of methyl *p*-nitrocinnamate monomers.

Information from the standard spectrum and the COSY experiments do not establish the stereochemistry of the substituents because vicinal cyclobutane protons have similar cis and trans couplings.[3] However, it is possible to assign the stereochemistry of the photoproduct from a NOESY spectrum, Figure 1, which shows interactions between H-2, H-3, and H-4. As such interactions only occur when protons are spatially close, the protons must be cis; the absence of interaction between these protons and H-1 indicates that the latter is on the other side of the cyclobutane, i.e., structure **3** is correct.

The structural and stereochemical assignment is buttressed by ancillary observations from the NOESY spectrum. The doublet at 7.49 ppm, the ortho protons of the aromatic group attached to C-1 (O_1 in Figure 1), shows polarization transfer to H-1, H-2, and H-4; the first of these is the result of a geminal interaction, while the others are vicinal (cis) interactions. Similarly, the doublet at 7.40 ppm, the ortho protons of the aromatic group attached to C-2 (O_2 in Figure 1), shows a geminal interaction with H-2 and a vicinal (cis) interaction with H-1. These observations show the aromatic rings to be trans to each other on the cyclobutane. The second COSY experiment, recorded to emphasize cross peaks arising from long-range couplings, showed a weak cross peak between the proton on C-4 and the low field *O*-methyl group. This peak indicates that the latter group is part of the carbomethoxy group attached to C-4. The higher field *O*-methyl group is therefore part of the carbomethoxy group on C-3. The upfield shift of this latter methyl group is probably caused by ring current shielding effects due to its position above the aromatic group at C-2.

The reassignment of the reported mixture as another head-to-head dimer of **1** shows that the regiochemical preference for this reaction path is greater than previously thought. There is no evidence of head-to-tail dimer formation.

Experimental Section

A solution of **1** in benzene was irradiated as described by Ishigami et al. and the mixture separated by column chromatography on silica gel. The observed chemical shifts and splitting patterns of the isolated photoproducts were in good agreement with values reported previously.[1]

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Supplementary Material Available: COSY spectrum of **3** (Figure 1) that shows coupling between cyclobutane protons and second COSY spectrum (Figure 2) optimized for detecting long-range couplings between ortho aromatic protons and H-1 and H-2 cyclobutane protons (4 pages). Ordering information is given on any current masthead page.

A Convenient Synthesis of 3,6-Disubstituted 3,6-Diazabicyclo[3.2.2]nonanes and 3,6-Diazabicyclo[3.2.1]octanes

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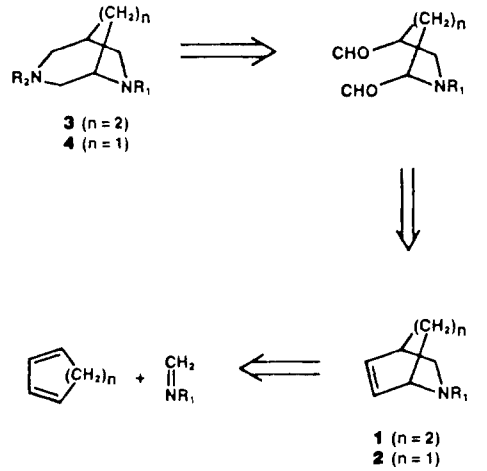
In connection with a project involving the synthesis of conformationally rigid ethylenediamine systems, we were interested in synthetic routes to 3,6-diazabicyclo[3.2.2]-nonanes (**3**) and 3,6-diazabicyclo[3.2.1]octanes (**4**). A literature search revealed that although the 3,6-diazabicyclo[3.3.1]nonane skeletal unit is present in some lupine alkaloids,[1] the simple bridged bicyclic systems **3** and **4** are unknown. We would like to describe a very convenient synthesis of these systems which allows for easy variation of the N-3 and N-6 substituents.

Retrosynthetically, 2-azabicyclo[2.2.2]oct-5-enes (**1**) and 2-azabicyclo[2.2.1]hept-5-enes (**2**) were regarded as convenient precursors to **3** and **4**, respectively, in which introduction of the 3-nitrogen of **3** and **4** could be accomplished by ozonolysis of the double bond to a dialdehyde and subsequent reductive amination.[2] The bridged, azabicyclic alkenes **1** and **2** could, in turn, be prepared by an aza Diels–Alder reaction.[3]



