dye precipitated as a copper-bronze solid: mp 233–235 °C; λ_{max} (CH_2Cl_2) 1190 nm (ϵ 270000); IR (KBr) 1590 (w), 1515, 1430, 1220, 1150 (br), 830, 755, 718 cm^{-1}.

Anal. Calcd for $C_{44}H_{39}BClF_4Te_2$: C, 56.2; H, 3.6, Te, 27.1. Found: C, 55.9; H, 3.5; Te, 26.5.

Preparation of 39. A solution of *p*-bromo-*N*,*N*-dimethylaniline (1.00 g, 5.00 mmol) in 5 mL of dry THF was added to magnesium turnings (0.24 g, 10 mg-atom) under an argon atmosphere. A small crystal of iodine (~10 mg) was added, and the mixture was warmed at reflux for 2 h. Telluropyrone **1** (0.20 g, 0.56 mmol) in 5 mL of dry THF was added dropwise. The mixture was stirred at reflux for an hour more. The THF solution was decanted from the magnesium turnings and concentrated. The residue was taken up in 5 mL of acetic acid, and 1 mL of 70% perchloric acid was added. The solution was added dropwise to 20 mL of cold water. The precipitate was collected by filtration and recrystallized from acetonitrile to give 0.26 g (81%) of **39** as a copper-bronze solid: IR (KBr) 1610, 1545, 1400, 1086, 810, 685 cm^{-1}.

Anal. Calcd for $C_{25}H_{22}ClNO_4Te$: C, 53.3; H, 3.9; N, 2.5. Found: C, 53.1; H, 3.7; N, 2.1.

Preparation of 40. *p*-(Dimethylamino)benzaldehyde (0.24 g, 1.6 mmol) and **2** (0.67 g, 1.5 mmol) were slurried in 3 mL of acetic anhydride. The mixture was heated on a steam bath for 4 min. The reaction mixture was cooled to ambient temperature, and 3 mL of acetonitrile was added. Chilling the solution induced crystallization of **40**, which was collected by filtration, washed with ether, and dried to give 0.63 g (72%) of shiny green needles: field desorption mass spectrum, *m/e* 492 (M^+, $C_{27}H_{24}NTe$).

Anal. Calcd for $C_{27}H_{24}BF_4NTe$: C, 56.2; H, 4.2; N, 2.4. Found: C, 56.1; H, 4.3; N, 2.5.

Preparation of 41. Aldehyde **43** (1.0 g, 5.3 mmol) and **2** (1.0 g, 2.0 mmol) in 5 mL of acetic anhydride were heated on a steam bath for 1.5 min. The reaction mixture was poured into 300 mL of ether, causing a gummy solid to precipitate. The ether was decanted, and the residue was dissolved in 5 mL of acetonitrile. The solution was diluted with 300 mL of ether, precipitating a solid. This procedure was repeated. The residue was dried under vacuum to give **41** as a friable foam (1.20 g, 90%): field desorption mass spectrum, *m/e* 532 (M^+, $C_{30}H_{28}NTe$).

Preparation of 42. 9-Formyljulolidine (**44**, 0.32 g, 1.6 mmol) and **2** (0.67 g, 1.5 mmol) were slurried in 3 mL of acetic anhydride. The mixture was allowed to stand for 4 h at ambient temperature and chilled. After 48 h, the reaction mixture was filtered, giving 0.81 g (86%) of **42** as bright copper needles: IR (KBr) 1625, 1520, 1100 (br), 1035, 758, 692 cm^{-1}.

Anal. Calcd for $C_{31}H_{28}BF_4NTe$: C, 59.2; H, 4.5; N, 2.2; Te, 20.3. Found: C, 58.8; H, 4.6; N, 2.2; Te, 20.3.

Preparation of 45. *p*-(Dimethylamino)cinnamaldehyde (0.28 g, 1.6 mmol) and **2** (0.67 g, 1.5 mmol) in 3 mL of acetic anhydride were warmed on a steam bath for 4 min. The reaction mixture was diluted with 3 mL of acetonitrile and chilled. The dye was collected by filtration, washed with ether, and dried to give 0.20 g (22%) of **45** as a maroon solid: field desorption mass spectrum, *m/e* 518 (M^+, $C_{29}H_{26}NTe$).

Anal. Calcd for $C_{29}H_{26}BF_4NTe$: C, 57.8; H, 4.3; N, 2.3. Found: C, 57.3; H, 4.2; N, 2.1.

Acknowledgment. We thank Dr. George A. Reynolds for many helpful discussions.

Registry No. **1**, 80697-46-7; **2**, 83710-66-1; **3**, 83710-67-2; **4**, 83710-69-4; **5**, 83710-70-7; **6**, 83710-72-9; **7**, 2340-23-0; **8**, 13586-30-6; **9**, 49655-20-1; **16**, 83711-01-7; **17**, 83710-81-0; **23**, 83710-75-2; **24**, 83710-83-2; **28**, 83710-77-4; **29**, 83710-85-4; **30**, 83710-79-6; **31**, 83710-87-6; **32**, 83710-89-8; **34**, 83710-91-2; **39**, 83710-93-4; **40**, 83711-03-9; **41**, 83710-95-6; **42**, 83710-97-8; **43**, 76529-12-9; **44**, 33985-71-6; **45**, 83710-99-0; 1,5-diphenyl-1,4-pentadiyn-3-one, 15814-30-9; Meldrum's acid, 2033-24-1; 1-chloro-2,6-diformylcyclohexene, 83710-73-0; *p*-bromo-*N*,*N*-dimethylaniline, 586-77-6; *p*-(dimethylamino)benzaldehyde, 100-10-7; *p*-(dimethylamino)-cinnamaldehyde, 6203-18-5.

