214 (20 850), 247 (34 350), 282 (4550), 334 (4350).

A methanolic solution (10 mL) of **26** (1.0 g, 3.1 mmol) was treated with 2 N NaOH (10 mL) at 0 °C. The resulting solid was collected by filtration and dried to give 750 mg (87%) of analytically pure ammiol: mp 210–212 °C. Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.84; H, 4.34. Found: C, 60.64; H, 4.48.

4,9-Dimethoxy-7-[(dimethylamino)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (27). A methylene chloride solution (50 mL) of 4,9-dimethoxy-7-(iodomethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one (1.19 g, 3.08 mmol) was treated with anhydrous dimethylamine for 5 min. After stirring for 3 h at room temperature, the solution was washed with H_2O (2 × 20 mL) and dried over Na_2SO_4. Evaporation gave an oil which was chromatographed over a Merck B Column in 10% MeOH/$CHCl_3$. Appropriate fractions were combined and the solvent removed in vacuo to give 0.90 g (97%) of a yellow oil which slowly crystallized: mp 107–109 °C; silica gel TLC R_f 0.35 in 10% $CH_3OH/CHCl_3$; IR ($CHCl_3$) 3120, 3080, 3060, 2790, 1650, 1630, 1620, 1595, 1545, 1485, 1385, 1075, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) 7.65 (d, 1 H, J = 2 Hz), 7.03 (d, 1 H, J = 2 Hz), 6.28 (s, 1 H, vinyl), 4.19 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.34 (s, 2 H, $CH_2N(CH_3)_2$) 2.38 (s, 6 H, $N(CH_3)_2$); mass spectrum, ions at m/e (relative intensity) 304 (11), 303 (60), 288 (25), 274 (9), 243 (10), 231 (8), 84 (10), 71 (12), 58 (100); UV (EtOH) λ_{max} (ϵ) 213 (20 300), 248 (35 150), 280 sh (4650), 333 (4450). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.63; H, 5.66; N, 4.66.

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Registry No. 1, 82-02-0; **2**, 93454-52-5; **4**, 668-10-0; **5**, 93454-53-6; **10**, 76301-19-4; **11**, 76301-20-7; **14**, 484-51-5; **15**, 4455-13-4; **16**, 7605-25-6; **17**, 76301-31-0; **18**, 76301-32-1; **19**, 93454-54-7; (*E*)-**20**, 88897-92-1; (*E*)-**21**, 93454-55-8; **24**, 76301-44-5; **25**, 88897-90-9; **26**, 93454-56-9; **27**, 76301-38-7; $MeSCH_2CO_2H$, 4455-13-4; $PhSCH_2CO_2H$, 7605-25-6; $(CH_3)_2NCH(OMe)_2$, 4637-24-5.

(*S*)-Tetrahydro-5-oxo-2-furancarboxylic Acid: A Chiral Derivatizing Reagent for Asymmetric Alcohols

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The use of (*S*)-tetrahydro-5-oxo-2-furancarboxylic (TOF) acid as a potential derivatizing reagent for the determination of the enantiomeric composition of chiral alcohols was investigated. A series of chiral alcohols of widely varying structural type were derivatized with this acid and compared with two widely used acids (*S*)-α-acetoxypropanoic and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic. The resolution of the diastereomeric esters was measured on five different capillary gas chromatographic (CGC) columns and one high-performance liquid chromatographic (HPLC) column. The ^{13}C NMR spectra of these derivatives were recorded and examined for possible correlations between configuration and carbon chemical shift values. The chromatographic data provide a starting point for the selection of a derivatizing agent and column combination applicable to the CGC analysis of chiral alcohol enantiomeric purity, and the HPLC data allow selection of a derivatizing agent and solvent system for the HPLC analytical or preparative resolution of a chiral alcohol. The ^{13}C NMR data provide information applicable to the assignment of the configuration to the resolved diastereomers.

Chiral alcohols and their derivatives are ubiquitous with numerous examples being found in the terpenoid family, the steroids, and particularly the field of insect pheromones.[1,2] Asymmetric alcohols occur as natural products and frequently as intermediates in the synthesis of chiral molecules.[2-12] The determination of the degree of chirality or enantiomeric excess (% ee) is critical both to the successful completion of an asymmetric synthesis and to the understanding of the results obtained from the biological evaluation of a chiral natural product. Many methods have been developed for the determination of the degree of enantiomeric purity of chiral alcohols, and although some preliminary success has been achieved in the direct gas chromatographic (GC) resolution of enantiomeric alcohols with chiral liquid phases,[13,14] the majority of gas chromatographic chiral alcohol resolutions utilize the formation of diastereomers with an enantiomerically pure chiral acid such as α-(alkanyloxy)propanoic,[15,16] α-hydroxy- and α-acetoxyalkanoic,[17] halogen-substituted α-(alkanoyloxy)-alkanoic,[18,19] (*S*)-α-acetoxypropanoic ((*S*)-lactic),[16,20-25] or

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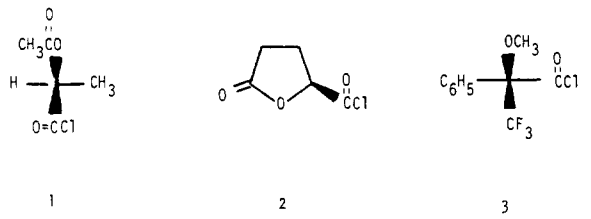
mandelic.[26] In addition *N*-trifluoroacetyl, (TFA)-L-alanyl,[27,28] drimanoyl and *trans*-chrysanthemoyl,[29] 3β-acetoxy-Δ⁵-etienoyl,[30] and 2-phenylpropanoyl[31] acid chlorides also have been utilized to prepare diastereomeric esters from chiral alcohols. Menthyl chloroformate[32] and (*R*)-(+)-1-phenylethyl isocyanate[33,34] also have been used as derivatizing agents.

