A Novel Heck Arylation Reaction: Rapid Access to Congeners of FR 900482

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Abstract: The C-6–C-7 bond of the epoxybenzazocine core of the antitumor FR 900482 series can be closed in high yield via a Heck arylation reaction of a 6-iodo-7,13-methylene seco precursor.

Recently, the isolation of two natural products containing the highly unusual 1,5-epoxybenzazocine[1] ring system has been reported.[2] In addition to their unique structure, FR 900482 (**1**) and FR 66979 (**2**) exhibit potent antitumor properties. Even more promising activity is manifested by the semisynthetic triacetate FK 973 (**3**).[2] This result suggests, but does not prove, that the free hydroxyl groups at C-5 and C-8 are not crucial for activity.[3] The activity of semisynthetic compounds (cf., **4** and **5**) demonstrates that free hydroxy groups at C-5 and C-12 are not critical for biological function.[4] Interestingly, derived decarbamoyl congener **11a** also evidences extremely potent activity.[4] By analogy to mitomycin K, the presence of the exocyclic olefin in **11a** may have ramifications on the possible mode of action by favoring the DNA alkylation.[5] In spite of the tantalizing relationship to the mitomycins[6] and leucoaziridinomitosenes,[7] no convincing evidence connecting the *in vivo* mechanism of action of the two drug structures has been offered.[8]

Not surprisingly, the potential of clinically useful aziridinoepoxybenzazocines, in concert with their novel and challenging structures of the natural and semisynthetic drugs, has brought forth many approaches aimed at achieving a total synthesis or gaining access to the generalized ring system.[9] Our focusing goal in undertaking the study described below was to accomplish the total synthesis of **1** (or **2**). In addition to attaining this primary goal, synthetic studies might reach various blocked versions of these compounds which seem to rival or surpass the natural products in terms of biological promise. Below, we describe a route to methylated congeners of the drugs. While falling short of the total synthesis, the chemistry which has been achieved reaches the active structural types in a particularly expeditious fashion.

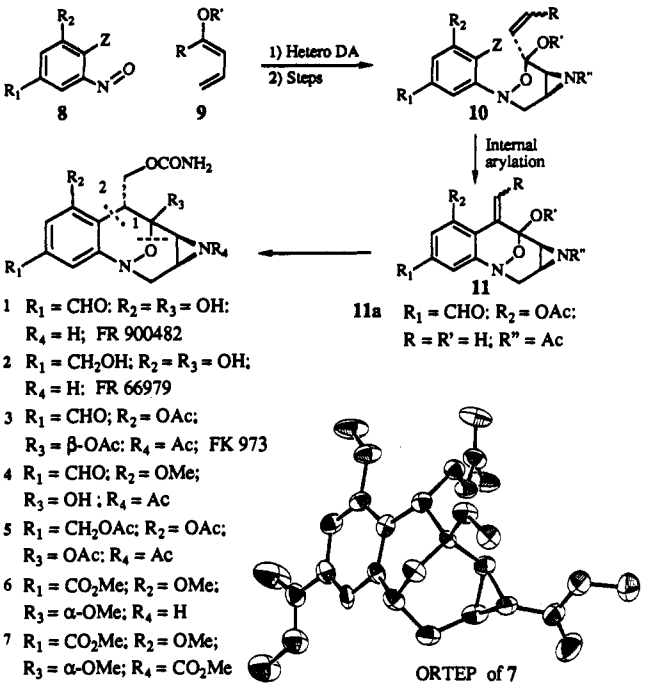
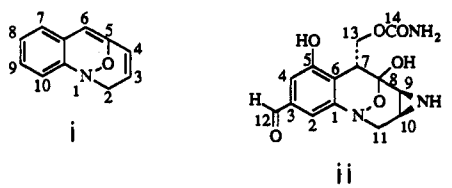


Figure 1.

Hitherto, all approaches, including the only successful total synthesis of **1** by Fukuyama,[10] have been founded on the logic implied in disconnection line 1 (see structures **1–7**, Figure 1). We came to consider the feasibility of a radically different construction, implied in disconnection line 2, wherein the benzoxazine ring system is established by intramolecular arylation of a suitably substituted seco system *bearing a fused aziridine* (cf. **10** → **11**). An attractive feature of this speculative proposal was that relevant prospective cyclization substrates might be rapidly assembled by cycloaddition of **8** and **9** followed by appropriate functionality adjustments. Herein, we report a synthesis of **6** through realization of this idea.

The requisite heterodienophile **12** was prepared following five straightforward steps (38% overall yield) from methyl vanillate:

(1) The nomenclature is based on a Chemical Abstract parent structure, 2*H*-1,5-epoxy-1-benzazocine (i). The numbering of FR 900482 (ii) in this manuscript will follow the convention used in the isolation paper (see ref 2a).



(2) (a) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyato, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108. (b) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. (c) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okumura, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *Ibid.* **1987**, *40*, 594. (d) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145.

(3) Alternatively, **3** could be viewed as leading to **1** by deacetylation.

(4) (a) Kohsaka, M.; et al. U.S. Patent 4 861 774, 1989. (b) Kohsaka, M.; et al. U. S. Patent 4 645 765, 1987.

(5) (a) Benbow, J. W.; Schulte, G. K.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 915. (b) Kohn, H.; Hong, Y. P. *J. Am. Chem. Soc.* **1990**, *112*, 4596.

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(8) Williams, R. M.; Rajski, S. R. *Tetrahedron Lett.* **1992**, *33*, 2929.

(9) (a) Yasuda, N.; Williams, R. M. *Tetrahedron Lett.* **1989**, *30*, 3397. (b) Goto, S.; Fukuyama, T. *Tetrahedron Lett.* **1989**, *30*, 6491. (c) Jones, R. J.; Rappoport, H. *J. Org. Chem.* **1990**, *55*, 1144. (d) McClure, K. F.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 850. (e) McClure, K. F.; Benbow, J. W.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 8185. (f) Dmitrienko, G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705.

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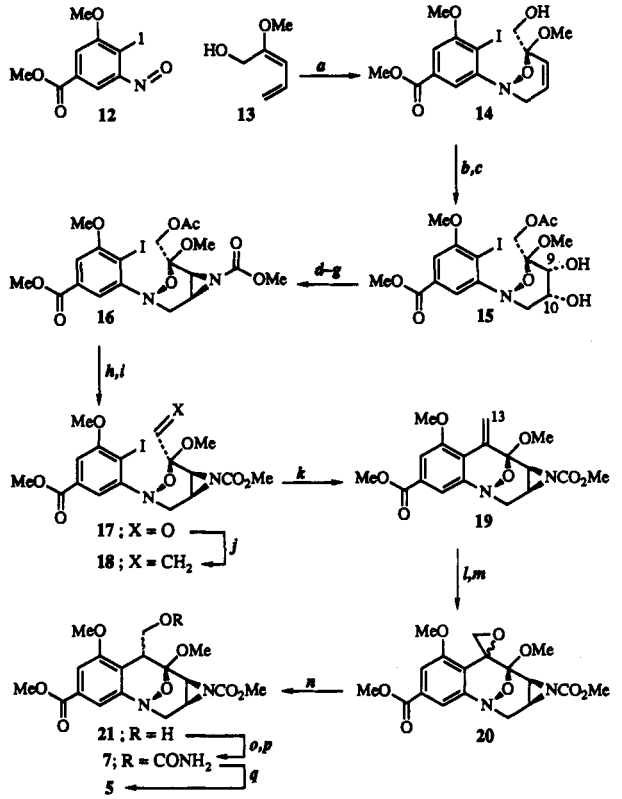
Scheme I[a]



