in. glass column of 2% OV-101. The GC parameters were set at 100 °C for 2 min and then rose 6 deg/min until the temperature reached 225 °C. Retention times and mass spectra were compared with those of authentic samples.

Diphenylmethane, deoxybenzoin, diphenylacetaldehyde, and *N,N'*-carbonyldiimidazole were commercially available (Aldrich). Benzyl methyl ether,[5] *cis*- and *trans*-stilbene oxide,[7] *meso*- and *d,l*-hydrobenzoin[3] benzylphenylcarbinol[8] and 1,1-diphenylethanol[8] were prepared by literature procedures.

***meso*-Hydrobenzoin Carbonate.** *meso*-Hydrobenzoin (2.0 g, 9.3 mmol) and *N,N'*-carbonyldiimidazole (1.6 g, 9.8 mmol) were dissolved in dry benzene (70 mL) and heated at reflux temperature for 3 h. After cooling, the benzene was washed with water (2 × 40 mL), dried (Na_2SO_4), and then removed by using a rotary evaporator to yield a colorless solid. Two recrystallizations from aqueous methanol gave **2a** (0.9 g, 40%), mp 125–126 °C (lit.[3] mp 126–127 °C).

***d,l*-Hydrobenzoin Carbonate.** This was prepared as above from *d,l*-hydrobenzoin, mp 109–110 °C (lit.[3] mp 110 °C).

Photochemical Reactions. Direct irradiations were carried out with a Rayonet Photochemical Reactor (Southern New England Ultraviolet Co.) equipped with 8 RPR 2537 lamps. An example of the general method is given for the photolysis of **2a**. *meso*-Hydrobenzoin carbonate (**2a**) (52 mg, 0.22 mmol) was dissolved in 6 mL of purified acetonitrile, placed in a quartz phototube, and sealed with a rubber septum. The mixture was sparged for 30 min with deoxygenated nitrogen for 30 min and then photolyzed for 60 min. After GC/MS data was obtained on the photolysate, the solvent was removed, and the residue was examined by NMR. The spectrum revealed singlets at 6.0 (unaltered starting material), 4.32 (**5a**), 4.0 (**7**), 3.92 (**6**) and 3.83 ppm (**5b**). The HPLC measurements were carried out by repeating the photolysis and then adding the internal standard prior to analysis.

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Syntheses of the Enantiomers of Carnitine and 4-Methylcarnitine via the Chromatographic Resolution of γ-(Dimethylamino)-β-hydroxy Ester Precursors

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It is well-established that L-(−)-carnitine, **1a**, plays a critical role in human energy metabolism via the transport of long-chain fatty acids into mitochondria.[1-3] Considerable recent work has focused on the development of inhibitors of this transport system.[1]

A number of preparations for the enantiomers of carnitine have previously been described. Most of these involved the formation of chiral salts and their sometimes-tedious separations by crystallization.[4] Additionally, the chiral-template approach has yielded several syntheses using chiral carbohydrates as a starting point (e.g., D-mannitol,[5] D- and L-arabinose,[6] or L-ascorbic acid[6,7]), but these provide only a single enantiomer from the natural sugar. More recent reports describe chemomicrobiological syntheses of D- or L-carnitine.[8]

As part of a program to develop carnitine analogues as possible modulators of fatty-acid transport, we recently reported a new synthesis of D,L-carnitine[9] as well as the preparation of several previously unknown racemic methylated analogues.[10] Herein we report the chromatographic resolution of ethyl 4-(dimethylamino)-3-hydroxybutanoate[9,11] (**3**) via the ester formed with (*S*)-(+)-α-methoxyphenylacetic acid.[12] The separated diastereomers are easily and efficiently converted to the enantiomers of carnitine. Furthermore, the utility of this method for obtaining the enantiomers of carnitine analogues is illustrated by the preparation and isolation of all four stereoisomers of 4-methylcarnitine via the chromatographic resolution of ethyl 4-(dimethylamino)-3-hydroxypentanoate.

