Total Synthesis of the Methanogenic Cofactors Methanofuran and Methanofuran *b*

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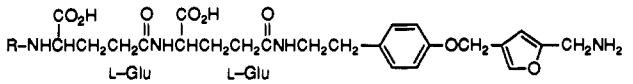
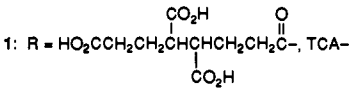
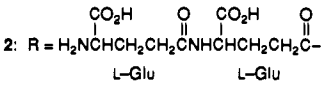
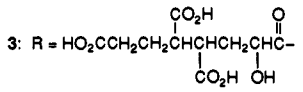
Abstract: Methanofuran, 3-{*p*-[(*N*-(*N*''-((4*R*,5*S*)- or (4*S*,5*R*)-4,5,7-tricarboxyheptanoyl)-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(aminomethyl)furan, and methanofuran *b*, 3-{*p*-[(*N*-(γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(aminomethyl)furan, are the first cofactors involved in the conversion of carbon dioxide to methane by the methanogenic bacteria *Methanobacterium thermoautotrophicum* and *Methanosarcina barkeri*, respectively. These two cofactors have now been synthesized, starting from glutamic acid, dimethyl glutarate, methyl 5-formyl-3-furoate, and tyramine. The synthetic compounds give the same NMR and mass spectra and biological activities as the natural cofactors.

Methanogenic bacteria[1] can convert carbon dioxide to methane by enzymatic processes,[2] employing six co-factors of known structures. The first such co-factor on the enzymatic pathway was assigned in these laboratories as methanofuran (**1**, MFR, from *Methanobacterium thermoautotrophicum*),[3] and subsequently two related compounds, methanofuran *b* (**2**, MFRb, from *Methanosarcina barkeri*)[4] and methanofuran *c* (**3**, from *Methanobrevibacter smithii*),[5] have been shown to be capable of serving the same function.





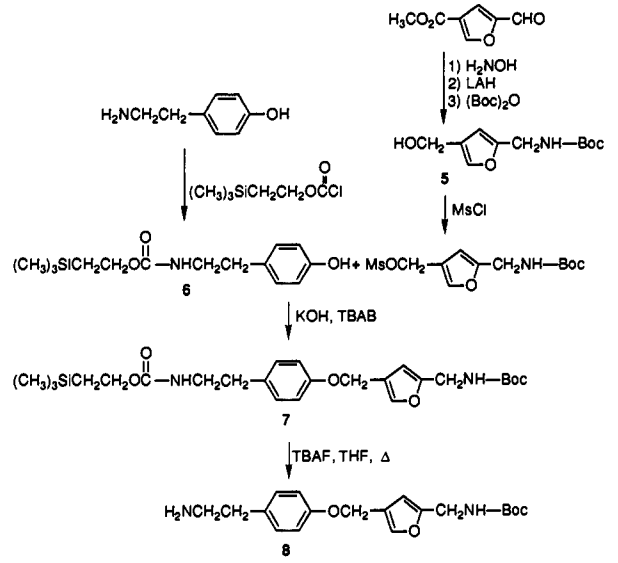




An available supply of these co-factors would facilitate more extensive studies of their mode of action, and we have, accordingly, undertaken their syntheses. We report here the first total syntheses of methanofuran and methanofuran *b*.

A key intermediate in both syntheses was **8**, prepared (Scheme I) by cleavage of the (trimethylsilyl)ethoxycarbonyl-protected precursor **7** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at 50 °C. Compound **7** was prepared by a Williamson ether synthesis from the corresponding phenol **6** (obtained by reaction of tyramine with (trimethylsilyl)ethoxycarbonyl chloride), 3-(mesyloxymethyl)-5-(((*tert*-butoxycarbonyl)amino)methyl)furan, tetrabutylammonium bromide (TBAB),

Scheme I



and solid potassium hydroxide in THF. The requisite furan was prepared from methyl 5-formyl-3-furoate by successive reactions with hydroxylamine, lithium aluminum hydride (LAH), *tert*-butoxycarbonyl (Boc) anhydride, and mesyl chloride.

For the synthesis of methanofuran *b* (**2**), the required tetra-γ-Glu derivative for coupling with **8** was **14**, which was obtained from sodium hydroxide saponification of the corresponding methyl ester **13**. The latter compound was obtained by dicyclohexylcarbodiimide (DCC) coupling of **11** and **12**. These two protected dipeptides were prepared by the routes shown in Scheme II. Starting material for all the monomeric Glu units was (*Z*)-Glu(OCH$_3$)OBu^t, prepared in three steps from glutamic acid.[6] Coupling of **14** with **8** (DCC) gave *tert*-butoxy-protected (Boc, *tert*-butyl esters) methanofuran *b*, which was cleaved to **2** with trifluoroacetic acid (TFA) (Scheme III).

The synthesis of methanofuran (**1**) followed a similar route, except that **8** was coupled with **28** (prepared by the route shown in Scheme IV) to give the protected methanofuran **29** (Scheme III), which was hydrolyzed (TFA) to **1**. The required tris(*tert*-butyl ester) of 4,5-dicarboxyoctanedioic acid (**26**) was prepared by the route shown in Scheme IV and coupled with the previously

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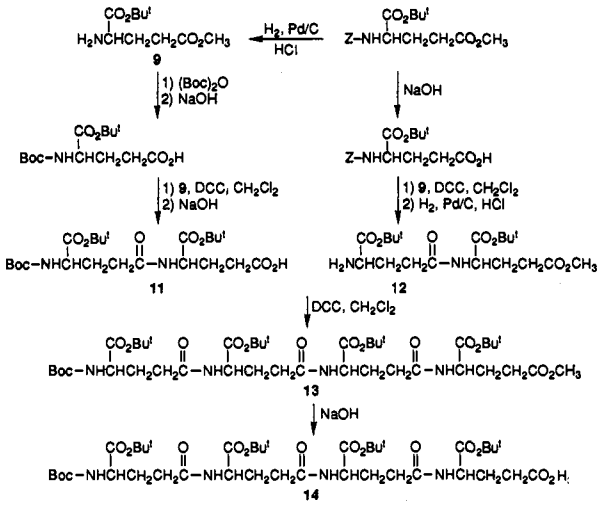
Scheme II



prepared protected dipeptide **12**. The starting tetramethyl ester **20a** for the synthesis of **26** was prepared by di-*tert*-butyl peroxide coupling of dimethyl glutarate[7] to give both *meso* and *D,L* isomers (Scheme V). The crystalline *meso* isomer (**20a**) was identified by X-ray crystallography, and the corresponding tetracarboxylic acid (TCA, **21**) was shown to be the isomer found in methanofuran by comparison of retention times on a chiral GC column of **20a**, a mixture of **20a** and **20b**, and the diazomethane-treated acidic hydrolysate of **1**. It has not yet been established whether the *R* or the *S* center is proximal to the adjacent Glu unit in methanofuran.

