Regioselective Synthesis of Isoquino[1,2-*b*][3]benzazepines (Homoprotoberberines) through 11-Membered-Ring Stilbene Lactams Obtained by Radical Macrocyclization†

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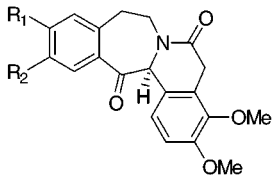
Silylated 11-membered-ring stilbene lactams **3** (*E* and *Z*) were easily prepared by intramolecular addition of an aryl radical to a trimethylsilylacetylene. Oxidation of their hindered stilbene double bonds with dioxiranes gave oxidative cleavage of their electron-rich aromatic rings. However, reduction of the amide to an amine functionality in both lactams (*E* and *Z*) triggers a regioselective [7,6]-transannular cyclization to isoquino[1,2-*b*][3]benzazepines (homoprotoberberines).

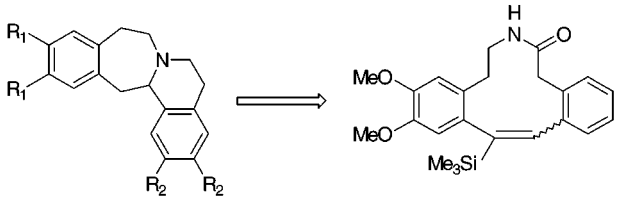
Introduction

Over the past few years, we have developed a new strategy for the synthesis of isoquinoline alkaloids, which is based on the use of 10-membered-ring stilbene lactams as key intermediates. These macrolactams, obtained by radical macrocyclization, could be regioselectively converted by [6,6]- or [7,5]-transannular cyclization into protoberberines or isoindolobenzazepines.[1a−d] In a continuation of our efforts to synthesize isoquinoline alkaloids for subsequent pharmacological evaluation, we envisioned that dioxygenated homoprotoberberines (isoquino[1,2-*b*][3]benzazepines) **1** and **2** might be interesting candidates (Scheme 1). Homoprotoberberines, such as puntarenine[2] and saulatine,[3] are isoquinoline alkaloids obtained from Berberidaceae plants.[4] Such structures are interesting from a synthetic and pharmacological point of view since they incorporate the [3]benzazepine moiety, which possesses important biological activity.[5] Homoprotoberberines have been the object of various synthetic approaches in which the key step is the formation of an isoquinoline ring under the Bischler−Napieralski conditions followed by intramolecular alkylation onto the isoquinoline nuclei.[6] We now report a regioselective synthesis of isoquino[1,2-*b*][3]benzazepines **1** and **2** that is based on the use of 11-membered-ring stilbene lactams

Scheme 1



Puntarenine R_1= R_2= -OCH_2O-
Saulatine R_1= R_2= OMe



1, R_1= OMe, R_2= H
2, R_1= H, R_2= OMe

3a, *E*
3b, *Z*

3 (*E* and *Z*) as key intermediates. These lactams, obtained by an 11-endo radical macrocyclization, may be regioselectively converted by [7,6]-transannular cyclization into homoprotoberberines **1** and **2**.

Results and Discussion

The precursor to the required 11-membered-ring lactams **3** is the *o*-(trimethylsilylethynyl)phenylacetamide **9**, which was prepared by starting from homoveratrylamine (**4**) and 2-iodobenzyl chloride (**6**), as shown in Scheme 2. Thus, condensation of the bromophenethylamine **5** with 2-iodophenylacetyl chloride (**7**),[7] prepared in three steps from **6**, in THF at room temperature in the presence of triethylamine gave phenylacetamide **8** in 91% yield. Treatment of the dihalogenated amide **8** with (trimethylsilyl)acetylene (1.5 equiv) in the presence of CuI (0.05 equiv) and $PdCl_2(PPh_3)_2$ (0.05 equiv) in triethylamine and THF as cosolvent at room temperature gave chemoselectively the *N*-(2-bromophenethyl)phenylacetamide **9** in 86% yield.