[a] (a) $NaHCO_3$, PhH, 80 °C, 15 min, 70%. (b) Catalytic OsO_4, NMO, $PhH/THF/H_2O$, 50 °C, 28 h, 90% based on recovered **14**. (c) AcCl, Py, CH_2Cl_2, −78 °C, 30 min, 63%. (d) Tf_2O, Py, CH_2Cl_2, 0 °C, 5 min; then Bu_4NN_3, DMF, 23 °C, 2 h, 75%. (e) Tf_2O, Py, CH_2Cl_2, 0–23 °C, 1 h, 84%. (f) Ph_3P, THF, 23 °C, 3 h; then aqueous (pH 10.5) NH_4OH, 15 min. (g) $ClCO_2Me$, Py, CH_2Cl_2, 0 °C, 10 min, 97% yield for f and g. (h) K_2CO_3, $MeOH/H_2O$, 23 °C, 1 h, 93%. (i) Swern oxidation, quant. (j) Ph_3PCH_3Br, $NaN(TMS)_2$, THF, −78–23 °C, 4 h, 83%. (k) Catalytic $Pd(PPh_3)_4$, 12 equiv of Et_3N, CH_3CN, 80 °C, 10 h, 90%. (l) Catalytic OsO_4, NMO, $THF/CH_2Cl_2/H_2O$, 23 °C, 44 h, 89%. (m) DIAD, Ph_3P, CH_2Cl_2, 23 °C, 36 h, 76%. (n) Catalytic $FeCl_3$, CH_2Cl_2, 23 °C, 40 min; then $LiAlH(O\text{-}t\text{-}Bu)_3$, THF, 0 °C, 5 min, 50%. (o) $ClCO_2Ph$, Py, CH_2Cl_2, 0 °C, 10 min, 89%. (p) NH_3, *i*-PrOH, 23 °C, 2 h, 86%. (q) K_2CO_2, $MeOH/H_2O$, 23 °C, 36 h, 67%.

(i) nitration,[11] (ii) triflation (Tf_2O/Py), (iii) iodine incorporation (NaI; DMSO; 70 °C), (iv) reduction (Zn/NH_4Cl), and (v) chromic acid oxidation. Heterodiene **13** was obtained in one step (55% yield) by reaction of the known 1-lithio-1-methoxybutadiene[12] with paraformaldehyde. Smooth cycloaddition occurred under the conditions shown providing a 70% yield of **14** (Scheme I).

The double-bond linkage in **14** was now targeted for aziridination by adaptation of previous methods in our mitomycin program[13]—in turn, influenced to no small extent by the earlier works of Kishi.[14] Stereoselective osmylation of the olefin was followed by selective acetylation of the primary alcohol (see compound **15**). Selective triflation at C-10 followed by azidolysis of the triflate set the stage for triflation of the C-9 alcohol. Reduction of the azide with triphenylphosphine[15] was followed by hydrolysis of the phospine imine. Carbomethoxylation of the resultant aziridine afforded compound **16**. The latter was converted to aldehyde **17** by deacetylation followed by Swern oxidation.[16] Systems of type **10** were obtained by Wittig reactions of this aldehyde. Here we focus on the parent vinyl compound.[17] Methylenation of **17** with methylenetriphenylphosphorane, under the conditions shown, afforded **18** which was to serve as the substrate for the all-critical attempt at cycloarylation.

*In the event, treatment of **18** with catalytic tetrakis(triphenylphosphine)Pd(0) in acetonitrile containing triethylamine*[18] *afforded a 90% yield of **19**.* The introduction of the carbamoyloxy function at C-13 proved to be more difficult than expected. It was accomplished in the somewhat lengthy, though decent-yielding, sequence shown. Osmylation of **19** produced a 6:1 mixture of diols (stereochemistry undetermined) which, on treatment with diisopropyl azodicarboxylate and triphenylphosphine,[19] gave rise to epoxides **20** (ca. 6:1). Treatment of the mixture—or the individual epoxides!—with catalytic $FeCl_3$[20] followed by immediate reduction of the resultant aldehyde afforded descarbamoyl FR 900482 analog **21**, from whence bis-carbamoyl derivative **7** was obtained by the usual 2 step sequence:[21] (i) carbophenoxylation and (ii) ammonolysis. The assignment of stereochemistry to compound **7** was vouchsafed by crystallographic means.[22] Finally, prolonged treatment of **7** with potassium carbonate/methanol afforded **6** in 67% yield.[23]

Attempts were then made to convert **6** to natural products **1** (or **2**). While the reduction of the methyl ester to the primary alcohol was demonstrated, the removal of the methyl ether "protective groups" proved to be incompatible with the preservation of the aziridine functionality. Nonetheless, the route described here is the most concise entry to the active structural series and could possibly lead to the total synthesis by the selection of alternate protecting groups on the oxygens of C-5 and C-8.

Experimental Section

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1420 ratio recording spectrometer and a Nicolet SX FTIR spectrometer. Low-resolution mass spectra were obtained using a Hewlett-Packard HP-5989A MS Engine mass spectrometer; high-resolution mass spectra were obtained using a Kratos MS80RFA mass spectrometer. Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker WM-250 or a General Electric QE-300 spectrometer. X-ray crystallographic diffraction measurements were made on an Enraf Nonius CAD4 fully automated diffractometer, and the structure solution was accomplished using a VAX 4000 workstation. Combustion analyses were performed by Robertson Laboratory, Inc.

Continous wave IR spectra were calibrated to 1601 cm^{-1} using a polystyrene film standard. All reported IR intensities are expressed subjectively as strong (s), medium (m), or weak (w). NMR chemical shifts are given in parts per million (ppm) downfield from internal tetramethylsilane (TMS) standard or relative to internal $CHCl_3$. Proton

(11) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015.

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(15) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) For a sixty year review, see: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.

(16) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(17) In a parallel study, the methyl enol ethers were shown to be competent substrates for the ensuing chemistry. A full account of this work will be provided in a subsequent report.

(18) For reviews of Heck arylations, see: (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (b) Heck, R. F. *Org. React.* (N.Y.) **1982**, *27*, 345.

(19) Robinson, P. L.; Barry, C. N.; Bass, W.; Jarvis, S. E.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 5396.

(20) Cf.: Corey, E. J.; Houpis, I. *J. Am. Chem. Soc.* **1990**, *112*, 8997.

(21) McLamore, W. M.; P'an, S. Y.; Bavley, A. *J. Org. Chem.* **1955**, *20*, 1379.

(22) Crystal data for **7**: orthorhombic space group $Pna2_1$ (No. 33); a = 13.5199(9) Å, b = 17.7879(9) Å, c = 16.819(1) Å, v = 4044.8(7) Å^3, Z = 4, with two molecules forming the asymmetric unit; R = 0.043 for 2349 unique observed [$I \geq 3s(I)$] reflections. Full details are given in the supplementary material.

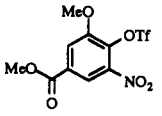
(23) For removal of acyl groups from aziridines, see: Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969; p 253 ff. (b) Heine, H. W.; Fetter, M. E.; Nicholson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202.

NMR (^{1}H NMR) are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; and m, multiplet), number of protons, and coupling constant(s) in hertz. Except for those high-resolution mass spectra indicated as requiring fast atom bombardment (FAB) ionization, all mass spectra were achieved by electron ionization (EI).

Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Methylene chloride, benzene, triethylamine, pyridine, and acetonitrile were distilled under a nitrogen atmosphere from calcium hydride. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under an inert atmosphere and stored over 3- or 4-Å molecular sieves. Solutions of *tert*-butyllithium in pentane were titrated regularly before use with 2,5-dimethoxybenzyl alcohol at 0 °C in THF.[24]

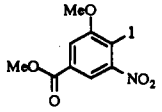
Chromatographic purifications were performed with EM Science (E. Merck) 230–400-mesh silica gel. Reactions and chromatography fractions were monitored and analyzed by thin layer chromatography (TLC) using EM Science (E. Merck) 250-μm 60 F_{254} silica plates.

3-Methoxy-5-nitro-4-(trifluoromethanesulfonyl)benzoic Acid Methyl Ester (A). To a stirred solution of 4-hydroxy-3-methoxy-5-nitro-4-benzoic acid methyl ester[11] (14.25 g, 62.7 mmol) in 125 mL of CH_2Cl_2 and 7.6 mL (94 mmol) of pyridine was added triflic anhydride (11.0 mL, 65 mmol) dropwise at 0 °C under an argon atmosphere. The resulting bronze



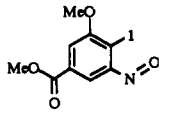
solution was stirred for 30 min at 0 °C before quenching the reaction with 100 mL of 2.5% aqueous HCl and extracting with CH_2Cl_2 (1 × 50 mL, then 2 × 25 mL). The combined CH_2Cl_2 extracts were washed with saturated aqueous Na_2CO_3 (2 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL) and dried over $MgSO_4$. Filtration through a 50-g plug of silica, rinsing with CH_2Cl_2, gave, on concentration, 20.0 g (88%) of A as a colorless solid: mp 79–80 °C; IR ($CHCl_3$) 1730 (s), 1550 (s), 1435 (s), 1350 (m), 1310 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.06 (s, 3H), 7.96 (d, 1H, J = 1.8 Hz), 8.29 (d, 1H, J = 1.8 Hz); MS (EI, 20 eV) m/z (M^+) 359 (31), 226 (100), 151 (21). Anal. Calcd for $C_{10}H_8F_3NO_8S$: C, 33.43; H, 2.24; N, 3.90. Found: C, 33.41; H, 2.03; N, 3.78.

4-Iodo-3-methoxy-5-nitrobenzoic Acid Methyl Ester (B). A stirred solution of triflate A (20.0 g, 55.6 mmol) and NaI (12.6 g, 84 mmol) in 40 mL of dimethyl sulfoxide (DMSO) was heated at 70 °C under an argon atmosphere for 39 h. The black reaction mixture was then cooled



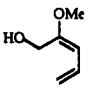
to room temperature; the reaction was quenched with 150 mL of saturated aqueous $Na_2S_2O_3$, and the mixture was filtered into a separatory funnel. The aqueous mixture was extracted with EtOAc (1 × 150 mL, 3 × 75 mL); the combined extracts were washed with saturated aqueous $NaHCO_3$ (3 × 75 mL), saturated aqueous $Na_2S_2O_3$ (1 × 75 mL), water (3 × 75 mL), and brine (1 × 75 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave 17 g of a yellow solid. Recrystallization (EtOAc/hexanes) and flash column chromatography (4:6) Et_2O/hexanes of the resultant mother liquor gave a combined total of 16.0 g (84%) of B as a yellow solid: mp 123–124 °C; R_f = 0.48 (8:2 Et_2O/hexanes); IR ($CHCl_3$) 1730 (s), 1545 (s), 1460 (m), 1370 (m), 1300 (s), 1260 (s), 1070 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.02 (s, 3H), 7.60 (d, 1H, J = 1.8 Hz), 7.92 (d, 1H, J = 1.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.86, 57.44, 85.96, 113.15, 117.26, 132.26, 155.43, 159.87, 164.52; MS (EI, 20 eV) m/z (M^+) 337 (100), 306 (15), 245 (21), 149 (27). Anal. Calcd for $C_9H_8INO_5$: C, 32.07; H, 2.39; N, 4.16. Found: C, 32.38; H, 2.30; N, 4.01.

4-Iodo-3-methoxy-5-nitrosobenzoic Acid Methyl Ester (12). To a stirred, hot (80 °C), yellow solution of B (8.0 g, 23.7 mmol) and ammonium chloride (476 mg, 8.9 mmol) in 25 mL of MeOH, 25 mL of THF, and 15 mL of H_2O was added, in one portion, 9.3 g of zinc dust. The resulting brown/grey suspension became noticeably exothermic but after 5 min,



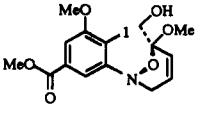
settled to a gentle reflux. After an additional 10 min, the yellow/white suspension was filtered into a separatory funnel, rinsing with hot EtOAc. The filtrate was washed with water (2×) and brine (1×) and concentrated to ca. 7 g of a yellow solid. The crude hydroxylamine thus generated was dissolved in 100 mL of acetone and 30 mL of water and cooled to 0 °C. To this cold, stirred solution was added dropwise 15 mL of Jones reagent (1.33 M, derived from dilution of a stock[25] 2.67 M solution with water) over 5 min. After an additional 10 min, 8 mL of 2-propanol was added; the ice bath was removed, and the mixture was allowed to warm to room temperature. After 20 min, Celite (10 g) was added and the greenish/brown suspension was filtered through a plug of Celite, rinsing with 700 mL of CH_2Cl_2. The CH_2Cl_2 filtrate was washed with water (2 × 200 mL) and concentrated *in vacuo* to 5 g of a green/brown solid. Purification by flash column chromatography (15:85 EtOAc/hexanes) gave 4.0 g (52%) of **12** as a bright green solid: mp 153–155 °C; IR ($CHCl_3$) 1730 (m), 1510 (m), 1440 (m), 1390 (m), 1300 (s), 1220 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.10 (s, 3H), 6.38 (d, 1H, J = 1.6 Hz), 7.68 (d, 1H, J = 1.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.73, 57.35, 102.35, 107.76, 115.41, 131.14, 160.40, 162.60, 165.46; MS (EI, 20 eV) m/z (M^+) 321 (100), 307 (27), 276 (28), 245 (37), 164 (35). Anal. Calcd for $C_9H_8INO_4$: C, 33.67; H, 2.51; N, 4.36. Found: C, 33.92; H, 2.27; N, 4.19.

2-Methoxy-2,4-pentadien-1-ol (13). To a stirred solution of 1-methoxy-1,3-butadiene (10.0 g, 0.12 mol) in 150 mL of THF was added *tert*-butyllithium (1.5 M in pentane, 85 mL, 0.13 mmol) *via* cannula over 35 min at −78 °C under an argon atmosphere. The resulting green/brown



solution was slowly allowed to warm to −20 °C over 1 h 45 min before cooling back to −78 °C. The argon line was momentarily removed along with the septum sealing the reaction vessel to facilitate the addition of 16 g of paraformaldehyde (dried overnight/P_2O_5 under high-vacuum) in one portion. The argon atmosphere was restored and the mixture stirred for 8 h at −78 °C before allowing it to warm overnight (9 h). The reaction was then quenched with dilute aqueous NH_4Cl (200 mL) and extracted with Et_2O (3 × 100 mL). The ether extracts were washed with water (2 × 75 mL) and brine (1 × 75 mL) and dried over K_2CO_3. Filtration and concentration by atmospheric distillation gave 9 g of a light yellow oil. Purification by high-vacuum (3 mm) distillation gave 7.5 g (55%) of **13** as a colorless liquid: bp 67–70 °C (3 mm); IR ($CHCl_3$) 3580 (m), 3400 (w), 1710 (m), 1650 (s), 1450 (m), 1400 (m), 1220 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.85 (t, 1H, J = 6.2 Hz), 3.63 (s, 3H), 4.29 (d, 2H, J = 6.2 Hz), 4.91 (dd, 1H, J = 10.2, 1.6 Hz), 5.10 (dd, 1H, J = 16.6, 1.6 Hz), 5.38 (d, 1H, J = 10.8), 6.48 (ddd, 1H, J = 16.6, 10.8, 10.2 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 54.26, 58.88, 102.09, 112.70, 131.02, 157.22. Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.15; H, 9.06.

