MTPA vs MPA in the Determination of the Absolute Configuration of Chiral Alcohols by ^{1}H NMR

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Molecular mechanics, semiempirical (AM1), and aromatic shielding effect calculations and DNMR experiments show that MTPA esters are constituted by three main conformers in close populations due to restricted rotation around the $C_\alpha-CO$ and $C_\alpha-Ph$ bonds. The small predominance of one conformer and the simultaneous operation of aromatic shielding and deshielding effects on the alcohol part, due to the orientation of the Ph ring, explains the small $\Delta\delta^{RS}$ values observed. A graphical description of the aromatic magnetic field distribution in the conformers of MTPA and MPA esters and its use to correlate the average chemical shifts with the absolute stereochemistry is presented. Comparison of MTPA with MPA (two conformers) as reagents for determination by NMR of absolute stereochemistry indicates that MTPA esters are intrinsically limited by the greater complexity of their conformational composition, yield very small $\Delta\delta^{RS}$ values, and are consequently less reliable for configurations assignment of chiral alcohols than MPA or other arylmethoxyacetic acid reagents such as *(R)*- and *(S)*-α-methoxy-α-(9-anthryl)acetic acids.

Introduction

The determination of absolute configuration by NMR is based on the derivatization of the compound to be investigated with the two enantiomers of a chiral reagent, typically an arylmethoxyacetic acid (AMAA), such as methoxyphenylacetic acid (MPA) or methoxytrifluoromethylphenylacetic acid (MTPA, Mosher's reagent), and comparison of the chemical shifts of the resulting diastereomers.[1,2] For the compounds in Figure 1, for example, the influence of the phenyl ring[3] leads to the NMR signals of L_1 and L_2 in the *(R)*-MTPA derivative to differ from those of the *(S)*-MTPA derivative, and the difference[4] $\Delta\delta^{RS} = \delta^R - \delta^S$ can be used to infer the absolute configuration at the chiral center to which L_1 and L_2 are attached. However, since the influence of the aromatic ring of the AMAA reagent depends on its precise orientation with respect to the "substrate" part of the molecule (i.e., the alcohol or amine part in the AMAA esters and amides, respectively), knowledge of the conformational characteristics of the diastereomers is essential if this empirically useful method is to be placed on a sound theoretical basis. Previous work along these lines[5] has led to the development of new AMAAs that are more efficient than MTPA and MPA[5b] and to the identification of more suitable conditions for NMR experiments.[5c] However, since the commercially available reagents MPA and MTPA are currently widely used for determination of absolute stereochemistry, in this paper we compare their fitness for this purpose.

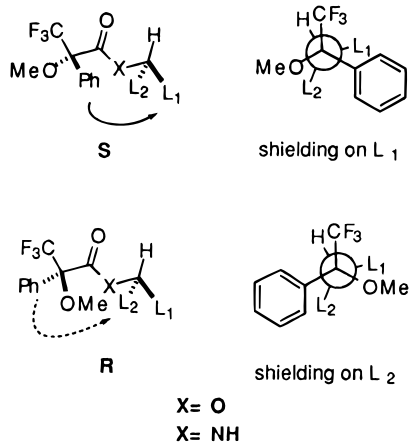

Figure 1.

MTPA is one of the most popular chirality recognition reagents,[6] probably because the quaternary character of its chiral center suppresses the risk of racemization[7] and because it allows stereochemistry to be studied by ^{19}F NMR[2a,8] as well as ^{1}H NMR spectroscopy. Quite fre-

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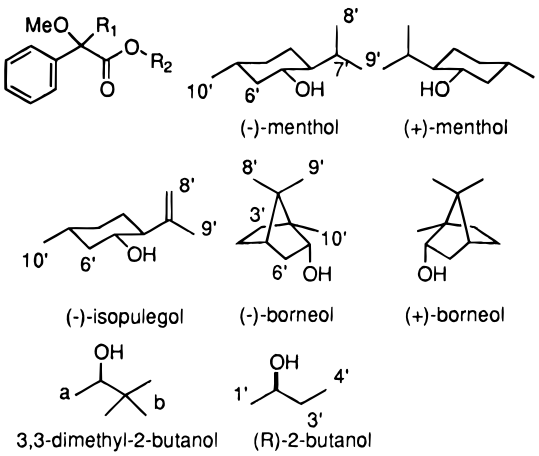

R_1	R_2	Compound[10]
CF_3	H	MTPA
H	H	MPA
CF_3	methyl	**1**
CF_3	3,3-dimethyl-2-butane	**2a**
H	3,3-dimethyl-2-butane	**2b**
CF_3	i-propyl	**3a**
H	i-propyl	**3b**
CF_3	(-)-menthyl	**4**
H	(-)-menthyl	**5**
CF_3	(-)-bornyl	**6**
CF_3	(-)-isopulegol	**7**
CF_3	(R)-2-butane	**8**
H	(-)-bornyl	**9**
H	(-)-isopulegol	**10**
H	(R)-2-butane	**11**
CF_3	(+)-bornyl	**12**
CF_3	(+)-menthyl	**13**
H	(+)-menthyl	**14**
H	(+)-bornyl	**15**

Figure 2.

quently, however, MTPA gives very small $\Delta\delta^{RS}$ values. When applied to alcohols the $\Delta\delta^{RS}$ obtained with MTPA are almost always smaller than those obtained with MPA. Such small separations of resonances make inference of chirality risky because solvent and concentration effects could well attain similar magnitudes, and indeed, some unexpected ^{1}H NMR results with MTPA have been reported.[9] In this paper, we explain the limitations of MTPA in comparison with MPA, on the basis of molecular mechanics, semiempirical and aromatic shielding effect calculations, and DNMR experiments on their esters (Figure 2).

Calculations

An MM study of rotation around the $C_\alpha-CO$ bond of the MTPA ester of methanol **(1)** found, as in the case of MPA esters,[5a] two low-energy rotamers: One *(sp)* with the $C_\alpha-CF_3$ and C=O groups synperiplanar and the other *(ap)* with those groups antiperiplanar (Figure 3). Earlier experimental and theoretical estudies[5a] suggested that in the $L_1L_2CHOC=O$ fragment the preferred conformers are those where the C(1′)−H bond is *gauche* to the O−CO bond and the C(1′)−O bond is *trans* to the $CO-C_\alpha$. Rotation around the $C_\alpha-Ar$ bond showed no clear preference for any particular ring orientation, whereas in MPA esters, the phenyl ring is in same plane as C−H (see Figure 3). However, more precise semiempirical calculations (AM1) on **1** identified three low-energy rotamers: one *ap* form *(ap1)* with the aryl ring coplanar with $C_\alpha-$OMe and two sp forms, *sp1* and *sp2*, that differ in the orientation of the aryl ring with respect to the $C_\alpha-CO$ bond. In these three low-energy conformations of MTPA esters, the $C_\alpha O-Me$ bond was found to be oriented in the same way as in MPA esters,[5] i.e., *anti* to the $C_\alpha-Ar$. These three forms are very close in energy and therefore must have almost equal populations. Table 1 lists the energy data for the more stable conformers and includes, for comparative purposes, those of *ap3* and *sp3* (see Figure 3) that are higher in energy.

Table 1. Calculated AM1 Data for the Main Conformers of the MTPA Ester of Methanol (1)

conformn	ΔE (kcal/mol)	Ph ring plane coplanar with
sp1	0.11	$C_\alpha-$OMe
sp2	0.00	$C_\alpha-$CO
sp3	2.05	$C_\alpha-CF_3$
ap1	0.01	$C_\alpha-$OMe
ap3	1.43	$C_\alpha-CF_3$

The data in Figure 4 show that the protons of substituent L_2 in the *(R)*-MTPA ester should be shielded by the aryl ring in rotamer *sp1* but deshielded in rotamer *sp2*, and those of substituent L_1 should be deshielded in rotamer *ap1* (Figure 4a and Table 1). In the conformers of the *(S)*-MTPA ester, the effects suffered by L_1 and L_2 are interchanged with respect to the *(R)*-ester. Thus, in the MTPA esters the shielding or deshielding effects in conformers *sp1* and *sp2* partially canceled each other, and the most marked effect in the ^{1}H NMR should be deshielding due to conformer *ap1*.

This situation is markedly different from that of MPA esters[5a] that have only two conformers, *ap* and *sp* (Figures 3 and 4b): In the *(R)*-MPA esters, L_1 is shielded and L_2 unaffected in *sp*, and L_2 is shielded and L_1 unaffected in *ap*. In keeping with the foregoing, all NMR signals for the alcohol part of the *(R)*- and *(S)*-MTPA esters of 3,3-dimethyl-2-butanol **(2a)**[2a] and 2-propanol **(3a)**[5b] lie downfield from the corresponding signals of the corresponding MPA esters **(2b, 3b)** (Figure 5). It is important to stress the overall deshielding effect of MTPA because deshielding effects have always been neglected in the interpretation of the NMR spectra of MTPA and MPA derivatives.