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† This paper is dedicated to Prof. Ian Scott on the occasion of his 70th birthday.

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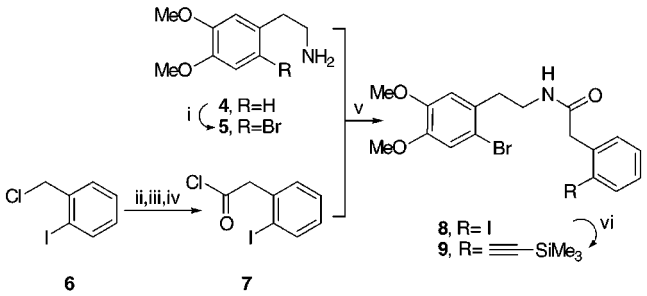
Scheme 2[a]



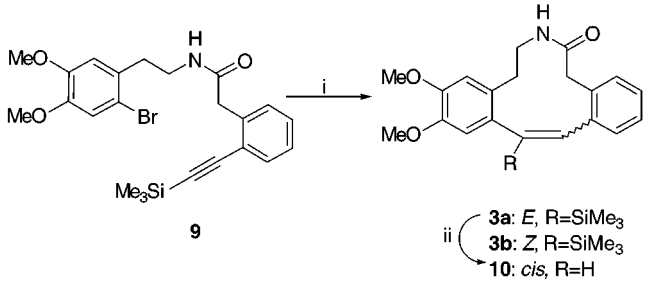
[a] Reagents: (i) Br_2, AcOH, ca. 20 °C, 98%; (ii) KCN, DMSO, 70 °C, 70%; (iii) NaOH, EtOH/H_2O, reflux, 87%; (iv) $SOCl_2$, ca. 20 °C; (v) Et_3N, THF, ca. 20 °C, 91%; (vi) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 86%.

The radical cyclization was performed by slow, dropwise addition of a solution of tributyltin hydride (2 equiv) and AIBN (20 wt %) in benzene to a 7 mM solution of phenylacetamide **9** in benzene by refluxing under argon. To our delight, cyclization occurred smoothly, and two isomeric stilbene macrolactams **3a** and **3b** were obtained in 50 and 25% yield.[8] This result contrasts with the one obtained in a similar cyclization to 10-membered-ring stilbene lactams, where a single geometric isomer of unknown stereochemistry was obtained.[1] The appearance of both *E* and *Z* stereoisomers for the 11-membered stilbene lactams could be due to lower geometrical constraint for the formation of the corresponding vinyl-radical intermediates due to the larger ring size.

With the macrolactams **3** prepared, we first attempted the transannular cyclization by following the various conditions developed for the case of 10-membered-ring lactams.[1] Unfortunately, when the 11-membered-ring lactams were subjected to either acidic conditions (treatment with hydriodic acid)[1c] or basic conditions (potassium *tert*-butoxide)[1a,b] or to tetrabutylammonium fluoride solution buffered with glacial acetic acid,[1c] only unidentified complex mixtures and/or recovered starting material were obtained. Curiously, when the *E* macrolactam **3a** was treated with sodium hydride (1.1 equiv) in DMF at room temperature, desilylation occurred to the *cis*-stilbene lactam **10** in low yield, thus reconfirming the assigned *E* geometry of **3a** (Scheme 3).[9]