Synthetic MFRb (**2**) was compared with the natural compound, isolated from *Methanosarcina barkeri*, by HPLC (retention times and coinjection), ^{1}H NMR, and FABMS/CID/MS. Most importantly, the biological activity in **2** as determined by an assay for methane production (Figure 1) was the same in the two samples, the two showing nearly identical production of methane with increasing amounts of cofactor. Two compounds with one or two γ-Glu units fewer than methanofuran *b* (**18** and **19**) were prepared from **16** and **17**, byproducts in the synthesis of **15** (Scheme VI). The smaller analogues had significant activity in the same bioassay (Figure 2). Compound **18**, with one fewer Glu unit than methanofuran *b*, has about 80% of the activity of methanofuran *b*, while compound **19**, with two fewer Glu units, has about 50% of the activity of methanofuran *b*.

Similarly, synthetic MFR (**1**) and the natural sample isolated from *Methanobacterium thermoautotrophicum* showed the same HPLC, ^{1}H NMR, and FABMS/CID/MS behavior in spite of the fact that synthetic **1** was a mixture of two diastereomers (from 4*R*,5*S*-TCA and 4*S*,5*R*-TCA) arising from use of *meso*-TCA. Moreover, the mixture of diastereomers displayed the same biological activity in an assay for methane production (Figure 1). Thus, the first CO_2-fixing enzyme in methanogenesis appears to be relatively promiscuous in its acceptance of co-factors. MFR, the coenzyme from *Methanobacterium*, saturates the enzyme system from this organism at about 8 μM, whereas MFRb, the coenzyme from *Methanosarcina*, saturates the *Methanobacterium* enzyme system at about 20 μM.

Experimental Section

NMR data (200 MHz for ^{1}H) are reported (δ) relative to tetramethylsilane or the sodium salt of 3-(trimethylsilyl)-1-propanesulfonic acid as internal standards. Fast atom bombardment (FAB) and chemical ionization (CI) mass spectrometry were carried out on ZAB-SE or 70-SE-4F instruments. The high-performance liquid chromatography (HPLC) system comprised a solvent delivery module and variable absorbance detector. Solutions were routinely dried with anhydrous $MgSO_4$ and then concentrated by removing the bulk of the solvent under reduced pressure by rotary evaporator and placing the sample under high vacuum until a constant weight was obtained. Compound purities were established by ^{1}H or ^{13}C NMR spectra (Figures 1S–26S). The S indicates that the spectra for the compounds with corresponding numbers are available as supplementary material. Melting points, determined on an oil immersion capillary melting point apparatus, are uncorrected.

Bioassays. The bioassay for methanofuran measured methanofuran-dependent methane formation from CO_2. This assay was performed as described[8] except that the following assay components were used: 100 mM K^+ PIPES buffer (pH 6.2), 15 mM $MgCl_2$, 5 mM ATP, 50 μL of cell extract (2 mg of protein), 4.4 mM titanium(III) citrate,[9] 10 μM tetrahydromethanopterin,[10] and 50 μM CoM-S-S-HTP.[11]

Methyl 5-Formyl-3-furoate Oxime. A solution of methyl 5-formyl-3-furoate[12] (3.5 g) and hydroxylamine hydrochloride (3.5 g) in pyridine (25 mL) and absolute EtOH (50 mL) refluxed for 3 h[13] and then was concentrated in vacuo. THF and 1:1 brine/0.1 N HCl were added, the two layers were separated, and the organic layer was washed with 1:1 brine/saturated $NaHCO_3$ solution and brine. The THF solution was dried and concentrated to give **3** (3.1 g, 81%) as a mixture of *syn* and *anti* isomers (ca. 2:1). Recrystallization from MeOH gave the major isomer: mp 173-174 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.87 (s, 3 H), 7.49 (s, 1 H), 7.61 (s, 1 H), 8.02 (s, 1 H), 8.04 (br s, 1 H); ^{13}C NMR ($CD_3)_2SO$ Figure 3S. Minor isomer: ^{1}H NMR ($CDCl_3$) δ 6.93 (s), 7.98 (s); ^{13}C NMR [$(CD_3)_2SO$] δ 110.3, 138.4, 149.0 (other expected ^{1}H and ^{13}C NMR signals for the minor isomer are apparently hidden under the signals of the major isomer); FABMS (on mixture of isomers) *m/z* (relative intensity) 170 (M + H, 100).

Anal. Calcd for $C_7H_8NO_4$ (M + H): 170.0453. Found: 170.0457 (M + H, HRFABMS on mixture).

5-(Aminomethyl)-3-furanmethanol (4). A solution of **3** (1.69 g, 10 mmol) in THF (25 mL) was added dropwise to a solution of LAH (0.78 g, 20 mmol) in THF (50 mL). The solution refluxed for 3 h and then was allowed to cool to room temperature. Water was added dropwise until excess LAH was decomposed. The solution was filtered and then continuously extracted with ether for 5 days. The ether solution was dried and concentrated to give 0.89 g (70%) of **4**: ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 2 H), 4.49 (s, 2 H), 6.20 (s, 1 H), 7.32 (s, 1 H); ^{13}C NMR ($CDCl_3$) Figure 4S; CIMS *m/z* (relative intensity) 127 (M^+, 34), 111 (100), 80 (30).

Anal. Calcd for $C_6H_9NO_2$ (M^+): 127.0633. Found: 127.0629 (M^+, HRCIMS).

5-((*tert*-Butoxycarbonyl)amino)methyl)-3-furanmethanol (5). To a stirred solution of **4** (0.51 g, 4 mmol) in dioxane (10 mL) and 0.1 N NaOH (10 mL) was added $(Boc)_2O$ (1.00 g, 4.6 mmol) (room temperature, 3 h). The usual workup gave 0.76 g (83%) of **5**: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.43 (br s, 1 H), 4.24 (d, 2 H, J = 5.8 Hz), 4.48 (s, 2 H), 5.01 (br s, 1 H), 6.24 (s, 1 H), 7.31 (s, 1 H); ^{13}C NMR ($CDCl_3$) Figure 5S; FABMS *m/z* (relative intensity) 228 (M + H, 44), 172 (100).

Anal. Calcd for $C_{11}H_{18}NO_4$ (M + H): 228.1236. Found: 228.1236 (M + H, HRFABMS).

The oxime could be converted directly to **5** in 72% yield by treatment of **3** with LAH as described above, followed by addition of $(Boc)_2O$ to the solution remaining after decomposition of excess LAH with water.

