partners as well as solvent effects will differentially affect the relative energies of the three transition states so favoring as a consequence a well-defined stereochemical outcome.

Synthesis of 3-Pyrrolines by an Intramolecular Wittig Reaction

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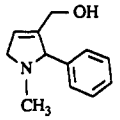
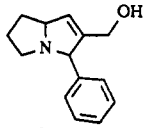
Intramolecular Wittig reactions have been applied successfully to the synthesis of unsaturated carbocycles and certain heterocycles.[1,2] This cyclization strategy has been used to prepare numerous β-lactam antibiotics[3] (i.e. cephalosporins, oxadethiacephams, olivanic acid derivatives, and thienamycin analogues). However, very few examples exist for the preparation of 3-pyrrolines using this methodology.[4] The preparation of unsaturated heterocycles by the intramolecular Wittig reaction typically requires an intermediate that contains the heteroatom and carbonyl moiety (Scheme I).

Cyclization is facilitated when the heteroatom attacks the electrophilic β-carbon of a vinylphosphonium[5] salt or phosphonate[6] to generate the ylide. This procedure works well when the heteroatom is oxygen, sulfur, or a resonance-delocalized nitrogen. However, in the case of aliphatic amines,[7] the preparation and storage of the required amino ketones (or amino aldehydes) can be problematic, thereby discouraging their use as practical intermediates.

This report demonstrates a novel, efficient method for the synthesis of *N*-alkyl-3-pyrrolines through an intramolecular Wittig reaction in which the starting material is a β-aminophosphonium salt. The 3-pyrroline 1 and pyrrolizine 2 were prepared by short convergent syntheses.



1

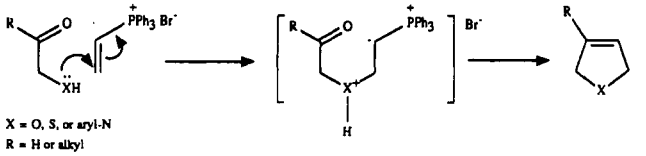


2

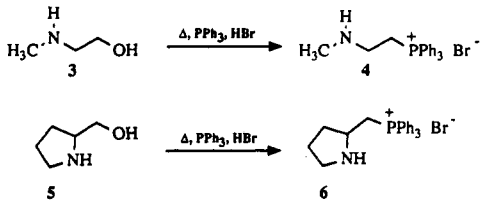
The β-aminophosphonium salts (*N*-methyl-β-aminoethyl)triphenylphosphonium bromide (4) and (2-pyrrolidinylmethyl)triphenylphosphonium bromide (6) were readily prepared from the appropriate β-amino alcohol by treatment with triphenylphosphine and HBr as described by Marxer[8] (Scheme II). The hydroxy ketone 8a was prepared by using a one-pot procedure (Scheme III). Treatment of α-bromophenylacetyl chloride [7b, from α-bromophenylacetic acid (7a) and thionyl chloride] with diazomethane and triethylamine in ether gave the diazo ketone 7c that was hydrolyzed in situ with aqueous trifluoroacetic acid (TFA) to give 8a. The hydroxy ketone 8a was purified by flash chromatography[9] and the hydroxyl moiety was protected by using dihydropyran (DHP) and a catalytic amount of TFA in dichloromethane. The resulting THP ether 8b could be stored for greater than 6 months if kept cold and free from light.

The intermediates 4 and 8b were smoothly coupled at room temperature in dichloromethane and triethylamine to give the crude amino ketone 9 (Scheme IV). Wittig cyclization was accomplished by the portion-wise addition of a THF solution of 9 to an excess of sodium hydride suspended in THF. The reaction products were partitioned between ethyl acetate and 5% aqueous HCl, which simultaneously separated the pyrroline from triphenylphosphine oxide and removed the THP protecting group. The alcohol 1 was an oil so it was converted to the crystalline carbamate 10 by treatment with isopropyl iso-