The mutual cancellation of the aromatic anisotropy effects of *sp1* and *sp2*, together with the fact that deshielding is usually smaller in magnitude than shielding, explains the observed small $\Delta\delta^{RS}$ values of MTPA esters and implies a degree of uncertainty in the interpretation of NMR shifts, which depends on the extent of that cancellation.

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(10) For simplification purposes and in coherence with previous papers (see ref 5), we will refer to these compounds by *(R/S)*-n, where *(R/S)* indicates the configuration at the chiral center of the auxiliary reagent (MPA or MTPA) and *n* is the digit that identifies the parent alcohol.

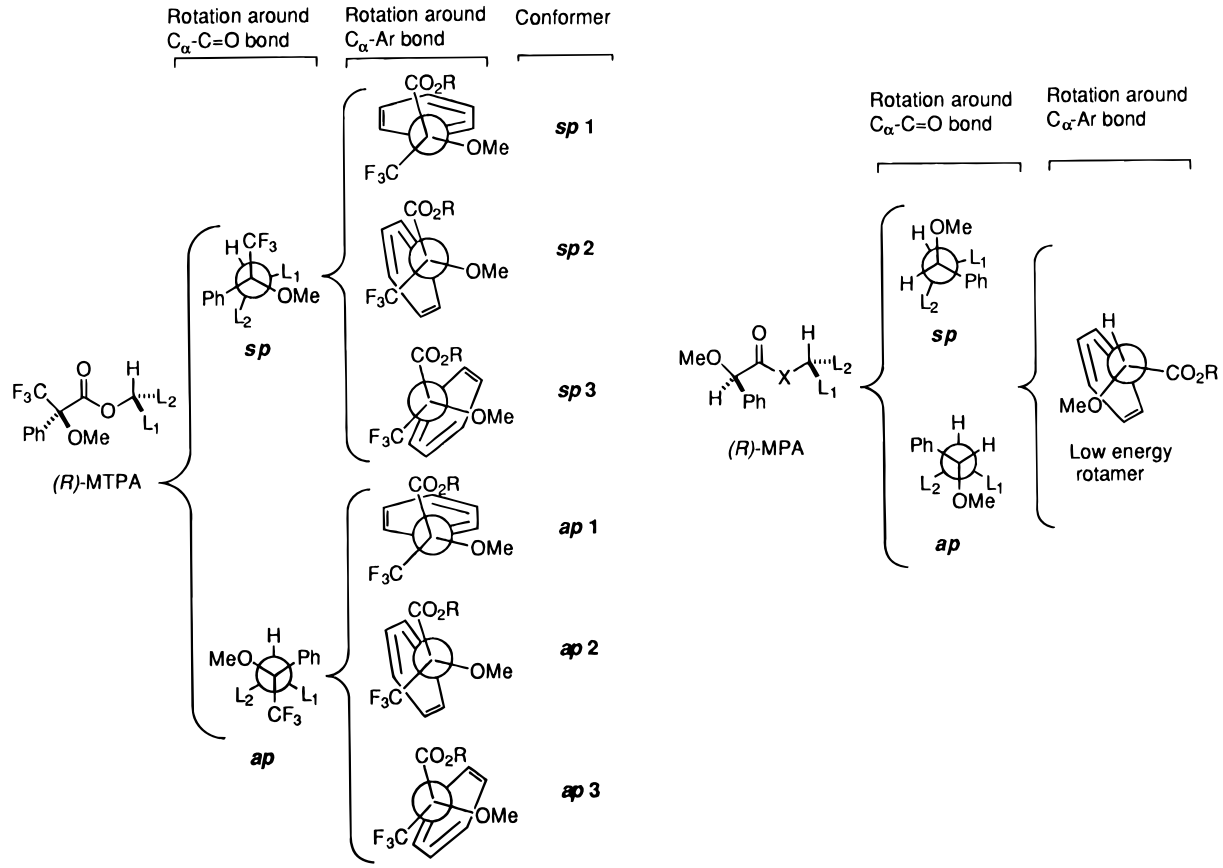


Figure 3. Energy-minimized conformations of *(R)*-MTPA and *(R)*-MPA esters. Newman projections along the C_α−CO bond (*sp* and *ap* conformers) and C_α−Ph bond (*sp1* and *sp3* and *ap1* to *ap3*).

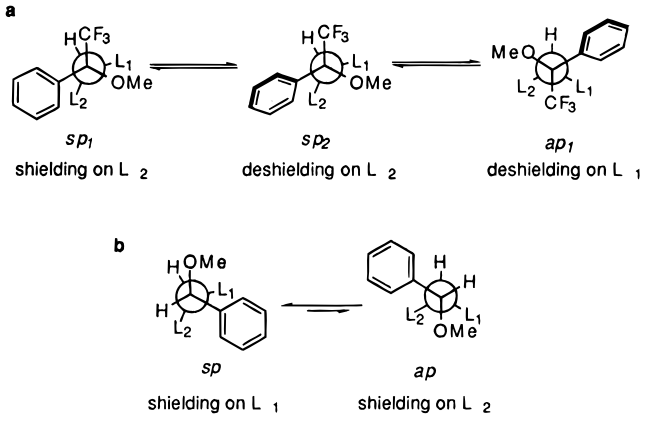


Figure 4. Low-energy conformations of (a) *(R)*-MTPA and (b) *(R)*-MPA methyl ester, as obtained by MM and AM1.

DNMR

The energy gaps among the three low energy conformers of **1** predicted by AM1 calculations (Table 1) suggested that changing their relative populations by varying temperature should cause changes in average NMR chemical shifts that could be predicted in the light of, and would therefore test, the above conclusions concerning the individual and joint effects of the conformers. As suitable test compounds for DNMR we chose the *(R)*- and *(S)*-MTPA derivatives of (−)-menthol (*(R)*-**4** and (*S*)-**4**), which have the advantages of easily identified NMR signals and unambiguous location of the protons affected by the aromatic ring in each rotamer.

Two additional reasons for selecting compounds **(4)** and (a) that AM1 calculations reproduced basically the same low-energy conformers and relative populations as for the methyl ester **(1)** (Table 2) and (b) that for the three low-energy conformers the predicted aromatic shielding or deshielding effects on H7′, H8′, and H9′ ($\Delta\sigma$ in Table 2, ring current increments calculated by a semiclassical model[3]) were sufficiently different, although smaller than those found for MPA esters, as to suggest that their contributions could be evaluated from the NMR spectrum of the equilibrium mixture.

Compound	R	Config.*	δa	δb
2a	CF_3	R,S	1.27	0.87
		R,R	1.20	0.90
2b	H	R,S	0.96	0.85
		R,R	1.13	0.65
3a	CF_3		1.35	1.28
3b	H		1.22	1.11

* Configuration at the acid and the alcohol chiral centre respectively

Figure 5.

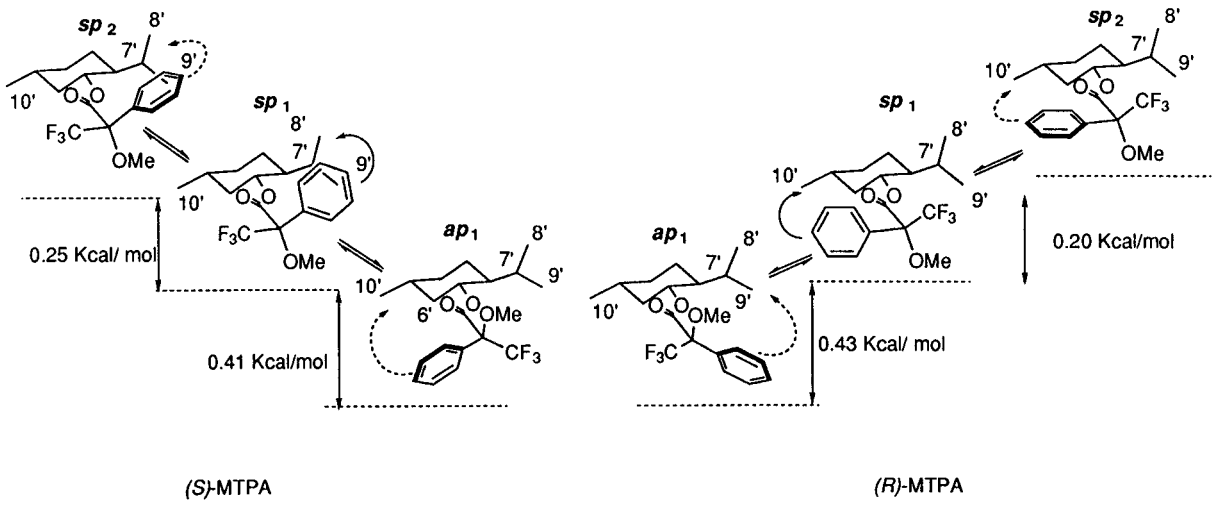


Figure 6. Equilibrium between the *sp* and *ap* rotamers of the *(S)*- and *(R)*-MTPA esters of menthol. Plain arrows show shielding effect and dashed arrows deshielding.

