riod, and then cooled to 0 °C. At 0 °C the reaction mixture was acidified with 10% HCl and extracted immediately with 2 × 200 mL of chloroform. The chloroform extracts were combined, washed with H_2O, and dried over anhydrous magnesium sulfate and concentration of the chloroform solution on a rotary evaporator yielded 5.0 g of an oil. The oil was chromatographed using silica gel G and elution with a methanol–ether solution afforded 3.1 g (76%) of an epimeric mixture of 15α- and 15β-11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 (**9**): NMR ($CDCl_3$) δ 0.91 (t), 1.05–1.93 (m) [23 H], 1.95–2.63 (m, 6 H), 2.65–3.95 (m, 4 H), and 7.10 [s (broad, CO_2H and OH), 2 H]; IR (neat) 1725 and 1665 cm^{-1}.

Anal. Calcd for $C_{19}H_{35}NO_4$: C, 66.82; H, 10.33; N, 4.10. Found: C, 66.84; H, 10.11; N, 4.03.

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Registry No.—**1**, 142-61-0; **2**, 62005-96-3; **3**, 4312-99-6; **4**, 62005-97-4; **5**, 62005-98-5; **6**, 62005-99-6; **7**, 62006-00-2; **8**, 62006-01-3; 15α-**9**, 62006-02-4; 15β-**9**, 62006-03-5; nitromethane, 75-52-5; ethylene glycol, 107-21-1; methyl 4-nitro-7,7-ethylenedioxydodecanoate, 62006-04-6; methyl 7-bromoheptanoate, 54049-24-0.

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Synthesis of L-Prolyl-L-leucylglycine Alkylamides[1]

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The synthesis of H-Pro-Leu-Gly-$NHCH_3$ and related alkylamido derivatives by a new general approach is described. The preferred conformation of H-Pro-Leu-Gly-$NHCH_3$ is assumed to be identical with that of H-Pro-Leu-Gly-NH_2. Also α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate β-methylamide and α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-glutamate β-methylamide were synthesized.

The C-terminal tripeptide of oxytocin, H-Pro-Leu-Gly-NH_2, has been suggested to be the natural factor inhibiting the release of melanocyte-stimulating hormone (MRIF). Indeed there exists an enzymic system in rat hypothalamic extracts which can form MRIF activity on using oxytocin as a substrate.[2,3] On the other hand, the replacement of a carboxamide proton in position 9 of oxytocin by a methyl group (a) eliminates the agonistic properties of the hormone, but not its binding capacity, and (b) exerts potent inhibitory oxytocin-induced avian vasodepressor response.[4] In view of these considerations, we thought it of interest to synthesize H-Pro-Leu-Gly-$NHCH_3$ and its analogues with enhanced lipophilicity (Table II) as possible agents of potent and selective clinical value. This paper provides experimental details on the synthesis of certain L-prolyl-L-leucylglycine alkylamides by a new general approach and some information concerning the conformation of H-Pro-Leu-Gly-$NHCH_3$.

Results and Discussion

Firstly, the tripeptide derivative, Z-Pro-Leu-Gly-$NHCH_3$, was synthesized in a stepwise manner using *N*-Trt-glycine[5] as the starting material. This compound was condensed via the mixed-anhydride method[6] with methyl-, ethyl-, and propylamine, respectively, yielding the corresponding *N*-alkylamido derivatives in good yields (Table I). Since methylamide has a very low boiling point, its hydrochloride salt, dissolved in tetrahydrofuran–water (6:4), was used alternatively. Liberation of the amine in situ was brought about by addition of triethylamine. In fact the latter modification enabled us also to prepare α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate β-methylamide and its L-glutamic analogue in satisfactory yield. On the contrary, prolonged reaction time of methylamine under anhydrous conditions facilitated the formation of the cyclic aspartoyl methylimide derivative. Its structure is based on elemental analysis and spectral data (see Experimental Section). As expected the ^1H NMR spectrum in Me_2SO-d_6 lacks aromatic protons. Since the NCH_3 protons are located under the large $(CH_3)_2SO$ peak, this solvent was replaced with CD_3OD and the NCH_3 protons were shown then clearly as a singlet in the region of δ 2.7. In contrast, the ^1H NMR spectrum of the noncyclic product (a) displays a doublet at δ 2.7 due to coupling with the amide proton and a singlet at δ 7.35 attributed to the aromatic protons.