High-performance liquid chromatography (HPLC) has been used albeit less frequently, for the separation of enantiomeric alcohols[35-37] and their derivatives.[38,39] Nuclear magnetic resonance (NMR) has been applied to the determination of the enantiomeric purity of free chiral alcohols and their α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) esters[40-42] using the elegant method of Mosher.[43,44]

The stereospecific synthesis of the Japanese beetle, *Popillia japonica* Newman pheromone,[45] involved the preparation of the (*R*)-(−)- and (*S*)-(+)-tetrahydro-5-oxo-2-furancarboxylic acids from the respective glutamic acids. The preparation of these chiral acids is known to be highly stereospecific[46,47] and thus provides highly pure chiral acids. The *S* enantiomer is prepared from the inexpensive naturally occurring (*S*)-glutamic acid and produces a potentially useful inexpensive derivatizing agent.

A series of chiral alcohols of widely varying structural types including simple aliphatic (which have been extensively studied by using (*S*)-α-acetoxypropanoic acid[15]) and aromatic alcohols, and examples likely to be utilized as synthetic intermediates for chiral syntheses were derivatized with the three acid chlorides (1–3) of Figure 1 to produce (*S*)-α-acetoxypropanoic (AP), (*S*)-tetrahydro-5-oxo-2-furancarboxylic (TOF), and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) esters, respectively. These diastereomeric esters were gas chromatographed on five capillary columns of differing polarity and one liquid crystal capillary column with the objective of producing data from which a combination of a derivatizing agent and column could be selected that would provide optimum resolution for a chiral alcohol of a particular structural type. MTPA derivatives have been used for HPLC separations,[38] but their gas chromatographic behavior has not been extensively studied.



1 2 3

Figure 1. Chiral derivatizing reagents.

High-performance liquid chromatographic (HPLC) evaluation of these diastereomeric esters was also undertaken since the AP derivatives had not been investigated in this manner. The choice of a derivatizing agent for HPLC is dependent on whether the application is analytical or preparative. In analytical applications, factors such as cost and molecular weight are secondary in priority to those of stability and detectability. In preparative applications, the molecular weight and cost of the derivatizing agent are very important. Throughput in grams per unit volume of solvent of the chiral alcohol portion of the derivative is lower for the higher molecular weight derivatizing agents and thus an inexpensive low molecular weight derivatizing reagent is desirable. The analytical and preparative use of these derivatizing agents was investigated.

The ^{13}C NMR spectra of the resolved esters were examined for correlation between configuration and the chemical shifts of particular carbon atoms in the pairs of diastereomers. The chemical shift differences between pairs of the diastereomers in ^{1}H[43,44] and ^{19}F[48] spectra by MTPA derivatives have been utilized extensively to determine configuration. The ^{13}C spectra were chosen because of the simplicity of the completely decoupled spectra, compared to the ^{1}H spectra, thus avoiding the difficulty of measuring small chemical shift differences of multiply coupled protons and the necessity of doing numerous proton decoupling experiments.

Results and Discussion

CGC and HPLC. The separation factors α and the elution orders for the diastereomeric esters are presented in Table I. An α value of 1.02 or greater is considered to be of practical application. CGC results: acetoxypropanoate (AP) esters chromatographed on polar or liquid crystal stationary phases are most suitable for aliphatic chiral alcohols I–IV, although the MTPA derivatives are usable on the polar and liquid crystal columns, whereas the TOF derivatives are unsuitable. In the cases of the acetylenic and olefinic alcohols V–XV, the choice of derivatizing agent will depend on the type of column available and vice versa. In general, the TOF derivative proved the most useful especially in those cases (VIII–XV) where the unsaturation is proximate to the chiral carbon. In cases in which the unsaturation is separated from the chiral carbon by one carbon (V–VII) the AP derivatives gave consistently higher α values, similar to the purely aliphatic alcohols. This result would indicate that in cases in which the unsaturation were removed from the chiral carbon by more than one carbon, AP derivatives would be more useful. With aromatic alcohols, the data indicate that the

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TOF derivative would be the one of choice. The MTPA derivative would be the one to choose in the case of a lactone alcohol (entry XVIII).

HPLC. These results follow the same general trend as the GC results with the AP derivatives having higher α values for the aliphatic (I–IV) and aliphatic-like (V–VII) alcohols, whereas the TOF derivatives are in general superior for the acetylenic and olefinic alcohols VIII–XV. The TOF derivatives also give better separations in cases of the aromatic alcohols XVI, whereas the MTPA derivative is superior in the case of entry XVIII.

There are some cases in which MTPA derivatives give a higher α in the HPLC separations, but the value for the TOF derivative was similar (i.e., see entries XII and XIII) and in a preparative application, the TOF derivative would be preferred for the reasons of cost and lower molecular weight discussed in the introduction.

The CGC elution orders indicate that in most cases the *RS* diastereomer elutes first, although there are examples (XII–XV) in which a reversal takes place, indicating a considerable change of conformation in the liquid phase. The reversal of elution order is strikingly apparent when the CGC data are compared to the HPLC data. The elution orders of the AP and MTPA derivatives are consistently the same in both CGC and HPLC with the earlier eluting diastereomer being the same. In the case of the TOF derivatives, the order of elution of diastereomers is the opposite for CGC and HPLC. This indicates that the solution conformation for the AP and MTPA derivatives is the same or at least similar for both CGC and HPLC, whereas for the TOF derivative the conformation is different for CGC vs. HPLC. These results imply that the conformational control exerted by the carbinyl hydrogens as described by Pirkle[49] is influenced strongly either by the higher temperatures and liquid phases of CGC and or by solute-adsorbent interactions in HPLC. Consideration of the range of polarities of the liquid phases studied indicates that intramolecular hydrogen bonding rather than strong interaction with the liquid phase controls the conformations in the CGC mode, whereas solute–solvent or solute–adsorbent interactions are important in the HPLC mode, particularly for the TOF esters. The parameters for HPLC separation on a preparative scale also were determined (see Experimental Section).

^{13}C NMR. The ^{13}C NMR chemical shift differences for the aliphatic diastereomeric esters are presented in Table II, and although the $\Delta RS - SS$ values for the AP and TOF derivatives are similar and significantly smaller than those for the MTPA derivatives, the values for the methyl c on the chiral carbon are large enough to be of diagnostic value. They are of opposite sign from those of the MTPA esters with the *RS* diastereomer occurring at higher field than the *SS*, indicating that the *SS* methyl group c is in the deshielding zone of one of the carbonyls in the AP and TOF esters but in the shielding zone of the phenyl ring in the MTPA esters.[50] The other carbons a and d that underwent significant but opposite chemical shifts from methyl c in the MTPA esters did not display any detectable shift in the AP and TOF derivatives.