Table 2. AM1 Relative Energies[a] and Aromatic Ring Current Increments Calculated for the Low-Energy Conformers of *(R)*- and *(S)*-MTPA Esters of (−)-Menthol (4)

config	conformn	ΔE (kcal/mol)	$\Delta\sigma(7')$	$\Delta\sigma(8')$	$\Delta\sigma(9')$
	sp1	0.41			
R	*sp2*	0.66			
	ap1	0.00	−0.3[b]	−0.1[b]	−0.2[b]
			−0.1[c]	−0.03[c]	−0.06[c]
	sp1	0.43	1.5[a]	0.45[a]	0.3[a]
S	*sp2*	0.63			
	ap1	0.00			

[a] In kcal/mol. [b] Shielding increments (in ppm) calculated by semiclassical model. [c] Idem by quantum mechanical model.

Table 3. Selected ^{1}H NMR Chemical Shifts (ppm) of *(S)*- and *(R)*-MTPA-Ester of (−)-Menthol (4) (in CS2/CD2Cl2-4/1)

conf	*T* (K)	H(6′e)	H(6′a)	H(7′)	Me(8′)	Me(9′)	Me(10′)
S	298	2.071	1.059	1.487	0.723	0.619	0.952
S	183	2.091	1.101	1.235	0.678	0.597	0.963
R	298	2.017	0.900	1.863	0.878	0.757	0.918
R	183	2.054	0.785	1.931	0.890	0.759	0.897

The calculations for the MTPA esters of **4** predict the presence of three conformers in equilibrium, *ap1*, *sp1*, and *sp2* with a slight predominance of *ap1* (Figure 6). In consequence, the ^{1}H-NMR spectrum of *(S)*-**4**, for example, should show deshielding of protons at positions 6′ and 10′ due to the contribution of conformer *ap1* (those protons lie in the phenyl plane), slight shielding of protons 7′, 8′, and 9′ due to *sp1*, and the opposite effect on the same protons due to *sp2*, and these effects should be enhanced at low temperature.

The DNMR data at 298 and 183 K (Table 3) corroborate these predictions. The signals of H(6′a), H(6′e), and Me(10′) in *(S)*-**4** shift to lower field due to the increased population of conformer *ap1*, and those of protons H(7′), Me(8′), and Me(9′) shift to higher field because of the enhanced predominance of *sp1* over *sp2* (the reverse in *(R)*-**4**).[11]

The extent of this deshielding of H(6′a), H(6′e), and Me(10′) in *(S)*-**4** can be judged by comparison with their signals in the NMR spectrum of the corresponding MPA ester *(R)*-**5** at 153 K (δH(6′a) = 1.10, δ(H6′e) = 2.09, and δ(Me10′) = 0.96 ppm *vs* 0.90, 1.90, and 0.89, respectively[12a]), which at this temperature is constituted almost exclusively by a single rotamer, *sp* (Figure 7), in which H(6′a), H(6′e), and Me(10′) are unaffected by the shielding cone of the aromatic ring.

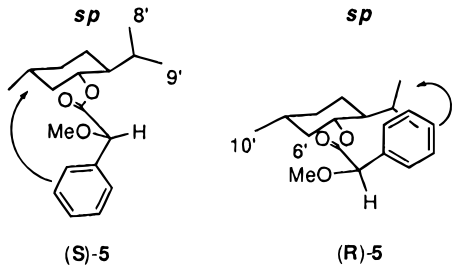


Figure 7. Low-energy rotamers of *(R)*- and *(S)*-MPA esters of (−)-menthol. Shielding effects shown by arrows.

An analogous reasoning applies to the *(R)*-MTPA ester *(R)*-**4**: at low temperature the increased population of *ap1* shifts the H(7′), Me(8′), and Me(9′) signals to lower field, and the increased predominance of *sp1* over *sp2* shifts the H(6′a) and Me(10′) signals to slightly higher field. In this case the extent of the deshielding of H(7′), Me(8′), and Me(9′) can be judged by comparison with their signals in the spectrum of *(S)*-**5** (1.87, 0.895, and 0.711 ppm, respectively[12b]), at which temperature *(S)*-**5** consists of single rotamer *(sp)* in which these protons are unaffected by the aromatic ring.

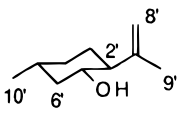
The above NMR data also show that temperature dependence of chemical shifts is much weaker for MTPA esters than for MPA esters. This is because the closer energies of the MTPA conformers (Table 2) mean that temperature-induced changes in conformer populations are smaller than for MPA and implies that contrary to what is observed in the case of MPA esters[13] not much improvement of $\Delta\delta$ values can be achieved by lowering the temperature.

In order to verify that the previous results can be generalized, the MTPA and MPA esters of (−)-isopulegol, (−)-borneol, and *(R)*-butan-2-ol (**6**−**11**, Figure 2) were prepared and their ^{1}H NMR spectra studied. Data in Table 4 show that the resonances of the alcohol part in

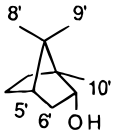
(11) The H(6′e) in *(R)*-**4** and *(S)*-**6**, H(6′a) in *(S)*-**7**, and H(3′) in *(R)*-**8** are affected by the anisotropic effect of the carbonyl, and its interference explains the high-field shift observed at lower anisotropic effect of the carbonyl, and its interference explains the high-field shift observed at lower temperature.

(12) (a) *(R)*-MPA ester of (−)-menthol (in CS_2 + CD_2Cl_2 − 4/1, T = 153 K): $\delta(10')$ = 0.898, δ(6′eq) = 1.9, and δ(6′ax) = 0.9 ppm. (b) *(S)*-MPA ester of (−)-menthol (in CS_2 + CD_2Cl_2 − 4/1, T = 153 K): $\delta(8')$ = 0.895 ppm, $\delta(9')$ = 0.681 ppm.

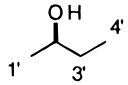
Table 4. Selected Chemical Shifts of *(R)*- and *(S)*-MPA and MTPA Esters of (−)-Isopulegol, (−)-Borneol, and *(R)*-2-Butanol at Room and Low Temperature



(-)-isopulegol



(-)-borneol



(R)-2-butanol

			δ(ppm)			δ(ppm)			δ(ppm)
(R)-MPA	*(R)*-**10**	H(2′)	2.005	*(R)*-**9**	H(8′)	0.845	*(R)*-**11**	H(3′)	1.425
		H(8′)	4.428/4.356[a]		H(9′)	0.815		H(4′)	0.663
		H(9′)	1.340		H(10′)	0.574			
		H(6′)	1.920/0.960[a,b]		H(5′)	1.609[b]		H(1′)	1.149[b]
		H(10′)	0.917[b]	H(6′)	2.254/0.879[a,b]				
(S)-MPA	*(S)*-**10**	H(2′)	2.060[b]	*(S)*-**9**	H(8′)	0.857[b]	*(S)*-**11**	H(3′)	1.520[b]
		H(8′)	4.638/4.606[a,b]		H(9′)	0.656[b]		H(4′)	0.824[b]
		H(9′)	1.550[b]	H(10′)	0.771[b]				
		H(6′)	1.735/0.865[a]		H(5′)	1.560		H(1′)	1.048
		H(10′)	0.878		H(6′)	2.180/0.629[a]			
(R)-MTPA	*(R)*-**7**	H(2′)	2.138 (2.183)[c]	*(R)*-**6**	H(8′)	0.930 (0.924)[c]	*(R)*-**8**	H(3′)	1.654/1.592[a,d] (1.634/1.582)[a,c]
		H(8′)	4.777/4.777 (4.804/4.779)[c]		H(9′)	0.881 (0.906)[c]		H(4′)	0.938 (0.955)[c]
		H(9′)	1.669 (1.662)[c]		H(10′)	0.874 (0.881)[c]			
		H(6′)	1.979/0.936[a] (1.934/0.835)[a,c]		H(5′)	1.665 (1.708)[c]		H(1′)	1.210 (1.193)[c]
		H(10′)	0.934 (0.917)[c]		H(6′)	2.390/0.918[a] (2.444/0.915)[a]			
(S)-MTPA	*(S)*-**7**	H(2′)	2.074 (2.078)[c]	*(S)*-**6**	H(8′)	0.927 (0.922)[c]	*(S)*-**8**	H(3′)	1.565/1.540 (1.569/1.521)[c]
		H(8′)	4.570/4.533 (4.475/4.423)[c]		H(9′)	0.876 (0.887)[c]		H(4′)	0.808 (0.717)[c]
		H(9′)	1.520 (1.494)[c]		H(10′)	0.765 (0.785)[c]			
		H(6′)	2.064/1.122[a,d] (2.041/1.184)[a,c]		H(5′)	1.700 (1.753)[c]		H(1′)	1.300 (1.330)[c]
		H(10′)	0.974 (0.977)[c]		H(6′)	2.404/1.054[a] (2.434/1.034)[a,c] *d*			

[a] eq/ax. [b] See ref 14. [c] Chemical shift at 183 K. [d] See ref 11.

the MTPA esters **6**−**8** are in all cases at lower field than in the corresponding MPA esters.[14] This was already found in the esters of menthol and described as the result of the presence in MTPA of conformers producing deshielding, which are absent in MPA esters.