3-(3,6-Dihyro-6-(hydroxymethyl)-6-methoxy-2*H*-1,2-oxazin-2-yl)-4-Iodo-5-methoxybenzoic Acid Methyl Ester (14). To a stirred, hot (80 °C) suspension of **12** (4.2 g, 13.1 mmol) and solid $NaHCO_3$ (6.6 g, 78.5 mmol) in 26 mL of benzene was added **13** (3 mL, 26 mmol). The resulting



mixture was vigorously stirred under a N_2 atmosphere for 15 min, cooled to room temperature, and filtered, rinsing with EtOAc. Concentration of the filtrate *in vacuo* and purification of the brown residue by flash column chromatography (4:6 EtOAc/hexanes) gave 4.0 g (70%) of **14** as a colorless solid: mp 148–150 °C; R_f = 0.33 (8:2 Et_2O/hexanes); IR($CHCl_3$) 3580 (w), 3400 (w), 1720 (s), 1580 (s), 1410 (s), 1340 (s), 1250 (s), 1110 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.34 (br t, 1H, J = 6.5 Hz), 3.60 (s, 3H), 3.47–3.93 (m, 4H), 3.94 (s, 3H), 3.96 (s, 3H),

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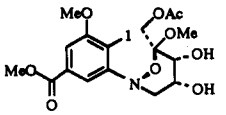
5.92 (dt, 1H, J = 10.0, 2.0 Hz), 6.36 (dt, 1H, J = 10.0, 3.2 Hz), 7.33 (d, 1H, J = 1.8 Hz), 7.81 (d, 1H, J = 1.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.33, 53.27, 54.21, 56.74, 66.62, 91.14, 101.79, 108.60, 114.85, 125.52, 129.63, 132.02, 153.19, 158.54, 166.18; MS (EI, 20 eV) m/z (M^+) 435 (40), 404 (17), 323 (90), 114 (100). Anal. Calcd for $C_{15}H_{18}INO_6$: C, 41.40; H, 4.17; N, 3.22. Found: C, 41.65; H, 4.14; N, 3.22.

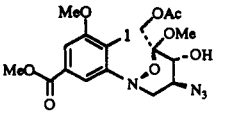
Diol Acetate 15. To a stirred, hot (50 °C) solution of **14** (7.0 g, 16.1 mmol) and 4-methylmorpholine *N*-oxide (3.7g, 32.2 mmol) in 33 mL of benzene, 12 mL of THF, and 4 mL of water was added a solution of OsO_4 (0.196 M in THF, 4.1 mL, 0.8 mmol) under a N_2 atmosphere. The



resulting mixture was vigorously stirred at 50 °C for 28 h (longer periods did not increase the percent conversion) before cooling to room temperature, quenching the reaction with saturated aqueous $NaHSO_3$ (100 mL), and extracting with EtOAc (4 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHSO_3$ (2 × 50 mL), water (2 × 50 mL), and brine (1 × 50 mL) and dried over Na_2SO_4. Filtration and concentration *in vacuo* gave a mixture of triols and starting olefin **14**. Recrystallization (EtOAc) and flash column chromatography (EtOAc) of the mother liquor gave a combined total of 4.4 g (58%) of a mixture of triols in a 5.5:1 ratio, as determined by proton magnetic resonance (^{1}H NMR). Recovered was 2.3 g (32%) of starting olefin **14**. While not chromatographically feasible, the triol isomers could be separated. The major isomer could be obtained from the recrystallization; the minor isomer required chemical methods. Conversion to a single 1,3-acetonide and a mixture of 1,2-acetonides (2-methoxypropene/TsOH/CH_2Cl_2), chromatographic separation (8:2 Et_2O/hexanes) isolating the lowest R_f (0.4 Et_2O) material, and removal of the acetonide (0.1 M TsOH/MeOH) gave the minor triol isomer as a colorless solid: mp 134–136 °C dec; R_f = 0.23 (EtOAc); IR ($CHCl_3$) 3530 (s), 1719 (s), 1577 (s), 1453 (s), 1430 (s), 1400 (s), 1337 (s), 1250 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (br s, 1H), 3.14 (br d, 2H, J = 14.2 Hz), 3.35 (s, 3H), 3.63 (dd, 1H, J = 12.8, 3.0 Hz), 3.70–4.10 (m, 5H), 3.95 (s, 3H), 3.97 (s, 3H), 7.36 (d, 1H, J = 1.0 Hz), 7.80 (d, 1H, J = 1.0 Hz); MS (EI, 20 eV) m/z (M^+) 469 (11), 349 (18), 336 (71), 320 (100). The major triol was isolated as a colorless solid: mp 141–143 °C dec; R_f = 0.24 (EtOAc); IR (KBr) 3420 (s), 2936 (s), 1720 (s), 1575 (s), 1400 (s), 1330 (s), 1250 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (br s, 1H), 2.61 (br s, 1H), 2.90 (br t, 1H, J = 11.0 Hz), 2.99 (d, 1H, J = 4.3 Hz), 3.24 (s, 3H), 3.42 (dd, 1H, J = 11.6, 4.7 Hz), 3.77 (dd, 1H, J = 12.0, 4.7 Hz), 3.85–3.92 (m, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 4.01 (t, 1H, J = 4.0 Hz), 4.48 (m, 1H), 7.32 (d, 1H, J = 1.4 Hz), 7.80 (d, 1H, J = 1.4 Hz); MS (EI, 20 eV) m/z (M^+) 469 (6), 336 (31), 320 (100); high-resolution MS m/z calcd for $C_{15}H_{20}INO_8$ (M^+) 469.0232, found 469.0246.

