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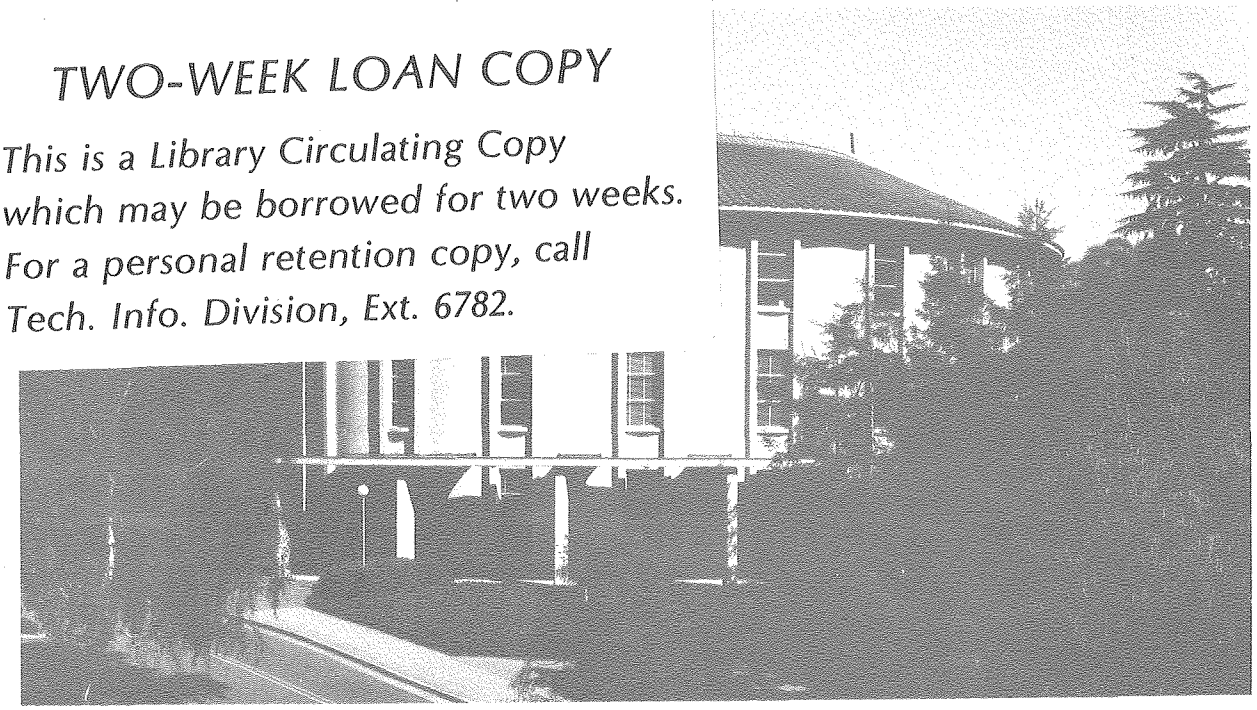

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DISCLAIMER

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

Abstract

Peptide cyclization via the p-nitrophenyl ester of 4-methyl-3-[4'-β-N-(N'-tert-butyloxycarbonyl-L-prolyl)-aminoethyl]phenoxy-pentanoic acid (9) has afforded a single cyclopeptide diastereomer, 9R-isopropyl-5S,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 5S,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 product known as the cyclopeptide alkaloids encompasses a group of over eighty polyamide plant bases which contain 13-, 14- or 15-membered rings.[1] Recently, experimental evidence suggesting their role as ionophores in plants[2,3,4] 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-hydroxystyryl amine, 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-hydroxyphenylalanyl, 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.

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-hydroxy-α-aminoacid 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 sidechain at C9. This study has lead to the synthesis of a new p-phencyclopeptine model 9R-isopropyl-5S,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 sidechain 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 isopropylpropiolate 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 dichroism (CD) and ^{1}H 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. The similarity of these spectral properties suggests similar conformations of these two p-phencyclopeptines which differ only by the isopropyl substituent at C9.

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 conformational similarity of p-phencyclopeptines 3d and 4 is even more evident from their ^{1}H NMR spectra. Recently, in an attempt to explain the metal ion affinity of these 14-membered ring cyclopeptides, the solution conformation of phencyclopeptine model 3d was studied by ^{1}H NMR spectroscopy.[11] This analysis utilized two dimensional J-resolved ^{1}H NMR spectroscopy to simplify the task of homonuclear decoupling experiments and has permitted straightforward assignment of the ^{1}H NMR spectrum of 3d (Table I).[11] Furthermore, spectral simulations have led to the formation of Karplus relationships for vicinal couplings. In this way the solution conformation of 3d was deduced.[11] The great similarity of the ^{1}H 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; only a single isomer is obtained.