2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**1a**), prepared by condensing 1,3-cyclohexadiene and methylene bisurethane in the presence of boron trifluoride–etherate in benzene,[4] was chosen as the aza Diels–Alder adduct precursor to the 3,6-diazabicyclo[3.2.2]nonanes (**3**). In essentially a "one-pot" procedure, a methanolic solution of **1a** was ozonolyzed at −78 °C and, after TLC analysis indicated the disappearance of starting material, the ozonide was quenched with dimethyl sulfide. The mixture was warmed to 0 °C and was treated with excess benzylamine hydrochloride and 3-Å molecular sieves and, after 4 h of stirring, excess sodium cyanoborohydride.[5] The mixture was filtered and the evaporated filtrate was carefully acidified (*HCN evolution!*) with aqueous 1 N HCl solution to destroy any amine–borane complexes and unreacted sodium cyanoborohydride. Following basification of the mixture, extractive workup, and chromatographic purification, 3-benzyl-6-carbethoxy-3,6-diazabicyclo[3.2.2]nonane (**3a**) was obtained in 33% distilled yield. Analogously, the corresponding 3-methyl analogue, **3b**, was prepared in identical yield by using methylamine hydrochloride in

(1) (a) *Chemistry of the Alkaloids*; Pelletier, S. W.; Van Norstrand Reinhold Company, New York, 1970. (b) Ohimiya, S.; Higashiyama, K.; Otomasu, H.; Haginiwa, J.; Murakoshi, I. *Chem. Pharm. Bull.* **1979**, *27*, 1055. (c) Bordner, J.; Ohmiya, S.; Otomasu, H.; Haginiwa, J.; Marakoshi, I. *Chem. Pharm. Bull.* **1980**, *28*, 1965.

(2) During the course of our synthetic investigations, a similar ozonolysis–reductive amination strategy was reported for the synthesis of 7,8-dicarbomethoxy-8-oxa-3-azabicyclo[3.2.1]octane, see: Kawaguchi, M.; Ohashi, J.; Kawakami, Y.; Yamamoto, Y.; Oda, J. *Synthesis* **1985**, 701. More recently, these authors have prepared piperazines and thiomorpholines by the same method, see: Kawaguchi, K.; Hayashi, O.; Hamada, M.; Yamamoto, Y.; Oda, J. *Agric. Biol. Chem.* **1987**, *51*, 435.

(3) For an excellent review, see: Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949.

(4) (a) Cava, M. P.; Wilkins, C. K.; Dalton, D. R.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772. (b) Borne, R. F.; Clark, R.; Holbrook, J. *J. Med. Chem.* **1973**, *16*, 853.

(5) Excess amine hydrochloride (10 equiv) and sodium cyanoborohydride (2.5 equiv) were used routinely, and no attempt was made to perform the reaction with more stoichiometric amounts of reagents.

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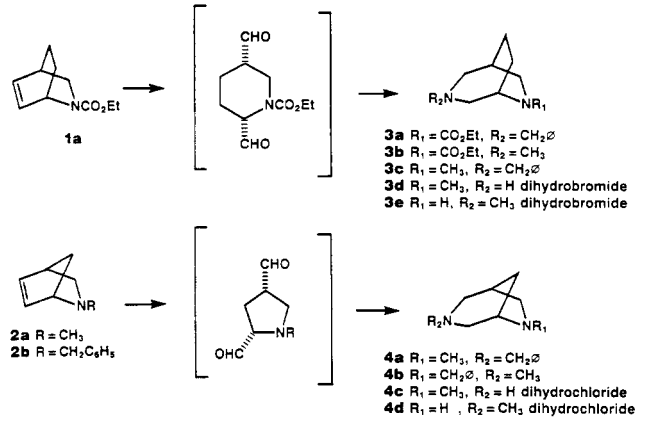
place of benzylamine hydrochloride in the reductive amination.

Several derivatives of **3a** and **3b** were also prepared. Lithium aluminum hydride reduction of the carbamate function of **3a** provided the 6-methyl derivative **3c**, which was subjected to catalytic hydrogenolysis in aqueous 1 N hydrochloric acid to remove the benzyl group, affording a hygroscopic dihydrochloride salt, which was converted to a more easily handled, nonhygroscopic dihydrobromide salt, **3d**. Additionally, hydrolysis of the carbamate group of **3b** in 33% hydrogen bromide solution in acetic acid at 70 °C gave the isomeric dihydrobromide salt **3e**.

