(C_1), 134.1, 130.4, 130.3, and 129.3 (aryl), 119.7 (C_2), 57.5 (oCH_3), 42.2 (CH_2), 30.3 ($C{=}CCOCH_3$), and 29.6 (CH_2COCH_3). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.81. Found: C, 72.16; H, 6.62.

Also isolated by extraction (i.e., removal) of the other seven components of the **1a–2c** photochemical reaction mixture with pentane or petroleum ether were the three ketones **18**, **19**, and **20**. These three ketones could be further isolated from components **13a,b**, **14**, **15**, **16**, **17a**, and **17b** by column chromatography on neutral alumina as described above.

Ketone 18, 2-phenacyl-5-methylfuran: IR (GC–FTIR) 1705 (s), 1605 (w), and 1267 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9 (2 H, m, ortho aryl), 7.3–7.2 (3 H, m, meta and para aryl), 6.3 (2 H, m, furyl), 3.1 (2 H, CH_2) and 2.21 (3 H, CH_3); MS (EI), m/z 200 (P, 15), 105 (100), and 77 (42). **Methylenedihydrofuran 19** was unstable to heat and air and was not obtained pure: IR (GC–FTIR) 1669 (s), 1570 (s), 1203 (m), and 903 cm^{-1}; ^1H NMR δ 7.9–7.8 (2 H, m), 7.8–7.7 (3 H, m, meta and para aryl), 3.39 (1 H, s, br, H_4), 4.90 (2 H, m, $C{=}CH_2$), and 2.38 (3 H, s, CH_3); MS (EI), m/z 200 (P, 100), 123 (78), and 77 (85). **Ketone 20, 3-benzoyl-2,5-dimethylfuran,** was obtained pure by HPLC: IR (GC–FTIR) 1694 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (2 H, m, ortho aryl), 7.38 (3 H, m, meta and pure aryl), 6.35 (1 H, s, H_4), 2.38 (3 H, s, C_2 CH_3), and 2.32 (3 H, s, C_5 CH_3); MS (EI); m/z 206 (P, 14), 129 (100), and 77 (40); ^{13}C NMR δ 196.9 (C=O) 133.6, 128.9, 128.7 (aryl), 155.8 (C_3), 151.9 (C_5), 123.8 (C_2), 108.7 (C_4), 29.8 (C_2 CH_3), and 13.3 (C_5 CH_3); MS (EI), m/z 200 (P, 60), 185 (100), 105 (40), and 77 (30). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.87. Found: C, 75.71; H, 8.68.

From the hexane-soluble extracts of the total reaction mixture after short-path distillation was also obtained via column chromatography on neutral alumina, eluting with hexane, the **2 + 2 furan cyclodimer 16**: IR (GC–FTIR) 1221, 1019, and 778 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 ($C{=}CCH_3$) and 1.45 (CCH_3); MS (EI), m/z 190 (P, 19), 95 (100), 43 (18). Later fractions from the alumina chromatography (with hexane) contained a mixture of ***exo*-phenyl- and *endo*-phenyloxetanes 16, 1,3-dimethyl-6-methoxy-6-phenyl-2,7-dioxabicyclo[3.2.0]hept-3-enes**: ^1H NMR ($CDCl_3$) δ 7.3 (5 H, m), 5.82 and 5.78 (1 H, m, OC=CH), 4.16 and 3.41 (1 H, br s, H_5 of *endo*-phenyl and *exo*-phenyl isomers), 3.08 (3 H, s, OCH_3 of both isomers), 1.80 and 1.71 (3 H, s, $C{=}CCH_3$ and CCH_3); MS (EI), m/z 232 (P, 20), 217 (63), and 136 (100).

Finally, there was obtained the ***E*,*Z* isomeric mixture of dienyl acetates 15**: IR (GC–FTIR) 1772, 1692, 1617, 1202 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (5 H, m, aryl), 5.92 (1 H, m), 5.83 (1 H, m), 3.15 (3 H, s, OCH_3), 2.22 (3 H, s, $C{=}CCH_3$), and 2.17 (3 H, s, $OOCCH_3$); MS (EI), m/z 232 (P, 20), 190 (100), 175 (35), and 43 (90).

Hydrolysis of *E* and *Z* Mixture 17a,b. To a solution of **17a,b** (0.1 g) in 90% aqueous THF was added 2 drops of concentrated HCl. The solution was allowed to stand for 4 h at 25 °C and was then poured onto 40 g of ice–water and extracted with 3 × 10 mL of dichloromethane. Washing of the combined extracts with water, drying (Na_2SO_4), and evaporation of the solvent gave an oil, **3-benzoylhexane-2,5-dione**: ^1H NMR ($CDCl_3$) δ 7.98 (2 H, d, ortho aryl), 7.59 (1 H, t, para aryl), 7.48 (2 H, t, meta aryl), 5.04 (1 H, t, $J_{3,4}$ = 7.1, H_3), 2.97 and 3.17 (1 H each, dd, $J_{4,3}$ = 7.1, $J_{4,4}$ = 8.2, H_4), 2.14 and 2.19 (3 H each, s, CH_3); IR (GC–FTIR) 1731 (vs), 1693 cm^{-1}; MS (EI), m/z 175 (3), 158 (20), 133 (30), 105 (100), 96 (20), 77 (50), 43 (65%); ^{13}C NMR ($CDCl_3$) δ 206.2 (C_5), 203.1 (C_2), 196.9 (PhC=O), 136.6 (1-aryl), 134.5 (para aryl), 129.6 (meta aryl), 129.4 (ortho aryl), 57.2 (C_3), 42.35 (C_4), 30.0 and 29.6 (CH_3).

