Dioxirane Epoxidation of 10-Membered-Ring Stilbene Lactams as Synthetic Precursors to Protoberberines

Gema Rodríguez, Luis Castedo, Domingo Domínguez,*,† and Carlos Saá*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Facultad de Química, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

Waldemar Adam and Chantu R. Saha-Möller

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

Received September 8, 1998

Silylated stilbene lactams **1**, prepared by intramolecular addition of an aryl radical to a trimethylsilylacetylene, were converted into protoberberines by dimethyldioxirane (DMD) epoxidation and subsequent acid-catalyzed cyclization of the epoxysilane with HCl. Treatment of the nonsilylated *trans*- and *cis*-stilbene derivatives with DMD afforded 13-hydroxytetrahydroprotoberberines and 13a-hydroxy-13-ketotetrahydroprotoberberines as the main products. Tetrahydroprotoberberines were also obtained in excellent yields by the reaction of both silylated and nonsilylated lactams with hydriodic acid.

Introduction

Over the past few years, we have developed a new strategy for the synthesis of isoquinoline alkaloids such as protoberberines[1] and isoindolobenzazepines.[2] Preliminary studies showed that the silylated stilbene lactam **1c**, obtained by 10-*endo* radical macrocyclization, can be regioselectively converted by transannular cyclization into products with either the isoindolobenzazepine or the protoberberine skeleton.[3] The protoberberine skeleton **3c** was obtained by epoxidation of **1c** with *m*-CPBA (3 equiv in CH_2Cl_2 under reflux) followed by acid-catalyzed opening of the epoxysilane **2c** with removal of trimethylsilanol (Scheme 1).

To synthesize tetrahydroprotoberberines with dioxygenated A or D rings for subsequent pharmacological evaluation, we pursued the new strategy[3,4] of preparing the protoberberines **3a** and **3b** from the stilbene macrolactams **1a** and **1b**. The radical reactions for the synthesis of **1a** and **1b** took place expectedly, but epoxidation of **1a** with *m*-CPBA led to a complex mixture of products. As potentially more effective epoxidizing agent, we decided to employ the recently popular dimethyldioxirane (DMD)[5,6] and its trifluoromethyl analogue TFD,[7] which combine high reactivity, neutral pH, and ease of workup. We report herein our results on the use of the stilbene macrolactams **1a** and **1b** to synthesize protoberberines by means of their intermediary epoxides, the latter readily available by dioxirane oxidation.

Results and Discussion

As precursors of the required stilbene macrolactams **1a** and **1b**, the *o*-(trimethylsilylethynyl)benzamides **8a** and **8b** were prepared from commercially available starting materials as shown in Schemes 2 and 3. Condensation of phenethylamines **4** with the acid chlorides **5** in THF at room temperature in the presence of triethylamine gave benzamides **6a** and **6b** in 87% and 77% yields, and bromination of **6a** and iodination of **6b** afforded the dihalogenated benzamides **7a** and **7b** (Scheme 2).

Treatment of **7a** and **7b** with (trimethylsilyl)acetylene (1.5 equiv) in the presence of CuI (0.05 equiv) and $(Ph_3P)_2$-$PdCl_2$ (0.05 equiv) in Et_3N at room temperature under argon afforded the *o*-(trimethylsilylethynyl)benzamides **8a** and **8b** chemoselectively in 83% and 80% yields (Scheme 3). Radical cyclization was performed by slow dropwise addition of a solution of tributyltin hydride (2 equiv) and AIBN (20 wt %) in benzene to a 5 mM solution of benzamide **8a** or **8b** in benzene refluxing under argon. The desired stilbene macrolactams **1a** and **1b** were obtained in 75% and 70% yields as single geometrical isomers of unknown configuration.[8]

As was mentioned above, epoxidation of **1a** with *m*-CPBA (3 equiv) in CH_2Cl_2 under reflux or at 0 °C led to a complex mixture of products (whereas with the same procedure 70% epoxidation of the unsubstituted lactam

† Fax: +34-981-595012. E-mail: qocsaa@usc.es, qomingos@usc.es.

(1) Bhakuni, D. S.; Jain, S. In *The Alkaloids*; Brossi, A., Ed.; New York: Academic Press: 1986; Vol. 28, pp 95−181.

(2) (a) Fajardo, V.; Elango, B.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39−42. (b) Valencia, E.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1984**, *25*, 599−602. (c) Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M. *Tetrahedron* **1984**, *40*, 3957−3962.

(3) Lamas, C.; Saá, C.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1992**, *33*, 5653−5654.

(4) Rodríguez, G.; Cid, M. M.; Saá, C.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1996**, *61*, 2780−2782.

(5) For a review of the chemistry of dioxiranes, see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205−211. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811−822. (d) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581−599. (e) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A., Weinkötz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105−109.

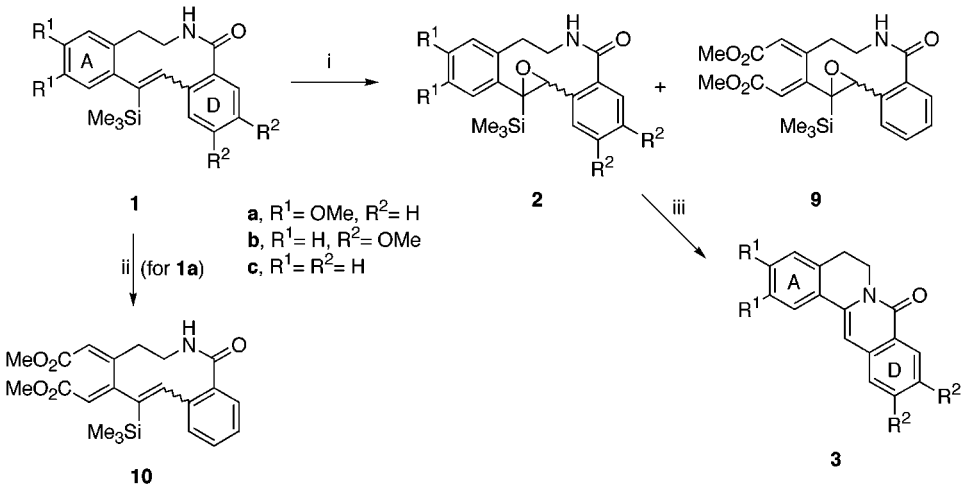
(6) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(7) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890−3891.

(8) NOE studies and molecular modeling did not allow to assign unequivocally the geometry of the isolated stereoisomer.

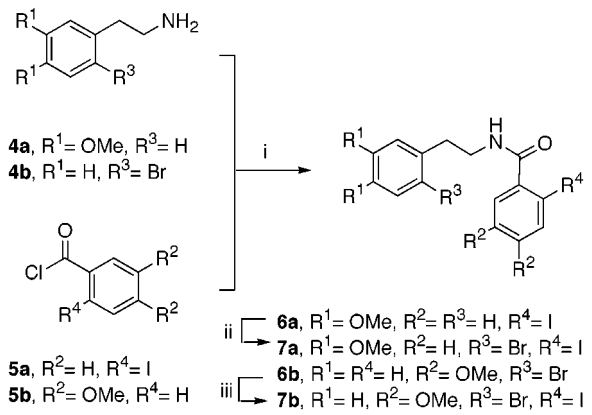
10.1021/jo981829n CCC: $18.00
Published on Web 01/09/1999

Scheme 1[a]



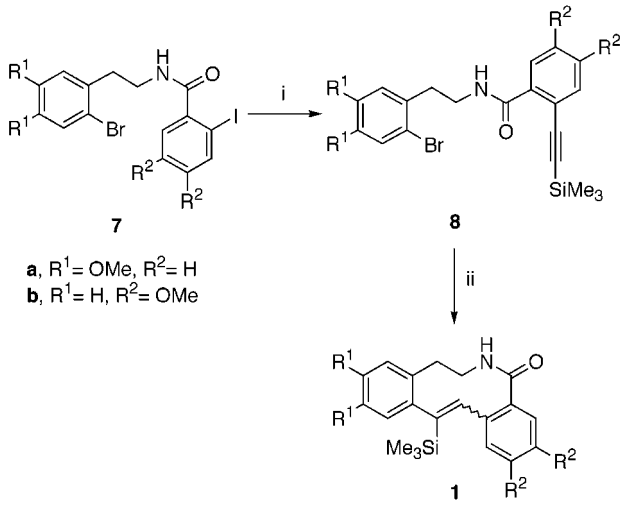
[a] Reagents: (i) DMD, acetone, ca. 20 °C; (ii) TFD, CH_2Cl_2, ca. 20 °C; (iii) HCl, MeOH, ca. 20 °C.

