A Remarkable Stereochemical Inversion in Some Heck Arylation Reactions. A Mechanistic Proposal

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Internal arylation reactions of enol ethers were used to form the 1,5-epoxybenzazocine ring system of FR 900482. An interesting inversion process was observed for Z-enol ethers.

Recently, we published[1] a synthesis of compound 2 which is a dimethyl ether methyl ester analog of the antitumor mitomycin-related alkaloid FR 900482 (1).[2] Our strategy was quite different from those which had previously been pursued[3] in attempting to synthesize 1. The key step in our program was a high-yielding internal arylation reaction of a seco system (cf. 3). Prior to this very successful Heck-like arylation using the *exo*-methylene substrate, 3, other cyclization candidates were screened. At the time, we were particularly desirous of achieving cyclization on a substrate equipped with useful functionality for installing the C-13 carbamoyloxy group of the target. As will be seen, the use of such substrates did not result in viable yields of Heck arylation products. However, some fascinating chemistry was discovered as is described in this account.

Given the considerations discussed above, enol ether functions were evaluated as aryl acceptors for the intramolecular Heck reaction.[4] Starting with the previously reported triol 5, the acetonide 6 was prepared with the dioxolane moiety serving, at the outset, as a model for the aziridine ring (Scheme 1). Swern oxidation[5] of the remaining hydroxyl group gave the aldehyde 7 which reacted with (methoxymethylidene)triphenylphosphorane to give, in surprisingly low yield (15% from 6), almost exclusively the (*Z*)-enol ether 8.

Reaction of 8 with 10% palladium on carbon in hot (80 °C) acetonitrile gave a 50% yield of what was later assigned (*vide infra*) as aldehyde 9 and 28% of the starting 8 (Scheme 2).[6] It was not clear why an enol ether was not reconstituted after arylation by β-hydride elimination. Of course, the possibility of adventitious hydrolysis of an intermediate enol ether could not be ruled out. Sodium borohydride reduction of aldehyde 9 gave an alcohol. Crystallographic analysis of the resulting alcohol[7] revealed a very interesting paradox. *The stereochemistry of the*

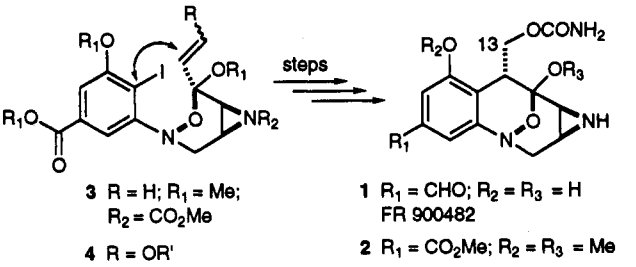
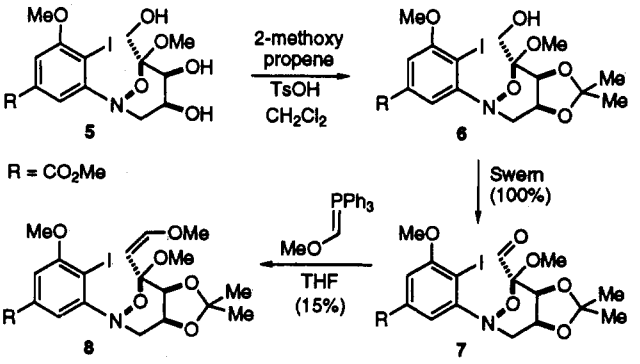
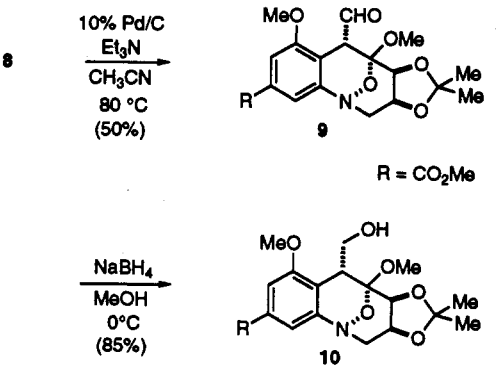


Figure 1.

Scheme 1



Scheme 2



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(1) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094.

(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) (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.; Rapoport, 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) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383. (g) Dmitrienko, G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705.

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

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

(6) For a review of Heck arylations with heteroatom-substituted olefins see: Doyle, D. G., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

(7) Experimental details, Pluto drawings, and tables containing fractional coordinates, temperature factors, bond distances and angles for all X-ray crystallographic analyses have been deposited with the Cambridge Crystallographic Data Centre. They can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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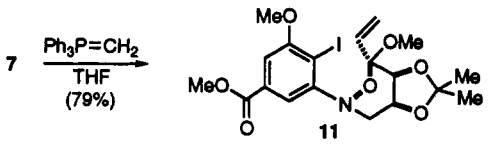
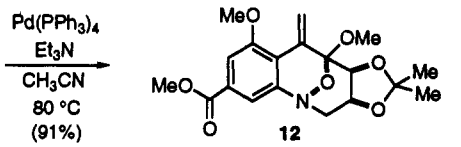
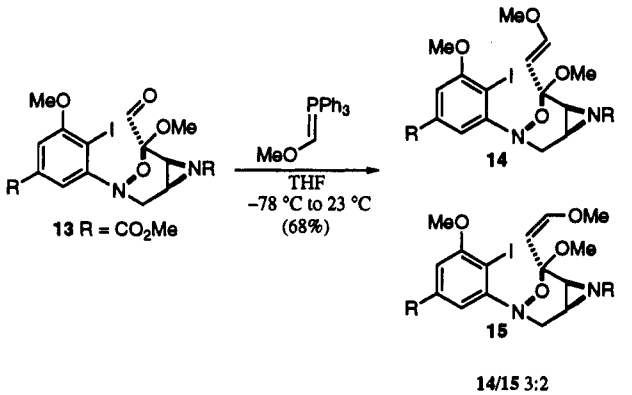
Scheme 3





Scheme 4



N–O bond oxygen relative to the dioxolane ring had been inverted (see structure 10).

This result was in contrast to the Heck arylation reaction of **3** (Figure 1), bearing an aziridine ring and an exocyclic methylene group. In this reaction no analogous inversion of the NO center had been observed. That the decisive difference lies in the use a methylene group as the aryl acceptor rather than in the tethering function (aziridine vs dioxolane) is seen from subsequent experiments.