Table III presents the ^{13}C NMR chemical shift differences for the diastereomeric olefinic esters. Although significant chemical shift differences between the diastereomers are present, the diagnostic value is somewhat limited due to the size of some of the shifts and the reversal of the relative field positions of the *RS* and *SS* diastereomers. Some patterns are apparent. The methyl c on the chiral carbon gave the expected and diagnostic shift difference in the MTPA derivatives, a smaller and less consistent but useful shift difference in the TOF derivatives, and no shift differences in the AP derivatives. The olefinic carbons had significant chemical shift differences in the AP and MTPA derivatives, the AP derivatives having the *SS* diastereomer at consistently higher fields than the *RS* for the AP derivatives of alcohols IX, X, XIV, and XV, whereas the olefinic carbons have opposite chemical differences for AP esters of alcohols VI and VII in which the olefinic function is one carbon removed from the center of chirality. In the MTPA derivatives of alcohols IX and X the two olefinic carbons are located at different relative field positions in the pairs of diastereomers. This seems to be the only case of a *Z* vs. *E* dependency of the chemical shift differences.

Table IV lists the chemical shift differences between the pairs of diastereomers of the AP, TOF, and MTPA esters of acetylenic alcohols. In molecules of this structural type, only the methyl c on the chiral carbon of the MTPA esters has any reliable diagnostic value with the acetylenic carbons producing some shift differences. In the case of the aromatic entry XVI, the shift differences for the asymmetric carbon are of diagnostic value in the AP and MTPA esters and the shift differences in all three esters of entry XVII are significant with the difference in the MTPA ester being the largest recorded.

Chemical shift differences between carbons of pairs of diastereomers in the acid portion of the esters were examined for diagnostically useful information of the type reported[48] for the ^{19}F spectra of MTPA derivatives. These results are presented in Table V, and although most of the chemical shift differences are small, they are consistent and some can be considered diagnostically useful. The values for carbons b and c of the TOF esters place the *SS* diastereomer at higher field than the *RS* diastereomers for the aliphatic alcohols and at lower field for the acetylenic and some of the olefinic entries. For the AP esters, the values for the three carbons examined a′, b′, and c′ again place the *SS* diastereomers at higher field than the *RS* for the aliphatic and olefinic esters where there is one carbon between the unsaturation and the chiral carbon. The carbonyl carbon of the MTPA diastereomeric esters displayed a small but definite shift.

The ^{13}C NMR spectra of the AP and MTPA esters of the lactone alcohol prepared by reduction of the ethyl ester[51] of (*R*)- or (*S*)-tetrahydro-5-oxo-2-furancarboxylic acid were examined and only the MTPA ester gave significant shift differences between the diastereomeric pairs with the chiral ring carbon and the adjacent exocyclic methylene carbon having $\Delta RS - SS$ values of −0.16 and 0.17, respectively. It was not possible to isolate the TOF ester of this alcohol.

Racemic dihydrobenzoin, entry XVII of Table I, was readily resolved (see Experimental Section) via recrystallization of the bis-TOF ester, thus providing ready access to the enantiomerically pure forms of this diol heretofore available only by a method based on spontaneous crystallization.[52] It may be possible to resolve other chiral alcohols by recrystallization when they form solid derivatives with TOF acid.

Although there are numerous reported preparations of (*R*)- and (*S*)-tetrahydro-5-oxo-2-furancarboxylic acid,[45–47]

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(50) The ^{1}H NMR spectrum of several diastereomeric pairs of MTPA esters showed that methyl group c of the *SS* diastereomer was shielded (occurred at higher field) than the methyl c of the *RS* diastereomer in accord with the model described by Dale.[44]
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Table I. Separation Factors (α)[a] for Diastereomeric Esters