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.

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 43 ppm has replaced the two C9-H resonances of 3d at 4.27 ppm (Hα) and 4.62 (Hβ). The assignment of the resonance at 4.43 ppm in 4, which lies equally between 4.27 and 4.62 ppm, to Hα or Hβ is not possible by comparison with the chemical shift values for Hα and Hβ in 3d.

The question of C9-stereochemistry was resolved by computer simulation of the C8-C9 spin system in 4. Using 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 4a,b).

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 (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 $^{3}J(8\alpha\text{-}9)$ 8.4 Hz; $^{3}J(8\beta\text{-}9)$ 0.0 Hz; $^{2}J(8\alpha\text{-}8\beta)$ -16.3 Hz and $^{3}J(9\text{-}9\underline{CH}(CH_3)_2)$ 4.9 Hz versus the predicted value of $^{3}J(8\alpha\text{-}9\beta)$ 10.3 Hz; $^{3}J(8\beta\text{-}9\beta)$ 0.0 Hz and $^{2}J(8\alpha\text{-}8\beta)$ -16.5 Hz used in Figure 4a. The predicted values for the S isomer (Figure 4b), $^{3}J(8\alpha\text{-}9\alpha)$ 1.5 Hz; $^{3}J(8\beta\text{-}9\alpha)$ 5.9 Hz and $^{2}J(8\alpha\text{-}8\beta)$ -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 disimilarity 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 shows no major conformational differences between the two cyclopeptides. Hence the ^1H NMR spectral data supports 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 Fig. 5. Based on these steric considerations, the obtention of the single isomer with R stereochemistry shown in 4 from the cyclization of the racemic active ester 9 is reasonable. Since the two diastereomer of 9 are present in equal amounts and only one cyclizes, 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, 9R-isopropyl-5S,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 alkaloid. 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 using internal Me_4Si ($\delta 0$) 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 INCOS data system was used for low resolution mass spectrometry while a CEC-110B instrument was used for high resolution. 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 x 50 cm column. fn 12 CD spectra were taken in acetonitrile on a homemade spectrometer.[12] 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, pyridine from BaO, and N,N'-dimethylacetamide from 4Å 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, 2 h at -5°C, 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 separated, the aqueous phase rinsed with Et_2O (2x20 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, 6H, J=7.3 Hz), 2.66 (m, 1H, J=7.3 Hz), 5.16 (s, 2H), 7.35 (s, 5H); IR (neat, cm^{-1}) 2225, 1710. 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-(N'-tert-butyloxycarbonyl-L-prolyl)-aminoethyl]phenoxy-3-pentenoate (7a) and (Z,E)-4-Methyl-3-[4'-β-N-(N'-tert-butyloxycarbonyl-L-prolyl)-aminoethyl]phenoxy-2-pentenoate (7b). Potassium hydride (2.07 g, 23.6% in oil, 12.2 mmol) was rinsed with 3x10 mL of dry THF. The KH was then resuspended in 5 mL THF, 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 hr the reaction mixture was dissolved in 150 mL of ethyl acetate and rinsed with 1M H_2SO_4 (1x40 mL), 50% sat. $NaHCO_3$ (1x40 mL), H_2O (1x30 mL), sat. NaCl (1x25 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 7a, δ 1.78 (s, 3H), 1.67 (s, 3H), 3.26 (s, 2H); 7b, δ 1.12 (d, 3H, J=7.3 Hz), 1.26 (d, 3H, J=7.3 Hz), 4.73 (s, 1H), 5.58 (s, 1H); 7a and 7b, 1.43 (s, 9H), 1.97-2.32 (m, 4H), 2.66-2.88 (m, 2H),

