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An Asymmetric Synthesis of *cis*-5-Alkylproline Derivatives[1]

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We have developed a versatile and convenient synthesis of *cis*-5-alkylprolinamides. Protection/activation of the α-carboxylic acid function of *N*-benzyloxycarbonyl-L-glutamic acid (Z-L-Glu-OH) by reaction with H_2CO to form an *N*-Z-oxazolidinone ring allowed the subsequent conversion of the side-chain carboxylic acid, through its acid chloride, into a series of alkyl ketones. Ammonolysis of the *N*-Z-oxazolidinone ring generated N^{α}-Z-amino acid amides which were converted into *cis*-5-alkylprolinamides by a reductive deprotection/cyclization step using H_2–Pd/C. The cyclization proceeds through a chiral 2-alkyl-Δ^1-pyrroline-5-carboxylic acid intermediate which induces a high degree of asymmetry (~95%) in the subsequent reduction to the desired *cis*-5-alkylprolinamides. These diastereomeric molecules may be purified to even higher enantiomeric excess by a simple recrystallization. Methyl-, ethyl-, butyl-, and benzyl-substituted proline analogues were prepared in high isomeric purity in this manner. By this route, 5-substituted proline derivatives are now readily available in high isomeric purity for use in conformation studies and analogue syntheses and as intermediates for the production of chiral reagents for asymmetric synthesis.

In conjunction with our studies on the asymmetric transformation of amino acids, we need a versatile and convenient synthesis of 5-alkyl-substituted prolinamides. Several previous syntheses of 5-methylproline have proceeded through 2-methyl-Δ^1-pyrroline-5-carboxylic acid by means of catalytic reduction.[2] The routes used to obtain the intermediates have made use of the base-catalyzed addition of diethyl acetamidomalonate to substrates such as methyl vinyl ketone,[3] 1,3-dichloro-2-butene,[4] and (through a Mannich intermediate) acetylacetone,[5] followed by acid-catalyzed hydrolysis and cyclization. Ammonolysis of methyl 2,5-dibromocaproate[6] has also been used for the preparation of 5-methylproline. All of these approaches to 5-methylproline led to mixtures of diastereomeric products which must be chemically resolved by multiple recrystallizations of the tartrate salts.[7] We now report a general and convenient asymmetric synthesis of 5-alkylproline derivatives which is analogous to the biosynthetic route from L-glutamic acid to proline through glutamic semialdehyde and chiral Δ^1-pyrroline-5-carboxylic acid.[8] Our procedure uses L-Glu as a chiral synthon for the preparation of optically pure 2-alkyl-Δ^1-pyrroline-5-carboxamides which are reduced stereoselectively to generate the new asymmetric center at C-2.

Table I. Physical Constants of Ketones 3

	substituent R	yield,[a,b] %	mp, °C	$[\alpha]^{25}_D$ (MeOH), deg	formula[d]
3a	H (2*S*)	82, 74	64–65	102*e*	$C_{15}H_{17}NO_5$
	H (2*R*)	58	61–63	−106[e]	$C_{15}H_{17}NO_5$
3b	CH_3	60, 72	45–46	82.5	$C_{16}H_{19}NO_5$
3c	*n*-C_3H_7	66	oil	67.9	$C_{18}H_{23}NO_5$·EtOAc
3d	C_6H_5	40, 33[c]	oil	63.7	$C_{21}H_{21}NO_5$

[a] Yield from diazoalkane reaction. [b] Yield from tetraalkyltin reaction. [c] Tetrabenzyltin obtained was not pure. [d] Elemental analyses agreed with calculated values (±0.4%). [e] Rotation carried out in $CHCl_3$.

