α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines[1]

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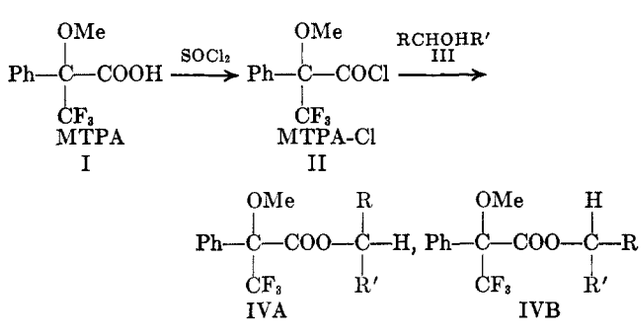
Diastereomeric esters and amides have been prepared from α-methoxy-α-trifluoromethylphenylacetyl chloride and various secondary alcohols and amines. The nmr spectra of the *R,R* and *S,S vs.* the *R,S* and *S,R* diastereomers show significantly different chemical shifts: 0.03–0.13 ppm in the proton region and 0.11–0.71 ppm in the fluorine region. By measuring the intensities of the nmr signals of the diastereomerically situated groups of esters and amides prepared from this enantiomerically pure reagent, satisfactory determinations of the enantiomeric composition of a number of alcohols and amines have been made. The use of the α-methoxy-α-trifluoromethylphenylacetyl derivative offers the distinct advantage, over other reagents having only proton resonances, that determinations of enantiomeric composition based upon fluorine resonances are usually more reliable, since the fluorine signals are simple and in an uncongested region. This is a absolute method, independent of optical rotation; accurate determinations can be made on 20-mg samples. Thus this reagent extends the application of this nmr technique. Furthermore, the reagent shows complete stability to racemization under prolonged reaction conditions. A practical synthesis and convenient resolution of the reagent have been developed.

Recent developments in methods for the determination of enantiomeric composition (optical purity) have been reviewed by Mislow and Raban.[2] Our interest in this problem is dictated by continuing studies on the asymmetric reduction of ketones with the necessity of determining the enantiomeric composition of the resulting chiral alcohols on relatively small samples.[3] In a previous paper[4] we reported on the applications and limitations of a series of mono-α-substituted phenylacetic acids for the nuclear magnetic resonance (nmr) and gas–liquid partition chromatographic (glpc) determination of enantiomeric composition.[5] The reagents previously studied do not give satisfactory results with hindered secondary carbinols because of epimerization at the α-carbon center of the acid moiety.[4,5] In addition, when nmr was used as the technique for quantitative measurement of diastereomer ratios, serious restrictions were often encountered owing to the overlapping of proton signals. In earlier studies on the determination of enantiomeric composition of partially active carbinols by glpc and nmr, it was recognized that α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, I) might be ideally suited for this purpose.[5] This reagent can react *via* its acid chloride (II) with chiral alcohols (III) to give a mixture of



diastereomeric esters (IVA and IVB) whose nmr spectrum can be used for quantitative analysis of the enantiomeric composition of the chiral alcohol from which it was made.

The advantages of this reagent for the determination of enantiomeric composition of a chiral alcohol are: (a) the generally excellent separation of both proton and fluorine nmr signals of the diastereomers IVA and IVB; (b) the presence of the trifluoromethyl group permitting the use of fluorine nmr, which occurs in an uncongested region of the spectrum; (c) its marked stability toward racemization even under severe conditions of acidity, basicity, and temperature; (d) its relative ease of preparation and resolution; (e) its inherent volatility which allows lower molecular weight derivatives to be purified, as well as analyzed, by glpc; (f) its versatility, *i.e.*, it may be used for determination of enantiomeric composition of primary and secondary amines as well as carbinols.

It should be re-emphasized[2,4] that this method is absolute and does not require that the carbinol or amine be previously resolved. Furthermore, the accuracy of the determination of enantiomeric composition by this method is not dependent in any way on the magnitude of the optical rotation; and yet one can calculate the maximum optical rotation from the rotation of a partially active sample and its enantiomeric composition as determined by this technique.

The nmr spectrum (Figure 1) of N-4-methyl-2-pentyl-α-methoxy-α-trifluoromethylphenylacetamide prepared from racemic materials, illustrates the advantage of using the signals from the trifluoromethyl group over those from the protons of an MTPA ester for nmr determination of enantiomeric composition. The signals for the isopropyl group, as well as for the α-methyl group, occur as two sets of doublets, one for the *R,S/S,R* enantiomeric pair and another for the *R,R/S,S* enantiomeric pair. Quite obviously, any

(1) We acknowledge with gratitude the support of this work by the U. S. Public Health Service (NIH GM 5248) and the National Science Foundation (GP 6738).

(2) M. Raban and K. Mislow, "Topics in Stereochemistry," Vol. II, N. L. Allinger and E. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, p 199.

(3) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964).

(4) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

(5) (a) K. Mislow and M. Raban, *Tetrahedron Lett.*, 4249 (1965). (b) M. Raban and K. Mislow, *ibid.*, 3961 (1966). (c) J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968). (d) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Amer. Chem. Soc.*, **90**, 4877 (1968). (e) D. J. Sandman and K. Mislow, *J. Org. Chem.*, **33**, 2924 (1968). (f) D. M. Feigl and H. S. Mosher, *Chem. Commun.*, 615 (1965). (g) D. W. Dull, Ph.D. Thesis, Stanford University, 1967.

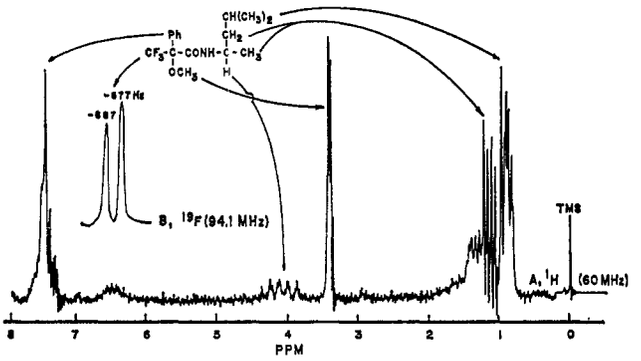


Figure 1.—The nmr spectrum of N-4-methyl-2-pentyl-α-methoxy-α-trifluoromethylphenylacetamide from racemic materials: (A) 60 MHz, ^{1}H, $CDCl_3$ solvent, TMS; (B) 94.1 MHz, ^{19}F, $CDCl_3$ solvent with trifluoroacetic acid internal standard.

