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Cyclopeptide Alkaloids. Synthetic, Spectroscopic and Conformational Studies of Phencyclopeptine Model Compounds

Dane Goff, J. Clark Lagarias, Willy C. Shih, Melvin P. Klein, and Henry Rapoport*

Department of Chemistry and Lawrence Berkeley Laboratory, University of California, Berkeley, California 94720

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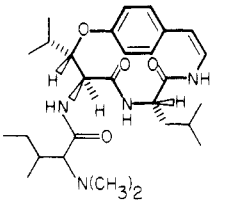
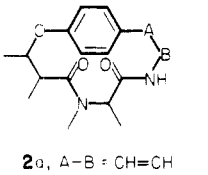
Peptide cyclization via the *p*-nitrophenyl ester of 4-methyl-3-[4′β-[[[*N*′-[(*tert*-butyloxy)carbonyl]-L-prolyl]-amino]ethyl]phenoxy]pentanoic acid (**9**) has afforded a single cyclopeptide diastereomer, (5*S*,9*R*)-9-isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**), in 36% yield. From the comparative analysis of the UV, IR, CD, and ^{1}H NMR spectra of **4** and cyclopeptide (5*S*)-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**3d**), of known geometry, the conformational identities of the 14-membered ring systems were ascertained. From these data the assignment of *R* stereochemistry at C9 for cyclopeptide **4** was deduced. Since the stereochemistry at C9 in the naturally occurring phencyclopeptines is the same, these results suggest a feasible route to the stereoselective total synthesis of the phencyclopeptines.

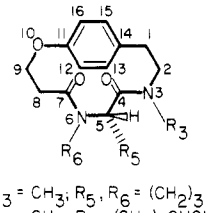
The class of natural products known as the cyclopeptide alkaloids encompasses a group of over 80 polyamide plant bases which contain 13-, 14-, or 15-membered rings.[1] Recently, experimental evidence suggesting their role as ionophores in plants[2-4] has generated further interest in the biology and chemistry of these compounds, particularly the 14-membered-ring phencyclopeptines.[5] Structurally, the *p*-phencyclopeptines are both *p*-cyclophanes and cyclodipeptides comprised of β-hydroxyamino acid, *p*-hydroxystyrylamine, and α-amino acid residues within the 14-membered ring. The β-hydroxyamino acid is commonly β-hydroxyleucine as in frangulanine (**1**); however, natural products containing β-(hydroxyphenyl)alanyl, β-hydroxyisoleucyl and *trans*-3-hydroxyprolyl residues have been identified.[1] The α-amino acid is also variable and for the most part limited to those with nonionic side chains (i.e., leucine, phenylalanine, tryptophan, proline). Functionalization of the benzylic position may vary in the natural products as shown in generalized structure **2**.

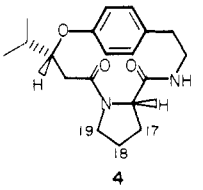


1



2 a, A–B = CH=CH
b, A–B = $COCH_2$
c, A–B = $CHOHCH_2$





4

3 a $R_3 = CH_3$; $R_5, R_6 = (CH_2)_3$
b $R_3 = CH_3$; $R_5 = (CH_3)_2CHCH_2$; $R_6 = H$
c $R_3 = R_6 = CH_3$; $R_5 = (CH_3)_2CHCH_2$
d $R_3 = H$; $R_5, R_6 = (CH_2)_3$
e $R_3 = R_6 = H$; $R_5 = (CH_3)_2CHCH_2$

Because of the complexity of the ring system with this functionality, the total synthesis of the phencyclopeptines is an interesting and difficult challenge. Two approaches to the synthesis of the phencyclopeptines have been described recently. Since any synthesis of the phenylcyclopeptines must rely on the success of the cyclization step, we chose to optimize the factors affecting ring closure of model compounds in an earlier study.[4] Using this methodology, the synthesis of phencyclopeptine models **3a–e** was successful via an active ester peptide cyclization. The approach employed by the French group has been to address the question of the stereochemistry of the β-hy-

(1) Tschesche, R; Kaussmann, E. V. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. XV, pp 165–203.
(2) Ravizzini, R. A.; Andreo, C. S.; Vallejos, R. H. *Plant Cell Physiol.* **1977**, *18*, 701.
(3) Kawai, K.; Nozawa, Y.; Ogihara, Y. *Experientia* **1977**, *33*, 1454.
(4) Lagarias, J. C.; Houghten, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202.
(5) The term phencyclopeptine was proposed as a reasonable and practical nomenclature system for these macrocyclic peptide alkaloids: Lagarias, J. C.; Goff, D.; Klein, F. K.; Rapoport, H. *J. Nat. Prod.* **1979**, *42*, 220.