Regioselective Functionalization.[1] β Substituent Effects on the Regioselectivity of Baeyer–Villiger Oxidations of 3-Substituted 2-Azabicyclo[2.2.2]octan-5-ones (Isoquinuclidin-5-ones)

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The regioselectivity of the Baeyer–Villager oxidation of *N*-carboalkoxy-2-azabicyclo[2.2.2]octan-5-ones **1** has been found to vary markedly as a function of the identity and stereochemistry of the substituent at the 3-position and the choice of peracid oxidant. With peracetic acid predominantly bridgehead (BH)-migrated lactones **2** were obtained from the ketones **1b** (R′ = *exo*-Me, 62% BH), **1e** (R′ = *exo*-CH_2OCOPh, 84% BH (TLC), and **1g** (R = *endo*-COOMe, 66% BH (TLC) and exclusively bridgehead migration from the ketones **1a** (R′ = H), **1c** (R′ = *exo*-Ph), and **1d** (R′ = *exo*-COOMe). The ketone **1f** (R = *endo*-Me) failed to undergo oxidation with peracetic acid. When *m*-chloroperbenzoic acid was used as the oxidant, greater amounts of methylene-migrated lactones **4** were obtained in every case examined. For ketones **1d** (R′ = *exo*-COOMe, 18% BH (TLC), and **1g** (R = *endo*-COOMe, 38% BH (TLC), methylene-migrated lactones **4** were the predominant lactones found. The change in migratory preference was especially notable with **1d** (R′ = *exo*-COOMe), which afforded 100% *bridgehead*-migrated lactone **2d** with peracetic acid but 82% *methylene*-migrated lactone **4d** with *m*-chloroperbenzoic acid. Migratory aptitudes for ketones **1** could not be correlated with ^{13}C NMR shifts of the carbonyl carbons of the ketones **1** when peracetic acid was used as the oxidant, but upfield shifts for the resonances of the ketone carbonyl carbons in **1d** (R′ = *exo*-COOMe) and **1g** (R = *endo*-COOMe) did correlate with a preference for methylene migration with *m*-chloroperbenzoic acid as the oxidant.

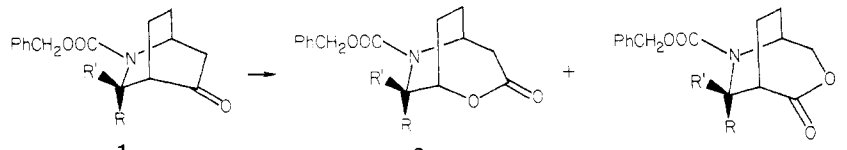
If regioselective insertion of oxygen between the methine and carbonyl carbon atoms of isoquinuclidin-5-ones **1** of known configuration at carbon 3 were to be effected, lactones **2**, the cyclized form of piperidines **3**, would be obtained (Scheme I). Such piperidines **3**, stereoselectively functionalized at positions 2, 3, and 6, are of potential use as synthons for elaboration of alkaloid natural products.[2-4]

(1) This research was supported by Grant No. CA 24596, awarded by the National Cancer Institute, DHEW, and American Cancer Society Grant No. IN 88J.

(2) Krow, G.; Johnson, C. *Synthesis* **1979**, 50–51.

0022-3263/82/1947-5239$01.25/0

Table I. 3-Substituent Effects on the Regiochemistry of Oxygen Insertion of *N*-Carbobenzoxyisoquinuclidin-5-ones 1

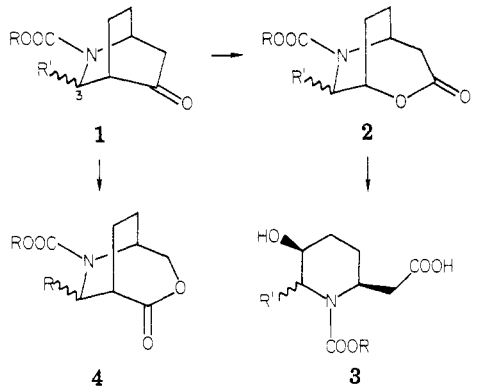


1 2 4

ketone	R	R′	peracid[a]	lactone ratio[b] 2	lactone ratio[b] 4	yield,[c] %	$^{13}C{=}O$ NMR shift,[d] δ
			(A) 3-Exo Substituents				
1a	H	H	PAA	100	0	90 (82)	211.08
			MCPBA	(69)	(31)	89 (80)	
			TFPAA	100	0	(61)	
			PNPBA	(67)	(33)	(78)	
1b	H	CH_3[e]	PAA	62 (76)	38 (24)	71 (60)	211.01
			MCPBA	50 (43)	50 (57)[f]	85 (73)	
1c	H	Ph	PAA	100	0	74 (38)	211.48
			MCPBA	60 (66)	40 (34)	83 (55)	
1d	H	COOMe	PAA	100	0	60 (38)	209.09
			MCPBA	(18)	(82)[g]	70 (59)	
1e	H	CH_2OCOPh	PAA	major (84)	(16)	78 (68)	
			(B) 3-Endo Substituents				
1f	CH_3	H	PAA			*h*	211.39
			MCPBA	81 (80)	19 (20)	(71)	
1g	COOMe	H	PAA	(66)	(34)[i]	57 (54)	208.94
			MCPBA	(38)	(62)[i]	91 (85)	