Synthesis

The α-carboxyl function of the inexpensive and readily available *N*-(benzyloxylcarbonyl)-L-glutamic acid (*N*-Z-L-Glu-OH) was simultaneously protected and mildly activated for subsequent ammonolysis by formation, in excellent yield, of the oxazolidinone, 1 (Scheme I).[9] The synthesis was also carried out with *N*-Z-D-Glu-OH (2*R*) in order to check the enantiomeric purity of the products. The γ-carboxyl function was converted to the crystalline

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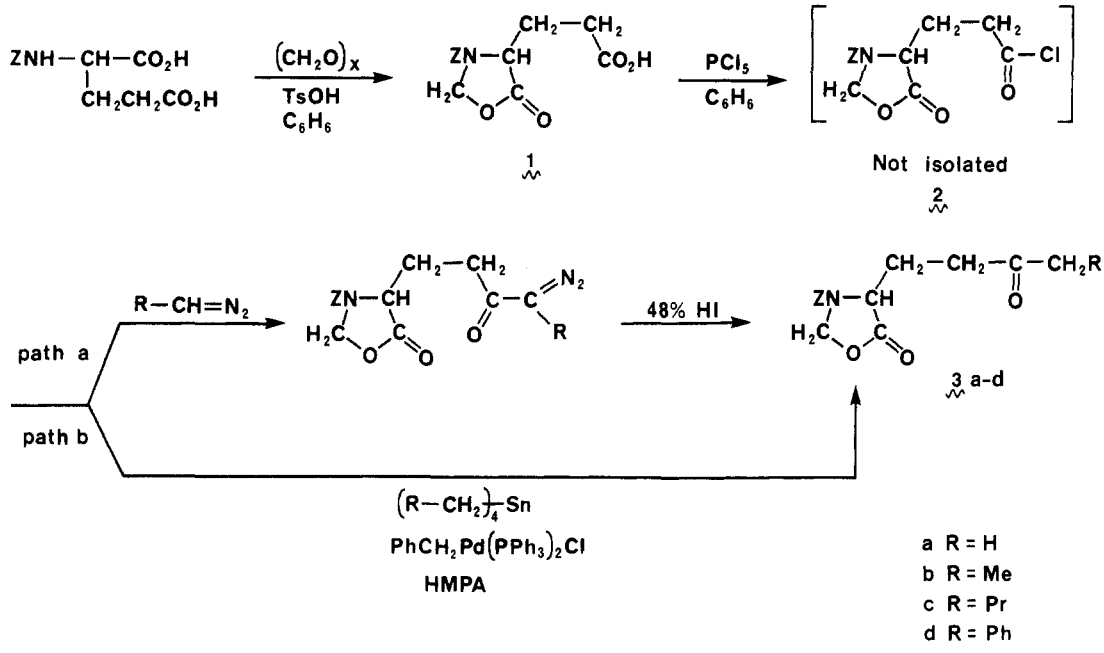
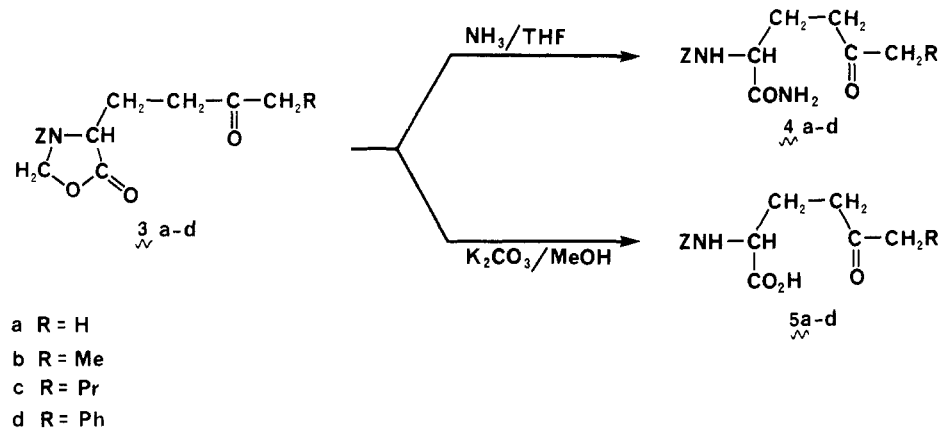
Scheme I



Scheme II



acid chloride (**2**) in situ with PCl_5.[10] Reaction of the acid chloride **2** with excess diazoalkanes formed the diazo ketones which were converted to the corresponding ketones **3a–d** by treatment with 48% HI (path a).[11]

Alternatively, the ketones (Table I) were obtained by reacting the acid chloride **2** with tetraalkyltin or tetraaralkyltin derivatives in the presence of $PhCH_2Pd(PPh_3)_2Cl$ catalyst[12] (path b) to form the alkyl or aralkyl ketones (**3a–d**). Neither procedure required purification of the intermediates. However, the latter procedure is preferable as the use of hazardous diazoalkanes is not involved.