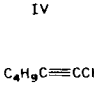
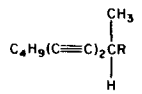
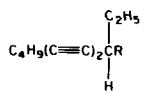
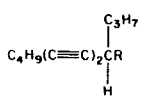
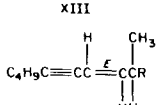
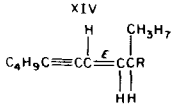
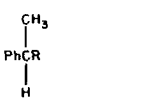
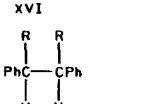
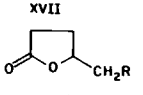
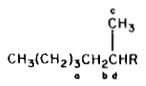
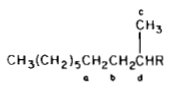
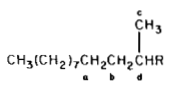
alcohol	R[c]	GC column type (temperature, °C) (elution order)[b]					
		BP-1[d]	DB-1[e]	CW20M[f]	SP-2340[g]	CpCC[h]	HPLC[i]
 I	AP	1.039 (85) (1)	1.172 (75) (1)	1.082 (60) (1)	1.055 (75) (1)	1.000 (75)	1.039 (*j*) (1)
	TOF	1.000 (125)	1.000 (115)	1.000 (140)	1.000 (160)	1.000 (120)	1.000 (*j*)
	MTPA	1.000 (125)	1.000 (115)	1.019 (100) (1)	1.008 (115) (1)	1.000 (110)	1.000 (*j*)
 II	AP	1.051 (140) (1)	1.061 (135) (1)	1.109 (100) (1)	1.113 (115) (1)	1.133 (110) (1)	1.131 (*j*) (1)
	TOF	1.000 (180)	1.000 (170) (1)[k]	1.000 (175)	1.029 (190) (1)	1.023 (160) (1)	1.088 (*j*) (2)
	MTPA	1.000 (180)	1.015 (175) (1)	1.047 (130) (1)	1.035 (150) (1)	1.047 (145) (1)	1.000 (*j*)
 III	AP	1.061 (160) (1)	1.054 (160) (1)	1.100 (120) (1)	1.109 (140) (1)	1.112 (135) (1)	1.156 (*j*) (1)
	TOF	1.000 (200)	1.000 (190)	1.000 (185)	1.029 (200) (1)	1.019 (180) (1)	1.092 (*j*) (2)
	MTPA	1.000 (200)	1.000 (190)	1.034 (150) (1)	1.022 (165) (1)	1.027 (160) (1)	1.000 (*j*)
 IV	AP	1.049 (180) (1)	1.060 (175) (1)	1.096 (140) (1)	1.100 (150) (1)	1.116 (155) (1)	1.145 (*j*) (1)
	TOF	1.000 (220)	1.013 (200) (1)	1.000 (200) (1)[k]	1.031 (215) (1)	1.031 (200) (1)	1.116 (*j*) (2)
	MTPA	1.000 (220)	1.000 (210)	1.000 (175)	1.000 (175)	1.025 (190) (1)	1.000 (*j*)
 V	AP	1.024 (160) (1)	1.023 (150) (1)	1.047 (125) (1)	1.037 (140) (1)	1.065 (125) (1)	1.126 (*j*) (1)
	TOF	1.062 (200) (1)	1.074 (175) (1)	1.103 (190) (1)	1.108 (205) (1)	1.116 (190) (1)	1.060 (*j*) (2)
	MTPA	1.000 (200)	1.020 (175) (2)	1.019 (155) (2)	1.044 (165) (2)	1.021 (160) (2)	1.000 (*j*)
 VI	AP	1.049 (160) (1)	1.052 (150) (1)	1.039 (110) (1)	1.076 (130) (1)	1.106 (125) (1)	1.098 (*j*) (1)
	TOF	1.021 (200) (1)	1.031 (175) (1)	1.047 (175) (1)	1.036 (200) (1)	1.055 (190) (1)	1.084 (*j*) (2)
	MTPA	1.000 (200)	1.000 (175)	1.000 (150)	1.000 (165)	1.000 (160)	1.000 (*j*)
 VII	AP	1.053 (160) (1)	1.061 (150) (1)	1.106 (110) (1)	1.096 (130) (1)	1.112 (125) (1)	1.155 (*j*) (1)
	TOF	1.000 (200)	1.029 (175) (1)	1.049 (175) (1)	1.060 (200) (1)	1.051 (190) (1)	1.075 (*j*) (2)
	MTPA	1.000 (200)	1.000 (175)	1.000 (150)	1.000 (165)	1.000 (160)	1.000 (*j*)
 VIII	AP	1.016 (180) (1)	1.021 (175) (1)	1.000 (150)	1.024 (160) (2)	1.000 (160)	1.000 (*j*)
	TOF	1.066 (220) (1)	1.075 (200) (1)	1.099 (200) (1)	1.086 (225) (1)	1.122 (200) (1)	1.240 (*j*) (2)
	MTPA	1.021 (220) (2)	1.030 (210) (2)	1.095 (175) (2)	1.109 (185) (2)	1.066 (170) (2)	1.222 (*j*) (2)
 IX	AP	1.021 (180) (1)	1.023 (175) (1)	1.039 (140) (1)	1.000 (150)	1.031 (160) (1)	1.000 (*j*)
	TOF	1.027 (220) (1)	1.030 (200) (1)	1.038 (200) (1)	1.038 (215) (1)	1.045 (200) (1)	1.113 (*j*) (2)
	MTPA	1.020 (220) (2)	1.023 (210) (2)	1.066 (165) (2)	1.087 (175) (2)	1.064 (170) (2)	1.079 (*j*) (2)
 X	AP	1.036 (180) (1)	1.035 (175) (1)	1.039 (140) (1)	1.036 (150) (1)	1.065 (160) (1)	1.099 (*j*) (1)
	TOF	*m*	1.046 (200) (1)	1.055 (200) (1)	*m*	*m* (200)	1.138 (*j*) (2)
	MTPA	*m*	*m*	1.000 (165)	1.031 (175) (1)	1.036 (170) (2)	1.068 (*j*) (2)

Table I (*Continued*)

alcohol	R[c]	GC column type (temperature, °C) (elution order)[b]					
		BP-1[d]	DB-1[e]	CW20M[f]	SP-2340[g]	CpCC[h]	HPLC[i]
 XI	AP	1.018 (180) (1)	1.022 (160) (1)	1.091 (150) (1)	1.135 (160) (1)	1.046 (160) (1)	1.000 (*j*)
	TOF	1.066 (220) (1)	1.066 (190) (1)	1.086 (210) (1)	1.053 (220) (1)	1.106 (200) (1)	1.333 (*j*) (2)
	MTPA	1.036 (220) (2)	1.036 (200) (2)	1.137 (185) (2)	1.173 (185) (2)	1.099 (180) (2)	1.309 (*j*) (2)
 XII	AP	1.027 (180) (2)	1.023 (175) (2)	1.111 (165) (2)	1.168 (160) (2)	1.079 (160) (2)	1.102 (*j*) (2)
	TOF	1.099 (220) (1)	1.094 (210) (1)	1.116 (210) (1)	1.086 (235) (1)	1.149 (200) (1)	1.259 (*j*) (2)
	MTPA	1.037 (220) (2)	1.039 (210) (2)	1.141 (185) (2)	1.175 (190) (2)	1.103 (185) (2)	1.295 (*j*) (2)
 XIII	AP	1.028 (190) (2)	1.028 (175) (2)	1.095 (165) (2)	1.157 (175) (2)	1.070 (170) (2)	1.146 (*j*) (2)
	TOF	1.100 (220) (1)	1.101 (210) (1)	1.125 (210) (1)	1.079 (240) (1)	1.166 (200) (1)	1.202 (*j*) (2)
	MTPA	1.036 (220) (2)	1.033 (210) (2)	1.153 (185) (2)	1.170 (195) (2)	1.106 (190) (2)	1.241 (*j*) (2)
 XIV	AP	1.000 (180)	1.000 (160)	1.029 (150) (2)	1.061 (160) (2)	1.000 (160)	1.000 (*j*) (2)
	TOF	1.000 (220)	1.000 (190)	1.049 (200) (1)	1.000 (225)	1.038 (200) (1)	1.192 (*j*) (2)
	MTPA	1.000 (220)	1.000 (200)	1.040 (175) (2)	1.058 (185) (2)	1.033 (180) (2)	1.116 (*j*) (2)
 XV	AP	1.000 (190)	1.000 (175)	1.059 (160) (2)	1.088 (165) (2)	1.039 (170) (2)	1.000 (*j*)
	TOF	1.059 (220) (1)	1.058 (210) (1)	1.051 (210) (1)	1.029 (235) (1)	1.068 (200) (1)	1.102 (*j*) (2)
	MTPA	1.012 (220) (2)	1.024 (210) (2)	1.064 (180) (2)	1.076 (190) (2)	1.044 (190) (2)	1.091 (*j*) (2)
 XVI	AP	1.000 (140)	1.000 (140)	1.000 (130)	1.042 (140) (2)	1.000 (120)	1.000
	TOF	1.090 (180) (1)	1.101 (175) (1)	1.115 (200) (1)	1.095 (200) (1)	1.137 (170) (1)	1.079 (*j*) (2)
	MTPA	1.022 (180) (2)	1.025 (175) (2)	1.060 (160) (2)	1.086 (165) (2)	1.052 (160) (2)	1.054 (*j*) (2)
 XVII	AP	1.000 (250)	1.020 (230) (2)	1.000 (240)	1.000 (240)	*m*	1.051 (*n*) (2)
	TOF	1.000 (290)	1.032 (280) (2)	*m*	*m* (240)	*m*	1.190 (*n*) (1)
	MTPA	1.000 (290)	1.000 (280)	*m*	*m* (240)	*m*	1.064 (*n*) (2)
 XVIII	AP	1.000 (160)	1.024 (145) (1)	1.000 (175)	1.000 (210)	1.000 (170)	1.000 (*o*)
	TOF	*m*	*m*	*m*	*m*	*m*	*m*
	MTPA	1.068 (200) (1)	1.091 (180) (1)	1.104 (200) (1)	1.097 (240)	1.157 (190) (2)	1.150 (*o*) (1)

