Table II. Crystal Data for Tetrafluoroaryl Azide 15

formula	$C_{23}H_{23}F_4N_3O_3S$
crystal system	$P\bar{1}$
space group	centric
a, Å	7.808 (2)
b, Å	9.611 (2)
c, Å	14.940 (3)
α, deg	104.925 (6)
β, deg	91.860 (6)
γ, deg	102.797 (5)
V, Å^3	1051.6 (8)
Z	2
density calcd, g/cm^3	1.539 g/cm^3
crystallizing solvent	ethyl acetate
crystal habit	prismatic (yellow)
crystal dimensions, mm	0.2 × 0.2 × 0.3
μ, cm^{-1}	2.11
transmission factor range	not applied
extinction	not applied
2θ limit, deg (octants)	46 ($+h\pm k\pm l$)
intensities (unique, R_i)	3285 (2397, 0.038)
intensities > $2.58\sigma(I)$	1690
R	0.046
R_w[for $w = 1/\sigma^2(F_o) + pF\sigma^2$]	0.053 (p = 0.010)
max density in ΔF map, e/Å^3	0.19

MS (EI) m/z 389 (M$^+$, 100), 374 (18), 297 (8), 195 (10), 120 (55), 92 (22); HRMS (EI) M$^+$ calcd for $C_{23}H_{19}NO_3S$ 389.1086, found 389.1095.

X-ray Crystallography. Crystals of **15** were obtained from ethyl acetate at room temperature. Diffraction data were measured at room temperature using a Syntex $P2_1$ diffractometer equipped with monochromated Mo radiation [λ (Kα) = 0.71073 Å]. Final cell dimensions were obtained by a least-squares fit to the automatically centered settings for at least 15 reflections. Three reference reflections monitored during the experiment showed no significant variation. Intensity data were corrected for Lorentz-polarization effects. Crystal data are listed in Table II. The average values of the normalized structure factors for **15** suggested a centric space group; this was confirmed by successful refinement.

The structure was solved by direct methods (SHELXS-86);[47] correct positions for all non-hydrogen atoms were deduced from an E map. Difference Fourier electron density maps gave positions for the hydrogen atoms; due to paucity of data, hydrogens were included as fixed contributors in idealized positions. In the final least-squares refinement cycle, anisotropic thermal coefficients were varied for non-hydrogen atoms and a common isotropic thermal parameter was varied for the hydrogens. The final difference Fourier map had no significant features. Atomic scattering factors, mass attenuation coefficients, and anomalous dispersion corrections were taken from ref 48.

Acknowledgment. We are grateful for support of this research through a grant from the National Institutes of Health (PHS RO1 DK15556). High-field NMR spectra and high-resolution mass spectra were obtained on instruments supported by grants from the National Institutes of Health (1531957 and GM27029) and the National Science Foundation (CHE 85-14500). We are indebted to Professor M. S. Platz (Ohio State University), Dr. G. M. Anstead, and Professor G. B. Schuster for many helpful discussions and insightful advice. We are especially thankful to D. J. Katzenellenbogen, M. Creiger, and L. Jablonski for technical assistance with various aspects of this project. We also thank K. E. Carlson for performing the estrogen receptor binding and photoinactivation assays and R. Srinivasan for valuable assistance with computational techniques.

Supplementary Material Available: Atomic numbering scheme for **15**, tables of atomic coordinates, thermal parameters, bond distances, and bond angles, and ^{1}H NMR spectra for compounds **8**, **2**, **21**, **22** (11 pages). Ordering information is given on any current masthead page.

(47) Sheldrick, G. M. SHELXS-86. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., and Goddard, R., Eds.; Oxford University Press: Oxford, 1985; pp 175-189.
(48) Ibers, J. A., Hamilton, W. C., Eds. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.

trans-3,4-Diaminopiperidines. Azacyclohexane Congeners of κ Agonist U-50488

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A variety of *trans*-3,4-diaminopiperidines were synthesized regio- and stereoselectively from 1-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine. These compounds are structurally related to the selective κ agonist U-50488. The two key reactions which determine the stereo- and regiochemistry of the final products involve the S_N2 ring opening of an epoxide and an aziridinium species. Reaction of secondary amines with epoxide **3** led to ca. 1.5:1 mixtures of amino alcohols **4** and **5**, while S_N2 attack by methylamine on aziridinium intermediate **6** occurs diastereoselectively at C-4 to give diamines **7**. Depending upon the isolation procedure, trimethylsilyl iodide cleavage of the carbobenzyloxy group in compounds **8** and **9** provides either *N*-benzyl compounds **12** and **13** or the unsubstituted piperidines **10** and **11**.