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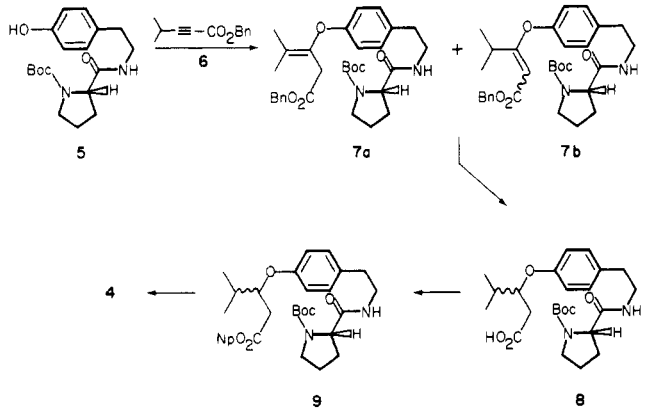
Scheme I



droxy-α-amino acid moiety early in their synthetic plan.[6,7] Despite these careful considerations, the preparation of the fully substituted phencyclopeptine nucleus proved unsuccessful.[8]

As a second part in our study directed toward the total synthesis of the phencyclopeptines, we now describe a method for the stereospecific introduction of the isopropyl side chain at C9. This study has lead to the synthesis of a new *p*-phencyclopeptine model (5*S*,9*R*)-9-isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**) which contains the natural product substitution pattern at C9. Comparative ^{1}H NMR analysis of cyclopeptide **3d**, which lacks the isopropyl side chain at C9, and cyclopeptide **4** has permitted the assignment of *R* stereochemistry at C9 for **4**.

Results and Discussion

The preparation of *p*-phencyclopeptine **4** was accomplished via the high dilution active ester cyclization method previously described.[4] Outlined in Scheme I, our synthetic approach utilized the readily available starting material, optically active phenol **5**.[4] In contrast to the spontaneous, high-yield reaction of **5** with benzyl propiolate and *N*-methylmorpholine as base,[4] the Michael addition of phenol **5** to isopropyl propiolate **6** under similar reaction conditions was unsuccessful.

Previous work[9] suggested that the Michael reaction was facilitated if the phenolate anion were preformed (by sodium metal in hot toluene) followed by addition of the acetylene ester. The reaction of *p*-cresol with **6** in this manner afforded the Michael adduct. This method proved infeasible for use with the protected phenol **5**, however, since the prolonged heating necessary to form the phenolate anion resulted in loss of the Boc nitrogen protecting group. This side reaction could be avoided by generating the potassium salt of phenol **5** with potassium hydride in THF at 0 °C. The soluble potassium salt of **5** then effectively added to **6** to give a mixture of isomeric phenoxypentenoates **7a** and **7b** in 37% yield. Catalytic hydrogenation of this mixture afforded the phenoxypentanoic acid **8** in 92% yield. Although a racemic mixture was obtained after reduction, no attempt was made to separate diastereomers at this step. Preparation of the *p*-nitrophenyl active ester **9** was accomplished with *p*-nitrophenyl trifluoroacetate in pyridine.[10] Subsequent removal of the Boc residue with anhydrous trifluoroacetic acid and cyclization as previously described[4] afforded the cyclic monomer **4** in 18% yield after chromatography and sublimation.

p-Phencyclopeptine **4** was characterized by high-resolution mass spectrometry, UV and IR absorption, circular

Table I. Comparative Spectral Data of (5*S*)-5,6-Trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**3d**) and (9*R*,5*S*)-9-Isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**)

	compd	
spectra	3d[a]	4
UV (MeOH) λ_{max}, nm (ϵ)	271 (568)	271 (614)
	276 (513)	276 (564)
IR ($CHCl_3$) λ_{max}, cm^{-1}	1675	1678
	1615	1612
CD (CH_3CN) $\Delta\epsilon_{max}$	−2.17 (271)	−1.18 (270)
(λ_{max}, nm)	−1.91 (277)	−1.14 (277)
^{1}H NMR ($CDCl_3$)[b]		
1α-H	2.86	2.86
1β-H	2.98	2.98
2α-H	3.78	3.78
2β-H	2.90	2.90
3-H	6.36	6.33
5β-H	4.29	4.29
8α-H	2.74	2.55
8β-H	2.20	2.16
9α-H	4.27	
9β-H	4.62	4.43
12,13-H's	7.19, 7.13	7.17, 7.14
15,16-H's	6.85	6.83
17α-H	2.34	2.34
17β-H	1.56	1.54
18α-H	1.93	1.93
18β-H	2.14	2.14
19α-H	3.50	3.48
19β-H	3.31	3.30
9α-$CH(CH_3)_2$		2.01
9α-$CH(CH_3)_2$		1.09, 1.11