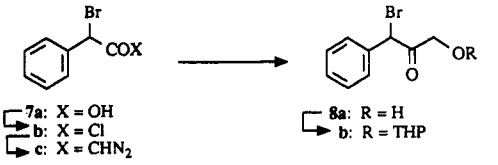
Scheme I



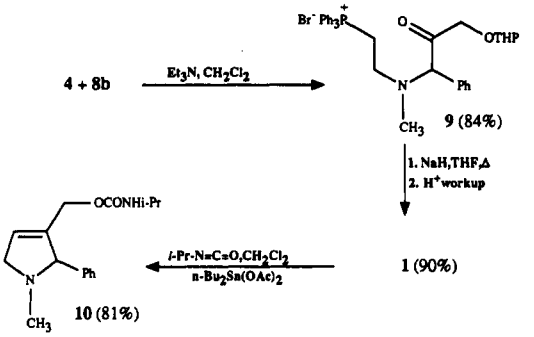
Scheme II



Scheme III



Scheme IV



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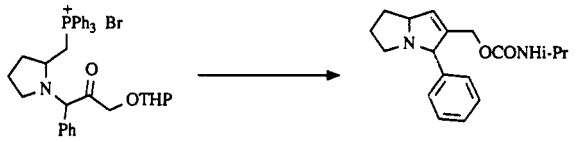
cyanate and a catalytic amount of di-*n*-butyltin diacetate in dichloromethane.

The pyrrolizine **2** was also prepared by this convergent approach from **6** and **8b**. The yield in the cyclization of **11** was lower because significant air oxidation of the pyrrolizine occurred during the course of the reaction and during workup. The free hydroxyl moiety was treated with isopropyl isocyanate (as before) to give the carbamate derivative **12** as a highly air sensitive pale yellow gum. All of the 3-pyrrolines prepared gave characteristic colors when treated with Ehrlich's reagent after brief exposure to iodine (thin layer chromatographic analysis). The Ehrlich pyrrole reaction has been used extensively in the identification of pyrrolizine alkaloids and their metabolites.[10]



11 **12**

Experimental Section

Melting points were determined in an open capillary and are uncorrected. IR spectra were determined on an FT-IR interferometer. All ^1H NMR spectra were obtained at 90 MHz. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

3-(Hydroxymethyl)-1-methyl-2-phenyl-3-pyrroline (1). A solution of **8b** (0.8 g, 2.25 mmol) in tetrahydrofuran (10 mL, distilled from sodium metal) was added portion-wise to a stirred solution of **4** (1 g, 2.5 mmol) and dichloromethane (10 mL, distilled from calcium hydride) at 25 °C. Triethylamine (2 mL) was added to the reaction in one portion, and the solution was stirred for 1 h (a greenish precipitate formed). The reaction mixture was concentrated in vacuo to a dark foam that was passed through a short flash column (230–400 mesh, 5 × 15 cm, eluted with 9:1 dichloromethane–methanol) to give 1.2 g (84%) of the crude intermediate **9** as a pale green foam. This intermediate was used immediately in the next reaction.

A solution of **9** (1 g, 1.88 mmol) in tetrahydrofuran (15 mL) was added portion-wise to a stirred suspension of sodium hydride (60% mineral oil suspension: 0.15 g, 3.62 mmol) and tetrahydrofuran (15 mL) at 25 °C under a positive pressure of argon. The reaction mixture was heated at reflux for ca. 45 min, which caused the greenish reaction mixture to become reddish. The reaction was cooled (5 °C) and carefully quenched with methanol (10 mL), filtered, and concentrated in vacuo to a dark gum. The residue was suspended in 5% aqueous hydrochloric acid (100 mL) and then extracted with ethyl acetate (2 × 100 mL). The acidic aqueous extract was basified to pH 9 with ammonium hydroxide solution, then extracted with dichloromethane (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give **1** (0.27 g, 90%) as a pale yellow oil: IR (neat) 3370, 2937, 2864, 2772, 1491, 1453, 1345, 1235 cm^{-1}; ^1H NMR δ 7.25 (s, 5 H), 5.7 (m, 1 H), 4.2 (m, 1 H), 3.85 (m, 1 H), 3.75 (sharp m, 2 H), 3.45 (s, 1 H), 3.3 (m, 1 H), 2.25 (s, 3 H).