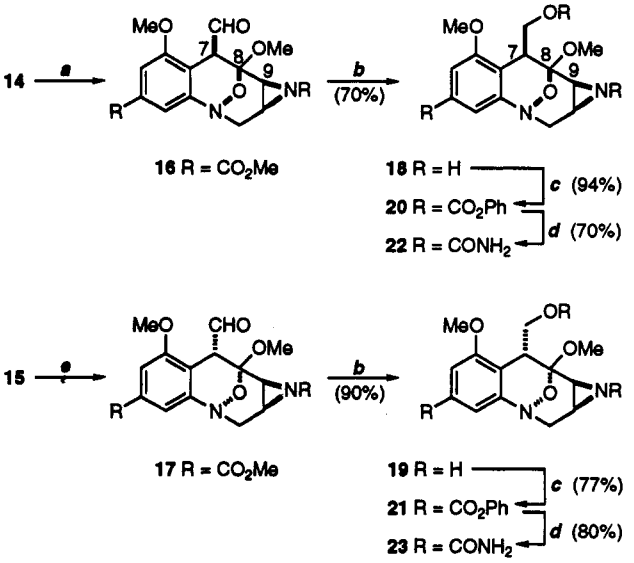
Reaction of aldehyde **7** with methylidenetriphenylphosphorane gave olefin **11** (Scheme 3). The latter upon reaction with catalytic tetrakis(triphenylphosphine)palladium(0) in triethylamine and acetonitrile gave a 91% yield of an exocyclic olefin **12**. The structure of **12** established by X-ray crystallography showed that the integrity of the N–O bond oxygen had been preserved in the arylation reaction.

When this chemistry was extended to enol ethers in aziridine-containing seco compounds, the same trend was observed. Addition of (methoxymethylidene)triphenylphosphorane to aldehyde **13** gave a 3:2 *E*/*Z* mixture of enol ethers **14** and **15** (68%), which could be separated. Each isomer was subjected to palladium-mediated cyclization (Scheme 4).

The *E*-isomer **14** produced aldehyde **16**. Under more forcing conditions the *Z*-isomer **15** gave aldehyde **17** (Scheme 5). The reactions were not catalytic in palladium, and the conversions were low yielding (13–15%). However, recovered starting material could be reprocessed.

It was initially assumed that the two aldehydes produced from **14** and **15** were simply epimers at C-7 (see structure **16** for numbering). Reduction of the aldehydes **16** and **17** with sodium borohydride gave the alcohols **18** and **19**. Following the standard two-step sequence[8] of carbophenoxylation and ammonolysis, the crystalline bis-carbamoyl derivatives **22** and **23** were obtained. X-ray crystallographic analysis of both **22** and **23** revealed that the difference between the two structures was not confined to the C-7 stereocenter but also extended to the relationship of the oxo bridge to the aziridine ring.

Scheme 5[a]



[a] Key: (a) $Pd_2(dba)_3$, Et_3N, PhH, 60 °C, 13% + 50% **14**; (b) $NaBH_4$, MeOH, 0 °C; (c) phenyl chloroformate, py, CH_2Cl_2, 0 °C; (d) NH_3, MeOH, 23 °C; (e) 10% Pd/C, Et_3N, CH_3CN, 85 °C, 14% + 57% **15**.

Assuming that the C-7 stereocenter was not being epimerized, and the C-8 center of the product was not suffering β-elimination/readdition of the hydroxylamine, it seems likely that the inversion of the bridging C-8 oxygen was occurring during the arylation step. Furthermore, this inversion is confined to the (*Z*)-enol ethers.[9] The other Heck arylation substrates reacted as expected without affecting the C-8 center (compare ORTEPs of **10**, **12**, **22**, and **23**, Figure 2).

To explain these results we start with the empirical finding that the compound with the (*Z*)-enol ether geometry was less reactive than the *E*-isomer. Thus, reactions of the *Z*-isomer required higher (20–40 °C) temperatures relative to the *E*-counterpart. It is recognized that, with the exception of α,β-unsaturated epoxides, palladium(0) is not known to insert into vinyl ether sites. However, perhaps, under the severe conditions employed, palladium(0) insertion in fact occurs to give the dynamic complexes **24**η^3 and **24**η^1 as transient intermediates. After rotation about the σ bond of **24**η^1 (top structure) and reclosure, the resultant *E*-enol ether **25** undergoes cyclization. Since the *Z*-isomer was recovered unchanged in the relationship of the aziridine and C-8 methoxy functions, the formation of intermediates **24**η^3 and **24**η^1 is apparently rate determining. *The critical feature of this argument is that the Z to E isomerization of the enol ether, which must precede cyclization, is intrinsically associated with inversion of the C-8–C-9 relationship.* This is shown in Scheme 6 for **15** going to **25**, but is also valid for the acetonide substrate **8**.

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

(9) For a related example in the palladium-catalyzed hydrogenolysis of allylic carbonates, see: Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 6090.