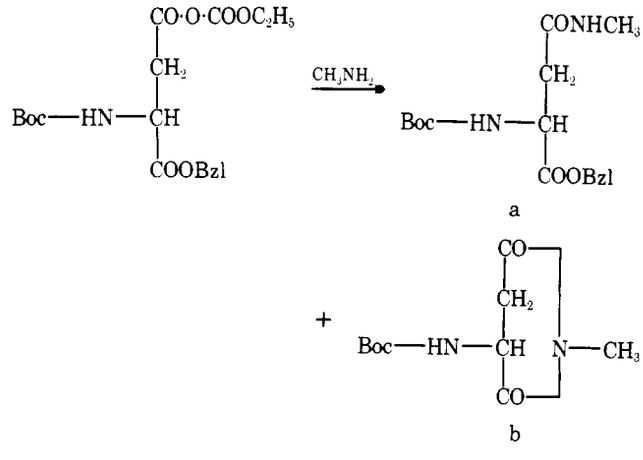


Table I. *N*-Tritylglycine Alkylamides and Deprotected Derivatives

Compd	Formula[a]	Mp, °C	Yield, %
Trt-Gly-NHCH$_2$CH$_3$[b]	$C_{23}H_{24}N_2O$	144–145	70
Trt-Gly-NH(CH$_2$)$_2$-CH$_3$[b]	$C_{24}H_{26}N_2O$	148–150	85
H-Gly-NHCH$_2$CH$_3$[c,d]	$C_{11}H_{18}N_2SO_4$	174–175	85
H-Gly-NH(CH$_2$)$_2$-CH$_3$[c,d]	$C_{12}H_{20}N_2SO_4$	140–141	82

[a] Analytical data were within ±0.4% for C, H, N. [b] Recrystallized from ethyl acetate–petroleum ether. [c] Isolated as the *p*-toluenesulfonate. [d] Recrystallized from ethanol.

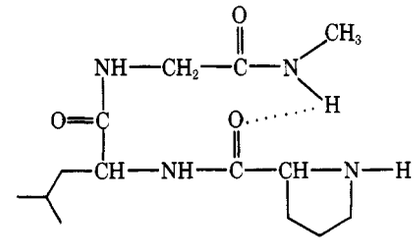
The tendency of aspartic acid amides and esters to imide formation is well known[7]. As the amide nitrogen of (a) becomes more nucleophilic, due to the methyl group, its cyclization to (b) proceeds in analogy to the proposed mechanism by Ondetti et al.[8] more readily.

Detritylation[5] of *N*-Trt-Gly-NHCH$_3$ (I) with *p*-toluenesulfonic acid afforded crystalline glycine methylamide *p-toluenesulfonate* (II). Similarly prepared Z-Gly-NHCH$_3$ was decarbobenzoxylated with HBr/AcOH to give glycine methylamide hydrobromide in high yield. Coupling of II with Z-Leu-OH by the *p*-nitrophenyl ester[9] produced Z-Leu-Gly-NHCH$_3$ (III) in crystalline form. The ^{1}H NMR spectrum shows characteristically a singlet at δ 7.15 for aromatic protons, a broad doublet at δ 0.9 for the methyl groups of the leucine residue, and a sharp doublet at δ 2.65 due to the methyl group coupled to the amide proton of the glycine residue. Compound III after deprotection with catalytic hydrogenolysis provided L-leucylglycine methylamide, which was isolated as the *p*-toluenesulfonate (IV). The latter was condensed in turn with Z-Pro-OH by the mixed-anhydride method[6] to give crystalline Z-Pro-Leu-Gly-NHCH$_3$ (V).