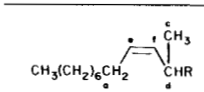
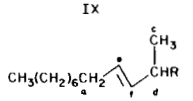
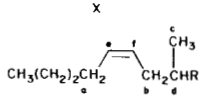
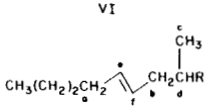
[a] $(RT_2 - T_0)/(RT_1 - T_0) = K'_2/K'_1$. [b] For the elution order designation: (1) = *RS* before *SS*; (2) = *SS* before *RS*. In each case, the derivatizing agent was of the *S* configuration and the first designator refers to the alcohol residue. [c] AP = (*S*)-(+)-acetoxypropanoic, TOF = (*S*)-(+)-tetrahydro-5-oxo-2-furancarboxylic, MTPA = (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic. For the GC data, the column operating temperature is recorded in parentheses after each α or separation factor. [d] Scientific Glass Engineering Inc. prepared BP-1, 12 m × 0.25 mm i.d. fused silica column. [e] J&W Scientific, Inc. prepared DB-1 12 m × 0.25 mm i.d. fused silica column. [f] Hewlett-Packard prepared Carbowax 20M, 15 m × 0.2 mm i.d. fused silica column. [g] Quadrex Corp. prepared SP-2340 ("007" Series), 14 m × 0.25 mm i.d. fused silica column with 0.25-μm film thickness. [h] CPCC, 15.2 m × 0.20 mm i.d. coated with 0.1% cholesteryl *p*-chlorocinnamate. When the column was operated below 150 °C, it was in a super-cooled state. [i] Lichrosorb EF54 (5 μm) silica gel 25 × 0.635 cm column. [j] Solvents for HPLC were as follows: AP = 8% by volume diethyl ether (E) in hexane (H); TOF = 20% ethyl acetate (EA) in hexane; MTPA = 0.75-1% diethyl ether in hexane except see footnotes *n* and *o*. [k] The peak from one diastereomer appeared as a shoulder on the side of the other, and although it was not possible to measure the *K'* for the shoulder, it was possible to determine which diastereomer eluted first. [m] No well-defined peaks were observed for the derivatives. [n] For these derivatives the solvents were as follows: AP = 20% E/H; TOF = 60% EA/H; MTPA = 8% E/H. [o] For these derivatives the solvent was 50% E/H.

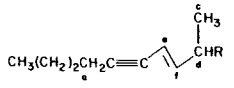
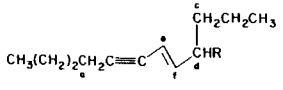
Table II. Significant[a] ^{13}C NMR Chemical Shift Differences of Diastereomeric Aliphatic Esters of TOF, AP, and MTPA Acids[b]

	R (*RS* – *SS*)											
	TOF				AP				MTPA			
alcohol	a	b	c	d	a	b	c	d	a	b	c	d
 I	*a*	0	−0.12	0	0	0.03	−0.1	0	−0.28	0	0.36	−0.18
 II	*a*	0	−0.10	0	0	0	−0.09	0	−0.33	−0.03	0.37	−0.20
 III	*a*	0	−0.11	0	0	0.04	−0.12	0	−0.33	0	0.37	−0.19
 IV	*a*	0	−0.11	0	0	0	−0.11	0	−0.32	0	0.37	−0.21

[a] Shift differences for other carbons were too small to be significant. Chemical shift differences are in ppm. [b] TOF = (*S*)-(+)-tetrahydro-5-oxo-2-furancarboxylic, AP = (*S*)-α-acetoxypropanoic, and MTPA = (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic.

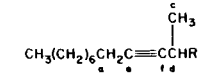
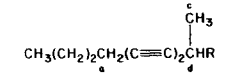
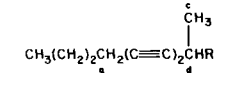
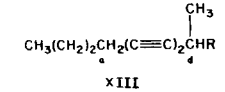
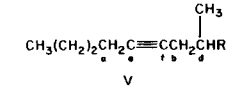
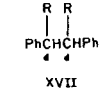
Table III. Significant[a] ^{13}C NMR Chemical Shift Differences of Diastereomeric Olefinic Esters of TOF, AP, and MTPA Acids[b]

	R (*RS* – *SS*)																	
	TOF						AP						MTPA					
alcohol	a	b	c	d	e	f	a	b	c	d	e	f	a	b	c	d	e	f
 IX	0		−0.05	0	0.05	−0.04	0.03		0	0.05	0	−0.06	0		0.16	0.15	−0.03	0.19
 X	0		−0.09	0	0.05	−0.05	0		−0.03	0	−0.16	−0.14	−0.03		0.24	−0.14	−0.38	0.19
 VI		0	0.05	−0.13	0.08	0.09	−0.06	0	−0.07	0	−0.05	0.1	−0.16	−0.08	−0.15	0.19	−0.17	−0.08
 VII	0	0	−0.10	0.02	0	0	0	−0.11	0	0	0.13	−0.16	−0.05	−0.15	0.16	−0.08	−0.19	−0.32