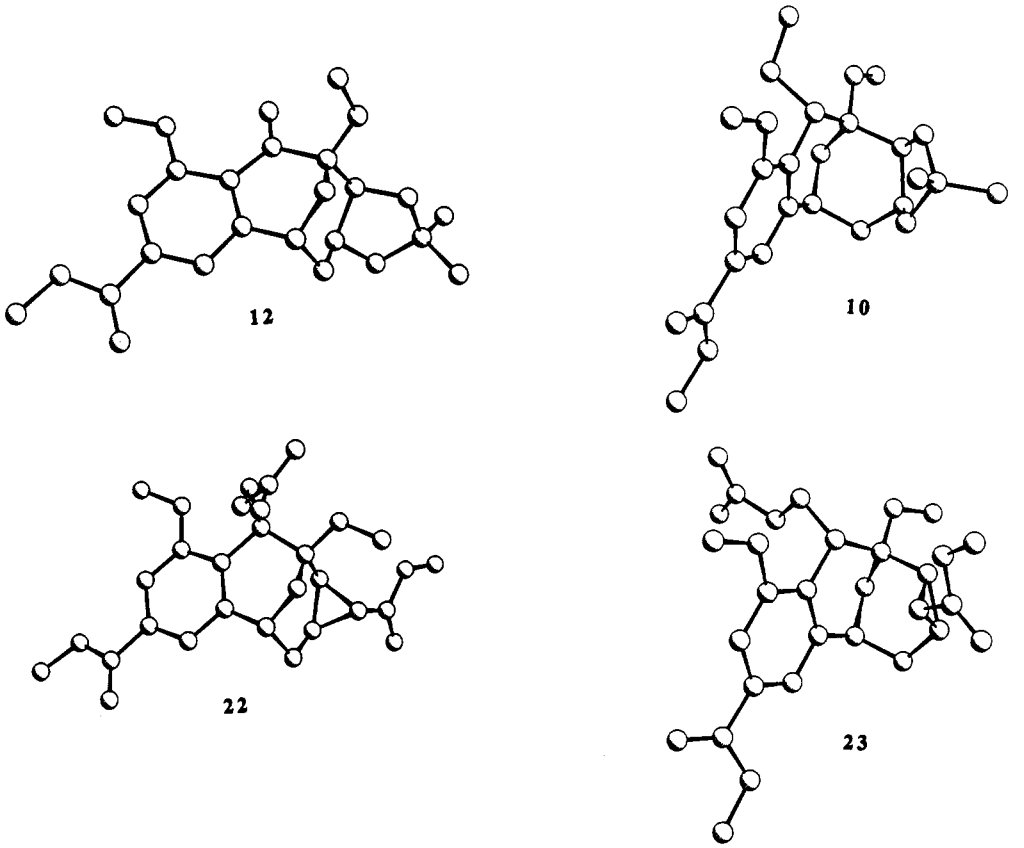
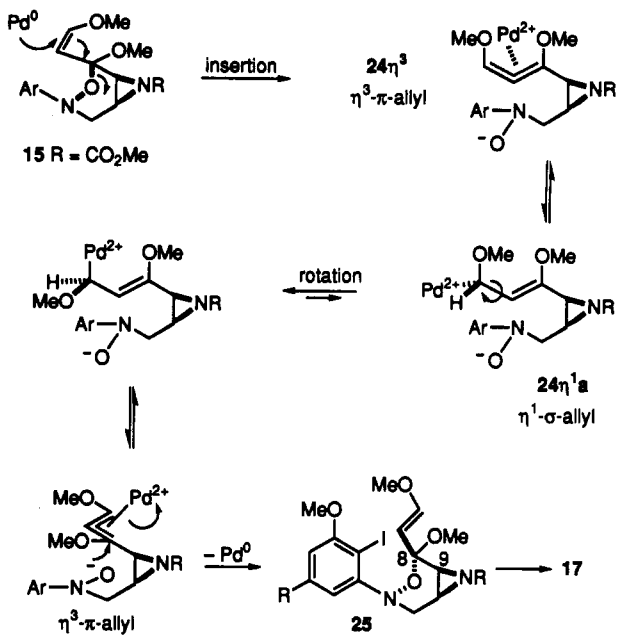


Figure 2. PLUTO representations.

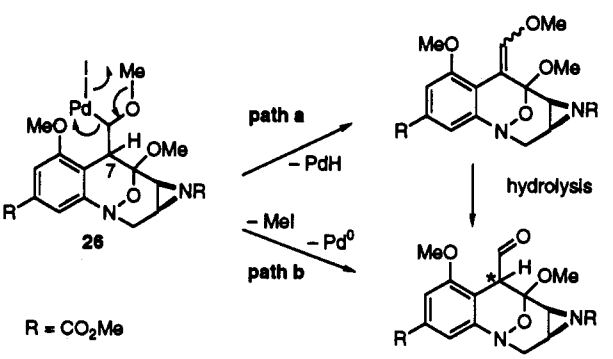
Scheme 6



We now turn to the surprising formation of aldehydes from the enol ether arylation reactions. We propose that an intermediate **26** is generated and that it undergoes an Arbuzov-like[10] (see path b, Scheme 7) unravelling, giving rise directly to an aldehyde. The stereochemistry of the aldehyde is seen to arise from a face-specific attack of the aryl group *anti* to the methoxy function at C-8 (on the rotamers where the enol ether extends away from the oxazine ring, see **14** and **25**). By this view, the integrity

(10) For a review of the Michaelis–Arbuzov rearrangement, see: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

Scheme 7



of the newly generated C-7 stereocenter is not lost through β-hydride elimination (path a). Thus, the fact that a particular enol ether starting material leads to a single aldehyde is accommodated.

While the mechanistic arguments presented here await further experimental verification, they do rationalize this surprising set of transformations. Also, the results suggest that under more forcing conditions, a broader range of allylic ether substrates than has thus far been realized can participate in palladium(0)-mediated chemistry.

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 measure-

ments were made on a four-circle Rigaku AFC5S fully automated diffractometer. The crystallographic structure solutions were accomplished using a Digital VAX station II/GPX workstation. Combustion analyses were performed by Robertson Laboratory, Inc., Madison, NJ 07940, and Galbraith Laboratories Inc., Knoxville, TN 37921-1750.

Continuous-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 an internal tetramethylsilane (TMS) standard or relative to internal $CHCl_3$. Proton NMR (^1H NMR) are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), number of protons, and coupling constant(s) in hertz. When appropriate, the multiplicities are preceeded by "br", indicating that the signal was broad. Except for those high-resolution mass spectra indicated as requiring fast atom bombardment (FAB) ionization, all mass spectra were achieved by electron ionization (EI).

Alcohol 6. Alcohol **6** was obtained from a mixture of the triol **5** and its isomer[1] by converting the two compounds to a mixture of 1,2 acetonides and a single 1,3 acetonide (2-methoxypropene/$TsOH/CH_2Cl_2$). Separation by flash column chromatography (8:2 Et_2O/hexanes) isolating the lowest R_f (0.4 Et_2O) material gave the alcohol **6** as a colorless solid: mp 82–85 °C; R_f = 0.4 (Et_2O); IR ($CHCl_3$) 1710 (s), 1580 (m), 1450 (m), 1400 (m), 1330 (m), 1250 (s), 1070 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.61 (s, 3 H), 2.52 (br t, 1 H, J = 6.8 Hz), 3.00 (m, 1 H), 3.46 (dd, 1 H, J = 12.2, 6.2 Hz), 3.55 (s, 3 H), 3.86–3.96 (m, 1 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 4.07 (dd, 1 H, J = 12.2, 7.0 Hz), 4.42 (d, 1 H, J = 5.2 Hz), 4.79 (m, 1 H), 7.34 (d, 1 H, J = 1.3 Hz), 7.89 (d, 1 H, J = 1.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.23, 27.94, 51.49, 52.41, 56.82, 57.97, 65.44, 72.12, 73.04, 90.52, 101.58, 108.79, 110.16, 114.54, 132.22, 151.99, 158.61, 166.13; MS (EI, 20 eV) m/z (M^+) 509 (33), 404 (22), 336 (100), 320 (80); high-resolution MS m/z calcd for $C_{18}H_{24}INO_8$ (M^+) 509.0545, found 509.0526.

