of the extent of shielding rather than invoke deshielding or a combination of shielding and deshielding. Theoretical justification for this view comes from the study

These interactions must be stereochemically directed and are significantly anisotropic by virtue of being through space (six bonds separate the interacting groups) and not because of some generalized influence of both chiral centers. We shall now consider a configuration correlation model for mandelate esters[33] which embodies these conclusions. The diastereomeric (*R*)-mandelate esters of secondary carbinols will be considered in the conformation shown in Figure 2, formulas **4A** and **4B**. The choice of this representation for the model is made on the basis of the preceding discussion and the following considerations. The correlation scheme should be represented if possible by a solitary model for each diastereomer. In this way we obviate the dubious analysis of positive and negative contributions from a large set of speculative conformers to the chemical shifts of the groups in these conformational mobile systems. Hydrogen bonding between the α-hydroxyl and carbonyl groups, as represented in Figure 2, incorporates an added constraint in the model for the mandelates which restricts the conformers under consideration. This single conformational model represents a crucial arrangement in which the α-phenyl substituent of the acid moiety is preferentially oriented towards the L^3 *vs.* L^2 groups attached to the carbinyl carbon of the alcohol moiety of each diastereomer. Thus in one diastereomer (**4A**) L^3 is juxtaposed with the α-phenyl group while in the alternate diastereomer, **4B**, it is L^2 which is juxtaposed with the α-phenyl.[34]

The proposed model positions the hydrogen attached to the carbinyl carbon in a region nonpreferentially shielded with respect to the alternate diastereomers. This is consonant with the observation that the chemical shift differences for these carbinyl protons are usually small.[28] Thus, the selection of **4** as the nmr correlation model for diastereomeric mandelates is founded upon its success in rationalizing the data as given in Tables I–III, as well as other unpublished examples.[35] This model provides an empirical correlation of extensive data which show that the mandelate diastereomer specified by **4A** will have the resonance for L^3 upfield (more shielded) from that for L^3 in the alternate diastereomer **4B**; at the same time diastereomer **4B** will have the resonance for L^2 upfield (more shielded) from that for L^2 in diastereomer **4A**. This is quickly and conveniently determined from the model by observing which group is juxtaposed with phenyl.

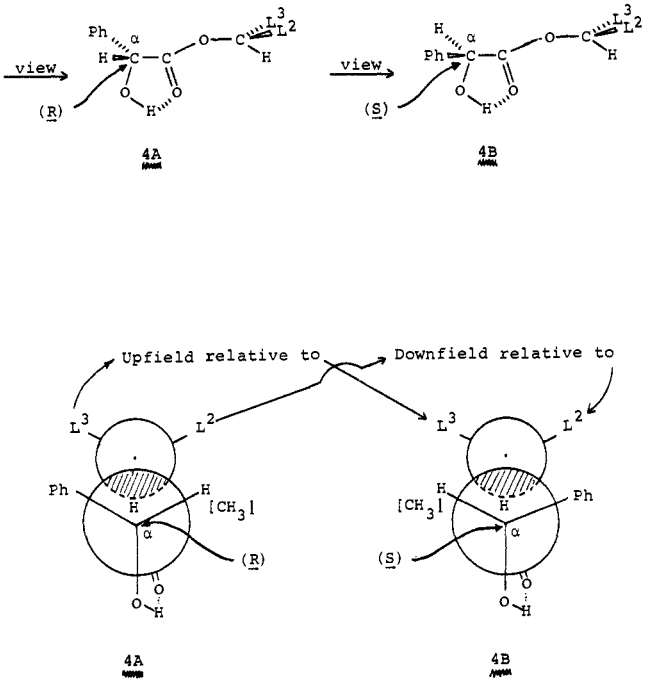
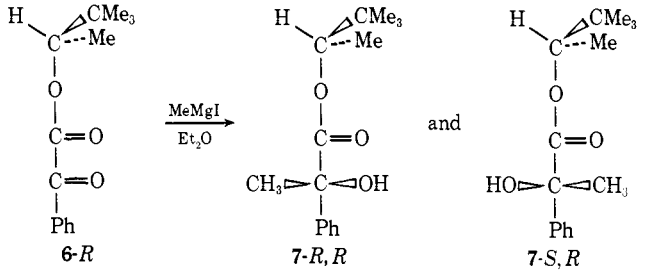


Figure 2. Configuration correlation model for (*R*)-mandelic acid derivatives (**4A**) and (*S*)-mandelic acid derivatives (**4B**)[34] and atrolactates, [CH_3] replacing α-H.