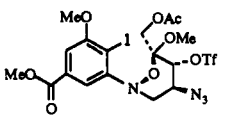
In practice, it was more convenient to carry the mixture of triols through a subsequent step. To a cold (–78 °C), stirred solution of the triol mixture (940 mg, 2.0 mmol) in 20 mL of CH_2Cl_2 and 1.45 mL (18.0 mmol) of pyridine was added slowly acetyl chloride (0.14 mL, 2.0 mmol) under a N_2 atmosphere. After 30 min, the cold bath was removed; the reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with aqueous NH_4Cl (2×), water (1 ×), and brine (1×) and dried over Na_2SO_4. Filtration and concentration *in vacuo* gave ca. 1.1 g of a light yellow foam. Purification by flash column chromatography (85:15 Et_2O/hexanes followed by EtOAc) gave 650 mg (63%) of diol acetate **15**, 130 mg of a mixture of peracetyl compounds, and 35 mg (4%) of the starting triol. Diol acetate **15** was isolated as a colorless solid: mp 170–180 °C dec; IR ($CHCl_3$) 3550 (m), 1710 (s), 1575 (s), 1455 (m), 1436 (m), 1408 (s), 1379 (m), 1336 (s), 1246 (s) cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) 2.18 (s, 3H), 2.50 (d, 1H, J = 9.9 Hz), 2.87 (t, 1H, J = 11.1 Hz), 3.24 (s, 3H), 3.44 (m, 2H), 3.74 (t, 1H, J = 4.0 Hz), 3.95 (s, 3H), 3.96 (s, 3H), 4.18 (d, 1H, J = 12.1 Hz), 4.47 (m, 1H), 4.53 (d, 1H, J = 12.1 Hz), 7.33 (d, 1H, J = 1.8 Hz), 7.79 (d, 1H, J = 1.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.76, 48.76, 52.35, 56.35, 56.74, 58.57, 64.94, 66.48, 91.46, 102.28, 108.61, 114.78, 131.91, 152.60, 158.77, 166.32, 171.39; MS (EI, 20 eV) m/z (M^+) 511 (64), 365 (23), 336 (100), 319 (72). Anal. Calcd for $C_{17}H_{22}INO_9$: C, 39.94; H, 4.34; N, 2.74. Found: C, 40.11; H, 4.31; N, 2.65.

Azido Alcohol. To a stirred, colorless solution of diol acetate **15** (1.4 g, 2.7 mmol) in 27 mL of CH_2Cl_2 and pyridine (0.70 mL, 8.6 mmol) was added dropwise triflic anhydride (0.46 mL, 2.7 mmol) at 0 °C under a N_2 atmosphere. The resulting yellow solution was stirred for 5 min at



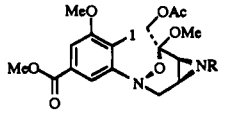
0 °C before being poured through a plug of silica, rinsing with 50 mL of CH_2Cl_2 and 80 mL of Et_2O. The filtrate was concentrated rapidly *in vacuo* to a yellow oil (the unstable triflate) which was diluted with 4 mL of DMF and added *via* cannula to a stirred solution of tetrabutylammonium azide[26] (4.5 g, 15.8 mmol) in 2.5 mL of DMF at room temperature. After 2 h, the reaction was quenched with water and the mixture extracted with EtOAc (4 × 50 mL). The organic extracts were washed with water (2 × 30 mL) and brine (1 × 30 mL) and dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography (6:4 Et_2O/hexanes) gave 1.1 g (75%) of the azido alcohol as a colorless foam: IR ($CHCl_3$) 2112 (s), 1721 (s), 1576 (m), 1408 (m), 1334 (m), 1247 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.04–3.08 (br m, 1H), 3.20 (br s, 1H), 3.38–3.52 (m, 2H), 3.42 (s, 3H), 3.82 (t, 1H, J = 4.6 Hz), 3.93 (s, 3H), 3.95 (s, 3H), 4.46 (br d, 1H, J = 12.6 Hz), 4.68 (br d, 1H, J = 12.6 Hz), 7.32 (d, 1H, J = 1.6 Hz), 7.78 (d, 1H, J = 1.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.89, 50.38, 52.44, 56.82 (2 C), 57.66, 59.65, 61.23, 91.38, 101.73, 108.96, 114.85, 132.05, 152.09, 158.81, 166.19, 170.91; MS (EI, 20 eV) m/z (M^+) 536 (2), 336 (100). Anal. Calcd for $C_{17}H_{21}IN_4O_8$: C, 38.07; H, 3.95; N, 10.45. Found: C, 38.30; H, 3.66; N, 10.30.

Azido Triflate. To a stirred solution of the azido alcohol (570 mg, 1.06 mmol) in 7.0 mL of CH_2Cl_2 and pyridine (0.18 mL, 2.12 mmol) was added triflic anhydride (0.21 mL, 1.3 mmol) dropwise at 0 °C under a N_2 atmosphere. The mixture was stirred for 5 min at 0 °C and for 1 h



at room temperature before we quenched the reaction with aqueous $NaHCO_3$ and extracted the mixture with EtOAc (3 × 100 mL). The organic extracts were washed with saturated aqueous NH_4Cl (2 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL) and dried over $MgSO_4$. Filtration, concentration, and purification of the orange residue by flash column chromatography (3:7 Et_2O/hexanes) gave 595 mg (84%) of the azido trifalte as a colorless foam: IR($CHCl_3$) 2116 (s), 1747 (s), 1721 (s), 1410 (s), 1332 (s), 1244 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.27 (br s, 1H), 3.44 (s, 3H), 3.58 (br d, 1H, J = 10.5 Hz), 3.96 (s, 3H), 3.97 (s, 3H), 4.18 (br s, 1H), 4.52 (d, 1H, J = 12.3 Hz), 4.58 (br s, 1H), 4.86 (br d, 1H, J = 7.0 Hz), 7.37 (d, 1H, J = 1.6 Hz), 7.75 (d, 1H, J = 1.6 Hz); MS (EI, 20 eV) m/z (M^+) 668 (17), 336 (100), 319 (67), 171 (30); high-resolution MS m/z calcd for $C_{18}H_{20}F_3IN_4O_{10}S$ (M^+) 667.9897, found 667.9853.

Acetate 16. To a stirred, colorless solution of the azido triflate (710 mg, 1.06 mmol) in 5.3 mL of THF was added triphenylphosphine (300 mg, 1.14 mmol) at room temperature. The resulting colorless mixture



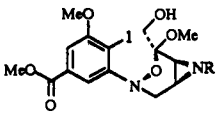
R= CO_2Me

was stirred for 3 h under a N_2 atmosphere, diluted with 8 mL of THF, and then treated with 4 mL of pH 10.5 aqueous NH_4OH. After 15 min, the reaction mixture was neutralized with aqueous NH_4Cl and extracted with EtOAc (4×). The organic extracts were washed with water (2×) and brine (1×) and dried over Na_2SO_4. Filtration and concentration *in vacuo* gave a colorless oil. The crude aziridine, thus generated, was diluted with 6 mL of CH_2Cl_2 and 260 μL (3.2 mmol) of pyridine and then cooled to 0 °C under a N_2 atmosphere. To this stirred, cold (0 °C), colorless solution was added dropwise methyl chloroformate (100 μL, 1.29 mmol). After 10 min, the reaction was quenched with dilute aqueous

(26) Brändström, A.; Lamm, B.; Palamertz, I. *Acta Chem. Scand., Ser. B* **1974**, *28B*, 699.

$NaHCO_3$ and the mixture extracted with EtOAc (3×). The combined extracts were washed with water (1×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration, and purification of the light yellow residue by flash column chromatography (85:15 Et_2O/hexanes) provided 570 mg (97%) of **16** as a colorless solid: mp 93–99 °C (becomes glassy at 70 °C); IR ($CHCl_3$) 1723 (s), 1577 (m), 1440 (m), 1408 (m), 1334 (m), 1294 (m), 1254 (s), 1242 (s) cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.05 (d, 1H, J = 6.6 Hz), 3.17 (br s, 1H), 3.40–3.46 (br m, 2H), 3.46 (s, 3H), 3.78 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 4.50 (d, 1H, J = 12.0 Hz), 4.64 (br s, 1H), 7.31 (d, 1H, J = 1.1 Hz), 7.77 (d, 1H, J = 1.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.72, 36.18, 36.82, 51.02, 52.24, 53.35, 53.74, 56.68, 62.87, 90.79, 98.42, 108.67, 114.90, 131.99, 152.13, 158.57, 162.60, 165.96, 170.19; MS (EI, 20 eV) m/z (M^+) 550 (15), 347 (21), 336 (81), 318 (98), 229 (100). Anal. Calcd for $C_{19}H_{23}IN_2O_9$: C, 41.47; H, 4.21; N, 5.09. Found: C, 41.73; H, 4.31; N, 4.95.