3.11-3.68 (m, 4H), 3.93-4.29 (m, 1H), 5.04 (s, 2H), 5.09 (s, 2H), 6.27 (s, 1H), 6.54 (s, 1H), 6.72-6.95 (m, 2H), 6.98-7.22 (m, 2H), 7.34 (s, 5H); MS m/e (rel intensity) 536 (0.8), 463 (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-(N'-tert-butyloxycarbonyl-L-prolyl)-aminoethyl]-phenoxypentanoic 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 for 37 h. After filtration and evaporation, 8 (376 mg, 92%) was obtained: NMR δ 0.98 (dd, 6H), 1.41 (s, 9H), 1.65-2.14 (m, 4H), 2.5-2.8 (m, 4H), 3.28-3.55 (m, 4H), 3.75 (m, 1H), 4.24 (m, 1H), 4.57 (m, 1H), 6.88 (d, 2H, J=7.3 Hz), 7.05 (d, 2H, J=8.1 Hz); MS m/e (rel. intensity) 448 (1.2), 375 (1.1), 347 (2.4) 234 (43.4), 70 (100). 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-(N'-tert-butyloxycarbonyl-L-prolyl)-aminoethyl]phenoxypentanoate (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 1M HCl (3x25 mL), 50% sat. $NaHCO_3$ (5x25 mL), sat. NaCl (1x10 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, 6H, J=6.6 Hz), 1.5-2.4 (m, 4H), 2.6-3.0 (m, 5H), 3.2-3.6 (m, 4H), 4.22 (m, 1H), 4.68 (m, 1H), 6.25 (s, 1H), 6.92 (d, 2H, J=8.8 Hz), 7.11 (d, 2H, J=8.8 Hz), 7.13 (d, 2H, J=9.5 Hz), 8.20 (d, 2H, J=9.5 Hz).

cyclo[4-Methyl-3-(4'-β-aminoethyl)phenyloxypentanoyl-L-prolyl]; 9R-Isopropyl-5S,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, then the solvent was evaporated and the residue 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: ^1H NMR (summarized in Table I and Figure 1); UV λ_{max} (ε) 271 nm (614), 276 (564); LRMS m/e (rel. intensity) 331 (3.3), 330 (14.8), 211 (12.2), 70 (100); HRMS m/e $C_{19}H_{26}N_2O_3$ requires 330.1943, found 330.1945; IR ($CHCl_3$) 1678, 1612 cm^{-1}.

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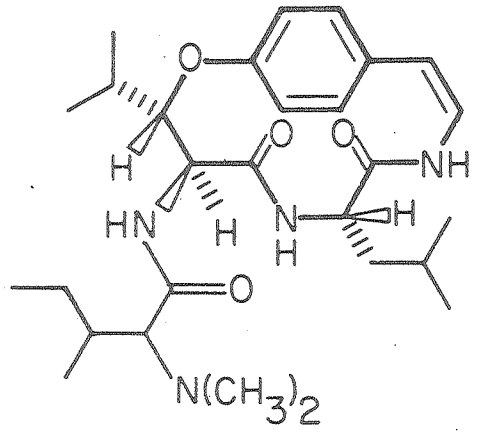

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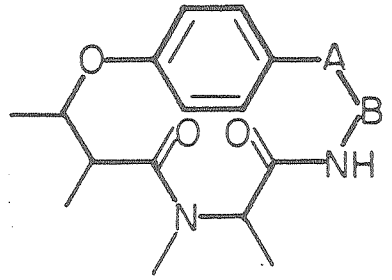
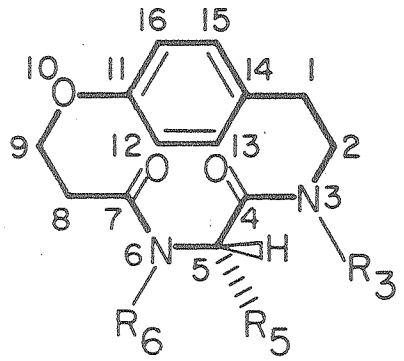
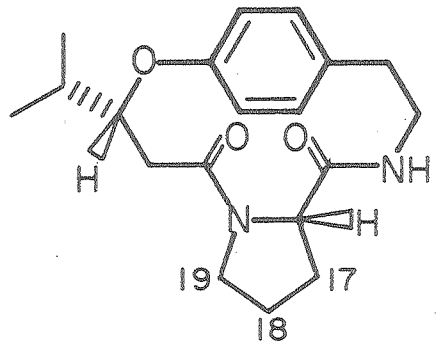


2a, A–B = CH=CH
b, A–B = $COCH_2$
c, A–B = $CHOHCH_2$



3a. $R_3 = CH_3$; $R_5, R_6 = (CH_2)_3$
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. $R_3 = R_6 = H$; $R_5 = (CH_3)_2CHCH_2$