Scheme 2[a]



[a] Reagents: (i) Et_3N, THF, ca. 20 °C; (ii) Br_2, AcOH, ca. 20 °C, 90%; (iii) I_2, $AgOCOCF_3$, $NaHCO_3$, CH_2Cl_2, ca. 20 °C, 75%.

Scheme 3[a]



[a] Reagents: (i) (trimethylsilyl)acetylene, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, ca. 20 °C, 80% (ii) *n*-Bu_3SnH, AIBN, benzene, reflux, 75%.

1c had been achieved).[3] We, therefore, attempted the epoxidation of the vinylsilane moiety with the more effective oxidant DMD. Indeed, addition of excess DMD (8 equiv) in several doses over 9 h at room temperature[9] afforded a 47% yield of the desired epoxysilane **2a** by DMD attack on the stilbene double bond. Also a 31% yield of the epoxymuconate diester **9** was obtained by oxidation of both the vinylsilane functionality and the electron-rich aromatic ring (Scheme 1).[10] Probably, epoxysilane **2a** is initially formed and subsequently oxidized by excess DMD to afford the epoxymuconate **9**. This is supported by the fact that treatment of authentic **2a** with 8 equiv DMD for 96 h produced **9** in 25% yield.[11]

Since the total consumption of **1a** required a large excess of DMD, epoxidation with the more reactive TFD was conducted. Treatment of a solution of **1a** in CH_2Cl_2 with 1.8 equiv of TFD (added in two doses) for 9 h at room temperature afforded the muconate diester **10** in 90% yield (Scheme 1). Instead of epoxidation of the hindered stilbene double bond, oxidative cleavage of the dimethoxylated aromatic ring took place. The cleavage of arenes by dioxiranes is known,[12] but that the olefinic double bond survives epoxidation by the very reactive TFD is unusual.[13] The sterically encumbered vinylsilane functionality and the activation of the aryl ring by the methoxy groups are responsible that for the sterically more demanding TFD only cleavage of **1a** to **10** (see mechanism below, Scheme 4) instead of epoxidation to **2a** and **9** is observed.

The cleavage of the dimethoxylated aromatic ring in **1a** by DMD is to be contrasted with its oxidation of methoxybenzenes, which readily undergo hydroxylation.[14] A possible mechanism is shown in Scheme 4, in which epoxidation of the electron-rich dimethoxylated double bond of ring A to a benzene oxide intermediate is

(9) Use of less DMD (1.1−4 equiv) led to incomplete consumption of the starting material (18% to 77% conversion) in 24 h.

(10) Regardless of the amount of DMD used, both **2a** and **9** appeared in the early stages of the reaction, as was shown by TLC monitoring.

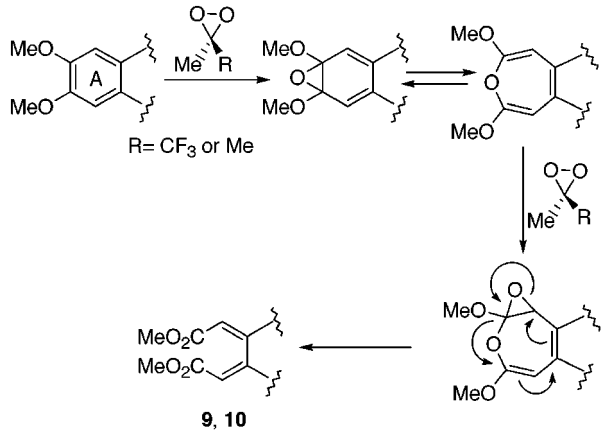
(11) 75% of starting epoxysilane **2a** was recovered unchanged.

(12) (a) Jeyaraman, R.; Murray, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 2462−2463. (b) Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Principe, T.; Curci, R. *Tetrahedron Lett.* **1990**, *31*, 6097−6100. (c) Altamura, A.; Fusco, C.; D'Accolti, L.; Mello, R.; Principe, T.; Curci, R. *Tetrahedron Lett.* **1991**, *32*, 5445−5448. (d) Murray, R. W.; Singh, M.; Rath, N. P. *J. Org. Chem.* **1997**, *62*, 8794−8799.

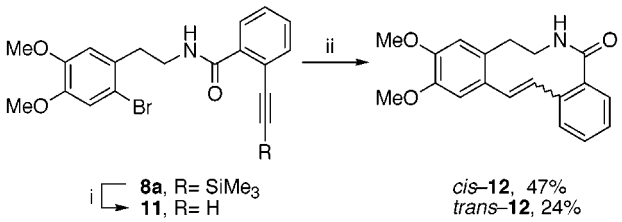
(13) We thank a reviewer to bring to our attention a precedent concerning the steric shielding to dioxirane epoxidation exercised by trimethylsilyl groups; Maynard, G. D.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 5480−5482.

(14) Adam, W.; Shimizu, M. *Synthesis* **1994**, 560−562.

Scheme 4



Scheme 5[a]



[a] Reagents: (i) K_2CO_3, MeOH, ca. 20 °C, 95%; (ii) *n*-Bu_3SnH, AIBN, benzene, reflux, 71%.

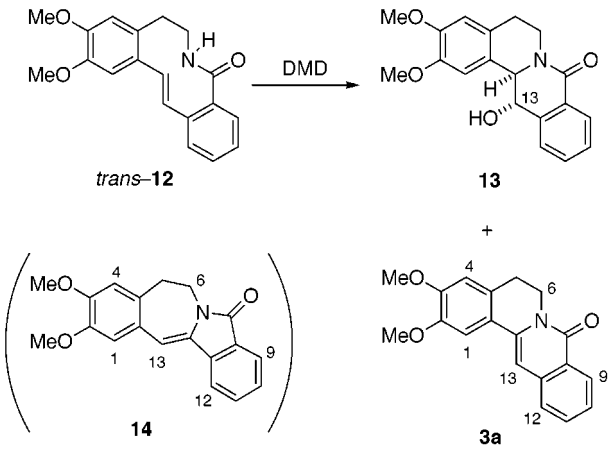
proposed, which equilibrates to the oxepin[12b−d] and a second epoxidation with subsequent ring-opening generates the muconate **10**.

In contrast, the epoxidation of the stilbene macrolactam **1b** afforded the epoxysilane **2b** almost quantitatively when treated at room temperature for 6 d with 5 equiv of DMD (added in several doses); no oxidative cleavage of the dimethoxylated aromatic ring was observed (Scheme 1). Thus, presumably the amide carbonyl group deactivates the dimethoxylated ring D sufficiently to prevent its electrophilic oxidation by DMD. The slow oxidation rate is again due to the bulky trimethylsilyl group, which hinders the approach of the dioxirane to the stilbene double bond. Most gratifying, addition of HCl to methanolic solutions of **2a** and **2b** afforded the desired protoberberines **3a**[15] and **3b** in quantitative yield (Scheme 1).

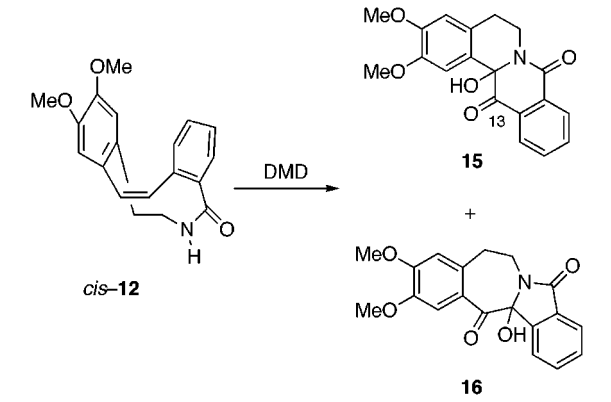
To assess the influence of the trimethylsilyl substituent and the olefin geometry on the epoxidation process, the unsilylated *cis*- and *trans*-stilbene macrolactams **12** were treated with DMD. Lactams **12** were prepared from ethynylbenzamide **11**, which was obtained in 95% yield by desilylation of benzamide **8a** with catalytic amounts of K_2CO_3 in MeOH at room temperature (Scheme 5). The radical macrocyclization of **11** followed the usual procedure and led to a mixture of *cis*- and *trans*-stilbene macrolactams **12** in 47% and 24% yields.[16] This is to be contrasted with the stereoselective formation of a single geometrical isomer when the silylated acetylene **8a** was cyclized to **1a** (Scheme 3) by the same procedure.