The replacement of carbon by a heteroatom in a drug template is a common strategy in medicinal chemistry. In our continuing efforts to elucidate the SAR of the unique κ opiate agonist U-50488,[1] we desired a variety of 4-aza analogs. If any of these compounds retained the desired analgesic activity and selectivity, they could provide access to a number of bis-ligands by attachment of an appropriate

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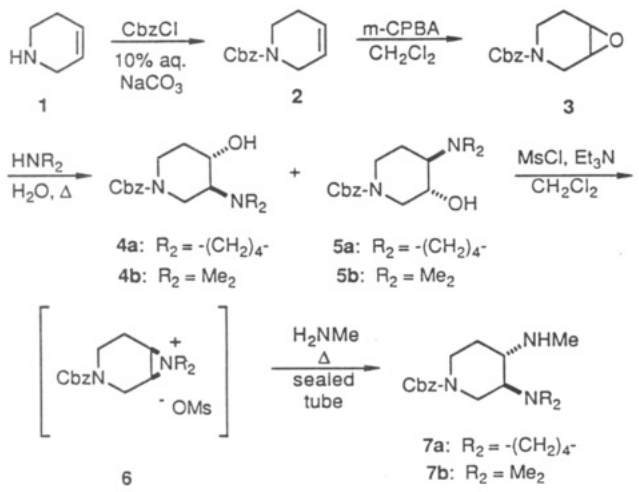
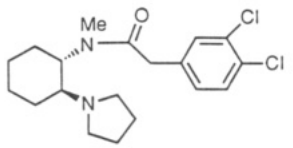
(1) Szmuszkovicz, J.; VonVoigtlander, P. F. *J. Med. Chem.* **1982**, *25*, 1125.

0022-3263/91/1956-3133$02.50/0

Scheme I



spacer to the piperidine nitrogen. With this general strategy in mind, we embarked on a synthesis of these 3,4-*trans*-diaminopiperidines.



U-50488

Results and Discussion

Commercially available 1,2,3,6-tetrahydropyridine (**1**) was protected as its carbobenzyloxy derivative **2** in quantitative yield. Treatment of **2** with *m*-CPBA gave epoxide **3** (92%) as a relatively stable oil.[2] Ring opening of **3** with pyrrolidine or dimethylamine led to mixtures of amino alcohols **4a**/**5a** and **4b**/**5b**, respectively. This lack of regioselectivity in the ring opening of epoxide **3** was inconsequential, because mesylation of the mixtures of aminoalcohols followed by ring opening of the aziridinium intermediates (**6**) by methylamine occurred regioselectively to give just one diastereoisomer (Scheme I). Diamines **7a** and **7b** were obtained in 97% and 90% yield, respectively. The structural assignments were confirmed by single crystal X-ray analysis of benzamide **8b** (vide infra).

Mechanistically these reactions bear some relation to the ring opening of cyclohexane and pyranose[3] epoxides with a few added complications. Piperidines typically exist predominantly in chair forms with the sterically undemanding lone pair in an axial position. In agreement with this, the structure of compound **8b** as determined by single-crystal X-ray crystallography clearly shows all three ring substituents in an equatorial or pseudoequatorial position. Since a N atom freely undergoes pyramidal inversion, a substituent can exchange rapidly between axial and equatorial positions. The inversion at nitrogen is usually faster than ring inversion.[4] But assuming some analogy with cyclohexane epoxides, piperidine epoxide **3** and aziridinium intermediate **6** might be expected to follow the Fürst–Plattner rule and ring open in a diaxial fashion via a chairlike transition state.[5] Since the carbobenzyloxy

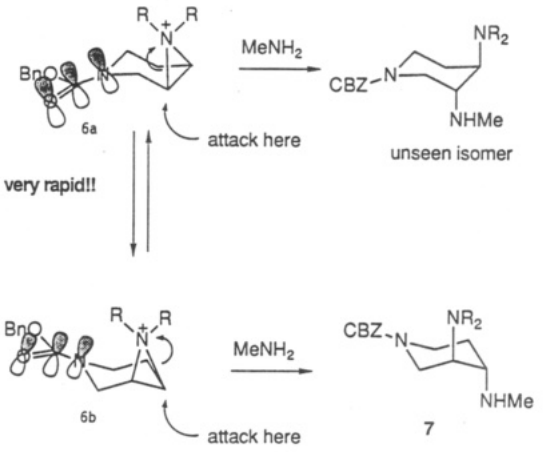
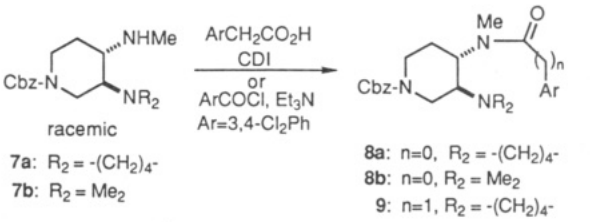


Figure 1.

group can adopt a pseudoequatorial position[6] in both aziridinium intermediates **6a** and **6b** also no diastereoselectivity was anticipated. The contrast in the behavior of the epoxides and aziridinium salts suggests that there must be other factors that are operating in hetero cyclohexanes.