Besides the stepwise synthesis of III and V (procedure A), a more convenient route to these compounds is by condensation of Z-Leu-Gly-OH[10] and Z-Pro-Leu-Gly-OH,[11] respectively, with methylamine hydrochloride as described above (procedure B). Both peptide derivatives, Z-Leu-Gly-NHCH$_3$ and Z-Pro-Leu-Gly-NHCH$_3$, obtained either by procedure A or B had identical melting points and optical values. Analogously, the coupling of Z-Pro-Leu-Gly-OH with ammonium chloride afforded Z-Pro-Leu-Gly-NH$_2$ identical with that prepared by another method.[11]

Finally, the desired H-Pro-Leu-Gly-NHCH$_3$ (VI) was obtained by catalytic deprotection of V and crystallized from ethyl acetate–petroleum ether as needles. Its structure (VI) was confirmed by spectral data. The mass spectrum displays a molecular ion at *m/e* 298 (M^+) corresponding to the molecular formula $C_{14}H_{26}O_3N_4$ (requires *m/e* 298). The ^{1}H NMR spectrum shows a sharp doublet methyl signal at δ 2.75 due to coupling with the glycine amide proton which shows up as a quartet at δ 7.25.

The IR spectrum ($CHCl_3$) displays a strong, broad band at 3340 cm^{-1} and a weak one at 3440 cm^{-1}. It is known that the 3300–3380-cm^{-1} region corresponds to hydrogen-bonded NH groups whereas the presence of NH bands in the 3430–3480-cm^{-1} region is evidence of the presence of free NH groups.[12] In this connection it should be mentioned that unpublished experiments at that time showed that Z-Pro-Leu-Gly-N(CH$_3$)$_2$ and its deprotected derivative show very weak absorption at the region of 3300–3380 cm^{-1}. Provided that secondary amides exist in the trans configuration the above findings suggest that the trans orientation of H-Pro-Leu-Gly-NHCH$_3$ agrees best with a hydrogen bonding between the trans carboxamide proton and the C=O of proline to form a



ten-membered β turn. This is in line with the proposed conformation of H-Pro-Leu-Gly-NH$_2$ by Walter et al.[13]

Experimental Section

Melting points were taken on a Buchi SMP-20 capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Laboratory of Microanalysis of National Hellenic Research Foundation, Athens, Greece. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6MG spectrometer. NMR spectra were obtained with a Hitachi Perkin-Elmer R-24 (60-MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in δ units using tetramethylsilane as the internal standard. Infrared spectra were recorded with a Perkin-Elmer 457 grating infrared spectrophotometer. Thin layer chromatography (TLC) was carried out on silica gel Si F chromatogram sheets with the solvent system I (BAWP), 1-butanol–acetic acid–water–pyridine (30:6:24:20), and the solvent system II (BE), benzene–ethanol (8:2), and visualized by UV, ninhydrin, and chlorine–tolidine reagent.

***N*-Tritylglycine Methylamide.** The following procedure is typical for the preparation of certain tritylglycine alkylamides which are listed in Table I.

To a solution of Trt-Gly-OH (12.98 g, 40 mmol) in 100 mL of THF, cooled to −10 °C, were added triethylamine (4.04 g, 40 mmol) and ethyl chlorocarbonate (4.34 g, 40 mmol). After 3 min a solution of 8.1 g (200% excess) of methylamine hydrochloride in 20 mL of THF–H_2O (6:4) was neutralized with 12.12 g of triethylamine and added immediately with vigorous shaking. Half an hour later the solvent was evaporated to dryness and the residue was taken up in CH_2Cl_2 (100 mL). This solution was washed with 3 × 50 mL of 5% $NaHCO_3$, then with water and dried (Na_2SO_4). After removal of the solvent, a residue of 10 g (80%) was obtained, mp 187–188 °C. This was recrystallized from ethanol–water (9:3) or ethyl acetate–petroleum ether (9:2) to give 9.4 g (75%) of the desired product,[14] mp 188–189 °C.