The oxazolidinone ketones **3a–d** were subjected to ammonolysis in THF to yield the desired keto amides **4a–d** in good yield (Table II). If the free carboxylic acid is desired (e.g., for the preparation of the free proline analogue), the oxazolidinone **3a** can be saponified to yield the keto acid **5a** (Scheme II).

Reduction of the protected keto amides (**4**) led to removal of the Z protecting group and cyclization to the intermediate 2-alkyl-Δ^1-pyrroline-5-carboxamide **6** (Scheme III), which could be observed as a UV-absorbing spot on TLC. When the reduction of **4a** was performed in MeOH, the reaction did not proceed further, and intermediate **6a** could be isolated. When the reduction was performed in the presence of acetic acid, however, asymmetric reduction took place and the 5-methylprolinamide (**7a**) was formed in good yield.

The extent of asymmetric induction was dependent on the catalyst used (Table III). If Adams' catalyst was used, the ratio of cis to trans products was approximately 7:3. When the catalyst was 10% Pd/C, or palladium black, prepared in situ from palladium acetate with MeOH/HOAc as solvent, predominant cis (2*S*,5*S*) product resulted. In this case, a single recrystallization from CH_2Cl_2 yielded the optically pure (2*S*,5*S*)-5-methylprolinamide (**7a**). Reduction of **4a** by transfer hydrogenation also gave

Table II. Physical Constants of Keto Amides 4

	substituent R	yield, %	mp, °C	$[\alpha]^{25}_D$, (MeOH), deg	formula[a]
4a	H (2*S*)	92	142–144	−4.0	$C_{14}H_{18}N_2O_4$
	H (2*R*)	60	137–139	3.02	$C_{14}H_{18}N_2O_4$
4b	CH_3	93	133–135	−4.17	$C_{15}H_{20}N_2O_4$
4c	*n*-C_3H_7	83	162–163	−4.32	$C_{17}H_{24}N_2O_4$
4d	C_6H_5	81	150–152	−1.29	$C_{20}H_{22}N_2O_4$

[a] Elemental analyses agreed with calculated values (±0.4%).