In some cases remote polar functionality can have a profound effect on the regioselectivity of epoxide ring-opening. For instance, the ring opening of *cis*- and *trans*-4-(benzyloxy)-1,2-epoxycyclohexane have been studied in detail.[7] The cis epoxide, being capable of chelation to Lewis acids, can be selectively opened in either direction depending on the conditions. However, the reactions in the present study were carried out under nonchelating conditions.

The 3,4-dichlorobenzamide and 3,4-dichlorophenylacetamide derivatives of trans diamines **7a** and **7b** were prepared in good yields according to standard procedures (eq 1). Our first attempt to remove the carbobenzyloxy



(1)

group of compound **8a** using TMSI under the conditions shown in eq 2 led to the isolation of the *N*-benzyl compound **12**. A closer look at this reaction revealed that the product obtained immediately after extractive isolation (saturated aqueous Na_2CO_3, CH_2Cl_2) was a mixture of compounds **8a**, **12**, and benzyl iodide (formed in situ during the TMSI deprotection).[8] We conclude that exposure of the crude reaction mixture to aqueous base resulted in some alkylation of the piperidine nitrogen by the benzyl iodide. This alkylation does not occur prior to the aqueous base treatment presumably because the piperidine nitrogen

(2) Compounds **2** and **3** have been prepared previously: Paioni, R.; Waldmeier, P. C.; Delini-Stula, A. *Drugs Future* **1987**, *12*, 126.

(3) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5467.

(4) Johnson, C. D. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J.; McKillop, A., Eds.; Pergamon Press: New York, 1984; Vol. 2, p 99.

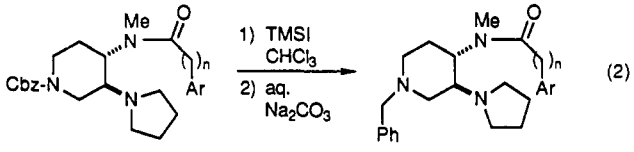
(5) Buchanan, J. G.; Sable, H. I. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 1, p 1.

(6) For a discussion of conformational aspects of piperidines see: Crabb, T. A.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1984**, *36*, 1. Ridell, F. G. *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: London 1980; Chapter 5.

(7) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1990**, *55*, 4265.

(8) For the mechanism of cleavage of N-carbobenzyloxy groups by HI and similar reagents see: (a) Ben-Ishai, D.; Berger, A. *J. Org. Chem.* **1952**, *17*, 1564. (b) Homer, R. B.; Moodie, R. B.; Rydon, H. N. *J. Chem. Soc.* **1965**, 4403. (c) Blaha, K.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1965**, *30*, 585.

is protected as its (trimethylsilyl)carbamate.[9] Piperidine **9** behaved similarly when treated with TMSI using this "basic" isolation procedure to give **13** (eq 2).

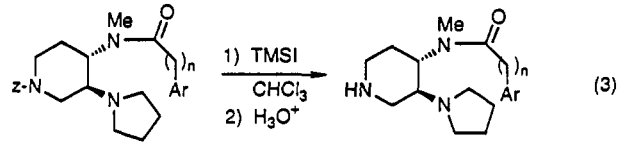


(2)

8a: n=0
9: n=1

12: n=0
13: n=1

Alternatively, when the crude cleavage products were promptly isolated by extraction into aqueous acid followed by neutralization and reextraction into methylene chloride, the "free", unalkylated piperidines **10** and **11** were obtained (eq 3). By using aqueous acid in the isolation procedure the free piperidine once formed is protonated thus preventing alkylation by benzyl iodide.



(3)

8a: n=0
9: n=1

10: n=0
11: n=1

Preliminary in vivo and in vitro testing of compounds **7**, **8a**, and **9–13** showed that they were only weak analgesics. These results did not warrant the continuation of this project into the area of bis-ligands.

Experimental Section

The following chemicals were obtained from commercial sources and were used without further purification: 1,2,3,6-tetrahydropyridine, benzyl chloroformate, trimethylsilyl iodide, pyrrolidine, 3-chloroperoxybenzoic acid, methanesulfonyl chloride, triethylamine, methylamine, 3,4-dichlorobenzoyl chloride, 1,1'-carbonyldiimidazole, 3,4-dichlorophenylacetic acid (Aldrich), diethyl ether (Fisher, reagent ACS, anhydrous), methylene chloride (Fisher, certified ACS). Tetrahydrofuran (Fisher, certified) was purified by refluxing over sodium benzophenone ketyl under nitrogen followed by distillation. Chloroform (Fisher, certified ACS) was purified just prior to use by washing with water followed by distillation from P_2O_5.

All reactions were carried out under a nitrogen atmosphere; "standard workup" refers to drying over $MgSO_4$, filtering, and concentrating.