Photochemical Reaction of Methyl Benzoate with 2,3,4,5-Tetramethylfuran (2d). A solution of ester **1a** (6 g, 0.04 mol) and 2,3,4,5-tetramethylfuran (**2d**)[13] (12 g, 0.10 mol) in spectrograde pentane (120 mL) was irradiated with a Rayonet chamber reactor using 254-nm lamps for 60 h. Evaporation of solvent and distillation of unreacted ester and furan left a yellow residue, which was short-path distilled to afford dione **22**, bp 70–80 °C (0.8 mm) (1.4 g, 41% based on unrecovered ester **1a**): ^1H NMR ($CDCl_3$) δ 8.00 (2 H, d, ortho aryl), 7.6–7.3 (3 H, m, aryl), 3.88 (3 H, s, OCH_3), 2.07 (6 H, s, CH_3CO), and 1.80 (6 H, s, CCH_3); ^{13}C NMR ($CDCl_3$) δ 216.0 (C=O), 199.3 (C=O), 143.9 (C=CO-CH_3), 132.7, 129.5, 128.2 (aryl), 114.8 (C=$COCH_3$), 51.9 (OCH_3), 14.9 ($COCH_3$), 17.2 (C=$OOCH_3$), 13.9, 13.8, 11.2, and 9.98 (CH_3C and CH_3C); MS (CI), m/z 260 (14), 245 (6), 217 (30), and 43 (100).

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Registry No. **1a**, 93-58-3; **2a**, 110-00-9; **2b**, 534-22-5; **2c**, 625-86-5; **2d**, 10599-58-3; **3a**, 117203-20-0; **3b**, 117305-67-6; **3d**, 117305-66-5; **4a**, 117203-21-1; **4d**, 61063-47-6; **5**, 56139-59-4; **6**, 117203-22-2; **7**, 117203-23-3; **9**, 720-75-2; **10a**, 117203-24-4; **10b**, 117203-25-5; **11**, 117203-26-6; **12**, 117203-27-7; **13a**, 117203-28-8; **13b**, 117226-18-3; **14**, 117203-35-7; **15**, 117203-34-6; *exo*-**16**, 117306-58-8; *endo*-**16**, 117203-33-5; **17a**, 117203-29-9; **17b**, 117203-30-2; **18**, 117203-31-3; **19**, 117203-32-4; **20**, 66685-28-7; **22**, 117203-36-8; $PhCO(CH_2)_2CO_2H$, 2051-95-8; furanaldehyde, 98-01-1; 3-benzoylhexane-2,5-dione, 81396-46-5; benzaldehyde, 100-52-7.

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Synthesis of Racemic (*E*)- and (*Z*)-2,3-Methanotyrosine: New Cyclopropane Analogues of Tyrosine

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Both (*E*)- and (*Z*)-2,3-methanotyrosine [(*E*)-2,3-MeTyr and (*Z*)-2,3-MeTyr] have been synthesized from the monoester **5**, which was prepared by cyclopropanation of the benzalmalonate **3**, followed by regioselective saponification and Curtius rearrangements to introduce the amino group stereoselectively. The *E* and *Z* configurations resulting unambiguously from these synthetic transformations were corroborated by the vicinal coupling constants of the cyclopropane ring protons. Ultraviolet spectroscopy confirmed the conjugative ability of the cyclopropane ring.

For some years now we have been engaged in the synthesis of 2,3-methano amino acids[1] both for incorporation into peptide hormones[2] in order to selectively restrict the peptide conformation[3] and stabilize amide bonds and as

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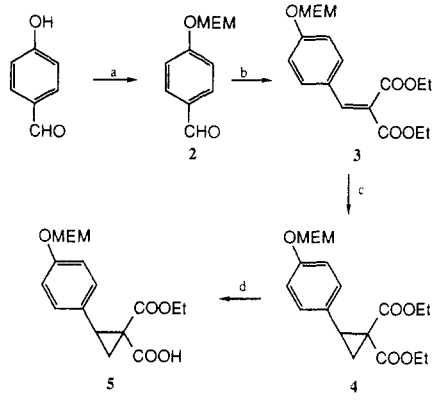
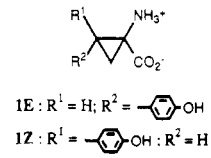
Scheme I[a]



[a] Reagents: (a) MEM-Cl, aqueous NaOH, CH_2Cl_2, PTC; (b) $CH_2(CO_2Et)_2$, $PipH^+Ac^-$, $PhCH_3$, Δ; (c) $(CH_3)_3SOI$, NaH, DMSO; (d) aqueous NaOH, 1.0 equiv, EtOH.

potential enzyme inhibitors[4] to use as mechanistic probes in studies of enzyme reactions.