 XIV	0	0	0	0	0	0	0	0	−0.09	−0.11	0	0.24	−0.06	−0.26	−0.08	
 XV	0	0	0	0	0	0	−0.04	0	−0.11	−0.10	0	0.33	0.09	−0.10	−0.34	

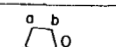
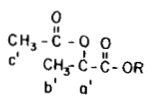
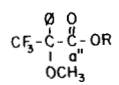
[a] Chemical shift differences in ppm. Shifts for other carbons are too small to be useful. [b] TOF = (*S*)-(+)-tetrahydro-5-oxo-2-furancarboxylic, AP = (*S*)-α-acetoxypropanoic, and MTPA = (*S*)-α-methoxy-2-(trifluoromethyl)phenylacetic acid.

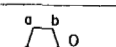
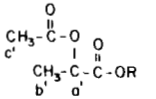
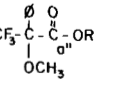
Table IV. Significant[a] ^{13}C NMR Chemical Shift Differences of Diastereomeric Acetylenic and Aromatic Esters of TOF, AP, and MTPA Acids[b]

	R (*RS* − *SS*)																	
	TOF						AP						MTPA					
alcohol	a	b	c	d	e	f	a	b	c	d	e	f	a	b	c	d	e	f
 VIII	0		0	0	0.1	0	0.06		0.04	0.05	0	−0.17	0.07		0.13	0.22	−0.14	−0.21
 XI	0		−0.03	−0.02	*c*	*c*	0		−0.03	0.04	*c*	*c*	0		0.21	0.24	*c*	*c*
 XII	0		0	0.02	*c*	*c*	0		0	0.03	*c*	*c*	0		0.24	0.38	*c*	*c*
 XIII	0		0	0	*c*	*c*	0		0	0	*c*	*c*	0		0.30	0.43	*c*	*c*
 V	0	0	−0.11	0.08	0.10	0	0	0	0	0	−0.20	−0.05	−0.11	−0.14	0.13	−0.11	−0.08	−0.38
 XVI		−0.21	0					−0.08	−0.21						0.38	0.04		
 XVII				0.16						0.16						0.86		

[a] Chemical shift differences are in ppm. Shifts for other carbons are too small to be significant. [b] TOF = (*S*)-(+)-tetrahydro-5-oxo-2-furancarboxylic, AP = (*S*)-α-acetoxypropanoic, and MTPA = (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic. [c] The acetylenic carbons did show chemical shift differences between diastereomers, but it was not possible to make precise peak assignments in these cases, thereby reducing the usefulness of these shift differences.

Table V. ^{13}C NMR Chemical Shift Differences[a] Induced in the Derivatizing Acids for Diastereomeric TOF, AP, and MTPA Acid Derivatives[b]

derivatizing acid		R (*RS* − *SS*)							
									
	a	0	0	0	0	0	0	0	0.07
	b	−0.11	−0.08	−0.09	−0.08	0	−0.03	0	0.19
	c	−0.05	−0.04	−0.02	−0.03	0.17	0.04	0.09	0.17
	a′	−0.04	−0.05	−0.06	−0.05	0	−0.03	0	0.08
	b′	−0.10	−0.05	−0.07	−0.08	−0.08	−0.06	−0.07	0.16
	c′	−0.10	−0.04	−0.07	−0.08	−0.16	−0.17	−0.21	0
	a″	−0.07	−0.07	−0.07	−0.06	−0.03	−0.05	−0.09	−0.13

		R (*RR* − *SS*)									
											
	a	0	0	0.06	0.07	0.18	0.07	0	0.16	0	*c*
	b	0.09	0.08	0.15	0.21	0.24	0.06	0.09	0.07	−0.16	*c*
	c	0.07	0.08	0.15	0.22	0.23	0.10	0.10	0.13	−0.21	*c*
	a′	−0.03	−0.08	0.05	0.04	0.04	0	0.05	0.03	0	−0.04
	b′	0.10	0	0.10	0.24	0.22	0	0	0.15	0	0
	c′	0	−0.06	−0.05	0	0	−0.08	0	0	0.05	0
	a″	−0.04	−0.11	−0.10	−0.12	−0.05	−0.08	−0.10	−0.24	−0.15	0.05

[a] Chemical shift differences are in ppm. Chemical shifts for other carbons are too small to be useful. [b] TOF = (*S*)-(+)-tetrahydro-5-oxo-2-furancarboxylic, AP = (*S*)-α-acetoxypropanoic, and MTPA = (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic. [c] It was not possible to isolate this derivative.

we encountered some difficulty in conducting these preparations on a large scale and after extensive investigation found that these difficulties were due to the facile conversion of the crude acid (produced by acidic nitrosation of the requisite glutamic acid) to its ethyl ester upon contact with solvents such as ethyl acetate, diethyl ether, or even chloroform containing small amounts of ethyl alcohol as a preservative. It was found that by avoiding these solvents and using ethanol-free chloroform during the preparation of the acid, reproducibly high yields of enantiomerically pure acid could be obtained. The enantiomeric purity of the *S* acid was determined by CGC analysis of the α-methylbenzylamides prepared from configurationally pure (*S*)-α-methylbenzylamine.

Conclusion

The chromatographic data presented allow for the selection of a derivatizing acid and column combination for a particular type of chiral alcohol that will provide a useful, practical determination of its enantiomeric composition and provides the necessary information for both analytical and preparative HPLC applications. In preparative HPLC applications in particular, both the AP and TOF esters proved to be quite useful, with the AP esters applicable to aliphatic chiral alcohols and the TOF esters to unsaturated alcohols. Even in those instances where the separation factors for the TOF and MTPA derivatives are comparable, the lower molecular weight of the TOF (125 vs. 233) and its much lower cost make it far more attractive for preparative applications, whereas the detectability of the MTPA derivatives would be clearly superior in analytical applications using an ultraviolet detector. The TOF derivative would be particularly useful for the resolution of multigram quantities of many chiral alcohol intermediates. The elution order data allow for the prediction, with high certainty, of diastereomer elution order for a wide variety of structural types of chiral alcohols.