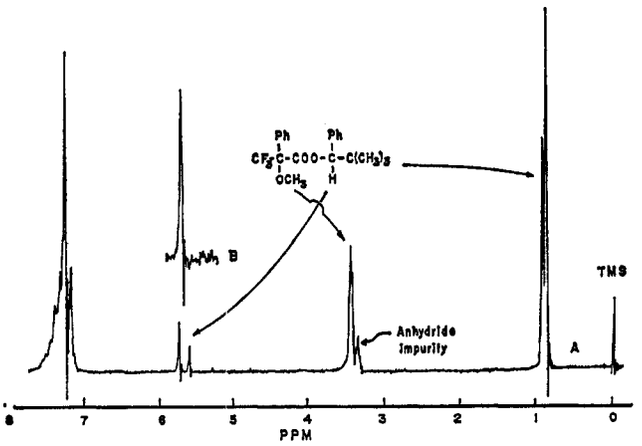


Figure 2.—(A) The 60-MHz proton nmr spectrum of diastereomeric esters from racemic phenyl-*t*-butylcarbinol and racemic α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA Cl). The anhydride impurity is absent when distilled MTPA Cl is used. (B) The α-carbinyl hydrogen signal of the single diastereomer from pure (+)-phenyl-*t*-butylcarbinol and MTPA Cl from pure (+) acid.

attempt at obtaining the relative proportions of these diastereomers by integration of proton signals would lead to very inaccurate results because of signal overlapping and perturbation. On the other hand, the fluorine nmr spectrum taken at 94.1 MHz is uncomplicated and shows a separation of 10 Hz for the signals for the two diastereomeric pairs, so that the relative areas of these signals can be obtained with reasonable accuracy by integration. It is of interest to note that the ^{19}F signals are broadened because of long range coupling with the protons of the methoxy group, and that the fluorine signals for the two diastereomeric pairs are not of the same intensity, although racemic materials were used in the synthesis (Figure 1).

When (*R*)-(+)-phenyl-*t*-butyl-carbinol, (*R*-III, R = phenyl, R′ = *t*-butyl, the pure isomer as measured by optical rotation) was treated with enantiomerically pure MPTA Cl (II), the signal for the α hydrogen of the carbinol moiety in the resulting ester IV was a singlet (Figure 2B), as was also the signal for the *t*-butyl group. However, when racemic phenyl-*t*-butylcarbinol, *RS*-III, was treated with racemic acid chloride, *RS*-II, the spectrum (Figure 2A) for the resulting mixture of diastereomeric ester pairs (*R,R*-IV + *S,S*-IV *vs.* *R,S*-IV + *S,R*-IV) showed grossly unequal signals for the respective α and *t*-butyl protons. The inequality of these signals is a consequence of the different rate of reaction of the reagent *R*-II with carbinol *R*-III to yield *R,R*-IV as compared to the rate of reaction of *R*-II with *S*-III to give *R,S*-IV. As has been discussed,[2] the rate of reaction of *S*-II with *S*-III to give *S,S*-IV, and of *S*-II with *R*-III to give *S,R*-IV will differ by exactly the same amount. We have observed that this difference may be quite large, especially when dealing with hindered carbinols. As has been pointed out,[2] therefore, when this reaction is being employed for the accurate determination of enantiomeric composition, it is imperative that (a) the reaction be quantitative with respect to the substrate (such as III) and (b) the reagent (such as II) be enantiomerically pure.

The nmr data for a number of esters and amides of MTPA are collected in Table I. The chemical shift differences between diastereotopic[6] protons was 0.03–0.13 ppm, while the range for the signals from the diastereotopic α-trifluoromethyl groups was 0.11–0.71 ppm. Such differences permitted precise integrations of the fluorine signals, but comparable precision in measuring the signals from the diastereotopic proton was not always possible because of overlapping or perturbation. When practical, though, the determinations were done for the sake of convenience by using the proton spectra.

Although these studies have been primarily with secondary carbinols, the chemical shift differences were substantial for the signals from both the diastereotopic methyl and trifluoromethyl groups of the ester from the tertiary alcohol methylphenyltrifluoromethylcarbinol.[5g,7] Thus this method should be generally applicable to those tertiary alcohols which are chiral at the carbinol center.

Furthermore, the chemical shift differences of the signals for the diastereotopic α hydrogens in the MTPA ester of neopentyl alcohol in benzene solvent differ by 0.15 ppm compared with 0.10 ppm for the analogous signals for the *o*-methylmandelate ester.[5a] However, this method will not always be applicable. Although the chemical shift differences were about 0.08 ppm for the diastereotopic hydrogens in the esters of benzyl and *o*-chlorobenzyl alcohols, the center bands were separated by only 2.4 Hz at 100 MHz; analysts of a sample which was not 100% deuterated would be virtually impossible. We have also made use of the reagent to confirm the enantiomeric purity of a sample of optically active neopentylamine-1-*d*.[8]

This method is much simpler than that used by Guthrie and Cram.[9] Two special examples will illustrate the utility of this method. A study was made some years ago of the asymmetric reduction of methyl *t*-butyl ketone by the Grignard reagent from the three (+)-1-halo-2-methylbutanes.[10] The synthetic yield of reduction product from the iodo compound was very low; the optical rotation and therefore the extent of asymmetric synthesis could not be determined. The crucial fraction from this reaction had

(6) For the definition of this terminology, see M. Raban and K. Mislow, "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, pp 1–37.
(7) G. A. Olah and C. V. Pittman, *J. Amer. Chem. Soc.*, **88**, 3310 (1966).
(8) G. Solladié, Stanford University, results to be published.
(9) R. D. Guthrie and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 5288 (1967).
(10) W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *ibid.*, **81**, 2779 (1959).

been saved; it was purified by glpc, and the enantiomeric composition of the methyl-*t*-butylcarbinol determined, by conversion to the MTPA ester, to be 7.5% e.e.[11] as compared with 13.4% e.e. and 11.7% e.e. respectively for the carbinols obtained by reduction with the chloro and bromo Grignard reagents.