Recently we reported[1c] the synthesis of (*Z*)-2,3-methanotyrosine ("*Z*-cyclopropyl tyrosine", **1Z**), which was



1E: $R^1 = H$; $R^2 =$

1Z: $R^1 =$: $R^2 = H$

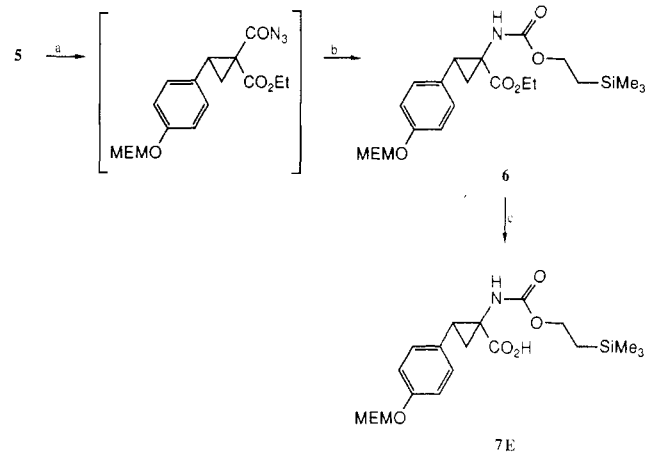
modeled on the route used earlier[1a] in the synthesis of (*Z*)-2,3-methanophenylalanine. This approach employed cyclopropanation of 4-benzylidene-2-phenyl-5(4*H*)-oxazolone and -thiazolone using diazomethane without isolation of the Δ^1-pyrazoline intermediates. This method suffered from a low yield deblocking of the amide and thioamide functions in the last step leading to the desired amino acids.

In an attempt to develop a more efficient, diastereoselective synthesis of both (*E*)- and (*Z*)-2,3-methanotyrosine (**1E**, **1Z**), we investigated a different synthetic approach, already recognized by other workers,[5] in which the key cyclopropanation is carried out on a 4-substituted benzalmalonate and the protected 1-amino group is subsequently introduced by using standard manipulations.

The method reported herein allowed both (*E*)- and (*Z*)-methanotyrosines to be synthesized by using as common intermediate the monoester **5** (Sheme I), prepared in 44% overall yield from 4-hydroxybenzaldehyde. In the first step, the (2-methoxyethoxy)methyl (MEM) ether[6] (**2**) was readily prepared by reaction of 4-hydroxybenzaldehyde with (2-methoxyethoxy)methyl chloride by using phase-transfer catalysis.[7] The MEM ether function provided the necessary protection of the phenolic hydroxyl group throughout the subsequent synthetic steps and was efficiently removed in nonaqueous acid (vide infra). Knoevenagel condensation of the protected 4-hydroxybenzaldehyde (**2**) with diethyl malonate gave the benzalmalonate **3**, which was cyclopropanated by using dimethylsulfoxonium methylide[8] to afford the desired cyclopropane derivative **4**. When dimethyl malonate was used in the Knoevenagel condensation, decarbomethoxylation to methyl 4-[(methoxyethoxy)methoxy]-cinnamate occurred, as evidenced by the disappearance of one of the methyl ester singlets in the ^1H NMR spectrum. Cyclopropanation of **3** with diazomethane did not yield **4**, but instead resulted in formation of a pyrazole derivative, apparently from the initially formed Δ^1-pyrazoline.[9]

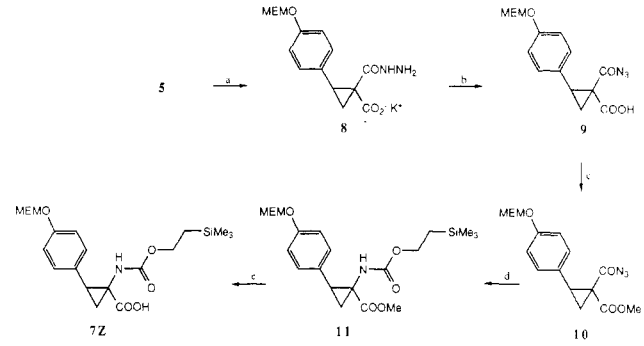
Treatment of **4** with 1 equiv of sodium hydroxide in ethanol resulted in selective hydrolysis of the less hindered ester function trans to the phenyl ring to yield the monoester **5**. It remained to convert either the carboxylic acid or ester function of **5** into a carbamate to obtain the desired (*E*)- and (*Z*)-2,3-methanotyrosine derivatives. Thus the azide afforded by reaction of **5** (Scheme II) with diphenyl

Scheme II[a]



[a] Reagents: (a) DPPA, TEA, $PhCH_3$; (b) $PhCH_3$, $(CH_3)_3SiCH_2CH_2OH$, Δ; (c) aqueous NaOH, EtOH, Δ.