Treatment of *trans*-**12** with 1.2 equiv of DMD for 8 h led to the 13-hydroxytetrahydroprotoberberine **13**[17] in 78% yield (Scheme 6). Epoxidation of the double bond followed by the opening of the epoxide ring due to nucleophilic attack by the nearby amide accounts for this transformation. When 1.5 equiv of DMD and a longer reaction time (24 h) were employed, a mixture of **13** (40%) and the protoberberine **3a**[15] (31%) was obtained,[18] and the latter compound was distinguished from the possible isoindolobenzazepine **14** by an HMBC NMR experiment that showed a three-bond coupling between H-13 and C-12 and no coupling between H-1 and C-13.

Scheme 6



Scheme 7



The epoxidation of the *cis*-**12** was more sluggish since its completion needed a larger excess of DMD (2.5 equiv) and a longer reaction time (2 d). The finding that *cis*-**12** is less reactive than its trans isomer is ascribable to its different molecular geometry: The trans isomer is flatter and has a more accessible stilbene bond than the U-shaped *cis*-**12** (Scheme 7), such that in the epoxidation of the latter the epoxidant has to approach the double bond between the two almost parallel aryl rings.[19] From the complex oxidation mixture, we only isolated the 13a-hydroxy-13-ketotetrahydroprotoberberine **15** in 21% yield. The presence of a small amount of the isoindolobenzazepine **16**[2a] was also observed (Scheme 7).[20] The formation of these overoxidized products can be ascribed to the

(15) Ninomiya, I.; Naito, T.; Takasugui, H.; *J. Chem. Soc., Perkin Trans. 1* **1975**, 1720−1724.

(16) Attempts to desilylate macrolactam **1a** under acid and basic conditions led to [6, 6]- and [7, 5]-azabicyclic products; Rodríguez, G.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1998**, *39*, 6551.

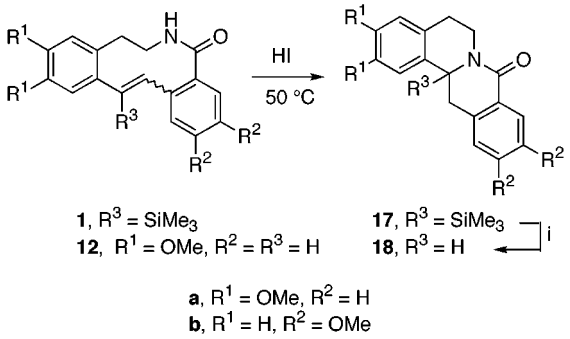
(17) Mardsen, R.; MacLean, D. B. *Can. J. Chem.* **1984**, *62*, 1392−1399.

(18) Compound **13** persists in acetone solution; however, in the presence of DMD, a slow dehydration takes place to afford **3a**.

(19) Geometry optimization was carried out by PM3 semiempirical calculations by using MacSpartan Plus 1.1.6, Wave Function, Irvine, CA, 1996.

(20) The isomeric structures **15** and **16** were identified by a combination of HMQC and HMBC NMR experiments.

Scheme 8[a]



[a] Reagents: (i) Bu_4NF, THF, ca. 20 °C.

large excess of DMD and the long reaction time. The absence of muconate confirms that oxidative cleavage of the dimethoxylated aromatic ring competes only if there is no other functionality capable of suffering oxidation in the molecule.

A comparison of epoxidation reactions between the silylated and nonsilylated stilbene macrolactams **1a** and **12** (*trans* and *cis*) clearly shows a different fate of the initially formed epoxides, which depends on the nature and substitution of the stilbene double bond. Thus, for *trans*- or *cis*-**12**, the intermediate epoxide suffers rapid ring-opening by nitrogen nucleophilic attack to afford the protoberberine skeletons (Schemes 6 and 7), whereas the epoxysilane **2a** remains intact and cyclization may be triggered at will by acid catalysis (Scheme 1).

Unexpectedly, we have also found that hydriodic acid treatment of the silylated stilbene macrolactams **1a** and **1b** and the nonsilylated stilbene macrolactams **12** led directly to the tetrahydroprotoberberines **17a**, **17b**, and **18a** (Scheme 8). Specifically, addition of 10 equiv of HI (57% in water) to solutions of **1a** and **1b** in benzene afforded almost quantitative yields of the silylated tetrahydroprotoberberines **17a** and **17b**, and both *cis*- and *trans*-stilbene macrolactams **12** gave under the same conditions **18a**[21] in 75% and 87% yields. In all cases only [6,6]-transannular cyclization occurred, in which the carbocation responsible for the intramolecular *N*-alkylation was generated regioselectively by protonation of the olefinic carbon atom farthest from the amide carbonyl group.[16] Desilylation of **17a** and **17b** by addition of tetrabutylammonium fluoride (1.5 equiv in THF) produced the tetrahydroprotoberberines **18a** and **18b** in 71% and 76% yields.

To sum up, we have shown that stilbene lactams with 10-membered lactam rings are versatile intermediates for the synthesis of protoberberine alkaloids. DMD epoxidation allows their easy conversion into protoberberines or oxyfunctionalized tetrahydroprotoberberines. Conveniently, hydriodic acid treatment of both silylated and nonsilylated stilbene macrolactams affords tetrahydroprotoberberines by regioselective [6,6]-transannular cyclization.

Experimental Section

General. All nonaqueous reactions were conducted under an inert atmosphere of argon gas, by using flame-dried glassware. Unless specified otherwise, solvents and reagents were commercially available chemicals and were used as received. Tetrahydrofuran (THF) and benzene were distilled from a sodium metal/benzophenone mixture. Dichloromethane, diisopropylethylamine and triethylamine were distilled from calcium hydride. Slow additions were carried out by using a syringe pump (Harvard 11). Melting points are uncorrected. ^1H, ^{13}C, and DEPT-NMR spectra were recorded in $CDCl_3$, unless specified; chemical shifts are reported as δ values in ppm vs tetramethylsilane (TMS).

***N*-[2-(2-Bromophenyl)ethyl]-3,4-dimethoxybenzamide (6b).** A solution of benzoyl chloride **5b** (0.55 g, 2.75 mmol) in THF (10 mL) was cannulated to a cold, stirred solution of 2-bromophenylethylamine **4b** (0.60 g, 3.02 mmol) and triethylamine (0.58 mL, 4.12 mmol) in THF (20 mL). Once addition was finished, stirring was continued for 2.5 h at room temperature (ca. 20 °C). The residue obtained by removal of volatiles under reduced pressure was dissolved in CH_2Cl_2 (10 mL), washed with 5% aqueous HCl (2 × 5 mL), dried over anhydrous Na_2SO_4, concentrated to dryness and recrystallized from CH_2Cl_2/ethyl ether to afford **6b** (0.84 g, 77%) as white plates, mp 99−101 °C. IR (KBr): ν 3246, 2923, 1629, 1513, 1232 cm^{-1}. ^1H NMR: δ 3.10 (t, J = 6.7 Hz, 2H), 3.69−3.76 (m, 2H), 3.91 (br s, 6H), 6.16−6.36 (m, 1H), 6.84 (d, J = 8.3 Hz, 1H), 7.07−7.21 (m, 1H), 7.22−7.27 (m, 3H), 7.40 (br s, 1H), 7.56 (d, J = 7.8 Hz, 1H). ^{13}C NMR: δ 35.7 (CH_2), 39.9 (CH_2), 55.9 (2 × CH_3), 110.2 (CH), 110.5 (CH), 119.2 (CH), 124.6 (C), 127.2 (C), 127.7 (CH), 128.3 (CH), 131.1 (CH), 132.9 (CH), 138.4 (C), 148.9 (C), 151.6 (C), 167.1 (C=O). MS *m*/*z* (relative intensity): 365 (M^+, 1), 363 (M^+, 1), 181 (9), 165 (100). Anal. Calcd for $C_{17}H_{18}BrNO_3$: C, 56.06; H, 4.98; N, 3.85. Found: C, 55.98; H, 4.98; N, 3.64.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2-iodobenzamide (7a).** A solution of Br_2 (2.35 g, 14.76 mmol) in glacial acetic acid (13 mL) was added dropwise to a stirred solution of **6a** (4.50 g, 10.94 mmol) in glacial acetic acid (20 mL) at 0 °C. Once addition was finished, the mixture was allowed to warm to room temperature, stirred for 6 h, poured into CH_2Cl_2 (50 mL), and washed successively with aqueous solutions of 10% $Na_2S_2O_5$ (3 × 30 mL), 10% KOH (3 × 30 mL), and saturated brine (3 × 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue obtained was crystallized from methanol to give 4.80 g of **7a** (90%) as white flakes, mp 158−160 °C. IR (KBr): ν 3276, 2925, 1635 cm^{-1}. ^1H NMR: δ 3.04 (t, J = 7.1 Hz, 2H), 3.68−3.75 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 5.86 (br s, 1H), 6.84 (s, 1H), 7.01 (s, 1H), 7.06−7.11 (m, 1H), 7.35 (m, 2H), 7.58 (d, J = 7.8 Hz, 1H). ^{13}C NMR: δ 35.3 (CH_2), 39.9 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 92.4 (C), 113.6 (CH), 114.3 (CH), 115.7 (CH), 128.1 (CH), 128.2 (CH), 129.9 (C), 131.1 (CH), 139.9 (CH), 142.1 (C), 148.4 (C), 148.6 (C), 169.4 (C=O). MS *m*/*z* (relative intensity): 491 (M^+, 4), 489 (M^+, 4), 244 (100), 242 (99), 231 (79). Anal. Calcd for $C_{17}H_{17}BrINO_3$: C, 41.66; H, 3.49; N, 2.86. Found: C, 41.45; H, 3.49; N, 2.77.