Furthermore this same model is applicable to atrolactate esters by the simple substitution of methyl for hydrogen in the α position of the acid moiety in Figure 2. Application of this atrolactate model can be illustrated by reference to Figure 1B, which is the spectrum of the mixture of diastereomeric methyl-*tert*-butylcarbinyl atrolactates resulting from the reaction of methylmagnesium iodide with racemic methyl-*tert*-butylcarbinyl benzoylformate. The following equation illustrates the reaction of the pure *R* isomer (**6**) to give a mixture of the *R,R* and *S,R* atrolactates (**7**)



in a 62 to 38 ratio.[36] The nmr spectrum of this product

of Johnson and Bovey,[32] whose plot of aromatic ring effects shows that deshielding effects drop off more rapidly with distance than shielding effects.

(32) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958). See also L. Jackmann and S. Sternhill, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, pp 94–98.

(33) In spite of the fact that the mandelates typically show larger diastereomer chemical shift differences than *O*-methylmandelates and MTPA derivatives, they are not well suited for use in configuration studies because of synthetic limitations and possible complications due to epimerization. Nevertheless, we shall discuss the mandelates first because they allow a more direct analysis for developing a configuration correlation model.

(34) In Figure 2 we have chosen to invert the configuration of the acid moiety in representing the alternate diastereomers **4A** and **4B**, so that one model represents the (*R*)-mandelate derivative while the other represents the (*S*)-mandelate derivative in the same manner as the data are presented in Table I. The model might have been represented by inverting the configuration of the alcohol moiety while retaining that of the mandelate portion constant. Since the nmr spectra of enantiomeric *R,R* and *S,S* stereoisomers are identical (in an achiral environment) as are *R,S* and *S,R* enantiomers, only two models are needed to represent the nmr spectra of the four stereoisomers.

(35) A subsequent publication will present our results on the LiAl(O-*t*-Bu)$_3$H reduction of a series of chiral benzoylformates to mandelates[2] all of whose configurations have not been rigorously established but which are satisfactorily rationalized by this model.

(36) The ratio of products given comes from the experiment of A. McKenzie and P. D. Ritchie, *Biochem. Z.*, **237**, 1 (1937). *Cf.* also V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956). We have repeated this asymmetric synthesis with benzoylformate ester prepared from a sample of methyl-*tert*-butylcarbinol containing an 11.7% excess of the *S*-(+) isomer. The (*S*)-(+)-atrolactic acid, isolated upon hydrolysis, $[\alpha]^{20}D$ +0.81 ± 0.05° (EtOH), indicates a 22 ± 2% asymmetric synthesis. We have also carried out the reaction using racemic benzoylformate and analyzed the mixture of diastereomers by nmr which showed a (*R,R* + *S,S*) to (*R,S* + *S,R*) ratio of 60:40 (Figure 1B, B. Braman, M.S. Thesis, Stanford University, Jan 1967). If the configuration of the predominant isomer can be ascertained by use of the currently proposed model it then becomes possible to determine both the extent and sense of an asymmetric synthesis such as this without direct recourse to optically active materials.

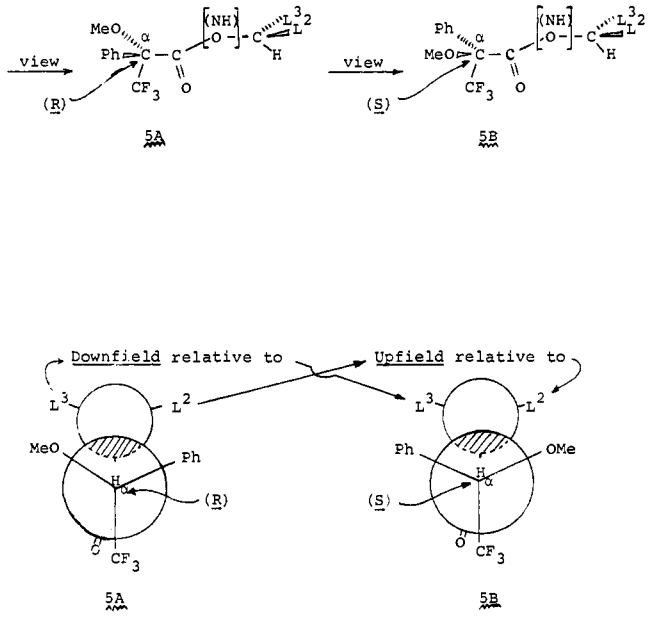


Figure 3. Configurational correlation model for (*R*)-MTPA derivatives (**5A**) and (*S*)-MTPA derivatives **5B**.