[a] PAA = 40% peracetic acid/acetic acid/sodium acetate; MCPBA = *m*-chloroperbenzoic acid/methylene chloride/sodium bicarbonate; TFPAA = trifluoroperacetic anhydride/89% hydrogen peroxide/disodium hydrogen phosphate; PNPBA = *p*-nitroperbenzoic acid/methylene chloride/sodium bicarbonate. [b] Ratios were determined from ^1H NMR spectra of reaction mixtures after workup to remove peracid and removal of solvent. Ratios after TLC isolation are in parentheses. [c] Yields are isolated from workup before TLC. Yields after TLC are in parentheses. [d] $CDCl_3$ solvent. [e] $PhCH_2$ = Et. [f] An observed 56:44 ratio for bridgehead to methylene-migrated lactones has been corrected for 20% of an 80:20 mixture of lactones **2f**/**4f**; the observed ratio after TLC isolation but before correction for **2f**/**4f** was 51:49. [g] See ref 4; Baxter and Holmes reported a **2d**/**4d** ratio of 0:100 and a **2e**/**4e** ratio of 0:100. Dr. Holmes has repeated this work and found a **2d**/**4d** ratio of 0:100 with MCPBA and a **2e**/**4e** ratio of 65:35 with the same peracid (personal communication). [h] No reaction occurred after one week at 25 °C. [i] Ratios were determined after TLC isolation of the lactones because of NMR overlap in the crude reaction mixture of peaks needed for isomer assignments.

Scheme I



1 2 4 3

With the goal of preparing lactones **2**, we undertook an examination of regiochemical outcomes for Baeyer–Villiger oxidations of a number of 3-exo- and 3-endo-substituted isoquinuclidin-5-ones **1** using peracetic acid and *m*-chloroperbenzoic acid as alternative oxidants.

At the inception of this work there was precedent for insertion of oxygen into bicyclo[2.2.2]octan-2-one with solely bridgehead migration by using peracetic acid as the oxidant.[5] However, in 1977 Baxter and Holmes[4] reported that **1d** (R′ = 3-*exo*-carbomethoxy) and **1e** (R′ = *exo*-CH_2OCOPh) with all peracids tried gave lactones **4** by exclusive methylene migration. In 1979 we reported[2] that ketone **1a** (R′ = H) gave solely bridgehead migration with peracetic acid but some methylene migration (31%) with *m*-chloroperbenzoic acid. We here report an expansion of our earliest study[2] including a reexamination of the earlier report of Baxter and Holmes.[4]

Results

The requisite *N*-carboalkoxyisoquinuclicin-5-ones **1** were prepared from the corresponding *N*-carboalkoxy-5,6-didehydroisoquinuclidines **5**[6] by using a previously described regioselective ketofunctionalization procedure.[7] Baeyer–Villiger oxidations of the ketones **1** were carried out with peracetic acid in sodium acetate buffered acetic acid or with excess *m*-chloroperbenzoic acid in sodium bicarbonate buffered methylene chloride to give lactones **2** and **4**, whose structures are consistent with ^1H NMR data (see Experimental Section). Ratios of the lactones **2**/**4** were determined by TLC isolation and, where possible, by comparison of the integrated areas for the methylene protons H-4,4′, δ 2.75–3.4) adjacent to the carbonyl group in the bridgehead-migrated lactones **2** with the methine proton

(3) (a) Natsume, M.; Ogawa, M. *Heterocycles* **1980**, 14, 169–173. (b) Natsume, M.; Ogawa, M. *Ibid.* **14**, 615–618. (c) Natsume, M.; Ogawa, M. *Ibid.* **1981**, *16*, 973–977.

(4) Baxter, A. J. G.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2343–2347.

(5) Meinwald, J.; Frauenglass, E. *J. Am. Chem. Soc.* **1960**, *82*, 5235–5239.

(6) (a) Krow, G.; Rodebaugh, R.; Grippi, M.; Pannella, H.; Carmosin, R. *J. Am. Chem. Soc.* **1973**, *95*, 5273–5280. (b) Cava, M. P.; Wilkins, C. K.; Dalton, D. R.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772–3775. (c) Krow, G. R.; Carey, J. T.; Cannon, K. C.; Henz, K. J. *Tetrahedron Lett.* **1982**, *23*, 2527–2528.

(7) (a) Krow, G. R.; Fan, D. M. *J. Org. Chem.* **1974**, *39*, 2674–2676. (b) Krow, G.; Rodebaugh, R.; Grippi, M.; Carmosin, R. *Synth. Commun.* **1972**, *2*, 211–212.

(H-1, δ 4.5–5.3) adjacent to the carbonyl group in the methylene-migrated lactones **4**. Reaction mixtures were analyzed after a mildly basic wash to remove acid but before TLC separation if possible; this was to reduce bias due to preferential hydrolysis of one of the lactone isomers.

Table IA shows the effects of 3-exo substituents and the choice of peracid on the regiochemistry of the Baeyer–Villager reaction of isoquinuclidin-5-ones **1a–e**. With peracetic acid as the oxidant, bridgehead carbon migration was favored in all cases studied, although with the 3-*exo*-alkyl substituents, R′ = methyl and R′ = hydroxymethylbenzoate of **1b** and **1e**, competitive methylene migration was observed. When *m*-chloroperbenzoic acid was used as the oxidant, methylene migration became increasingly competitive with bridgehead migration; indeed, methylene migration was clearly preferred when R′ = COOMe in **1d**.[8] The ratio of lactones **2e**/**4e** changed from 60:40 to 40:60 upon TLC as the major bridgehead-migrated lactone **2e** was preferentially hydrolyzed during isolation.[9] In the oxidation of **1a** replacement of peracetic acid (acetic acid, $pK_a = 4.5$)[10a] by the much stronger, but structurally similar, trifluoroperacetic acid (trifluoroacetic acid, $pK_a = -3.0$)[10b] does not affect the total preference for isolation of bridgehead-migrated lactone **2a**; similarly, replacement of *m*-chloroperbenzoic acid (*m*-chlorobenzoic acid, $pK_a = 3.82$)[10a] by *p*-nitroperbenzoic acid (*p*-nitrobenzoic acid, $pK_a = 3.41$)[10a] led to the same 2:1 preference for bridgehead migration. Although not shown in Table I (see supplementary material), the ethyl, phenyl, and 2,2,2-trichloroethyl analogues of benzylcarbamate **1a** gave the same preference for lactone **2a** (100% with peracetic acid, 62–69% with *m*-chloroperbenzoic acid) upon oxidation.

