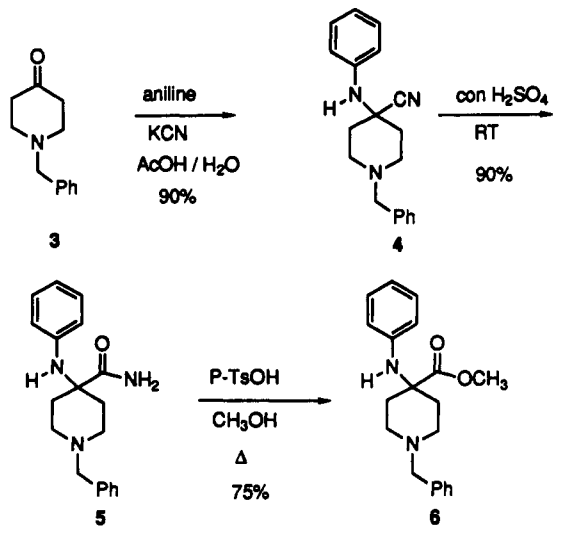
Scheme I



Methanolysis of the nitrile would be the most direct way to convert **4** to **6**. We and others[3] have found, however, that while some **6** is formed, the dominant products from such attempts derive from reversal of the Strecker addition. The alternative has been[3] hydrolysis to the difficult-to-handle amino acid, followed by methylation of the carboxylate salt. The esterification is a competition between O-methylation and N-methylation, resulting in mediocre yields.

There are scattered reports[4] of the direct alcoholysis of amides to the corresponding methyl esters. After some experimentation, we found that *p*-toluenesulfonic acid monohydrate gave the cleanest conversion of **5** to **6**. The reaction, slow in refluxing methanol, is best run in a sealed bottle. The optimal temperature for the conversion of **5** to **6** is 105 °C, at which temperature the reaction takes 36 h. We expect that less hindered amides will react more rapidly. (**CAUTION**: A volatile material, presumably dimethyl ether,[4b] is formed during the methanolysis. The reaction should be run behind a shield, and pressure bottles should be opened slowly, after cooling.)

With these modifications, ester **6**, the key intermediate for the synthesis of carfentanil (**2**), is available in 61% overall yield from *N*-benzyl-4-piperidone (**3**).

Experimental Section

4-(Phenylamino)-1-(phenylmethyl)-4-piperidinecarbonitrile (4). A mixture of 1-benzyl-4-piperidone (**3**) (17.01 g, 90 mmol), KCN (14.64 g, 225 mmol), aniline (12.57 g, 135 mmol), acetic acid (450 mL), and water (75 mL) was maintained at 45 °C with irradiation from an ultrasonic cleaning bath, for 45 h. The mixture was cooled and then poured over 200 g of ice in 600 mL of concentrated aqueous NH_4OH. An additional 15 mL of NH_4OH was added to complete neutralization (pH = 7 by pH paper). The mixture was extracted with $CHCl_3$ (3 × 150 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from Et_2O to give nitrile **4** as a white solid (23.7 g, 90%), mp = 145–146 °C (lit.[3] mp = 145–146 °C).

4-(Phenylamino)-1-(phenylmethyl)-4-piperidinecarboxamide (5). Nitrile **4** (15.0 g, 51.5 mmol) was added portionwise to 400 mL of concentrated H_2SO_4 at rt. After 48 h the mixture was cooled and then added slowly to 400 g of ice in 1300 mL of concentrated aqueous NH_4OH. The resultant white precipitate was filtered, washed with water, and vacuum dried to give amide **5** (14.35 g, 90%), mp = 190–191 °C. ^1H NMR (δ): 7.38–7.22 (m, 5 H); 7.19 (t, 2 H, J = 7.7 Hz); 6.87 (bs, 1 H); 6.80 (t, 1 H, J = 7.5 Hz); 6.63 (d, 2 H, J = 7.7 Hz); 5.43 (bs, 1 H); 4.02 (s, 1 H); 3.48 (s, 2 H); 2.74 (dt, 2 H, J = 12.1, 2.1 Hz); 2.31 (dt, 2 H, J = 3.9, 12.6 Hz); 2.10 (dt, 2 H, J = 2.0, 11.9 Hz); 1.92 (bd, 2 H, J = 12.2 Hz). ^{13}C NMR (δ): 178.7, 144.0, 138.5, 129.4, 129.2, 128.4, 127.3, 119.5, 116.4, 63.2, 58.5, 49.0, 31.7; MS (*m*/*z*, rel intensity): 309 (17.6), 266 (9.7), 265 (62.5), 264 (100), 216 (54.6), 172 (28.4).