***N*-[2-(2-Bromophenyl)ethyl]-2-iodo-4,5-dimethoxybenzamide (7b).** A suspension of **6b** (4.01 g, 11.0 mmol), iodine (3.07 g, 12.1 mmol), $AgOCOCF_3$ (2.67, 12.1 mmol), and $NaHCO_3$ (1.02, 12.1 mmol) in CH_2Cl_2 (110 mL) was stirred for 12 h at room temperature and the solids removed by filtration. The organic layer was washed with an aqueous solution of 10% $Na_2S_2O_5$ (2 × 60 mL) and saturated brine (2 × 60 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the residue by flash column chromatography (1:1 EtOAc/hexane) yielded **7b** (4.04 g, 75%) as white flakes, mp 118−120 °C (EtOAc). IR (KBr): ν 3292, 2916, 1640, 1253, 1208, 1021 cm^{-1}. ^1H NMR: δ 3.13 (t, J = 7.0 Hz, 2H), 3.70−3.77 (m, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 5.97−6.11 (m, 1H), 6.91 (s, 1H), 7.07−7.18 (m, 1H), 7.20 (s, 1H), 7.22−7.38 (m, 2H), 7.55 (d, J = 7.9 Hz, 1H). ^{13}C NMR: δ 35.4 (CH_2), 39.8 (CH_2), 56.0 (CH_3), 56.2 (CH_3), 80.9 (C), 111.7 (CH), 122.0 (CH), 124.6 (C), 127.6 (CH), 128.3 (CH), 131.1 (CH), 132.9 (CH), 134.1 (C), 138.1 (C), 149.0 (C), 150.4 (C), 168.8 (C=O). MS *m*/*z* (relative intensity): 491 (M^+, 2), 489 (M^+, 2), 291 (100). Anal. Calcd for $C_{17}H_{17}BrINO_3$: C, 41.66; H, 3.49; N, 2.86. Found: C, 41.86; H, 3.49; N, 2.74.

(21) (a) Warrener, R. N.; Liu, L.; Russell, R. A. *Chem. Commun.* **1997**, 2173-2174. (b) Lenz, G. R. *J. Org. Chem.* **1974**, *39*, 2846−2851.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2-[(trimethylsilyl)ethynyl]benzamide (8a).** A mixture of **7a** (4.00 g, 8.16 mmol), $(Ph_3P)_2PdCl_2$ (0.29 g, 0.41 mmol), CuI (0.08 g, 0.41 mmol), and (trimethylsilyl)acetylene (1.8 mL, 12.74 mmol) in 120 mL of Et_3N was stirred for 6 h at room temperature and passed through a pad of Celite to remove solids. The filtrate was concentrated and the residue dissolved in CH_2Cl_2 (40 mL). The resulting solution was washed with 5% aqueous HCl (2 × 20 mL) and saturated brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the residue by flash chromatography on silica gel (1:2 EtOAc/hexane) afforded **8a** (3.10 g, 83%), which was crystallized from MeOH as white plates, mp 113−115 °C (MeOH). IR (KBr): ν 3328, 2957, 2153, 1632, 1533, 841 cm^{-1}. ^1H NMR: δ 0.24 (s, 9H), 3.02 (t, J = 7.4 Hz, 2H), 3.68 (m, 2H), 3.76 (s, 3H), 3.83 (s, 3H), 6.77 (s, 1H), 7.00 (s, 1H), 7.37−7.46 (m, 2H), 7.51−7.54 (m, 1H), 7.89 (br s, 1H), 8.12 (d, J = 7.2 Hz, 1H). ^{13}C NMR: δ −0.3 (CH_3), 35.6 (CH_2), 40.0 (CH_2), 55.9 (CH_3), 56.1 (CH_3), 101.9 (C), 103.6 (C), 113.5 (CH), 114.0 (CH), 115.5 (CH), 119.3 (C), 129.1 (CH), 130.1 (CH), 130.2 (C), 130.5 (CH), 133.9 (CH), 135.1 (C), 148.2 (C), 148.4 (C), 165.8 (C═O). MS m/z (relative intensity): 461 (M^+, 3), 459 (M^+, 3), 380 (20), 244 (100), 242 (98). Anal. Calcd for $C_{22}H_{26}BrNO_3Si$: C, 57.39; H, 5.69; N, 3.04. Found: C, 57.10; H, 5.95; N, 3.30.

***N*-[2-(2-Bromophenyl)ethyl]-4,5-dimethoxy-2-[(trimethylsilyl)ethynyl]benzamide (8b).** A mixture of **7b** (3.00 g, 6.11 mmol), $(Ph_3P)_2PdCl_2$ (0.22 g, 0.31 mmol), CuI (0.08 g, 0.31 mmol) and (trimethylsilyl)acetylene (1.3 mL, 9.17 mmol) in DMF (20 mL) and Et_3N (50 mL) was stirred for 12 h at room temperature and passed through a pad of Celite to remove solids. The filtrate was concentrated and dissolved in CH_2Cl_2 (40 mL). The resulting solution was washed with 5% aqueous HCl (2 × 20 mL) and saturated brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the residue by flash chromatography on silica gel (1:2 EtOAc/hexane) afforded **8b** (2.26 g, 80%), which was crystallized from MeOH as white powder, mp 51−53 °C (MeOH). IR (KBr): ν 3384, 2953, 2135, 1631, 1024, 846 cm^{-1}. ^1H NMR: δ 0.24 (s, 9H), 3.10 (t, J = 7.4 Hz, 2H), 3.67−3.75 (m, 2H), 3.93 (s, 3H), 3.96 (s, 3H), 6.95 (s, 1H), 7.05−7.30 (m, 3H), 7.55 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 8.16 (br s, 1H). ^{13}C NMR: δ −0.2 (CH_3), 36.1 (CH_2), 40.0 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 100.5 (C), 104.0 (C), 111.9 (C), 112.7 (CH), 115.5 (CH), 124.5 (C), 127.6 (CH), 128.2 (CH), 128.4 (C), 131.1 (CH), 132.8 (CH), 138.4 (C), 149.6 (C), 150.4 (C), 165.3 (C═O). MS m/z (relative intensity): 461 (M^+, 2), 459 (M^+, 2), 262 (27), 261 (100).