***p*-[β-(((Trimethylsilylethoxy)carbonyl)amino)ethyl]phenol (6).** To ((trimethylsilyl)ethoxy)carbonyl chloride, made from β-(trimethylsilyl)-ethanol (5.91 g, 50 mmol) and phosgene,[14,15] cooled in an ice–water bath was added tyramine (6.85 g, 50 mmol) in dioxane (50 mL) and NaOH (2.0 g, 50 mmol) in water (25 mL). After being stirred for about 1.5

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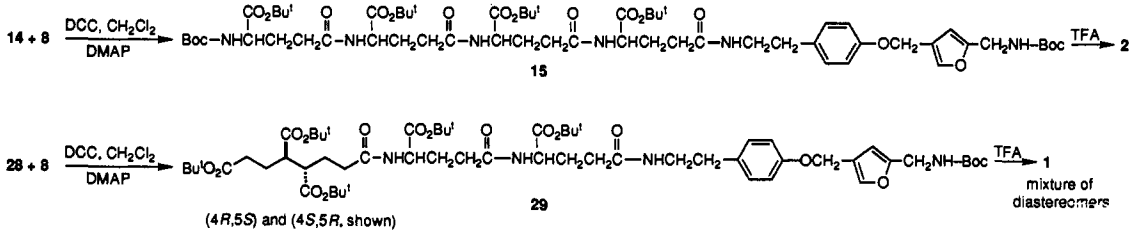
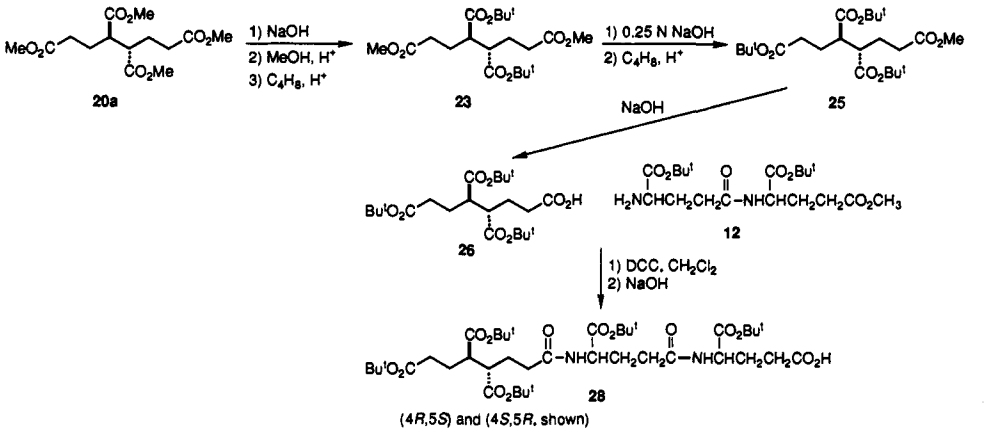
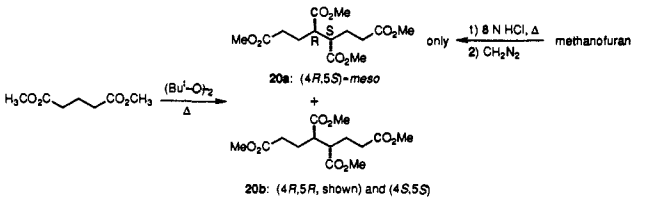
Scheme III



Scheme IV



Scheme V



h while warming to room temperature, the solution was concentrated in vacuo. Ether and water were added and separated, and the ether layer was extracted with 0.5 N NaOH. The combined aqueous layers were neutralized with aqueous HCl, and the aqueous layer was extracted with ether. The ether layer was washed with brine, dried, and concentrated to give 7.76 g (55%) of **6** as a tan oil: ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.96 (t, 2 H, J = 8.4 Hz), 2.71 (t, 2 H, J = 6.8 Hz), 3.38 (q, 2 H, J = 6.8 Hz), 4.16 (t, 2 H, J = 8.4 Hz), 6.79 (d, 2 H, J = 8.2 Hz), 7.00 (d, 2 H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) Figure 6S; FABMS m/z (relative intensity) 563 (2M + H, 7), 326 (14), 282 (M + H), 254 (100).

Anal. Calcd for $C_{14}H_{24}NO_3Si$ (M + H): 282.1525. Found: 282.1521 (M + H, HRFABMS).

3-{*p*-[β-((((Trimethylsilyl)ethoxy)carbonyl)amino)ethyl]phenoxymethyl}-5-(((*tert*-butyloxycarbonyl)amino)methyl)furan (7). Mesyl chloride (0.23 mL, 3.0 mmol) was added to a solution of **5** (0.57 g, 2.5 mmol) and triethylamine (0.47 mL, 3.4 mmol) in THF (25 mL) cooled in an ice–water bath. After being stirred for 30 min, this solution was vacuum filtered (to remove triethylamine hydrochloride) directly into a mixture of **6** (0.70 g, 2.5 mmol), powdered KOH (0.50 g, ca. 7.5 mmol), and tetra-*n*-butylammonium bromide (0.13 g, 0.4 mmol) in THF (25 mL) previously cooled in an ice-water bath. The mixture was allowed to warm to room temperature, and, after being stirred for 3 h, the solution was filtered and concentrated in vacuo. The remaining oil was dissolved in ether and worked up in the usual way to give 1.22 g of crude **7**, a portion of which was purified by RP-HPLC (4:1 MeOH/H_2O): ^{1}H NMR ($CDCl_3$) Figure 7S; ^{13}C NMR ($CDCl_3$) δ −1.5, 17.8, 28.4, 35.4, 37.8, 42.3, 61.9, 63.0, 107.5, 114.9, 122.1, 129.8, 131.3, 140.2, 153.3, 156.7, 157.2; FABMS m/z (relative intensity) 491 (M + H, 84), 363 (100).

Anal. Calcd for $C_{25}H_{39}N_2O_6Si$ (M + H): 491.2557. Found: 491.2559 (M + H, HRFABMS).

3-[*p*-(β-Aminoethyl)phenoxymethyl]-5-(((*tert*-butoxycarbonyl)amino)-methyl)furan (8). To a solution of crude **7** (0.98 g, ca. 2.0 mmol) in THF (25 mL) was added TBAF (5.0 mL, 1.0 M in THF, Aldrich). This

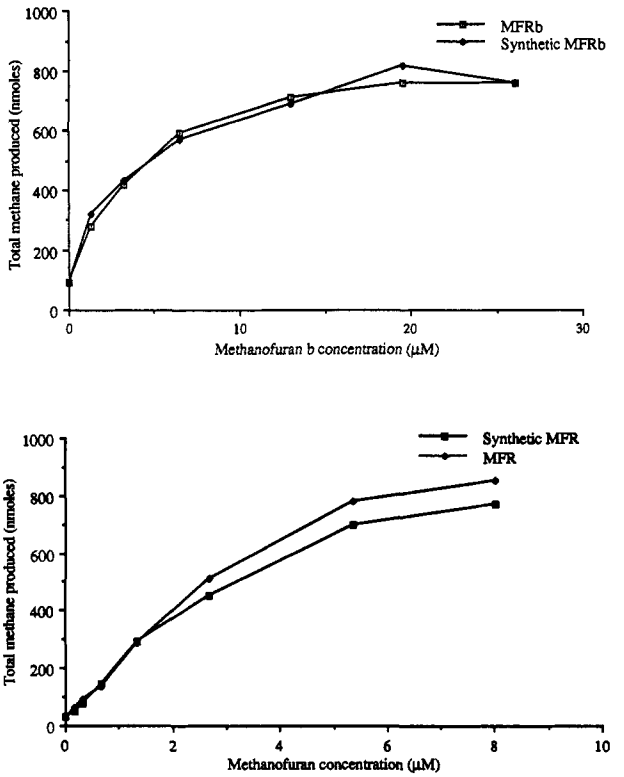


Figure 1. Stimulation of methane production. Top, by methanofuran *b* (MFRb); bottom, by methanofuran (MFR).