Aldehyde 7. To a stirred, cold (−78 °C) solution of oxalyl chloride (38 μL, 432 μmol) in 0.7 mL of CH_2Cl_2 was added slowly a solution of dimethyl sulfoxide (67 μL, 863 μmol) in 0.32 mL of CH_2Cl_2 under a N_2 atmosphere. A solution of alcohol **6** (110 mg, 0.22 mmol) in 1.0 mL of CH_2Cl_2 was then added dropwise *via* cannula. After ca. 15 min triethylamine (0.18 mL, 1.29 mmol) was added slowly to dissolve 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 **7** as a colorless foam. The crude aldehyde **7** was carried on without purification.

(*Z*)-Enol Ether 8. To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (78 mg, 0.23 mmol) in 0.3 mL of THF was added 0.23 mL of a solution of sodium bis(trimethylsilyl)amide (1.0 M) at 0 °C under a N_2 atmosphere. The resulting red solution–suspension was then warmed to room temperature and allowed to stir for 30 min. The (methoxymethylidene)triphenylphosphorane thus generated was cooled to −23 °C (CO_2/CCl_4), at which point a solution of the crude aldehyde **7** (ca. 95 mg, 0.19 mmol) in 1.0 mL of THF generated as before (*vide supra*) was added dropwise under a N_2 atmosphere. The cold bath was then removed, and reaction mixture was allowed to warm to room temperature. After 10 h at room temperature, the reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with water (2×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration *in vacuo*, and purification of the residue by flash column chromatography (7:3 Et_2O/hexanes) provided 15 mg of **8** (15% from **6**) as a colorless foam: R_f = 0.30 (8:2 Et_2O/hexanes), 0.48 (Et_2O); IR ($CHCl_3$) 1716 (s), 1650 (m), 1575 (m), 1459 (m), 1408 (m), 1364 (m), 1337 (m), 1252 (s), 1110 (m), 1097 (m), 1060 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3 H), 1.45 (s, 3 H), 2.86–2.93 (m, 1 H), 3.45–3.55 (m, 1 H), 3.48 (s, 3 H), 3.68 (s, 3 H), 3.92 (s, 3 H), 3.95 (s, 3 H), 4.60–4.67 (m, 2 H), 4.81 (d, 1 H, J = 7.0 Hz), 6.17 (d, 1 H, J = 7.0 Hz), 7.30 (d, 1 H, J = 1.3 Hz), 7.93 (d, 1 H, 1.3 Hz); MS (EI, 20 eV) m/z (M^+) 535 (1), 404 (10), 124 (100); high-resolution MS m/z calcd for $C_{20}H_{26}INO_8$ (M^+) 535.0702, found 535.0709.

Aldehyde 9. To a stirred solution of the (*Z*)-enol ether **8** (9 mg, 17 μmol) in 0.3 mL of acetonitrile and triethylamine (7 μL, 50 μmol) was added 16 mg of 10% palladium on carbon at room temperature. The resulting suspension was then vigorously stirred under an argon atmosphere at 80 °C in a sealed tube for 18 h. After being cooled to room temperature, the reaction mixture was passed through a small plug of silica, rinsing with copious amounts of EtOAc. Concentration of the filtrate *in vacuo* and purification of the residue by flash column chromatography (65:35 Et_2O/hexanes) gave 2.5 mg (28%) of the starting **8** and 3.3 mg (50%) of aldehyde **9** as a colorless film: R_f = 0.25 (8:2 Et_2O/hexanes) 0.41 (Et_2O); IR ($CHCl_3$) 1725 (s), 1566 (m), 1463 (m), 1437 (m), 1354 (m), 1306 (m), 1241 (m), 1109 (m), 1066 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 1.19 (s, 3 H), 3.51 (s, 3 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 3.91–3.96 (m, 2 H), 4.37 (m, 2 H), 4.56 (d, 1 H, J = 7.6 Hz), 7.24 (s, 1 H), 7.32 (s, 1 H), 9.47 (d, 1 H, J = 4.0 Hz); MS (EI, 20 eV) m/z (M^+) 393 (66), 256 (88), 149 (65), 73 (100); high-resolution MS m/z calcd for $C_{19}H_{23}NO_8$ (M^+) 393.1424 found 393.1414.

Alcohol 10. To a stirred solution of the aldehyde **9** (3.5 mg, 8.8 μmol) in ca. 0.3 mL of MeOH was added sodium borohydride (1 mg, 26 μmol) at 0 °C. The resulting colorless solution was stirred under a N_2 atmosphere for 10 min before the reaction was quenched with water. The cold bath was removed; the reaction mixture was stirred for an additional 10 min, and then the mixture was extracted with EtOAc (4×). The combined organic extracts were washed with water (2×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration *in vacuo*, and purification of the light yellow residue by flash column chromatography (Et_2O) gave 3 mg (85%) of alcohol **10** as a colorless solid. Crystals suitable for X-ray analysis[11] could be obtained of compound **10** by slow evaporation of an ethereal (Et_2O) solution at 23 °C: mp 162–163 °C; R_f = 0.32 (8:2 EtOAc/hexanes), 0.20 (Et_2O); IR ($CHCl_3$) 3550 (w), 1719 (s), 1567 (s), 1462 (m), 1377 (m), 1355 (m), 1307 (m), 1272 (s), 1240 (s), 1166 (m), 1095 (m), 1065 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 3 H), 1.17 (s, 3 H), 3.02 (dd, 1 H, J = 10.2, 3.2 Hz), 3.56 (s, 3 H), 3.68–3.94 (m, 5 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 4.36 (dd, 1 H, J = 7.9, 3.6 Hz), 4.62 (d, 1 H, J = 7.9 Hz), 7.22 (s, 1 H), 7.23 (s, 1 H); MS (EI, 20 eV) m/z (M^+) 395 (29), 380 (100), 278 (85); high-resolution MS m/z calcd for $C_{19}H_{25}NO_8$ (M^+) 395.1580, found 395.1583. NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3 H), 1.45 (s, 3 H), 2.86–2.93 (m, 1 H), 3.45–3.55 (m, 1 H), 3.48 (s, 3 H), 3.68 (s, 3 H), 3.92 (s, 3 H), 3.95 (s, 3 H), 4.60–4.67 (m, 2 H), 4.81 (d, 1 H, J = 7.0 Hz), 6.17 (d, 1 H, J = 7.0 Hz), 7.30 (d, 1 H, J = 1.3 Hz), 7.93 (d, 1 H, 1.3 Hz); MS (EI, 20 eV) m/z (M^+) 535 (1), 404 (10), 124 (100); high-resolution MS m/z calcd for $C_{20}H_{26}INO_8$ (M^+) 535.0702, found 535.0709.