For the synthesis of the 3,6-diazabicyclo[3.2.1]octanes (**4**), the potential bridged, bicyclic precursor, *N*-carbethoxy-2-azabicyclo[3.2.1]hept-5-ene, the homologue of **1a** used in the synthesis of the 3,6-diazabicyclo[3.2.2]octanes, could not be prepared because of the polymerization of cyclopentadiene under the conditions of the Lewis acid catalyzed aza Diels–Alder reaction.[6] We, therefore, chose the *N*-alkyl-2-azabicyclo[2.2.1]hept-5-enes **2a,b** as precursors, which were prepared very conveniently by the aqueous method of Grieco using cyclopentadiene, aqueous formaldehyde, and the amine hydrochloride.[7] Subjection of **2a** to the ozonolysis–reductive amination procedure described above, but as its hydrochloride salt to prevent oxidation of the nitrogen, led to a 40% yield of **4a** using benzylamine hydrochloride in the reductive amination. In the workup procedure, it was crucial to use more vigorous acidic conditions than those used in the cases of **3a** and **3b**, since **4a** contains two basic nitrogens and thus forms stronger amine–borane complexes. Conversion of the *N*-benzyl bridged, bicyclic alkene **2b** to **4b** was also accomplished but in poorer yield (18%). Crystalline dihydrochloride derivatives **4c** and **4d** were prepared by catalytic hydrogenolysis of **4a** and **4b**, respectively, in methanol containing hydrochloric acid.



In summary, the first synthesis of the 3,6-diazabicyclo[3.2.2]nonane (**3**) and 3,6-diazabicyclo[3.2.1]octane (**4**) frameworks has been accomplished by ozonolysis and subsequent reductive amination of 2-azabicyclo[2.2.2]-oct-5-ene **1a** and 2-azabicyclo[2.2.1]hept-5-enes **2a,b**, respectively. The modest overall yield of this transformation is compensated by the fact that it is performed essentially in a "one-pot" operation and that the precursors **1a**, **2a**, and **2b** can be conveniently prepared on a large scale in one step from readily available materials. In addition, these cis dialdehyde intermediates may serve as interesting precursors to functionalized pyrrolidine and piperidine derivatives (i.e., proline and homoproline).

Experimental Section

^{1}H NMR spectra were determined with a Varian T-60, Varian EM 390, Bruker WM-250, or Varian XL300 spectrometer. Chemical shifts are expressed in ppm relative to internal tetramethylsilane (60- and 90-MHz spectra), $CDCl_3$, or D_2O (250- and 300-MHz spectra). ^{13}C NMR spectra were determined at 75.429 MHz on a Varian XL-300 or at 62.84 MHz on a Bruker WM-250 spectrometer using the 77 ppm resonance of $CDCl_3$ as the internal standard. The ^{13}C chemical shifts in D_2O were not measured directly with an internal standard and the values may vary slightly depending upon the variability of the lock signal. Significant ^{1}H NMR data are tabulated in order (number of protons, multiplicity, coupling constant (Hertz)). Exact masses were determined on an A.E.I.-MS30 mass spectrometer. Elemental analyses were performed by the Pfizer Analytical Chemistry Department. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus.

Solvents were commercially available and used directly unless otherwise noted. Recrystallized sodium cyanoborohydride was purchased from Alfa. Ozonolyses were performed on a Welsbach ozinator. Solvents were removed with a rotary evaporator.

Flash chromatography was performed with 32–63-μm silica gel (Woelm) according to the method described by Still et al.[8] Analytical thin-layer chromatography (TLC) was performed on 250-μm, 2.5 × 10 cm silica gel plates (Analtech) using phosphomolybdic acid, potassium permanganate, or iodoplatinate for visualization.

2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (1a). Following the procedure of Cava,[4a] with the Borne modification,[4b] 50.0 g (0.32 mol) of methylene bisurethane and 31 mL (26.1 g, 0.33 mol) of 1,3-cyclohexadiene were condensed in 415 mL of benzene in the presence of 10.0 g (8.7 mL) of boron trifluoride–etherate to provide 25.0 g (43%) of 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene as a clear liquid, bp 74–75 °C (0.2 Torr) [lit.[4b] bp 130–134 °C (10 Torr)].

2-Methyl-2-azabicyclo[2.2.1]hept-5-ene (2a). Following the procedure of Grieco,[7] a mixture of 7.11 g (0.105 mol) of methylamine hydrochloride, 11.9 g (0.147 mol) of aqueous 37% formaldehyde solution, 13.9 g (0.211 mol) of cyclopentadiene, and 30 mL of water was stirred vigorously for 16 h at room temperature. The mixture was diluted with 50 mL of water, and the separated oil was removed by extraction with ether (4 × 30 mL). The aqueous layer was basified by the addition of 6 g of KOH pellets and the mixture was extracted with ether (4 × 30 mL). Drying of the combined extracts (K_2CO_3) and evaporation of the solvent afforded 6.29 g (55%) of 2-methyl-2-azabicyclo[2.2.1]hept-5-ene (**2a**) as an oil: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.3–1.7 (3 H, m), 2.19 (3 H, s), 2.94 (1 H, br s), 2.21 (1 H, dd, J = 9 and 3), 3.80 (1 H, br s), 6.0–6.5 (2 H, m).