Methyl 4-(Phenylamino)-1-(phenylmethyl)-4-piperidinecarboxylate (6). Amide **5** (4.65 g, 15.0 mmol), *p*-toluenesulfonic acid monohydrate (10.0 g, 52 mmol), and methanol (55 mL) were sealed in a glass pressure vessel and maintained at 105 °C (internal) for 36 h. (**CAUTION**: PRESSURE BUILD-UP! The reaction should be run behind a shield.) The vessel was cooled and vented. The solvent was evaporated, the residue was taken to pH = 8 (pH paper) with concentrated aqueous NH_4OH, and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), evaporated, and chromatographed on silica gel to give 3.63 g (75%) of ester **6**, TLC R_f = 0.64 (10% CH_3OH/CH_2Cl_2), as a clear viscous oil. On standing in the refrigerator and seeding, this material crystallized, mp = 80–80.5 °C (lit.[3f] mp = 80.5 °C). The ^{13}C and ^1H NMR spectra for **6** are identical with those recently reported,[3a] with the exception that the peak at 3.56 (5, 3 H) cited should be 3.56 (s, 3 H).

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Registry No. **2**, 59708-52-0; **3**, 3612-20-2; **4**, 968-86-5; **5**, 1096-03-3; **6**, 61085-60-7; aniline, 62-53-3.

(6) A general experimental procedure was recently published: Taber, D. F.; Hoerrner, R. S.; Hagen, M. D. *J. Org. Chem.* **1991**, *56*, 1287.

The Tautomerism of a Phosphono Enamine

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The Emmons reaction, a popular modification of the Wittig reaction because of the ease of removal of the water-soluble byproducts, typically involves the formation of a diethoxyphosphono intermediate such as **1**. This is converted by a strong base to an anion and treated with a ketone or aldehyde to provide the desired olefin from the elimination of a more oxygenated phosphorus species. We have used such an approach in the synthesis of unsaturated 1-pyrrolines, **2**, identified in the venom of the ant *Megalomyrmex foreli*.[1] Thus, the butylpyrroline phosphonate intermediate **3** was readily prepared by phosphonylation of the anion of the corresponding 2-methyl-1-pyrroline under conditions of kinetic control. The Emmons product of this material and hexanal or 2-hexenal produced the required venom alkaloids, **2**.

Several groups preparing phosphono intermediates with a nitrogen substituent have characterized them with divergent results. Russian and American groups have prepared examples corresponding to **4** and **5**, with the proportions of the *E* and *Z* isomers varying with various substituents.[2] In light of the observations below, it is

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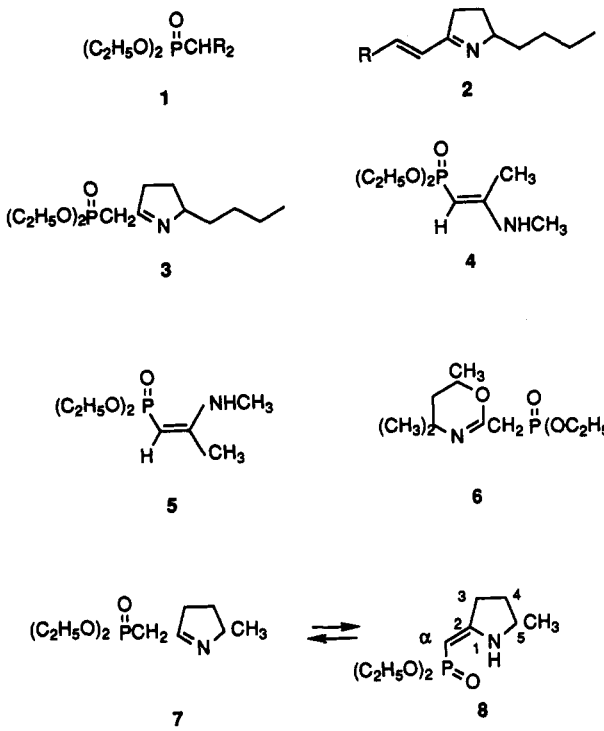
(2) (a) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1973**, *38*, 820. (b) Alikin, A. Y.; Liorber, B. G.; Sokolov, M. P.; Razumov, A. I.; Zykova, T. V.; Salakhutdinov, R. A. *Z. Obsch. Khim.* **1982**, *52*, 316.