4

Scheme I

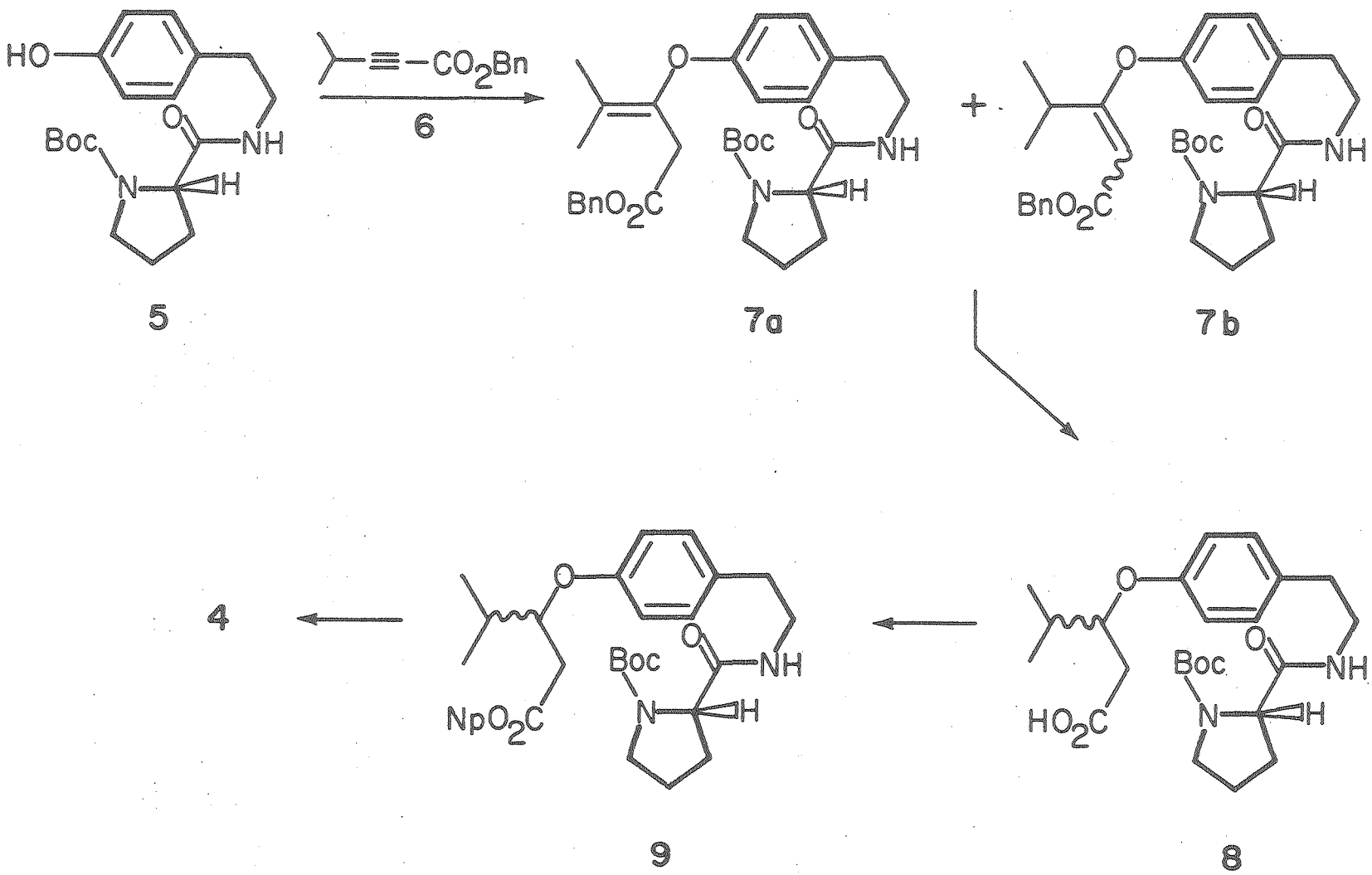


Table 1. Comparative Spectra of 5S,6-Trimethylene-8-deamino-1,2-dihydro-p-phencyclopeptine (3d) and 9R-Isopropyl-5S,6-trimethylene-8-deamino-1,2-dihydro-p-phencyclopeptine (4).

Spectra	3d[a]	4
UV(MeOH)		
λ_{max}, nm(ε)	271(568) 276(513)	271(614) 276(564)
IR($CHCl_3$)		
λ_{max}, cm^{-1}	1675 1615	1678 1612
CD(CH_3CN)		
$\Delta\varepsilon_{max}(\lambda_{max}, nm)$	-2.17(271) -1.91(277)	-1.18(270) -1.14(277)
^1H NMR($CDCl_3$)[b]		
assignment	δ, ppm	
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-$C\underline{H}(CH_3)_2$	———	2.01
9α-$C\underline{H}(CH_3)_2$	———	1.09,1.11

a. The UV, IR, CD and ^1H NMR spectra of 3d were first reported in in reference 4.

b. The ^1H NMR spectra chemical shift values are reported in ppm from TMS. The complete ^1H NMR spectral assignments of 3d is described in reference 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 C5-H pointing up (see Figure 5).