The NMR taken at low temperature are also in good agreement with the previous results on the conformational equilibrium of MTPA esters (Figure 4a and Figure 6). Thus, the low-temperature NMR data presented in Table 4 show protons H(2′) and H(8′) in the *(R)*-MTPA ester of isopulegol (*(R)*-**7**) and H(6′) and H(10′) in the *(S)*-MTPA ester (*(S)*-**7**) are shifted to lower field as a result of increase of relative population of *ap1*, while protons H(6′) and H(10′) in the *(R)*-MTPA ester and H(7′), H(8′), and H(9′) in the *(S)*-MTPA ester are shifted to higher field due to the increase of *sp1* over *sp2*.

Analogously, the MTPA esters of borneol show a clear lower field shift at low temperature of H(9′) and H(10′) in the *(R)*-MTPA (*(R)*-**6**) and of H(5′) and H(6′) in the *(S)*-MTPA ester (*(S)*-**6**). Similar results are observed in the case of *(R)*-2-butanol. The NMR spectra show shifts to higher field for protons H(4′) in the *(S)*- and H(1) in the *(R)*-MTPA ester ((*S*)-**8** and *(R)*-**8**) and to lower field for H(1) in the *(S)*- and H(4) in the *(R)*-MTPA ester.

Finally, to ensure that the relatively small chemical shift differences reported in this study are not due to associations in solution, we checked the absence of concentration effects and the symmetry of the chemical shifts for enantiomeric pairs. Thus, the NMR spectra of *(R)*- and *(S)*-MTPA esters of (−)-menthol (in $CDCl_3$, T = 300 K) were repeated at concentrations ranging from 1 to 8 mg/mL and found to be practically identical. For its part, the ^{1}H NMR spectra of *(R)*- and *(S)*-MTPA and MPA esters of (+)-borneol **(12, 15)** and (+)-menthol **(13, 14)** were taken and found to be identical to those of their enantiomeric pairs already discussed, proving that solute−solute complexes do not play a role in these results.

Discussion

Quite frequently, researchers use no other criteria to choose between MPA or MTPA as reagents for configuration assignment by NMR than their availability off the shelf. However, the significant differences in conformational composition between MTPA esters and the corresponding MPA derivatives have important consequences for the recognition of configuration.

Esters of MTPA and MPA exhibit similar conformational behavior in regard to rotation around the C_α−CO bond, but the freedom of rotation around the C_α−Ar bond is quite different. In MPA esters, the aryl ring is rotated in such a way (coplanar to C−H (Figure 3)) that shielding

(13) (a) *(S)*-MPA ester of (−)-menthol (in CS_2 + CD_2Cl_2 − 4/1, T = 298 K): $\delta(7') = 1.25$ ppm, $\delta(8') = 0.65$ ppm, $\delta(9') = 0.42$ ppm. (b) *(R)*-MPA ester of (−)-menthol (in CS_2 + CD_2Cl_2 − 4/1, T = 298 K): $\delta(10') = 0.88$ ppm.

(14) Protons H(6′) in *(R)*-**10**, H(5′) and H(6′) in *(R)*-**9**, H(1′) in *(R)*-**11**, H(2′), H(8′), and H(9′) in *(S)*-**10**, H(8′), H(9′), and H(10′) in *(S)*-**9**, and H(3′) and H(4′) in *(S)*-**11** are unaffected by the shielding cone of the phenyl ring, and their chemical shifts are taken as reference for comparison with MTPA esters.

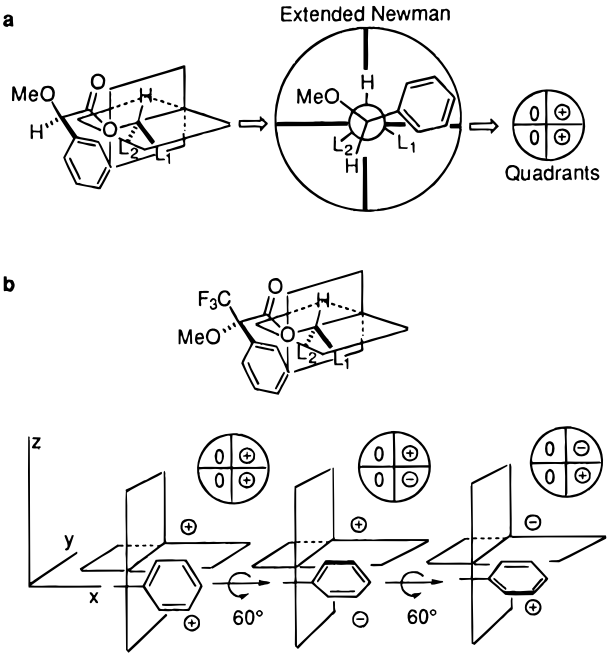


Figure 8.

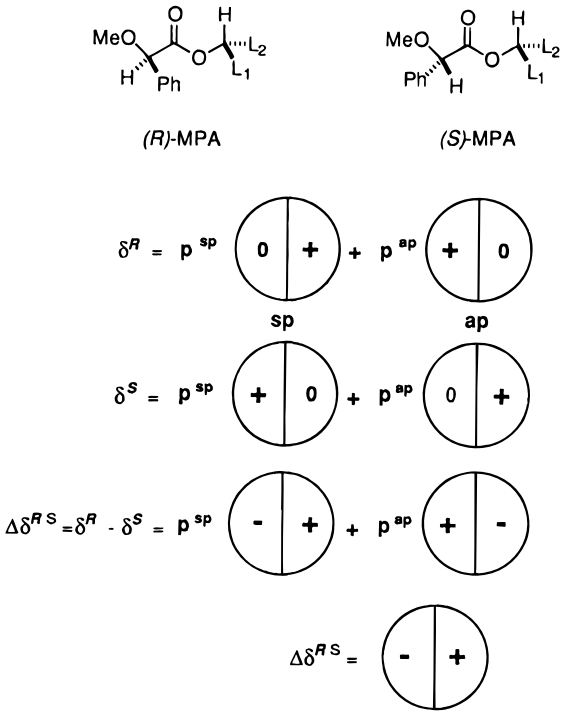


Figure 9.

is the only possible effect on substituents L_1/L_2 (Figure 4a). However, different orientations of the phenyl ring are present in the three representative conformers of the MTPA esters, and so the prediction of the average anysotropic effect is more complex. Figure 8a shows, in perspective and extended Newman projections, the orientation of the aromatic ring for each rotamer, and in quadrants, the distribution of the magnetic field (+ indicates shielding, and 0 no effect).

In accordance with this situation, the chemical shifts of L_1/L_2 in *(R)*- and *(S)*-MPA esters are represented in Figure 9 as a function of the magnetic field distribution, the location of L_1 and L_2 in those quadrants, and the relative population (p) of *sp* and *ap* conformers: Thus, in the *(R)*-MPA ester, L_1 is shielded in conformer *sp* and unaffected in the *ap* while the *(S)*-ester is shielded in the *ap* and unaffected in the *sp*. As the *sp* rotamer is predominant in esters, L_1 will resonate in the *(R)*-MPA ester at higher field than in the *(S)*-MPA ester. Substituent L_2 residues on the other side of the molecule and should therefore resonate in the *(S)*-MPA ester at higher field than in the *(R)*-ester. In MPA amides the predominant rotamer is *ap*, and consequently L_1 in amides takes the place of L_2 in esters and *vice versa*. The classical conformational model used for interpretation of the NMR data of MPA esters and amides and its correlation with the absolute stereochemistry are in fact simplified versions of this scheme where the unaffected region/rotamer are simply not examined.

When restricted rotation around the C_α-Ar bond is considered the resulting spatial distribution of shielding/deshielding areas is more complicated than in MPA. Figure 8b shows in quadrants projected on the $x-z$ plane the expected field distribution (+ indicates shielding, − deshielding, and 0, no effect) when the ring is rotated along the *x* axis in 60° steps.