Aldehyde 9. To a stirred solution of the (*Z*)-enol ether **8** (9 mg, 17 μmol) in 0.3 mL of acetonitrile and triethylamine (7 μL, 50 μmol) was added 16 mg of 10% palladium on carbon at room temperature. The resulting suspension was then vigorously stirred under an argon atmosphere at 80 °C in a sealed tube for 18 h. After being cooled to room temperature, the reaction mixture was passed through a small plug of silica, rinsing with copious amounts of EtOAc. Concentration of the filtrate *in vacuo* and purification of the residue by flash column chromatography (65:35 Et_2O/hexanes) gave 2.5 mg (28%) of the starting **8** and 3.3 mg (50%) of aldehyde **9** as a colorless film: R_f = 0.25 (8:2 Et_2O/hexanes) 0.41 (Et_2O); IR ($CHCl_3$) 1725 (s), 1566 (m), 1463 (m), 1437 (m), 1354 (m), 1306 (m), 1241 (m), 1109 (m), 1066 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 1.19 (s, 3 H), 3.51 (s, 3 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 3.91–3.96 (m, 2 H), 4.37 (m, 2 H), 4.56 (d, 1 H, J = 7.6 Hz), 7.24 (s, 1 H), 7.32 (s, 1 H), 9.47 (d, 1 H, J = 4.0 Hz); MS (EI, 20 eV) m/z (M^+) 393 (66), 256 (88), 149 (65), 73 (100); high-resolution MS m/z calcd for $C_{19}H_{23}NO_8$ (M^+) 393.1424 found 393.1414.

Alcohol 10. To a stirred solution of the aldehyde **9** (3.5 mg, 8.8 μmol) in ca. 0.3 mL of MeOH was added sodium borohydride (1 mg, 26 μmol) at 0 °C. The resulting colorless solution was stirred under a N_2 atmosphere for 10 min before the reaction was quenched with water. The cold bath was removed; the reaction

(11) Experimental details of the X-ray analysis have been deposited with the Cambridge Crystallographic Data Centre. See ref 7.

mixture was stirred for an additional 10 min, and then the mixture was extracted with EtOAc (4×). The combined organic extracts were washed with water (2×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration *in vacuo*, and purification of the light yellow residue by flash column chromatography (Et_2O) gave 3 mg (85%) of alcohol **10** as a colorless solid. Crystals of compound **10** suitable for X-ray analysis[11] could be obtained by slow evaporation of an ethereal (Et_2O) solution at 23 °C: mp 162–163 °C; R_f = 0.32 (8:2 EtOAc/hexanes), 0.20 (Et_2O); IR ($CHCl_3$) 3550 (w), 1719 (s), 1567 (s), 1462 (m), 1377 (m), 1355 (m), 1307 (m), 1272 (s), 1240 (s), 1166 (m), 1095 (m), 1065 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 3 H), 1.17 (s, 3 H), 3.02 (dd, 1 H, J = 10.2, 3.2 Hz), 3.56 (s, 3 H), 3.68–3.94 (m, 5 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 4.36 (dd, 1 H, J = 7.9, 3.6 Hz), 4.62 (d, 1 H, J = 7.9 Hz), 7.22 (s, 1 H), 7.23 (s, 1 H); MS (EI, 20 eV) m/z (M^+) 395 (29), 380 (100), 278 (85); high-resolution MS m/z calcd for $C_{19}H_{25}NO_8$ (M^+) 395.1580, found 395.1583.

Olefin 11. The crude aldehyde **7** (ca. 110 mg, 0.22 mmol) generated above was dissolved in 1.0 mL of THF and cooled to −78 °C under a N_2 atmosphere. To this stirred, cold solution was added a 0.4 M solution (the salts were allowed to settle) of the methylene ylide (0.57 mL, 0.23 mmol) in THF generated from methyltriphenylphosphonium bromide and sodium bis(trimethylsilyl)amide (1.0 M in THF). The cold bath was removed after the addition, and the reaction mixture was allowed to warm to room temperature. After 2 h at room temperature, the reaction was quenched with aqueous NH_4Cl, and the mixture was 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 (2:8 EtOAc/hexanes) provided 87 mg (79% from **6**) of **11** as a colorless solid: mp 146–148 °C; R_f = 0.38 (6:4 Et_2O/hexanes); IR ($CHCl_3$) 1650 (s), 1620 (s), 1590 (s), 1570 (s), 1490 (m), 1450 (m), 1340 (s), 1190 (s), 1100 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.63 (s, 3 H), 3.09 (m, 1 H), 3.38 (s, 3 H), 3.38–3.48 (m, 1 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 4.27 (d, 1 H, J = 4.7 Hz), 4.57 (m, 1 H), 5.50 (d, 1 H, J = 17.8 Hz), 5.53 (d, 1 H, J = 11.3 Hz), 6.17 (dd, 1 H, J = 17.8, 11.3 Hz), 7.32 (s, 1 H), 7.92 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.42, 27.87, 51.08, 52.25, 56.69 (2C), 71.98, 75.89, 90.29, 101.90, 108.20, 110.47, 114.67, 119.72, 131.92, 136.01, 152.27, 158.56, 166.17; MS (EI, 20 eV) m/z (505 (73), 404 (100), 320 (33); high-resolution MS m/z calcd for $C_{19}H_{24}INO_7$ (M^+) 505.0596, found 505.0578. Anal. Calcd for $C_{19}H_{24}INO_7$: C, 45.16; H, 4.79; N, 2.77. Found: C, 45.21; H, 4.45; N, 2.60.