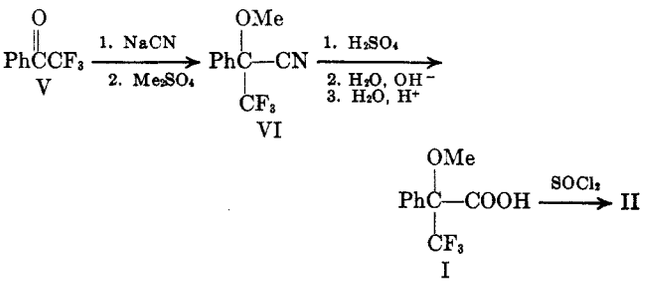
The resolution and determination of maximum rotation for methyltrifluoromethylcarbinol has presented difficulties. The initially reported resolution[12] gave material of $[\alpha]^{25}D$ −2.6° (neat). Analysis by glpc of the *o*-methylmandelate esters[5d,13] gave a calculated value of $[\alpha]^{27}D$ −5.6° (neat) for the pure enantiomer. This value was subsequently revised[14] to $[\alpha]^{25}D$ −5.8° (neat) based on a combination of further resolution and glpc analysis *via* the *o*-methylmandelates. It now seems certain that some racemization of the *o*-methylmandeloyl moiety had taken place during the preparation of the diastereomeric esters, thereby leading to a calculated value which was high. Formation of the (+)- and (−)-MTPA esters of partially active methyltrifluoromethylcarbinol and analysis of their nmr spectra and gas chromatograms gave maximum rotation values of $[\alpha]^{24}D$ −5.15 ± 0.09° and −5.07 ± 0.08° (neat) respectively. Preparative glpc resolution of the mixture of diastereomeric esters made from pure (−)-MTPA and racemic methyltrifluoromethylcarbinol gave a recovered (−) ester which contained 1.5 ± 0.5% of the other diastereomer. Lithium aluminum hydride reduction of this ester regenerated methyltrifluoromethylcarbinol, $\alpha^{25}D$ −6.19° (neat). Correcting for the amount of (+) enantiomer present gives a value of $\alpha^{24}D$ −6.39°, $\alpha^{25}D$ −5.07 ± 0.09° (neat, d_4^{25} 1.263) for the totation of the pure enantiomer. These limits of error include the uncertainty in determining the signal areas, the optical rotation, and the density.

A study of the data in Table I shows certain relationships between chemical shifts and configuration within closely related series. However, in general it seems premature to speculate on these relationships with the limited data available. One conclusion, which applies to the diastereomeric esters of the aliphatic alcohols so far studied, is as follows: when the signal(s) from the R group attached to the carbinol carbon on one isomer (IVA) is shifted downfield with respect to the signal(s) for this same R group in the other diastereomer (IV B), the reverse will be true for the signal(s) from the R′ group; *i.e.*, when the signals for the R group are shielded, those for the R′ group will be relatively deshielded.

Table II compares the enantiomeric composition (% e.e.) of a number of compounds determined by optical rotation and by the nmr method. The agreement, which is at worst within 1%, confirms the reliability of MTPA as a general reagent for the determination of enantiomeric composition of alcohols and amines. The accuracy of the method can be improved in specific cases by careful standardization of procedures and especially by the use of multiple-scanning summation techniques.

The recommended procedure for the preparation of the diastereomeric derivatives, either esters or amides, is described in the experimental section. Since treatment of the acid, I, with thionyl chloride can give some acid anhydride, which is very much less reactive than the acid chloride II, it is recommended that the acid chloride be vacuum distilled before use. It can be stored in sealed vials and used as needed. Generally a full molar excess of the acid chloride was taken if undistilled material was employed; this is unnecessary when the distilled acid chloride is used, since it has been observed that 0.2 molar excess, and in one case 0.02 molar excess, was sufficient to achieve complete reaction. Analytical determinations were routinely conducted starting with 0.1 to 0.2 mmol of carbinol, *i.e.*, about 20 mg of an alcohol such as phenyl-*t*-butylcarbinol, although initial experiments were carried out on larger amounts.

Racemic α-methoxy-α-trifluoromethylphenylacetic acid[15] (MTPA) was made from phenyl trifluoromethyl ketone[16] (I) by cyanide addition in 1,2-dimethoxyethane (glyme) solvent followed by methylation with dimethylsulfate to give VI, which was distilled and then hydrolyzed in two stages without isolation of the intermediate amide to give MTPA in high over-all yield. This procedure is preferable to hydrolysis of the cyanohydrin to give α-hydroxy-α-trifluoromethylphenylacetic acid followed by resolution and then methylation.[15]



The acid (I) is readily resolved *via* crystallization of the α-phenylethylamine salts from ethanol. Using both isomers of the resolving agent, 70% of the acid may be obtained in either the enantiomerically pure (+) or (−) form. The optically active distilled acid chloride (II) is formed in nearly quantitative yield by refluxing with excess thionyl chloride for 50 hr.

Pirkle and Beare[17] have concluded that (−)-methyl α-hydroxy-α-trifluoromethylphenylacetate has the absolute *R* configuration based upon correlation of its nmr chemical shift in (−)-1-naphthylethylamine with those of (*R*)-(−)-methyl mandelate, (*R*)-(−)-methyl atrolactate, and (*R*)-(+)-methyl α-hydroxy-α-trichloromethylphenylacetate. Since α-hydroxy-α-trifluoromethylphenylacetic acid [(+) in methanol and water, (−) in chloroform] is converted to (−)-methyl α-hydroxy-α-trifluoromethylphenylacetate (neat) and (+)-methyl α-methoxy-α-trifluoromethylphenylacetate (neat), which is converted into (+)-α-methoxy-α-trifluoromethylphenylacetic acid, it follows that all of these have the *R* configuration based on this evidence. Preliminary circular dichroism studies[18] are

(11) Per cent enantiomeric excess (% e.e.) by definition is the per cent excess of the preponderant enantiomer over the racemate.
(12) J. W. Crawford, *J. Chem. Soc.*, 4280 (1965).
(13) D. M. Feigl, Ph.D. Thesis, Stanford University, 1965.
(14) J. W. Crawford, *J. Chem. Soc.*, 2322 (1967).
(15) D. L. Dull and H. S. Mosher, *J. Amer. Chem. Soc.*, **89**, 4230 (1967).
(16) K. T. Dishart and R. Levine, *ibid.*, **78**, 2268 (1956); also commercially available.
(17) W. H. Pirkle and S. D. Beare, *Tetrahedron Lett.*, 2579 (1968). There is a typographical error on page 258; the symbol with formula 2 should be *R*-(−).
(18) W. Voetler and E. Bunnenberg, private communication.