Results and Discussion

As shown in Scheme I, compound **3** was esterified to (*S*)-(+)-α-methoxyphenylacetic acid by using dicyclohexylcarbodiimide and (dimethylamino)pyridine in CH_2Cl_2[13] to give a 1:1 mixture of diastereomers **5a** and **5b**. The two diastereomers were readily distinguished by ^1H NMR in that the dimethylamino resonances occurred at 2.27 and 2.13 ppm for **5a** and **5b**, respectively. Flash chromatography of this mixture on silica gel using 40:5:1 hexane/ethyl acetate/Et_3N as eluent afforded (after two passes) 76% of pure **5b** and 60% of pure **5a** (isolated chromatographed yields).

The lower yield for **5a** resulted from trailing of the leading band **5b** during chromatography (such that several fractions of **5a** were contaminated with small amounts of **5b**). However, it should be noted that the elution order may be reversed (so that the precursor to **1a** is contained

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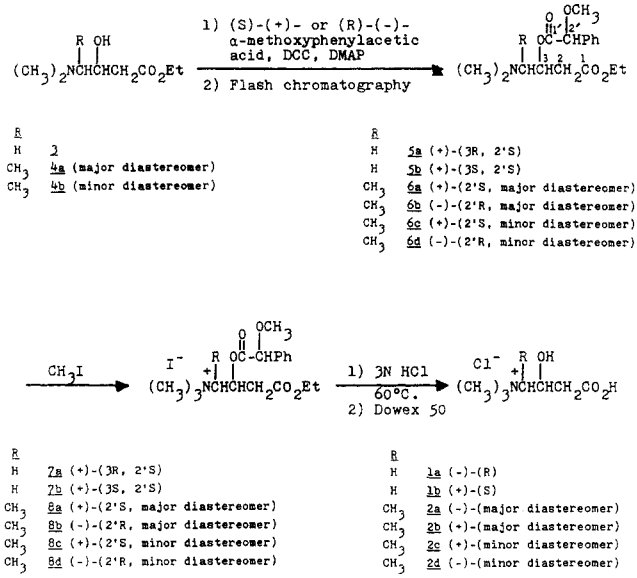
Scheme I



in the leading band) by using (*R*)-(−)-α-methoxyphenylacetic acid as the resolving agent.

Compounds **5a** and **5b** were then quantitatively quaternized with CH_3I/acetone to give **7a** and **7b**, respectively. These diesters were completely hydrolyzed in 3 N HCl at 60 °C to provide **1a** or **1b** in 90–93% yield. The resolving agent may be easily recovered (75–80% recovery) in optically pure form at this point.

Final purification of **1a** and **1b** was achieved by ion-exchange chromatography (Dowex 50) to give L-(−)-carnitine chloride (**1a**) in 54% overall yield from **3** and D-(+)-carnitine chloride (**1b**) in 71% overall yield from **3**.

Our early preparations of **5a** and **5b** utilized (*S*)-(+)-α-methoxyphenylacetyl chloride (from the acid and $SOCl_2$)[14] and also provided high yields. However, the chromatographic purification of **5a**, the trailing isomer and precursor to L-carnitine, was complicated in this case by the coelution of a small amount of byproduct, which was not characterized. No complications of this nature occurred with the DCC-mediated preparations of **5a** and **5b**.

The general approach described above was then used to prepare the enantiomers of 4-methylcarnitine (**2a–d**). Thus a diastereomeric mixture of ethyl 4-(dimethylamino)-3-hydroxypentanoate (**4a** and **4b**), prepared as previously reported,[10] was separated on a silica flash chromatography column to provide pure **4a** (major diastereomer) and **4b** (minor diastereomer) in relative amounts of 3:1. These diastereomers were readily distinguished by their ^1H NMR spectra (as well as TLC) in that the chemical shifts for the $CHCH_3$ methyl doublets differed by 0.12 ppm. It should be noted that the relative stereochemistries of these diastereomeric *d,l* pairs and the absolute stereochemistries of the final 4-methylcarnitine stereoisomers were not determined.