1-(Carbobenzyloxy)-1,2,3,6-tetrahydropyridine (2).[2] 1,2,3,6-Tetrahydropyridine (4.17 g, 50.0 mmol) was combined with 10% aqueous Na_2CO_3 (3 mL) and cooled to 0 °C. Benzyl chloroformate (8.53 g, 50.0 mmol) was added dropwise over a 1-h period. The resulting yellow suspension was stirred for 2 h at 0 °C. The reaction mixture was then diluted with 100 mL of brine and extracted several times with ether. Standard workup afforded 10.8 g (99%) of **2** as a colorless oil: ^{1}H NMR (200 MHz) δ 2.16 (broad s, 2 H), 3.55 (t, J = 8, 2 H), 3.94 (m, 2 H), 5.13 (s, 2 H), 5.60 (m, 1 H), 5.81 (m, 1 H), 7.34 (s, 5 H); IR (film) 1700 (CO) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1104.

1-(Carbobenzyloxy)-3,4-epoxypiperidine (3).[2] To a cooled (0 °C) solution of 1-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine (**2**) (0.70 g, 3.2 mmol) in 10 mL of CH_2Cl_2 was added *m*-CPBA (0.77 g, 4.5 mmol) dissolved in 20 mL of CH_2Cl_2. The colorless reaction mixture was allowed to warm to room temperature while stirring. After 4 h, the reaction mixture was washed with 5% aqueous K_2CO_3 (3×) and brine. Standard workup provided 0.69 g (92%) of **3** as a colorless oil: ^{1}H NMR (200 MHz) δ 1.9 (broad m, 2 H), 3.25 (m, 2 H), 3.5 (m, 1 H), 3.6–4.0 (m, 3 H), 5.1 (s, 2 H), 7.3 (s, 5 H); IR (film) 1700 (CO) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1043.

(9) Sakaitani, M.; Ohfuney, Y. *J. Org. Chem.* **1990**, *55*, 870.

1-(Carbobenzyloxy)-*trans*-4-pyrrolidinyl-3-hydroxypiperidine (5a) and 1-(Carbobenzyloxy)-*trans*-3-pyrrolidinyl-4-hydroxypiperidine (4a). A solution of **3** (8.16 g, 35.0 mmol) and pyrrolidine (7.47 g, 105 mmol) in 6 mL of water was heated at 90 °C for 8 h. The cooled reaction mixture was diluted with 150 mL of ether and then washed with saturated aqueous Na_2CO_3 (2 × 60 mL) and brine (1 × 60 mL). Standard workup gave 10.5 (98%) of **4a** and **5a** (~2:1 mixture of diastereoisomers as estimated by ^{1}H NMR; the exact identity of the major and minor isomers remains uncertain) as a yellow oil. These diastereoisomers could not be separated by preparative TLC: ^{1}H NMR (300 MHz, 100 °C in DMSO-d_6 (mixture of **4a** and **5a**) δ 1.38 (m, 1 H), 1.65 (m, 4 H), 1.84 (m, 2 H), 2.177, 2.40, 2.59, 2.64 (series of m, total of 4 H), 3.07 (m, 1 H), 3.28–3.78 (m, 5 H), 5.06 (s, 2 H, CH_2Ph), 7.34 (m, 5 H, ArH); IR (film) 3450 (OH), 1700 (CO) cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}N_2O_3$ 304.1787, found 304.1787.

1-(Carbobenzyloxy)-4-(dimethylamino)-3-hydroxypiperidine (5b) and 1-(Carbobenzyloxy)-3-(dimethylamino)-4-hydroxypiperidine (4b). 1-(Carbobenzyloxy)-3,4-epoxypiperidine (**3**) (3.5 g, 15 mmol) was combined with 40% aqueous dimethylamine (25 mL) and heated to 50 °C for 5 h. The cooled reaction mixture was diluted with 100 mL saturated aqueous Na_2CO_3. This aqueous solution was saturated with solid NaCl and then extracted repeatedly with ether. Standard workup provided 3.3 g (78%) of regioisomers **5b** and **4b**. Integration of the ^{1}H NMR indicated that the regioisomers were obtained in a ratio of 1.5:1. The two isomers were separable by column chromatography (silica gel; $CHCl_3$/MeOH/NH_4OH, 94:5:1). Based on routine analysis of the ^{1}H NMR of the two fractions, it was not possible to determine which of the two regioisomers, **5b** or **4b**, was the major or minor isomer:

Major isomer: ^{1}H NMR (200 MHz) δ 1.49 (m, 1 H, CH), 2.04 (m, 1 H, CH), 2.34 (s, 6 H, N(CH_3)$_2$), 2.69 (m, 2 H, CH_2), 3.52 (dt, J = 4, 10, 1 H, CH), 4.20 (broad m, 2 H, 2 CH), 5.12 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, ArH); IR (film) 3450 (broad, OH), 1700 (CO) cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}N_2O_3$ 278.1630, found 278.1624.

Minor isomer: ^{1}H NMR (200 MHz) δ 1.40 (m, 1 H, CH), 1.72 (broad d, J = 12, 1 H, CH), 2.27 (s, 6 H, N(CH_3)$_2$), 2.30 (m, 1 H, CH), 2.65 (m, 2 H, CH_2), 3.40 (m, 1 H, CH), 4.31 (broad m, 1 H, CH), 4.48 (broad m, 1 H, CH), 5.13 (s, 2 H, CH_2Ph), 7.35 (s, 5 H, ArH); IR (film) 3450 (broad, OH), 1690 (CO) cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{23}N_2O_3$ 279.1709, found 279.1714.