2,3,5,7a-Tetrahydro-6-(hydroxymethyl)-5-phenyl-1*H*-pyrrolizine (2). Compounds **6** and **8b** were reacted in a manner analogous to the method described for **1** to give the pyrrolizine **2** as a highly air sensitive pale yellow oil (20%) that was used immediately in the next reaction (see **12**).

[2-(Methylamino)ethyl]triphenylphosphonium Bromide (4). Hydrobromic acid (48%, 42 mL, 0.373 mol) was added portionwise (cautiously at first) to a stirred solution of 2-(methylamino)ethanol (5 mL, 0.0622 mol) and triphenylphosphine (16.3 g, 0.0622 mol) in benzene (25 mL) at 5 °C. The reaction mixture was heated to ca. 150 °C, which caused the benzene and most of the water to evaporate to give a melt. The melt was heated to 200–210 °C for ca. 1 h and then at 150 °C for 3 h. The reaction was allowed to cool to room temperature and dissolved in water (100 mL) and then extracted with ethyl acetate (3 × 100 mL). The acidic aqueous fraction was basified to pH 8 with a sodium carbonate–sodium bicarbonate solution, then extracted with dichloromethane (6 × 150 mL), dried (Na_2SO_4), and concentrated in vacuo to give 16.7 g, (67%) of **4** as a white hygroscopic solid (store in a desiccator): mp (ethanol/ether) 219–223 °C (lit.[8] mp 235.5–237.5 °C); IR ($CHCl_3$) 3264, 3018, 2934, 2450, 1588, 1485, 1439, 1113, 998 cm^{-1}; ^1H NMR δ 7.85 (sharp m, 15 H), 3.95 (m, 2 H), 2.95 (m, 2 H), 2.45 (s, 1 H), 2.2 (s 3 H).

(*S*)-2-(Hydroxymethyl)pyrrolidine (5). A suspension of *l*-proline (10 g, 0.0868 mol) in tetrahydrofuran (100 mL, distilled from sodium metal) was added cautiously (portion-wise) to a stirred suspension of lithium aluminum hydride (6.6 g, 0.174 mol) in ether (100 mL) at −10 °C under a positive pressure of argon. The reaction was allowed to warm to room temperature (25 °C), stirred for 16 h and then cooled (ice bath). The cold reaction mixture was quenched with the sequential addition of water (7 mL), 15% sodium hydroxide solution (7 mL), and water (21 mL) and then filtered (washed with tetrahydrofuran). The combined filtrates were concentrated in vacuo to give a yellow oil that was distilled to give 5.8 g (66%) of **5** as a clear oil: bp 68–69 °C, 1.25 mmHg (lit.[11] bp 74–76 °C, 2 mmHg); IR (neat) 3306, 3121, 2874, 1458, 1373, 1106, 1051 cm^{-1}; ^1H NMR δ 4.0 (s, 2 H), 3.45 (m, 3 H), 3.0 (t, J = 6 Hz, 2 H), 1.7 (m, 4 H).

(2-Pyrrolidinylmethyl)triphenylphosphonium Bromide (6). The method used for **4** gave **6** as a white hygroscopic solid (60%, store in a desiccator): mp (dichloromethane–methanol) 174–175 °C; IR ($CHCl_3$) 3058, 2962, 2732, 2695, 2511, 1588, 1438, 1265, 1111 cm^{-1}; ^1H NMR δ 7.8 (sharp m, 15 H), 4.3–3.5 (complex m, 3 H), 2.7 (m, 3 H), 1.8 (m, 4 H); FABMS, m/e 346 (M^+ − Br). Anal. Calcd for $C_{23}H_{25}BrNP$: C, 64.80; H, 5.91; N, 3.78. Found: C, 64.63; H, 5.92; N, 3.78.