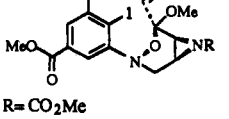
Alcohol 16a. To a stirred solution of acetate **16** (570 mg, 1.04 mmol) in 10 mL of MeOH were added 1 drop of water and a catalytic amount of K_2CO_3 at room temperature. The resulting colorless solution was



R= CO_2Me

stirred for 1 h at room temperature; the reaction was quenched with dilute aqueous NH_4Cl, and the mixture was extracted with EtOAc (3×). The organic extracts were washed with water (2×) and brine (1×) and dried over Na_2SO_4. Filtration, concentration, and purification of the residue by flash column chromatography (7:3 EtOAc/hexanes) gave 490 mg (93%) of alcohol **16a** as a colorless solid: mp 178–180 °C; IR ($CHCl_3$) 1722 (s), 1577 (m), 1440 (m), 1407 (m), 1333 (m), 1293 (m), 1255 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.51 (br s, 1H), 3.11 (d, 1H, J = 6.6 Hz), 3.16–3.22 (m, 1H), 3.30–3.50 (br m, 2H), 3.55 (s, 3H), 3.79 (s, 3H), 3.82–4.06 (m, 2H), 3.92 (s, 3H), 3.95 (s, 3H), 7.32 (d, 1H, J = 1.7 Hz), 7.79 (d, 1H, J = 1.7 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 35.89, 36.71, 51.27, 52.31, 53.65, 53.76, 56.73, 64.86, 90.67, 99.32, 108.76, 114.93, 132.11, 152.31, 158.57, 162.77, 166.01; MS (EI, 20 eV) m/z (M^+) 508 (8), 336 (100), 320 (30), 187 (27). Anal. Calcd for $C_{17}H_{21}IN_2O_8$: C, 40.17; H, 4.16; N, 5.51. Found: C, 40.45; H, 4.22; N, 5.41.

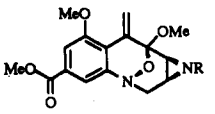
Olefin 18. To a stirred, cold (–78 °C) solution of oxalyl chloride (40 μL, 464 μmol) in 0.7 mL of CH_2Cl_2 was added slowly a solution of dimethyl sulfoxide (70 μL, 925 μmol) in 200 μL of CH_2Cl_2 under a N_2 atmosphere. A solution of alcohol **16a** (118 mg, 232 μmol) in 1.4 mL



R= CO_2Me

of CH_2Cl_2 and 20 μL of DMSO was then added dropwise *via* cannula. After ca. 15 min, 195 μL, (1.39 mmol) of triethylamine was added slowly, dissolving the colorless salt precipitate. The lightly colored solution was stirred for 30 min at –78 °C and for 30 min at 0 °C, the reaction was quenched with water, and the mixture was extracted with EtOAc (4×). The combined extracts were washed with aqueous NH_4Cl (1×), water (1×), and brine (1×) and dried over Na_2SO_4. Filtration and concentration *in vacuo* gave ca. 110 mg of a lightly colored foam. The crude aldehyde **17**, thus generated, was dissolved in 1.3 mL of THF and cooled to –78 °C under a N_2 atmosphere. To this stirred, cold solution was added 620 μL (248 μmol) of a 0.4 M solution (the salts were allowed to settle) in THF of the methylene ylide generated from methyltriphenylphosphonium bromide and sodium bis(trimethylsilyl)amide. The cold bath was removed after the addition, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 4 h at room temperature before the reaction was quenched with aqueous NH_4Cl and the mixture extracted with EtOAc (3×). The combined organic extracts were washed with water (2×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography (65:35 Et_2O/hexanes) provided 98 mg (83%) of **18** as a colorless foam: R_f = 0.29 (7:3 Et_2O/hexanes); IR ($CHCl_3$) 1721 (s), 1576 (m), 1440 (s), 1408 (s), 1334 (m), 1293 (s), 1255 (s), 1119 (m), 1098 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.94 (d, 1H, J = 6.5 Hz), 3.14 (br t, 1H, J = 5.9 Hz), 3.30 (s, 3H), 3.35 (br d, 1H, J = 12.0 Hz), 3.51 (br d, 1H, J = 12.0 Hz), 3.78 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 5.53 (dd, 1H, J = 11.1, 1.0 Hz), 5.61 (dd, 1H, J = 17.8, 1.0 Hz), 6.09 (dd, 1H, J = 17.8, 11.1 Hz), 7.30 (d, 1H, J = 1.7 Hz), 7.83 (d, 1H, J = 1.7 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 36.71, 39.54, 50.82, 52.29, 53.13, 53.77, 56.72, 90.56, 99.60, 108.41, 114.99, 120.02, 131.99, 135.51, 152.75, 158.66, 162.91, 166.19; MS (EI, 20 eV) m/z (M^+) 504 (2), 183 (54), 155 (100); high-resolution MS m/z calcd for $C_{18}H_{21}IN_2O_7$ (M^+) 504.0392, found 504.0375.

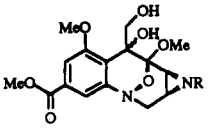
Exocyclic Olefin 19. A stirred solution of **18** (98 mg, 0.19 mmol), triethylamine (0.32 mL, 2.3 mmol), and catalytic tetrakis(triphenylphosphine)palladium(0) (ca. 5 mg, 4 μmol) in 2.4 mL of acetonitrile was heated at 80 °C in a sealed tube under an argon atmosphere for 10 h.



R= CO_2Me

The reaction mixture turned dark orange after ca. 10 min, and the catalyst plated out on the walls of the tube as a shiny layer of palladium metal upon completion of the reaction. The reaction mixture was cooled to room temperature; the reaction was quenched with aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (4×). The organic extracts were washed with aqueous $NaHSO_3$ (1×), water (1×), and brine (1×) and dried over $MgSO_4$. Filtration, concentration, and purification of the orange residue by flash column chromatography (45:55 Et_2O/hexanes) gave 66 mg (90%) of **19** as a colorless solid: mp 193–194 °C; R_f = 0.29 (8:2 Et_2O/hexanes); IR ($CHCl_3$) 1722 (s), 1567 (m), 1463 (m), 1440 (s), 1415 (m), 1357 (m), 1347 (m), 1315 (m), 1291 (s), 1278 (s), 1242 (s), 1226 (m), 1064 (m), 1048 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.77 (d, 1H, J = 6.8 Hz), 2.86 (dt, 1H, J = 6.8, 1.7 Hz), 3.54 (s, 3H), 3.60 (dd, 1H, J = 14.8, 6.1 Hz), 3.77 (s, 3H), 3.92 (s, 3H), 3.94 (m, 1H), 3.99 (s, 3H), 5.97 (d, 1H, J = 1.0 Hz), 6.87 (d, 1H, J = 1.0 Hz), 7.19 (d, 1H, J = 1.4 Hz), 7.30 (d, 1H, J = 1.4 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 33.74, 38.65, 51.44, 52.30, 52.89, 53.95, 55.70, 95.11, 106.74, 114.33, 116.26, 118.31, 130.01, 133.11, 146.87, 159.31, 162.46, 166.07; MS (EI, 20 eV) m/z (M^+) 376 (100), 359 (38), 345 (50), 329 (43), 301 (41), 276 (29), 269 (39), 156 (36). Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.44; H, 5.31; N, 7.27.