The major and minor diastereomers, **4a** and **4b**, were esterified to (*S*)-(+)-α-methoxyphenylacetic acid as described above to provide **6a** (plus a diastereomer) and **6c** (plus a diastereomer). Each compound was readily distinguished from its diastereomer as a result of significant chemical shift differences (0.13 ppm) between the dimethylamino singlets in the ^1H NMR spectra. However, in this case the R_f values for the diastereomer mixtures were considerably closer than those for **5a** and **5b**, and tailing of the leading isomer (**6a** or **6c**) made it difficult to obtain reasonable yields of pure trailing isomer. Therefore, only pure leading isomer was carried forward. (Mixed fractions may be rechromatographed or hydrolyzed and recycled). In order to obtain the other stereochemistries, additional **4a** or **4b** was esterified to (*R*)-(−)-α-methoxyphenylacetic acid to provide **6b** (plus a diastereomer) and **6d** (plus a diastereomer). Compounds **6b** and **6d** (the enantiomers of **6a** and **6c**, respectively) were now the leading isomers during chromatography and were isolated in pure form. Pure enantiomers **6a–d** were then each carried on, as described previously, to provide the stereoisomers of 4-methylcarnitine (**2a–d**) in ca. 40% overall yield from **4a** or **4b**.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM 360 (60 MHz) or GE 300-WB FT-NMR (300 MHz) spectrometer. IR spectra were obtained on a Beckman Acculab 2 spectrophotometer. Preparative flash chromatographic separations were performed on EM Reagents silica, 230–400 mesh, at flow rates of 2 in./min. All solvents were distilled prior to use. Optical rotations were performed at ambient temperature on a Perkin-Elmer 141 polarimeter in 1-dm cells of 1-mL capacity. Unless otherwise indicated, R_f values were obtained by using Fisher Redi-Plates, silica gel, 5 × 10 cm (0.25-mm layer). Elemental analyses were performed at Atlantic Microlab of Atlanta, GA.

(+)-(3*R*,2′*S*)- and (+)-(3*S*,2′*S*)-Ethyl 4-(Dimethylamino)-3-[(2-methoxy-2-phenylacetyl)oxy]butanoate (5a and 5b, Respectively). A solution containing **3** (630 mg, 3.6 mmol), DCC (1.15 g, 5.57 mmol), (*S*)-(+)-α-methoxyphenylacetic acid (0.62 g, 3.73 mmol), and (dimethylamino)pyridine (0.46 g, 3.77 mmol) in CH_2Cl_2 (15 mL) was stirred for 24 h at room temperature. The solution was filtered, the DCU washed on the filter with ether, and the solvent removed on a rotary evaporator. The residue was triturated with 40:5:1 hexane/ethyl acetate/Et_3N (15 mL) and the mixture filtered. After removal of the solvent from the filtrate, this trituration process was repeated. The residue (now free of most DCU) was flash chromatographed (5 × 13 cm column, 40:5:1 hexane/ethyl acetate/Et_3N) to provide 455 mg (76%) of **5b** (R_f 0.79, ether): ^1H NMR ($CDCl_3$) δ 7.6–7.2 (m, 5 H, aromatic), 5.41 (m, 1 H, CH_2CHCH_2), 4.73 (s, 1 H, $CHOCH_3$), 4.07 (q, 2 H, OCH_2CH_3), 3.44 (s, 3 H, OCH_3), 2.9–2.1 (m, 4 H, CH_2CHCH_2), 2.13 (s, 6 H, $(CH_3)_2N$), 1.22 (t, 3 H, OCH_2CH_3); IR (liquid film) 1722 (C=O) cm^{-1}; $[\alpha]^{25}_D$ +27.4° (*c* 1.22, $CHCl_3$).

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.19; H, 7.81; N, 4.28.

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Further elution gave 305 mg of a mixture of **5a** and **5b** followed by 153 mg of pure **5a** (R_f 0.55, ether). The mixed fractions were again subjected to flash chromatography (3 × 13 cm column) using the same eluent to provide an additional 200 mg of pure **5a** and 60 mg of a mixture of **5a** and **5b**. The total yield of pure **5a** was 353 mg (60%): ^{1}H NMR ($CDCl_3$) δ 7.6–7.2 (m, 5 H, aromatic), 5.38 (m, 1 H, CH_2CHCH_2), 4.75 (s, 1 H, $CHOCH_3$), 3.90 (q, 2 H, OCH_2CH_3), 3.43 (s, 3 H, OCH_3), 2.7–2.2 (m, 4 H, CH_2CHCH_2), 2.27 (s, 6 H, $N(CH_3)_2$), 1.12 (t, 3 H, OCH_2CH_3); IR (liquid film) 1715 (C=O) cm^{-1}; $[\alpha]^{25}_D$ +56.4° (*c* 1.10, $CHCl_3$).