2-Benzyl-2-azabicyclo[2.2.1]hept-5-ene (2b). Following the procedure of Grieco,[7] a mixture of 5.0 g (0.0348 mol) of benzylamine hydrochloride, 3.95 g (0.0487 mol) of aqueous 37% formaldehyde solution, 4.6 g (0.0696 mol) of cyclopentadiene, and 10 mL of water was stirred vigorously for 16 h at room temperature. The mixture was diluted with 20 mL of water, and the separated oil was removed by extraction with ether (2 × 20 mL). The aqueous layer was basified by the addition of 4 g of KOH pellets, and the turbid mixture was extracted with ether (3 × 25 mL). Drying (K_2CO_3) of the combined extracts and evaporation of the solvent afforded 6.69 g (theory = 6.38 g)[9] of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**2b**) as an oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.3–1.8 (3 H, m), 2.95 (s, 1 H), 3.3–3.1 (1 H, m), 3.49 (2 H, centroid of AB pattern, J = 14), 3.85 (1 H, s), 6.05–6.2 (m, 1 H), 6.35–6.5 (m, 1 H), 7.25–7.5 (5 H, m).

3-Benzyl-6-carbethoxy-3,6-diazabicyclo[3.2.2]nonane (3a). A stream of ozone was passed through a 1.2-L methanol solution of 40.0 g (0.22 mol) of 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**1a**) at −78 °C for 5.5 h. At this time, the reaction mixture became blue, and consumption of starting olefin was indicated by TLC (1:1 EtOAc/hexane). Nitrogen was bubbled through the mixture to remove excess ozone and then 100 mL of dimethyl sulfide was added dropwise before being allowed to warm slowly to 0 °C.

(6) Gaitanopoulos, D. E.; Weinstock, J. *J. Heterocycl. Chem.* **1985**, *22*, 957.
(7) Larson, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(9) The excess weight was due to trapped solvent, as indicated by NMR.

Following 4 h of additional stirring at 0 °C, 200 g (1.39 mol) of benzylamine hydrochloride and 200 g of activated 3-Å molecular sieves were added and the mixture was stirred mechanically for 4 h at room temperature under N_2. The mixture was then cooled to 0 °C and was treated with 200 mL of a methanolic solution of 69.8 g (1.11 mol) of sodium cyanoborohydride added dropwise over 40 min, and additional stirring was continued for 5 h at room temperature. The mixture was then filtered, and the insoluble material was washed well with methanol. The filtrate was concentrated to an oil, cooled to 0 °C, and carefully acidified (*HCN evolution!*)[10] with 500 mL of aqueous 1 N HCl solution with stirring. After the effervescence had ceased (4 h), sodium hydroxide pellets were added carefully at 0 °C until the mixture was basic (pH 13). The oil that had separated was removed in a separatory funnel and combined with 5 × 100-mL EtOAc extracts of the aqueous layer, which were then dried (K_2CO_3) and evaporated. Partial fractional distillation of the oil (60 °C, 2 Torr) to remove excess benzylamine and chromatography of the undistilled residue (63 g) on 290 g of silica gel using an EtOAc–hexane eluant (1:9 to 3:7) afforded 22.2 g of 3-benzyl-6-carbethoxy-3,6-diazabicyclo[3.2.2]nonane (**3a**) (R_f 0.65; EtOAc–hexane, 1:1) as an oil. The product was further purified by short-path distillation to provide 21.1 g (33%) of **3a** as a pale yellow oil, bp 166–168 °C (0.1 Torr): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.20 and 1.24 (3 H, 2 t, J = 7), 1.4–1.6 (1 H, m), 3.55 and 3.56 (3 H, 2 s), 4.12 and 4.13 (2 H, 2 q, J = 7), 7.2–7.4 (5 H, m); IR ($CHCl_3$) 1673 cm^{-1}; MS, m/e 288 (M^+), 245, 197, 134, 91.

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.41; H, 8.20; N, 9.66.