10,11-Dimethoxy-13-trimethylsilyl-5,6,7,8-tetrahydrodibenzo[*c*,*g*]azecin-5-one (1a). A solution of *n*-Bu_3SnH (175 μL, 0.69 mmol) and AIBN (40 mg, 20 wt % of **8a**) in benzene (12 mL) was added over 5 h by means of a syringe pump to a solution of **8a** (0.20 g, 0.43 mmol) in dry, degassed benzene (75 mL) kept at reflux. After complete addition, reflux was kept up for another 4 h. The solvent was evaporated to dryness and the residue was dissolved in CH_3CN (30 mL). This solution was washed with hexane (3 × 15 mL), then concentrated and the obtained residue chromatographed on silica gel (1:2 EtOAc/hexane). Macrolactam **1a** (125 mg, 75%) was obtained as white needles, mp 158−160 °C (EtOAc). IR (KBr): ν 3340, 2928, 1644, 1506, 839 cm^{-1}. ^1H NMR: δ 0.19 (s, 9H), 2.44 (dd, J = 4.1, 14.2 Hz, 1H), 3.03−3.06 (m, 1H), 3.09−3.14 (m, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 4.21−4.25 (m, 1H), 5.62 (dd, J = 4.3, 9.3 Hz, 1H), 6.63 (s, 1H), 6.70 (s, 1H), 7.09 (s, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.42 (dt, J = 1.4, 7.5 Hz, 1H), 7.69 (dd, J = 1.0, 7.5 Hz, 1H). ^{13}C NMR: δ −0.5 (CH_3), 32.8 (CH_2), 43.8 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 110.1 (CH), 114.1 (CH), 127.0 (CH), 127.6 (CH), 128.3 (CH), 129.9 (CH), 131.1 (C), 137.9 (C), 138.4 (C), 138.5 (C), 145.3 (CH), 147.0 (2 × C), 151.4 (C), 170.8 (C═O). MS m/z (relative intensity): 381 (M^+, 22), 353 (26), 308 (91), 292 (44), 262 (26), 73 (100). Anal. Calcd for $C_{22}H_{27}NO_3Si$: C, 69.25; H, 7.13; N, 3.67. Found: C, 69.06; H, 7.35; N, 3.59.

2,3-Dimethoxy-13-trimethylsilyl-5,6,7,8-tetrahydrodibenzo[*c*,*g*]azecin-5-one (1b). A solution of *n*-Bu_3SnH (308 μL, 1.14 mmol) and AIBN (50 mg, 20 wt % of **8b**) in benzene (15 mL) was added over 5 h by means of a syringe pump to a solution of **8b** (0.25 g, 0.54 mmol) in dry, degassed benzene (70 mL) kept at reflux. After complete addition, reflux was kept up for another 4 h. The solvent was evaporated to dryness and the residue was dissolved in CH_3CN (35 mL). This solution was washed with hexane (3 × 20 mL), then concentrated and the obtained residue chromatographed on silica gel (1:1 EtOAc/hexane). Macrolactam **1b** (146 mg, 70%) was obtained as white needles, mp 182−184 °C (EtOAc/ Et_2O). IR (KBr): ν 3403, 2948, 1653, 1500, 843 cm^{-1}. ^1H NMR: δ −0.15 (s, 9H), 2.51−2.57 (m, 1H), 2.98−3.15 (m, 2H), 3.94 (s, 6H), 4.24−4.34 (m, 1H), 5.54−5.57 (m, 1H), 6.75 (s, 1H), 7.03 (s, 1H), 7.10−7.24 (m, 5H). ^{13}C NMR: δ −0.3 (CH_3), 33.8 (CH_2), 44.0 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 109.7 (CH), 111.1 (CH), 126.3 (CH), 126.5 (CH), 126.6 (CH), 130.9 (CH), 131.2 (C), 131.3 (C), 139.2 (C), 144.3 (CH), 146.4 (C), 148.6 (C), 150.3 (C), 153.3 (C), 170.9 (C═O). MS m/z (relative intensity): 381 (M^+, 14), 309 (22), 308 (100), 292 (44), 73 (56). Anal. Calcd for $C_{22}H_{27}NO_3Si$: C, 69.25; H, 7.13; N, 3.67. Found: C, 68.92; H, 6.99; N, 3.57.

General Procedure for the Epoxidation of Macrolactams 1a, 1b, and 12 with Dimethyldioxirane. Doses of a cooled solution (−78 °C) of dimethyldioxirane (DMD) in acetone (0.050−0.084 M),[6] dried over molecular sieves, were rapidly added at room temperature to a stirred solution of the appropriate macrolactam in the same solvent until complete consumption of the starting material (TLC monitoring). The solvent was evaporated to dryness and the residue was subjected to silica gel chromatography.

10,11-Dimethoxy-12b-trimethylsilyl-5,6,7,8,12b,13a-hexahydrodibenzo[*c*,*g*]oxireno[2,3-*e*]-5-one (2a) and Methyl-2-{1a-trimethylsilyl-2-[(*E*)-1-(methyloxycarbonyl)-methylidene]-7-oxo-1a,2,3,4,5,6,7,11b-octahydrobenzo-[*c*]oxireno[2,3-*e*]azecin-3-yliden}acetate (9). A solution (16 mL) of 0.078 M DMD (1.25 mmol) in acetone was added to 60 mg (0.16 mmol) of **1a** in acetone (1 mL) within 9 h. Removal of the solvent (20 °C, 740 Torr), followed by preparative TLC of the residue on silica gel (1:2 EtOAc/hexane), afforded 37 mg (47%) of **2a** and 25 mg (31%) of **9**, both as white plates. Epoxysilane **2a**: mp 163−165 °C (EtOAc/hexane). IR (KBr): ν 3312, 2954, 1636, 1510, 842 cm^{-1}. ^1H NMR: δ −0.23 (s, 9H), 2.61 (dd, J = 3.9, 14.4 Hz, 1H), 3.04 (dt, J = 4.9, 12.4 Hz, 1H), 3.30−3.41 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.11 (s, 1H), 4.29−4.40 (m, 1H), 6.18−6.23 (m, 1H), 6.66 (s, 1H), 6.95 (s, 1H), 7.36−7.50 (m, 3H), 7.68 (d, J = 7.2 Hz, 1H). ^{13}C NMR: δ −1.7 (CH_3), 39.6 (CH_2), 44.3 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 62.7 (C), 69.6 (CH), 109.0 (CH), 114.6 (CH), 126.4 (CH), 128.4 (2 × CH), 129.7 (C), 130.7 (CH), 134.3 (C), 134.8 (C), 135.5 (C), 147.6 (C), 147.8 (C), 169.0 (C═O). MS m/z (relative intensity): 397 (M^+, 13), 308 (44), 307 (62), 292 (100). Muconate **9**: mp 150−152 °C (EtOAc/hexane). IR (KBr): ν 3315, 2923, 1727, 1642, 524 cm^{-1}. ^1H NMR: δ −0.11 (s, 9H), 2.27−2.36 (m, 1H), 2.95 (dd, J = 1.8, 12.4 Hz, 1H), 3.38−3.48 (m, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 4.00 (s, 1H), 4.18−4.25 (m, 1H), 5.90−5.94 (m, 1H), 6.08 (s, 1H), 6.15 (s, 1H), 7.36−7.44 (m, 3H), 7.55−7.58 (m, 1H). ^{13}C NMR: δ −0.8 (CH_3), 40.7 (CH_2), 42.3 (CH_2), 51.3 (CH_3), 51.4 (CH_3), 61.6 (C), 68.1 (CH), 116.3 (CH), 123.9 (CH), 127.3 (CH), 127.5 (CH), 128.7 (CH), 130.2 (CH), 133.1 (C), 135.5 (C), 153.3 (C), 158.4 (C), 165.0 (C═O), 166.1 (C═O), 168.6 (C═O). MS m/z (relative intensity): 429 (M^+, 4), 292 (41), 280 (54), 133 (49), 73 (100). HRMS calcd for $C_{22}H_{27}NO_6Si$ 429.16076, found 429.16125.