Anal. Calcd for $C_{22}H_{22}N_2O$: C, 80.00; H, 6.66; N, 8.48. Found: C, 80.32; H, 6.85; N, 8.17.

Glycine Methylamide *p*-Toluenesulfonate. A mixture of tritylglycine methylamide (3.8 g, 20 mmol) and *p*-toluenesulfonic acid monohydrate (3.8 g, 20 mmol) in 60 mL of ethanol was heated for 5 min under reflux. The solvent was then evaporated to dryness and the solid residue was collected by filtration, repeatedly washed with ether, and finally recrystallized from 2-propanol–ether to give 5 g (96%) of product, mp 180–181 °C.

Anal. Calcd for $C_{10}H_{16}N_2O_4S$: C, 46.15; H, 6.15; N, 10.76. Found: C, 46.18; H, 6.41; N, 10.47.

Carbobenzoxy-L-leucylglycine Methylamide. To a magnetically stirred solution of glycine methylamide *p*-toluenesulfonate (1.93 g, 5 mmol) and *N*-methylmorpholine (0.5 g, 5 mmol) in DMF (12 mL) was added Z-Leu-ONp (1.93 g, 5 mmol). After 24 h the solvent was evaporated in vacuo and the remaining oily residue solidified by addition of water (60 mL) while cooling. The solid product was filtered and washed with 1 N HCl (50 mL), 5% $NaHCO_3$ (50 mL), and water. Crystallization from ethyl acetate–petroleum ether (7:3) gave 1.75 g (75%) of product, mp 124–125 °C, $[\alpha]^{24}_D$ −12.5° (*c* 1, DMF).

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.89; H, 7.46; N, 12.53. Found: C, 60.42; H, 7.31; N, 12.24.

L-Leucylglycine Methylamide *p*-Toluenesulfonate. A solution of Z-Leu-Gly-NHCH$_3$ (1.45 g, 5 mmol) in ethanol (50 mL) was subjected to catalytic hydrogenolysis over 250 mg of PdO. The evolution of CO_2 ceased after 3 h, the reaction mixture was filtered, and the solvent was evaporated to dryness yielding an oily product (0.86 g) homogeneous to TLC. The oil was then dissolved in dry ether (10 mL) and added *p*-toluenesulfonic acid *monohydrate* (0.96 g). After about 10 min the solvent was evaporated under vacuum and the remaining residue crystallized by addition of THF (10 mL), yield 1.3 g (68%), mp 172–175 °C.

Anal. Calcd for $C_{16}H_{27}N_3O_5S \cdot \frac{1}{2}H_2O$: C, 50.26; H, 7.32; N, 10.99. Found: C, 50.62; H, 6.96; N, 10.69.

Carbobenzoxy-L-prolyl-L-leucylglycine Methylamide. Procedure A. To a solution of Z-Pro-OH (0.78 g, 3.2 mmol) and trieth-

Table II. L-Prolyl-L-leucylglycine Alkylamide Derivatives

Peptide	Formula[a]	$[\alpha]^{24}_D$[b]	Mp, °C	Yield, %
Z-Pro-Leu-Gly-$NHCH_2CH_3$[c,d]	$C_{23}H_{34}N_4O_5$	−49.85°	163–165	64
Z-Pro-Leu-Gly-$NHCH_2CH_2CH_3$[c,d]	$C_{24}H_{36}N_4O_5$	−46.2°	110–111	55
H-Pro-Leu-Gly-$NHCH_2CH_3$[d]	$C_{15}H_{28}N_4O_3$	−41.4°	101–102	79
H-Pro-Leu-Gly-$NHCH_2CH_2CH_3$[d]	$C_{16}H_{30}N_4O_3$	−40.2°	112–113	84

[a] Analytical data were within ±0.4% for C, H, N. [b] As 1% solution in DMF. [c] By procedure B. [d] Recrystallized from ethyl acetate–petroleum ether.