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Scheme III

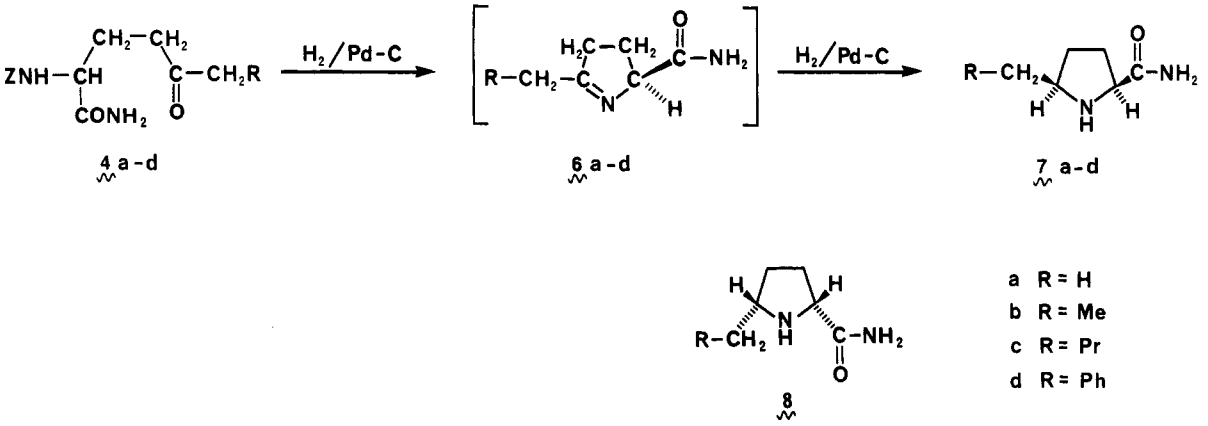

Table III. Asymmetric Reduction Results

	substituent R	yield,[a-d] %	cis/trans[a-d]	mp,[e] °C	$[\alpha]^{25}_D$ (MeOH),[e] deg	formula[f]
7a	H	89,[a] 83,[b] 82,[c] 80[d]	95/5,[a] 95/5,[b] 85/15,[c] 70/30,[d]	58–60	−66.9	$C_6H_{12}N_2O$
7b	CH_3	98,[a] 75,[b]	75/25,[a] 80/20[b]	63–65	−53.3	$C_7H_{14}N_2O$·HOAc
7c	n-C_3H_7	82,[a]	90/10,[a] 90/10,[b]	74–75	−53.1	$C_9H_{18}N_2$·HOAc
7d	C_6H_5	85[b]	90/10[b]	90–92	−3.6	$C_{12}H_{10}N_2O$·HOAc
8	H	83	92/8[b]	97–99[g]	63.1	$C_6H_{12}N_2O$·0.6HOAc[g]

[a] Pd (black) was used as catalyst. [b] 10% Pd/C was used as catalyst. [c] 10% Pd/C in EtOH/HOAc (2:1) with cyclohexene as H_2 source. [d] Adams' catalyst. [e] Data for the recrystallized cis isomer. [f] Elemental analyses agreed with calculated values (±0.4%). [g] Obtained as the acetate salt; C, 51.99; H, 8.82; N, 17.66.

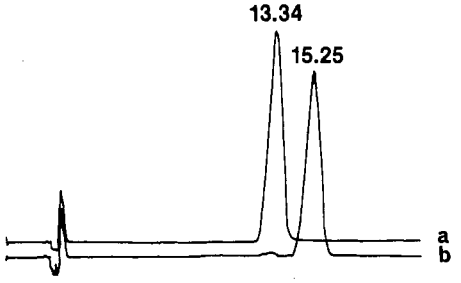

Figure 1. Demonstration of enantiomeric purity of **7a**. The HPLC traces (t_R in min) of the diastereomeric GITC derivatives (see Experimental Section) of the enantiomers **7a** (trace a) and **8** (trace b) demonstrate that no significant racemization occurred at the C^α-position during the cyclization/reduction step. The apparent presence of ~1% of **7a** in trace b is in accord with our detection by the GITC procedures (22% CH_3CN eluent) of up to 1% L-Glu in lots of the D-Glu starting material for **8**.

predominantly the cis isomer (Table III). Reduction of **4b–d** to (2*S*,5*S*)-5-alkyl- or 5-aralkylprolinamides also proceed well. If the protected keto acid (e.g., **5a**) is used as precursor, *cis*-5-alkylprolines will result.

The absence of the corresponding diastereomer, (2*S*,5*R*)-5-methylprolinamide, was confirmed by NMR and amino acid analysis (see Experimental Section). Enantiomeric purity was established by the preparation of (2*R*,5*R*)-5-methylprolinamide (**8**) (from D-glutamic acid) and the subsequent HPLC characterization of the two enantiomers after derivatization with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate[14] (Figure 1). This experiment very clearly demonstrates the absence of racemization at the α-position during this reaction sequence.

Proline residues have important conformational properties in polypeptides and proteins, and the study of proline analogues with unusual steric constraints is of interest.[15] This convenient and general route to optically pure *cis*-5-alkyl- or *cis*-5-aralkylproline derivatives makes such analogues readily available for peptide hormone analogue studies.