TABLE I

NMR CHEMICAL SHIFTS OF DIASTEREOMERIC ESTERS AND AMIDES OF (+)-α-METHOXY-α-TRIFLUOROMETHYLPHENYLACETIC ACID[a]

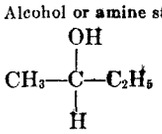
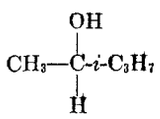
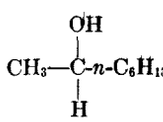
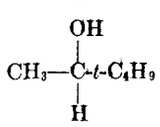
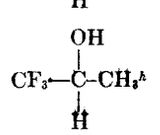
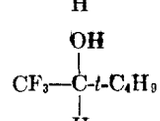
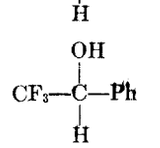
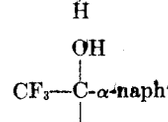
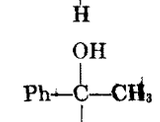
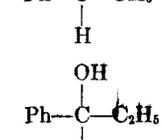
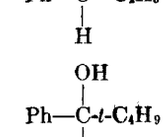
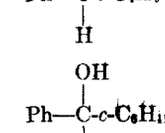
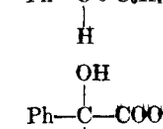
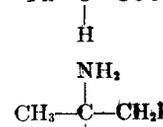
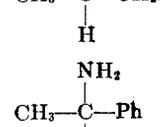
Alcohol or amine structure	Registry no.	Configuration,[b] R or S	Chemical shifts of diastereomers in Hz downfield of TMS or TFA[c]				
			CF_3	OCH_3	H	CH_2	Other
	20445-05-0	R (−)	539	214[d]	306	73	56[e]
	20445-06-1	S (+)	532	216	306	79	48
	20445-07-2	R (−)	581	212[d]	299.5	72.3	55.5[f]
	20445-08-3	S (+)	565	214	299.5	77	51
	20445-09-4	R (−)	576	213	278	...	...
	20445-10-7	S (+)	546	213	278	...	...
	20445-11-8	R (−)	601	211[d]	292.3	71.2	53.8[g]
	20445-12-9	S (+)	581	214	294.3	75.3	51
	20445-13-0	R (+)	422	212	328	82.5	−240[i]
	20445-14-1	S (−)	395	209	328	89.5	−265
	20445-15-2	...	600	216	318	...	53[g]
		...	600	210	320	...	58
	20445-16-3	S (+)	551	208	381.2	...	−1106[i,j]
	20445-45-2	R (−)	501	216	376.8	...	−1086
	20445-17-4	...	562	208	...	...	100[i]
		...	495	219	...	...	117
	20445-18-5	...	547	213	366	96.5	...
		...	499	208	369	93	...
	20445-19-6	...	537	206	356.2	...	48.7[e]
		...	501	211	351.5	...	54
	20445-20-9	R (+)[k]	670	209[d]	345.5	...	53[g]
	20445-21-0	S (−)	623	210	337.5	...	56
	20445-22-1	S (−)[k]	−682[i]	210	336	...	...
	20445-23-2	R (+)	−648	205	342	...	...
	20455-46-3	S (+)	270	213	368	...	227[m]
	20455-47-4	R (−)	263	222	368	...	227
	20445-24-3	R (−)	695	192	260	66	...
	20445-25-4	S (+)	648	195	260	70	...
	20445-26-5	R (+)	710	198	308	83.7	...
	20445-27-6	S (−)	687	201	308	87.6	...

TABLE I (*Continued*)

Alcohol or amine structure	Registry no.	Configuartion,[b] R or S	Chemical shifts of diastereomers in Hz downfield of TMS or TFA[c] CF₂	OCH₃	H	CF₃	Other
$CH_3-\underset{\underset{H}{\vert}}{\overset{\overset{NH_2}{\vert}}{C}}-\alpha$-aaphthyl	20445-28-7	(+)	739	195	359	98.5	...
		(−)	695	197	359	101.5	...
$CH_3-\underset{\underset{H}{\vert}}{\overset{\overset{NH_2}{\vert}}{C}}-i\text{-}C_4H_9$	20445-29-8	...	687	204	248	66.0	...
		...	677	204	248	69.5	...
$CH_3-\underset{\underset{Ph}{\vert}}{\overset{\overset{OH}{\vert}}{C}}-CF_3$	20445-30-1	...	575	212	...	131	−462[f]
		...	535	216	...	132.5	−462

[a] See Experimental Section for details of experimental conditions. If an entry is preceeded by a (−), it indicates that the signal was upfield from the TFA standard rather than downfield. The values refer to 94.1 MHz, ^{19}F and 60 MHz, ^1H nmr. [b] The configuration and/or sign of rotation of the alcohol or amine used for preparation of the ester or amide is indicated. No entry indicates that racemic alcohol or amine was used. [c] The diastereomer with furthest downfield α-CF_3 signal is listed first. Where identical values are given for both diastereomers, the differences in chemical shifts was 0.2 Hz or less or the coupling pattern was so complex that small differences which existed could not be determined by direct inspection of the spectra. [d] The assignment of the signals to the appropriate diastereomers was ambiguous and may be reversed. [e] The terminal methyl proton signal of the ethyl group. [f] The terminal methyl proton signal of the isopropyl group. [g] The proton signal of the *t*-butyl group. [h] Carbon tetrachloride solvent used instead of deuteriochloroform. [i] The fluorine signal of the carbinyl trifluoromethyl group. [j] External trifluoroacetic acid standard. [k] See ref 20. [l] *c*-C_6H_{11} represents the cyclohexyl group. [m] The methyl proton signal of the carbomethoxy group.