6-Carbethoxy-3-methyl-3,6-diazabicyclo[3.2.2]nonane (3b). Following the same procedure used for the synthesis of 3-benzyl-6-carbethoxy-3,6-diazabicyclo[3.2.2]nonane, 10 g (0.55 mol) of 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**1a**) was ozonolyzed and subjected to reductive amination using 37.3 g (0.552 mol) of methylamine hydrochloride and 17.3 g (0.276 mol) of sodium cyanoborohydride in the presence of 38 g of activated 3-Å molecular sieves. After workup, the crude reaction mixture (13.2 g) was purified by silica gel chromatography (10-cm height, 12-cm diameter) using 5% MeOH/$CHCl_3$ as eluant to provide 3.89 g (33%) of 6-carbethoxy-3-methyl-3,6-diazabicyclo[3.2.2]nonane (**3b**) as a pale yellow oil (R_f 0.31, 5% MeOH/$CHCl_3$): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 and 1.18 (3 H, 2 t, J = 7), 1.37–1.50 (1 H, m), 2.205 and 2.21 (3 H, 2 s), 2.73–2.93 (2 H, m), 3.15–3.27 (1 H, m), 4.05 (2 H, q, J = 7); IR ($CHCl_3$) 1672 cm^{-1}. The analytical sample was obtained on the hydrobromide salt, which was prepared by dissolving 817 mg of **3b** in 1.5 mL of solution of 33% HBr in acetic acid and crystallization from ether after removal of the solvent, mp 194–197 °C.

Anal. Calcd for $C_{11}H_{21}BrN_2O_2$: C, 45.06; H, 7.22; N, 9.55. Found: C, 44.79; H, 7.06; N, 9.33.

3-Benzyl-6-methyl-3,6-diazabicyclo[3.2.2]nonane (3c). To a suspension of 6.32 g (0.167 mol) of lithium aluminum hydride in 1.5 L of ether was added dropwise over 45 min a 200-mL ether solution of 20.96 g (0.73 mol) of 3-benzyl-6-carbethoxy-3,6-diazabicyclo[3.2.2]nonane (**3a**). After a gentle reflux period of 2 h, the mixture was chilled to 0 °C and carefully quenched by the sequential addition of 6.32 mL of water, 6.32 mL of aqueous 15% aqueous NaOH solution, and 19.0 mL of water. The salts were removed by filtration and were washed well with ether. The filtrate was dried (K_2CO_3) and evaporated to a clear oil, which was distilled to provide 15.13 g (90%) of 3-benzyl-6-methyl-3,6-diazabicyclo[3.2.2]nonane (**3c**) as a clear liquid, bp 120–122 °C (0.1 Torr): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.5–1.7 (1 H, m), 1.8–2.0 (3 H, m), 2.4 (3 H, s), 3.55 (2 H, centroid of AB pattern, J = 15), 7.2–7.4 (5 H, m); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 22.7, 24.7, 31.8, 44.1, 57.2, 57.4, 58.1, 62.1, 62.5, 126.8, 128.2, 140.0.

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.42; H, 9.59; N, 12.08.

6-Methyl-3,6-diazabicyclo[3.2.2]nonane Dihydrobromide (3d). A 330-mL 1 N HCl solution of 15.13 g (0.066 mol) of 3-benzyl-6-methyl-3,6-diazabicyclo[3.2.2]nonane (**3c**) was hydrogenated at 30 psi in the presence of 2.6 g of 10% Pd/C for 3 h. After filtration of the catalyst and concentration of the filtrate, the oily residue was stirred for 2 h in a 1-L methanol (containing a little water) suspension of 250 g of Amberlite CG-400II ion-exchange resin (Fluka), which was prewashed sequentially with water, aqueous 1 N NaOH solution, water, and methanol. The resin was then filtered and washed well with methanol, and the filtrate was acidified with 140 mL of aqueous 48% HBr solution. The solvent was removed and the residue was crystallized from isopropyl alcohol to yield 14.89 g (75%) of 6-methyl-3,6-diazabicyclo[3.2.2]nonane dihydrobromide (**3d**) as a white solid, mp 295–300 °C (dec): ^{1}H NMR (D_2O, 300 MHz) δ 1.95–2.25 (3 H, m), 2.35–2.54 (1 H, m), 2.60–2.72 (1 H, m), 2.03 (3 H, s) 3.40–4.07 (7 H, m); ^{13}C NMR (D_2O, 75 MHz) δ 18.3, 28.0, 43.3, 52.5, 56.9, 57.5.

Anal. Calcd for $C_8H_{18}N_2Br_2$: C, 31.81; H, 6.01; N, 9.27. Found: C, 31.72; H, 5.89; N, 9.23.