ylamine (0.32 g, mmol) in THF (10 mL), cooled to −10 °C, was added ethyl chlorocarbonate (0.35 g, 3.2 mmol). After 3 min a mixture of L-leucylglycine methylamide *p*-toluenesulfonate (1.2 g, 3.2 mmol), *N*-methylmorpholine (0.44 mL), and water (1 mL) in THF (10 mL) was added with shaking. The reaction mixture was permitted to remain for 1 h at room temperature. Then the solvent was evaporated under vacuum and the residue was taken up in CH_2Cl_2, washed with 5% $NaHCO_3$ and H_2O, and dried (Na_2SO_4). The solvent was removed leaving an oil, which was crystallized (needles) from ethyl acetate–petroleum ether: yield 0.95 g (75%); mp 155–156 °C; $[\alpha]^{24}_D$ −52.6° (*c* 1, DMF).

Procedure B. To a chilled solution of Z-Pro-Leu-Gly-OH (4.19 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in THF (20 mL) was added ethyl chlorocarbonate (1.1 g, 10 mmol). After 3 min a solution of methylamine hydrochloride (2.02 g, 30 mmol) in 10 mL of THF–H_2O (6:4) was neutralized with triethylamine (3.03 g, 30 mmol) and mixed immediately with the anhydride. After 5 min the solvent was evaporated under vacuum and residue was taken up in CH_2Cl_2 and treated as described above: yield 2.76 g (64%); mp 155–156 °C; $[\alpha]^{24}_D$ −52.2° (*c* 1, DMF); IR (KBr) 3320, 3280, 1690, 1660, 1560 cm^{-1}; NMR ($CDCl_3$) δ 0.9 [br d, $(CH_3)_2C$], 1.6–2.3 (br signal, 9 H, 3 CH_2, $CHCH_2$), 2.7 (d, J = 6 Hz, 3 H, NCH_3), 3.5 (poorly resolved triplet, 1 H, α-CHPro), 3.8 (d, J = 6 Hz, 2 H, α-CH_2Gly, collapsed to a singlet on exchange with D_2O), 4.25 (br signal, 1 H, α-CHLeu), 5 (s, 2 H, $ArCH_2$), 7.2 (s, 5 H, C_6H_5), 7–7.8 (br signal, 3 H, 3 CONH, D_2O exchangeable); mass spectrum *m/e* 432 (molecular ion), 417, 402, 401, 389, 375, 344, 343, 317.

Anal. Calcd for $C_{22}H_{32}N_4O_5$: C, 61.11; H, 7.40; N, 12.96. Found: C, 60.76; H, 7.18; N, 12.63.

L-Prolyl-L-leucylglycine Methylamide. A solution of Z-Pro-Leu-Gly-$NHCH_3$ (0.71 g, 1.6 mmol) in ethanol (50 mL) was hydrogenolyzed over 100 mg of PdO and the resulting oily product crystallized (needles) from ethyl acetate–petroleum ether: yield 250 mg (58%); mp 117–118 °C; $[\alpha]^{24}_D$ −45.4° (*c* 1, DMF); IR (KBr) 3290, 2950, 1650–1630, 1560–1540 cm^{-1}; NMR ($CDCl_3$) δ 0.9 [br d, 6 H, $(CH_3)_2C$], 1.5–2.2 (br, 9 H, 3 CH_2, $CHCH_2$), 2.75 (d, J = 6 Hz, 3 H, CH_3), 3.6–3.9 (br s, 3 H, α-CHPro, α-CH_2Gly), 4.3 (poorly resolved signal, 1 H, α-CHLeu, on exchange with D_2O becomes apparent triplet), 7.25 (q, J = 6 Hz, 1 H, CONHCH$_3$), 7.75 (br t, 1 H, α-CH_2GlyNH), 8.1 (br d, J ~ 7 Hz, 1 H, α-CHLeuNH); mass spectrum *m/e* 298 (molecular ion), 283, 281, 268, 266, 265, 242, 211, 210, 186, 183, 155.

Anal. Calcd for $C_{14}H_{26}N_4O_3$: C, 56.37; H, 8.72; N, 18.79. Found: C, 56.10; H, 8.71; N, 18.76.