Exo Olefin 12. A stirred solution of **11** (44 mg, 87 μmol), triethylamine (0.14 mL, 1.0 mmol), and catalytic (ca. 5 mg, 4 μmol) tetrakis(triphenylphosphine)palladium(0) in 1.0 mL of acetonitrile was heated at 80 °C in a sealed tube under an argon atmosphere for 10 h. 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 was cooled to room temperature and quenched with aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (4×). The organic extracts were washed with aqueous sodium bisulfite ($NaHSO_3$) (1×), water (1×), and brine (1×) and dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography (45:55 Et_2O/hexanes) gave 30 mg (91%) of **12** as a colorless solid. Crystals suitable for X-ray analysis[11] of **12** could be obtained by slow evaporation of an ethereal (Et_2O) solution at 23 °C: mp 201–202 °C; R_f = 0.24 (6:4 Et_2O/hexanes), 0.57 (Et_2O), 0.45 (8:2 Et_2O/hexanes); IR ($CHCl_3$) 1720 (s), 1570 (m), 1460 (m), 1440 (m), 1340 (m), 1350 (m), 1300 (m), 1250 (s), 1130 (s), 1080 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.63 (s, 3 H), 3.38–3.58 (m, 2 H), 3.48 (s, 3 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 4.12 (m, 1 H), 4.26 (d, 1 H, J = 4.6 Hz), 5.88 (s, 1 H), 6.92 (s, 1 H), 7.28 (s, 1 H), 7.35 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.73, 28.46, 51.22, 52.32, 54.24, 55.70, 68.57, 77.43, 99.86, 107.83, 110.80, 114.90, 117.12, 120.43, 130.00, 133.28, 146.06, 158.87, 166.00; MS (EI, 20 eV) m/z (M^+) 377 (8), 362 (32), 43 (100); high-resolution MS m/z calcd for $C_{19}H_{23}NO_7$ (M^+) 377.1474, found 377.1500. Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.76; H, 6.38: N, 3.63.

Enol Ethers 14 and 15. The crude aldehyde **13**[1] (ca. 211 mg, 0.42 mmol) was dissolved in 1.5 mL of THF and cooled to −78 °C under a N_2 atmosphere. To this stirred, cold solution was added a 0.5 M solution (the salts were allowed to settle over 40 min) of (methoxymethylidene)triphenylphosphorane (1.2 mL, 2.4 mmol) in THF prepared from (methoxymethyl)triphenylphosphonium chloride and a THF solution of sodium bis(trimethylsilyl)amide (1.0 M). The cold bath was removed after the addition, and reaction mixture was allowed to warm to room temperature. After 13 h at room temperature, the reaction was quenched with aqueous NH_4Cl, and the mixture was 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 brown residue by flash column chromatography (7:3 Et_2O/hexanes) provided 91 mg (41%) of **14** and 60 mg (27%) of **15**.

14 was isolated as a colorless foam/film: R_f = 0.5 (Et_2O); IR ($CHCl_3$) 1720 (s), 1651 (m), 1577 (m), 1452 (m), 1440 (s), 1408 (s), 1334 (m), 1295 (s), 1119 (m), 1097 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.94 (d, 1 H, J = 6.5 Hz), 3.16–3.32 (br m, 1 H), 3.30–3.54 (br m, 2 H), 3.32 (s, 3 H), 3.62 (s, 3 H), 3.78 (s, 3 H), 3.92 (s, 3 H), 3.95 (s, 3 H), 5.02 (d, 1 H, J = 13.2 Hz), 6.83 (d, 1 H, 13.2 Hz), 7.31 (d, 1 H, J = 1.7 Hz), 7.80 (d, 1 H, 1.7 Hz); ^{13}C NMR δ 36.73, 40.80, 50.54, 52.35, 53.33, 53.80, 56.06, 56.79, 90.82, 99.94, 100.77, 108.55, 115.20, 132.12, 152.40, 152.81, 158.75, 162.98, 166.27; MS (EI, 20 eV) m/z (M^+) 534 (24), 321 (18), 168 (67), 138 (100). Anal. Calcd for $C_{19}H_{23}IN_2O_8$: C, 42.71; H, 4.34; N, 5.24. Found: C, 42.81; H, 4.40; N, 4.96.

15 was isolated as a colorless foam: R_f = 0.35 (Et_2O); IR ($CHCl_3$) 1720 (s), 1660 (m), 1576 (m), 1465 (m), 1453 (m), 1440 (m), 1408 (m), 1334 (m), 1292 (s), 1255 (s), 1119 (m), 1093 (s) 1055 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.14–3.24 (m 2 H), 3.30 (d, 1 H, J = 6.6 Hz), 3.40 (s, 3 H), 3.60–3.70 (m, 1 H), 3.70 (s, 3 H), 3.77 (s, 3 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 4.69 (d, 1 H, J = 7.0 Hz), 6.20 (d, 1 H, 7.0 Hz), 7.30 (d, 1 H, J = 1.7 Hz), 7.87 (d, 1 H, 1.7 Hz); ^{13}C NMR δ 36.66, 39.12, 51.24, 52.21, 53.19, 53.68, 56.74, 60.62, 90.62, 100.60, 103.23, 108.41, 115.69, 132.08, 149.87, 152.83, 158.52, 163.13, 166.19; MS (EI, 20 eV) m/z (M^+) 534 (15), 321 (10), 168 (55), 138 (100). Anal. Calcd for $C_{19}H_{23}IN_2O_8$: C, 42.71; H, 4.34; N, 5.24. Found: C, 43.00; H, 4.33; N, 4.96.

(±)-(1aα,3β,8β,9β,9aα)-1-Carbomethoxy-8-formyl-1,1a,2,8,9,-9a-hexahydro-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]-benzazocine-5-carboxylic Acid Methyl Ester (16). To a stirred solution of **14** (60 mg, 0.11 mmol) in triethylamine (16 μL, 110 μmol) and 1.1 mL of benzene was added tris(dibenzylideneacetone)dipalladium(0) (150 mg, 0.16 mmol) at room temperature. The resulting purple solution was then heated at 60 °C overnight (8 h). While the reaction was warming the palladium metal fell out of solution as a dark blue-black precipitate. Vigorous stirring of the heterogeneous mixture was therefore maintained during the remainder of the reaction. From thin-layer chromatographic analysis it was not clear whether the reaction progressed much further after the palladium had precipitated. Furthermore, heating of the reaction mixture was of questionable import; the reaction seemed to give some of the desired aldehyde even at room temperature. After the reaction was finalized by cooling to room temperature, the insolubles were filtered off using a small plug of silica. The filtrate was then concentrated *in vacuo* to a yellow-orange residue laden with the former palladium ligand dibenzylideneacetone. Purification by flash column chromatography (7:3 Et_2O/hexanes) gave 30 mg (50%) of the starting enol ether **14** and aldehyde **16** (ca. 6 mg; 13%) contaminated with a few impurities. As full characterization of **16** was not practical, generally the aldehyde was reduced to alcohol **18** using the conditions described below.