[a] The UV, IR, CD, and ^{1}H NMR spectra of **3d** were first reported in ref 4. [b] The ^{1}H NMR spectra chemical shift values are reported in parts per million from Me_4Si. The complete ^{1}H NMR spectral assignment of **3d** is described in ref 11. The assignments of α and β refer to the spatial geometry of geminal hydrogens with relation to the plane of the 14-membered ring; β has been defined as above the plane of the 14-membered ring when the molecule is oriented with the C5 H pointing up (see Figure 5).

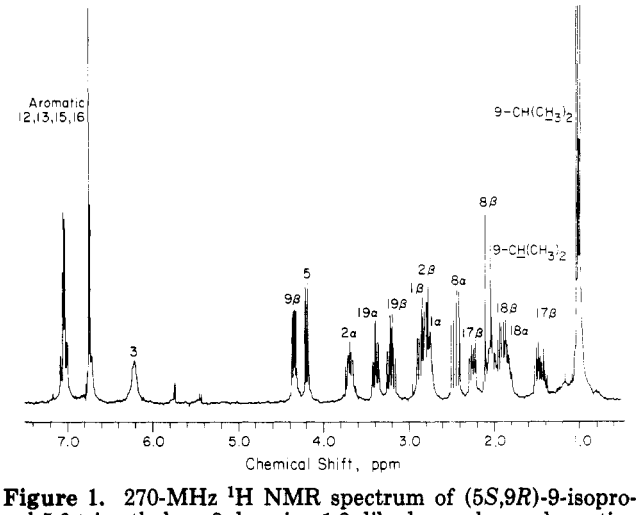


Figure 1. 270-MHz ^{1}H NMR spectrum of (5*S*,9*R*)-9-isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**).

(6) Marchand, J.; Rocchiccioli, F.; Pais, M.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1972**, 4699.
(7) Frappier, F.; Rocchiccioli, F.; Jarreau, F.-X.; Pais, M. *Tetrahedron* **1978**, *34*, 2911.
(8) Rocchiccioli, F.; Jarreau, F.-X.; Pais, M. *Tetrahedron* **1978**, *34*, 2917.
(9) Ruhemann, S.; Beddow, F. *J. Chem. Soc.* **1900**, 984.
(10) Sakakibara, S.; Inukai, N. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1231.

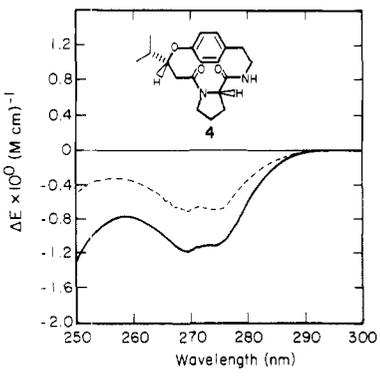


Figure 2. Circular dichroism spectra of (5*S*,9*R*)-9-isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**), 11.1×10^{-3}M in CH_3CN: —, no added salts; —, 1.09×10^{-2}M $NaClO_4$; - - -, 1.20×10^{-2} M $Mg(ClO_4)_2$.

dichroism (CD), and ^1H NMR spectroscopy (Table I, Figures 1 and 2). For comparative purposes, the spectral properties of **4** are contrasted with those of the previously synthesized *p*-phencyclopeptine **3d** in Table I. Conformational analysis of *p*-phencyclopeptine **3d**, based on the X-ray structure determination of **3a** and comparative spectroscopic analysis of *p*-phencyclopeptines **3a** and **3d** (^1H NMR, ^{13}C NMR, and two-dimensional *J*-resolved ^1H NMR spectroscopy), is consistent with the trans geometry for both amide bonds (N6–C7, N3–C4).[11] The similarity of the spectral properties of **3d** and **4** (Table I) strongly suggests that the two *p*-phencyclopeptines, which differ only by the isopropyl substituent at C9, have identical amide geometry and overall conformation.