1 2 3 4 5 6 7 8

interesting that, since resonances differing by 1 Hz in the NMR spectra could be distinguished, there was no rapid interconversion of these materials. Malone and Meyers[3] reported that the oxazine 6 showed infrared and NMR characteristics of the imine and phosphonomethylene groups, but no evidence of an enamine.

In the light of such divergent interpretations of the structure of these products, it seemed desirable to characterize the functionality of 3 more fully. To simplify the study of the structures by NMR spectra, the investigation was switched to compound 7, available by analogous phosphonylation of 2,5-dimethylpyrroline with diethyl chlorophosphonate. The required pyrroline was most conveniently prepared from the corresponding pyrrolidine by a familiar halogenation/dehydrohalogenation sequence.[4] So produced, 7 eluted as a single peak under a variety of gas chromatographic conditions. FTIR spectra of the eluting material showed the characteristic enamine absorption at 1622 cm^{-1}. Additionally, in solution, both infrared and NMR spectra showed peaks characteristic of an NH group. Broadening of the peaks of both ^1H and ^{13}C spectra taken at room temperature suggested that a chemical exchange between two species was involved. In spectra taken at lower temperatures this broadening was eliminated and, at −59 °C, a set of peaks evidently associated with one form was much reduced in intensity. A saturation transfer experiment at room temperature identified the affected protons.[5] Irradiation of the N^{1}H decreased the intensity of the two doublets centered at 3.5 and 3.05 ppm. Difference spectra, Figure 1, demonstrated the results very clearly. Chemical characterization of the product required that there be a double bond, for reduction of the material by hydrogen produced a dihydro derivative with the anticipated mass and NMR spectra.

Evidence quoted to this point suggests the occurrence of the imine–enamine tautomerism between 7 and 8, but

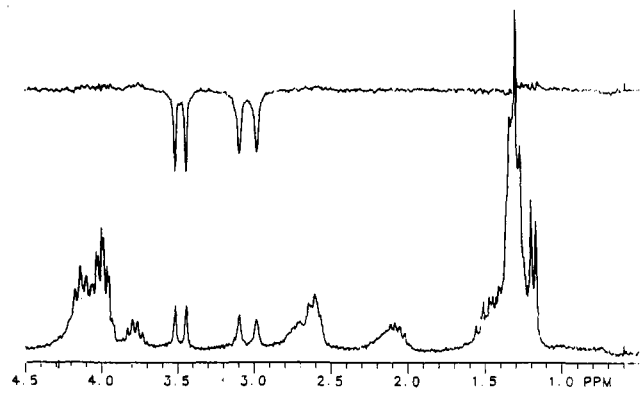


Figure 1. Upfield portion of ^1H spectrum of 7/8 and the difference spectrum with irradiation of the N^{1}H at 7.13 ppm.

Table I

atom	^1H	^{13}C	^1J(CH)	other couplings	other nuclei
			7		
1					$\delta(^{15}N)$ 210
2		168.6		^2J(CP) 8.1	
3	2.71 2.58	38.3	131		
4	1.39	30.7	132		
5	3.94	67.7	141		
α	3.06	32.2	128	^1J(CP) 134 ^2J(HP) 22.2	
CH_3	1.28	21.8	129		
ethoxy CH_2	3.96	62.2	148	^2J(CP) 10.3 ^3J(HP) 3.5	$\delta(^{31}P)$ 19
CH_3	1.30	16.3	128	^3J(CP) 3.5	
			8		
1	7.13				$\delta(^{15}N)$ 79
2		167.9		^2J(CP) 5.1	
3	2.50 2.03	33.5	133	^3J(CP) 18.6	
4	1.38	30.4	134		
5	3.70	54.5	142		
α	3.51	60.9	159	^1J(CP) 198 ^2J(HP) 14.5	
CH_3	1.10	21.5	128		
ethoxy CH_2	4.00	60.5	148	^3J(HP) 3.3	$\delta(^{31}P)$ 24
CH_3	1.30	16.28	128	^3J(CP) 3.5	

neither ^1H nor ^{13}C spectra showed peaks characteristic of =CH atoms. One-bond coupling values were therefore sought to provide a more reliable indication of the presence of a double bond, for this coupling is proportional to the amount of s character in the carbon atom.[6] A heteronuclear J-resolved spectrum[7] showed couplings near 130 Hz for all ^{13}C resonances except a doublet centered at 61 ppm, which had ^1J(CH) values anticipated of a vinyl CH, 160 Hz. Comparison of the separation of the two peaks of this doublet at two field strengths, 4.7 and 7.05 T, showed it to be 199 Hz at both 50 and 75 MHz, and therefore the result of one-bond coupling to the phosphorus atom. The doublet can thus be assigned to C-α of 8.