(±)-(1aα,3aα,8aα,9aα,9aα)-1-Carbomethoxy-8-formyl-1,1a,2,8,9,-9a-hexahydro-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]-benzazocine-5-carboxylic Acid Methyl Ester (17). To a stirred solution of (*Z*)-enol ether **15** (70 mg, 0.13 mmol) in triethylamine (27 μL, 190 μmol) and 1.3 mL of acetonitrile was added 80 mg of 10% palladium on carbon at room temperature. The resulting suspension was then vigorously stirred under an argon atmosphere at 85 °C in a sealed tube for 22 h. After being cooled to room temperature the reaction mixture was passed through a small plug of silica, rinsing with copious amounts of EtOAc. Concentration of the filtrate *in vacuo* and purification by flash column chromatography (Et_2O) gave 40 mg (57%) of the starting **15** and 7 mg (14%) of aldehyde **17** as a colorless foam: R_f = 0.23 (Et_2O); IR ($CHCl_3$) 1729 (s), 1587 (s), 1439 (s), 1356 (s), 1319 (m), 1296 (s), 1278 (s), 1241 (s), 1187 (s), 1150 (m), 1139 (m),

1106 (s), 1043 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.88 (dd, 1 H, J = 6.5, 1.6 Hz), 3.30 (d, 1 H, J = 6.5 Hz), 3.60 (s, 3 H), 3.64 (s, 3 H), 3.80–3.93 (m, 2 H), 3.82 (s, 3 H), 3.90 (s, 3 H), 3.99 (d, 1 H, J = 4.3 Hz), 7.18 (br s, 2 H), 9.45 (d, 1 H, J = 4.3 Hz); MS (EI, 20 eV) m/z (M$^+$) 392 (71), 347 (48), 316 (27), 45 (100); high-resolution MS m/z calcd for $C_{18}H_{20}N_2O_8$ (M$^+$) 392.1220, found 392.1240.

(±)-(1aα,3β,8β,9β,9aα)-1-Carbomethoxy-1,1a,2,8,9,9a-hexahydro-8-(hydroxymethyl)-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylic Acid Methyl Ester (18). To a stirred solution of aldehyde **16** (11 mg, 28 μmol) in ca. 3 mL of MeOH was added sodium borohydride (3 mg, 79 μmol) at 0 °C. The resulting cloudy solution was stirred under a N_2 atmosphere for 10 min before the reaction was quenched with water. The cold bath was removed; the reaction mixture was stirred for an additional 10 min, and then the mixture was extracted with EtOAc (3×). The combined organics were washed with water (2×) and brine (1×) and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave 12 mg of a light yellow film. Purification by flash column chromatography (9:1 Et_2O/hexanes) gave 7.5–8 mg (70%) of alcohol **18** as a colorless foam: R_f = 0.32 (Et_2O); IR ($CHCl_3$) 3558 (w), 1722 (s), 1439 (m), 1418 (m), 1355 (m), 1295 (s), 1276 (s), 1240 (s), 1194 (m), 1127 (m), 1044 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.62–2.63 (m, 2 H), 3.12 (dd, 1 H, J = 10.4, 3.2 Hz), 3.36 (dd, 1 H, 7.7, 2.1 Hz), 3.58–3.92 (m, 4 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 7.17 (d, 1 H, J = 1.3 Hz), 7.24 (d, 1 H, J = 1.3 Hz); MS (EI, 20 eV) m/z (M$^+$) 394 (14), 347 (46), 45 (100); high-resolution MS m/z calcd for $C_{18}H_{22}N_2O_8$ (M$^+$) 394.1376, found 394.1389.

(±)-(1aα,3aα,8aα,9aα,9aα)-1-Carbomethoxy-1,1a,2,8,9,9a-hexahydro-8-(hydroxymethyl)-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylic Acid Methyl Ester (19). To a stirred solution of aldehyde **17** (10 mg, 25 μmol) in ca. 3 mL of MeOH was added sodium borohydride (3 mg, 79 μmol) at 0 °C. The resulting colorless solution was stirred under a N_2 atmosphere for 10 min before the reaction was quenched with water. The cold bath was removed; the reaction mixture was stirred for an additional 10 min, and then the mixture was extracted with EtOAc (3×). The combined organics were washed with water (2×) and brine (1×) and dried over $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (8:2 EtOAc/hexanes) gave 9 mg (90%) of alcohol **19** as a colorless film: R_f = 0.24 (8:2 EtOAc/hexanes); IR ($CHCl_3$) 3550 (w), 1721 (s), 1586 (m), 1463 (m), 1439 (s), 1353 (s), 1332 (m), 1308 (m), 1194 (m), 1279 (s), 1240 (s), 1182 (m), 1146 (m), 1106 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.83 (dd, 1 H, J = 6.5, 1.9 Hz), 2.94 (dd, 1 H, J = 10.0, 3.8 Hz), 3.25 (d, 1 H, J = 6.5 Hz), 3.45 (dd, 1 H, 7.6, 2.4 Hz), 3.59 (s, 3 H), 3.67–3.86 (m, 4 H), 3.71 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 7.06 (d, 1 H, J = 1.3 Hz), 7.20 (d, 1 H, J = 1.3 Hz); MS (EI, 20 eV) m/z (M$^+$) 394 (100), 347 (42), 329 (23); high-resolution MS m/z calcd for $C_{18}H_{22}N_2O_8$ (M$^+$) 394.1376, found 394.1350.

(±)-(1aα,3β,8β,9β,9aα)-1-Carbomethoxy-8-[[(carbophenoxy)oxy]methyl]-1,1a,2,8,9,9a-hexahydro-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylic Acid Methyl Ester (20). To a stirred solution of **18** (7 mg, 18 μmol) in pyridine (5 μL, 62 μmol) and 0.36 mL of CH_2Cl_2 was added phenyl chloroformate (4 μL, 32 μmol) at 0 °C under a N_2 atmosphere. After 10 min, the reaction was quenched with aqueous Na_2CO_3, and the mixture was 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 colorless residue by flash column chromatography (3:1 Et_2O/hexanes) provided 8.7 mg (94%) of the phenyl carbonate **20** as a colorless film: R_f = 0.5 (Et_2O); IR ($CHCl_3$) 1758 (m), 1724 (s), 1587 (m), 1439 (m), 1355 (m), 1299 (s), 1439 (s), 1279 (s), 1239 (s), 1127 (m), 1109 (m), 1070 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.63–2.65 (m, 2 H), 3.62 (dd, 1 H, J = 6.6, 3.2 Hz), 3.66 (t, 1 H, J = 3.0 Hz), 3.75–3.84 (m, 1 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 4.26 (dd, 1 H, J = 10.9, 3.3 Hz), 4.78 (dd, 1 H, J = 10.9, 6.6 Hz), 7.14–7.39 (m, 7 H); MS (EI, 20 eV) m/z (M$^+$) 514 (2), 376 (13), 45 (100); high-resolution MS m/z calcd for $C_{25}H_{26}N_2O_{10}$ (M$^+$) 514.1587, found 514.1577.