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

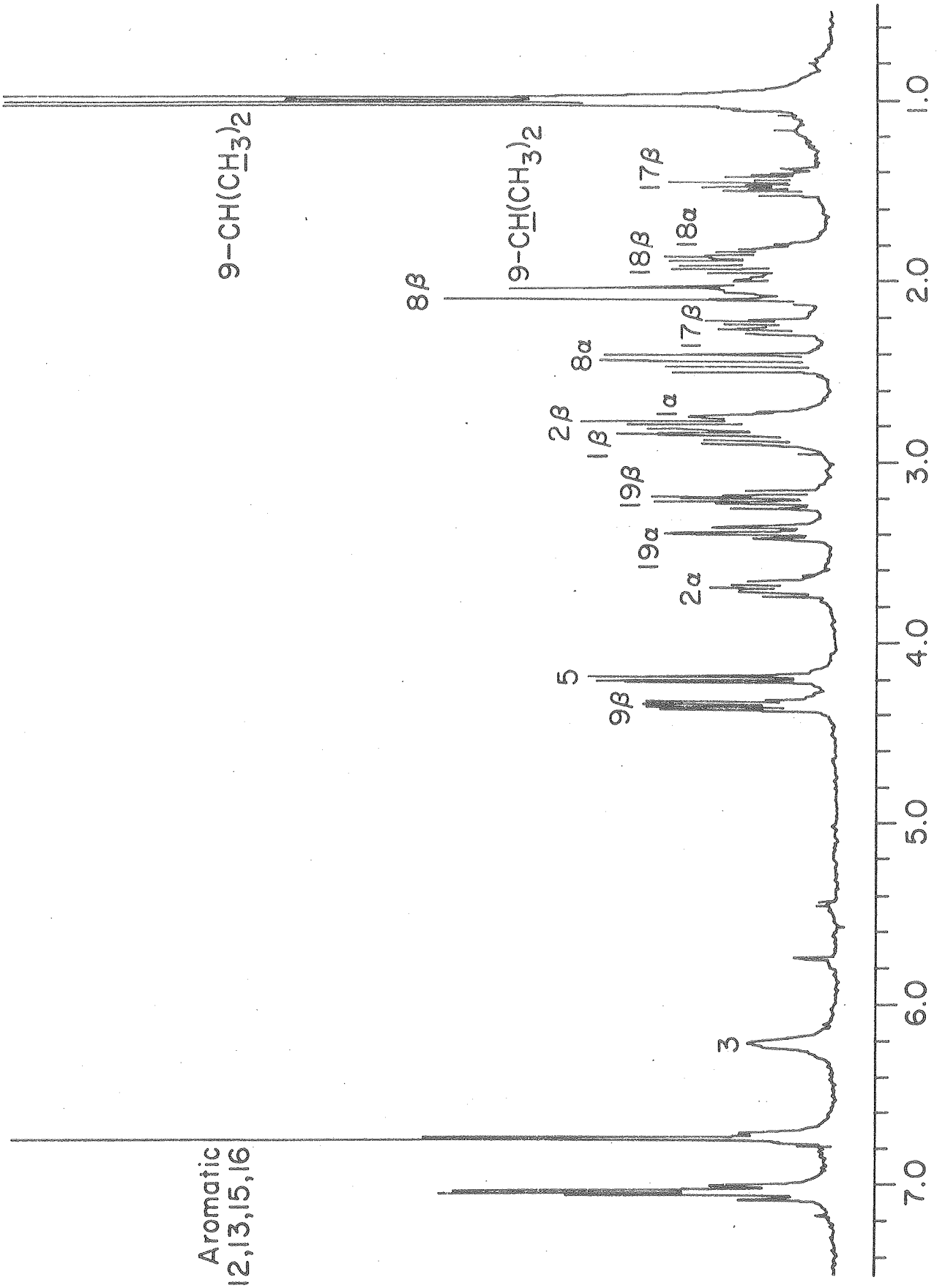

Aromatic
12,13,15,16
3
9β
5
2α
19α
19β
1β
2β
1α
8α
17β
8β
18α
18β
17β
9-CH(CH3)2
9-CH(CH3)2
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Chemical Shift, ppm

Fig. 1

Figure 2. Circular dichroism spectra of 9R-isopropyl-5S,6-trimethylene-8-deamino-1,2-dihydro-p-phencyclopeptine (4), 1.11×10^{-3}M in CH_3CN; —— no added salts; ——, 1.09×10^{-2}M $NaClO_4$; ---- 1.20×10^{-2}M $Mg(ClO_4)_2$.