3-Methyl-3,6-diazabicyclo[3.2.2]nonane Dihydrobromide (3e). A mixture of 852 mg of 6-carbethoxy-3-methyl-3,6-diazabicyclo[3.2.2]nonane (**3b**) and 15 mL of 33% HBr solution in acetic acid was heated to 70 °C for 4 h. Evaporation of the solvent and trituration of the solid residue in 2-propanol afforded 951 mg (78%) of 3-methyl-3,6-diazabicyclo[3.2.2]nonane (**3e**) as a fluffy, tan solid, mp 297–300 °C: ^{1}H NMR (250 MHz, D_2O) δ 2.02 (4 H, m), 2.58–2.68 (1 H, m), 3.04 (3 H, s), 3.45–3.75 (4 H, m), 3.85–4.15 (3 H, m); ^{13}C NMR (63 MHz, D_2O) δ 18.5, 19.6, 27.2, 45.1, 45.9, 48.0, 58.4, 62.7.

Anal. Calcd for $C_8H_{18}N_2Br_2$: C, 31.81; H, 6.01; N, 9.27. Found: C, 31.46; H, 5.82; N, 9.11.

3-Benzyl-6-methyl-3,6-diazabicyclo[3.2.1]octane (4a). A solution of 5.07 g (46.4 mmol) of 2-methyl-2-azabicyclo[2.2.1]-hept-5-ene (**2a**) in 30 mL of dioxane was treated with 20 mL of a 4.5 N solution of hydrogen chloride in dioxane. After removal of the solvent, the residue was dissolved in 100 mL of methanol, and the mixture was ozonolyzed at −78 °C until a blue color persisted. At this time, 14 mL (11.8 g, 190 mmol) of dimethyl sulfide was added, and the mixture was allowed to warm slowly to 0 °C. The mixture was transferred to a three-neck flask equipped with a mechanical stirring apparatus and 66.6 g (464 mmol) of benzylamine hydrochloride and 50 g of activated 3-Å molecular sieves were added at 0 °C. The suspension was stirred for 16 h, as the ice bath was allowed to melt, and then was rechilled to 0 °C before being treated with 14.6 g (232 mmol) of solid sodium cyanoborohydride. Following a slow warming to room temperature over a 4.5-h period, the insoluble material was removed by filtration, and the filtrate was evaporated. The residue was diluted with 150 mL of water and was carefully acidified by the dropwise addition of 200 mL of aqueous 6 N HCl solution (*HCN evolution!*),[10] and the resulting mixture was stirred for 16 h at room temperature before being carefully basified (pH 14) with NaOH pellets. The mixture was extracted with EtOAc (4 × 200 mL), and the extracts were dried (K_2CO_3), evaporated, and the excess benzylamine was removed by partial fractional distillation under high vacuum. Purification of the undistilled residue by chromatography (7-cm diameter, 16-cm height) using $CHCl_3$/MeOH/concentrated aqueous NH_4OH (89:10:1) as eluant and then by distillation [bp 105–106 °C (0.5 Torr)] afforded 4.00 g (40%) of 3-benzyl-6-methyl-3,6-diazabicyclo[3.2.1]octane (**4a**) as a pale yellow oil (R_f 0.1; 89:10:1 $CHCl_3$/MeOH/concentrated aqueous NH_4OH): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.44 (1 H, d, J = 10), 1.9–2.0 (1 H, m), 2.10 (2 H, d, J = 8), 2.2–2.3 (1 H, m), 2.41 (3 H, s), 2.70 (2 H, d, J = 10), 2.9–3.1 (3 H, m), 3.50 (2 H, centroid of AB q, J = 12), 7.15–7.35 (5 H, m); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 35.4, 36.8, 37.7, 54.9, 57.7, 58.3, 58.7, 62.3, 126.8, 128.0, 128.8, 138.8; HRMS, found 216.1628, calcd for $C_{14}H_{20}O_2$ 216.1641.

6-Benzyl-3-methyl-3,6-diazabicyclo[3.2.1]octane (4b). Following the same procedure for the synthesis of **4a**, 8.44 g (45.6 mmol) of *N*-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**2b**) was ozonolyzed as its hydrochloride salt and, following reduction of the ozonide, the crude dialdehyde was subjected to reductive amination using 30.8 g (456 mmol) of methylamine hydrochloride and 14.3 g (228 mmol) of sodium cyanoborohydride. After workup, the crude product was purified by chromatography (7-cm diameter, 15-cm height) using 94:5:1 to 89:10:1 $CHCl_3$/MeOH/concentrated aqueous NH_3 as eluant and then by distillation [bp 104–107 °C (0.5 Torr)] to provide 1.77 g (18%) of 6-benzyl-3-methyl-3,6-diazabicyclo[3.2.1]octane (**4b**) (R_f 0.15; 89:10:1 $CHCl_3$/MeOH/concentrated aqueous NH_3) as a pale yellow oil:

(10) The hydrogen cyanide gas was bubbled directly into a trap containing KOH and Chlorox.