solution was heated in a water bath at 50 °C for 3 h and then was cooled to room temperature and concentrated in vacuo. Ether was added, and the solution was washed with 0.5 N NaOH and water. The ether solution was extracted twice with 0.1 N HCl. The combined aqueous layer were neutralized with aqueous NaOH, saturated with salt, and extracted twice with ether. The ether layer was washed with brine, dried, and concentrated to give 0.32 g of slightly impure **8**, a portion of which was purified by RP-HPLC (MeOH): ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.71 (m, 2 H), 2.93 (q, 2 H, J = 6.8 Hz), 4.24 (d, 2 H, J = 5.8 Hz), 4.84 (s, 2 H), 6.30 (s, 1 H), 6.88 (d, 2 H, J = 8.2 Hz), 7.10 (d, 2 H, J = 8.2 Hz), 7.39 (s,

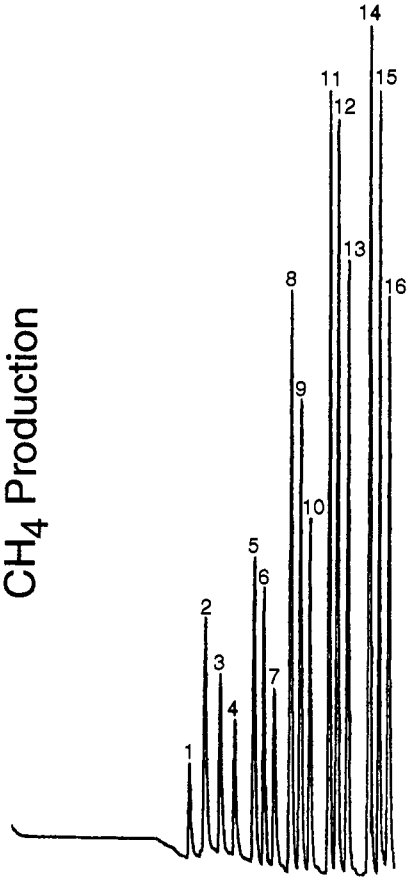
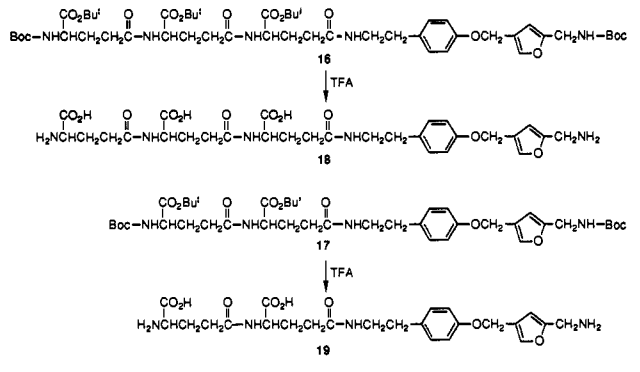


Figure 2. Relative amounts of methane produced with synthetic cofactors, in sets of three contiguous experiments. Peak 1 shows negative control; peaks 2, 5, 8, 11, and 14 show reaction with methanofuran *b*; peaks 3, 6, 9, 12, and 15 show reaction with methanofuran *b* lacking one Glu unit; and peaks 4, 7, 10, 13, and 16 show reaction with methanofuran *b* lacking two Glu units.

Scheme VI



1 H); ^{13}C NMR ($CDCl_3$) Figure 8S; FABMS *m/z* (relative intensity) 347 (M + H, 100), 291 (42).

Anal. Calcd for $C_{19}H_{27}N_2O_4$ (M + H): 347.1971. Found: 347.1965 (M + H, HRFABMS).

α-*tert*-Butyl γ-Methyl L-Glutamate (9). A solution of α-*tert*-butyl γ-methyl *N*-(benzyloxycarbonyl)-L-glutamate[6] (8.76 g, 25 mmol) was hydrogenated for 8 h over 5% Pd/C (1.75 g) in MeOH to which had been added 1 M HCl in MeOH (25.0 mL). This product was then filtered and concentrated in vacuo, water was added, and the solution was washed with CH_2Cl_2. The aqueous solution was neutralized with aqueous $NaHCO_3$ and then extracted twice with CH_2Cl_2. The CH_2Cl_2 solution was dried and concentrated to leave 4.85 g (89%) of **9** as a colorless oil: ^1H NMR ($CDCl_3$) Figure 9S; ^{13}C NMR ($CDCl_3$) δ 28.6, 30.4, 31.0, 81.6, 174.2, 175.4; FABMS *m/z* (relative intensity) 218 (M + H, 100), 162 (84).

Anal. Calcd for $C_{10}H_{20}NO_4$ (M + H): 218.1392. Found: 218.1387 (M + H, HRFABMS).

Although **9** could be stored in a freezer for several days without decomposition, over a period of several months the amine cyclized to *tert*-butyl pyroglutamate.

***N*-(*tert*-Butoxycarbonyl)-γ-L-glutamyl-L-glutamic Acid, α,α′-Di-*tert*-butyl γ-Methyl Triester (10).** To a solution of α-*tert*-butyl *N*-(*tert*-butoxycarbonyl)-L-glutamate (1.52 g, 5.0 mmol, from treatment of **9** with $(Boc)_2O$ followed by hydrolysis with aqueous NaOH) and **9** (1.09 g, 5.0 mmol) in CH_2Cl_2 cooled in an ice–water bath was added DCC (1.13 g, 5.5 mmol). This solution was then allowed to warm to room temperature and was stirred overnight. The usual workup gave 2.21 g (88%) of **10**: ^{13}C NMR ($CDCl_3$) Figure 10S; FABMS *m/z* (relative intensity) 503 (M + H, 66), 447 (6), 403 (28), 391 (7), 347 (20), 335 (19), 291 (100), 228 (16), 162 (37), 130 (29), 116 (30).

Anal. Calcd for $C_{24}H_{43}N_2O_9$ (M + H): 503.2969. Found: 503.2973 (M + H, HRFABMS).

***N*-(*tert*-Butoxycarbonyl)-γ-L-glutamyl-L-glutamic Acid, α,α′-Di-*tert*-butyl Ester (11).** To a solution of **10** (2.01 g, 4.0 mmol) in 2:1 MeOH/water (25 mL) was added NaOH (0.17 g, 4.25 mmol) with stirring at room temperature for 2 h. The usual workup gave 1.23 g (63%) of **11**: ^{13}C NMR ($CDCl_3$) Figure 11S; FABMS *m/z* (relative intensity) 489 (M + H, 26), 433 (4), 406 (11), 389 (17), 377 (7), 333 (15), 321 (20), 277 (100), 214 (12), 148 (53), 130 (42).

Anal. Calcd for $C_{23}H_{41}N_2O_9$ (M + H): 489.2812. Found: 489.2811 (M + H, HRFABMS).