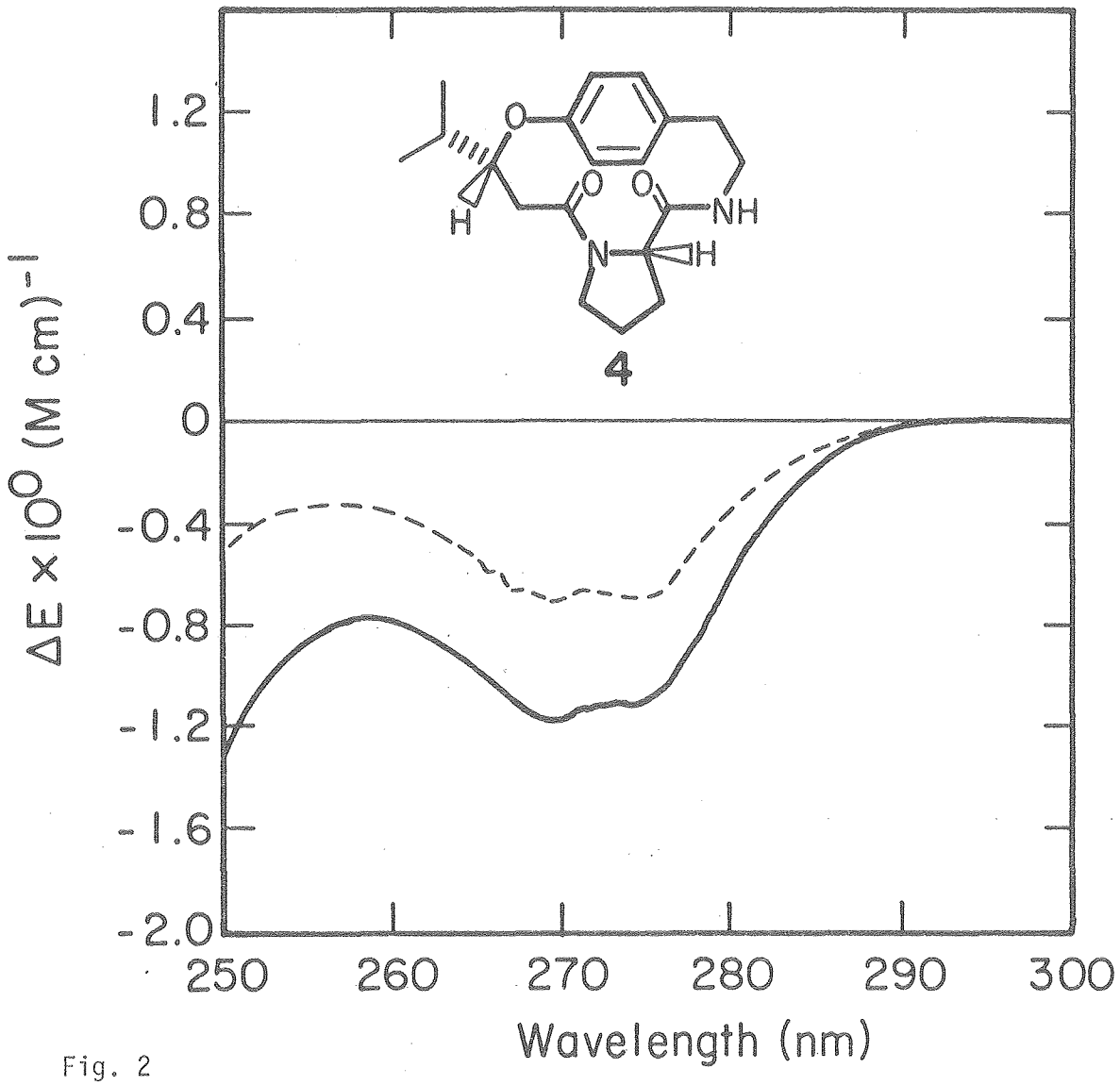

1.2
0.8
0.4
0
-0.4
-0.8
-1.2
-1.6
-2.0
ΔE x 10^0 (M cm)^-1
250
260
270
280
290
300
Wavelength (nm)
O
O
O
NH
H
N
H
4