mixture (**7**-*R*,*R* and **7**-*S*,*R*) should be the same within experimental limits as that given in Figure 1B.[36] Since the starting ester (**6**-*R*) has the *R* configuration, *tert*-butyl must be assigned to L^3 and methyl to L^2 in Figure 2. According to the atrolactate model (Figure 2 with CH_3 replacing α-H) we must associate that *tert*-butyl group responsible for the relatively upfield signal (Figure 1B) with that diastereomer model which has phenyl and *tert*-butyl juxtapositioned, namely **4A**. Thus application of this model predicts that the major diastereomer which has the relatively upfield *tert*-butyl resonance must be *R*,*R* (*i.e.*, **4A**, L^3 = *t*-Bu, L^2 = CH_3) in accord with the known stereochemical course of this reaction.[17,36,37]

The correlation model (Figure 2) for mandelate esters, which applies to the atrolactates by replacing the α hydrogen with a methyl, also extends to *O*-methylmandelates by replacement of OH in **4** by OCH_3. This extended model successfully correlates the sense of nonequivalence for all of the *O*-methylmandelates reported in Table I. The success of the same model for mandelates and atrolactates on the one hand, and *O*-methylmandelates on the other means that hydrogen bonding between the α-hydroxyl and carbonyl groups, with resulting restriction of this portion of the structure, is not necessary to the success of the correlation model. Nevertheless, the diastereomer chemical-shift differences for the α-methoxy-α-phenylacetate types are typically smaller than these for the corresponding α-hydroxy types studied (Table III) and indeed we feel that this reflects a less rigid structure for these α-methoxy derivatives. Although the chemical-shift differences are decreased for the *O*-methylmandelates, compared to the mandelates, the differences are still sufficient to be useful for correlation studies.

Chiral MTPA esters retain the same general chemical shift pattern for the resonances of the L^2 and L^3 groups as observed in the mandelates; however, the sense of nonequivalence is reversed. This reversal of the correlation pattern in replacing the α hydrogen of the mandelates and *O*-methylmandelates with an α-trifluoromethyl group emphasizes the important role of the electronegative CF_3 group in determining the conformations of such esters.[38] Therefore, the model in Figure 2 for the "mandelates" has been formulated in Figure 3 for the MTPA derivatives as required to accommodate this reversal in observed sense of nonequivalence. In this representation the α-trifluoromethyl group, instead of the α-methoxy group, more or less eclipses the carbonyl.[39] The conformation at the carbinyl carbon is again arranged to have the carbinyl hydrogen located in the same relative position in each diastereomer, thus causing L^2 to be juxtaposed with phenyl in **5A** and L^3 in **5B**. Model **5A** represents that diastereomer of (*R*)-(+)-MTPA which has the signal for L^2 upfield (and the signal for L^3 downfield) relative to the signals for the same groups in **5B**, the alternate diastereomer. In this representation the diastereomers **5A** and **5B** have been generated by inverting the configuration at the α carbon of the acid moiety rather than at the carbinyl center.[34]

The explicit statement of the nmr configuration correlation model for MTPA derivatives is as follows;[25] that diastereomeric ester (or amide)[23] prepared from (*R*)-(+)-MTPA and a chiral secondary alcohol (or analogous primary amine) which shows the upfield signal for the group L^2 (and the downfield signal for the group L^3) compared to the signals for the same groups in the alternate diastereomer, is represented formally by configuration **5A**. The alternate diastereomer **5B** prepared from the same chiral substrate and (*S*)-(−)-MTPA will show the upfield signal for the L^3 group (and downfield signal for the L^2 group) compared to the alternate diastereomer.[40] The final configurational designation follows simply from the application of the Cahn–Ingold–Prelog nomenclature scheme[27] to the formula with the appropriate L^2 and L^3 substitutions.[41]

(37) The same conclusion is reached by considering the relatively upfield minor doublet due to the CH_3 group which is juxtaposed to phenyl in **4B**. Alternatively this analysis could be based on the relatively downfield signals associated with the groups in this model which are remote from phenyl; *i.e.*, L^2 = CH_3 in **4A** and L^3 = *t*-Bu in **4***B*.