^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (1 H, d, J = 9), 1.92 (2 H, d, J = 11), 2.10 (1 H, d, J = 9), 2.28 (3 H, s), 3.88 (2 H, centroid of AB q, J = 13) 7.1–7.7 (5 H, m); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 35.0, 35.4, 45.4, 57.0, 57.1, 58.4, 60.8, 126.6, 128.1, 128.5, 140.0; HRMS, found 216.1588, calcd for $C_{14}H_{20}N_2$ 216.1626.

6-Methyl-3,6-diazabicyclo[3.2.1]octane Dihydrochloride (4c). A mixture of 3.00 g of 3-benzyl-6-methyl-3,6-diazabicyclo[3.2.1]octane (**4a**), 75 mL of methanol, and 5 mL of concentrated aqueous hydrochloric acid was hydrogenated at 50 psi in the presence of 1 g of 10% Pd/C for 7 h. The catalyst was removed by filtration and the filtrate was evaporated to a solid which was triturated in *i*-PrOH and ether to afford 2.43 g (88%) of 6-methyl-3,6-diazabicyclo[3.2.1]octane dihydrochloride (**4c**), mp 266–269 °C: ^{1}H NMR (D_2O, 300 MHz) δ 2.22 (1 H, d, J = 13), 2.3–2.5 (1 H, m), 3.06 (3 H, s), 3.45 (1 H, s), 3.53 (1 H, d, J = 13), 3.77 (1 H, d, J = 13), 4.18 (1 H, s); ^{13}C NMR (D_2O + NaOD,[11] 63 MHz) δ 35.1, 37.0, 41.3, 48.4, 50.4, 58.3; 61.0; HRMS, found 126.1162, calcd for $C_7H_{14}N_2$ 126.1157.

3-Methyl-3,6-diazabicyclo[3.2.1]octane Dihydrochloride (4d). Following the same procedure for the synthesis of **4c**, 1.01 g of 6-benzyl-3-methyl-3,6-diazabicyclo[3.2.1]octane (**4b**) was hydrogenated to provide 0.78 g (84%) of 3-methyl-3,6-diazabicyclo[3.2.1]octane dihydrochloride (**4d**), mp 259–261 °C: ^{1}H NMR (D_2O, 250 MHz) δ 2.05–2.2 (1 H, m), 2.28 (1 H, d, J = 13), 2.98 (3 H, s), 3.04 (1 H, s), 3.35–3.8 (5 H, m), 3.88 (1 H, d, J = 13), 4.38 (1 H, s); ^{13}C NMR (D_2O, 63 MHz) δ 33.0, 33.6, 44.8, 48.2, 55.0, 55.5, 58.6.

Anal. Calcd for $C_7H_{14}N_4 \cdot 2HCl \cdot 0.5\ H_2O$: C, 40.40; H, 8.23; N, 13.46. Found: C, 40.20, H, 7.89; N, 13.32.

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Registry No. 1, 3693-69-4; **2a**, 95019-15-1; **2b**, 112375-05-0; **3a**, 112375-06-1; **3b**, 112375-07-2; **3c**, 112375-08-3; **3d**, 112375-09-4; **3e**, 112375-10-7; **4a**, 112375-11-8; **4b**, 112375-12-9; **4c**, 112375-13-0; **4d**, 112375-14-1; methylene bisurethane, 3693-53-6; 1,3-cyclohexadiene, 592-57-4; methylamine, 74-89-5; cyclopentadiene, 542-92-7; benzylamine hydrochloride, 3287-99-8.

(11) The ^{13}C NMR of the dihydrochloride salt was poorly resolved due to the equilibrium between the various protonated species. A resolved spectrum was obtained on the free diamine by in situ neutralization with NaOD.