***N*-γ-L-Glutamyl-L-glutamic Acid, α,α′-Di-*tert*-butyl γ-Methyl Triester (12).** A solution of *N*-(benzyloxycarbonyl)-γ-L-glutamyl-L-glutamic acid, α,α′-di-*tert*-butyl γ-methyl triester[16] (2.68 g, 5.0 mmol), was hydrogenated for 5 h over 5% Pd/C (2.0 g) in MeOH to which had been added 1 M HCl in MeOH (5.0 mL). The usual workup gave 1.77 g (88%) of **12** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.47 (s, 18 H), 1.80–2.30 (m, 10 H), 3.36 (m, 1 H), 3.68 (s, 3 H), 4.51 (m, 1 H), 6.71 (br d, 1 H); ^{13}C NMR ($CDCl_3$) Figure 12S; FABMS *m/z* (relative intensity) 403 (M + H, 100), 347 (12), 291 (37).

Anal. Calcd for $C_{19}H_{35}N_2O_7$ (M + H): 403.2444. Found: 403.2451 (M + H, HRFABMS).

***N*-(*tert*-Butoxycarbonyl)-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl-L-glutamic Acid, α,α′,α″,α‴-Tetra-*tert*-butyl γ-Methyl Pentaester (13).** To a solution of **11** (0.49 g, 1.0 mmol) and **12** (0.40 g, 1.0 mmol) in CH_2Cl_2 cooled in an ice-water bath was added DCC (0.23 g, 1.1 mmol). This mixture was then allowed to warm to room temperature and was stirred overnight. The usual workup gave 0.74 g (85%) of **13**: ^{13}C NMR ($CDCl_3$) Figure 13S; FABMS *m/z* (relative intensity) 873 (M + H, 25), 773 (37), 717 (23), 661 (14), 605 (11), 588 (9), 549 (35), 486 (14), 420 (24), 357 (38), 291 (33), 259 (25), 228 (63), 196 (30), 168 (72), 162 (100), 130 (100), 114 (78).

Anal. Calcd for $C_{42}H_{73}N_4O_{15}$ (M + H): 873.5072. Found: 873.5096 (M + H, HRFABMS).

3-{*p*-[(*N*-((*tert*-Butoxycarbonyl)-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(((*tert*-butoxycarbonyl)amino)methyl)furan, Tetra-*tert*-butyl Ester (15). To a solution of **13** (0.65 g, ca. 0.75 mmol) in 2:1 MeOH/water (25 mL) was added NaOH (32 mg, 0.8 mmol) with stirring at room temperature for 2 h. Workup gave 0.40 g of *N*-(*tert*-butoxycarbonyl)-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl-L-glutamic acid, α,α′,α″,α‴-tetra-*tert*-butyl ester (**14**) contaminated with *N*-(*tert*-butoxycarbonyl)-γ-L-glutamyl-γ-L-glutamyl-L-glutamic acid, α,α′,α″-tri-*tert*-butyl ester and *N*-(*tert*-butoxycarbonyl)-γ-L-glutamyl-L-glutamic acid, α,α′-di-*tert*-butyl ester as indicated by RP-TLC: FABMS *m/z* (relative intensity) 859 (M + H, 11), 759 (22), 703 (16), 647 (9), 591 (8), 574 (9), 535 (24), 472 (10), 406 (27), 343 (28), 277 (47), 259 (22), 214 (41), 196 (23), 168 (57), 148 (96), 130 (100), 114 (68).

Anal. Calcd for $C_{41}H_{71}N_4O_{15}$ (M + H): 859.4916. Found: 859.4901 (M + H, HRFABMS).

To a solution of **8** (70 mg) and **14** (170 mg) in CH_2Cl_2 cooled in an ice-water bath were added DCC (40 mg) and 4-(dimethylamino)pyridine (3 mg). This solution was then allowed to warm to room temperature and was stirred overnight. The mixture was filtered, methylene chloride was removed on a rotary evaporator, ether was added, and the solution was extracted with 0.1 N HCl and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to give 220 mg of crude **15**. This material was purified by RP-HPLC (3:1 MeOH/water) to give pure **16** (21 mg), **17** (10 mg), and **15** (46 mg). For **15**: ^1H NMR ($CDCl_3$) δ 7.41 (s, 1 H), 7.14 (d, 2 H), 6.86 (d, 2 H), 6.31 (s, 1 H), 4.85 (s, 2 H), 1.46 (s, 18 H), 1.44 (s,

(16) Kovacs, J.; Schmit, G. N.; Johnson, B. J. *Can. J. Chem.* **1969**, *47*, 3690–3693.

18 H), 1.42 (s, 18 H), and Figure 15S; FABMS m/z (relative intensity) 1187 (M + H, 31), 1087 (100), 1031 (39), 975 (12), 931 (8).

Anal. Calcd for $C_{60}H_{95}N_6O_{18}$ (M + H): 1187.6703. Found: 1187.6764 (M + H, HRFABMS).

3-{p-[(N-((*tert*-Butoxycarbonyl)-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(((*tert*-butoxycarbonyl)amino)methyl)furan, tri-*tert*-butyl ester (16): ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 45 H), 1.62-1.97 (m, 2 H), 2.07-2.50 (m, 10 H), 2.76 (t, 2 H, J = 7.0 Hz), 3.26–3.58 (m, 2 H), 4.10–4.28 (m, 1 H), 4.28 (d, 2 H, J = 7.0 Hz), 4.35–4.57 (m, 2 H), 4.84 (s, 2 H), 5.11 (br t, 1 H), 5.36 (br d, 1 H, J = 9.0 Hz), 6.31 (s, 1 H), 6.67 (br d, 1 H, J = 9.0 Hz), 6.86 (d, 2 H, J = 7.2 Hz), 7.12 (d, 2 H, J = 7.2 Hz), 7.12–7.32 (m, 2 H), 7.41 (s, 1 H); ^{13}C NMR ($CDCl_3$) Figure 16S; FABMS m/z (relative intensity) 1002 (M + H, 29), 902 (100), 846 (34), 802 (8), 790 (9), 746 (10).

Anal. Calcd for $C_{51}H_{80}N_5O_{15}$ (M + H): 1002.5651. Found: 1002.5591 (M + H, HRFABMS).

3-{p-[(N-((*tert*-Butoxycarbonyl)-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(((*tert*-butoxycarbonyl)amino)methyl)furan, di-*tert*-butyl ester (17): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.45 (s, 9 H), 1.46 (s, 18 H), 1.68–1.98 (m, 2 H), 2.08–2.43 (m, 6 H), 2.76 (t, 2 H, J = 7.0 Hz), 3.29–3.59 (m, 2 H), 4.09–4.26 (m, 1 H), 4.28 (d, 2 H, J = 7.0 Hz), 4.36–4.52 (m, 1 H), 4.85 (s, 2 H), 4.97 (br t, 1 H), 5.29 (br d, 1 H, J = 9.0 Hz), 6.31 (s, 1 H), 6.56–6.67 (m, 2 H), 6.87 (d, 2 H, J = 7.2 Hz), 7.12 (d, 2 H, J = 7.2 Hz), 7.41 (s, 1 H); ^{13}C NMR ($CDCl_3$) Figure 17S; FABMS m/z (relative intensity) 817 (M + H, 21), 717 (100), 661 (34), 617 (13), 561 (20), 505 (24).

Anal. Calcd for $C_{42}H_{65}N_4O_{12}$ (M + H): 817.4599. Found: 817.4577 (M + H, HRFABMS).