That the UV spectra of **3d** and **4** both show absorption maxima at 271 and 276 nm and have small extinction coefficients is particularly characteristic of the 14-membered-ring system.[4] The absorption maxima of acyclic precursors and cyclic oligomers display ≥5-nm red shifts and greatly enhanced extinction coefficients.[4] The similarity of the IR spectra of cyclopeptides **3d** and **4** in the carbonyl absorption bands also reveals configurational identity. The CD spectra of the two cyclopeptides are similar, with the ion-selective metal ion binding properties of **4** (Figure 2) mimicking that of **3d**.[4]

The great similarity of the ^1H NMR spectra of cyclopeptides **3d** and **4** has permitted facile assignment of the newly prepared *p*-phencyclopeptine (Table I). From this special comparison, there is no evidence for the presence of a mixture of isomers in the cyclopeptide **4**.[12] Despite the structural differences in the two peptides caused by the C9 substituent, no difference is evident in the chemical shift or line shapes of resonances attributed to the proline ring hydrogens (C5,17,18,19), the aromatic moiety (C12,13,15,16), and the C1–C2 methylenes for both cyclopeptides. Slight differences are observed in the chemical shifts of the C8 hydrogens of **4** due to the effect of the isopropyl group on C9. This effect is greatest on the 8α-H resonance which is shifted from 2.74 ppm in **3d** to 2.55 ppm in **4**. The 8β-H resonance is affected to a lesser extent, 2.20 ppm in **3d** as compared with 2.16 ppm in **4**.

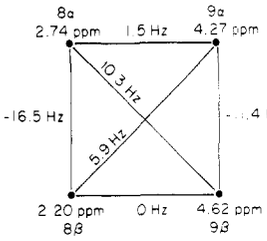


Figure 3. Chemical shift values and coupling constants for (5*S*)-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**3d**).

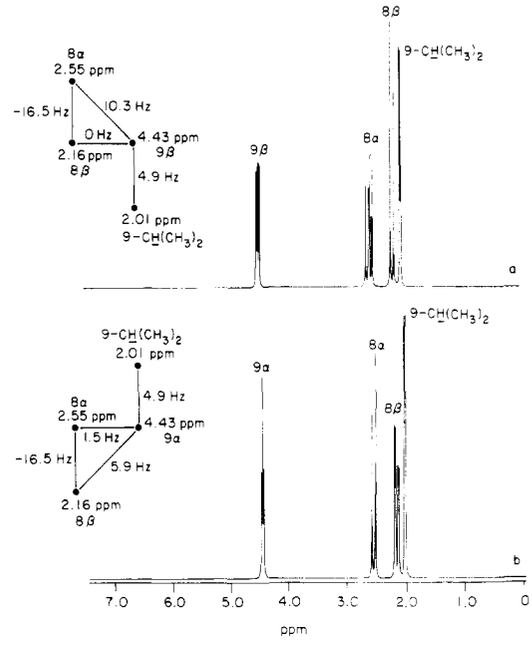


Figure 4. Computer simulation of the ^1H NMR spectrum of the C8–C9 spin system of (5*S*,9*R*)-9-isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**). Coupling constants were obtained from **3d** (Figure 3); chemical shift values obtained from **4** (Table I); line widths for simulations are 2 Hz. (a) Spectrum obtained by replacing the 9α-hydrogen of **3d** with $CH(CH_3)_2$. The insert shows the chemical shift and coupling constant patterns used for simulation. (b) Spectrum obtained by replacing the 9β-hydrogen of **3d** with $CH(CH_3)_2$.

The major difference between the two spectra is the lack of one of the C9 hydrogen resonances in the spectrum of **4**. In this spectrum, a single C9 H resonance at 4.43 ppm has replaced the two C9 H resonances of **3d** at 4.27 (H_α) and 4.62 ppm (H_β). The assignment of the resonance at 4.43 ppm in **4**, which lies equally between 4.27 and 4.62 ppm, to H_α or H_β is not possible by comparison with the chemical shift values for H_α and H_β in **3d**.

The question of C9 stereochemistry was resolved by computer simulation of the C8–C9 spin system in **4**. By use of the coupling constants for the C8–C9 spin system of **3d**, obtained from the previous conformational study (Figure 3),[11] and the observed values for the chemical shifts in **4** (Table I), two computer simulations of the C8–C9 spin system of **4** were generated (Figure 4).