In Table IB are the results of oxidation of two 3-endo-substituted isoquinuclidin-5-ones, **1f–g**. With peracetic acid, the 3-*endo*-methyl ketone **1f** failed to react; however, the 3-*endo*-carbomethoxy ketone **1g** with peracetic acid did afford about a 2:1 mixture of the bridgehead/methylene-migrated lactones **2g**/**4g**. With *m*-chloroperbenzoic acid and 3-*endo*-methyl ketone **1f** there was a 4:1 preference **2f**/**4f** favoring bridgehead migration, while 3-*endo*-carbomethoxy ketone **1g** gave a 4:6 preference of **2g**/**4g** with methylene migration being favored.

The bridgehead vs. methylene carbon migration ratios of Table I may have been influenced to some extent by partial hydrolysis of the product lactones during the initial mildly basic wash to remove peracid. Although efforts were made to minimize the loss of lactone, nevertheless, product losses were appreciable and in the 40% range in one case (lactones **2g**/**4g**). Observations of the lactone ratios before and after column chromatography indicate that the methylene-migrated lactone was generally lost to a greater extent than the bridgehead-migrated lactone.[9] One exception was bridgehead-migrated lactone **2e**, which was lost to a greater extent than methylene-migrated lactone **4e**. Even if the unaccounted products of Table I are hydrolyzed methylene-migrated lactones **4**, the general thrust of our observations remains that 3-substituents β[11] to a potentially migrating carbon atom play a major role in determining the regiochemistry of oxygen insertion during the Baeyer–Villiger oxidation of ketones **1**.

The regiochemistry of the Baeyer–Villiger oxidation of the 3-exo-substituted isoquinuclidin-5-ones **1a–e** should be a function of the inductive effect of the 3-exo substituents rather than a steric effect. However, when peracetic acid was used as the oxidant, it was not possible to observe a corelation between ^{13}C NMR chemical shifts of the carbonyl carbons and the tendency to obtain methylene-migrated lactones **4**.[12] The results for oxidation of **1d** and **1g** with *m*-chloroperbenzoic acid do indicate an increased preference for methylene migration related to an upfield shift of the ketone carbonyl resonance by the carbomethoxy groups (δ 1.99 and 2.14, respectively). However, the 3-substituent effect for oxidation of ketones **1a–e** need not be purely a function of through-bond electronic interactions such as ^{13}C NMR shifts might measure,[13] and clearly, steric effects influence the regiochemical outcome for oxidations of the 3-endo-substituted ketones **1f,g**.[14]

Experimental Section

Infrared spectra were measured with a Perkin-Elmer 137 sodium chloride spectrophotometer. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE. Unless otherwise specified, proton NMR spectra were obtained in $CDCl_3$ solutions with Me_4Si as an internal standard by using a Perkin-Elmer R-32 90-MHz spectrometer; ^{13}C NMR spectra were recorded on a Varian XL-100 instrument operating at 25.2 MHz by using a Nicolet NTCFT 1180 pulse system. Samples were measured in 5-mm tubes in $CDCl_3$ solution with a deuterium pulse lock; $CDCl_3$ was assigned as 76.9 ppm as the standard, and chemical shift values were computer generated. High-resolution (360 MHz) NMR spectra were recorded at the University of Pennsylvania Middle Atlantic NMR facility, G. McDonald, director. Exact mass measurements were taken on an RMH-2 Hitachi-Perkin Elmer mass spectrometer at an ionization energy of 70 eV at the University of Pennsylvania Mass Spectrometry Center, D. T. Terwilliger, director. Routine mass spectra were obtained by R. Dumphy on a Perkin-Elmer RMU-6H spectrometer. Dry column chromatography was performed by using Woelm dry column silica gel (activity III) with fluorescent indicator. Thin-layer chromatography was conducted by using Analtech silica gel GF plates containing a fluorescent indicator; ethyl acetate was used to extract lactones from the TLC plates. Lactone ratios determined by NMR integration have a precision of no worse than ±4%. Peracetic acid (40%) was prepared from acetic acid and 30% hydrogen peroxide. *N*-carboalkoxy-5,6-dehydroisoquinuclidines **5** and *N*-carboalkoxyisoquinuclidin-5-ones **1** were prepared by using our previously described procedures.[4,6,7]

Baeyer–Villager Oxidations. Method A. Peracetic Acid. To the appropriate *N*-carboalkoxy-2-azabicyclo[2.2.2]octan-5-one **1** (1.0 mmol) in 1 mL of acetic acid containing 0.1 g of sodium acetate was added 1 mL of 28% peracetic acid. After the mixture

(8) (a) Lee, J. B.; Uff, B. C. *Q. Rev., Chem. Soc.* **1967**, *21*, 429–457. (b) Grudzinski, Z.; Roberts, S. M.; Howard, C.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1182–1186. These authors have noted the role of peracid in reaction regioselectivity of the Baeyer–Villiger reaction.

(9) Preferential acid or base hydrolysis of one of a pair of diastereomeric lactones formed during Baeyer–Villiger oxidation has been noted previously. See, for example: (a) Newton, R. F.; Roberts, S. F. *Tetrahedron* **1980**, *36*, 2163–2196. (b) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; DiGiorgio, J. B. *J. Org. Chem.* **1978**, *43*, 3904–3916.