3-{p-[(N-(γ-L-Glutamyl-γ-L-glutamyl-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(aminomethyl)furan (Methanofuran *A*, 2). To **15** (10 mg) was added TFA (0.5 mL). After 30 min, TFA was evaporated under N_2 flow to give 5.8 mg of a white powder. This material was purified by RP-HPLC (93:7 water/MeCN containing 0.7 g/L ammonium formate) to give 4.2 mg (65%) of pure **2**: ^{1}H NMR (D_2O) δ 1.24–1.42 (m, 14 H), 2.48 (t, 2 H, J = 7.0 Hz), 2.77 (t, 2 H, J = 7.0 Hz), 3.42 (t, 2 H, J = 7.0 Hz), 3.77 (t, 1 H, J = 7.0 Hz), 4.02–4.18 (m, 3 H), 4.22 (s, 2 H), 5.03 (s, 2 H), 6.68 (s, 1 H), 7.01 (d, 2 H, J = 7.8 Hz), 7.22 (d, 2 H, J = 7.8 Hz), 7.68 (s, 1 H); FABMS m/z (relative intensity) 763 (M + H, 100); FABMS/CID/MS for synthetic and natural **2**, Figure 2S.

Anal. Calcd for $C_{34}H_{47}N_6O_{14}$ (M + H): 763.3150. Found: 763.3163 (M + H, HRFABMS).

3-{p-[(N-(γ-L-Glutamyl-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]-phenoxymethyl}-5-(aminomethyl)furan (18). A sample of **16** was treated with TFA to give, after purification by RP-HPLC, **18**: ^{1}H NMR (D_2O) δ 1.79–2.34 (m, 8 H), 2.41 (t, 2 H, J = 7.5 Hz), 2.57 (t, 2 H, J = 7.5 Hz), 2.80 (t, 2 H, J = 6.5 Hz), 3.32–3.52 (m, 2 H), 4.08 (t, 1 H, J = 6.5 Hz), 4.22 (s, 2 H), 4.20–4.22 (m, 2 H), 5.01 (s, 2 H), 6.68 (s, 1 H), 7.00 (d, 2 H, J = 8.4 Hz), 7.23 (d, 2 H, J = 8.4 Hz), 7.68 (s, 1 H); FABMS m/z (relative intensity) 634 (M + H, 100).

Anal. Calcd for $C_{29}H_{40}N_5O_{11}$ (M + H): 634.2724. Found: 634.2721 (M + H, HRFABMS).

3-{p-[(N-(γ-L-Glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(aminomethyl)furan (10). A sample of **17** was treated with TFA to give, after purification by RP-HPLC, **19**: ^{1}H NMR (D_2O) δ 7.67 (s, 1 H), 7.22 (d, 2 H), 6.99 (d, 2 H), 6.67 (s, 1 H), 3.43 (t, 2 H), 2.73 (5, 2 H), 2.53 (t, 2 H), 2.27 (t, 4 H), and Figure 19S; FABMS m/z (relative intensity) 505 (M + H, 100).

Anal. Calcd for $C_{24}H_{33}N_4O_8$ (M + H): 505.2298. Found: 505.2309 (M + H, HRFABMS).

Tetramethyl (3*R*,4*S*)-1,3,4,6-Hexanetetracarboxylate (20a). Free-radical-induced coupling of dimethyl glutarate (200 g)[7] gave 34.89 g of a mixture of **20a** and **20b** (1:1) by ^{13}C NMR analysis. When this mixture was dissolved in approximately 50 mL of ether and cooled in a freezer overnight, crystals formed which were isolated by filtration and washed with cold ether–hexane solution to give 6.85 g of an off-white powder. Analysis of this powder by ^{13}C NMR indicated that it consisted of a single isomer: mp 73–74 °C (ether):[17] ^{1}H NMR ($CDCl_3$) δ 1.71–2.04 (m, 4 H), 2.25–2.41 (m, 4 H), 2.68–2.82 (m, 2 H), 3.66 (s, 6 H), 3.71 (s, 6 H); ^{13}C NMR ($CDCl_3$) Figure 20aS; FABMS m/z (relative intensity) 319 (M + H, 54), 287 (100), 227 (7).

Anal. Calcd for $C_{14}H_{23}O_8$ (M + H): 319.1393. Found: 319.1395 (M + H, HRFABMS).

Single-Crystal X-ray Diffraction Analysis of 20a. The colorless, prismatic data crystal of **20a**, dimensions 0.2 × 0.4 × 0.5 mm^3, was grown from an ethyl acetate solution. Preliminary X-ray photographs confirmed triclinic symmetry, space group $P1$ or $P\bar{1}$, a = 8.389(2), b = 8.727(3), and c = 6.050(2) Å, α = 104.62(3)°, β = 102.88(2)°, and γ = 103.06-(2)°. Crystal density indicated one molecule of composition $C_{14}H_{20}O_8$ in the unit cell (Z = 1). All unique diffraction intensities with $2\theta > 51°$ were collected on an Enraf–Nonius CAD4 automated κ-axis diffractometer using graphite monochromated Mo radiation (0.710 73 Å) and ω/θ scans. Of the 1481 independent intensities measured (R_i = 0.011), 1205 observed data ($I > 2.58\sigma(I)$) were used in subsequent calculations. Average values of the normalized structure factors suggested the centric space group, $P\bar{1}$, which was later confirmed by refinement. The structure was solved using direct methods, SHELXS-86; correct positions for all non-hydrogen atoms were deduced from an E-map. Subsequent least-squares refinement and difference Fourier syntheses, SHELX-76, revealed hydrogen atom positions. In the final cycle of least squares, non-hydrogen atoms were refined with anisotropic thermal coefficients, hydrogen atoms were refined with isotropic thermal coefficients, and an empirical isotropic extinction parameter was varied. Successful convergence was indicated by the maximum shift/error for the last cycle. A final analysis of variance between observed and calculated structure factors showed no systematic errors. Additional crystallographic information is available in the supplementary material.

Tetramethyl (3*R*,4*R*)- and (3*S*,4*S*)-1,3,4,6-Hexanetetracarboxylate (20b). Column chromatography using CH_2Cl_2 as the eluent was performed on a portion of the filtrate remaining after crystallization of **20a**. Although **20a** and **20b** were not completely separated, the latter cuts were enriched in **20b** so that crystallization from hexane gave pure **20b**: mp 58–59 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.91–2.01 (m, 4 H), 2.29–2.42 (m, 4 H), 2.75–2.80 (m, 4 H), 3.67 (s, 3 H), 3.69 (s, 6 H), 3.70 (s, 3 H); ^{13}C NMR ($CDCl_3$) Figure 20bS; FABMS m/z (relative intensity) 319 (M + H, 45), 287 (100), 227 (7).

Anal. Calcd for $C_{14}H_{23}O_8$ (M + H): 319.1393. Found: 319.1395 (M + H, HRFABMS).

Determination of Relative Stereochemistry of 20 in Methanofuran. GC analysis with an Alltech Chirasil-Val III (25 m × 0.32 mm) capillary column comparing **20a**, a mixture of **20a** and **20b**, and the tetracarboxylate derived from acidic hydrolysis of methanofuran[3] followed by treatment with diazomethane showed that the hydrolysate of **1** contains **21**.