Synthesis and Evidence for the Stability of a Glycerophosphochloridate: *rac*-1-*O*-Hexadecyl-2-*O*-(methylcarbamyl)-*sn*-glycero-3-phosphorochloridocholine

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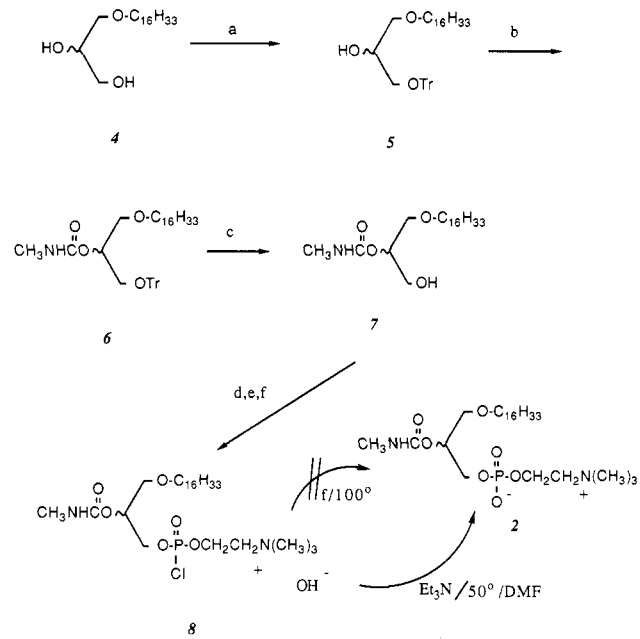
The carbamyl moiety has been reported[1] to be resistant to phospholipase hydrolysis. As part of our ongoing study[2]

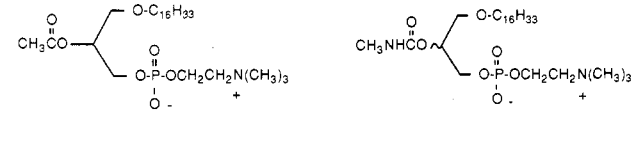
(1) Gupta, C. M.; Bali, A. *Biochim. Biophys. Acta* **1981**, *663*, 506.

Scheme I[a]



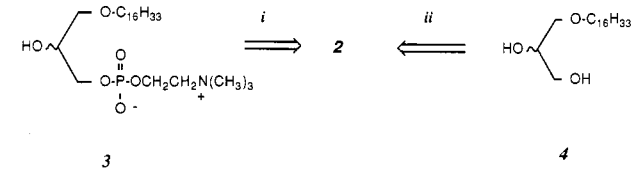
[a] (a) TrCl/hexanes/reflux; (b) CH_3NCO/DMAP/CH_2Cl_2; (c) $BF_3 \cdot 2MeOH/CH_2Cl_2$; (d) $POCl_3/CHCl_3/Et_3N$; (e) C_5H_5N/choline tosylate; (f) H_2O.

of the diverse properties of alkylglycerolipids such as platelet-activating factor **1** (PAF), the 2-methylcarbamyl analogue **2** was envisioned as meeting the strict size re-



quirements[2a-c,3] for activity imposed on moieties at the glycerol *sn*-2 position.[4] It also has the potential to be a biologically nonhydrolyzable PAF analogue, since analogue **2** might prove to be stable to hydrolysis by the acetylhydrolase[5] that degrades PAF.

Two synthetic routes to the desired methylcarbamyl analogue **2** are (i) directly from the lyso phospholipid **3** and (ii) de novo from chimyl alcohol **4**. Reaction of the lyso



phospholipid with methyl isocyanate[1,6] initially resulted

(2) (a) Wykle, R. L.; Miller, C. H.; Lewis, J. C.; Schmitt, J. D.; Smith, J. A.; Surles, J. R.; Piantadosi, C.; O'Flaherty, J. T. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 1651. (b) Wykle, R. L.; Surles, J. R.; Piantadosi, C.; Salzer, W. L.; O'Flaherty, J. T. *FEBS Lett.* **1982**, *141*, 29. (c) Blank, M. L.; Cress, E. A.; Lee, T.-C.; Malone, B.; Surles, J. R.; Piantadosi, C.; Hajdu, J.; Snyder, F. *Res. Commun. Chem. Pathol. Pharmacol.* **1982**, *38*, 3. (d) Surles, J. R.; Wykle, R. L.; O'Flaherty, J. T.; Salzer, W. L.; Thomas, M. J.; Snyder, F.; Piantadosi, C. *J. Med. Chem.* **1985**, *28*, 73. (e) O'Flaherty, J. T.; Surles, J. R.; Redman, J.; Jacobson, D.; Piantadosi, C.; Wykle, R. L. *J. Clin. Invest.* **1986**, *78*, 381. (f) For a report on receptor binding and biological stability studies: O'Flaherty, J. T.; Redman, J. F., Jr.; Schmitt, J. D.; Ellis, J. M.; Surles, J. R.; Marx, M. H.; Piantadosi, C.; Wykle, R. L. *Biochem. Biophys. Res. Commun.* **1987**, *147* (1), 18.

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(5) Blank, M. L.; Lee, T.-C.; Fitzgerald, V.; Snyder, F. *J. Biol. Chem.* **1981**, *256*, 175.

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