Fig. 2

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

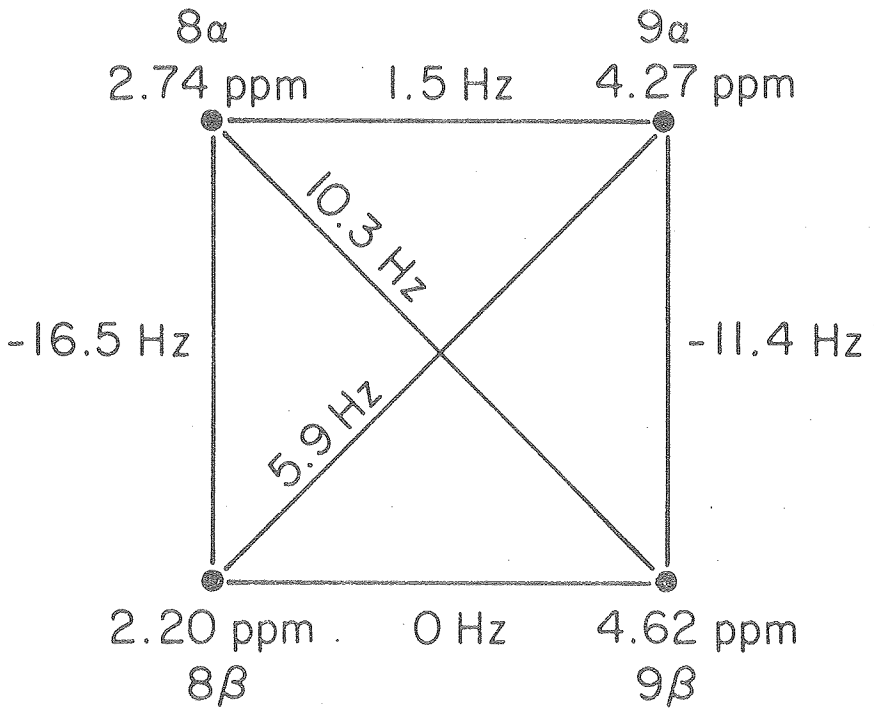

8α
2.74 ppm
1.5 Hz
9α
4.27 ppm
10.3 Hz
-16.5 Hz
-11.4 Hz
5.9 Hz
2.20 ppm
8β
0 Hz
4.62 ppm
9β