Application of these concepts to MTPA esters, formed by three main conformers in close populations (see Figure 4a), is shown in the equations of Figure 10 where the chemical shift of a substituent L_1/L_2 is represented as a combination of the field distribution for each conformer and its relative population (*p*). Thus, in the *(R)*-MTPA ester, L_1 is located in the deshielded region (−) in conformer *ap1* and in an unaffected area (0) in *sp1* and *sp2* while in the *(S)*-MTPA ester L_1 is in the shielded area in *sp1* (+), in a deshielded one (−) in *sp2*, and unaffected (0) by the ring anisotropy in *ap1*. In regard to relative populations, we have established that *sp1* is slightly more populated than *sp2*, and therefore the average NMR shows for L_1 a small shift to lower field in the *(R)*-MTPA ester and a very small shift to higher field in the *(S)*-ester: L_1 should resonate in the *(R)*-ester at slightly lower field than in the *(S)*-ester, and $\Delta\delta^{RS}$ has to be small. These predictions are graphically illustrated in Figure 10 and show a perfect coincidence with the experimental data reported in the literature for a large number of MTPA esters.

Conclusions

The determination of the absolute stereochemistry by NMR is based on the selective influence of the aromatic group on the substituents of the substrate so that good knowledge of the structures of the main conformers, their relative population, and contribution to the NMR of the exchange average mixture is necessary to predict the result. Large $\Delta\delta^{RS}$ values and reliable configuration assignments are related to the predominance of one NMR-significant conformer over the others.

In the case of MPA esters these conditions are fulfilled: there are only two main conformers, their populations are sufficiently different and the aromatic field distribution is clear cut. Therefore, the prediction of absolute stereochemistry is straightforward by use of the simplified conformational model that considers only the shielding conformer.

In contrast, in MTPA esters the conformational composition and NMR contribution of each conformer to the average shifts is much more complicated. In MTPA esters, the predominant conformer, *ap*, produces shielding—quantitatively less important than deshielding—and so the values of $\Delta\delta^{RS}$ are so small that slight perturbations of the equilibria due to steric interactions or

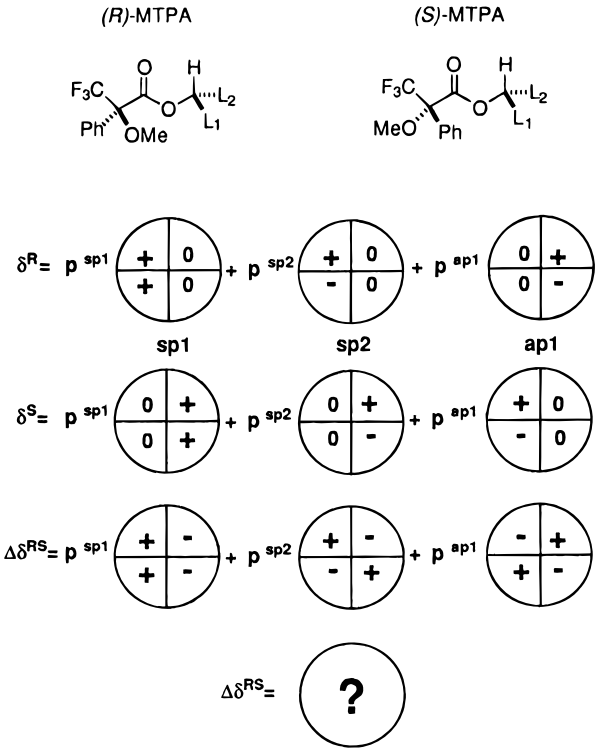


Figure 10.

experimental factors as solvent or concentration effect could affect the balance and therefore the reliability of the prediction of the absolute stereochemistry. A few examples of hindered alcohols where the sign of the shifts observed in the MTPA esters cannot be explained on the basis of the simplified model have been described in the literature.[9]

In conclusion, the use of MTPA is limited by its intrinsic unfavorable conformational characteristics and by the presence of shielding and deshielding effects that partially cancel each other, leading to diminished $\Delta\delta$ values. As a whole, in the case of secondary alcohols, MTPA is clearly less reliable than MPA or the other arylmethoxyacetic acid reagents recently introduced, such as *(R)*- and *(S)*-α-methoxy-α-(9-anthryl)acetic acids.[5]

Experimental Section

Computational Methods. Molecular mechanics (employing the CV force field[15]) and AM1 were performed by the Insight II package on a Silicon Graphics Iris computer. Initial molecular geometries were generated from the Builder Module of Insight II; 3D coordinates were then generated from the bond lengths, bond angles, and dihedral angles by the DG-II package.[16] The conformational space of each compound was scanned by MM optimization of the sterically allowed conformations around key single bonds. Analysis of conformational transitions, identification of the low-energy conformers, and calculation of the energy barriers between these conformers were all carried out by MM with an additional harmonic term of the form $k(1 + \cos(n\theta - \theta_0)$ included in the force field. The energies of conformations were minimized in Cartesian coordinate space by the block-diagonal Newton−Raphson method; minima corresponded to root mean square energy gradients < 0.001 kcal/mol Å. The ground-state energies of the geometries were then calculated by AM1 using the MOPAC 6.0 program. For all compounds, full geometry optimization used the Broyden−Fletcher−Goldfarb−Shanno (BFGS) method and the PRECISE option.[17]

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of samples in 4:1 CS_2/CD_2Cl_2 (4 mg in 0.5 mL) were recorded in Bruker AMX 500 and WM 250 NMR spectrometers. Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) in all cases. The NMR spectra were repeated at concentrations from ca. 8 mg/mL up to ca. 1 mg/mL to prove the absence of concentration effects.

1D ^{1}H NMR spectra: size 32 K, pulse length 2.8 ms (30°), 16 acquisitions.

1D ^{13}C NMR spectra: size 64 K, pulse length 3.5 ms (30°), 1024 acquisitions.

2D COSY spectra: sequence, D1−90−t1−90−t2; relaxation delay D1 = 0.5 s; D2 = 4 ms, 90° pulse, 8.5 μs. 2D NOESY spectrum: sequence, D1−90−t1−90−τ_{min}−90−t2; relaxation delay D1 = 0.5 s; mixing time (τ_{mix}) 0.5 s; 90° pulse 8.5 μs; TPPI-mode, NS = 64.

For DNMR spectroscopy, the probe temperature was controlled by a standard unit calibrated with a methanol reference; samples were allowed to equilibrate for 15 min at each temperature before the spectra were recorded. To ensure that cooling−heating cycles are reversible, ^{1}H NMR spectra were repeated at room temperature immediately after the low-temperature experiments.

General Procedures. Preparation of diastereomeric esters from the alcohol and *O*-methylmandelic acid and methoxy-2-(trifluoromethyl)phenylacetic acid was carried out with DCC−DMAP (esters).[2b] The reaction mixture was filtered to remove the dicyclohexylurea and the ester purified by flash chromatography on silica gel, eluting with dichloromethane. Further purification was accomplished by HPLC (μ-Porasil, 3 mm × 250 mm, hexane−ethyl acetate).

(−)-Menthyl (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetate ((*S*)-4: HPLC t_R = 9.73 min (hexane−ethyl acetate, 96−4, 2 mL/min, μ-Porasil); [α] = −61.5 (*c* = 0.005, Cl_3CH); ^{1}H NMR (500.13 MHz, $CS_2Cl_2CD_2$ (4:1)) δ (ppm) 7.42−7.27 (m, 5H), 4.77 (ddd, *J* = 4.32, 10.81 Hz, 1H), 3.49 (s, 3H), 2.07 (m, 1H), 1.71−1.62 (m, 2H), 1.54−1.45 (m, 2H), 1.38−1.32 (m, 1H), 1.09−0.98 (m, 2H), 0.95 (d, *J* = 6.56 Hz, 3H), 0.92−0.83 (m, 1H), 0.72 (d, *J* = 7.03 Hz, 3H), 0.62 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 15.5, 20.5, 21.9, 22.8, 35.3, 31.4, 34.0, 40.5, 46.7, 55.4, 77.2, 125.8, 127.2, 128.3, 129.5, 132.8, 166.2; IR (NaCl) 2955, 2870, 1741, 1257, 1171, 1120, 1081, 996, 949 cm^{-1}; MS (E/I) *m*/*z* 372 (M^+).