(3*R*,4*S*)-1,3,4,6-Hexanetetracarboxylic Acid (21). To a solution of **20a** (31.8 g, 0.10 mol) in THF (500 mL) was added NaOH (18.0 g, 0.45 mol) dissolved in water (100 mL). The solution was heated at 50 °C, overnight, allowed to cool to room temperature, and concentrated in vacuo. Some water was added to the material and then aqueous HCl was added until the solution was acidic. Within 1 material began to precipitate. The mixture was cooled in a refrigerator and then filtered to give 6.84 g of material. The filtrate was concentrated and more material precipitated; filtration gave an additional 3.12 g of product for a total of 9.96 g (68%) of **21**: mp 210–212 °C;[19] ^{1}H NMR (D_2O) δ 1.77–1.95 (m, 4 H), 2.45 (q, 4 H, J = 6.3 Hz), 2.68–2.77 (m, 2 H); ^{13}C NMR (D_2O) Figure 21S; FABMS m/z (relative intensity) 263 (M + H, 100), 245 (53), 227 (51), 209 (26).

Anal. Calcd for $C_{10}H_{15}O_8$ (M + H): 263.0767. Found: 263.0768 (M + H, HRFABMS).

Dimethyl (4*R*,5*S*)-4,5-Dicarboxyoctanedioate (22). To a solution of **21** (6.55 g, 25.0 mmol) in methanol (100 mL) was added a solution of 5 N HCl in methanol (10 mL).[20] This solution was kept at room temperature for 1 h and then was concentrated in vacuo. Recrystallization from water gave 3.47 g of product, and the filtrate was concentrated to yield 0.82 g more for a total of 4.29 g (59%) of **22**: ^{1}H NMR (CD_3OD) δ 1.75–1.93 (m, 4 H), 2.30–2.45 (m, 4 H), 2.54–2.66 (m, 2 H), 3.65 (s, 6 H); ^{13}C NMR (CD_3OD) Figure 22S; FABMS m/z (relative intensity) 313 (M + Na, 68), 291 (M + H, 100), 273 (71), 259 (12), 241 (49), 227 (11), 209 (29).

Anal. Calcd for $C_{12}H_{19}O_8$ (M + H): 291.1080. Found: 291.1073 (M + H, HRFABMS).

Dimethyl (4*R*,5*S*)-4,5-Di-(*tert*-butoxycarbonyl)octanedioate (23). A solution of **22** (4.35 g, 15.0 mmol) in CH_2Cl_2/THF (9:1, 1000 mL) was cooled in an ice–water bath, sulfuric acid (5.0 mL) was added, and then

(17) A melting point of 48–59 °C was reported[7] for what was presumably a mixture of **20a** and **20b**, while a melting point of 73 °C was reported[18] for one isomer of **20** whose unassigned stereochemistry was probably that of **20a**.

(18) Blood, C. T.; Linstead, R. P. *J. Chem. Soc.* **1952**, 2255–2262.

(19) A melting point of 216–217 °C was reported[18] for one isomer of 1,3,4,6-hexanetetracarboxylic acid whose unassigned stereochemistry was probably that of **21**.

(20) Sell, W. J.; Jackson, H. *J. Chem. Soc.* **1899**, *75*, 507–518.

the solution was saturated with isobutylene. After 5 days, $NaHCO_3$ was added, and workup in the usual way gave 4.49 g (74%) of **23**: mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 1.47 (s, 18 H), 1.75–1.93 (m, 4 H), 2.25–2.40 (m, 4 H), 2.47–2.57 (m, 2 H), 3.67 (s, 6 H); ^{13}C NMR ($CDCl_3$) Figure 23S; FABMS m/z (relative intensity) 403 (M + H, 16), 347 (11), 291 (100), 273 (40), 259 (8), 241 (16), 227 (5), 209 (7).

Anal. Calcd for $C_{20}H_{35}O_8$ (M + H): 403.2332. Found: 403.2333 (M + H, HRFABMS).

Methyl Hydrogen (4*R*,5*S*)- and (4*S*,5*R*)-4,5-Di-(*tert*-butoxycarbonyl)-octanedioate (24). To a solution of **23** (4.02 g, 10.0 mmol) in MeOH (25 mL) was added 1.0 M NaOH (2.5 mL) with stirring at room temperature for 5 h. The usual workup gave 0.96 g (25%) of **24**: ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.47 (s, 9 H), 1.74–1.96 (m, 4 H), 2.23–2.45 (m, 4 H), 2.48–2.57 (m, 2 H), 3.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) Figure 24S; FABMS m/z (relative intensity) 389 (M + H, 14), 333 (17), 277 (100), 259 (55), 245 (13), 241 (25), 227 (30), 209 (18).

Anal. Calcd for $C_{19}H_{33}O_8$ (M + H): 389.2175. Found: 389.2174 (M + H, HRFABMS).

***tert*-Butyl Methyl (4*R*,5*S*)- and (4*S*,5*R*)-4,5-Di-(*tert*-butoxycarbonyl)-octanedioate (25).** A solution of **24** (0.97 g, 2.5 mmol) in CH_2Cl_2 (200 mL) was cooled in an ice–water bath, sulfuric acid (1.0 mL) was added, and the solution was saturated with isobutylene. After 3 days, $NaHCO_3$ was added, and workup in the usual way gave 1.10 g (99%) of **25**: mp 55–57 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.47 (s, 18 H), 1.71–1.91 (m, 4 H), 2.14–2.39 (m, 4 H), 2.45–2.56 (m, 2 H), 3.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) Figure 25S; FABMS m/z (relative intensity) 445 (M + H, 8), 389 (8), 333 (24), 277 (100), 259 (46), 245 (29), 241 (14), 227 (34), 209 (17).

Anal. Calcd for $C_{23}H_{41}O_8$ (M + H): 445.2801. Found: 445.2796 (M + H, HRFABMS).

***tert*-Butyl Hydrogen (4*R*,5*S*)- and (4*S*,5*R*)-4,5-Di-(*tert*-butoxycarbonyl)octanedioate (26).** To a solution of **25** (0.89 g, 2.0 mmol) in MeOH (30 mL) was added 1.0 M NaOH (2.2 mL) with stirring at room temperature overnight. The usual workup gave 0.55 g (64%) of **26**: ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.47 (s, 18 H), 1.70–1.94 (m, 4 H), 2.15–2.44 (m, 4 H), 2.47–2.57 (m, 2 H); ^{13}C NMR ($CDCl_3$) Figure 26S; FABMS m/z (relative intensity) 431 (M + H, 18), 375 (26), 319 (38), 263 (100), 245 (54), 227 (39), 209 (15).

Anal. Calcd for $C_{22}H_{39}O_8$: 431.2645 (M + H). Found: 431.2630 (M + H, HRFABMS).