1-(Carbobenzyloxy)-*trans*-4-(methylamino)-3-pyrrolidinylpiperidine (7a). To a cooled (0 °C) solution of amino alcohols **4a** and **5a** (9.79 g, 32.2 mmol) and triethylamine (3.58 g, 35.4 mmol) in 150 mL of CH_2Cl_2 was added methanesulfonyl chloride (4.06 g, 35.4 mmol) dropwise. The reaction mixture was stirred for 15 min at 0 °C and for 2 h at room temperature. The solvent was removed by rotary evaporation, and 70 mL of cold (–78 °C), anhydrous methylamine was added. The resultant solution was transferred to a pressure reactor and heated (70 °C external) for 18 h. The cooled reaction mixture was dissolved in 150 mL of CH_2Cl_2 and washed with saturated aqueous Na_2CO_3 (2 × 50 mL). Standard workup gave 9.92 g (97%) of **7a** as a golden oil: ^{1}H NMR δ 1.30 (m, 1 H), 1.73 (s, 4 H), 2.00 (m, 1 H), 2.42 (s, 3 H, NCH_3), 2.30–2.60 (m, 7 H), 2.87 (m, 2 H, Cbz-NCH_2), 4.10 (m, 2 H, NC*H* and N*H*), 5.13 (s, 2 H, OCH_2Ph), 7.34 (s, 5 H, ArH); IR (film) 3550 (br, OH), 3310 (m, NH) cm^{-1}; MS (EI) m/z 317 (M$^+$).

For analytical testing purposes the bis(hydrochloride) salt was prepared: mp 230–231 °C dec; HRMS (EI) calcd for $C_{18}H_{27}N_3O_2$ 317.2103, found 317.2099. Anal. Calcd for $C_{18}H_{29}N_3O_2Cl_2$: C, 55.39; H, 7.49; N, 10.76; Cl, 18.16. Found: C, 55.36; H, 7.51; N, 10.85; Cl, 18.41.

1-(Carbobenzyloxy)-4-(methylamino)-3-(dimethylamino)piperidine (7b). Prepared according to the procedure described above for **7a** (90%); ^{1}H NMR (200 MHz) δ 2.1 (broad m, 2 H, CH_2), 2.3 (s, 6 H, N(CH_3)$_2$, 2.45 (s, 3 H, NCH_3), 2.5 (m, 1 H, CH), 2.7 (m, 2 H, CH_2), 3.5 (m, 1 H, NC*H*), 4.25 (broad m, 2 H, 2 CH), 5.2 (s, 2 H, CH_2), 7.3 (s, 5 H, ArH); IR (film) 3330 (NH), 1705 (CO) cm^{-1}; MS (EI) 291 (M$^+$); HRMS (FAB) calcd for $C_{16}H_{26}N_3O_2$ 292.2025, found 292.2015.

1-(Carbobenzyloxy)-4-(*N*-methyl-3',4'-dichlorobenzamido)-3-(dimethylamino)piperidine (8b). To a cooled (0 °C) solution of diamine **7b** (0.69 g, 2.4 mmol) and triethylamine (0.24

g, 2.6 mmol) in ether (30 mL) was added 3,4-dichlorobenzoyl chloride (0.54 g, 2.6 mmol) in four portions. The cold bath was removed after completion of the addition, and the resulting white suspension was stirred for 18 h. The reaction mixture was then diluted with 25 mL of ether and washed with saturated aqueous Na_2CO_3 and brine. Standard workup provided a yellow oil. The crude product was purified by radial chromatography (silica gel; $CHCl_3$/MeOH/NH_4OH, 95:4:1) to give **8b** as a yellow oil (0.80 g, 73%).

The crystalline hydrochloride of this compound was prepared by its addition to ethereal HCl and subsequent crystallization from 1:1 methanol/ether: mp 148–150 °C; ^1H NMR (200 MHz) δ 1.65 (broad m, 2 H, CH_2), 2.15 (broad s, 1 H, CH), 2.40 (s, 6 H, $N(CH_3)_2$), 2.76 (s, 3 H, NCH_3), 2.80–3.10 (broad m, 2 H, 2 CH), 4.25 (broad m, 1 H, CH), 4.48 (m, 1 H, CH), 4.77 (m, 1 H, CH), 5.20 (s, 2 H, CH_2), 7.25 (m, 2 H, ArH), 7.35 (s, 5 H, ArH), 7.50 (m, 1 H, ArH); IR (film) 1705 (carbamate CO), 1642 (amide CO) cm^{-1}; MS (EI) m/z at 463 (M^+). Anal. Calcd for $C_{23}H_{27}N_3O_3Cl_2$·HCl: C, 55.14; H, 5.59; N, 8.39; Cl, 21.28. Found: C, 54.91; H, 5.70; N, 8.17; Cl, 21.09.