TABLE II

COMPARISON OF ENANTIOMERIC COMPOSITION DETERMINED BY OPTICAL ROTATION AND NMR ANALYSIS OF DIASTEREOMERIC MTPA DERIVATIVES

Alcohol or amine Structure	Mmoles	Per cent enantiomeric excess[a,b] Optical Rotation	Nmr of MTPA derivative A-60, ^1H	HA-100, ^{19}F
$CH_3CH(OH)C_2H_5$	0.23	82.4	82.0	...
$CH_3CH(OH)$-*n*-C_6H_{11}	2.3	96.1	...	96.5
$CH_3CH(OH)$-*i*-C_3H_7	4.6	95.5	95.0	...
	5.7	95.5	95.0	95.3
$CH_3CH(OH)$-*t*-C_4H_9	0.35	7.8	7.5	...
$CH_3CH(OH)CF_3$	0.48	75.8[e]	75	...
	0.36	97[e]	98	...
$PhCH(OH)CF_3$	5.6	45.2	45.5	...
	0.15	45.2	44.9	...
$PhCH(OH)$-*c*-C_6H_{11}	0.26	78.5	77.5	79.0
$PhCH(OH)$-*t*-C_4H_9	6.7	100	100[d]	...
	0.14	100	100[d]	...
$PhCH(OH)COOCH_3$	0.12	67.1	67.0	67.3
$PhCH(NH_2)CH_3$	25	100	100[d]	100
	0.43	42.2	42.4	...
$PhCH_2CH(NH_2)CH_3$	16	100	100[d]	100
	0.22	100	100[d]	100
$PhCH(NH_2)$-α-Naph	5.8	36.4[c]	35.0	36.0

[a] By definition, per cent enantiomeric excess (% e.e.) equals the per cent of the predominant isomer in excess of the racemate. [b] Proton resonance determined on Varian Associates A-60 spectrometer and ^{19}F resonance determined either on Varian Associates DP-60 (56.4 MHz) or HA-100 (94.1 MHz) spectrometers under conditions given in the Experimental Section. The precision of all determinations was better than ±1%. [c] Composition of the enantiomer mixture was determined by quantitative mixing of the two pure enantiomers. [d] Signals for only one diastereomer observed. [e] Rotation of pure enantiomer based on $\alpha^{24}D$ −6.39° (neat, l = 1) obtained by preparative glpc resolution of the MTPA ester followed by lithium aluminum hydride regeneration.

also best interpreted in terms of the *R*-(+) configuration for (+)-MTPA. However, our experience with aberrant ORD curves for these same derivatives[15] makes it seem at least possible that the same factors which render the ORD data unreliable for establishing the configuration in this particular series might also be operating in these other methods. Therefore we prefer to leave the question of the absolute configuration of the MTPA reagent open until chemical proof, such as that obtained for the secondary trifluoromethylcarbinols,[19] has been obtained.

Experimental Section

Nmr Measurements.—The proton nmr spectra were obtained at 36° on a Varian Associates A-60 spectrometer using, except where otherwise specified, deuteriochloroform solvent and approximately 3% tetramethylsilane (TMS) as an internal standard. The fluorine nmr spectra were obtained with Varian HA-100 (94.1 MHz) and DP-60 (54.6 MHz) spectrometers using a solvent mixture of 80% deuteriochloroform and approximately 20% trifluoroacetic acid (TFA) by volume as an internal standard added immediately prior to making the determination. The precise chemical shift was dependent upon the amount of TFA added; therefore, the values in Table I have been recorded only to the nearest hertz, for fluorine. Although we experienced few difficulties with the potentially destructive trifluoroacetic acid as an internal standard, it might be preferable to use it as an external standard, or to substitute another neutral standard in certain cases. However, the TFA has a significant effect on the chemical shift differences. Thus the α-CF_3 signals are shifted upfield, when the TFA is external, from the position when the TFA is internal. The chemical shift differences between diastereomers are larger when internal TFA is used. The difference for the α-CF_3 signals for the diastereomeric 2-butyl esters (Table I, example 1) is 7 Hz when TFA is internal and 1-2 Hz when external. Determinations of diastereomer ratios were usually based on machine integrals; accurate values were dependent upon very careful machine tuning, although this was less critical for the determinations using the fluorine signals where large chemical shift differences were observed. When proton signals were resolved, measuring relative peak heights gave answers which corresponded to those obtained by machine integration. This procedure was much simpler and was used when it was established that it was reliable in a specific case. The glpc separations and analyses were performed with a Varian Aerograph A-90-P3 instrument using a 30 ft × 3/8 in., 30% STAP column on 60/80 DMGS-W support.

Alcohols and Amines.—Racemic trifluoromethyl-*t*-butylcarbinol,[20] phenyltrifluoromethylcarbinol[20] α-naphthyltrifluoromethylcarbinol[21] were made by lithium aluminum hydride reduction of

(19) H. Peters and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968).
(20) D. M. Feigl and H. S. Mosher, *ibid*, **33**, 4242 (1968).
(21) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **89**, 5485 (1967).

the corresponding ketones. Methylphenyltrifluoromethylcarbinol[7] was made in 89% yield by the action of phenylmagnesium bromide on methyltrifluoromethyl ketone. Other carbinols and both isomers of α-phenylethylamine (Norse Chemical Corporation), α-(1-naphthyl)ethylamine (Aldrich Chemical Co.), and α-benzylethylamine (Mann Research Laboratories) were commercially available. Partially active (+)-phenyltrifluoromethylcarbinol,[20] phenylcyclohexylcarbinol,[22] phenylethylcarbinol,[7] and phenyl-*t*-butylcarbinol[20] were obtained by asymmetric reduction of the corresponding ketones. Optically active methylethylcarbinol,[23] methylisopropylcarbinol,[24] and methyl-*n*-hexylcarbinol[25] were obtained by classical resolutions.