Fig. 3

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

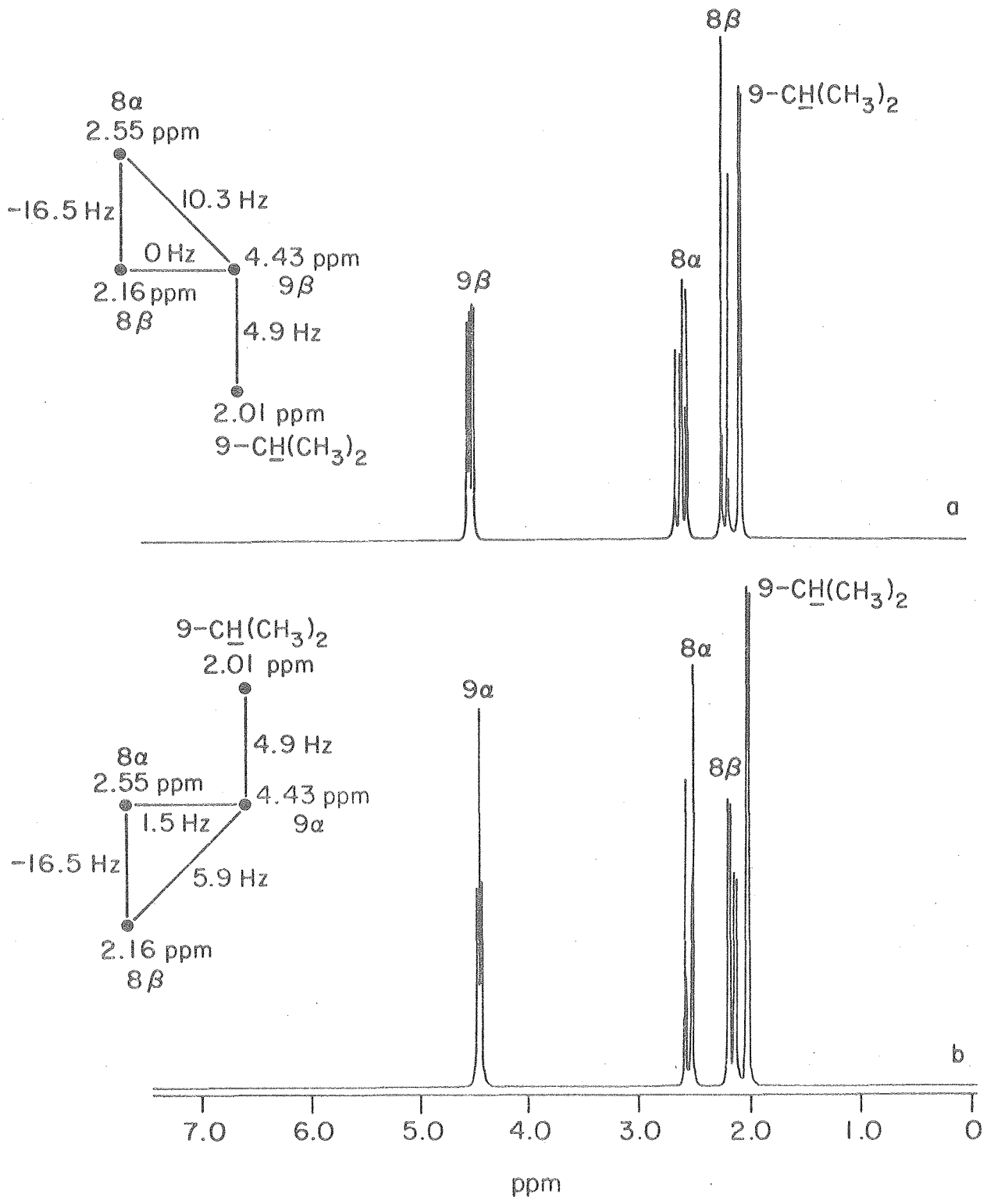
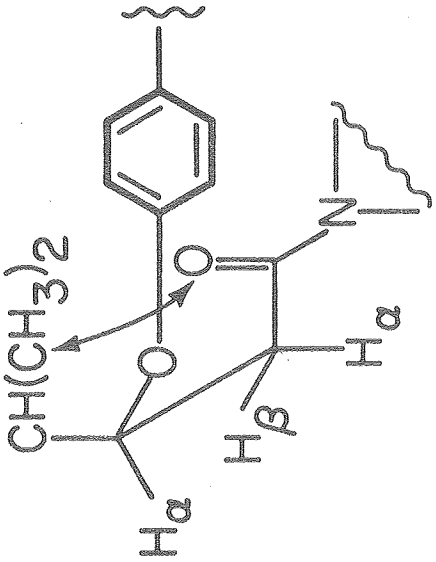
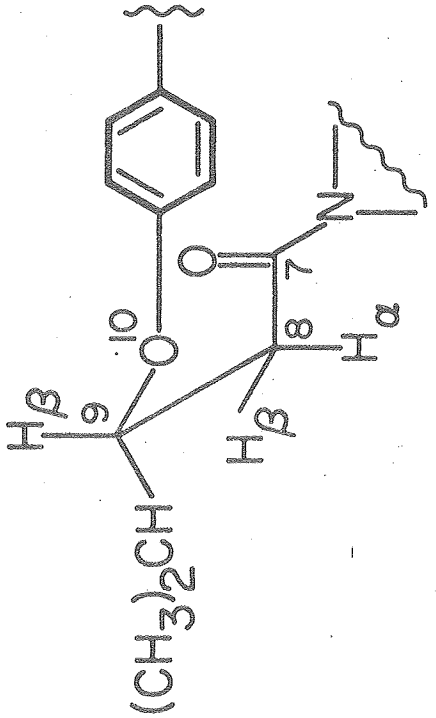

8α
2.55 ppm
-16.5 Hz
10.3 Hz
0 Hz
4.43 ppm
9β
2.16 ppm
8β
4.9 Hz
2.01 ppm
9-CH(CH3)2
9β
8α
8β
9-CH(CH3)2
a
9-CH(CH3)2
2.01 ppm
4.9 Hz
8α
2.55 ppm
4.43 ppm
9α
1.5 Hz
-16.5 Hz
5.9 Hz
2.16 ppm
8β
9α
8α
8β
9-CH(CH3)2
b
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

Fig. 4

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.



b



a

Fig. 5