The ^{13}C NMR data demonstrate the elegance of the assignment of configuration provided by MTPA derivatives that has found such widespread application, and it provides information on a wide variety of structural types of alcohols, thereby extending the scope of application of this derivatizing reagent. The AP and TOF derivatives as applied to determination of configuration by NMR are clearly inferior to the MTPA derivatives, but using the data presented, it should be possible to distinguish with certainty between the resolved *RS* and *SS* diastereomers using ^{13}C NMR.

The chromatographic and ^{13}C NMR data provide new information for MTPA and AP esters that should extend their usefulness and demonstrates that (*S*)-tetrahydro-5-oxo-2-furancarboxylic acid is a valuable new addition to the arsenal of chiral alcohol derivatizing agents and could prove useful as a reagent for other chiral molecules such as amines and mercaptans.

Experimental Section

The CGC separations were carried out on Varian 3700 and 1400 gas chromatographs equipped with user-designed all-glass capillary split-inlet systems with carrier gas (He) flow rates of 18 cm/s and a split ratio of 100:1. The output of the flame ionization detectors were interfaced to a Nicolet 1180 data system. Chromatographic conditions were adjusted so that the partition coefficient (k') of both diastereomers in each case was >2.5.

High-performance liquid chromatography was done at a flow rate of 1.5–2.0 mL/min using a Waters Associates M6000 solvent delivery system, a Rheodyne 905-19 injector for sample introduction, and a Waters Associates R401 differential refractometer detector. Reagent grade degassed solvents were used. Mass spectra were recorded on a Finnigan 1015S chemical ionization mass spectrometer using either methane or isobutane as reagent gases. The samples were introduced via a solid probe inlet. The spectra were in complete agreement with the assigned structures; i.e., the base peak was generated by cleavage of the asymmetric carbon–oxygen bond and either was that from the protonated acid derivatizing reagent in the cases of the aliphatic alcohols or was that from the positively charged alcohol portion of the molecule in the cases of the unsaturated alcohols. In those cases where sufficient separation by HPLC provided pure samples of each diastereomer, the mass spectra were identical. Proton and carbon magnetic resonance spectra were recorded in $CDCl_3$ on a Nicolet 300-MHz spectrometer. The ^1H spectra were in compliance with the assigned structures with the MTPA derivatives displaying nonequivalence for several of the protons in some of the molecules as would be expected.[44] Racemic alcohols were resolved as their TOF derivatives, a portion was saponified, and the enantiomerically pure alcohols were converted to AP and MTPA esters. Configurations were assigned by examination of the ^1H NMR signals of the methyls c on the chiral carbons of the MTPA esters according to the model described by Dale.[44]

Infrared spectra were recorded with a Perkin-Elmer 467 spectrophotometer as 2% w/v solutions in CCl_4. The recorded spectra were in complete agreement with the assigned structures with the AP and MTPA derivatives having one carbonyl absorption and the TOF derivatives having two. The *E* olefinic chiral alcohols displayed strong absorptions at or near 950 cm^{-1}, consistent with their assignment as the trans *E* isomers.

Capillary Preparation. The glass capillary column, used for the preparation of the CpCC column, was drawn from 1 m × 2.0 mm i.d. × 6.5 mm o.d. soda lime tubing (Kimble, USA) on a GDM-1 (Schimadzu Ltd., Japan) glass drawing apparatus using a 100:1 draw ratio. The capillary was etched by flushing with anhydrous HCl (Matheson, USA) for 15 min, sealing the ends, and heating at 300 °C for 16 h. After being etched, the capillary was purged at 190 °C with dry N_2 for 24 h. The etched column was coated by the static method as described.[53]

All the capillary columns used were of fused silica with the exception of the CpCC column, which was soft glass. The DB-1 column was 12 m × 0.25 mm i.d. and was purchased from J&W Scientific, Inc., Rancho Cordova, CA. The BP-1 column was 12 m × 0.25 mm i.d. and was purchased from Scientific Glass Engineering, Inc., Austin, TX.

The Carbowax 20M fused-silica column was 15 m × 0.02 mm i.d. and was purchased from Hewlett-Packard (Avondale, PA). The SP-2340 column (14 m × 0.025 mm i.d. coated with a 0.25-μm film thickness was purchased from Quadrex Corp., New Haven, CN. The cholesteryl *p*-chlorocinnamate (CpCC)[54] column (15 m × 0.02 mm i.d. coated with 0.1% CpCC) was prepared in our laboratory. Each column was conditioned for 2 h at 200 °C prior to use.

Liquid Chromatographic Column. High-performance liquid chromatography was done on a 0.635 × 25 cm column packed[55] with Lichrosorb EF54 (5 μm) silica gel.

Preparation of (*S*)-Tetrahydro-5-oxo-2-furancarboxylic Acid. The (*S*)-(+)-glutamic acid (73.5 g, 0.5 mol) (Sigma Chemical Co., No. G-1251) was suspended in 800 mL of H_2O at room temperature. $NaNO_2$ (45 g, 0.65 mol) was added all at once. The temperature rose about 5 °C, and the presence of HNO_2 was noted and some N_2 evolution occurred. The temperature was lowered to 15–18 °C, and 300 mL of 2 N HCl was added dropwise over 3 h. The clear solution was stirred at room temperature overnight. The H_2O was removed under vacuum at 40–50 °C, and the oily solid was extracted with 500–700 mL of hot acetone and filtered. The acetone filtrate was dried over Na_2SO_4, the drying agent removed by filtration, and the acetone evaporated. After removal of the last traces of acetone under pump vacuum, addition of a few seed crystals induced crystallization. The solid was taken up in about 1600 mL of hot ethanol-free chloroform (the ethanol was removed by washing with concentrated H_2SO_4, H_2O, and