***N*-[(4*R*,5*S*)- and (4*S*,5*R*)-4,5,7-Tri-(*tert*-butoxycarbonyl)heptanoyl]-γ-L-glutamyl-L-glutamic Acid, α,α′-Di-*tert*-butyl γ-Methyl Triester (27).** To a solution of **26** (0.44 g, 1.0 mmol) and **12** (0.40 g, 1.0 mmol) in CH_2Cl_2 cooled in an ice–water bath was added DCC (0.23 g, 1.1 mmol). This solution was then allowed to warm to room temperature and was stirred overnight. Workup in the usual way gave 0.86 g of crude **27**, which was purified by column chromatography using CH_2Cl_2 to give 0.59 g (73%) of pure **27**: ^1H NMR ($CDCl_3$) δ 0.78–2.44 (m, 16 H), 1.43 (s, 9 H), 1.46 (s, 27 H), 1.48 (s, 9 H), 2.46–2.55 (m, 2 H), 3.68 (s, 3 H), 4.45–4.57 (m, 2 H), 6.16 (br d, 1 H, J = 9.0 Hz); FABMS m/z (relative intensity) 815 (M + H, 28), 759 (8), 703 (4), 647 (5), 591 (9), 535 (100), 517 (25).

Anal. Calcd for $C_{41}H_{71}N_2O_{14}$: 815.4905 (M + H). Found: 815.4881 (M + H, HRFABMS).

***N*-[(4*R*,5*S*)- and (4*S*,5*R*)-4,5,7-Tri-(*tert*-butoxycarbonyl)heptanoyl]-γ-L-glutamyl-L-glutamic Acid, α,α′-Di-*tert*-butyl Ester (28).** To a solution of **27** (0.41 g, 0.5 mmol) in 2:1 MeOH/H_2O (10 mL) was added 0.1 M NaOH (5.0 mL) with stirring at room temperature for 2 h. The solution was concentrated in vacuo and washed with ether, and then the aqueous layer was neutralized with 0.1 N HCl, saturated with salt, and extracted twice with ether. The combined ether layers were washed with brine, dried, and concentrated to give 0.06 g of crude **28**. The ether solution from washing of the basic aqueous layer was found to contain a mixture of **27** and **28**. After this solution was concentrated in vacuo, repeated trituration with hexane and decantation of the hexane solution removed most of **27** to leave 0.25 g of **28**: ^1H NMR ($CDCl_3$) δ 0.78–2.44 (m, 16 H), 1.43 (s, 9 H), 1.46 (s, 27 H), 1.48 (s, 9 H), 2.46–2.55 (m, 2 H), 4.45–4.57 (m, 2 H), 6.16 (br d, 1 H, J = 9.0 Hz); FABMS m/z (relative intensity) 823 (M + Na, 42), 801 (M + H, 33), 745 (8), 689 (5), 633 (8), 577 (14), 521 (100), 503 (21).

Anal. Calcd for $C_{40}H_{69}N_2O_{14}$: 801.4749 (M + H). Found: 801.4751 (M + H, HRFABMS).

3-{*p*-[(*N*-(*N*″-(4*R*,5*S*)- and (4*S*,5*R*)-4,5,7-Tri-(*tert*-butoxycarbonyl)-heptanoyl)-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(((*tert*-butoxycarbonyl)amino)methyl)furan, Di-*tert*-butyl Ester (29). To a solution of **8** (50 mg) and **28** (100 mg) in CH_2Cl_2 cooled in an ice–water bath were added DCC (26 mg) and 4-(dimethylamino)pyridine (2 mg). This solution was then allowed to warm to room temperature and was stirred overnight. The usual workup gave 135 mg of material which was purified by RP-HPLC (17:3 MeOH/water) to give 45 mg (32%) of pure **29**: ^1H NMR ($CDCl_3$) δ 1.11–2.40 (m, 16 H), 1.43 and 1.44 (s, 9 H), 1.45 (s, 36 H), 1.47 and 1.50 (s, 9 H), 2.47–2.62 (m, 2 H), 2.74 and 2.76 (t, 2 H, J = 7.0 Hz), 3.28–3.58 (m, 2 H), 4.28 (d, 2 H, J = 7.0 Hz), 4.38–4.58 (m, 2 H), 4.85 (s, 2 H), 6.31 (s, 1 H), 6.36 (br d, 1 H, J = 9.0 Hz), 6.70–6.85 (m, 2 H), 6.85 and 6.86 (d, 2 H, J = 7.2 Hz), 7.02 (br t, 1 H, J = 8.6 Hz), 7.11 and 7.12 (d, 2 H, J = 7.2 Hz), 7.40 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.0, 26.3, 26.7, 28.0, 28.1, 28.3, 28.9, 29.0, 29.1, 29.3, 29.7, 31.8, 32.0, 32.5, 32.7, 32.9. 33.0, 34.1, 34.9, 37.8, 47.8, 47.9, 48.2, 51.7, 51.8, 52.0, 52.2, 61.9, 80.3, 81.1, 81.2, 81.4, 81.7, 82.0, 82.2, 82.4, 82.6, 107.4, 114.7, 122.2, 129.7, 131.6, 140.1, 153.1, 155.5, 157.1, 171.0, 171.1, 171.3, 171.6, 171.8, 171.9, 172.1, 172.2, 172.3, 172.6, 172.7, 173.0; FABMS m/z (relative intensity) 1129 (M + H, 73), 1029 (100), 973 (91), 917 (73), 861 (55), 805 (45), 749 (36).

Anal. Calcd for $C_{59}H_{93}N_4O_{17}$ (M + H): 1129.6536. Found: 1129.6536 (M + H, HRFABMS).

3-{*p*-[(*N*-(*N*″-((4*R*,5*S*)- and (4*S*,5*R*)-4,5,7-Tricarboxyheptanoyl)-γ-L-glutamyl-γ-L-glutamyl)-β-amino)ethyl]phenoxymethyl}-5-(aminomethyl)furan (Methanofuran, 1). To **29** (10.0 mg) was added TFA (0.5 mL). After 30 min, TFA was removed under N_2 flow to give 5.5 mg of a white powder, which was purified by RP-HPLC (93:7 water/MeCN containing 0.7 g/L ammonium formate) to give 4.0 mg (60%) of pure **1**: ^1H NMR (D_2O) δ 1.12–2.83 (m, 18 H), 3.35–3.52 (m, 2 H), 3.66–3.82 (m, 2 H), 4.22 (s, 2 H), 4.26–4.40 (m, 2 H), 5.00 (s, 2 H), 6.67 (s, 1 H), 6.99 (d, 2 H, J = 7.8 Hz), 7.21 (d, 2 H, J = 7.8 Hz), 7.68 (s, 1 H), and Figure 1Sa; FABMS m/z (relative intensity) 749 (M + H, 100); FABMS/CID/MS Figure 1S.

Anal. Calcd for $C_{34}H_{45}N_4O_{15}$ (M + H): 749.2881. Found: 749.2890 (M + H, HRFABMS).

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Supplementary Material Available: FABMS/CID/MS spectra for **1** and **2**; ^1H NMR spectra for **1** (synthetic), **7**, **9**, **15**, **19**, **29**; ^{13}C NMR spectra for methyl 5-formyl-3-furoate oxime, **4–6**, **8**, **10–13**, **16**, **17**, **20a**, **20b**, **21–26**; tables of positional parameters (Table IS), thermal parameters (Table IIS), and selected distances and angles (Tables IIIS) for **20a** (33 pages); observed and calculated structure factors for **20d** (Table IVS) (9 pages). Ordering information is given on any current masthead page.