(−)-Menthyl *(R)*-methoxy-2-(trifluoromethyl)phenylacetate ((*R*)-4): HPLC t_R = 9.87 min (hexane−ethyl acetate, 96−4 mL/min, μ-Porasil); [α] = −10.2 (*c* = 0.026, Cl_3CH); ^{1}H NMR (500.13 MHz, $CS_2 + Cl_2CD_2$ (4:1)) δ (ppm) 7.40−7.28 (m, 5H), 4.76 (ddd, *J* = 4.32, 10.86 Hz, 1H), 3.44 (s, 3H), 2.02 (m, 1H), 1.86 (m, 1H), 1.71−1.66 (m, 2H), 1.52−1.44 (m, 1H), 1.43−1.37 (m, 1H), 1.09−1.01 (m, 1H), 0.93−0.82 (m, 2H), 0.92 (d, *J* = 6.54 Hz, 3H), 0.88 (d, *J* = 7.01 Hz, 3H), 0.76 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 15.5, 20.7, 21.9, 22.8, 25.7, 31.4, 33.9, 40.0, 46.6, 55.3, 77.4, 121.2, 125.8, 127.6, 128.3, 129.5, 132.5, 166.4; IR (NaCl) 2978, 2869, 1732, 1256, 1170, 1120, 1081, 949 cm^{-1}; MS (E/I) *m*/*z* 372 (M^+).

(−)-Bornyl *(R)*-2-methoxy-2-(trifluoromethyl)phenylacetate ((*R*)-6): HPLC t_R = 13.35 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 1.8 (*c* = 0.013, Cl_3CH); ^{1}H NMR (500.13 MHz, $CS_2 + Cl_2CD_2$ (4:1)) δ (ppm) 7.39−7.25 (m, 5H), 4.97 (ddd, *J* = 2.28, 5.65, 9.82 Hz, 1H), 3.47 (s, 3H), 2.39 (dddd, *J* = 3.31, 4.59, 9.82, 14.26 Hz, 1H), 1.78 (ddd, *J* = 3.63, 9.02, 13.26 Hz, 1H), 1.69 (m, 1H), 1.67 (t, *J* = 4.25 Hz, 1H), 1.30−1.20 (m, 1H), 1.07 (ddd, *J* = 4.63, 9.45, 12.13 Hz, 1H), 0.92 (dd, *J* = 3.48, 13.86 Hz, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 13.5, 18.8, 19.5, 26.9, 27.8, 36.5, 44.8, 47.8, 48.7, 55.3, 83.1, 125.8, 127.5, 128.4, 129.5, 132.5, 166.8; IR (NaCl) 2952, 2881, 2121, 1746, 1595, 1487, 1459, 1379, 1266, 1175, 1119, 1080, 1025, 993, 883 cm^{-1}; MS (E/I) *m*/*z* 370 (M^+). Anal. Calcd for $C_{20}H_{25}O_3F_3$: C, 64.83; H, 6.81; O, 12.96; F, 15.4. Found: C, 64.58; H, 7.03; F, 15.65.

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(16) Cioslowski, J.; Kertesz, M. *QCPE Bull.* **1987**, *7*, 159.
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(−)-Bornyl *(S)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(S)*-6): HPLC t_R = 13.57 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = −47.6 (*c* = 0.016, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.44−7.29 (m, 5H), 5.00 (ddd, *J* = 2.19, 3.29, 7.97 Hz, 1H), 3.47 (s, 3H), 2.40 (dddd, *J* = 3.36, 4.48, 9.89, 13.65 Hz, 1H), 1.75 (m, 2H), 1.70 (t, *J* = 4.35 Hz, 1H), 1.22 (m, 2H), 1.05 (dd, *J* = 3.42, 13.87 Hz), 0.93 (s, 1H), 0.88 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 13.2, 18.8, 19.5, 26.9, 27.9, 36.4, 44.8, 47.8, 49.1, 55.3, 82.9, 121.4, 126.0, 127.5, 128.4, 129.5, 132.7, 166.8; IR (NaCl) 2955, 2875, 1747, 1593, 1483, 1460, 1379, 1268, 1175, 1119, 1080, 996, 884, 839, 770 cm^{-1}; MS (E/I) *m*/*z* 370 (M^+); HRMS(EI) $C_{20}H_{25}O_3F_3$ obsd 370.176 53, calcd 370.175 579 Δ*m* 0.95 mu.

***(R)*-2-Methoxy-2-(trifluoromethyl)phenylacetate of isopulegol (*(R)*-7):** HPLC t_R = 13.54 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 37.0 (*c* = 0.024, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.41−7.25 (m, 5H), 4.96 (ddd, *J* = 4.41, 10.91 Hz, 1H), 4.78 (m, 2H), 3.42 (s, 3H), 2.14 (ddd, *J* = 3.83, 12.42, 10.90 Hz, 1H), 1.98 (m, 1H), 1.74 (dq, *J* = 3.02, 13.39 Hz, 1H), 1.70 (m, 1H), 1.67 (s, 3H), 1.54 (m, 2H), 1.39 (dq, *J* = 3.59, 10.23 Hz, 1H), 0.93 (d, *J* = 6.58 Hz, 3H), 0.94 (m, 1H); ^{13}C NMR (62.9 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 20.3, 31.8, 32.2, 34.9, 40.4, 50.8, 77.0, 113.0, 121.5, 126.1, 128.1, 128.6, 129.9, 133.3, 146.5, 165.9; IR (NaCl) 3076, 2951, 2928, 2962, 2119, 1744, 1651, 1496, 1451, 1382, 1263, 1175, 1120, 1085, 1020, 992, 958, 895 cm^{-1}; MS (E/I) *m*/*z* 370 (M^+). Anal. Calcd for $C_{20}H_{25}O_3F_3$: C, 64.83; H, 6.81; O, O 12.96; F, 15.4. Found: C, 64.51; H, 6.63; F, 15.52.

***(S)*-2-Methoxy-2-(trifluoromethyl)phenylacetate of isopulegol (*(S)*-7):** HPLC t_R = 13.51 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = −15.8 (*c* = 0.0105, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.39−7.25 (m, 5H), 4.95 (ddd, *J* = 4.44, 10.93 Hz, 1H), 4.57 (m, 1H), 4.53 (m, 1H), 3.42 (s, 3H), 2.07 (m, 1H), 2.06 (m, 1H), 1.70 (m, 2H), 1.55 (m, 1H), 1.52 (s, 3H), 1.37 (dq, *J* = 3.59, 10.20 Hz, 1H), 1.12 (dd, *J* = 12.01, 23.20 Hz, 1H), 0.97 (d, *J* = 6.53 Hz, 3H), 0.94 (m, 1H); ^{13}C NMR (62.9 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 20.3, 22.8, 331.6, 32.3, 40.9, 55.6, 76.7, 113.0, 128.1, 128.6, 129.8, 145.5, 165.5; IR (NaCl) 3077, 2936, 2863, 2121, 1745, 1639, 1602, 1497, 1452, 1379, 1265, 1166, 1118, 1013, 995, 954, 900, 846, 775 cm^{-1}; MS (E/I) *m*/*z* 370 (M^+); HRMS(EI) $C_{20}H_{25}O_3F_3$ obsd 370.176 81, calcd 370.175 579 Δ*m* 1.23 mu.

***(R)*-2-Butyl *(R)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(R)*-8):** HPLC t*R* = 14.09 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 25.3 (*c* = 0.215, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.42−7.22 (m, 5H), 4.98 (m 1H), 3.47 (s, 3H), 1.65 (m, 1H), 1.59 (m, 1H), 1.21 (d, *J* = 6.25 Hz, 3H), 0.94 (t, *J* = 7.44 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 9.3, 19.3, 28.5, 55.3, 75.3, 121.2, 125.8, 127.4, 128.3, 129.5, 132.7, 166.2; IR (NaCl) 3070, 2974, 2942, 2881, 2845, 1746, 1596, 1456, 1382, 1267, 1175, 1117, 1013, 993, 960, 858, 775, 712 cm^{-1}; MS (E/I) *m*/*z* 290 (M^+). Anal. Calcd for $C_{14}H_{17}O_3F_3$: C, 57.91; H, 5.91; O, 16.54; F, 19.65. Found: C, 57.70; H, 5.78; F, 19.35.

***(R)*-2-Butyl *(S)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(S)*-8):** HPLC t_R = 14.76 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = −42.5 (*c* = 0.012, Cl_3CH; ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.43−7.29 (m, 5H), 4.97 (m, 1H), 3.47 (s, 3H), 1.57 (m, 1H), 1.54 (m, 1H), 1.30 (d, *J* = 6.27 Hz, 3H), 0.81 (t, *J* = 7.47 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 9.6, 18.9, 28.5, 55.3, 75.4, 121.2, 127.5, 128.4, 129.5, 132.7, 166.3; IR (NaCl) 3075, 2970, 2945, 2857, 1747, 1599, 1456, 1385, 1268, 1175, 1117, 1085, 1016, 996, 1963, 857 cm^{-1}; MS (E/I) *m*/*z* 290 (M^+); HRMS(EI) $C_{14}H_{17}O_3F_3$ obsd 290.114 17, calcd 290.112 979 Δ*m* 1.19 mu.