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saturated $NaHCO_3$, drying over Na_2SO_4/K_2CO_3, and distillation). A gummy, insoluble oil present was best removed by stirring the mixture with Na_2SO_4 (the gummy residue seems to cling to the Na_2SO_4) while it was allowed to cool to room temperature. The drying agent was removed by filtration, the chloroform volume was reduced to about 300 mL, a few seed crystals were added, and the solution was chilled in the freezer (-20 °C). The first crop of crystalline acid (44 g) had a melting point of 70-72 °C. Evaporation of the chloroform produced a second crop (3 g) of acid of mp 70-73 °C producing a total yield of 47 g (72%). The specific rotation ($[\alpha]^{25}_D$ 16.02° (c 4.6, MeOH) (lit.[45] $[\alpha]^{25}_D$ 14.39° (c 4.7, MeOH))), and the melting point can be used as a measure of the enantiomeric purity of the acid, but a more reliable and precise method was used to prepare the amide with (S)-α-methylbenzylamine (Hexcel Corp., Zeeland, MI) that has been purified by threefold recrystallization of its tartrate salt[56] as follows. The acid was converted to the acid chloride,[45] and a small sample (0.100-0.250 g) in 10-20 mL of methylene chloride was treated with triethylamine (0.100-0.250 mL) and the (S)-α-methylbenzylamine (0.09-0.18 g). Workup by dilution with ether, washing with H_2O and $NaHCO_3$, and drying over Na_2SO_4 gives the amides. The *RS* amide had a melting point of 114-116 °C, while the *SS* amide was an oil that would not crystallize. Gas chromatographic analysis on the DB-1 capillary column gave *K'* values for the *SS* and *RS* amides of 5.07 and 5.38, respectively: IR (Nugol) 1775, 1660, 1390, 1240, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (3, d), 2.5-2.6 (4, m), 4.75-4.85 (1, t), 5.1-5.2 (1, m), 7.2-7.4 (5, m); MS (CI), *m/z* (relative abundance) 233 $(M)^+$ (*SS*, 20; *RS*, 50) 234 $(M + 1)^+$ (*SS* + *RS* 100).

The possibility of converting the crude acid directly to the acid chloride (after removal of the last traces of acetone under vacuum) was investigated by heating this crude acid with excess thionyl chloride[45] followed by distillation of the product. The acid chloride was obtained in 81% overall yield with an enantiomeric purity of 95.7%. The melting point of the acid is not a good measure of enantiomeric purity since samples of acid with a melting point of from 67 to 74 °C, produced acid chloride of high >99% enantiomeric purity.

Derivative Preparation. The acid chloride of the derivatizing acids were prepared by the following published methods: (S)-α-acetoxypropanoyl chloride (acid from Aldrich Chemical Co.),[57] (S)-tetrahydro-5-oxo-2-furancarboxyl chloride,[45] and (R)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[44] (the acid was purchased from Aldrich Chemical Co.). The diastereomeric esters were prepared as follows: (S)-α-acetoxypropanoates and (S)-tetrahydro-5-oxo-2-furancarboxylates; 100 μL of a 2 M solution of the acid chloride in methylene chloride was added to a cold mixture of 20 μL of the chiral alcohol and 80 μL of pyridine. The mixture was allowed to come to room temperature with stirring, two drops of 1 N hydrochloric acid and several milliliters of hexane were added, the layers were separated, and the organic layer was dried by passage through sodium sulfate. The (S)-α-methoxy-α-(trifluoromethyl)phenyl acetates were prepared similarly by using the neat acid chloride and no methylene chloride.

Resolution of Racemic Dihydrobenzoin. Racemic dihydrobenzoin (prepared from the meso form by the published procedure[58]) (10.71 g, 0.05 mol) was placed in a 500-mL flask with 200 mL of dry methylene chloride and 9.7 mL (0.12 mol) of pyridine and chilled in an ice bath. (S)-Tetrahydro-5-oxo-2-furancarboxyl chloride dissolved in 50 mL of methylene chloride was added dropwise. The mixture was stirred at room temperature overnight and worked up by extraction with water, 5% HCl, saturated $NaHCO_3$ drying over Na_2SO_4, and recrystallized from benzene (100% yield). Typically 100 mL of benzene is used for each gram of bis-TOF derivative, and this yields from 7.2 to 10.6 g (65.6 to 96.7%) of >99% pure *RRSS* diastereomer from one recrystallization. If a small amount of *SSSS* diastereomer remains in the product, a second recrystallization from 50 mL of benzene produces product of >99% purity. Evaporation of the mother liquor from several recrystallizations leaves the *SSSS* diastereomer with from 23 to 14g *RRSS* diastereomer. This material can be purified by preparative HPLC or alternatively could be purified by saponification to the diol and resolution with the *R* enantiomer of TOF acid. The pure *RS* diastereomer was saponified by stirring 11 g (0.025 mol) with 10 g of NaOH in 250 mL of ethanol and 25 mL of water for 24 h. The mixture was diluted with two volumes of water and extracted several times with ether. The combined ether extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent after removal of the drying agent gave 5 g (93%) of pure (*R,R*)-dihydrobenzoin of 100% ee. Rederivatization of a small sample with (S)-TOF acid chloride and analysis by capillary GC on the DB-1 column showed no racemization had occurred. The resolved *RR* enantiomer had a specific rotation $[\alpha]^{25}_D$ 96.8° (c 1.3, ethanol) (lit.[52] $[\alpha]^{25}_D$ 96.5° (c 1.6, ethanol)).

Preparative High-Performance Liquid Chromatography. In a preparative separation of entry VIII with $3 < K' < 5$ a resolution of 3 was obtained with a 50-mg injection and a resolution of 0.9 with 250-mg injection of the racemic TOF ester. This was done on a 2.54 × 25 cm column packed[55] with Bio-Sil A, 2-10 M, operated at a flow of 9.9 mL/min of 20% ethyl acetate/hexane.

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Circular Dichroic Detection in the HPLC of Chiral Molecules: Direct Determination of Elution Orders

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The use of a dichrograph as a detector in the HPLC of chiral molecules is presented; the sign of the CD at a suitable wavelength is used to determine the absolute configuration of the fractions eluted, i.e., the elution order, by means of sector rules or nonempirical models. A general procedure for selecting the wavelength for the CD detection is presented. The advantages of such a method are discussed.

Polarimetric[1] and circular dichroic[2] (CD) detectors for HPLC instruments have been recently described: the usefulness of these devices is due to their selectivity (the detector will "observe" only chiral molecules) and to the

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