(38) ORD–CD studies[14] have been interpreted in terms of conformations of mandelates and *O*-methylmandelates which have the α-hydroxy or α-methoxy eclipsed with the carbonyl group. This study also concluded (on the basis of an enhanced optically active, $n\rightarrow\pi^*$, homoconjugated carbon phenyl transition) that the α-trifluoromethyl group instead of the methoxy group of MTPA esters is essentially eclipsed with the carbonyl in the crucial (although not necessarily major) conformation to account for the observed ORD effect.[39]

(39) For effective shielding of L^2 or L^3 by the phenyl group the α-CF_3-carbonyl conformation need not be prefectly eclipsed but can be substantially skewed from coplanarity.

(40) In order to avoid misinterpretation it should be unequivocally stated that we do not claim models **4** and **5** to be preferred ground-state conformations of the molecules under consideration. These models have been constructed *a posteriori;* they may in fact represent an effective average of many conformations or may represent a minor conformation in which differential shielding of the L^2 and L^3 groups is most effective. Alternatively, these structures may represent minor conformations for which, however, there are no reasonable alternatives functioning in a counteracting sense. It also remains possible that this is merely a fortuitous array which does not embody the significant conformational contributions of the molecules under observation.

(41) The explicit statement in terms of the *R*–*S* nomenclature scheme for MTPA derivatives is as follows: that ester (or amide) prepared from (*R*)-(+)-MTPA and a chiral secondary alcohol (or corresponding primary amine) which shows the upfield signal for the L^2 group (and the downfield signal for the L^3 group) relative to the alternate diastereomer will be the *R*, *R* diastereomer if the Cahn–Ingold–Prelog nomenclature sequence is [O or NH] > L^3 > L^2 > H, or the *R*,*S* diastereomer if the sequence is [O or NH] > L^2 > L^3 > H. If (*S*)-(−)-MTPA is used in preparing the derivative, the same chemical shift patterns would indicate the nmr equivalent *S*,*S* or *S*,*R* diastereomers, respectively.

Although we have not made a systematic experimental investigation of other chiral α-substituted phenylacetic acids, a survey of random cases available in these laboratories from other studies has shown agreement with the general model as formulated in Figures 2 and 3.

Inspection of Table I of ref 8 shows that in 10 of the 18 entries for MTPA esters and amides the differences in chemical shifts for the externally diastereotopic α-OCH_3 resonance was less than 4 Hz (at 100 MHz, 0.05 ppm or less). With one exception, which is an ester of a tertiary alcohol, these derivatives with small diastereotopic chemical-shift differences for the α-OCH_3 resonance do not have an aromatic group on the carbinyl carbon while those with a significant chemical-shift difference generally do. This can be rationalized by correlation models **5A** and **5B** in which L^3 is assigned to the aryl group; the upfield α-OCH_3 shift in these compounds can be correlated then with that diastereomer in which the α OCH_3 is shielded by the juxtaposed L^3 aryl group.

Since the OCH_3 signal in MTPA derivatives is an unresolved quartet due to long-range couplings with the α-CF_3 groups, these generally small diastereomeric chemical-shift differences have not been of great value. Nevertheless we have observed that these signals are significantly shifted and separated by the lanthanide-shift reagents. This technique will certainly prove to be a valuable adjunct to the present studies.[29]

The separations of signals for diastereotopic α-CF_3 groups generally are not larger for MTPA derivatives when the carbinyl carbon carries an aryl substituent. Therefore, correlation models **5A** and **5B** are not directly applicable to rationalizing these observations on the α-CF_3 diastereomer chemical-shift differences,[29] since in these representations CF_3 is positioned equally between L^3 and L^2. Nevertheless we find, in the cases we have studied[8] where the configurations are known, that the α-CF_3 signal for **5B** is upfield (with respect to trifluoroacetic acid, TFA) from that of **5A**. These data were largely collected using internal TFA which we now know has a large effect on the absolute ^{19}F chemical shift value and on the magnitude of ^{19}F diastereomer chemical-shift differences; in one case, at least, causing a reversal in resonance positions. Further data on this point are being collected using external TFA standard. If this correlation is sustained with additional examples, it should prove useful and complementary to the proton nmr correlation presented herein.

Experimental Section

Instruments. Nmr determinations were performed on Varian T-60, A-60, and HR-100 MHz instruments, as appropriate for the required resolution, with TMS internal standard in ether $CDCl_3$ or CCl_4 solvent. Optical rotations were determined either visually on a Zeiss polarimeter to ±0.02° with center-filled tubes or electronically on a Perkin–Elmer Model 141 to ±0.002°.