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.23; H, 7.81; N, 4.28.

(+)-(3*R*,2′*S*)- and (+)-(3*S*,2′*S*)-Ethyl 3-[(2-Methoxy-2-phenylacetyl)oxy]-4-(trimethylammonio)butanoate Iodide (7a and 7b, Respectively). In a typical preparation, a solution containing diastereomer **5a** or **5b** (350 mg, 1.08 mmol) and CH_3I (307 mg, 2.20 mmol) in 10 mL of acetone was stirred overnight (16–18 h). The solvent was removed in vacuo to provide **7a** or **7b** (97% and 99% yields, respectively) as a foamy residue, which appeared pure on the basis of the ^{1}H NMR spectrum. Crude **7a** was crystallized from 1:1 EtOH/Et_2O (without heating) to give white flakes, mp 117–118 °C: ^{1}H NMR ($CDCl_3$) δ 7.7–7.1 (m, 5 H, aromatic), 6.0–5.4 (m, 1 H, CH_2CH), 4.93 (s, 1 H, $CHOCH_3$), 4.7–3.5 (m, 4 H, NCH_2 and OCH_2CH_3), 3.42 (s, 12 H, $N(CH_3)_3$ and OCH_3), 2.73 (d, 2 H, CH_2CO_2Et), 1.17 (t, 3 H, OCH_2CH_3); IR (KBr) 1723, 1706 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +17.4° (*c* 1.03, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}INO_5$: C, 46.46; H, 6.07; N, 3.01; I, 27.27. Found: C, 46.43; H, 6.08; N, 3.00; I, 27.35.

Crude **7b** was crystallized from 1:1 EtOH/Et_2O (without heating) to give pale yellow crystals, mp 65–68 °C: ^{1}H NMR ($CDCl_3$) δ 7.7–7.0 (m, 5 H, aromatic), 5.9–5.2 (s, 1 H, CH_2CH), 4.8 (s, 1 H, $CHOCH_3$), 4.6–3.4 (m, 4 H, OCH_2CH_3 and NCH_2), 3.7 (q, 2 H, OCH_2CH_3 from EtOH), 3.40 (s, 3 H, OCH_3), 3.12 (s, 9 H, $N(CH_3)_3$), 2.9 (d, 2 H, CH_2CO_2Et), 1.27 (t, 3 H, OCH_2CH_3), 1.25 (t, 3 H, OCH_2CH_3 from EtOH); IR (KBr) 1736, 1719 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +71.6° (*c* 0.97, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}INO_5 \cdot C_2H_5OH$: C, 46.97; H, 6.70; N, 2.74; I, 24.81. Found: C, 46.72; H, 6.51; N, 2.72; I, 24.73.

(*R*)-(−)- and (*S*)-(+)-3-Hydroxy-4-(trimethylammonio)butanoic Acid Chloride (1a and 1b, Respectively). In a typical preparation, diester **7a** or **7b** (139 mg, 0.30 mmol) was dissolved in 8 mL of 3 N HCl, heated at 60 °C for 2 h, and allowed to stand at ambient temperature overnight (16 h). The resulting mixture was extracted with $CHCl_3$ (3 × 5 mL) to remove (*S*)-(+)-α-methoxyphenylacetic acid (75–80% recovery). The aqueous layer was concentrated to dryness in vacuo (40 °C). The residue was purified and converted to the chloride form by chromatography on a Dowex 50X8-200 column (H^+ form, 6 × 1.5 cm). The column was eluted with H_2O until the eluent was no longer yellow (200 mL) followed by 2 N HCl. The fractions containing product (500 mL) were detected by spotting the eluent on a silica TLC plate without elution and staining with I_2. These were concentrated to provide 53 mg (90%) of **1a** or **1b** as a clear oil. In each case the ^{1}H NMR spectrum was identical with that for D,L-carnitine.