1-(Carbobenzyloxy)-*trans*-4-(*N*-methyl-3′,4′-dichlorobenzamido)-3-pyrrolidinylpiperidine (8a). Prepared as described above for **8b** except that the crude product was purified by column chromatography (silica gel; ether and ether/MeOH/NEt_3, 90:3:2) to give 5.58 g (90%) of **8a** as a golden oil: ^1H NMR δ 1.74 (broad s, 6 H), 2.60–2.95 (m, 6 H), 2.76 (s, 3 H, NCH_3), 4.26 (m, 2 H), 4.40 (m, 1 H), 4.73 (m, 1 H), 5.15 (s, 2 H, CH_2Ph), 7.22 (m, 1 H, ArH), 7.36 (s, 5 H, ArH), 7.48 (m, 2 H, ArH); IR (film) 1705 (CO), 1640 (CO) cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{30}Cl_2N_2O_3$ 490.1664, found 490.1673.

For analytical and biological testing purposes the hydrobromide salt was prepared: mp 183–184 °C; HRMS (FAB) calcd for $C_{25}H_{30}Cl_2N_2O_3$ 490.1664, found 490.1673.

1-(Carbobenzyloxy)-*trans*-4-(*N*-methyl-3′,4′-dichlorophenylacetamido)-3-pyrrolidinylpiperidine (9). A solution of 3,4-dichlorophenylacetic acid (2.85 g, 13.9 mmol) and 1,1′-carbonyldiimidazole (2.25 g, 13.9 mmol) in 100 mL of THF was stirred for 2 h at ambient temperature. Diamine **7a** (4.00 g, 12.6 mmol) in 50 mL of THF was added dropwise using a syringe. The resultant solution was stirred for 20 h. The reaction mixture was dissolved in 300 mL of ether and washed with saturated aqueous Na_2CO_3 (2 × 100 mL). Standard workup gave 6.41 g of a golden oil. The crude product was purified by column chromatography (silica gel; ether and ether/MeOH/NEt_3, 90:3:2) to give 5.00 g (79%) of **9** as a yellow, viscous oil: ^1H NMR δ 1.65 (m, 4 H), 1.85 (m, 1 H), 2.59 (m, 2 H), 2.60–3.00 (m, 4 H), 2.79 (s, 3 H, NCH_3), 3.41 (m, 1 H), 3.68 (m, 3 H), 4.22 (m 1 H), 4.37 (m, 1 H), 4.75 (m, 1 H), 5.13 (s, 2 H, CH_2Ph), 7.20 (m, 1 H, ArH), 7.35 (broad s, 7 H, ArH); IR (film) 1705 (CO), 1640 (CO) cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{32}Cl_2N_3O_3$ 504.1821, found 504.1800.

For analytical purposes the hydrochloride salt was prepared: mp 123 °C. Anal. Calcd for $C_{26}H_{32}N_3O_3Cl_2$·HCl·$^1/_2H_2O$: C, 56.76; H, 6.05; N, 7.64; Cl, 19.34. Found: C, 56.69; H, 6.20; N, 7.62; Cl, 19.27.

General Procedure for the CBz Cleavage Using TMSI. *trans*-4-(*N*-Methyl-3′,4′-dichlorobenzamido)-3-pyrrolidinylpiperidine (10). A stirred solution of compound **8a** (470 mg, 0.960 mmol) in 15 mL of $CHCl_3$ was cooled to 0 °C and treated dropwise with trimethylsilyl iodide (479 mg, 2.40 mmol). The solution was stirred for 30 min at 0 °C and for 18 h at room temperature. Isolation: The $CHCl_3$ solution was diluted with ether (100 mL) and extracted with 10% aqueous HCl (3 × 25 mL). The aqueous HCl layers were combined, neutralized with solid Na_2CO_3, and extracted with CH_2Cl_2 (3 × 30 mL). Standard workup gave 218 mg (64%) of **10** as a yellow oil: ^1H NMR δ 1.76 (m, 6 H), 2.30–3.35 (m, 9 H), 2.80 (s, 3 H, NCH_3), 2.45 (m, 1 H), 4.68 (dt, J = 4, 11, 1 H, C*H*NCO), 7.24 (m, 1 H, ArH), 7.48 (m, 2 H, ArH); IR (film) 3300 (br, NH), 1630 (CO) cm^{-1}; MS (FAB) $[M + H]^+$ at m/e 356, 358.

For analytical purposes the bis(methanesulfonate) salt was prepared: mp 177 °C dec. Anal. Calcd for $C_{19}H_{31}N_3O_7Cl_2S_2$: C, 41.61; H, 5.70; N, 7.66; S, 11.69; Cl, 12.93. Found: C, 41.44; H, 5.70; N, 7.78; S, 11.54; Cl, 13.09.