2,3-Dimethoxy-12b-trimethylsilyl-5,6,7,8,12b,13a-hexahydrodibenzo[*c*,*g*]oxireno[2,3-*e*]-5-one (2b). A solution (3.5 mL) of 0.078 M DMD (0.30 mmol) in acetone was added to 23 mg (0.060 mmol) of **1b** in acetone (0.5 mL) (see General Procedure). After 6 d, removal of the solvent (20 °C, 740 Torr), followed by preparative TLC of the residue on silica gel (1:1 EtOAc/hexane), afforded 23 mg (96%) of **2b** as a white powder. IR (film): ν 3315, 2923, 1637, 1508, 842, 754 cm^{-1}. ^1H NMR: δ −0.19 (s, 9H), 2.72 (dd, J = 3.9, 14.1 Hz, 1H), 3.05 (dt, J = 4.8, 12.2 Hz, 1H), 3.29−3.41 (m, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 4.09 (s, 1H), 4.39−4.51 (m, 1H), 6.03−6.08 (m, 1H), 6.95 (s, 1H), 7.03−7.31 (m, 4H), 7.39−7.42 (m, 1H). ^{13}C NMR: δ −1.6 (CH_3), 35.6 (CH_2), 44.2 (CH_2), 56.0 (CH_3), 56.2 (CH_3), 63.3 (C), 69.0 (CH), 108.9 (CH), 111.0 (CH), 125.6 (CH), 127.2 (2 × CH), 127.8 (C), 127.9 (C), 131.4 (CH), 137.9

(C), 142.6 (C), 148.8 (C), 150.9 (C), 169.0 (C=O). MS *m/z* (relative intensity): 397 (M^+, 12), 308 (77), 307 (78), 292 (100), 193 (98), 73 (100). HRMS calcd for $C_{22}H_{27}NO_6Si$ 397.17093, found 397.17070.

Methyl-2-{7-trimethylsilyl-5-[(*Z*)-1-(methyloxycarbonyl)methylidene]-1-oxo-1,2,3,4,5,6-hexahydro-2-benzazecin-6-yliden}acetate (10). A cold solution of methyl(trifluoro)-dioxirane[7] (0.51 M in trifluoro-2-propanone, 0.12 mL, 0.060 mmol) was added to a solution of **1a** (20 mg, 0.050 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 3.5 h, another 0.06 mL of TFD (0.030 mmol) was added and TLC monitoring showed that the starting material had been consumed after 9 h. Removal of the solvent (20 °C, 740 Torr), followed by preparative TLC on silica gel (1:2 EtOAc/hexane), afforded 20 mg of **10** (90%) as a pale yellow powder. IR (film): ν 3306, 2952, 1725, 1651, 1250, 844, 754 cm^{-1}. ^1H NMR: δ −0.09 (s, 9H), 2.25 (ddd, J = 4.4, 12.8, 15.3 Hz, 1H), 2.63−2.66 (m, 1H), 3.22 (tt, J = 4.2, 13.9 Hz, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 3.99−4.03 (m, 1H), 5.40−5.42 (m, 1H), 5.91 (s, 1H), 5.97 (d, J = 1.8 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.39 (dt, J = 1.3, 7.5 Hz, 1H), 7.45 (s, 1H), 7.51 (dd, J = 1.0, 7.6 Hz, 1H). ^{13}C NMR: δ 0.4 (CH_3), 33.2 (CH_2), 40.8 (CH_2), 51.3 (2 × CH_3), 117.5 (CH), 118.4 (CH), 126.8 (CH), 127.4 (CH), 127.9 (CH), 129.9 (CH), 137.2 (C), 137.5 (C), 140.2 (C), 149.1 (CH), 155.3 (C), 157.0 (C), 166.0 (C=O), 166.1 (C=O), 170.3 (C=O). MS *m/z* (relative intensity): 413 (M^+, 2), 354 (100).

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2-(ethynyl-)benzamide (11).** Potassium carbonate (15 mg, 0.11 mmol) was added to a stirred solution of **8a** (1.00 g, 2.16 mmol) in MeOH (50 mL), and the reaction mixture was kept at room temperature for 15 min. After removal of volatiles under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), and this solution was washed with 5% aqueous HCl (3 × 25 mL) and saturated brine (3 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was recrystallized from methanol to give 3.10 g (95%) of **11** as yellow needles, mp 161−163 °C (MeOH). IR (KBr): ν 3283, 3238, 2910, 2099, 1638 cm^{-1}. ^1H NMR: δ 3.01 (t, J = 7.0 Hz, 2H), 3,28 (s, 1H), 3.69−3.76 (m, 2H), 3.79 (s, 3H), 3.83 (s, 3H), 6.78 (s, 1H), 7.00 (s, 1H), 7.24 (br s, 1H), 7.38−7.54 (m, 3H), 7.94 (d, J = 7.2 Hz, 1H). ^{13}C NMR: δ 35.2 (CH_2), 39.9 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 82.0 (C), 83.4 (CH), 113.6 (CH), 114.2 (CH), 115.6 (CH), 118.4 (C), 129.3 (CH), 129.5 (CH), 130.2 (C), 130.4 (CH), 134.0 (CH), 136.6 (C), 148.2 (C), 148.4 (C), 166.3 (C=O). MS *m/z* (relative intensity): 389 (M^+, 6), 387 (M^+, 6), 244 (100), 242 (96). HRMS calcd for $C_{19}H_{18}BrNO_3$ 387.04700, found 387.04814.

10,11-Dimethoxy-5,6,7,8-tetrahydrodibenzo[*c*,*g*]azecin-5-one (12). A solution of *n*-Bu_3SnH (364 μL, 1.35 mmol) and AIBN (50 mg, 20 wt % of **11**) in benzene (40 mL) was added within 5 h by means of a syringe pump, to a solution of **11** (0.25 g, 0.64 mmol) in dry, degassed benzene (100 mL) kept at reflux. Once addition was complete, reflux was kept up for another 4 h. The solvent was evaporated to dryness and the resulting residue was dissolved in CH_3CN (30 mL). This solution was washed with hexane (3 × 15 mL), then concentrated and the obtained residue chromatographed on silica gel (1:2 EtOAc/hexane). Macrolactams *cis*-**12** (91 mg, 47%, R_f = 0.14) and *trans*-**12** (35 mg, 24%, R_f = 0.57) were obtained as white powder and white plates after recrystallization from EtOAc/hexane and EtOAc, respectively. *cis*-**12**: mp 65−67 °C (EtOAc/hexane). ^1H NMR: δ 2.67 (dd, J = 2.8, 13.2 Hz, 1H), 2.92 (dt, J = 4.8, 13.2 Hz, 1H), 3.27−3.34 (m, 1H), 3.52 (s, 3H), 3.86 (s, 3H), 4.02−4.19 (m, 1H), 5.97 (d, J = 11.0 Hz, 1H), 6.20 (s, 1H), 6.74 (s, 1H), 6.78 (d, J = 11.9 Hz, 1H), 6.89 (d, J = 11.9 Hz, 1H), 7.21−7.29 (m, 2H), 7.36−7.42 (m, 1H), 7.55 (d, J = 7.7 Hz, 1H). ^{13}C NMR: δ 33.7 (CH_2), 43.1 (CH_2), 55.6 (CH_3), 55.7 (CH_3), 111.5 (CH), 112.9 (CH), 127.6 (CH), 128.8 (C), 129.7 (C), 129.8 (CH), 130.0 (CH), 130.1 (CH), 130.2 (CH), 133.7 (C), 133.8 (C), 136.5 (CH), 147.7 (C), 149.3 (C), 168.7 (C=O). MS *m/z* (relative intensity): 309 (M^+, 100), 308 (34), 165 (30). HRMS calcd for $C_{19}H_{19}NO_3$ 309.13649, found 309.13616. *trans*-**12**: mp 223−225 °C (EtOAc). IR (KBr): ν 3285, 2928, 1633, 1508 cm^{-1}. ^1H NMR δ 2.26−2.50 (m, 1H), 2.91−3.15 (m, 1H), 3.76−3.83 (m, 1H), 3.89 (s, 3H), 3.94 (s, 3H), 4.01−4.33 (m, 1H), 5.68−5.72 (m, 1H), 6.46 (d, J = 16.6 Hz, 1H), 6.71 (s, 1H), 6.97 (s, 1H), 7.29−7.43 (m, 4H), 7.68 (d, J = 7.2 Hz, 1H). ^{13}C NMR: δ 31.1 (CH_2), 43.7 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 108.1 (CH), 114.1 (CH), 125.8 (CH), 127.5 (CH), 128.7 (CH), 130.0 (2 × CH), 130.8 (C), 131.9 (C), 137.3 (C), 137.7 (C), 140.2 (CH), 148.3 (C), 148.4 (C), 172.0 (C=O). MS *m/z* (relative intensity): 309 (M^+, 100), 308 (39), 265 (20), 165 (35). HRMS calcd for $C_{19}H_{19}NO_3$ 309.13649, found 309.13624.