(+)-α-Methoxy-α-trifluoromethylphenylacetic Acid (MTPA) (I).—Phenyl trifluoromethyl ketone (159 g, 0.915 mol, Columbia Organic Chemicals Co.), powdered sodium cyanide (77 g, 1.57 mol) and 1,2-dimethoxyethane (glyme, 400 ml, freshly distilled, bp 85°) were mixed at room temperature and stirred for 1.5 hr. The temperature initially rose to about 40°. Dimethyl sulfate (150 g, 1.12 mol) was added dropwise over a 5-hr period at such a rate that the temperature did not exceed about 60°. Pentane (200 ml) was added to the cooled reaction mixture, the precipitated salts were removed by filtration, the solvent was evaporated, and the residue was distilled to give α-methoxy-α-trifluoromethylphenylacetonitrile (192 g, 97.5% yield, bp 85–89° (20 mm); 39–40° (2 mm), Water (50 ml) was carefully added to a mixture of the nitrile (192 g) and concentrated sulfuric acid (600 ml). After heating the two-layer mixture on the steam bath for 2 hr with occasional shaking, it became homogeneous. It was heated for an additional 4 hr. The hydrolysis mixture was cooled and extracted with a total of 1 l. of a 3:1 mixture of ether–benzene in three portions. The solvent was evaporated to give a dark residue which was vigorously refluxed with sodium hydroxide (120 g in 400 ml of water) for 3 hr. The cooled mixture was extracted with ether (2 25-ml portions from which 18.7 g, 11% yield of amide was recovered upon evaporation) and the aqueous layer acidified with sulfuric acid. The acidified layer was extracted with a 3:1 ether–benzene mixture and the extracts were dried ($MgSO_4$), the solvent evaporated, and the residue was distilled to give MTPA (131.7 g, 63% yield), bp 105–110° (1 mm).

Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.28; H, 3.87. Found: C, 51.24; H, 4.03.

Resolution of α-Methoxy-α-trifluoromethylphenylacetic Acid.—Racemic MTPA (87.3 g), (+)-α-phenylethylamine (45.0 g, $\alpha^{25}D$ 37.34°, neat, l = 1) and ethanol (300 ml) were mixed. The salt which formed immediately was dissolved by heating on the steam bath, and the solution was insulated and allowed to cool slowly without being disturbed for 48 hr. The salt was collected by filtration, washed with a minimum of cold ethanol, and recrystallized twice from ethanol to give 29.0 g, mp 195–198°, $[\alpha]^{26}D$ 59.1 ± 1.1° (*c* 1.32, EtOH). Reprocessing solids from the filtrate gave an additional 14.5 g, $[\alpha]^{19}D$ 62.5 ± 1.6° (*c* 1.23, EtOH). These combined crystals were decomposed with dilute hydrochloric acid and the regenerated acid extracted with ether. The extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue distilled to give the (+) was acid, 28.6 g, bp 116–118° (1.5 mm), $[\alpha]^{25}D$ 68.5 ± 1.3° (*c* 1.49, CH_3OH). The more soluble salt fractions were decomposed in the usual manner and the isolated acid treated with (−)-α-phenylethylamine (30 g, $[\alpha]^{25}D$ −36.34°, neat l = 1) in ethanol (230 ml). Processing the salt as above gave a total of 55.4 g, $\alpha^{28}D$ −60° ± 2° (*c* 1, EtOH) which was decomposed as above to give 34.7 g, bp 115–117° (1.5 mm), $[\alpha]^{24}D$ −71.8 ± 0.6° (*c* 3.28, CH_3OH). The total recovery on the resolution was 72%.

α-Methoxy-α-trifluoromethylphenylacetyl Chloride (II).—(+)-MPTA (41.0 g), thionyl chloride (75 ml, distilled practical grade) and sodium chloride (0.5 g) were refluxed together for 50 hr. After excess thionyl chloride was removed by vacuum evaporation, the residue was distilled to give 43.8 g, 90% yield, bp 54–56° (1 mm), $[\alpha]^{24}D$ 129.0 ± 0.2 (*c* 5.17, CCl_4), $\alpha^{25}D$ −10.0 ± 0.1° (neat, l = 1). Shorter reaction times result in a second higher-boiling product, bp 130–155° (1 mm), which was identified as the anhydride.

2,2,2-Trifluoroacetophenone Cyanohydrin.—The following procedure was used when the cyanohydrin was isolated. A solution of 81.6 g (1.23 mol) of potassium cyanide in 300 ml of water and 60 ml of ethanol in a 2-l flask was kept between 0 and 5° while 216 g (1.22 mol) of 2,2,2-trifluoroacetophenone (Peninsular Chemical Research) was added dropwise with stirring over a period of 40 min. A solution of 72 ml of 96% sulfuric acid and 180 ml of water was added with maintenance of the temperature below 10°. After the mixture had warmed to room temperature, it was extracted with ether. After drying ($MgSO_4$), the ether was evaporated to give a solid residue which was recrystallized from hexane: 208.7 g (83% yield); mp 75–77°; ir ν_{max}^{KBr} 3380, 1450, 1260, 1210, 1175, 1125, 1010, 930, 760, 740, and 695 cm^{-1}.

Anal. Calcd for $C_9H_6F_3NO$: C, 53.73; H, 3.06; N, 6.96. Found: C, 53.45; H, 2.85; N, 6.79.

α-Hydroxy-α-trifluoromethylphenylacetamide.—2,2,2-Trifluoroacetophenone cyanohydrin (138 g, 0.68 mol) was dissolved in 96% sulfuric acid (1.5 l) at room temperature. After 15 min, the solution was poured onto ice and the product extracted with ether. The extract was washed with water, dried ($MgSO_4$), and the ether removed to give, after recrystsllization from hexane–benzene, 134.6 g (83% yield) of the amide: mp 102–103°; ir ν_{max}^{KBr} 3530, 3400, 3200, 1700, 1570, 1260, 1190, 1170, 980, 950, 750, and 700 cm^{-1}.

Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.67. Found: C, 49.40; H, 3.73.

α-Hydroxy-α-trifluoromethylphenylacetic Acid.—A solution of α-hydroxy-α-trifluoromethylphenylacetamide (107.5 g) in water (700 ml) containing potassium hydroxide (132 g) was refluxed for 4.5 hr. The amide is acidic enough so that it dissolves in the base, and the progress of the hydrolysis was followed by noting ammonia evolution. The cooled solution was poured onto ice and hydrochloric acid. The product was extracted with ether, dried ($MgSO_4$), and recrystallized from benzene: 92.5 g (85%); mp 110.5–111.5°; ir ν_{max}^{KBr} 3400, 3060, 1740, 1210, 1180, 1120, 1000, 950, and 700 cm^{-1}.

Anal. Calcd for $C_9H_7F_3O_3$: C, 49.10; H, 3.20. Found: C, 49.35; H, 3.25.

Alternatively, the acid can be obtained by direct hydrolysis of the nitrile by heating it with 12 times its volume of concentrated hydrochloric acid for 4 hr at 110° in a Carius tube: yield 84%.