(10) (a) "CRC Handbook of Chemistry and Physics", 58th ed.; CRC Press: West Palm Beach, FL, 1977–1978; p D-150. Badea, F. "Reaction Mechanisms in Organic Chemistry"; Abacus Press: Tunbridge Wells, Kent, England, 1977; p 205.

(11) For a recent example of inductive inhibition of σ participation by a cyano substituent β to a potentially migrating center, see: Apeloig, Y.; Arad, D.; Lenoir, D.; Schleyer, P. v. R. *Tetrahedron Lett.* **1981**, *22*, 879–882.

(12) (a) Noyori, R.; Kobayashi, H.; Sato, T. *Tetrahedron Lett.* **1980**, *21*, 2573–2576. (b) Noyori, R.; Sato, T.; Kobayashi, H. *Ibid.* **1980**, *21*, 2569–2572. These authors, in a study of through-bond electronic effects on the regioselectivity of trifluoroperacetic acid mediated Baeyer–Villiger oxidations of a series of 8-oxabicyclo[3.2.1]octan-3-ones for which steric influences were considered to be absent, found ^{13}C NMR shifts for the carbonyl signals of the ketones to be an indication of the transmission of electronic effects of substituents X and to correlate with the regiochemistry of oxygen insertion.

(13) For recent discussions of the mechanisms of transmission of polar effects in σ-bonded systems, see: (a) Stock, L. M. *J. Chem. Educ.* **1972**, *49*, 400–404. (b) Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1–20. Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 369–379.

(14) For a recent review of the Baeyer–Villiger reaction and mechanistic discussion, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697–2724.

was stirred in the dark for 24 h, 10 mL of methylene chloride was added, and the solution was washed with saturated aqueous sodium sulfite (4 × 5 mL) followed by saturated aqueous sodium bicarbonate (2 × 5 mL). By the general procedure the following oxidations were carried out with peracetic acid.

6-(Benzyloxycarbonyl)-2-oxa-3-oxo-6-azabicyclo[3.2.2]nonane (2a). Ketone **1a** (400 mg, 1.53 mmol) after 18 h afforded 338 mg (80%) of lactone **2a**: bp 145–150 °C (0.025 torr); NMR ($CDCl_3$) δ 7.3 (5 H, s), 5.15 (2 H, s), 4.58 (br, H-1), 4.48 (br, H-5), 4.00 (dt, J = 13, 2 Hz, H-7n), 3.55 (dd, J = 13, 4 Hz, H-7x), 3.15 (dt, J = 17, 2 Hz, H-4′), 2.75 (dd, J = 17, 2 Hz, H-4), 2.3–1.8 (br, 4 H). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.24; N, 5.09. Found: c, 65.38; H, 6.31; N, 5.23.

***N*-Carbethoxy-2-oxa-3-oxo-6-aza-7-*exo*-methylbicyclo[3.2.2]nonane (2b) and *N*-Carbethoxy-2-oxo-3-oxa-6-aza-7-*exo*-methylbicyclo[3.2.2]nonane (4b).** An 80:20 mixture of *N*-carbethoxy-3-*exo*-methyl ketone **1b** and *N*-carbethoxy-3-*endo*-methyl ketone **1f** (76 mg, 0.36 mmol) after 72 h afforded 50 mg of a mixture, which after preparative TLC (ether, two developments) afforded 10 mg of ketones **1b** and **1f** R_f 0.6). Lactone **2b**: 32 mg (49%); R_f 0.16; mp 92–94 °C (ether); NMR ($CDCl_3$) δ 4.55–3.97 (br, 5H), 3.30 (br d, J = 20 Hz, H-4′), 2.72 (dm, J = 20 Hz, H-4), 2.43–1.50 (m, 4 H), 1.42–0.97 (m, 6 H); high-resolution mass spectrum, m/e 227.1153 (calcd $C_{11}H_{17}NO_4$ 227.1158). Lactone **4b**: 10 mg (15%); R_f 0.21); mp 86–87 °C (ether); NMR ($CDCl_3$) δ 4.65–3.50 (br, 6 H), 3.00 (br, H-1), 2.20 (m, 4 H), 1.50–1.00 (m, 6 H); high-resolution mass spectrum, m/e 227.1158 (calcd for $C_{11}H_{17}NO_4$ 227.1158). Comparison of integrated intensities of H-4,4′ of lactone **2b** with twice the value of H-1 of lactone **4b** for the crude mixture of lactones before chromatography indicated an initial 62:38 mixture of lactones **2b**/**4b**. Ketone **1f** does not undergo oxidation with peracetic acid under the reaction conditions (vide infra).

***N*-Carbobenzoxy-2-oxa-3-oxo-6-aza-7-*exo*-phenylbicyclo[3.2.2]nonane (2c).** The *exo*-phenyl ketone **1c** (200 mg, 0.6 mmol) after 24 h afforded 156 mg (74%) of TLC- and NMR-homogeneous lactone **2c** as a yellow oil. TLC (ether) purification gave 80 mg (38%) of lactone **2c** as a white crystalline solid: mp 154–155 °C (ether); NMR ($CDCl_3$) δ 7.32 (s, 10 H), 5.50 (br, H-7n), 5.10 (br, 2 H), 4.78 (br, H-1), 4.63 (br, H-5), 3.40 (dm, J = 17 Hz, H-4′), 2.84 (dd, J = 17, 2 Hz, H-4), 2.4–1.6 (m, 4 H); mass spectrum, m/e 351. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.98. Found: C, 71.59; H, 6.12; N, 4.03.