Scheme III[a]



[a] Reagents: (a) (i) $KHCO_3$, EtOH, water; (ii) $NH_2NH_2 \cdot H_2O$, EtOH, Δ; (b) 1 M H_2SO_4, $NaNO_2$, Et_2O; (c) CH_2N_2, Et_2O; (d) $PhCH_3$, Δ, $(CH_3)_3SiCH_2CH_2OH$; (e) aqueous NaOH, EtOH.

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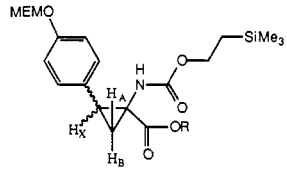
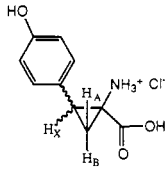
Table I. ^{1}H NMR Spectral Data of 2,3-Methanotyrosine Derivatives



6 : R = Et [a]
7 : R = H [a]
11: R = Me [a]

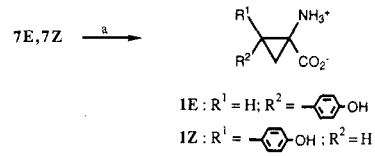


1 [b]

cmpd	chemical shift, δ						coupling constants, Hz		
	Ar	H_N	H_X	H_B	H_A	R	J_{AB}	J_{AX}	J_{BX}
1E	7.01; 6.63 (2 d)		2.82 (t)	1.90 (dd)	1.64 (dd)		−6.8	10.4	8.7
1Z	7.07; 6.71 (2 d)		2.99 (t)	1.82 (dd)	1.64 (dd)		−7.0	8.2	10.1
6	7.32; 7.01 (2 d)	5.82 (s)	2.88 (t)	2.18 (dd)	1.62 (dd)	3.82; 0.91	−5.4	9.7	8.4
11	7.18–6.89 (m)	5.02 (s)	2.91 (t)	2.03 (m)	1.67 (m)	3.72 (s)			
7E	7.19; 6.88 (2 d)	5.64 (s)	2.78 (t)	2.03 (dd)	1.51 (dd)		−5.4	9.8	8.4
7Z	7.11; 7.01 (2 d)	4.80 (s)	2.98 (t)	2.18 (m)	1.75 (m)				

[a] Solvent $CDCl_3$; int ref TMS group. [b] Solvent D_2O; int ref *p*-dioxane.

Scheme IV[a]



[a] Reagents: (a) (i) 4 N HCl–dioxane, anisole, *m*-cresol; (ii) $NaHCO_3$, H_2O (pH 5.6).

phosphazidate[10] was uneventfully converted to the 2-(trimethylsilyl)ethyl carbamate **6** after Curtius rearrangement followed by alcoholysis of the resulting isocyanate with 2-(trimethylsilyl)ethanol in 53% overall yield. 2-(Trimethylsilyl)ethanol, not surprisingly, gave higher yields of **6** than did *tert*-butyl alcohol. Furthermore, the [2-(trimethylsilyl)ethoxy]carbonyl protecting group[11] offers additional orthogonality to the protection scheme, being readily removed by either acidolysis or by treatment with tetraalkylammonium fluorides. Vigorous alkaline hydrolysis of the hindered ester function of **6** readily gave the (*E*)-2,3-methanotyrosine derivative **7E**.

The synthesis of (*Z*)-2,3-methanotyrosine was accomplished by using a somewhat longer route (Scheme III). Since **5** failed to give a well-characterized hydrazide, we found that the potassium salt of **5** could be converted to the hydrazide **8** in refluxing ethanolic hydrazine solution. Nitrosation of **8** yielded the azide **9**, which was esterified directly with diazomethane followed by rearrangement. This route was used because we found that Curtius rearrangement of the ester **10** was considerably more efficicient than that of the acid **9**. The fully blocked (*Z*)-2,3-methanotyrosine (**11**) was thus obtained in 40% overall yield from the monoester **5**. Saponification of **11** then furnished the desired carboxylic acid **7Z** uneventfully. Cleavage of the MEM ether and [2-(trimethylsilyl)ethoxy]carbonyl blocking groups from **7E** and **7Z** was accomplished by using 4 N HCl in dioxane (Scheme IV). Both (*E*)- and (*Z*)-2,3-methanotyrosines were obtained as zwitterions upon neutralization of their hydrochloride salts and recrystallization from water.

Table II. ^{13}C NMR Spectral Data of 2,3-Methanotyrosine Derivatives

cmpd	chemical shifts, δ				
	C_1	C_2	C_3	C_4	C_5
1E	39.9	30.6	17.0		170.1
1Z	38.8	29.2	17.0		172.3
6	40.9	34.5	20.4	156.9	170.0
11	39.2	31.9	21.1	156.4	172.3
7E	40.7	35.5	21.1	157.5	174.0
7Z	39.3	33.0	22.3	156.9	177.8

[a] Solvent $CDCl_3$; int ref $CDCl_3$, 77.0 ppm. [b] Solvent D_2O; int ref *p*-dioxane, 66.7 ppm.