Diols 19a and 19b. To a stirred solution of exocyclic olefin **19** (98 mg, 0.26 mmol) and 4-methylmorpholine *N*-oxide (61 mg, 0.52 mmol) in 1.5 mL of THF, 200 μL of CH_2Cl_2, and 250 μL of water was added a solution of OsO_4 (0.196 M in THF, 92 μL, 18 μmol) at room temperature under a N_2 atmosphere. The reaction vessel was then sealed with a plastic cap



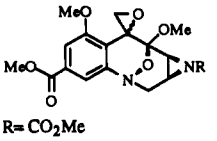
R= CO_2Me

and warmed gently with a water bath in order to maintain a homogeneous solution. After 20 min, the bath was removed without precipitating the reactants. The yellow solution was allowed to stir at room temperature for 44 h before quenching the reaction with aqueous $NaHSO_3$ and extracting with EtOAc (4×). The combined extracts were washed with aqueous $NaHSO_3$ (2×), water (1×), and brine (1×) and dried over Na_2SO_4. Filtration, concentration, and purification of the residue by flash column chromatography (8:2 EtOAc/hexanes) gave a combined total of 95 mg (89%) of a mixture of diols **19a** and **19b** in a 4.5:1 ratio (^1H NMR). The major diol isomer **19a** was isolated as a colorless foam: R_f = 0.38 (EtOAc); IR ($CHCl_3$) 1724 (s), 1575 (m), 1440 (m), 1293 (s), 1276 (s), 1129 (m), 1110 (m), 1037 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.12 (dd, 1H, J = 9.6, 5.5 Hz), 2.80 (dt, 1H, J = 6.7, 2.4 Hz), 3.30 (d, 1H, J = 6.7 Hz), 3.42 (s, 1H), 3.68 (dd, 1H, J = 14.8, 6.3 Hz), 3.76–3.90 (m, 1H), 3.78 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 4.24 (dd, 1H, J = 12.0, 9.6 Hz), 4.47 (dd, 1H, J = 12.0, 5.5 Hz), 7.23 (d, 1H, J = 1.3 Hz), 7.31 (d, 1H, J = 1.3 Hz); MS (EI, 20 eV) (no parent ion) m/z 347, 319, 234, 220, 208; high-resolution MS (FAB) calcd for $C_{18}H_{23}N_2O_9$ (M + H^+) 411.1404, found 411.1405.

The minor diol isomer **19b** was isolated as a colorless film: R_f = 0.46 (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 2.77 (dt, 1H, J = 6.8, 2.8 Hz),

2.94 (dd, 1H, J = 9.9, 3.8 Hz), 3.46 (d, 1H, J = 6.8 Hz), 3.67 (dd, 1H, J = 14.9, 6.4 Hz), 3.76 (s, 3H), 3.76–3.87 (m, 2H), 3.81 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 4.11 (dd, 1H, J = 11.7, 3.8 Hz), 4.29 (s, 1H), 7.16 (d, 1H, J = 1.4 Hz), 7.29 (d, 1H, J = 1.4 Hz); MS (EI, 20 eV) m/z (M^+) 410 (16), 379 (34), 331 (16), 220 (100).

Epoxides 20. In general, the conversion of the 1,2-diol to spiro epoxide **20** could be achieved starting with either a mixture or with a given diol isomer. Described below are the details of the transformation using the major diol isomer.

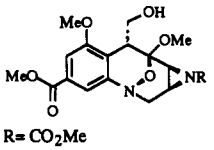


R= CO_2Me

To a stirred solution of major diol isomer **19a** (75 mg, 182 μmol) and triphenylphosphine (53 mg, 0.20 mmol) in 900 μL of CH_2Cl_2 was added 40 μL, (201 μmol) of DIAD (diisopropyl azodicarboxylate) at room temperature under a N_2 atmosphere. The reaction vessel was sealed with a plastic cap and stirred in the dark for 36 h. The reaction mixture was then concentrated *in vacuo*, and the brown residue was purified by flash column chromatography (85:15 Et_2O/hexanes) to give 55 mg (76%) of **20** as a colorless solid: mp 215–217 °C; R_f = 0.3 (Et_2O); IR ($CHCl_3$) 1724 (s), 1576 (m), 1439 (m), 1418 (m), 1348 (m), 1309 (m), 1294 (m), 1274 (m), 1243 (m), 1121 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.69 (d, 1H, J = 6.5 Hz), 2.85 (dt, 1H, J = 6.5, 2.5 Hz), 3.25 (d, 1H, J = 6.6 Hz), 3.65–3.76 (m, 2H), 3.70 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.39 (d, 1H, J = 6.6 Hz), 7.21 (s, 2H), MS (EI, 20 eV) m/z (M^+) 392 (100), 347 (19), 319 (30), 234 (70); high-resolution MS m/z calcd for $C_{18}H_{20}N_2O_8$ (M^+) 392.1220, found 392.1200.

Epoxide **20** derived from minor diol isomer **19b** was isolated as a colorless solid: mp 196–199 °C; R_f = 0.44 (Et_2O); IR ($CHCl_3$) 1725 (s), 1579 (m), 1463 (m), 1454 (m), 1439 (s), 1418 (m), 1347 (m), 1311 (m), 1294 (s), 1275 (s), 1243 (s), 1120 (s), 1057 (m), 990 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87 (dt, 1H, J = 6.5, 2.6 Hz), 3.09 (d, 1H, J = 6.5 Hz), 3.64 (d, 1H, J = 6.6 Hz), 3.68–3.92 (m, 3H), 3.70 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 7.18 (d, 1H, J = 1.0 Hz), 7.22 (d, 1H, J = 1.0 Hz); MS (EI, 20 eV) m/z (M^+) 392 (16), 279 (32), 167 (37), 149 (100).

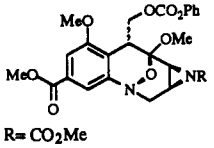
Alcohol 21. Rearrangement of epoxide **20** with $FeCl_3$ produced the same intermediate aldehyde, as determined by ^1H NMR ($CDCl_3$ δ 9.95 (d, C*H*O)), starting with either epoxide isomer. This being the case, it was often more convenient to carry out the reaction on a mixture of isomers. Delineated below is a general procedure for the sequence.