***N*-Carbobenzoxy-2-oxa-3-oxo-6-aza-7-*exo*-carbomethoxybicyclo[3.2.2]nonane (2d).** *N*-Carbobenzoxy-3-*exo*-carbomethoxy ketone **1d**[4] (52 mg, 0.16 mmol) after 72 h afforded 32 mg (60%) of lactone **2d**[15] as a yellow oil, which after TLC (ether) gave a clear oil of R_f 0.2: NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.30, 5.20 (2 s, 2 H), 4.5–5.0 (br, 3 H), 3.6, 3.8 (2 s, 3 H), 3.20 (dm, J = 17 Hz, H-4′), 2.78 (dd, J = 17, 2 Hz, H-4), 2.5–1.6 (br, 4 H); high-resolution mass spectrum, m/e 333.1210 (calcd for $C_{17}H_{19}NO_6$ 333.1211).

(*N*-Carbobenzoxy-2-oxa-3-oxo-6-azabicyclo[3.2.2]nonan-7-*exo*-yl)methyl Benzoate (2e) and (*N*-Carbobenzoxy-2-oxo-3-oxa-6-azabicyclo[3.2.2]nonan-7-*exo*-yl)methyl Benzoate (4e). *N*-Carbobenzoxy-3-*exo*-methyl benzoate ketone **1e** (25 mg, 0.63 mmol) after 48 h afforded 20 mg of a crude mixture of lactones **2e** and **4e** in which the presence of lactone **4e** was indicated by an enhancement of absorption at δ 3.30 of the crude NMR spectrum. Separation of the lactone mixture by preparative TLC (2:1 hexane/ethyl acetate) afforded (R_f 0.2) 15 mg (57%) of lactone **2e** [NMR ($CDCl_3$) δ 8.0, 7.37 (m, 10 H), 5.20 (s, 2 H), 4.1–4.8 (br, 3 H), 3.31 (dm, J = 17 Hz, H-4′), 2.75 (dd, J = 17, 2 Hz, H-4), 2.4–1.90 (br, 4 H); high-resolution mass spectrum m/e 409.1523 (calcd for $C_{23}H_{23}NO_6$ 409.1524)] and 3 mg (11%; R_f 0.27) of the known lactone **4e**;[4] high-resolution mass spectrum, m/e 409.1522 (calcd for $C_{23}H_{23}NO_6$ 409.1524).

Attempted Peracetic Acid Oxidation of *N*-Carbobenzoxy-3-*endo*-methyl-2-azabicyclo[2.2.2]octan-5-one (1f). The 3-*endo*-methyl ketone **1f** (120 mg, 0.57 mmol) afforded 84–91% starting material after 1 week. No lactonic product was isolated.

***N*-Carbobenzoxy-2-oxa-3-oxo-6-aza-7-*endo*-carbomethoxybicyclo[3.2.2]nonane (2g) and *N*-Carbobenzoxy-2-oxo-3-oxa-6-aza-7-*endo*-carbomethoxybicyclo[3.2.2]nonane (4g).** *N*-Carbobenzoxy-3-*endo*-carbomethoxy ketone **1g** (67 mg, 0.21 mmol) after 1 week afforded 40 mg of a mixture which upon preparative TLC (ether, R_f 0.2) afforded 25 mg (35%) of lactone **2g**: NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.3, 5.2 (2 s, 2 H), 4.5–5.3 (br, 3 H), 3.6, 3.86 (2s, 3 H), 3.35 (dm, J = Hz, H-4′), 2.81 (dm, J m= 17 Hz, H-4), 2.5–1.4 (br, 4 H); high-resolution mass spectrum, m/e 333.1213 (calcd for $C_{17}H_{19}NO_6$ 333.1211). The ratio of lactones **2g**/**4g** in the crude reaction mixture could not be accurately determined because of overlap in the proton NMR spectrum of absorptions for OMe and H-1 of **4g** and H-4,4′ of **2g**.

Baeyer–Villiger Oxidations with *m*-Chloroperbenzoic Acid. General Procedure. Method B. To the appropriate *N*-carboalkoxy-2-azabicyclo[2.2.2]octan-5-one 1 (0.5 mmol) in 20 mL of methylene chloride were added *m*-chloroperbenzoic acid (1.2 mmol, 85% by iodometric titration) and 0.09 g of sodium bicarbonate (1.1 mmol). The mixture was stirred in the dark for 3–5 days and then washed with saturated aqueous sodium sulfite (4 × 5 mL) followed by cold saturated aqueous sodium bicarbonate (2 × 5 mL). The organic layer was dried and filtered, and the solvent was removed in vacuo to afford a crude mixture of lactones **2** and **4**. Further purification was effected by preparative thin-layer chromatography with ether as the developing solvent. Products were separated from the column support with warm ethyl acetate. The following oxidations were performed by the general procedure.

***N*-Carbobenzoxy-2-oxa-3-oxa-6-azabicyclo[3.2.2]nonane (2a) and *N*-Carbobenzoxy-2-oxo-3-oxa-6-azabicyclo[3.2.2]nonane (4a).** Ketone **1a** (190 mg, 0.73 mmol) after 42 h afforded 200 mg of a mixture of lactones. Preparative TLC (2:1 ethyl acetate/hexane) afforded 110 mg (55%) of lactone **2a** at R_f 0.26 and 50 mg (25%) of lactone **4a** at R_f 0.4: NMR ($CDCl_3$) δ 7.30 (s, 5 H), 5.15 (s, 2 H), 4.65 (br, H-5), 4.3 (br, H-4,4′), 3.85 (dt, J = 14, 2 Hz, H-7n), 3.55 (dd, J = 14, 5 Hz, H-7x), 3.10 (br, H-1), 2.3–1.8 (br, 4 H). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.24; N, 5.09. Found: C, 65.62; H, 6.12; N, 4.87.