All of the intermediates and final products were characterized by high field ^{1}H and ^{13}C NMR and the results are summarized in Tables I and II. Chemical shifts, spin-splitting patterns, and coupling constants of (*E*)- and (*Z*)-2,3-methanotyrosine were consistent with the configurational outcome of the synthetic manipulations discussed above and showed the expected similarities with the corresponding stereoisomers of 2,3-methanophenylalanine.[1a] The cyclopropane proton H_X appeared as well-resolved triplets and the geminal H_A and H_B protons appeared as doublets of doublets in all of the derivatives except **11** and **7Z**, appearing in these as broad multiplets. This difference may be due to s-cis/s-trans isomerism of the carbamate moiety in **11** and **7Z**, possibly induced by the vicinal phenyl ring. Unambiguous assignment of the cyclopropane ring protons in **6**, **1E**, and **1Z** was allowed by their chemical shifts and coupling constants, since H_X is always downfield of H_A and H_B due to deshielding by the phenyl ring and there is no exception to the rule that, for the vicinal protons of cyclopropanes, J_{cis} is always larger than J_{trans}.[12] Assignment of H_X, H_A, and H_B in **11** and **7Z** was possible by analogy with **6** and **7E** and by comparison with the corresponding (*Z*)-2,3-methanophenylanine derivatives. Interestingly, the coupling constants of **1E** and **1Z** are virtually identical with those of (*E*)- and (*Z*)-2,3-methanophenylalanine,[1a] respectively.

Some useful trends are evidenced by the ^{13}C NMR spectra (Table II). While both C_1 and C_2 of the *E* isomers appear downfield of the same atoms in the *Z* isomers, the

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Table III. UV Absorption of Amino Acids 1 and of L-Tyrosine[a]

amino acid	λ (nm)	ε
L-Tyr	200.5	14412
	223.5	8332
	274.5	1300
(*E*)-2,3-MeTyr (**1E**)	201.0	18768
	227.0	9164
	276.0	1176
(*Z*)-2,3-MeTyr (**1Z**)	201.0	24270
	229.5	12076
	274.5	1238

[a] 5×10^{-5} M in 0.1 N HCl.

reverse is true of C_3 (except in the amino acids, **1**) and of the carbonyl carbon atoms C_5. Notably, the (*E*)- and (*Z*)-2,3-methanophenylalanine derivatives[1a] exhibited the same trends. This suggests that ^{13}C chemical shifts may be a valuable method for the diastereochemical assignments of 2,3-methanoamino acid isomers.

The conjugative ability of the cyclopropane ring, due to partial character of the ring bonds, was examined by UV spectroscopy in the amino acids (**1**) using L-tyrosine as a reference (Table III). The n → π* transition band of L-tyrosine (223.5 nm) experienced considerable bathochromic and hyperchromic effects both in **1E** and **1Z** (3.5 and 6.0 nm bathochromic increments, respectively). This phenomenon was exhibited by derivatives of (*E*)- and (*Z*)-2,3-methanophenylalanine as well and has been attributed to conjugation of the carbonyl group with the aromatic ring through the cyclopropane ring.[2a] The expected greater degree of conjugation in **1Z** vis a vis **1E** is shown by the greater intensity and the larger bathochromic shift of the n → π* band. A significant hyperchromic effect is also revealed by the π → π* transition band near 200 nm. Double beam measurements[2a,13] showed that the π → π* and n → π* bands of **1** can be isolated by difference UV spectroscopy. This may allow the identification of 2,3-methanotyrosines in peptides incorporating them.

Incorporation of the stereoisomers **1E** and **1Z** into Leu^5-enkephalin is now in progress in this laboratory.

Experimental Section

All melting points (uncorrected) were taken on a Thomas Hoover melting point apparatus. ^1H and ^{13}C NMR spectra were recorded with a JEOL FX 90Q (operating at 100.0 and 22.5 MHz) or a Bruker AM 250 (operating at 250.0 and 62.9 MHz) spectrometer, using tetramethylsilane (TMS) or the trimethylsilyl group or *p*-dioxane (3.53 ppm downfield from TMS) as internal standards for ^1H NMR and *p*-dioxane (66.7 ppm downfield from TMS) or $CDCl_3$ (77.0 ppm downfield from TMS) as internal standards for ^{13}C NMR. Ultraviolet spectra were taken on a Gilford response UV–vis spectrophotometer at the same concentration of 2,3-methano and saturated (L-Tyr) amino acids.

TLC was performed on Whatman precoated silica gel plates with the following solvent systems (v/v): (I) EtOAc–hexanes (1:1), (II) EtOAc–hexanes (2:3); (III) $CHCl_3$–EtOH–acetic acid (90:10:1), (IV) EtOAc–acetic acid (100:1); (V) *n*-BuOH–acetic acid–water (4:1:5), upper layer; (VI) $CHCl_3$–MeOH–acetic acid (5:2:1).