13-Hydroxy-2,3-dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (13) and 2,3-Dimethoxy-6,8-dihydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (3a). A solution (2.0 mL) of 0.087 M DMD (0.18 mmol) in acetone was added to 31 mg (0.12 mmol) of *trans*-**12** in acetone (0.5 mL) within 24 h (see General Procedure). Removal of the solvent (20 °C, 740 Torr), followed by preparative TLC of the residue on silica gel (1:2 EtOAc/hexane) afforded 16 mg (40%, R_f = 0.31) of **13** and 11 mg (31%, R_f = 0.19) of **3a**, which were recrystallized from EtOAc/hexane as a creamy powder and white plates, respectively. Hydroxyprotoberberine **13**, ^1H NMR: δ 2.76−2.97 (m, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.65−4.66 (broad s, 2H), 4.97−5.01 (m, 1H), 6.76 (s, 1H), 6.98 (s, 1H), 7.42−7.48 (m, 1H), 7.59 (dt, J = 1.4, 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 8.11 (dd, J = 1.1, 7.7 Hz, 1H). ^{13}C NMR: δ 30.1 (CH_2), 39.2 (CH_2), 55.9 (CH_3), 56.1 (CH_3), 61.5 (CH), 71.7 (CH), 111.6 (CH), 111.8 (CH), 123.6 (CH), 124.0 (C), 127.5 (C), 128.0 (CH), 128.3 (CH), 129.0 (C), 132.3 (CH), 140.7 (C), 147.3 (C), 148.3 (C), 164.2 (C=O). MS *m/z* (relative intensity): 325 (M^+, 13), 192 (100). Protoberberine **3a**: mp 167−169 °C (EtOAc/hexane) [lit[15] 191−192 °C (MeOH)]. IR (film): ν 2924, 1643, 1514, 1271 cm^{-1}. ^1H NMR, HMQC, and HMBC: δ 2.95 (t, J = 6.2 Hz, 2H, H-5), 3.95 (s, 3H, OMe), 4.00 (s, 3H, OMe), 4.37 (t, J = 6.2 Hz, 2H, H-6), 6.75 (s, 1H, H-4), 6.89 (s, 1H, H-13), 7.28 (s, 1H, H-1), 7.41−7.47 (m, 1H, H-10), 7.55−7.66 (m, 2H, H-11 and H-12), 8.43 (d, J = 8.1 Hz, 1H, H-9). ^{13}C NMR and DEPT: δ 28.1 (CH_2, C-5), 39.8 (CH_2, C-6), 56.1 (OCH_3), 56.3 (OCH_3), 101.5 (CH, C-13), 108.0 (CH, C-1), 110.5 (CH, C-4), 122.4 (C, C-13b), 124.6 (C, C-8a), 125.9 (CH, C-12), 126.2 (CH, C-10), 128.0 (CH, C-9), 128.8 (C, C-4a), 132.3 (CH, H-11), 136.7 (C, C-12a), 137.5 (C, C-13a), 148.5 (C, C-3), 150.4 (C, C-2), 162.2 (C=O, C-8). MS *m/z* (relative intensity): 307 (M^+, 83), 293 (21), 292 (100).

13a-Hydroxy-2,3-dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8,13-dione (15) and 13a-Hydroxy-10,11-dimethoxy-7,8,13,13a-tetrahydro-5*H*-benzo-[4,5]azepino[2,1-*a*]isoindol-5,13-dione (16). A solution (4.0 mL) of 0.087 M DMD (0.34 mmol) in acetone was added to 42 mg (0.14 mmol) of *cis*-**12** in acetone (1 mL) within 48 h (see General Procedure). Removal of the solvent (20 °C, 740 Torr), followed by preparative TLC of the residue on silica gel (1:1 EtOAc/hexane), afforded 10 mg (21%, R_f = 0.20) of **15** and 3 mg (7%, R_f = 0.27) of **16** as white powders. Oxoprotoberberine **15**, IR (film): ν 3371, 2927, 1679, 1634, 1516, 1456, 1261, 758 cm^{-1}. ^1H NMR, HMQC, and HMBC: δ 2.74 (dd, J = 3.1, 16.4 Hz, 1H, H-5), 3.09−3.16 (m, 1H, H-5), 3.65 (dt, J = 4.2, 12.8 Hz, 1H, H-6), 3.86 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.05 (br s, 1H, OH), 4.91 (m, 1H, H-6), 6.64 (s, 1H, H-4), 7.01 (s, 1H, H-1), 7.70 (t, J = 7.7 Hz, 1H, H-10), 7.79 (t, J = 7.7 Hz, 1H, H-11), 8.09 (d, J = 7.7 Hz, 1H, H-12), 8.27 (d, J = 7.7 Hz, 1H, H-9). ^{13}C NMR and DEPT: δ 27.6 (CH_2, C-5), 37.1 (CH_2, C-6), 56.0 (OCH_3), 56.1 (OCH_3), 84.8 (C, C-13a), 110.3 (CH, C-1), 111.8 (CH, C-4), 124.9 (C, C-13b), 126.7 (CH, C-12), 128.7 (C + CH, C-4a and C-9), 130.2 (C, C-12a), 131.5 (C, C-8a), 133.0 (CH, C-11), 135.3 (CH, C-10), 147.5 (C, C-2), 149.8 (C, C-3), 161.7 (C=O, C-8), 191.4 (C=O, C-13). MS *m/z* (relative intensity): 339 (M^+, 23), 323 (65), 308 (49), 292 (87), 206 (100). Benzazepinone **16**, ^1H NMR: δ 2.70−2.77 (m, 1H), 3.01−3.15 (m, 1H), 3.41−3.50 (m, H + OH), 3.86 (s, 3H), 3.90 (s, 3H), 4.91−4.99 (m, 1H), 6.64 (s, 1H), 7.18 (s, 1H), 7.65−7.81 (m, 2H), 8.06 (dd, J = 1.1, 7.6 Hz, 1H), 8.28 (dd, J = 1.1, 7.6 Hz, 1H). ^{13}C NMR: δ 28.1 (CH_2), 38.1 (CH_2), 55.9 (CH_3), 56.1 (CH_3), 89.2 (C), 111.3 (2 × CH), 125.1 (C), 126.6 (CH), 128.5 (CH), 129.4 (C), 129.5 (C), 131.3 (C), 132.8 (CH), 134.8 (CH), 147.5 (C), 149.8 (C), 157.1 (C=O), 181.9 (C=O). MS *m/z* (relative intensity): 339 (M^+, 31), 338 (82), 322 (100), 244 (53).

2,3-Dimethoxy-6,8-dihydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (3a). A solution of 37% aqueous HCl (0.5 mL) was added to a solution of **2a** (9 mg, 0.02 mmol) in MeOH (2 mL). After stirring for 12 h at room temperature, the solvent was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (5 mL). This solution was washed with 10% aqueous NaOH (2 × 3 mL) and saturated brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of the residue by preparative TLC on silica gel (1:1 EtOAc/hexane) gave **3a** (7.0 mg) almost quantitatively.

10,11-Dimethoxy-6,8-dihydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (3b). A solution of 37% aqueous HCl (0.5 mL) was added to a solution of **2b** (15 mg, 0.03 mmol) in MeOH (2 mL). After stirring for 12 h at room temperature, the solvent was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (6 mL). This solution was washed with 10% aqueous NaOH (2 × 3 mL) and saturated brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the residue by preparative TLC on silica gel (1:1 EtOAc/hexane) gave 11.0 mg of **3b** (95%) as a white powder. ^{1}H NMR: δ 3.01 (t, J = 6.1 Hz, 2H), 4.01 (s, 3H), 4.02 (s, 3H), 4.38 (t, J = 6.1 Hz, 2H), 6.94 (s, 1H), 6.97 (s, 1H), 7.28−7.36 (m, 3H), 7.51−7.54 (m, 1H), 7.81 (s, 1H). ^{13}C NMR: δ 28.6 (CH_2), 39.6 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 102.5 (CH), 106.1 (CH), 107.8 (CH), 119.0 (C), 124.6 (CH), 126.8 (CH), 127.7 (CH), 128.4 (CH), 128.9 (C), 130.4 (C), 132.0 (C), 135.1 (C), 136.1 (C), 153.5 (C), 161.3 (C=O). MS *m*/*z* (relative intensity): 307 (M^+, 100), 292 (80).