Carbobenzoxyglycine Methylamide. This compound was prepared from carbobenzoxyglycine (2.1 g, 10 mmol) by exactly the same procedure described for the tritylglycine analogue, yield 1.44 g (65%), mp 107–108 °C.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.30; N, 12.61. Found: C, 59.10; H, 6.12; N, 12.42.

Glycine Methylamide Hydrobromide. The above product, Z-Gly-$NHCH_3$ (2.22 g, 10 mmol), was stirred for 1 h with 10 mL of 2 N HBr in glacial acetic acid. During this time most of the hydrobromide precipitated. The precipitation was completed by addition of 60 mL of anhydrous ether. The solid material was collected by filtration, repeatedly washed with ether, and finally recrystallized from 2-propanol–ether, yield 1.6 g (95%), mp 126–128 °C.

Anal. Calcd for $C_3H_9N_2OBr$: C, 28.91; H, 7.22; N, 22.48. Found: C, 28.80; H, 7.19; N, 22.40.

α-Benzyl N^{α}-*tert*-Butyloxycarbonyl-L-aspartate β-Methylamide. To a chilled solution of α-benzyl Boc-L-asparate[15] (1.61 g, 5 mmol) and triethylamine (0.5 g, 5 mmol) was added 0.55 g (5 mmol) of ethyl chlorocarbonate. After 2 min a solution of methylamine hydrochloride (1.01 g, 200% excess) and triethylamine (2.1 mL) in 10 mL of THF–H_2O (6:4) was added with vigorous shaking. The reaction mixture remained at room temperature for 2 min and the solvent was evaporated under vacuum. The remaining residue was solidified from ethanol–water (2:10) and cooled for 24 h. Then it was filtered and washed with 5% $NaHCO_3$ and water: yield 1.4 g (40%); mp 108–109 °C; $[\alpha]^{24}_D$ −16.1° (*c* 1, CH_3OH); NMR ($CDCl_3$) δ 1.4 [s, 9 H, $(CH_3)_3C$], 2.7 (br d, 5 H, NCH_3, CH_2), 4.6 (complex m, 1 H, COCHN), 5.15 (s, 2 H, $ArCH_2$), 5.7 (br d, 1 H, OCONH), 6.3 (br signal, 1 H, CONH), 7.35 (s, 5 H, C_6H_5).

Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.71; H, 7.14; N, 8.33. Found: C, 60.45; H, 7.11; N, 8.29.

When dry methylamine (300% excess) was used and the reaction mixture permitted to remain at room temperature for 1 h the main product was found to be the Boc-aspartoylmethylimide derivative (b): yield 66%; mp 195–197 °C; $[\alpha]^{24}_D$ +2.9° (*c* 1, CH_3OH); NMR spectrum of the cyclic product in $(CD_3)_2SO$ does not exhibit absorption for aromatic protons, δ 1.4 [s, 9 H, $(CH_3)_3C$], 4.25 (complex m, 1 H, NCOCHN), 6.65 (br d, 1 H, OCONH).

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 56.60; H, 7.54; N, 13.20. Found: C, 56.49; H, 7.51; N, 13.10.

α-Benzyl N^{α}-*tert*-Butyloxycarbonyl-L-glutamate-β-methylamide. This compound was prepared in a manner similar to that used in the synthesis of α-benzyl Boc-L-aspartate-β-methylamide: yield 77%; mp 89–90 °C; $[\alpha]^{24}_D$ −24.2° (*c* 1, CH_3OH).

Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.71; H, 7.42; N, 8.00. Found: C, 61.20; H, 7.39; N, 7.92.

Carbobenzoxy-L-prolyl-L-leucylglycinamide. Coupling of Z-Pro-Leu-Gly-OH (629 mg, 1.5 mmol) with ammonium chloride (240 mg, 4.5 mmol) was done by the same reactions described above. The solid product resulting from the evaporation of THF was collected by addition of 5% $NaHCO_3$ solution and washed with water. It was dried over P_2O_5 and triturated with ethyl acetate: yield 0.4 g (64%); mp 162–163 °C; $[\alpha]^{24}_D$ −74.1° (*c* 2, 95% C_2H_5OH); reported[11] mp 163–163.5 °C; $[\alpha]^{24}_D$ −73.3° (*c* 2, 95% C_2H_5OH).