Anhydrous $MgSO_4$ or K_2CO_3 (Baker) was used to dry the organic solutions during workups; 60–230-mesh (Baker) and 32–63 μM (Wöelm) silica gel were used for gravity and flash chromatography, respectively. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

All reactions were carried out under a nitrogen atmosphere.

Materials. (2-Methoxyethoxy)methyl chloride, Aliquat 336, *p*-hydroxybenzaldehyde, diethyl malonate, piperidine, trimethylsulfoxonium iodide, diazald, and 2-(trimethylsilyl)ethanol were purchased from Aldrich, 50% NaH in mineral oil from Alfa, and 4 N HCl in dioxane from Pierce. Dimethyl sulfoxide (Fisher) was distilled from KOH under reduced pressure prior to use, tetrahydrofuran from sodium metal, and toluene from calcium chloride; all other solvents were reagent grade and were used without further purification.

4-[(2-Methoxyethoxy)methoxy]benzaldehyde. (2). To a solution of *p*-hydroxybenzaldehyde (27.5 g, 0.225 mol) and 50% NaOH (18 mL) in water (180 mL), containing 5.1 mL of Aliquat 336, was added dropwise MEM-C (12.9 mL, 0.113 mol) in CH_2Cl_2 (180 mL). The reaction mixture was stirred overnight at room temperature. After separation from the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 × 180 mL). The combined organic extracts were washed with 10% Na_2CO_3 (3 × 180 mL) and brine (2 × 100 mL), dried, and evaporated under reduced pressure to give a red oil, which was eluted through a layer of silica gel (25 g) with EtOAc–hexanes (1:1). Upon solvent removal, 18.13 g (77%) of **2** was afforded, as a yellow oil; ^1H NMR ($CDCl_3$) δ 3.35 (s, 3 H, OCH_3), 3.38–3.48 (m, 2 H, OCH_2), 3.52–3.62 (m, 2 H, OCH_2), 5.34 (s, 2 H, $PhOCH_2$), 7.15 (d, J = 8.7 Hz, 2 H, Ar H), 7.82 (d, J = 8.8 Hz, 2 H, Ar H), 9.88 (s, 1 H, CHO).

Diethyl 4-[(2-Methoxyethoxy)methoxy]benzalmalonate (3). A solution of **2** (18 g, 85.6 mmol), diethyl malonate (110 mmol, 16.9 mL), piperidine (0.85 mL), and acetic acid (0.44 mL) in toluene (40 mL was heated to reflux overnight with azeotropic removal of water. Dilution with toluene (100 mL) was followed by acidic (1 N $KHSO_4$, 3 × 50 mL) and basic (5% $NaHCO_3$, 3 × 50 mL) washes. Evaporation of the dried organic phase gave 30 g (100%) of a yellow oil, which was distilled in vacuo (bp 227–229 °C (0.03 Torr)) to give 27.9 g (93%) of **3**: R_f(I) 0.68; ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz), 6 H, $CO_2CH_2CH_3$), 3.36 (s, 3 H, OCH_3), 3.45–3.62 (m, 2 H, OCH_2), 3.74–3.88 (m, 2 H, OCH_2), 4.32 (dq, J = 7 Hz, 4 H, $CO_2CH_2CH_3$), 5.29 (s, 2 H, $PhOCH_2$), 7.03 (d, J = 8.8 Hz, 2 H, Ar H), 7.42 (d, J = 9.1 Hz, 2 H, Ar H), 7.66 (s, 1 H, CH=C); ^{13}C NMR 13.9, 14.1, 58.9, 61.3, 61.5, 67.9, 71.6, 93.3, 116.4, 124.4, 126.6, 131.4, 141.5, 159.2, 164.3, 166.8.

Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.44; H, 6.87.

Diethyl 2-[4-[(2-Methoxyethoxy)methoxy]phenyl]cyclopropane-1,1-dicarboxylate (4). A solution of dimethylsulfoxonium methylide was prepared under N_2 from a 50% NaH mineral oil dispersion (1.62 g, 68 mmol), trimethylsulfoxonium iodide (14.9 g, 68 mmol), and DMSO (100 mL). After 20 min, a solution of **3** (21.7 g, 61.0 mmol) in THF (100 mL) was added dropwise over 20 min and after being stirred for 1 h at room temperature and 1 h at 50 °C, the solution was poured into ice-cold water (200 mL) and extracted with ether (3 × 200 mL). The combined ethereal extracts were washed with brine, dried, and evaporated to an oil, which was distilled in vacuo to afford 17.1 g (76%) of pure **4**; bp 175–180 °C (0.02 Torr); R_f(I) 0.74; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 3 H, cis $CO_2CH_2CH_3$), 1.28 (t, J = 7 Hz, 3 H, trans $CO_2CH_2CH_3$), 1.66 (dd, 1 H, ▽H), 2.11 (dd, 1 H, ▽H), 3.16 (ps t, 1 H, ▽H), 3.35 (s, 3 H, OCH_3), 3.46–3.58 (m, 2 H, OCH_2), 3.70–3.80 (m, 2 H, OCH_2), 3.87 (q, J = 7 Hz, 2 H, cis $CO_2CH_2CH_3$), 4.23 (q, J = 7 Hz, 2 H, trans $CO_2CH_2CH_3$), 5.21 (s, 2 H, OCH_2O), 6.92 (d, J = 8.8 Hz, 2 H, Ar H) 7.13 (d, J = 8.5 Hz, 2 H, Ar H); ^{13}C NMR δ 13.7, 14.1, 18.8 (▽CH_2), 31.7 (▽CH), 37.3 (▽C), 58.9, 61.0, 61.5, 67.7, 71.6, 93.6, 116.0, 128.1, 129.7, 156.6, 166.6, 169.8.