Table IV. Diagnostic NMR[a] Signals for 5-Alkylprolinamides 7

		^1H spectrum (δ ppm)	
compd	alkyl group[b]	H_a (J, Hz)[b]	H_b (on C_5)
7a	*cis*-CH_3	1.25 d (6)[c]	4.01 m
	trans-CH_3	1.25 d (6)[c]	4.05 m
7b	*cis*-CH_3CH_2	0.9959 t (7.5)	3.96 m
	trans-CH_3CH_2	0.967 t (7.5)	4.00 m
7c	*cis*-$CH_3(CH_2)_3$	0.908 t (6.8)	4.136 m
7d	*cis*-$PhCH_2$	2.83 d (6.6)	3.94 m
8	*cis*-CH_3	1.20 d (6)	3.83 m
	trans-CH_3	1.20 d (6)	3.90 m

[a] Proton spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer of the amino acid acetate salt in $CDCl_3$. [b] The protons designated H_a are in italics. [c] The resonances given for the corresponding free acids, *cis*-5-methylproline·HCl and *trans*-5-methylproline·HCl in D_2O, are 1.44 (d, J = 6.6, H_a); 4.50 (m, H_b) and 1.42 (d, J = 6.8, H_a); 4.50 ppm (m, H_b), respectively.[7]

Experimental Section

^1H and ^{13}C NMR spectra were recorded on Brucker WM-300 and WH90 spectrophotometers, respectively (see Table IV). Melting points were determined on a Thomas-Hoover apparatus and are corrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter in a 1-dm microcell at 25 °C. *N*-Z-L-Glu-OH was purchased from Vega Biochemical. Tetramethyltin, tetraethyltin, and tetrabutyltin were purchased from Alfa. Tetrabenzyltin was purchased from Organometallics, Inc. Diazoalkanes,[13] benzyl bis(triphenylphosphine)palladium chloride,[12] and oxazolidinone[9] **7** were prepared as described. All other reagents were from Aldrich or Mallinckrodt and were used without further purification.

Amino Acid Analyses. Amio acid analyses were performed on a Beckman 119CL automatic analyzer after hydrolysis in 6 N HCl for 18 h. The buffer sequence was pH 3.25 (50 min), 4.12 (17 min), 6.40 (113 min). Using this sequence the retention times

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for *cis*-5-methylproline and *trans*-5-methylproline were 45.5 and 49.7 min, respectively. A slightly different buffer sequence was used previously to separate these isomers.[11] The *cis*-5-ethylproline and *trans*-5-ethylproline isomers had retention times of 55.7 and 63.2 min, respectively. It was determined that these hydrolysis conditions led to a small amount of the trans material. This isomerization was found to be time-dependent by analysis of the hydrolysate of pure *cis*-5-methylprolinamide (6 N HCl, 110 °C) in sealed tubes at various time periods.

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidinepropionyl Chloride (2).[9] PCl_5 (13.9 g, 66.6 mmol) was added to a solution of oxazolidinone[10] 1 (19.5 g, 66.6 mmol) in 60 mL of benzene (dried over molecular sieves) at 0 °C, and the mixture was stirred at 0 °C for 1 h during which time the reaction mixture became homogeneous. The solvent was removed under vacuum, and the $POCl_3$ byproduct was codistilled with 2 × 25 mL dry toluene to give the solid acid chloride.

General Procedure for 3. Method A. To a cooled solution of acid chloride 2 (6.2 g, 20 mmol) in 30 mL of dry benzene was added excess diazoalkane (30 mmol) in ether (caution). The reaction mixture was stirred at 0 °C for 0.5 h and the excess diazoalkane and solvents were removed at the water aspirator to give a yellow syrup. The syrup was dissolved in 150 mL of $CHCl_3$, shaken with 48% HI in portions (8 mL, 8 mL, 9 mL), washed with water, 2% $Na_2S_2O_3$, water, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a brown solid. Chromatography of the solid on a silica gel column with EtOAc/hexane (2:3) gave the pure compound.

Method B. To a solution of 67 mmol of the acid chloride 2 in 30 mL of HMPA (toxic) was added the tetraalkyltin (67.32 mmol) and $PhCH_2Pd(PH_3)_2Cl$ (40 mg, 0.033 mmol).[12] The reaction mixture was heated at 65 °C for 4 h, diluted with water, and extracted with EtOAc. The EtOAc layer was washed with H_2O, 5% $NaHCO_3$, H_2O, 5% $NaHSO_4$, H_2O, and brine and was dried over Na_2SO_4. The EtOAc was filtered and concentrated to give an oil. Filtration of the oil through a silica gel column with EtOAc/hexane (2:3) gave the pure product.