Figure 4a represents the computer simulation of **4** resulting from replacement of the 9α-H with the isopropyl group (i.e., the *R* isomer) while Figure 4b shows the spectrum obtained by substituting isopropyl for the 9β-H

(11) On the basis of the X-ray structure determination of **3a**, showing trans–trans amide geometry of the cyclopeptide (J. Bordner, private communication), the solution conformation of **3a** was inferred. The ^1H NMR spectral similarity of **3a** and **3d**, especially with respect to the vicinal coupling constants, has led to the assignment of similar overall conformations to the two cyclopeptides (Shih, W. C. Ph.D. Thesis, University of California, Berkeley, 1979). This conclusion is further supported by the ^{13}C NMR spectral analyses of the two cyclopeptides by the method of: Siemion, I. Z.; Wieland, T.; Pook, K-H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 702. The details of these conformational studies, including the ^1H NMR and ^{13}C NMR spectral study and the X-ray analysis, will be included in a future report.

(12) Only a single isomer was obtained, and none of the other fractions appeared to be cyclopeptides. Favored ring closure of only one of two acyclic diastereomeric peptides has literature precedence, e.g.: (a) Brady, S. F; Varga, S. L.; Freidinger, R. M.; Schwenck, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101; (b) Rich, D. H.; Bhatnagar, P.; Mathiaparanam, P.; Grant, J. A.; Tam, J. P. *Ibid.* **1978**, *43*, 296.

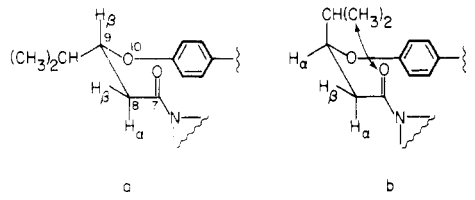


Figure 5. Conformational depiction of the two possible stereoisomers at C9: (a) *R* configuration as in **4**; (b) *S* configuration, with arrow indicating transannular interaction.

(*S* isomer). That good agreement between the computer simulation of Figure 4a and the experimentally obtained spectrum of **4** (Figure 1) was observed, whereas Figure 4b poorly approximates the measured spectrum, provided strong evidence for the *R* stereochemical assignment. The measured values for the constants for the C8–C9 spin system of **4** are $^3J(8\alpha\text{–}9)$ = 8.4 Hz, $^3J(8\beta\text{–}9)$ = 0.0 Hz, $^2J(8\alpha\text{–}8\beta)$ = −16.3 Hz, and $^3J(9\text{–}9\text{-}CH(CH_3)_2)$ = 4.9 Hz vs. the predicted values of $^3J(8\alpha\text{–}9\beta)$ = 10.3 Hz, $^3J(8\beta\text{–}9\beta)$ = 0.0 Hz, and $^2J(8\alpha\text{–}8\beta)$ = −16.5 Hz used in Figure 4a. The predicted values for the *S* isomer (Figure 4b), $^3J(8\alpha\text{–}9\alpha)$ = 1.5 Hz, $^3J(8\beta\text{–}9\alpha)$ = 5.9 Hz, and $^2J(8\alpha\text{–}8\beta)$ = −16.5 Hz, are in much poorer agreement with the experimental values.

Because the values of the coupling constants reflect the conformation of the C8–C9 system, the disparity of the experimental and the predicted values for the *S* isomer (Figure 4b) would represent a major conformational dissimilarity between **3d** and **4** at C8–C9. Examination of molecular models also shows that major changes in the C8–C9 geometry would effect significant changes in the conformation of the entire *p*-phencyclopeptine. The spectral data show no major conformational differences between the two cyclopeptides. Hence the ^1H NMR spectral data support the assignment of *R* stereochemistry at C9 as shown in **4**.

This assignment of the *R* stereochemistry is also consistent with the observation that the 8α-H resonance is shifted more dramatically than the 8β-H resonance, consistent with an α-isopropyl group at C9 in **4** (see earlier discussion). In the previous conformation analysis of **3d**, the quasi-axial conformation of the 9β-hydrogen was deduced.[11] Substitution of this hydrogen with an isopropyl group would introduce an unfavorable transannular (quasi-diaxial) interaction between the C7 carbonyl and a 9β-isopropyl group (*S* configuration). No such steric compression would be observed in the case where the isopropyl group is in the (*R*)-9α configuration. These possibilities are illustrated in Figure 5. On the basis of these steric considerations, the obtention of the single isomer with the *R* stereochemistry shown in **4** from the cyclization of the racemic active ester **9** is reasonable. Since the two diastereomers of **9** are present in equal amounts and only one cyclizes,[12] the ring closure of this isomer proceeds in 36% yield.