(−)-Bornyl *(R)*-2-methoxy-2-phenylacetate (*(R)*-9): HPLC t_R = 13.06 min (hexane−ethyl acetate, 96−4, 2 mL/min, μ-Porasil); [α] = −70.1 (*c* = 0.007, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.33−7.20 (m, 5H), 4.80 (ddd, *J* = 2.04, *J′* = 3.46, *J″* = 9.99 Hz, 1H), 4.62 (s, 1H), 3.33 (s, 3H), 2.25 (dddd, *J* = 3.34, 4.70, 9.99, 13.58 Hz, 1H), 1.78−1.65 (m, 2H), 1.61 (t, *J* = 4.50 Hz, 1H), 1.18−1.11 (m, 2H), 0.88 (dd, *J* = 3.48, 13.71 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 12.9, 18.6, 19.4, 26.6, 27.7, 36.3, 44.7, 47.6, 48.8, 57.1, 80.3, 82.7, 127.1, 128.4, 128.5, 136.7, 170.9; IR (NaCl) 2982, 2915, 2882, 1748, 1644, 1452, 1387, 1276, 1179, 1113, 1025, 943, 803, 773, 730, 697; MS (E/I) *m*/*z* 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67; O, 15.88. Found: C, 75.46; H, 8.67.

(−)-Bornyl *(S)*-2-methoxy-2-phenylacetate (*(S)*-9): HPLC t_R = 12.81 min (hexane−ethyl acetate, 96−4, 2 mL/min, μ-Porasil); [α] = 12.8 (*c* = 0.013 Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD32 (4:1)) δ (ppm) 7.33−7.20 (m, 5H), 4.77 (ddd, *J* = 2.24, 3.39, 9.86 Hz, 1H), 4.63 (s, 1H), 3.34 (s, 3H), 2.18 (dddd, *J* = 3.33, 4.68, 9.81, 13.68 Hz, 1H), 1.82 (ddd, *J* = 4.43, 9.50, 13.70 Hz, 1H), 1.65 (dddd, *J* = 4.38, 7.75, 16.60 Hz, 1H), 1.56 (t, *J* = 4.57 Hz, 1H), 1.22 (tq, *J* = 2.21, 12.78 Hz, 1H), 0.98 (ddd, *J* = 4.49, 9.51, 12.32 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H), 0.63 (dd, *J* = 3.38, 13.73 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 13.2, 28.6, 19.4, 26.8, 27.6, 36.2, 44.5, 47.7, 48.6, 57.1, 80.6, 82.5, 127.0, 128.4, 136.5, 170.8; IR (NaCl) 2953, 2880, 2823, 1748, 1732, 1452, 1276, 1179, 1113, 1025, 936, 804, 773, 730; MS (E/I) *m*/*z* 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67; O, 15.88. Found: C, 75.45; H, 8.65.

***(S)*-2-Methoxy-2-phenylacetate of isopulegol (*(S)*-10):** HPLC t_R = 18.45 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 15.1 (*c* = 0.066 Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2, Cl_2CD_2 (4:1)) δ (ppm) 7.28−7.18 (m, 5H), 4.73 (ddd, *J* = 4.37, 10.89 Hz, 1H), 4.64 (m, 1H), 4.61 (m, 1H), 4.52 (s, 1H), 3.27 (s, 3H), 2.06 (ddd, *J* = 3.55, 10.83, 12.31 Hz, 1H), 1.74 (dddd, *J* = 1.87, 2.56, 4.44, 12.18 Hz, 1H), 1.65 (m, 2H), 1.56 (m, 3H), 1.45 (m, 1H), 0.88 (d, *J* = 6.55 Hz, 3H), 0.87 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 19.2, 21.8, 30.2, 31.2, 33.9, 39.8, 50.5, 57.2, 74.3, 82.7, 111.9, 127.1, 128.3, 128.4, 136.5, 145.9, 170.1; IR (NaCl) 3076, 3027, 2930, 2868, 2826, 1745, 1650, 1591, 1493, 1456, 1373, 1368, 1262, 1203, 1179, 1113, 1035, 1005, 916, 849, 798, 774 cm^{-1}; MS (E/I) *m*/*z* 302 (M^+); HRMS(EI) $C_{19}H_{26}O_3$ obsd 302.188 12, calcd 302.188 194 Δ*m* = −0.07 mu.

***(R)*-2-Methoxy-2-phenylacetate of isopulegol (*(R)*-10):** HPLC t_R = 20.36 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = −50.8 (*c* = 0.0385, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.27−7.17 (m, 5H), 4.66 (ddd, *J* = 4.38, 10.90 Hz, 1H), 4.53 (s, 1H), 4.43 (m, 1H), 4.36 (m, 1H), 3.28 (s, 3H), 2.01 (ddd, *J* = 3.76, 10.84, n12.49 Hz, 1H), 1.92 (dddd, *J* = 1.88, 3.57, 4.30, 12.13 Hz, 1H), 1.65−1.59 (m, 2H), 1.51−1.43 (m, 1H), 1.34 (m, 3H), 1.29 (dddd, *J* = 3.60, 12.58, 13.44 Hz, 1H), 0.96 (m, 1H), 0.92 (d, *J* = 6.54 Hz, 3H), 0.91 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 19.0, 21.8, 30.5, 31.3, 33.9, 40.3, 50.4, 57.2, 74.6, 82.7, 111.8, 127.3, 128.3, 128.4, 136.5, 145.4, 170.3; IR (NaCl) 3071, 2926, 2867, 1745, 1643, 1587, 1452, 1373, 1262, 1204, 1178, 1113, 997, 891, 850, 733 cm^{-1}; MS (E/I) *m*/*z* 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67; O, 15.88. Found: C, 75.32; H, 8.62.

***(R)*-2-Butyl *(S)*-2-methoxy-2-phenylacetate (*(S)*-11:** [α] = −32 (*c* = 0.0185, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.30−7.21 (m, 5H), 4.74 (m, 1H), 4.57 (s, 1H), 3.32 (s, 3H), 1.52 (m, 2H), 1.05 (d, *J* = 6.26 Hz, 3H), 0.82 (t, *J* = 7.44 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 9.5, 19.1, 28.6, 57.2, 73.2, 82.8, 127.1, 127.3, 128.5, 128.6, 136.55, 170.5; MS (E/I) *m*/*z* 222 (M^+); HRMS(EI) $C_{13}H_{18}O_3$ obsd 222.126 64, calcd 222.125 594 Δ*m* 1.04 mu.

***(R)*-2-Butyl *(R)*-2-methoxy-2-phenylacetate (*(R)*-11):** [α] = 3.4 (*c* = 0.0095, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.30−7.22 (m, 5H), 4.72 (m, 1H), 4.56 (s, 1H), 3.31 (s, 3H), 1.43 (m, 2H), 1.15 (d, *J* = 6.26 Hz, 3H), 0.66 (t, *J* = 7.43 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 9.1, 19.4, 28.5, 57.2, 73.2, 82.7, 127.2, 128.5, 128.6, 136.6, 170.5; MS (E/I) *m*/*z* 222 (M^+). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, H 8.17; O, 21.6. Found: C, 70.38; H, 8.33.

(+)-Bornyl *(R)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(R)*-12): HPLC t_R = 13.61 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 55.2 (*c* = 0.021, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.44−7.29 (m, 5H), 5.00 (ddd, *J* = 2.19, 3.29, 7.97 Hz, 1H), 3.47 (s, 3H), 2.40 (dddd, *J* = 3.36, 4.48, 9.89, 13.65 Hz, 1H), 1.75 (m, 2H), 1.70 (t, *J* = 4.35 Hz, 1H), 1.22 (m, 2H), 1.05 (dd, *J* = 3.42, 13.87 Hz), 0.93 (s, 1H), 0.88 (s, 3H), 0.77 (s,

3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 13.2, 18.8, 19.5, 26.9, 27.9, 36.4, 44.8, 47.8, 49.1, 55.3, 82.9, 121.4, 126.0, 127.5, 128.4, 129.5, 132.7, 166.8; IR (NaCl) 2960, 2875, 1745, 1454, 1373, 1267, 1171, 1118, 1023, 762, 712 cm^{-1}; MS (E/I) *m*/*z* 370 (M^+). Anal. Calcd for $C_{20}H_{25}O_3F_3$: C, 64.83; H, 6.81; O, 12.96; F, 15.4. Found: C, 64.62; H, 6.53; F, 15.52.