Resolution of α-Hydroxy-α-trifluoromethylphenylacetic Acid with (+)-α-(1-Naphthyl)ethylamine.—A mixture of 22.0 g (0.1 mol) of racemic α-hydroxy-α-trifluoromethylphenylactic acid and 17.2 g (0.1 mol) of (+)-α-(1-naphthyl)ethylamine (Aldrich Chemical Co.), $\alpha^{20}D$ 81.35° (neat, l = 1) in 80 ml of 6:1 benzene-ethanol was prepared. Heat was evolved and the salts precipitated immediately. Two recrystallizations of this material from the same solvent system gave 7.5 g of salt, $[\alpha]^{22}D$ 15.5 ±1.2° (*c* 1.68, ethanol). In a trial resolution, material with this rotation remained unchanged on further recrystallization. Decomposition of this fraction with dilute hydrochloric acid and recrystallization of the product from hexane–benzene gave, in three fractions, 4.09 g, mp 123–124°. All fractions had $[\alpha]^{20}D$ −22.5 ± 0.7° (*c* 2.70, chloroform), $[\alpha]^{20}D$ 31.1 ± 0.7° (*c* 2.76, water) within experimental error, indicating that the initial product was probably stereochemically homogeneous. Concentration of the mother liquors gave two additional salt fractions of 3.09 g, $[\alpha]^{23}D$ 14.3 ± 0.6° (*c* 2.93, ethanol), and 12.6 g, $[\alpha]^{22}D$ 0.0° (*c* 5.5, ethanol). Decomposition of these fractions gave, after recrystallization, 1.0 g, $[\alpha]^{20}D$ −23.2 ± 0.7° (*c* 2.93, chloroform), and 5.4 g, $[\alpha]^{22}D$ 8.8 ± 0.6° (*c* 3.62, chloroform). Decomposition of the remaining salt fractions gave, after recrystallization, 4.3 g, $[\alpha]^{19}D$ 9.3 ± 0.3° (*c* 3.56, chloroform).

A subsequent exploratory resolution with (−)-α-phenylethylamine in methylene chloride was also successful.

Methyl α-Hydroxy-α-trifluoromethylphenylacetate.—A solution of the α-hydroxy acid (92.5 g) in methanol (350 ml) was saturated with dry hydrogen chloride and refluxed for 3 hr; the esterification mixture was cooled, resaturated, refluxed for an additional 2.5 hr, and allowed to stand at room temperature overnight. After distilling the methanol, the residue was taken up in ether, washed with saturated salt solution and sodium bicarbonate, dried ($MgSO_4$), and the product distilled: 82.7 g (84%); bp 86–92° (2–3 mm); ir ν_{max}^{film} 3470, 1745, 1450, 1435, 1300, 1235, 1170, 1125, 1075, 1000, 955, 800, 770, 735, and 710 cm^{-1}.

Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.28; H, 3.87. Found: C, 51.22; H, 4.02.

(22) R. McLeod, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960).

(23) A. W. Ingersoll, *Org. Reactions*, **2**, 403 (1944).

(24) Pickard and Kenyon, *J. Chem. Soc.*, **101**, 620 (1912).

(25) R. L. Shriner and J. H. Young, *J. Amer. Chem. Soc.*, **52**, 3332 (1930).

(+)-α-Hydroxy-α-trifluoromethylphenylacetic acid, $[\alpha]^{19}D$ 9.3° ($CHCl_3$, 40% enantiomerically pure), gave methyl ester (83% yield), $\alpha^{19}D$ 6.90 ± 0.06° (neat, l = 1).

Methyl α-Methoxy-α-trifluoromethylphenylacetate.—A mixture of the α-hydroxy ester (82.7 g), dry silver oxide (98.7 g), methyl iodide (550 g), Dreirite (94 g), and glass beads was stirred vigorously under reflux for 50 hr. The reaction mixture was filtered, the solid was extracted with ether, and the extracts and filtrate were distilled to give 78.5 g, bp 93–96° (4 mm).

Anal. Calcd for $C_{11}H_{11}F_3O_3$: C, 53.22; H, 4.46. Found: C, 53.33; H, 4.60.

Optically active acid, $[\alpha]^{22}D$ 8.8° ($CHCl_3$, 39.1% enantiomerically pure), was converted in 90% yield into (−)-methyl α-methoxy-α-trifluoromethylphenylacetate, $\alpha^{20}D$ −48.64 ± 0.04° (neat, l = 1), $[\alpha]^{21}D$ −37.5 ± 0.02° (c 4.48, acetone).

Racemic methyl ester methyl ether was hydrolyzed by refluxing with a 1:3:16 mixture by weight of potassium hydroxide, ethanol, and water for 45 min to give α-methoxy-α-trifluoromethylphenylacetic acid identical with that obtained by the direct procedure. There was no racemization of the optically active methyl ester methyl ether under the same conditions.

Preparation of Esters and Amides of MTPA.—The synthesis of N′-α-(1-naphthyl)ethyl-α-methoxy-α-trifluoromethylphenylacetamide will illustrate the procedure for the preparation of both esters and amides in gram quantities when only the undistilled acid chloride was available. The synthesis of phenyltrifluoromethylcarbinyl α-methoxy-α-trifluoromethylphenylacetate will illustrate the procedure, used for the preparation of milligram amounts, which is recommended as a general procedure for use in determining the enantiomeric composition of either alcohols or amines. Purification of the final product, if required, can be done either by preparative glpc, by column chromatography on silica gel using benzene solvent, or by preparative tlc. Separation of diastereomers can take place by these methods, and care must be exercised that both isomers are completely collected. All key compounds gave satisfactory analyses, and all compounds gave spectra consistent with their assigned structures, taking into consideration nmr nonequivalence of diastereotopic groups.

N-α′-(1-Naphthyl)ethyl-α-methoxy-α-trifluoromethylphenylacetamide.—A sample of partially active (−)-α-naphthylethylamine, 1.09 g, $[\alpha]^{24}D$ −37.32° (c 7, EtOH), was added to a mixtur of undistilled MTPA Cl (prepared by refluxing 3.7 g of (+)-MTPA and excess thionyl chloride for 5 hr and then removing the excess thionyl chloride *in vacuo*) dissolved in carbon tetrachloride (17 ml) and pyridine (5 ml). The mixture was refluxed for 90 min and the crude product (2.6 g) isolated by acidifying, extracting, washing with base, drying, and evaporating the solvent. A sample was removed for nmr analysis (Table I) and the remainder recrystallized from hexane–benzene.