In summary, asymmetric induction occurring during peptide cyclization of **9** has permitted the isolation in 36% yield of a single isomer, (5*S*,9*R*)-9-isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (**4**), with the natural phencyclopeptine stereochemistry at C9. Because of the availability of starting materials and the stereospecificity of the cyclization, this approach offers a promising synthetic route to the phencyclopeptine class of cyclopeptide alkaloids. Two steps remain to complete the total synthesis of the phencyclopeptine system by this approach—the incorporation of the C1–C2 double bond and the incorporation of a nitrogen atom in the 8β-position. Experiments along these lines are currently being considered.

Experimental Section

Methods. All reactions were performed under a nitrogen atmosphere. Final organic extracts were dried over Na_2SO_4 and evaporated in vacuo with a rotary evaporator. ^1H NMR spectra were taken in $CDCl_3$ solution by using internal Me_4Si (δ 0) on a Varian HR-220 instrument or a homemade 270-MHz spectrometer based on a Bruker 63-kG magnet with a Nicolet 1180 data system. UV spectra were taken in methanol on a Cary 118 instrument. A Model AEI-MS12 mass spectrometer with an INCOS data system was used for low-resolution mass spectrometry while a CEC-110B instrument was used for high-resolution spectra. IR spectra were recorded on a Perkin-Elmer Model 283 spectrometer. Thin-layer chromatography was done on Analtech silica gel GF plates (250 μm), column chromatography utilized E. M. Merck silica gel (70–230 mesh), and ion-exchange chromatography was done with a mixed-bed resin of Bio-Rex AG501-X8-D (20–50 mesh) on a 1.5 × 50 cm column. CD spectra were taken in acetonitrile on a homemade spectrometer. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Materials. The following solvents were routinely distilled prior to use: tetrahydrofuran from sodium benzophenone ketyl, pyrdine from BaO, and *N,N*-dimethylacetamide from 4-Å molecular sieves under reduced pressure.

Benzyl 4-Methyl-2-pentynoate (6). To 64 mL (0.15 mol) of *n*-butyllithium in hexane was added 90 mL of anhydrous ethyl ether. The solution was cooled to −20 °C whereupon 15 mL (0.15 mol) of 3-methyl-1-butyne was added. The solution was then cooled to −30 °C. Upon precipitation of the lithium acetylide, 29 mL (0.20 mol) of benzyl chloroformate was added. The mixture was stirred 2 h at −30 °C, 2 h at −20 °C, and 2 h at −5 °C and then allowed to warm to room temperature over 1 h. The reaction mixture was then poured into 80 mL of ice–water, the organic phase was separated, the aqueous phase was rinsed with Et_2O (2 × 20 mL), and the combined organic layers were dried, evaporated, and then distilled to remove excess benzyl chloroformate and give 13.7 g (45%) of crude **6**. This material was chromatographed (SiO_2, 500 g, benzene) to give 9.16 g (31%) of pure **6**: NMR δ 1.20 (d, 6 H, *J* = 7.3 Hz), 2.66 (m, 1 H, *J* = 7.3 Hz), 5.16 (s, 2 H), 7.35 (s, 5 H); IR (neat) 2225, 1710 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.2; H, 7.0. Found: C, 76.9; H, 6.9.