2-Bromo-2-phenylacetyl Chloride (7b). A solution of α-bromophenylacetic acid (**7a**) (20 g, 0.093 mol) in thionyl chloride (33 mL, 0.465 mol) was stirred at reflux for 2 days. The thionyl chloride was distilled to give the crude acid chloride that was distilled to give 20.2 g (93%) of **7b** as a light yellow oil: bp 135–137 °C, ca. 20 mmHg; IR (neat) 3066, 3033, 2980, 1799, 1766, 1494, 1455, 1194, 980 cm^{-1}; ^1H NMR δ 7.55 (sharp m, 5 H), 5.75 (s, 1 H).

1-Bromo-3-diazo-1-phenyl-2-propanone (7c). A solution of **7b** (4.7 g, 0.0203 mol) in ether (20 mL) was added dropwise to a stirred solution of diazomethane (0.3 M solution in ether, 135 mL, 0.0406 mol) and triethylamine (3 mL, 0.021 mol) at 5 °C. The evolution of nitrogen gas was observed. The reaction was stirred at this temperature for 1 h and then concentrated in vacuo to a yellow oil that was chromatographed (silica eluted with 4:1 hexane–ethyl acetate) to give **7c** (2.2 g, 46%) as a light yellow solid: mp 80–81 °C; IR (mineral oil) 3070, 2936, 2415, 2182, 1752, 1632, 1351, 1132 cm^{-1}; ^1H NMR δ 7.35 (m, 5 H), 5.65 (s, 1 H), 5.32 (s, 1 H). Anal. Calcd for $C_9H_7BrN_2O$: C, 45.21; H, 2.95; Br, 33.42; N, 11.71. Found: C, 45.39; H, 3.00; Br, 33.28; N, 11.79.

1-Bromo-3-hydroxy-1-phenyl-2-propanone (8a). A solution of α-bromophenylacetyl chloride (**7b**) (7.4 g, 0.0317 mol) in ether (50 mL) was added dropwise to a stirred solution of diazomethane (300 mL, 0.3 M solution in ether) and triethylamine (4.4 mL, 0.0317 mol) at 5 °C. The reaction was stirred at this temperature for 2 h, then water (100 mL) and trifluoroacetic acid (35 mL, slowly) were added in tandem and the solutions stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo to a ca. 100-mL volume and then stirred at 25 °C for 3 h (substantial nitrogen gas evolved). The mixture was partitioned between ethyl acetate and water. The ethyl acetate fraction was dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Flash chromatography (230–400 mesh, 7 × 30 cm, eluted with 7:3 hexane–ethyl acetate) gave **8a** (3.4 g, 47%) as a thick light yellow oil: IR (neat) 3379, 2920, 1742, 1452, 1254, 1036 cm^{-1}; ^1H NMR δ 7.38 (sharp m, 5 H), 5.56 (s, 1 H), 5.06 (br s, 1 H), 4.50 (s, 2 H); HRMS (CI) for $C_9H_9BrO_2$ calcd 228.9864, found 228.9868.

Tetrahydro-2-[(3-bromo-2-oxo-3-phenylpropyl)oxy]pyran (8b). Trifluoroacetic acid (10 drops) was added to a stirred solution of **8a** (2 g, 0.00873 mol) and dihydropyran (1.6 mL, 0.0175

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mol) in dichloromethane (30 mL, distilled from calcium hydride) at 5 °C under a positive pressure of argon in the dark. The reaction was stirred at 25 °C for 3 h and then concentrated in vacuo to a dark oil. Flash chromatography (230–400 mesh, 7 × 30 cm, eluted with hexane–ethyl acetate 8:1) gave **8b** having R_f = 0.31 (2.3 g, 83%) as a light-sensitive, pale yellow oil: IR (neat) 2943, 2869, 1736, 1494, 1454, 1202, 1131, 1078, 1036 cm^{-1}; ^1H NMR δ 7.4 (sharp m, 5 H), 5.8 (s, 1 H), 4.4 (m, 3 H), 3.65 (m, 2 H), 1.6 (m, 6 H); HRMS (EI) for $C_{14}H_{17}BrO_3$ calcd 311.02824, found 311.02704.