Registry No.—*N*-Trityl-Gly methylamide, 62029-66-7; Trt-Gly-OH, 5893-05-0; methylamine HCl, 593-51-1; Gly methylamide *p*-toluenesulfonate, 62029-67-8; carbobenzoxy-L-Leu-Gly methylamide, 62029-68-9; Z-Leu-ONp, 1738-87-0; L-Leu-Gly methylamide *p*-toluenesulfonate, 62029-70-3; Z-L-Pro-L-Leu-Gly methylamide, 62029-71-4; Z-Pro-OH, 1148-11-4; Z-Pro-Leu-Gly-OH, 7801-38-9; L-Pro-L-Leu-Gly-$NHCH_3$, 62029-72-5; Z-Gly-$NHCH_3$, 21855-72-1; Z-Gly-OH, 1138-80-3; Gly-$NHCH_3$ HBr, 62029-73-6; α-benzyl N^{α}-Boc-L-Asp-β-$NHCH_3$, 62029-74-7; α-benzyl Boc-L-Asp, 30925-18-9; Boc-aspartoyl methylimide derivative, 62029-75-8; α-benzyl N^{α}-Boc-L-Glu-$NHCH_3$, 62029-76-9; Z-L-Pro-L-Leu-Gly-NH_2, 14485-80-4; Trt-Gly-$NHCH_2CH_3$, 62029-77-0; Trt-Gly-$NH(CH_2)_2CH_3$, 62029-78-1; H-Gly-$NHCH_2CH_3$ *p*-toluenesulfonate, 62029-80-5; H-Gly-$NH(CH_2)_2CH_3$ *p*-toluenesulfonate, 62029-82-7; Z-Pro-Leu-Gly-$NHCH_2CH_3$, 62029-83-8; Z-Pro-Leu-Gly-$NH(CH_2)_2CH_3$, 62029-84-9; H-Pro-Leu-Gly-$NHCH_2CH_3$, 62029-85-0; H-Pro-Leu-Gly-$NH(CH_2)_2CH_3$, 62029-86-1; ethylamine, 75-04-7; propylamine, 107-10-8.

References and Notes

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A Synthesis of (±)-*trans*-Chrysanthemic Acid

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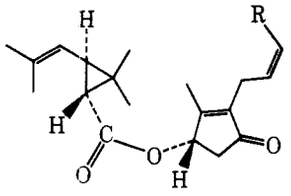
A synthesis of (±)-*trans*-chrysanthemic acid (8) from eucarvone (1) is described. Ozonolysis of 3-methylcar-4-en-2-one (2) in methanol at −78 °C followed by reduction with dimethyl sulfide and treatment with methanolic hydrogen chloride effects cleavage of the alkene, decarbonylation, and formation of acetal 3 in a single synthetic stage.

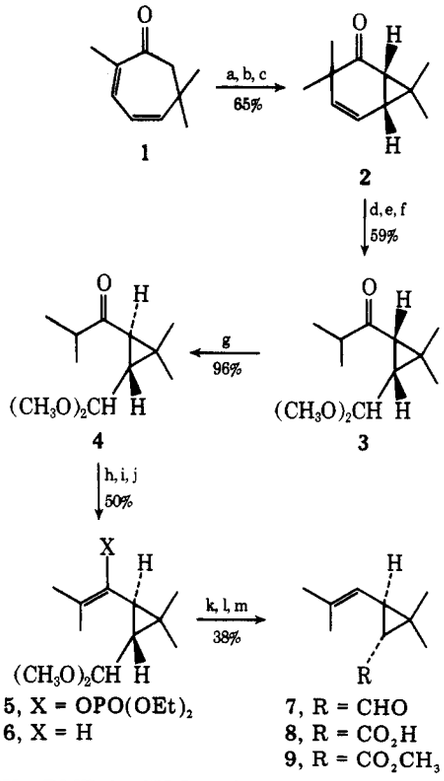
Pyrethrins are a family of naturally occurring insecticides from *Chrysanthemum cineriaefolium* (pyrethrum daises) which exhibit low mammalian toxicity and ready biodegradability.[1] Pyrethrins, such as pyrethrin I, are esters of *trans*-