(±)-(1aα,3aα,8aα,9aα,9aα)-1-Carbomethoxy-8-[[(carbophenoxy)oxy]methyl]-1,1a,2,8,9,9a-hexahydro-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylic Acid Methyl Ester (21). To a stirred solution of alcohol **19** (8 mg, 20 μmol) in pyridine (5 μL, 62 μmol) and 0.40 mL of CH_2Cl_2 was added phenyl chloroformate (4 μL, 32 μmol) at 0 °C under a N_2 atmosphere. After 10 min, the reaction was quenched with aqueous Na_2CO_3, and the mixture was 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 and concentration *in vacuo* gave ca. 12 mg of a colorless residue. Purification of the crude material by flash column chromatography (Et_2O) provided 8 mg (77%) of the phenylcarbonate **21** as a colorless film: R_f = 0.52 (8:2 EtOAc/hexanes); IR ($CHCl_3$) 1760 (s), 1722 (s), 1587 (s), 1439 (s), 1355 (s), 1277 (s), 1237 (s), 1152 (m), 1108 (m), 1072 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.85 (br d, 1 H, J = 6.5 Hz), 3.28 (d, 1 H, J = 6.5 Hz), 3.59 (s, 3 H), 3.59–3.90 (m, 3 H), 3.68 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 4.43 (br d, 1 H, J = 10.7 Hz), 4.75 (dd, 1 H, J = 10.7, 7.1 Hz), 7.09-7.40 (m, 7 H); MS (EI, 20 eV) m/z (M$^+$) 514 (38), 285 (48), 156 (34), 57 (100); high-resolution MS m/z calcd for $C_{25}H_{26}N_2O_{10}$ (M$^+$) 514.1587, found 514.1591.

(±)-(1aα,3β,8β,9β,9aα)-8-[[(Aminocarbonyl)oxy]methyl]-1-carbomethoxy-1,1a,2,8,9,9a-hexahydro-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylic Acid Methyl Ester (22). To a flask charged with 8.8 mg (17 μmol) of the phenyl carbonate **20** and containing a magnetic stir bar was added a saturated (ca. 16% at 25 °C) solution of ammonia in MeOH (0.5 mL) at room temperature. The flask was sealed with a plastic cap, and the colorless contents were stirred for 30 min. Concentration *in vacuo* and purification of the residue by flash column chromatography (8:2 EtOAc/hexanes) gave 5.3 mg (70%) of a colorless solid. Crystals suitable for X-ray analysis[11] of **22** could be obtained by slow evaporation of a chloroform solution at 23 °C: mp 256–258 °C (browns on heating and decomposes to a red liquid upon final melting); R_f = 0.39 (9:1 EtOAc/hexanes), 0.47 (EtOAc); IR ($CHCl_3$) 3500 (w), 3400 (w), 1720 (s), 1580 (m), 1460 (m), 1430 (m), 1340 (m), 1290 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.59–2.68 (m, 2 H), 3.44–3.82 (m, 3 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.18 (dd, 1 H, J = 11.0, 3.3 Hz), 4.53 (br s, 2 H), 4.61 (dd, 1 H, J = 11.0, 5.8 Hz), 7.18 (d, 1 H, J = 1.2 Hz), 7.23 (d, 1 H, J = 1.2 Hz); MS (EI, 20 eV) m/z (M$^+$) 437 (11), 376 (100), 345 (49), 301 (45); high-resolution MS m/z calcd for $C_{19}H_{23}N_3O_9$ (M$^+$) 437.1434, found 437.1430.

(±)-(1aα,3aα,8aα,9aα,9aα)-8-[[(Aminocarbonyl)oxy]methyl]-1-carbomethoxy-1,1a,2,8,9,9a-hexahydro-7,9-dimethoxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylic Acid Methyl Ester (23). To a flask charged with 6 mg (12 μmol) of the phenyl carbonate **21** and containing a magnetic stir bar was added a saturated (ca. 16% at 25 °C) solution of ammonia in MeOH (0.5 mL) at room temperature. The flask was sealed with a plastic cap, and the colorless contents were stirred for 1 h. Concentration *in vacuo* and purification of the colorless residue by flash column chromatography (9:1 EtOAc/hexanes) gave 4 mg (80%) of a colorless solid. Crystals suitable for X-ray analysis[11] of **23** could be obtained by slow evaporation of a EtOAc/CH_2Cl_2 solution at 23 °C: mp 202–204 °C (browns on heating at ca. 180 °C and decomposes on melting); R_f = 0.28 (9:1 EtOAc/hexanes), 0.32 (EtOAc); IR ($CHCl_3$) 3546 (w), 3426 (w), 1722 (s), 1585 (m), 1439 (m), 1355 (m), 1339 (m), 1279 (s), 1240 (m), 1109 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.83 (dd, 1 H, J = 6.5, 1.7 Hz), 3.24 (d, 1 H, J = 6.5 Hz), 3.42 (dd, 1 H, J = 5.9, 2.1 Hz), 3.59 (s, 3 H), 3.65 (s, 3 H), 3.67–3.89 (m, 2 H), 3.90 (s, 6 H), 4.34 (dd, 1 H, J = 10.9, 2.1 Hz), 4.54 (br s, 2 H), 4.61 (dd, 1 H, J = 10.9, 5.9 Hz), 7.07 (d, 1 H, J = 1.4 Hz), 7.19 (d, 1 H, J = 1.4 Hz). A low-resolution mass spectrum showing the parent could not be obtained by electron ionization (EI) or by chemical ionization (CI); high-resolution MS (FAB) calcd for $C_{19}H_{23}N_3O_9$ (M + H$^+$), 438.1513, found 437.1557.

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