1-Methyl-2-phenyl-3-[[((2-propyl)carbamoyl)oxy]-methyl]-3-pyrroline (10). 2-Propyl isocyanate (0.32 mL, 0.0033 mol) was added in one portion to a stirred solution of **1** (0.25 g, 0.00132 mol) and di-*n*-butyltin diacetate (2 drops) in dichloromethane (10 mL, distilled from calcium hydride) at 25 °C under a positive pressure of argon. The reaction was stirred for 1.5 h and then concentrated in vacuo to give an oil that was flash chromatographed (230–400 mesh, 5 × 25 cm, eluted with 3:2 ethyl acetate–dichloromethane) to give a pale yellow solid. The solid was recrystallized from dichloromethane–hexane to give **10** (0.29 g, 81%) as a white fluffy solid: mp 66–67 °C; IR ($CHCl_3$) 3338, 2968, 2773, 1719, 1453, 1247, 1168 cm^{-1}; ^1H NMR δ 7.3 (s, 5 H), 5.85 (m, 1 H), 4.6–3.25 (complex m, 7 H), 2.4 (s, 3 H), 1.15 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.05; H, 8.13; N, 10.20.

2,3,5,7a-Tetrahydro-5-phenyl-6-[[((2-propyl)carbamoyl)-oxy]methyl]-1*H*-pyrrolizine (12). Compound **2** was converted to **12** by using the procedure described for **10**. Compound **12** was obtained as a highly air sensitive pale yellow gum (70%): IR ($CHCl_3$) 3443, 2967, 2873, 1715, 1509, 1455, 1229, 1084 cm^{-1}; ^1H NMR δ 7.25 (s, 5 H), 5.80 (s, 1 H), 4.40 (m, 4 H), 3.75 (m, 2 H), 3.20 (m, 1 H), 2.75 (m, 1 H), 1.73 (m, 4 H), 1.10 (d, J = 6 Hz, 6 H); CIMS, m/e 197 (53), 198 (64), 301 (M + 1, 100). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found C, 72.19; H, 7.74; N, 9.38.

Acknowledgment. This research was supported in part by the National Cancer Institute (CA-22935, CM-67698, and CM-27570) and the General Medical Institute (GM-7145), DHHS. We thank Dr. A. M. Bergmann of SUNY at Buffalo, Chemistry Instrumentation Center, for HRMS determinations.

Registry No. 1, 135733-62-9; 2, 135733-63-0; 3, 109-83-1; 4, 34477-69-5; 5, 23356-96-9; 6, 135733-64-1; 7a, 4870-65-9; 7b, 19078-72-9; 7c, 135733-67-4; 8a, 116204-25-2; 8b, 135733-69-6; 9, 135733-65-2; 10, 135733-66-3; 11, 135733-70-9; 12, 135733-68-5; H-Pro-OH, 147-85-3; *i*-PrNCO, 1795-48-8; 3,4-dihydro-2*H*-pyran, 110-87-2.

Supplementary Material Available: ^1H NMR spectra (90 MHz) for compounds **8a**, **8b**, and **12** (3 pages). Ordering information is given on any current masthead page.