Lactones 2b and 4b. An 80:20 mixture of *N*-carbethoxy-3-*exo*- and -3-*endo*-methyl ketones **1b** and **1f** (122 mg, 0.57 mmol) after 24 h afforded 124 mg of a mixture. TLC purification afforded 14 mg of ketones **1b** and **1f**, 42 mg (37%) of lactones **2b**/**2f**, and 40 mg (35%) of lactones **4b**/**4f**. It was not possible to separate **2b** from **2f** or **4b** from **4f**; however, a **2b**,**f**/**4b**,**f** ratio of 56:44 was determined from the NMR spectrum by comparison of the combined integrated areas of H-4,4′ for **2b**,**f** (δ 3.30 and 2.72) with twice that of H-1 of **4b**,**f** (δ 3.00). In order to correct for the presence of **1f** in the reaction mixture the observed **2b**,**f**/**4b**,**f** ratio was corrected for 20% of an 80:20 ratio of **2f**/**4f**. The ratio of **2b**/**4b** is 50:50 by NMR before chromatography and 43:57 after TLC.

Lactone 2c and *N*-Carbobenzoxy-2-oxo-3-oxa-6-aza-7-*exo*-phenylbicyclo[3.2.2]nonane (4c). *N*-Carbobenzoxy-3-*exo*-phenyl ketone **1c** (400 mg, 1.2 mmol) after 72 h afforded 385 mg of a mixture of lactones. Preparative TLC (2:1 hexane/ethyl acetate, triple development) gave 150 mg (36%) at R_f 0.33 of the lactone **2c** and 79 mg (19%) R_f 0.48 of the lactone **4c**: mp 123–125 °C (ether); NMR ($CDCl_3$) δ 7.30 (s, 10 H), 5.38 (br, H-7n), 5.11 (br, 2 H), 4.79 (br, H-5), 4.33 (br t, J = 14 Hz, H-4,4′), 3.31 (br, H-1), 2.46–1.49 (br, 4 H). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.98. Found: C, 71.55; H, 6.00; N, 3.92. NMR analysis of the crude mixture of lactones indicated a 60:40 ratio of **2c**/**4c** by comparison of the integrated intensities for H-4,4′ of **2c** with twice that of H-1 of **4c**.

Lactones 2d and 4d. *N*-Carbobenzoxy-3-*exo*-carbomethoxy ketone **1d** (75 mg, 0.23 mmol) after 72 h afforded 53 mg of a mixture of lactones. Preparative TLC (ether) gave 8 mg (11%) at R_f 0.23 of lactone **2d** and 36 mg (48%) at R_f 0.30 of lactone **4d**.[4] The ratio of lactones **2d**/**4d** in the crude reaction mixture could not be accurately determined by proton NMR because of partial overlap of the methyl ester signals at δ 3.60 with those of H-1 of **4d** at δ 3.40 and H-4 of **2d** at δ 3.35.

Lactones 2e and 4e. *N*-Carbobenzoxy-3-*exo*-methyl benzoate ester ketone **1e** (100 mg, 0.25 mmol) after 72 h afforded 80 mg of a lactone mixture. TLC (2:1 hexane/ethyl acetate, triple development) gave 17 mg (17%) at R_f 0.20 of the lactone **2e** and 26 mg (25%) at R_f 0.28 of the lactone **4e**. A **2e**/**4e** ratio of 60:40 in the crude lactone mixture was determined by NMR comparison

(15) It has been reported[4] that lactone **2c** could not be obtained with sodium acetate buffered peracetic acid in acetic acid at 2 °C but that the lactone **4c** was obtained.

of the integrated intensities of H-4,4′ of **2e** with twice that of H-1 of **4e**.[16]

***N*-Carbobenzoxy-2-oxa-3-oxo-6-aza-7-*endo*-methylbicyclo[3.2.2]nonane (2f) and *N*-Carbobenzoxy-2-oxo-3-oxa-6-aza-7-*endo*-methylbicyclo[3.2.2.]nonane (4f).** *N*-Carbobenzoxy-3-*endo*-methyl ketone **1f** (152 mg, 0.55 mmol) after 64 h afforded 140 mg of a mixture. Preparative TLC (1:1 hexane/ether) afforded at R_f 0.31 ketone **1f** (18 mg), at R_f 0.11 was 82 mg (51%) of lactone **2f** [NMR ($CDCl_3$) δ 7.45 (s, 5 H), 5.23 (s, 2 H), 4.7–4.4 (m, 2 H), 4.15 (br, H-7x), 2.95 (td, H-4,4′), 2.6–1.5 (br, 4 H), 1.40 (d, J = 7 Hz, 3 H);[17] IR (neat) 1690, 1730 cm^{-1}; high-resolution mass spectrum, m/e 289.1293, (calcd for $C_{16}H_{19}NO_4$ 289.1314)], and at R_f 0.13 was 19 mg (12%) of lactone **4f**: NMR ($CDCl_3$) δ 7.39 (s, 5 H), 5.21 (s, 2 H), 4.93–4.53 (m, H-5), 4.33 (m, H-4,4′), 4.03 (br, H-7x), 3.05 (m, H-1), 2.43–1.53 (br, 4 H), 1.34 (d, J = 6 Hz, 3 H); high-resolution mass spectrum, m/e 289.1307, calcd for $C_{16}H_{19}NO_4$ 289.1314. It was not possible to accurately determine the ratio **2f**/**4f** from the NMR spectrum of the crude reaction mixture because of overlap of H-1 of **4f** with H-4 of **2f**.

(16) Professor A. Holmes, University Chemical Laboratory, Cambridge, has found a 65:35 ratio of **2e**/**4e** with *m*-chloroperbenzoic acid/sodium bicarbonate (46% yield); personal communication.

(17) An NMR comparison of **2f** with a spectrum of the corresponding *N*-carbethoxy analogue provided by Professor M. Natsume, Research Foundation Itsuu Laboratory, Tokyo, Japan, was positive (see ref 3).