Enantiomers **1a** and **1b** were each crystallized from 1:1 EtOH/Et_2O to provide white, hygroscopic powders. For enantiomer **1a**: mp 134–136 °C; $[\alpha]^{25}_D$ −21.8° (*c* 1.00, H_2O) (lit.[4f] mp 142 °C, $[\alpha]^{25}_D$ −23.7°). For enantiomer **1b**: mp 135–137 °C; $[\alpha]^{25}_D$ +23.1° (*c* 1.65, H_2O) (lit.[4f] mp 142 °C, $[\alpha]^{25}_D$ +23.7°).

The $CHCl_3$ extracts containing recovered resolving agent were concentrated to dryness, and the residue was passed through a short silica gel column (ether eluent). The solvent was removed from the resulting solution and the residue crystallized from hexane to provide a white solid, mp 64.5–66 °C: $[\alpha]^{20}_D$ +143.8° (*c* 1.000, EtOH) [lit.[15] mp 64–65 °C, $[\alpha]^{25}_D$ +149.4° (*c* 0.964, EtOH)].

Ethyl 4-(Dimethylamino)-3-hydroxypentanoate (4a and 4b). A mixture of diastereomers **4a** and **4b** was prepared according to a procedure that we previously reported.[10] Typically, the separation of 2 g of this mixture on a silica flash chromatography column (31.5 × 3.0 cm column, 20:5:1 hexane/EtOAc/Et_3N eluent) provided 85% of the applied mass as two fractions. The leading fraction (R_f 0.42, alumina, $CHCl_3$ eluent) contained 1.28 g of major diastereomer **4a**, and the trailing fraction (R_f 0.31, alumina, $CHCl_3$ eluent) contained 0.42 g of the minor diastereomer **4b**, representing a 3:1 ratio for formation of these diastereomers. (Note that relative amounts of **4b** are higher than previously observed.)[10] The complete characterization of **4a** has been reported.[10] For minor diastereomer **4b**: ^{1}H NMR ($CDCl_3$) δ 4.4–3.5 (m, 3 H, OCH_2CH_3 and $CHOH$), 3.3–2.7 (m, 1 H, OH), 2.7–2.1 (m, 3 H, CH_3CH and CH_2CO_2Et), 2.24 (s, 6 H, $N(CH_3)_2$), 1.28 (t, 3 H, OCH_2CH_3), 1.02 (d, 3 H, $CHCH_3$); IR (KBr) 3450 (OH), 1725 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.22; H, 10.12; N, 7.39.

Preparation of the Four Stereoisomers of Ethyl 3-[(2-Methoxy-2-phenylacetyl)oxy]-4-(trimethylammonio)pentanoate Iodide (8a–d). In a typical preparation, **4a** and **4b** (500 mg, 2.65 mmol) were each esterified with (*S*)-(+)-α-methoxyphenylacetic acid, and the resulting diastereomers were separated via flash chromatography (5 × 13 cm column) as described above for the preparations of **5a** and **5b**. However, in this case the fractions containing the pure leading diastereomer were isolated, and those mixed fractions enriched in the leading isomer were combined and chromatographed on a second flash column (3 × 23 cm column). The latter process was repeated once to provide, from an average run, 210 mg (47%) of pure **6a** (R_f 0.70, ether eluent) or **6c** (R_f 0.63, ether eluent), respectively. In each case the purity of the leading diastereomer was readily determined by TLC and ^{1}H NMR, the latter exhibiting significantly different chemical shift values (0.13 ppm) for the $N(CH_3)_2$ singlet of the diastereomers. For **6a**: ^{1}H NMR ($CDCl_3$) δ 7.57–7.10 (m, 5 H, aromatic), 5.6–5.2 (m, 1 H, $CHCH_2$), 4.71 (s, 1 H, $CHOCH_3$), 4.06 (q, 2 H, OCH_2CH_3), 3.43 (s, 3 H, OCH_3), 2.80–2.10 (m, 3 H, $CHCH_3$ and CH_2CO_2Et), 2.07 (s, 6 H, $N(CH_3)_2$), 1.21 (t, 3 H, OCH_2CH_3), 0.66 (d, 3 H, $CHCH_3$); IR (liquid film) 1745 (shoulder), 1733 (C=O) cm^{-1}; $[\alpha]^{21}_D$ +47.9° (*c* 1.07, $CHCl_3$). For **6c**: ^{1}H NMR ($CDCl_3$) δ 7.60–6.90 (m, 5 H, aromatic), 5.53–4.87 (m, 1 H, $CHCH_2$), 4.71 (s, 1 H, $CHOCH_3$), 4.08 (q, 2 H, OCH_2CH_3), 3.42 (s, 3 H, OCH_3), 3.13–2.18 (m, 3 H, $CHCH_3$ and CH_2CO_2Et), 2.09 (s, 6 H, $N(CH_3)_2$), 1.24 (t, 3 H, OCH_2CH_3), 0.55 (d, 3 H, $CHCH_3$); IR (liquid film) 1745 (shoulder), 1732 (C=O) cm^{-1}; $[\alpha]^{21}_D$ +39.6° (*c* 0.930, $CHCl_3$).