A Reconsideration of the Cleavage of Ellman's Reagent (5,5′-Dithiobis(2-nitrobenzoic acid)) in the Presence of Dioctadecyldimethylammonium Chloride Surfactant Vesicles

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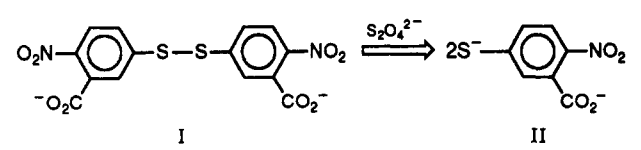
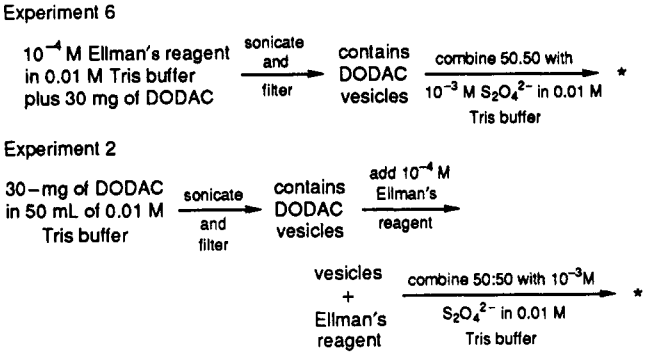
During the process of attempting to find a reaction system that could be used to measure the occurrence of structural modifications of surfactant vesicular bilayers in aqueous solution by chemical kinetics, we repeated experiments 2–6 of Table III of a previous study by Moss and co-workers on the cleavage of Ellman's reagent (I) by dithionite (Scheme I) in the presence of dioctadecyldimethylammonium chloride (DODAC) vesicles.[2]

Scheme I



I II

Scheme II[a]



[a]* Follow rate of appearance of absorbance (λ_{max} = 440 nm) in a spectrophotometer.

Experiment 2 of this table involved the cosonication of 10^{-4} M Ellman's reagent with 10^{-3} M DODAC in pH 8, 0.01 M aqueous Tris buffer μ = 0.01 (KCl) followed by combination of the resulting solution 50:50 with 10^{-3} M ($S_2O_4^{2-}$) also in Tris buffer, μ = 0.01 (KCl) inside a UV–vis spectrophotometer thermostated at 25 °C[2] (see Scheme II). A biphasic kinetic appearance of yellow color (λ_{max} = 450 nm) was observed. The fast kinetic phase was over in a few seconds and was interpreted to involve a bimolecular reaction between dithionite and that portion of the substrate (Ellman's reagent) that is adsorbed onto the outer DODAC vesicular surface and remains in contact with the outer vesicular–aqueous interface.[3] The 450-nm absorbance peak is attributed to the formation of Ellman's anion (II) (Scheme I; λ_{max} = 440 nm (ϵ = 13,600)).[2] The slow kinetic phase lasted about 1 h and was interpreted to involve cleavage of the remaining portion of the substrate, which was encapsulated within the vesicles formed by the sonication process by buffer supplied hydroxide since the $S_2O_4^{2-}$ was believed to be unable to pass through the DODAC vesicular bilayer. The reported pseudo first-order rate constant[2] at pH 8 for this slow phase ($k = 5.09 \times 10^{-4}$ s^{-1}) is within experimental error equal to that reported earlier[4] for the reaction of Ellman's reagent with hydroxide at pH 8 ($k = 7.8 \times 10^{-4}$ s^{-1}). Experiment 2 of this same table was identical with that of 6 except that the substrate was added after sonication of the DODAC in the buffer but prior to combination with the $S_2O_4^{2-}$ solution in the spectrometer (see Scheme II). In this case only a single rapid kinetic phase was reported to take place at 450 nm

(1) Chemistry teacher, Flagstaff High School.

(2) Moss, R. A.; Swarup, S.; Zhang, H. *J. Am. Chem. Soc.* **1988**, *110*, 2914.

(3) The cleavage of Ellman's reagent is significantly faster in the presence of DODAC vesicles than alone in aqueous solution. Also, Ellman's reagent experiences a 12-nm hypsochromic shift in its major aqueous absorption band in the presence of DODAC vesicles. These results were earlier reported to be due to substrate and reactant electrostatic adsorption onto the anionic outer vesicular surface prior to reaction.

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