Anal. Calcd for $C_{22}H_{20}NF_3O_2$: C, 68.23; H, 5.17; N, 3.62. Found: C, 68.35; H, 5.32; N, 3.60.

Before recrystallization of the product, both nmr and ir spectra showed that acid anhydride was present (*cf.* Figure 2A).

Phenyltrifluoromethylcarbinyl α-Methoxy-α-trifluoromethylphenylacetate.—Phenyltrifluoromethylcarbinol [0.0262 g, 0.148 mmol, $\alpha^{25}D$ 18.51° (neat, l = 1)] and distilled (+)-MTPA Cl (0.0379 g, 0.15 mmol) were mixed with carbon tetrachloride (5 drops) and dry pyridine (5 drops) and allowed to stand in a stoppered flask for 12 hr. Water (1 ml) was added and the reaction mixture transferred to a separatory funnel with ether (20 ml). The ether solution, after washing successively with dilute hydrochloric acid, saturated sodium carbonate solution, and water, was dried ($MgSO_4$), filtered, evaporated, and the residue was dissolved in deuteriochloroform for nmr analysis. A larger sample prepared by the same procedure was purified by glc (retention times of the diastereomers 20.0 and 21.8 min, 220°, helium flow rate 94 cm^3/min).

Anal. Calcd for $C_{18}H_{14}O_3F_6$: C, 55.11; H, 3.59. Found: C, 55.34; H, 3.70.

Methylphenyltrifluoromethylcarbinyl α-Methoxy-α-trifluoromethylphenyl Acetate.—When the general procedure was applied to the tertiary alcohol, methylphenyltrifluoromethylcarbinol,[7] the yield was negligible but was 20% when refluxed for 14 hr in excess pyridine. The ester was purified by glpc; the diastereomers had retention times of 20.6 and 22.2 min on a 5-ft × 0.25-in., 20% silicone M rubber column at 155° and a helium flow rate of 64 ml/min.

Methyl-*t*-butylcarbinyl-α-Methoxy α-trifluoromethylphenylacetate.—Methyl-*t*-butylcarbinol (0.036 g, $\alpha^{25}D$ 0.49 ± 0.02° (neat, l = 1), obtained from the asymmetric reduction of methyl *t*-butyl ketone by Grignard reagent from (+)-1-iodo-2-methylbutane,[10] distilled MTPA Cl (0.111 g, from pure (+) acid), and pyridine (0.5 ml) were allowed to stand for 1 hr. Water was added to the cooled mixture which was then extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and dilute sodium carbonate solution, dried ($MgSO_4$), and evaporated to give a residual oil. This oil was analyzed by nmr as reported in Table II.

Methyltrifluoromethylcarbinyl α-Methoxy-α-trifluoromethylphenylacetate.—A sample of methyltrifluoromethylcarbinol (0.0554 g, $\alpha^{19}D$ −4.85° (neat, l = 1) was treated with distilled MPTA-Cl (0.1815 g, prepared from pure (+) acid) and pyridine (0.5 ml) for one hour. Water was added and the mixture extracted with ether (20 ml). The ether extract was washed with dilute hydrochloric acid, sodium carbonate solution, and water, and dried ($MgSO_4$). The residue on evaporation was analyzed both by glpc and nmr as reported in Table II.

Preparative Glpc Resolution of Methyltrifluoromethylcarbinol.—(−)-MTPA (100% e.e.) was converted to the distilled acid chloride. This (−)-MTPA-Cl (12.6 g, 100% e.e. as analyzed by nmr of the (+)-α-phenylethylamide), methyltrifluoromethylcarbinol (6.9 g, Columbia Organic Chemical Company), and carbon tetrachloride (5 ml) were mixed with resulting spontaneous cooling. The solution was cooled to −70°, and dry pyridine (5 ml) was added. The reaction mixture was warmed to room temperature and then heated 1 hr at 100°, cooled, and diluted with ether. The ether extract was washed with dilute hydrochloric acid, dilute sodium carbonate, and water, dried ($MgSO_4$), and distilled to give 9.1 g, bp 71–72° (1 mm). A series of injections of 0.1-ml samples with separate collection of the diastereomers (retention times 48 and 54 min respectively, 30 ft × 3/8 in. STAP column at 150° helium flow rate 55 ml/min) gave the predominant isomer (3.41 g) which by glpc analysis was shown to include 1.5 ± 0.5% of its diastereomer. This mixture was reduced by lithium aluminum hydride in dibutyl ether. The dibutyl ether solution of the product obtained by working up the mixture was distilled and the distillate purified by glpc (SE-30 column 20 ft × 3/8 in., 103°, helium flow rate 58 ml/min, retention time 9.8 min). The glpc purified carbinol was subjected to a vacuum transfer (to preclude the presence of impurities resulting from any "bleeding" of the column) to give (−)-methyltrifluoromethylcarbinol [0.87 g, $\alpha^{25}D$ −6.19 ± 0.02° (neat, l = 1), corrected for e.e., $\alpha^{25}D$ −6.39 ± 0.09°]. This material showed no significant impurities when analyzed on SE-30, STAP, Carbowax 20M-TPA, and 4000 columns. This carbinol (0.0431 g) was reconverted to the MTPA ester using distilled MTPA-Cl 100% e.e. Analysis by both nmr and glpc gave a 99.0:1.0 ± 0.5 diastereomer ratio, thereby confirming the activity of the carbinol and proving that no racemization had taken place during these transformations. The major uncertainty in both determinations is in the base line for the minor component; there cannot be less than 1.0% of the minor component but there might be a maximum of 2.0%.

Registry No.—2,2,2-Trifluoroacetophenone cyanohydrin, 20445-04-9; (+)-I, 20445-31-2; (−)-I, 17257-71-5; II, 20445-33-4; α-hydroxy-α-trifluoromethylphenylacetamide, 20445-34-5; α-hydroxy-α-trifluoromethylphenylacetic acid, 20445-35-6; methyl α-hydroxy-α-trifluoromethylphenylacetate, 20445-36-7; methyl α-methoxy-α-trifluoromethylphenylacetate, 20445-37-8.