Similarly, **4a** and **4b** were each esterified to (*R*)-(−)-α-methoxyphenylacetic acid and the products chromatographed exactly as above to provide similar yields of the enantiomers of **6a** and **6c**, namely, **6b** and **6d**, respectively. (Note that **6b** and **6d** were now the leading isomers during chromatography.) Accordingly, the R_f values as well as ^{1}H NMR and IR spectra were identical with those for **6a** and **6c**. For **6b**: $[\alpha]^{21}_D$ −45.2° (*c* 0.470, $CHCl_3$). For **6d**: $[\alpha]^{23}_D$ −39.7° (*c* 1.03, $CHCl_3$).

Oily products **6a–d** were not further characterized but were each (150 mg, 0.45 mmol) converted to the quaternary ammonium iodides **8a–d**, respectively, in quantitative yields as described above for the preparations of **7a** and **7b**. The crude products were crystallized from 1:1 EtOH/Et_2O as before and characterized. For **8a**: mp 122.5–124 °C; $[\alpha]^{25}_D$ +40.4° (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.6–7.2 (m, 5 H, aromatic), 5.75–5.2 (m, 1 H, $CHCH_2$), 4.8 (s, 1 H, $CHOCH_3$), 4.65–3.7 (m, 3 H, $CHCH_3$ and OCH_2CH_3), 3.38 (s, 3 H, OCH_3), 3.24 (s, 9 H, $N(CH_3)_3$), 3.03–2.65 (m, 2 H, CH_2CO_2Et), 1.46 (d, 3 H, $CHCH_3$), 1.23 (t, 3 H, OCH_2CH_3); IR (KBr) 1743, 1725 (C=O) cm^{-1}.

Anal. Calcd for $C_{19}H_{30}INO_5$: C, 47.61; H, 6.31; N, 2.92; I, 26.47. Found: C, 47.62; H, 6.34; N, 2.92; I, 26.50.

For **8b**: mp 121.5–123 °C; $[\alpha]^{25}_D$ −40.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR and IR spectra were identical with those for **8a**.

Anal. Calcd for $C_{19}H_{30}INO_5$: C, 47.61; H, 6.31; N, 2.92; I, 26.47. Found: C, 47.46; H, 6.32; N, 2.86; I, 26.59.

For **8c**: mp 140–142 °C; $[\alpha]^{23}_D$ +48.0° (*c* 0.830, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45–7.10 (m, 5 H, aromatic), 5.95–5.5 (m, 1 H, $CHCH_2$), 4.73 (s, 1 H, $CHOCH_3$), 4.5 (q, 1 H, CH_3CH), 4.12 (q, 2 H, OCH_2CH_3), 3.38 (s, 3 H, OCH_3), 3.0–2.6 (m, 2 H, CH_2CO_2Et), 1.4–1.1 (m, 6 H, $CHCH_3$ and OCH_2CH_3); IR (KBr) 1753 (shoulder), 1735 (C=O) cm^{-1}.