A heteronuclear correlation experiment[6] showed that the carbon resonance which gave rise to these peaks is correlated to that of the proton of chemical shift 3.5 ppm, one of the pair shown by the saturation transfer to be involved in the chemical exchange. The other proton, with a chemical shift of 3.06, is borne by the carbon represented by the doublet centered at 32.1 ppm, with ^1J(CP) of 128 Hz. DEPT spectra[5] showed the two carbons to be methine

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(4) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1979**, *20*, 1031.
(5) Nakanishi, K. *One-Dimensional and Two-Dimensional NMR Spectra by Modern Pulse Techniques*; University Science Books: Mill Valley, CA, 1990; p 26.
(6) Kalinowski, H.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Wiley: New York, 1988; p 495.
(7) Martin, G. E.; Zektzer, A. S. *Two-Dimensional NMR Methods for Establishing Molecular Connectivity*; VCH: New York, 1988; p 20.

and methylene, respectively. Both ^1J(HC) and ^1J(CP) for the carbon at 60.9 ppm are substantially larger than the corresponding values for the carbon at 32.1 ppm, and clearly show that the two resonances arise from olefinic and aliphatic carbons, respectively.

The exchanging system is thus shown to comprise enamine–imine tautomers. Complete assignment of the magnetic resonance of all the atoms except oxygen (Table I) supports this interpretation. The very different ^{15}N chemical shifts, 211 and 79 ppm, require that they arise from imine and enamine groups, respectively.[8] The large vicinal coupling between the phosphorus and C-3 implies a *Z* configuration of the double bond of 8.[9] This configuration is consistent with the appearance in the infrared spectrum of an intramolecular hydrogen bond at 3318 cm^{-1}. Although the concentrations of 7 and 8 are nearly equal to 30 °C, at −60 °C the enamine, 8, predominates. There is no evidence for the occurrence of the *E* isomer of 8.

To provide further confirmation of these assignments, ^1H and ^{13}C spectra were obtained of the product after the $CDCl_3$ solution was shaken with D_2O. The peaks corresponding to the α-^1H and ^{13}C disappeared from the spectra immediately, with no other peaks affected.

Enamines are characterized by an upfield shift of the resonances of both the β-^1H and ^{13}C as a result of resonance contribution of $N^+{=}CCH^-$.[10] The further upfield shifts are evidently to be ascribed to the polarizability of the phosphonyl group, stabilizing the negative charge on the β carbon.[11]

Earlier studies have shown that the proportion of enamine and imine in these tautomeric systems is very sensitive to the effect of substituents.[12] In the examples quoted above, it is likely that the olefinic peaks which would have provided evidence for the existence of the enamine isomer of 6 were obscured in the 60-MHz spectrum by the ethoxyl resonances. The contrast of the facile exchange observed here with the apparent static character of the noncyclic systems noted above[2] is quite striking.

Experimental Section

Gas chromatographic analyses were carried out using a 30 m × 0.5-mm i.d. open DB-17 column (1-μm film thickness). The temperature for the analyses was programed from 60–215 °C at 10°/min, and the carrier gas flow rate was 15 mL/min. On a given day, retention temperatures were reproducible to 1 °C. Preparative gas chromatography was conducted with a 2 m × 5-mm i.d. column packed with 10% OV-17 on 100–120 mesh Supelcoport. ^1H and ^{13}C NMR spectra were obtained from $CDCl_3$ solutions at 4.7 and 7 T; ^{31}P NMR spectra were obtained at 4.7 T, while ^{15}N spectra were obtained at 7 T. Solutions for ^1H and ^{13}C spectra included tetramethylsilane as an internal reference (0 ppm); for ^{15}N, nitromethane (380 ppm, NH_3 = 0 ppm); for ^{31}P, external phosphoric acid (0 ppm). Assignments were made on the basis of homo- and heteronuclear correlation spectra, consistent with DEPT spectra. Multiplets ascribed to coupling with ^{31}P were confirmed by comparison of spectra obtained at 4.7 and 7.05 T. Electron-impact mass spectra were obtained using an GC/MS equipped with a 25 m × 0.31-mm i.d. HP-5 column. High-resolution mass spectra were obtained with a double-focusing mass spectrometer.