R= CO_2Me

To a stirred, colorless solution of epoxide **20** (32 mg, 81 μmol) in 1.0 mL of CH_2Cl_2 was added a catalytic amount of $FeCl_3$ at room temperature. The resulting yellow solution was stirred for 40 min under a N_2 atmosphere, diluted with CH_2Cl_2, and rapidly passed through a small plug of silica, rinsing with 8:2 Et_2O/hexanes. Concentration of the filtrate gave the intermediate aldehyde as a colorless solid. As the aldehyde had demonstrated a tendency to epimerize, it was necessary to proceed with the subsequent reduction as quickly as possible. The crude aldehyde was thus dissolved in 1 mL of THF and cooled to 0 °C under a N_2 atmosphere. To this cold, stirred solution was added 800 μL of a solution (0.2 M) of lithium tri-*tert*-butoxyaluminohydride in THF. After 5 min, the reaction mixture was diluted with THF and quenched with saturated aqueous NH_4Cl. The aqueous mixture was vigorously stirred for several minutes before extracting with EtOAc (3×). The combined organic extracts were washed with water (2 ×) and brine (1 ×) and dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography (7:3 EtOAc/hexanes) gave 16 mg (50%) of alcohol **21** as a colorless film: R_f = 0.17 (Et_2O), 0.33 (8:2 EtOAc/hexanes); IR ($CHCl_3$) 1722 (s), 1580 (m), 1439 (m), 1416 (m), 1351 (m), 1318 (m), 1277 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.94 (br s, 1H), 2.84 (dt, 1H, J = 6.6, 2.1 Hz), 3.16 (d, 1H, J = 6.6 Hz), 3.40 (dd, 1H, J = 5.2, 1.8 Hz), 3.64–3.89 (m, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 4.22 (br m, 1H), 4.54 (br m, 1H), 7.22 (d, 1H, J = 1.2 Hz), 7.27 (d, 1H, J = 1.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.95, 34.97, 44.67, 51.58, 52.35, 53.92 (2 C), 56.00, 58.90, 93.86, 106.12, 114.70, 118.39, 129.93, 148.25, 157.86, 162.75, 166.26; MS (EI, 20 eV) m/z (M^+) 394 (100), 347 (29), 329 (28), 256 (44), 236 (40); high-resolution MS m/z calcd for $C_{18}H_{22}N_2O_8$ (M^+) 394.1376, found 394.1387.

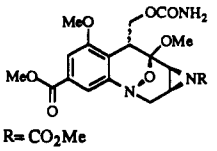
Carbonate 21a. To a stirred solution of **21** (12 mg, 30 μmol) in 300 μL of CH_2Cl_2 and 7 μL, (91 μmol) of pyridine was added phenyl chloroformate (7 μL, 91 μmol) at 0 °C under a N_2 atmosphere. After



R= CO_2Me

10 min, the reaction was quenched with aqueous Na_2CO_3 and the mixture extracted with EtOAc (3×). The combined organic extracts were washed with saturated aqueous Na_2CO_3 (2×), water (1×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration, and purification of the yellow residue by flash column chromatography (6:4 Et_2O/hexanes) provided 14 mg (89%) of the phenylcarbonate as a colorless film: R_f = 0.59 (Et_2O); IR ($CHCl_3$) 1762 (s), 1723 (s), 1583 (m), 1491 (m), 1462 (m), 1452 (m), 1439 (s), 1417 (m), 1353 (m), 1323 (m), 1279 (s), 1239 (s), 1170 (m), 1127 (m), 1111 (m), 1069 (m), 1061 (m), 1046 (m), 988 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.62 (dt, 1H, J = 6.5, 2.0 Hz), 2.82 (d, 1H, J = 6.5 Hz), 3.58 (br d, 1H, J = 6.0 Hz), 3.62–3.91 (m, 2H), 3.67 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 4.67 (dd, 1H, J = 11.5, 1.0 Hz), 5.51 (dd, 1H, J = 11.5, 6.0 Hz), 6.92 (d, 2H, J = 8.1 Hz), 7.19–7.30 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.96, 34.63, 42.14, 51.76, 52.37, 53.58, 53.98, 55.72, 64.12, 93.22, 105.69, 114.09, 116.94, 120.82, 125.98, 129.38, 130.10, 147.79, 150.98, 152.45, 158.09, 162.57, 166.37; MS (EI, 20 eV) m/z (M^+) 514 (5), 376 (8), 329 (8), 45 (100); high-resolution MS m/z calcd for $C_{25}H_{26}N_2O_{10}$ (M^+) 514.1587, found 514.1598.

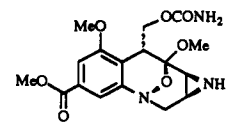
Urethane 7. To a flask charged with 15 mg (29 μmol) of phenyl carbonate **21a** and containing a magnetic stir bar was added a saturated solution of ammonia in 2-propanol (0.5 mL) at room temperature. The



R= CO_2Me

flask was sealed with a plastic cap, and the colorless contents were stirred for 2 h. Concentration *in vacuo* and purification of the residue by flash column chromatography (85:15 EtOAc/hexanes) gave 11 mg (86%) of a colorless solid. Crystals suitable for X-ray analysis of **7** could be obtained by slow evaporation (48 h) of an acetonitrile solution: mp 197–199 °C; R_f = 0.12 (Et_2O), 0.46 (EtOAc); IR ($CHCl_3$) 1724 (s), 1583 (m), 1439 (m), 1353 (m), 1338 (m), 1323 (m), 1279 (s), 1127 (m), 1109 (m) cm^{-1}; ^1HNMR (250 MHz, $CDCl_3$) δ 2.83–2.93 (m, 2H), 3.58–3.72 (m, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 3.87 (s, 3H), 3.90–3.96 (m, 1H), 3.91 (s, 3H), 4.51 (br s, 2H), 4.57 (dd, 1H, J = 11.5, 1.6 Hz), 5.08 (dd, 1H, J = 11.5, 6.6 Hz), 7.19 (d, 1H, J = 1.4 Hz), 7.20 (d, 1H, J = 1.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.08, 34.91, 41.28, 51.51, 52.31, 53.38, 53.99, 55.64, 60.90, 93.63, 105.68, 113.90, 117.69, 129.88, 147.60, 156.23, 158.25, 162.72, 166.41; MS (EI, 20 eV) m/z (M^+) 437 (41), 376 (100), 345 (88), 329 (54), 301 (49); high-resolution MS m/z calcd for $C_{19}H_{23}N_3O_9$ (M^+) 437.1434, found 437.1448.

Aziridine 6. To a stirred solution of urethane **7** (6 mg, 13 μmol) in MeOH (and a drop of CH_2Cl_2 for solubility) were added 1 drop of water and a catalytic amount of K_2CO_3 at room temperature. The resulting



colorless solution was stirred for 36 h at room temperature; the reaction was quenched with dilute aqueous NH_4Cl, and the mixture was extracted with EtOAc (4×). The organic extracts were washed with water (2×) and brine (1×) and dried over Na_2SO_4. Filtration, concentration, and

purification of the residue (ca. 5 mg) by flash column chromatography (9:1 $CHCl_3$/MeOH) gave 3.5 mg (67%) of aziridine **6** as a colorless film: R_f = 0.22 (9:1 $CHCl_3$/MeOH); IR ($CHCl_3$) 3542 (w), 3416 (w), 1721 (s), 1582 (s), 1462 (m), 1436 (m), 1417 (m), 1354 (s), 1339 (s), 1323 (s), 1278 (s), 1241 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.34–2.39 (m, 1H), 2.48–2.50 (m, 1H), 3.52 (s, 3H), 3.64–3.84 (m, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.52 (br s, 2H), 4.72 (dd, 1H, J = 11.4, 2.1 Hz), 4.92 (dd, 1H, J = 11.4, 7.0 Hz), 7.19 (d, 1H, J = 1.4 Hz), 7.21 (d, 1H, J = 1.4 Hz); MS (EI, 20 eV) m/z (M^+) 379 (30), 318 (67), 301 (47), 287 (100); high-resolution MS m/z calcd for $C_{17}H_{21}N_3O_7$ (M^+) 379.1380, found 379.1408.

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Supplementary Material Available: PLUTO drawings and tables containing fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors for the X-ray analysis of compound **7** (18 pages). Ordering information is given on any current masthead page.