Anal. Calcd for $C_{19}H_{30}INO_5$: C, 47.61; H, 6.31; N, 2.92; I, 26.47. Found: C, 47.70; H, 6.36; N, 2.88; I, 26.43.

For **8d**: mp 140–142 °C; $[\alpha]^{23}_D$ −45.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR and IR spectra were identical with those for **8c**.

Anal. Calcd for $C_{19}H_{30}INO_5$: C, 47.61; H, 6.31; N, 2.92; I, 26.47. Found: C, 47.49; H, 6.34; N, 2.90; I, 26.63.

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Preparation of the Racemic Minor Diastereomer of 3-Hydroxy-4-(trimethylammonio)pentanoic Acid Chloride (2). Minor diastereomer **4b** was quaternized with CH_3I and hydrolyzed in concentrated HCl to form racemic minor diastereomer **2** according to the procedure reported[10] for the preparation of racemic major diastereomer **2** from **4a**. Yields were essentially the same as those observed for the major diastereomer. For racemic minor diastereomer **2**: mp 190–192 °C dec ($EtOH/Et_2O$); ^1H NMR (D_2O) δ 4.93–4.40 (m, 1 H, $CHOH$), 3.46 (q, 1 H, $CHCH_3$), 3.1 (s, 9 H, $N(CH_3)_3$), 2.56 (d, 2 H, CH_2CO_2H), 1.37 (m, 3 H, $CHCH_3$); IR (KBr) 1718 (C=O) cm^{-1}.

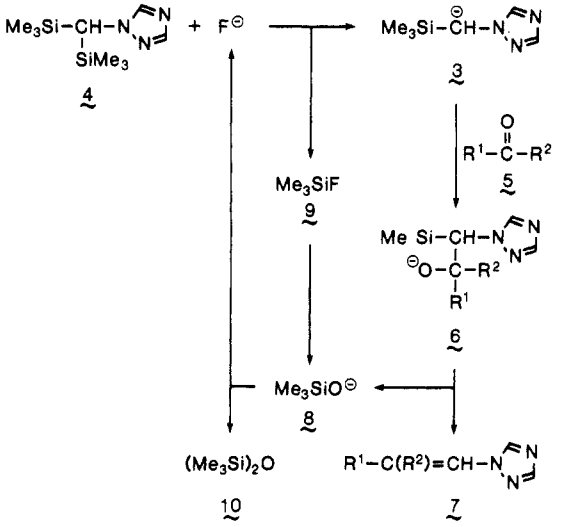
Anal. Calcd for $C_8H_{18}NO_3Cl \cdot {}^1/_4H_2O$: C, 44.44; H, 8.62; N, 6.48. Found: C, 44.47; H, 8.66; N, 6.46.

This unusually hygroscopic salt was also analyzed as the tetraphenylborate derivative:[15] mp 156–160 °C dec (acetone/H_2O). Anal. Calcd for $C_{32}H_{38}NO_3B$: C, 77.57; H, 7.73; N, 2.83. Found: C, 77.53; H, 7.75; N, 2.83.

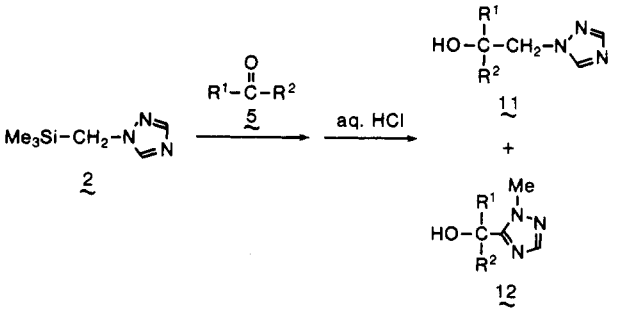
Preparation of the Four Stereoisomers of 3-Hydroxy-4-(trimethylammonio)pentanoic Acid Chloride (2a–d). Compounds **8a–d** were each hydrolyzed in 3 N HCl and purified by ion-exchange chromatography according to the procedure used above for the syntheses of **1a** and **1b** to provide 90% yields of 4-methylcarnitines **2a–d**, respectively. The hygroscopic products were crystallized from 1:1 $EtOH/Et_2O$ to provide white solids. For enantiomers **2a** and **2b**, the 300-MHz ^1H NMR spectra were identical with that for the racemic major diastereomer of **2** (previously reported).[10] Additionally, for **2a**: mp 190–191 °C dec ($EtOH/Et_2O$); $[\alpha]^{23}_D$ −11.6° (*c* 0.870, H_2O). For **2b**: mp 188.5–190 °C dec ($EtOH/Et_2O$); $[\alpha]^{23}_D$ +11.6° (*c* 0.830, H_2O).