General Procedure for the Cyclization of the Macrolactams 1a, 1b, *cis*-, and *trans*-12a with Hydriodic Acid. A sample of 57% aqueous HI (10 mmol) was added to a solution of the macrolactam (1 mmol) in benzene (15 mL). After stirring for 3 h at 50 °C, the reaction mixture was allowed to cool to room temperature and the solvent was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (10 mL), and this solution was washed with 10% aqueous NaOH (2 × 5 mL) and saturated brine (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by flash chromatography on silica gel with 1:1 or 1:2 ethyl acetate/hexane as eluent, followed by recrystallization.

13a-Trimethylsilyl-2,3-dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (17a). A sample of 57% aqueous HI (1.4 mL, 10.48 mmol) was added to a solution of **1a** (0.40 g, 1.05 mmol) in benzene (15 mL), see General Procedure. Purification by flash chromatography (1:2 EtOAc/hexane) and recrystallization from ethyl ether/hexane gave 0.39 g (97%) of **17a** as white plates, mp 108−110 °C (Et_2O/hexane). IR (film): ν 2957, 1640, 1517, 1258, 843 cm^{-1}. ^{1}H NMR δ −0.17 (s, 9H), 2.74−3.05 (m, 3H), 3.24 (d, J = 15.4 Hz, 1H), 3.39 (d, J = 15.4 Hz, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 5.19−5.25 (m, 1H), 6.64 (s, 2H), 7.20 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.44 (dt, J = 1.4, 7.3 Hz, 1H), 8.06 (dd, J = 1.0, 7.5 Hz, 1H). ^{13}C NMR: δ −0.2 (CH_3), 29.0 (CH_2), 37.9 (CH_2), 40.5 (CH_2), 55.8 (CH_3), 56.1 (CH_3 + C), 107.9 (CH), 111.8 (CH), 124.9 (C), 126.7 (CH), 127.4 (CH), 128.1 (CH), 130.4 (C), 131.8 (CH), 132.6 (C), 135.8 (C), 146.9 (C), 147.7 (C), 163.7 (C=O). MS *m*/*z* (relative intensity): 381 (M^+, 1), 366 (18), 309 (21), 308 (100). Anal. Calcd for $C_{22}H_{27}NO_3Si$: C, 69.25; H, 7.13; N, 3.67. Found: C, 69.40; H, 7.01; N, 3.63.

13a-Trimethylsilyl-10,11-dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (17b). A sample of 57% aqueous HI (0.35 mL, 2.62 mmol) was added to a solution of **1b** (0.10 g, 0.26 mmol) in benzene (5 mL), see General Procedure. Purification by flash chromatography (1:1 EtOAc/hexane) and recrystallization from ethyl ether/hexane gave 99 mg (99%) of **17b** as white plates, mp 155−157 °C (Et_2O/hexane). IR (KBr): ν 2956, 1637, 1595, 1248, 838 cm^{-1}. ^{1}H NMR: δ −0.14 (s, 9H), 2.84−3.13 (m, 3H), 3.23 (d, J = 15.4 Hz, 1H), 3.36 (d, J = 15.4 Hz, 1H), 3.94 (s, 6H), 5.15−5.23 (m, 1H), 6.67 (s, 1H), 7.10−7.23 (m, 4H), 7.60 (s, 1H). ^{13}C NMR: δ −0.1 (CH_3), 29.5 (CH_2), 37.8 (CH_2), 39.9 (CH_2), 56.1 (2 × CH_3), 56.4 (C), 109.2 (CH), 110.5 (CH), 123.1 (C), 124.6 (CH), 125.4 (CH), 126.5 (CH), 129.4 (C), 129.5 (CH), 132.6 (C), 141.1 (C), 148.4 (C), 152.0 (C), 163.7 (C=O). MS *m*/*z* (relative intensity): 381 (M^+, 5), 309 (20), 308 (100). Anal. Calcd for $C_{22}H_{27}NO_3Si$: C, 69.25; H, 7.13; N, 3.67. Found: C, 69.37; H, 7.07; N, 3.55.

2,3-Dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (18a). A sample of 57% aqueous HI (34 μL, 0.26 mmol) was added to a solution of cis-**12** (8 mg, 0.03 mmol) in 1 mL of benzene. After stirring for 13 h at 50 °C, the reaction was worked up as usually. Purification by preparative TLC on silica gel (1:1 EtOAc/hexane) and recrystallization from ethyl ether/ ethyl acetate gave 6 mg (75%) of **18a** as white prisms, mp 114−116 °C (Et_2O/EtOAc) [lit[21b] 143−145 °C (MeOH)].

With the same amounts of starting materials and the same purification steps, trans-**12** gave 7.0 mg (87%) of **18a**. IR (film): ν 2925, 1645, 1515, 1258 cm^{-1}. ^{1}H NMR: δ 2.74−3.03 (m, 4H), 3.22 (dd, J = 3.7, 15.7 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 4.86 (dd, J = 3.7, 13.3 Hz, 1H), 4.97−5.02 (m, 1H), 6.69 (s, 1H), 6.72 (s, 1H), 7.24−7.27 (m, 1H), 7.35−7.49 (m, 2H), 8.14 (dd, J = 1.4, 7.6 Hz, 1H). ^{13}C NMR: δ 29.2 (CH_2), 38.1 (CH_2), 38.7 (CH_2), 55.0 (CH), 55.9 (CH_3), 56.1 (CH_3), 108.8 (CH), 111.4 (CH), 126.8 (CH), 127.2 (C), 127.3 (CH), 127.6 (C), 128.6 (CH), 129.1 (C), 131.8 (C), 137.3 (C), 147.9 (C), 148.0 (C), 164.6 (C=O). MS *m*/*z* (relative intensity): 309 (M^+, 100), 308 (89), 294 (37), 118 (30), 90 (30).

2,3-Dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (18a). Tetrabutylammonium fluoride (1.1 mL, 1.1 mmol, 1 M in THF) was added to a solution of **17a** (0.28 g, 0.73 mmol) in THF (10 mL) and the resulting mixture was stirred at room temperature for 15 min. After solvent concentration, the residue was dissolved in CH_2Cl_2 (10 mL) and washed (3 × 10 mL), and the organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness, and chromatographed on silica gel with 1:2 EtOAc/hexane as eluent. After recrystallization from ethyl ether/ethyl acetate, the tetrahydroprotoberberine **18a** (0.16 g, 71%) was obtained as white prisms.[21b]

10,11-Dimethoxy-6,8,13,13a-tetrahydro-5*H*-isoquino[3,2-*a*]isoquinolin-8-one (18b). Tetrabutylammonium fluoride (0.66 mL, 0.66 mmol, 1M in THF) was added to a solution of **17b** (0.25 g, 0.66 mmol) in THF (5 mL) and the resulting mixture was stirred at room temperature for 5 min. After solvent concentration, the residue was dissolved in CH_2Cl_2 (10 mL) and washed (3 × 10 mL), and the organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness and chromatographed on silica gel with 1:1 EtOAc/hexane as eluent. After recrystallization from ethyl ether/ethyl acetate, the tetrahydroprotoberberine **18b** (0.15 g, 76%) was obtained as white prisms, mp 158−160 °C (Et_2O). IR (film): ν 2940, 1637, 1595 cm^{-1}. ^{1}H NMR: δ 2.67−2.78 (m, 4H), 3.00−3.07 (m, 1H), 3.78 (s, 6H), 4.71−4.82 (m, 2H), 6.59 (s, 1H), 7.08−7.12 (m, 4H), 7.51 (s, 1H). ^{13}C NMR: δ 29.6 (CH_2), 37.2 (CH_2), 38.4 (CH_2), 55.3 (CH), 55.9 (CH_3), 56.0 (CH_3), 109.1 (CH), 110.5 (CH), 121.4 (C), 125.7 (CH), 126.5 (CH), 126.6 (CH), 128.8 (CH), 130.9 (C), 134.9 (C), 135.9 (C), 148.0 (C), 151.7 (C), 164.5 (C=O). MS *m*/*z* (relative intensity): 309 (M^+, 49), 308 (13), 178 (100), 150 (92). HRMS calcd for $C_{19}H_{19}NO_3$ 309.13649, found 309.13589.

Acknowledgment. We are grateful for financial support from the Dirección General de Enseñanza Superior (Project PB95-0824), the Xunta de Galicia (Project XUGA 20907-B96), and the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm Peroxidchemie). G. Rodríguez thanks the Xunta de Galicia for a predoctoral fellowship and for a 4 month research stay at the University of Würzburg.

Supporting Information Available: Copies of the ^{1}H NMR and ^{13}C NMR spectra of all new compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981829N