(+)-Bornyl *(S)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(S)*-12): HPLC t_R = 13.61 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = −1.3 (*c* = 0.0175, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.39−7.25 (m, 5H), 4.97 (ddd, *J* = 2.28, 5.65, 9.82 Hz, 1H), 3.47 (s, 3H), 2.39 (dddd, *J* = 3.31, 4.59, 9.82, 14.26 Hz, 1H), 1.78 (ddd, *J* = 3.63, 9.02, 13.26 Hz, 1H), 1.69 (m, 1H), 1.67 (t, *J* = 4.25 Hz, 1H), 1.30−1.20 (m, 1H), 1.07 (ddd, 4.63, 9.45, 12.13 Hz, 1H), 0.92 (dd, *J* = 3.48, 13.86 Hz, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 13.5, 18.8, 19.5, 26.9, 27.8, 36.5, 44.8, 47.8, 48.7, 55.3, 83.1, 125.8, 127.5, 128.4, 129.5, 132.5, 166.8; IR (NaCl) 2954, 2875, 1745, 1475, 1453, 1380, 1271, 1159, 1118, 1083, 1025, 1010, 995, 886, 856, 728 cm^{-1}; MS (E/I) *m*/*z* 370 (M^+); HRMS-(EI) $C_{20}H_{25}O_3F_3$ obsd 370.174 37, calcd 370.175 579 Δm −1.21 mu.

(+)-Menthyl *(R)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(R)*-13): HPLC t_R = 12.49 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 61.4 (*c* = 0.0155, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.42−7.27 (m, 5H), 4.77 (ddd, *J* = 4.32, 10.81 Hz, 1H), 3.49 (s, 3H), 2.07 (m, 1H), 1.71−1.62 (m, 2H), 1.54−1.45 (m, 2H), 1.38−1.32 (m, 1H), 1.09−0.98 (m, 2H), 0.95 (d, *J* = 6.56 Hz, 3H), 0.92−0.83 (m, 1H), 0.72 (d, *J* = 7.03 Hz, 3H), 0.62 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 15.5, 20.5, 21.9, 22.8, 35.3, 31.4, 34.0, 40.5, 46.7, 55.4, 77.2, 125.8, 127.2, 128.3, 129.5, 132.8, 166.2; IR (NaCl) 2954, 2863, 1745, 1264, 1173, 1118, 1025, 994 cm^{-1}; MS (E/I) *m*/*z* 372 (M^+). Anal. Calcd for $C_{20}H_{27}O_3F_3$: C, 64.48; H, 7.31; O, 12.89; F, 15.31. Found: C, 64.27; H, 7.34; F, 15.03.

(+)-Menthyl *(S)*-2-methoxy-2-(trifluoromethyl)phenylacetate (*(S)*-13): HPLC t_R = 12.97 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 15.5 (*c* = 0.021, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.40−7.28 (m, 5H), 4.76 (ddd, *J* = 4.32, 10.86 Hz, 1H), 3.44 (s, 3H), 2.02 (m, 1H), 1.86 (m, 1H), 1.71−1.66 (m, 2H), 1.52−1.44 (m, 1H), 1.43−1.37 (m, 1H), 1.09−1.01 (m, 1H), 0.93−0.82 (m, 2H), 0.92 (d, *J* = 6.54 Hz, 3H), 0.88 (d, *J* = 7.01 Hz, 3H), 0.76 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 15.5, 20.7, 21.9, 22.8, 25.7, 31.4, 33.9, 40.0, 46.6, 55.3, 77.4, 121.2, 125.8, 127.6, 128.3, 129.5, 132.5, 166.4; IR (NaCl) 2945, 2864, 1744, 1264, 1175, 1116, 1020, 991 cm^{-1}; MS (E/I) *m*/*z* 372 (M^+); HRMS(EI) $C_{20}H_{27}O_3F_3$ obsd 372.192 31, calcd 372.191 229 Δm 1.08 mu.

(+)-Menthyl *(S)*-2-methoxy-2-phenylacetate (*(S)*-14): HPLC t_R = 19.05 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 107.3 (*c* = 0.042, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.30−7.20 (m, 5H), 4.53 (s, 1H), 4.51 (ddd, *J* = 4.32, 10.81 Hz, 1H), 3.30 (s, 3H), 1.90 (dddd, *J* = 2.08, 3.77, 11.97 Hz, 1H), 1.66−1.61 (m, 1H), 1.56 (dq, *J* = 3.42, 13.34 Hz, 1H), 1.46−1.37 (m, 1H), 1.29−1.20 (m, 2H), 0.98−0.90 (m, 2H), 0.89 (d, *J* = 6.55 Hz, 3H), 0.85−0.76 (m, 1H), 0.65 (d, *J* = 6.91 Hz, 3H), 0.42 (d, *J* = 6.86 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 15.4, 20.4, 21.8, 25.3, 31.2, 34.1, 40.7, 46.9, 57.1, 75.1, 82.7, 127.3, 128.3, 128.5, 136.5, 170.3; IR (NaCl) 2951, 2930, 2868, 2826, 1745, 1672, 1591, 1456, 1389, 1368, 1262, 1203, 1179, 1113, 1035, 1005, 916, 849 cm^{-1}; MS (E/I) *m*/*z* 304 (M^+); HRMS(EI) $C_{19}H_{28}O_3$ obsd 304.203 14, calcd 304.203 844 Δm −0.70 mu.

(+)-Menthyl *(R)*-2-methoxy-2-phenylacetate (*(R)*-14): HPLC t_R = 18.28 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 16.9 (*c* = 0.047, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.30−7.20 (m, 5H), 4.59 (ddd, *J* = 4.38, 10.89 Hz, 1H), 4.57 (s, 1H), 3.31 (s, 3H), 1.74−1.59 (m, 4H), 1.42−1.28 (m, 2H), 1.05−0.95 (m, 1H), 0.85 (d, *J* = 6.37 Hz, 3H), 0.82 (d, *J* = 6.90 Hz, 3H), 0.79 (m, 2H), 0.64 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 16.0, 20.5, 21.7, 23.2, 26.1, 31.2, 34.1, 40.1, 46.7, 57.1, 75.1, 82.7, 126.9, 128.4, 128.5, 136.4, 170.3; IR (NaCl) 2951, 2930, 2868, 2826, 1745, 1672, 1591, 1493, 1456, 1389, 1368, 1262, 1203, 1179, 1113, 1035, 1005, 916 cm^{-1}; MS (E/I) *m*/*z* 304 (M^+). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.95; H, 9.28; O, 15.77. Found: C, 75.24; H, 9.01.

(+)-Bornyl *(S)*-2-methoxy-2-phenylacetate (*(S)*-15): HPLC t_R = 21.41 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = 64.2 (*c* = 0.047, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.33−7.20 (m, 5H), 4.80 (ddd, *J* = 2.04, 3.46, 9.99 Hz, 1H), 4.62 (s, 1H), 3.33 (s, 3H), 2.25 (dddd, *J* = 3.34, 4.70, 9.99, 13.58 Hz, 1H), 1.78−1.65 (m, 2H), 1.61 (t, *J* = 4.50 Hz, 1H), 1.18−1.11 (m, 2H), 0.88 (dd, *J* = 3.48, 13.71 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 12.9, 18.6, 19.4, 26.6, 27.7, 36.3, 44.7, 47.6, 48.8, 57.1, 80.3, 82.7, 127.1, 128.4, 128.5, 136.7, 170.9; IR (NaCl) 3065, 2952, 2880, 2827, 1747, 1590, 1455, 1389, 1306, 1262, 1200, 1183, 1114, 1025, 997, 771 cm^{-1}; MS (E/I) *m*/*z* 302 (M^+); HRMS(EI) $C_{19}H_{26}O_3$ obsd 302.188 07, calcd 302.188 194 Δm −0.12 mu.

(+)-Bornyl *(R)*-2-methoxy-2-phenylacetate (*(R)*-15): HPLC t_R = 21.99 min (hexane−ethyl acetate, 96−4, 2 mL/min, Spherisorb S5W 5 μm); [α] = −17.7 (*c* = 0.066, Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ (ppm) 7.33−7.20 (m, 5H), 4.77 (ddd, *J* = 2.24, 3.39, 9.86 Hz, 1H), 4.63 (s, 1H), 3.34 (s, 3H), 2.18 (dddd, *J* = 3.33, 4.68, 9.81, 13.68 Hz, 1H), 1.82 (ddd, *J* = 4.43, 9.50, 13.70 Hz, 1H), 1.65 (dddd, *J* = 4.38, 7.75, 16.60 Hz, 1H), 1.56 (t, *J* = 4.57 Hz, 1H), 1.22 (tq, *J* = 2.21, 12.78 Hz, 1H), 0.98 (ddd, *J* = 4.49, 9.51, 12.32 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H), 0.63 (dd, *J* = 3.38, 13.73 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 13.2, 28.6, 19.4, 26.8, 27.6, 36.2, 44.5, 47.7, 48.6, 57.1, 80.6, 82.5, 127.0, 128.4, 136.5, 170.8; IR (NaCl) 3064, 2952, 2880, 2826, 1746, 1591, 1455, 1373, 1303, 1262, 1193, 1182, 1114, 1024, 997, 887, 823 cm^{-1}; MS (E/I) *m*/*z* 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67; O, 15.88. Found: C, 75.18; H, 8.33.

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Supporting Information Available: ^{1}H NMR spectra for compounds **4** and **6**−**15** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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