For enantiomers **2c** and **2d**, the 300-MHz ^1H NMR spectra were identical with that for the racemic minor diastereomer of **2** (given above). Additionally, for **2c**: mp 199.5–200.5 °C dec ($EtOH/Et_2O$); $[\alpha]^{22}_D$ +17.4° (*c* 1.07, H_2O). For **2d**: mp 204.5–205.5 °C dec ($EtOH/Et_2O$); $[\alpha]^{22}_D$ −16.9° (*c* 0.830, H_2O).

Scheme I



Scheme II



A Novel Route to 1-Vinyl-1,2,4-triazoles by the Fluoride-Catalyzed Peterson Reaction of 1-[Bis(trimethylsilyl)methyl]-1,2,4-triazole with Carbonyl Compounds

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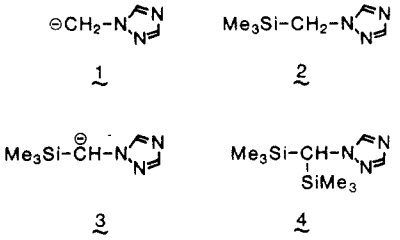
We recently found that the reaction of carbonyl compounds with (1,2,4-triazol-1-yl)methyl anion (**1**) generated from the fluoride-induced desilylation of 1-[(trimethylsilyl)methyl]-1,2,4-triazole (**2**) leads to 2-(1,2,4-triazol-1-yl)ethanols.[1] We now report that 1,2,4-triazol-1-yl(trimethylsilyl)methyl anion (**3**), generated from fluoride-induced desilylation of 1-[bis(trimethylsilyl)methyl]-1,2,4-triazole (**4**), reacts with carbonyl compounds **5** to give 1-vinyl-1,2,4-triazoles **7** in good yields.



Results and Discussion

Preparation of 1-[Bis(trimethylsilyl)methyl]-1,2,4-triazole (4). Treatment of 1,2,4-triazole with bis(trimethylsilyl)chloromethane[2] in the presence of potassium carbonate in DMF at 60 °C gave **4** (61%) accompanied by **2** (4%), which could be removed by flash chromatography. The formation of **2** is considered to proceed via **4**, which undergoes nucleophilic attack by the 1,2,4-triazol-1-yl anion under the reaction conditions to cause cleavage of the carbon–silicon bond. Prolongation of the reaction time to more than 40 h decreased the yield of **4** but increased the formation of **2**.

Fluoride-Catalyzed Reaction of 1-[Bis(trimethylsilyl)methyl]-1,2,4-triazole (4) with Carbonyl Compounds 5. 1-[Bis(trimethylsilyl)methyl]-1,2,4-triazole (**4**) reacted smoothly with carbonyl compounds **5** in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) in THF at −20 °C to give the 1-vinyl-1,2,4-triazoles **7** in good yields. The results are summarized in the Table I. Although 1 equiv of base is generally necessary for silicon elimination of a β-silylethanol,[3] the formation of **7** proceeded with a catalytic amount of TBAF. This catalytic Peterson reaction can be explained by the process shown in the Scheme I. Fluoride anion induced desilylation of **4** generates the anion **3** by addition to the carbonyl compound **5**, leading to β-silylethoxide **6**. The subsequent elimination reaction of **6** affords the 1-vinyl-1,2,4-triazole **7** and the alkoxide **8**, which reacts with the fluorosilane **9** to regenerate fluoride anion. In other work, it has been reported that bis(trimethylsilyl)methyl isothiocyanate[4] undergoes a similar fluoride-catalyzed Pe-

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