Reagents. (+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride was prepared and used according to the literature.[8] Benzoylformic acid was converted to the acid chloride by use of oxalyl chloride[42] and (*S*)-(+)-*O*-methylmandelic acid[43] was converted to the acid chloride *via* formation of the sodium salt and subsequent treatment with oxalyl chloride.[44]

(*R*)-(+)-MTPA Derivatives. The following procedure was routinely used for the small scale preparation of MTPA derivatives for nmr studies. (*R*)-(+)-MTPA[2,1,45] was converted to the (+)-acid chloride[8,46] and distilled. It is indefinitely stable when stored in a sealed ampoule. The reaction was carried out in a dry 10 × 75 mm test tube fitted with rubber septum.[47] The reagents were injected *via* syringe into the test tube in the following order: dry pyridine (300 μl, 300 mg); (+)-MTPA-Cl[46] (35 mg, 26 μl, 0.14 mmol); carbon tetrachloride (300 μl);[48] and the substrate alcohol or amine (0.10 mmol). The reaction mixture was then shaken and allowed to stand at room temperature until the reaction was complete as evidenced by no more formation of crystalline pyridine hydrochloride.[49] After reaction was complete, excess 3-dimethylamino-1-propylamine (*ca.* 0.20 mmol, 20 mg, 24 μl) was added[50] and the mixture allowed to stand for 5 min. It was then diluted with ether, washed (cold dilute HCl, cold saturated Na_2CO_3, and saturated NaCl), and dried ($MgSO_4$). The filtered ether solution was concentrated, carbon tetrachloride added to the residue and the concentration repeated a second and third time in order to remove the last traces of ether. The nmr spectrum was taken of this residue.[51]

Acknowledgment. We are especially grateful to Dr. Lois Durham for her helpful and critical discussions during this research, for her expert supervision of the Stanford nmr laboratory, and for her unfailing cooperation during the collection of the nmr data reported here.

(42) M. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **64**, 329 (1942).
(43) D. G. Neilson and D. A. V. Peters, *J. Chem. Soc.*, 1519 (1962).
(44) G. Stork and T. Clark, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961).
(45) Available from Aldrich Chemical Co., Milwaukee, Wis.; Norse Laboratories, Santa Barbara, Calif.; Fluka A. G., Buchs, Switzerland.
(46) Enantiomerically pure (*R*)-(+)-MTPA is converted to (*S*)-(+)-acid chloride: $[\alpha]^{24}D$ +134.0 ± 0.5° (*c* 6.46, CCl_4), $\alpha^{25}D$ +90.70 ± 0.03° (neat, *l* 1½). The solution rotation is as previously reported, but the previously reported[8] rotation of $\alpha^{25}D$ −10.0° (neat, *l* 1) was in error. Note that according to the nomenclature rules (*R*)-(+)-MTPA gives (*S*)-(+)-MTPA-Cl.
(47) The test tubes were dried in an oven at 150° and stored along with the serum caps in a desiccator.
(48) The formation of a precipitate at this point indicates that the pyridine was wet. A slight opalescence can be tolerated but a definite precipitate requires that the reaction can be abandoned and repeated with dry reagents.
(49) The reaction with primary amines is complete in a few minutes; unhindered secondary alcohols such as 2-propanol in less than 10 min, most other secondary alcohols in 12 hr or less. Phenyl-*tert*-butylcarbinol reaction was complete in approximately 48 hr, but there was inappreciable reaction with di-*tert*-butylcarbinol after 2 weeks at room temperature.
(50) This converts unreacted MTPA-Cl, or MTPA anhydride, which may be formed in the reaction and which is difficultly hydrolyzed, into the basic amide which is subsequently removed in the acid wash. The reaction may warm and the pyridine hydrochloride dissolve upon addition of this base. Other diamines such as β-diethylaminoethylamine should be equally suitable. If the chiral substrate being derivatized carries a basic substituent (as for instance, 1-dimethylamino-2-propylamine) then this step should be omitted or an alternate work-up procedure devised.
(51) If the product required further purification it was passed through a small column of silica gel using benzene as eluant. Purification or analysis may be done by gas chromatography using an STAP column on 60–80 DMGS-W support, 6 ft × 0.25 in. for analysis and 30 ft × ⅜ in. for preparative separation.