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.84; H, 7.30.

(*Z*)-1-(Ethoxycarbonyl)-2-[4-[(2-Methoxyethoxy)methoxy]phenyl]cyclopropanecarboxylic Acid (5). To a solution of **4** (14.8 g, 40.4 mmol) in EtOH (27 mL) was added dropwise a 50% NaOH solution (3.17 g, 39.6 mmol), diluted to 27 mL with water. The resulting solution was stirred for 48 h at room temperature, the EtOH was evaporated, and the remaining solution was diluted with water (20 mL) and extracted with Et_2O (2 × 50 mL). The aqueous phase was acidified to pH 2 with $KHSO_4$ and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried, and evaporated to a colorless oil, 11.8 g (95%, corrected for recovered starting material). Purification by elution through a silica gel column (4.0 × 40 cm) with 1% acetic acid in EtOAc afforded 10.5 g (78%) of pure **5** as an oil: R_f(III) 0.73; ^1H NMR ($CDCl_3$) δ 0.77 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 2.20–2.45 (m, 2 H, 2▽H), 2.90 (ps t, 1 H, ▽H), 3.36 (s, 3 H, OCH_3), 3.45–3.59 (m, 2 H, OCH_2), 3.71–3.81 (m, 2

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H, OCH_2), 4.30 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 5.24 (s, 2 H, OCH_2O), 7.07 (ps q, 4 H, Ar H); ^{13}C NMR δ 13.2, 21.3 (∇CH_2), 33.6 (∇CH), 39.9 (∇C), 58.9, 62.3, 67.7, 71.6, 93.5, 116.1, 127.4, 130.4, 157.0, 170.7, 172.8.

***N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*O*-[(2-methoxyethoxy)methyl]-(*E*)-2,3-methanotyrosine Ethyl Ester (6).** A solution of **5** (8.96 g, 26.5 mmol), triethylamine (5.91 mL, 42.4 mmol), and DPPA (6.28 mL 29.2 mmol) in toluene (200 mL) was heated to reflux for 1 h. After cooling, 2-(trimethylsilyl)ethanol (5.7 mL, 39.8 mmol) was added the solution was stirred for 20 h and washed with 10% citric acid (2 × 50 mL) and 10% $NaHCO_3$ (2 × 50 M). The aqueous washes were combined and extracted with ether (2 × 100 mL). The organic phases were combined, dried, and evaporated to an oil. Purification by flash chromatography (6.5 × 25 cm column) using EtOAc–hexanes (2:3) as the eluent yielded 6.32 g (53%) of pure **6** in fractions (1500–2300 mL), as an oil, R_f(II) 0.70.

***N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*O*-[(methoxyethoxy)methyl]-(*E*)-2,3-methanotyrosine (7E).** To a solution of **6** (0.55 g, 1.2 mmol) in EtOH (5 mL) was added a solution of NaOH (0.69 g, 1.7 mmol) in water (5 mL). The reaction mixture was heated to reflux for 2 h, then stirred at room temperature for 20 h, and worked up as described for **5**. The resulting solid was recrystallized from Et_2O–hexanes, giving 0.37 g (70%) of **7E**: mp 98–102 °C; R_f(II) 0.11.

Anal. Calcd for $C_{20}H_{31}NO_7Si$: C, 56.45; H, 7.34; N, 3.29. Found: C, 56.39; H, 7.35; N, 3.27.