Lactones 2g and 4g. *N*-Carbobenzoxy-3-*endo*-carbomethoxy ketone **1g** (75 mg, 0.23 mmol) after 72 h afforded 90% unreacted ketone **1g**. After 3 weeks, 70 mg of a mixture was obtained which upon preparative TLC afforded 11 mg of ketone **1g**, 21 mg (32%; R_f 0.21) of lactone **2g** and 34 mg (53%; R_f = 0.32) of lactone **4g**. A ratio of **2g**/**4g** could not be accurately determined by proton NMR analysis of the crude reaction mixture.

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Registry No. **1a**, 69386-57-8; **1b**, 83681-60-1; **1c**, 83681-61-2; **1d**, 65961-22-0; **1e**, 65961-25-3; **1f**, 83681-62-3; **1g**, 83709-53-9; **2a**, 69386-58-9; **2b**, 83681-63-4; **2c**, 83681-64-5; **2d**, 83681-65-6; **2e**, 83681-66-7; **2f**, 83681-67-8; **2g**, 83709-54-0; **4a**, 69386-59-0; **4b**, 83681-69-0; **4c**, 83681-70-3; **4d**, 65961-28-6; **4e**, 65961-29-7; **4f**, 83681-68-9; **4g**, 83709-55-1; PAA, 79-21-0; MCPBA, 937-14-4; trifluoroacetic anhydride, 407-25-0.

Supplementary Material Available: Spectral data, experimental details, and analytical data are available for **1b,c,f,g**, for the trifluoroperacetic acid and *p*-nitroperbenzoic acid oxidations of **1a**, for the preparation of the *N*-carbophenoxy- and *N*-(2,2,2-trichloroethoxy)carbonyl analogues of **1a** and the oxidation of these, and for the *N*-carbethoxy analogues of **1a** with peracetic and *m*-chloroperbenzoic acids (11 pages). Ordering information is given on any current masthead page.

Synthesis of (Polyfluoroalkyl)pyrroles and -porphyrins

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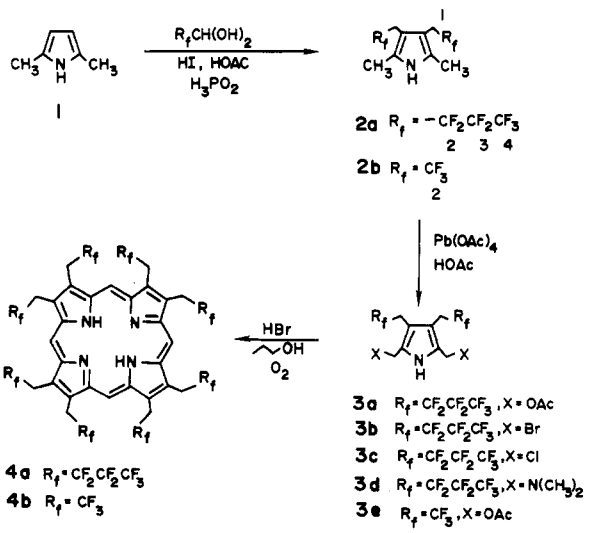
Octakis(1*H*,1*H*-heptafluorobut-1-yl)porphyrin **4a** has been prepared by acid-catalyzed self-condensations of 2,5-disubstituted acetoxymethyl, bromomethyl, and chloromethyl derivatives of 2,5-dimethyl-3,4-bis(1*H*,1*H*-heptafluorobut-1-yl)pyrrole (**2a**). The 2,5-bis[(dimethylamino)methyl] derivative **3e** failed to undergo a similar conversion to **4a**. Octakis(1*H*,1*H*-trifluoroeth-1-yl)porphyrin **4b** was prepared from the bis(acetoxymethyl)pyrrole **3e**, the lead tetraacetate oxidation product of **2b**. Pyrroles **2a,b** were obtained from the reductive alkylation of 2,5-dimethylpyrrole with the corresponding polyfluoro aldehyde hydrates. An alternate, more efficient conversion to porphyrin **4a** was achieved by the acid-catalyzed condensation of formaldehyde with 2,5-diiodopyrrole **6**. Pyrrole **6** was readily obtained from **2a** by oxidation with excess sulfuryl chloride and hydrolysis in aqueous THF followed by iodinative decarboxylation of the intermediate dicarboxypyrrole **5**.

In connection with a research program directed toward the preparation of perfluorinated porphyrins we report facile syntheses of octakis(1*H*,1*H*-heptafluorobut-1-yl)-porphyrin **4a** and octakis(1*H*,1*H*-trifluoroeth-1-yl)-porphyrin **4b**, two novel, polyfluorinated analogues of octabutyl and octaethylporphyrin. Each synthesis employs a functionalized derivative of the 2,5-dimethyl-3,4-bis-(polyfluoroalkyl)pyrroles **2a,b** as key intermediates in unprecedented pyrrole condensations leading to porphyrin.

Pyrroles **2a,b** were obtained from readily available 2,5-dimethylpyrrole by reductive alkylation with heptafluorobutyraldehyde hydrate and trifluoroacetaldehyde hydrate (Scheme I). This general alkylation procedure which is an extention of the pyrrole alkylations described by MacDonald[1,2] has proven to be of great utility in the preparation of tetrasubstituted pyrroles.

The oxidation of **2a,b** with lead tetraacetate in acetic acid at room temperature afforded the stable bis(acetoxymethyl) derivatives **3a,e** in nearly quantitative yields. Heating of **3a,e** under reflux with HBr in aqueous alcohol in the presence of oxygen provided porphyrins **4a,b**, which precipitated from the reaction mixture in 20% and 31% yields, respectively.

Scheme I



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