Benzyl 4-Methyl-3-[4′β-[[[*N*′-[(*tert*-butyloxy)carbonyl]-L-prolyl]amino]ethyl]phenoxy]-3-pentenoate (7a) and Benzyl (*Z,E*)-4-Methyl-3-[4′β-[[[*N*′-[(*tert*-butyloxy)carbonyl]-L-prolyl]amino]ethyl]phenoxy]-2-pentenoate (7b). Potassium hydride (2.07 g, 23.6% in oil, 12.2 mmol) was rinsed with dry THF (3 × 10 mL). The KH was then resuspended in 5 mL of THF, the mixture was cooled to 0 °C, phenol **5** (4.07 g, 12.2 mmol) was added, and immediately after gas evolution ceased, acetylenic ester **6** (5.11 g, 25.3 mmol) was introduced. The flask was then warmed to room temperature. After 1 h the reaction mixture was dissolved in 150 mL of ethyl acetate and rinsed with 1 M H_2SO_4 (1 × 40 mL), 50% saturated $NaHCO_3$ (1 × 40 mL), H_2O (1 × 30 mL), and saturated NaCl (1 × 25 mL), dried, and evaporated. The residue (8.4 g) was chromatographed (SiO_2, 300 g; benzene/Et_2O, 1/1) to give a mixture of **7a** and **7b** (2.42 g, 37%) as a white glass: NMR for **7a** δ 1.78 (s, 3 H), 1.67 (s, 3 H), 3.26 (s, 2 H), 5.04 (s, 2 H, benzyl); for **7b** δ 1.12 (d, 3 H, *J* = 7.3 Hz), 1.26 (d, 3 H, *J* = 7.3 Hz), 4.73 (s, 1 H), 5.58 (s, 1 H), 5.09 (s, 2 H, benzyl, 6.27 and 6.54 (2 s, 1 H, olefinic); for **7a** and **7b** δ 1.43 (s, 9 H), 1.97–2.32 (m, 4 H), 2.66–2.88 (m, 2 H), 3.11–3.68 (m, 4 H), 3.93–4.29 (m, 1 H), 6.72–6.95 (m, 2 H), 6.98–7.22 (m, 2 H), 7.34 (s, 5 H); mass spectrum, *m/e* (relative intensity) 536 (0.8), 4.63 (0.5), 437 (3.5), 322 (34.6), 70 (100). Anal. Calcd for $C_{31}H_{40}N_2O_6$: C, 69.4; H, 7.5; N, 5.2. Found: C, 69.2; H, 7.6; N, 5.2.

4-Methyl-3-[4′β-[[[*N*′-[(*tert*-butyloxy)carbonyl]-L-prolyl]amino]ethyl]phenoxy]pentanoic Acid (8). A mixture of benzyl pentenoates **7a** and **7b** (477 mg, 0.89 mmol) and Pd/C (10%, 191 mg) in 20 mL of THF was shaken with hydrogen at 20 psi of H_2 for 37 h. After filtration and evaporation, **8** (376 mg, 92%) was obtained: NMR δ 0.98 (dd, 6 H), 1.41 (s, 9 H), 1.65–2.14 (m, 4 H), 2.5–2.8 (m, 4 H), 3.28–3.55 (m, 4 H), 3.75 (m, 1 H), 4.24

(m, 1 H), 4.57 (m, 1 H), 6.88 (d, 2 H, J = 7.3 Hz), 7.05 (d, 2 H, J = 8.1 Hz); mass spectrum, m/e (relative intensity) 448 (1.2), 375 (1.1), 347 (2.4), 234 (43.4), 70 (100). Anal. Calcd for $C_{24}H_{36}N_2O_6$: C, 64.3; H, 8.1; N, 6.2. Found: C, 63.4; H, 8.1; N, 6.0.

p-Nitrophenyl 4-Methyl-3-[4′β-[[[N′-[(tert-butyloxy)carbonyl]-L-prolyl]amino]ethyl]phenoxy]pentanoate (9). A mixture of the acid 8 (340 mg, 0.76 mmol) and p-nitrophenyl trifluoroacetate[10] (270 mg, 1.14 mmol) in 15 mL of pyridine was stirred for 14 h at room temperature. After evaporation, the residue was dissolved in 50 mL of ethyl acetate and washed with 1 M HCl (3 × 25 mL), 50% saturated $NaHCO_3$ (5 × 25 mL), and saturated NaCl (1 × 10 mL), dried, and evaporated. The resulting yellow oil was chromatographed (SiO_2, 50 g; EtOAc/toluene, 2/1) to give 9 (413 mg, 95%) as an equal mixture of diastereomers: NMR δ 1.04 (d, 6 H, J = 6.6 Hz), 1.42 (s, 9 H), 1.5–2.4 (m, 4 H), 2.6–3.0 (m, 5 H), 3.2–3.6 (m, 4 H), 4.22 (m, 1 H), 4.68 (m, 1 H), 6.25 (s, 1 H), 6.92 (d, 2 H, J = 8.8 Hz), 7.11 (d, 2 H, J = 8.8 Hz), 7.13 (d, 2 H, J = 9.5 Hz), 8.20 (d, 2 H, J = 9.5 Hz).