2-[(Diethylphosphono)methyl]-5-methyl-2-pyrroline (7). A solution containing 8.6 g (87 mmol) of 2,5-dimethylpyrrolidine in 100 mL of MeOH and 200 mL of 5% sodium hypochlorite solution was stirred for 2 h at room temperature. Following the addition of 10 g of NaOH, the mixture was heated on a steam bath for 1 h, cooled, and extracted with 3 × 70 mL of ether. The combined ether extracts were dried over anhydrous K_2CO_3 and carefully distilled to provide 4.0 g of 2,5-dimethyl-1-pyrroline (49% yield): bp 110–114 °C.[13] A solution containing 0.50 g (50 mmol) of 2,5-dimethyl-1-pyrroline in 2 mL of THF was added over 15 min to a solution containing 10 mmol of lithium diisopropylamide at −78 °C in 5 mL of THF (from 1.40 mL of diisopropylamine and 6.25 mL of 1.6 M *n*-butyllithium) under a nitrogen atmosphere. After 1 h, a solution containing 0.85 g (6.1 mmol) of diethyl chlorophosphate in THF was added slowly and the mixture was stirred for 3 h. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and warmed to room temperature. After the addition of 10 mL of ether, the aqueous layer was separated, and the organic mixture was dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo provided 1.1 g of a mixture of which 85% was a single component with a long retention time, which was purified by preparative gas chromatography. Pure material so prepared had an NMR spectrum closely resembling that of the original crude product: IR (GC-FTIR or CCl_4) 3318, 1622, 1281, 1040, 951, and 787 cm^{-1}, unchanged by dilution of the sample. The IR of the neat liquid showed an additional band at 3220 cm^{-1}; MS *m/z* (rel intensity) 233 (21, M^+), 218 (29), 190 (15), 162 (14), 160 (15), 150 (11), 144 (18), 122 (53), 97 (100), 96 (29), 95 (19), 94 (37), 82 (44), 81 (15), 80 (62), and 54 (21); HRMS *m/z* 233.1184 M^+ ($C_{10}H_{20}O_3NP$, calcd 233.1181).

Hydrogenation of 7/8. A small portion (ca. 200 mg) of the crude product above was taken up in hexane and hydrogenated over 0.4 g of 5% Rh/Al_2O_3 for 8 h. After filtration and removal of the solvent in vacuo gas chromatographic analysis revealed the presence of a single major component (85%): IR 2967, 2881, 1397, 1267, 1099, 949, and 806 cm^{-1}; ^1H NMR δ 4.1 (m, CH_2O), 3.3 (m, H-2), 3.1 (m, H-5), 2.0 (m, α-H, H-3), 1.6 (m, H-4), 1.29 (t, J = 7.0 Hz, CH_3CH_2O), 1.12 (d, J = 6.6, C-5 CH_3); ^{13}C NMR δ 61.4 (OCH_2, ^2J(CP) = 6 Hz), 53.9 (C-5), 53.6 (C-2, ^2J(CP) = 4 Hz), 32.9 (α, ^1J(CP) = 137 Hz), 32.6 (C-3, ^3J(CP) = 12 Hz), 32.5 (C-4), 21.6 (C-5 CH_3), 16.4 (CH_3CH_2O, ^3J(CP) = 6 Hz); MS *m/z* 235 (4, M^+), 220 (9), 192 (5), 179 (13), 164 (8), 98 (11), 97 (70), 85 (8), 84 (100), 83 (8), 82 (50), 81 (12), 70 (32), 68 (17), 57 (41), 55 (15), 43 (11); HRMS *m/z* 235.1336 M^+ ($C_{10}H_{22}O_3NP$, calcd 235.1337).

(8) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; Wiley: New York, 1979; p 29.
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Synthesis of Antibiotic Stilbenes Using Organomanganese Arene Complexes

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The two antibiotic metabolites isolated from strain H_b of Xenorhabdus, a genus of bacteria symbionts which live in the guts of parasitic nematodes,[1-3] have been identified as the homologous *trans*-hydroxystilbene derivatives **1a** and **1b**.[2,3] In order to conduct further biological testing of antibiotics **1a** and **1b**,[4] we sought an expedient synthesis based on the readily available 1,3-dimethoxy-2-alkylbenzenes. We envisioned that the direct nucleophilic at-

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