***trans*-4-(*N*-Methyl-3′,4′-dichlorophenylacetamido)-3-pyrrolidinylpiperidine (11).** A solution of compound **9** (400 mg, 0.794 mmol) in 10 mL of $CHCl_3$ was treated with trimethylsilyl iodide (397 mg, 1.98 mmol) according to the general procedure. Isolation as described for compound **10** gave 200 mg (68%) of **11** as a colorless oil: ^1H NMR δ 1.67 (m, 6 H), 2.65 (m, 4 H), 2.72 (m, 4 H), 2.86 (s, 3 H, NCH_3), 3.09 (m, 1 H), 3.26 (m, 1 H), 3.71 (m, 2 H, NCH_2CO), 4.70 (dt, J = 4, 12, 1 H, C*H*NCO), 7.15 (m, 1 H, ArH), 7.38 (m, 2 H, ArH); IR (film) 3300 (br, NH), 1640 (CO) cm^{-1}; MS (FAB) $[M + H]^+$ at m/e 370, 372.

For analytical purposes the bis(methanesulfonate) salt was prepared: mp 165 °C dec. Anal. Calcd for $C_{20}H_{33}N_3O_7Cl_2S_2$: C, 42.70; H, 5.91; N, 7.47; S, 11.40; Cl, 12.60. Found: C, 42.61; H, 5.99; N, 7.31; S, 11.56; Cl, 12.44.

1-Benzyl-*trans*-4-(*N*-methyl-3′,4′-dichlorobenzamido)-3-pyrrolidinylpiperidine (12). A solution of **8a** (529 mg, 1.08 mmol) in 10 mL of chloroform was treated with trimethylsilyl iodide (539 mg, 2.70 mmol) as described in the general procedure. Isolation: After stirring overnight, the reaction mixture was quenched by the addition of methanol (5 mL). The solvent was removed in vacuo, and the crude residue was partitioned between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, and the aqueous phase was back extracted with CH_2Cl_2 (25 mL). Standard workup gave 600 mg of a yellow oil. After standing for 2 days, the oil was purified by radial chromatography (silica gel; 95:4:1 $CHCl_3$/MeOH/NH_4OH) to give 383 mg (86%) of **12** as a colorless oil: ^1H NMR δ 1.69 (m, 6 H), 2.10 (m, 1 H), 2.48 (m, 3 H), 2.78 (s, 3 H, NCH_3), 2.85–3.10 (m, 4 H), 3.57 (m, 3 H), 4.58 (m, 1 H, C*H*NCO), 7.31 (m, 6 H, ArH), 7.46 (m, 2 H, ArH); IR (film) 1640 (CO) cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{29}N_3OCl_2$ 446.1766, found 446.1746.

1-Benzyl-*trans*-4-(*N*-methyl-3′,4′-dichlorophenylacetamido)-3-pyrrolidinylpiperidine (13). A solution of **9** (1.00 g, 1.98 mmol) in 30 mL of $CHCl_3$ was treated with trimethylsilyl iodide (794 mg, 3.97 mmol) as described in the general procedure. Isolation as described for compound **12** gave 800 mg of a yellow oil. The crude product was purified by radial chromatography (silica gel, 95:5 ether/NEt_3) to give 686 mg (75%) of **13** as a colorless oil: ^1H NMR δ 1.61 (m, 6 H), 1.90 (m, 1 H), 2.06 (m, 2 H), 2.54 (m, 2 H), 2.67 (m, 1 H), 2.83 (s, 3 H, NCH_3), 2.84 (m, 2 H), 3.05 (m, 1 H), 3.52 (dd, J = 12, 20, 2 H, CH_2Ar), 3.68 (dd, J = 14, 20, 2 H, CH_2Ar), 4.60 (m, 1 H, C*H*NCO), 7.11 (m, 1 H, ArH), 7.30 (s, 5 H, ArH), 7.32 (m, 2 H, ArH); IR (film) 1640 (CO) cm^{-1}; MS (FAB) $[M + H]^+$ at m/e 460, 462.

For analytical purposes the bis(methanesulfonate) salt was prepared: mp 230-231 °C. Anal. Calcd for $C_{27}H_{39}N_3O_7S_2Cl_2$: C, 49.69; H, 6.02; N, 6.44; S, 9.83; Cl, 10.86. Found: C, 49.46; H, 5.99; N, 6.41; S, 9.66; Cl, 10.71.

X-ray Structure Determination of Compound 8b. One asymmetric unit contains the formula $C_{23}H_{27}N_3O_3Cl_2$·HCl·$^1/_2$-(H_2O), with formula wt = 473.4 × 36.46 × 9.0. Crystal data are: monoclinic; space group $P2_1/c$; Z = 4; a = 13.745 (4), b = 15.092 (2), c = 12.144 (2) Å, β = 100.24 (4)°, V = 2479 (2) Å^3. The calculated density = 1.37 g cm^{-3}.