***cyclo*-[[4-Methyl-3-[4′β-[(aminoethyl)phenyl]oxy]pentanoyl]-L-prolyl]; (5S,9R)-9-Isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-p-phencyclopeptine (4).** The active ester 9 (521 mg, 0.91 mmol) was dissolved in 15 mL of anhydrous TFA at 0 °C. After 1 h the solvent was removed in vacuo to give an oil (776 mg) which was dissolved in 575 mL of N,N-dimethylacetamide. This solution was added by a metering pump over a period of 50 h to 600 mL of pyridine, mechanically stirred and maintained at 90 °C. The solution was stirred and heated an additional 10 h, the solvent was evaporated, and the residue was dissolved in methanol and passed through a mixed-bed ion-exchange resin. The first 100 mL of eluant was collected, evaporated, and chromatographed on Sephadex LH-20 (200 g, MeOH). Fractions 1 (47 mg), 2 (187 mg), and 3 (65 mg) were collected. Fraction 3 was sublimed at 120 °C (0.02 mm) to give 62 mg of a yellow glass. Following TLC ($CHCl_3$/MeOH, 20/1) two bands were isolated with R_f's of 0.65 and 0.56 in a 5/1 mass ratio. the R_f 0.65 band was cyclopeptide 4 (52 mg, 18% yield from total educt). The minor component (R_f 0.56) was not a 14-membered-ring cyclopeptide and was not further characterized. For cyclopeptide 4: ^{1}H NMR, summarized in Table I and Figure 1; UV λ_{max} 271 nm (ε 614), 276 (564); low-resolution mass spectrum, m/e (relative intensity) 331 (3.3), 330 (14.8), 211 (12.2), 70 (100); high-resolution mass spectrum calcd for $C_{19}H_{26}N_2O_3$ m/e 330.1943, found m/e 330.1945; IR ($CHCl_3$) 1678, 1612 cm^{-1}.

Registry No. 3d, 69100-22-7; **4**, 75266-53-4; **5**, 68898-89-5; **6**, 75266-54-5; **7a**, 75266-55-6; **(E)-7b**, 75266-56-7; **(Z)-7b**, 75266-57-8; **8** (isomer 1), 75266-58-9; **8** (isomer 2), 75266-59-0; **9** (isomer 1), 75266-60-3; **9** (isomer 2), 75266-61-4; 3-methyl-1-butyne, 598-23-2; benzyl chloroformate, 501-53-1.

L-Vinylglycine

Ali Afzali-Ardakani[1] and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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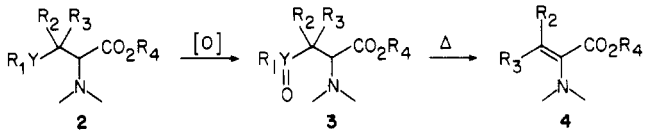
Optically pure L-vinylglycine (1) has been synthesized from L-methionine in 54% overall yield. The process consists in first preparing N-[(benzyloxy)carbonyl]methionine methyl ester (9) which is then oxidized to methyl 2-[[(benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butyrate (10). Thermal syn elimination followed by acid hydrolysis then gives L-vinylglycine.

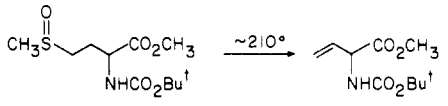
Vinylglycine (1), which has been isolated in the partially racemized D form from mushrooms,[2] has been the subject of numerous biochemical studies and has been postulated as an intermediate in the enzymatic conversions of homoserine to threonine[3] and α-ketobutyrate.[4] It was first synthesized in 1974[5] as the racemic material in very poor yield and partially resolved to D-vinylglycine with L-amino acid oxidase or baker's yeast.[5a] Subsequently, in a related approach, the synthesis of racemic 1 was described from acrolein in an overall yield of 15%.[6] In this report, we present a convenient and high-yield synthesis of optically pure L-vinylglycine and some of its derivatives.

One of the early[7] methods for the synthesis of unsaturated amino acid derivatives makes use of olefin formation through syn elimination from selenoxides.[8] Thus dehydroalanine derivatives were prepared from selenocysteine derivatives, and similarly, α,β-unsaturated amino acid derivatives and dehydropeptides have been prepared by syn elimination of sulfoxides[9] (**2** → **3** → **4**). The relatively mild conditions effective in the latter instances (80–140 °C) presumably result from the ease of removal of the α-proton.



2 **3** **4**

When sulfoxide elimination was applied to the formation of β,γ-unsaturated amino acid derivatives where the reactivity of the α-proton could not be exploited, much more drastic conditions were used.[8] Thus methyl 2-[[(tert-butyloxy)carbonyl]amino]-3-butenoate (6) was obtained by



5 **6**

passing a dilute solution of sulfoxide 5 in xylene through a hot tube at 200–210 °C; no optical activity data were reported for product 6.

Our interest in vinylglycine required a method for the preparation of optically pure material and on a scale compatible with its use as a synthetic intermediate. Therefore we undertook a study of its formation from

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