pyrethrin I, R = CH_3, C_2H_5, or $CH{=}CH_2$

chrysanthemic acid (8) and various rethrolone alcohols.[2] A number of syntheses of *trans*-chrysanthemic acid (8) have been reported[3] presumably because of the usefulness of this substance in the preparation of commercial pyrethrins for pest insect control. We wish to report herein a synthesis of (±)-*trans*-chrysanthemic acid (8) from eucarvone (1).

Eucarvone (1), readily available from carvone,[4] upon alkylation using sodium amide in 1,2-dimethoxyethane (DME) followed by methyl iodide affords a 4:1 mixture of 3-methylcar-4-en-2-one (2) and 2,6,6,7-tetramethylcyclohepta-2,4-dienone, respectively.[5] These two ketones can be separated by preparative gas chromatography;[5] however, while investigating various methods of cleaving the alkenes in this mixture we discovered that the cycloheptadienone could be oxidized at an appreciably faster rate than ketone 2. Therefore, if this mixture of enones is stirred in a homogeneous solution of osmium tetroxide (catalytic amount) and sodium chlorate (2.62 equiv) in aqueous *tert*-butyl alcohol for 18 h,[6] followed by workup and simple bulb-to-bulb distillation, 3-methylcar-4-en-2-one (2) is then obtained pure in 65% overall yield from eucarvone (1). Ozonolysis of ketone 2 in methanol at −78 °C followed by reduction of the ozonide with dimethyl sulfide[7] and treatment with methanolic hydrogen chloride over anhydrous calcium sulfate affords keto acetal 3 in 59% yield. Methanolic hydrogen chloride not only converts the aldehyde group to an acetal, but it also affects decarbonylation of the intermediate nonenolizable β-keto aldehyde. Epimerization of keto acetal 3 using potassium *tert*-butoxide in dry *tert*-butyl alcohol gives keto acetal 4 in 96% yield. Treatment of keto acetal 4 with lithium diisopropylamide (1.1 equiv) in anhydrous tetrahydrofuran (THF) at −78 °C followed by diethyl chlorophosphate (1.1 equiv) at 0–25 °C produces enol phosphate 5 in 62% yield.[8] Reduction of enol phosphate 5 utilizing lithium metal (16 equiv) in anhydrous ethylamine in the presence of dry *tert*-butyl alcohol affords alkene 6 in 81% yield.[9] Hydrolysis of acetal 6 by simply stirring in aqueous acetone for 12 h gives aldehyde 7 in 98% yield. Oxidation of aldehyde 7 with chromium trioxide in wet pyridine for 78 h according to the procedure of Raphael and co-workers[3] produces (±)-*trans*-chrysanthemic acid (8) in 42% yield.[3] Other



a, $NaNH_2$, DME; b, CH_3I; c, OsO_4 cat., $NaClO_3$, H_2O, *t*-BuOH; d, O_3, CH_3OH, −78°C; e, $(CH_3)_2S$; f, CH_3OH, HCl cat., $CaSO_4$; g, KO-*t*-Bu, *t*-BuOH; h, $LiN(i\text{-}Pr)_2$, THF; i, $(EtO)_2POCl$; j, Li, $EtNH_2$, *t*-BuOH; k, acetone, H_2O; l, CrO_3, pyridine, H_2O; m, CH_2N_2, Et_2O.

oxidizing agents were tried including Jones reagent[10] and silver oxide;[12] however, these latter methods proved to be less efficient than chromium trioxide in wet pyridine. Synthetic *trans*-chrysanthemic acid (8) was esterified to (±)-methyl