A clear plate 0.09 × 0.17 × 0.30 mm was mounted on a Siemens $P1$ diffractometer controlled by a Harris computer. Graphite monochromatized Cu Kα radiation was used, (λ(cu Kα) = 1.5418 Å), with $2\theta_{max}$ = 138°. Intensity data were measured at low temperature (T = 123 (2) K) using 1°/min θ–2θ step scans with scan widths >3.4°. Of 4566 unique reflections measured, 3369 had intensities >2σ. Ten reflections periodically monitored showed no trend towards deterioration, $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics +(0.024I)^2, where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least-squares fit of Kα_1 2θ values (λKα_1 = 1.5402) for 25 high 2θ reflections.[10] An Lp correction appropriate for a monochromator with 50% perfect character was applied, and the data were also corrected for absorption (μ = 3.5 mm^{-1})[11] The structure was solved by direct methods, using DIREC.[12] Hydrogens, except for one water hydrogen, were found in difference maps. Least-squares refinement included coordinates for all atoms and anisotropic thermal parameters for nonhydrogen atoms, except for the water

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oxygen, which was kept isotropic. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle and Turner,[13] and, for hydrogen, from Stewart, Davidson, and Simpson.[14] In the final refinement cycle, all shifts were $<0.2\sigma$. The final difference Fourier peaks were <0.30 e Å^{-3}, except those very close to known atoms.

One water hydrogen is located on a center of symmetry. The water molecule is half-populated; however, if both centrically related waters happened to be present in the same cell, they would share this hydrogen, and be separated by a fairly short hydrogen-bond distance, 2.645 (5) Å. The other water hydrogen was not found in difference Fouriers, but must be located between the water oxygen and the chlorine ion because these atoms are hydrogen-bonded (d = 3.16 Å). The nitrogen of the N-dimethyl group is protonated, and hydrogen-bonds to the chlorine ion with a distance of 3.043 (3) Å. There is also a close intermolecular contact between the ortho chlorine on the aromatic ring and the carbonyl oxygen of the amide group in the molecule related by: $-x, y + {}^1/_2, 1{}^1/_2 - z$. The final agreement index R = 0.079 for all 4566 reflections, and the standard deviation of fit = 2.14. The CRYM system of computer programs was used.[12] The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. In addition, tables of bond lengths and angles, torsion angles, and close intermolecular contacts are available as supplementary material.

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Supplementary Material Available: Additional X-ray data and ^{1}H NMR for compounds **4**, **5**, **7b**, **8a**, and **12** (12 pages). Ordering information is given on any current masthead page.

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Preparation, Alkylation Reactions, and Conformational Analysis of Esters of Phospholanic Acid. Preparation and Reactivity of (2*S**,5*S**)-1,2,5-Tribenzyl-1-oxophospholane

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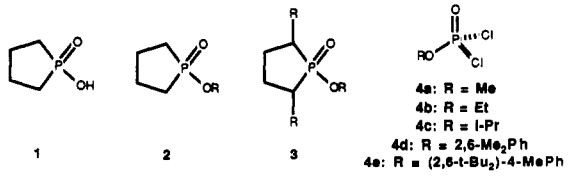
Optimum conditions for the reaction of 1,4-butanediyldimagnesium dibromide and alkyl phosphorodichloridates are described. The general geometric requirements of the cyclization reaction transition state are discussed. Alkylation reactions of phospholanate esters **2b** and **2c** are reported. Conformational analysis of various phospholanate esters is discussed in terms of $^3J_{PC}$ and $^3J_{PH}$ data, NOE experiments, and crystal structures of related phospholane derivatives. *trans*-2,5-Dibenzyl phosphinate esters **15b** and **15c** were converted to (2*S**,5*S**)-1,2,5-tribenzyl-1-oxophospholane **18** by reductive alkylation. Phosphine oxide **18** was shown to participate in an olefination reaction with 4-*tert*-butylcyclohexanone.

Phospholanic acid (**1**, 1-hydroxy-1-oxophospholane; tetramethylenephosphinic acid) represents the parent compound of a class of saturated five-membered ring phosphinic acid derivatives.[1] Since phosphinate esters can be converted by straightforward methods into substances of potential utility to organic and organometallic chemistry, we initiated an investigation of the development of practical methods for the preparation of phospholanate esters **2** and ring alkylated derivatives **3**. This paper describes the chemistry and conformational analysis of racemic phosphinate esters **2** and **3**. Future publications will address the preparation of these materials in chiral form.



1 2 3

Classical methods of preparation of phosphorus(IV) derivatives of phospholane have involved reaction of 1,4-butanediyldimagnesium dibromide with amidous phosphorodichloridates,[2] intramolecular Arbuzov reaction of 4-chlorobutyl diethyl phosponite,[3] and McCormack cycloaddition of 1,3-butadiene with phosphorus trichloride.[4] Each of these methods suffered from low overall yield.

In an attempt to establish a practical alternative for the preparation of phospholanic esters, we investigated reactions of alkyl phosphorodichloridates[5] **4** with 1,4-butanediyldimagnesium dibromide.[6] During the course of these studies two independent reports describing the preparation

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