General Procedure for 4. To a solution of 3 (35 mmol) in 500 mL of distilled THF was added at 0 °C concentrated NH_4OH (160 mL). The reaction mixture was stirred at 0 °C for 5 h, then at 25 °C overnight. Evaporation of the solvent followed by recrystallization from hot EtOAc gave the desired product.

General Procedure for 7. A total of 1.8 mmol of 4 was dissolved in a mixture of 25 mL of MeOH and 2.5 mL of glacial acetic acid. The catalyst (100 mg) was added and the reduction under H_2 at atmospheric pressure was followed by TLC. Upon completion of the reaction, the mixture was filtered through Celite, concentrated to dryness, and flash chromatographed (CH_2Cl_2/MeOH; 3:1). Recrystallization from CH_2Cl_2 gave the desired product.

Assay for Enantiomeric Purity. The enantiomeric (2*S*,5*S*)- and (2*R*,5*R*)-5-methylprolinamides were characterized by HPLC analysis after derivatization by the GITC procedure.[14] A solution of ~5 mg of the amino acid amide was dissolved in 2.5 mL of 0.4% Et_3N. To this aqueous solution was added 2.5 mL of a solution of 0.5% 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate in CH_3CN. After ~20 min at room temperature, the resulting diastereomeric thiourea adducts were analyzed by reversed-phase HPLC on a 5-μm C-18 column (4.5 × 250 mm; Altex) using isocratic elution (30% CH_3CN, eluent 0.03 M in NH_4OAc, pH 4.5) and absorption at 250 nm.

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Perhydroazulenes. 6. 4-Keto Derivatives with Bridgehead Methyl Substituents[1]

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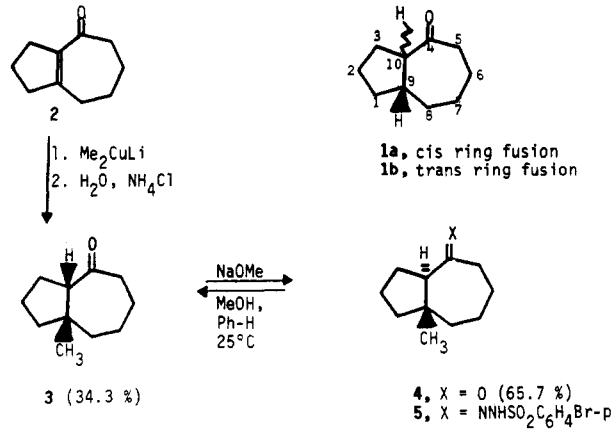
The two 9-methyl stereoisomers 3 and 4 and the two 10-methyl stereoisomers 8 and 9 of 4-ketoperhydroazulene have been prepared and fully characterized by means of spectra, analyses, and crystal structures. Several routes, including the selective methylation of the enone 2 to form the unsaturated ketone 12, were used (Schemes II and III) to form the 10-methyl compounds 8 and 9. Methylation of the lithium enolate (7) of 4-ketoperhydroazulene yielded a mixture of monoalkylated products containing 97% of the cis isomer 8 and 3% of the trans isomer 9. Probable conformations for the enolates and alkylated products obtained in this study are discussed.

To continue our study[2-4] of the synthesis and conformation of 4-ketoperhydroazulene derivatives 1 (Scheme I), we have examined the stereochemistry and conformation of the products formed when a methyl group is introduced at either of the two bridgehead positions C9 or C10. The 9-methyl ketones 3 and 4 were obtained by the previously described[5] addition of lithium dimethylcuprate to the enone 2.[2] The stereoisomeric products were separated by HPLC and the equilibrium composition (34.2% 3 and 65.7% 48 reported[5a] ca. 1:2) was measured in a C_6H_6–MeOH mixture (1:1 v/v) at 25.0 °C in the presence

Scheme I



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