***N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*O*-[(methoxyethoxy)methyl]-(*Z*)-2,3-methanotyrosine Methyl Ester (11).** The potassium salt of **5** was prepared by neutralization to pH 7.0 of a solution of **5** (13.4 g, 39.7 mmol) in EtOH (67 mL) and water (27 mL) using 5% $KHCO_3$ (78 mL). The solution was evaporated to dryness and reevaporated twice from EtOAc and cyclohexane. The resulting solid was heated to reflux with $NH_2NH_2{\cdot}H_2O$ (83% solution in water, 81 mL) in EtOH (14 mL) for 24 h. The residue obtained upon evaporation was dissolved in water and the solution lyophilized to give a quantitative yield (15.4 g) of hydrazide **8**: ^{13}C NMR (D_2O) 17.1 (∇CH_2), 30.5 (∇CH), 39.1 (∇C), 57.9, 67.3, 70.9, 93.3, 116.4, 129.0, 130.7, 155.0, 169.9, 176.8. To a solution of **8** (39.7 mmol) and $NaNO_2$[14] (3.0 g, 43.6 mmol) in water (120 mL) was added ether (240 mL) and, after cooling to 0 °C, a 1 M solution of sulfuric acid (83.4 mL). The two-phase mixture was stirred for 2 h at 5 °C. The aqueous phase was separated and extracted with ether (3 × 120 mL). The combined etheral extracts were washed with brine (2 × 100 mL), dried, and evaporated in vacuo to afford the azide **9** as a yellow oil (10.6 g, 80%), R_f(III) 0.73.[15] Reaction of **9** with ethereal diazomethane, generated from diazald (7.5 g, 35 mmol) according to the optimized procedure of Hudlicky,[16] gave a nearly quantitative yield of methyl ester **10**. This was heated to reflux in toluene (150 mL) for 30 min. After cooling, 2-(trimethylsilyl)ethanol (6.8 mL, 47.4 mmol) was added and refluxing was continued overnight. The solution was evaporated to an oil, which was purified by flash chromatography on a silica gel column (4.0 × 30 cm) using EtOAc–hexane (2:3) as eluant. Pure **11** was afforded in fractions (1300–2000 mL) as an oil, 6.9 g (50%, from **9**): R_f(I) 0.56.

***N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*O*-[(2-methoxyethoxy)methyl]-(*Z*)-2,3-methanotyrosine (7Z).** This compound was prepared as described for **7E**, by reaction of **11** (6.2 g, 14.0 mmol) with NaOH (21 mmol) in water–ethanol (1:1) (24 mL). Purification of the product was effected by elution through a silica gel column (2.5 × 23 cm) with 1% acetic acid in EtOAc. Evaporation of the fractions (300–500 mL) containing the product, followed by recrystallization of the resulting solid from EtOAc–hexanes, afforded 4.52 g (76%) of **7Z**: mp 88–90 °C; R_f(IV) 0.66.

Anal. Calcd for $C_{20}H_{31}NO_7Si$: C, 56.45; H, 7.34; N, 3.29. Found: C, 56.63; H, 7.38; N, 3.41.

(*E*)-2,3-Methanotyrosine (1E). To a solution of **7E** (0.62 g, 1.4 mmol) and *m*-cresol (1.0 mL) in dioxane (9 mL) was added dropwise 4 N HCl in dioxane (10 mL) at 0 °C. The reaction mixture was stirred for 24 h at room temperature and evaporated to an oil, which was triturated with ether to give a solid. Recrystallization from 2-propanol–ether afforded 0.17 g (53%) of **1E**·HCl, mp 201–210 °C. A solution of this (60 mg, 0.26 mmol) in water (0.5 mL) was adjusted to pH 5.5 with $NaHCO_3$. The precipitate formed was collected and washed with water (0.2 mL), 2-propanol (0.5 mL), and EtOAc (1.0 mL). Recrystallization from water afforded 32 mg (64%) of pure **1E**: mp 211–212 °C dec; R_f(V) 0.38, R_f(VI) 0.23.

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.00; H, 5.77; N, 7.24.

(*Z*)-2,3-Methanotyrosine (1Z). This compound was prepared as described for **1E**, starting from 0.30 g (0.7 mmol) of **7Z**. Conversion of the hydrochloride salt (0.10 g, 0.44 mmol) to the zwitterion **1Z** gave, after recrystallization from water, 56 mg (67%) of (*Z*)-2,3-methanotyrosine, mp 203–204 °C dec; R_f(V) 0.39, R_f(VI) 0.25.

Anal. Calcd for $C_{10}H_{11}NO_3$; C, 62.16; H, 5.74; N, 7.25. Found: C, 61.98; H, 5.82; N, 7.16.

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Registry No. **1E**, 87856-51-7; **1E**·HCl, 117942-52-6; **1Z**, 74214-39-4; **1Z**·HCl, 111314-74-0; **2**, 117942-41-3; **3**, 117942-42-4; **4**, 117942-43-5; **5**, 117942-44-6; **6**, 117942-45-7; **7E**, 117942-50-4; **7Z**, 117942-51-5; **8**, 117942-46-8; **9**, 117942-47-9; **10**, 117942-48-0; **11**, 117942-49-1; $CH_2(CO_2Et)_2$, 105-53-3; $(CH_3)_3SOI$, 1174-47-6; $(CH_3)_3SiCH_2CH_2OH$, 2916-68-9; *p*-hydroxybenzaldehyde, 123-08-0.

(14) The use of a larger excess of $NaNO_2$ is not recommended, since nitrosation of the phenyl ring may occur.

(15) The azide decomposed on the TLC plate; only the R_f of the major spot is reported.

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