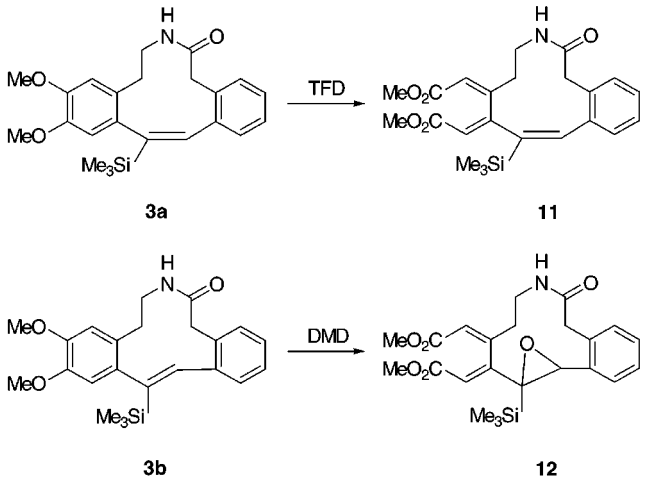
Geometrical constraints were suspected as the reason for the failure of [7,6]-transanular cyclization, and we decided to epoxidize the vinylsilane moiety of lactams **3** with dioxiranes.[1d,10] Accordingly, the *E* lactam **3a** was treated with an excess (8 equiv) of DMD[11] over 30 h at room temperature, but unfortunately, unchanged starting material was completely recovered. Therefore, epoxidation with the more reactive TFD[12] was then tried (Scheme 4) by treatment of a solution of the *E* lactam **3a** in CH_2Cl_2 with 1.8 equiv of TFD at room temperature over 16 h. However, the muconate **11** was obtained in 83% yield by oxidative cleavage of the dimethoxylated

Scheme 3[a]



[a] Reagents: (i) AIBN, *n*-Bu_3SnH, benzene, reflux, 75%; (ii) NaH, DMF, ca. 20 °C, 36%.

Scheme 4



aromatic ring, but no epoxidation of the hindered double bond was observed, analogous to the 10-membered lactam.[1d] In contrast, addition of an excess (7.9 equiv) of DMD in several doses over 5 days at room temperature to an acetone solution of the *Z* lactam **3b** afforded the epoxymuconate diester **12** in moderate yield. The formation of muconate **11** suggests that steric factors play an important role in preventing the epoxidation of the *E* macrolactam **3a**, since the bulky trimethylsilyl group hinders the approach of the sterically sensitive TFD to the double bond, and therefore, oxidation of the electron-rich aromatic ring becomes competitive. Nonetheless, formation of epoxymuconate diester **12** was due to the oxidation of both the vinylsilane functionality and the electron-rich aromatic ring. Probably, epoxidation of the more accessible double bond of **3b**, as compared to **3a**, occurred first, and the epoxysilane intermediate was subsequently oxidized by excess DMD to the epoxymuconate **12**. These results are similar to the ones observed in the case of the 10-membered-ring stilbene lactam homologues.[1d]

These interesting but inappropriate results for our goals led us to look for another possibility to modify the

(7) 2-Iodophenylacetic acid was prepared by a modification of the published procedure: Dippy, F. J.; Lewis, R. H. *J. Chem. Soc.* **1936**, 644−649. (b) For an alternative synthetic procedure, see: Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4845−4850.

(8) The assignment of the geometry of the silylated stilbene lactams is based on NOE studies.

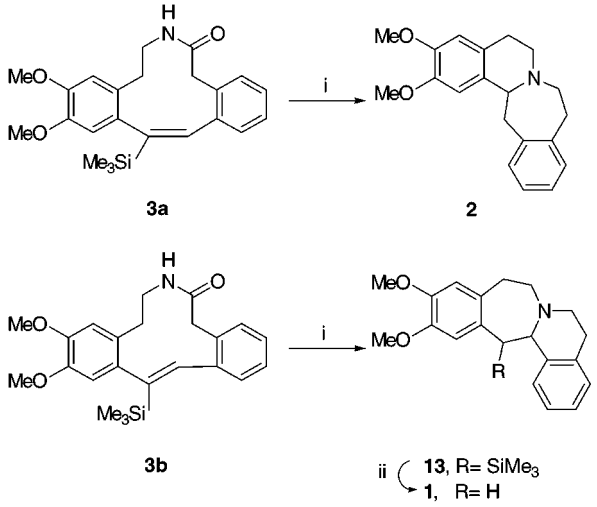
(9) The formation of desilylated product is rationalized by invoking the amidate and further iminosilyl ether formation due to the singular spatial disposition of both groups. Final hydrolytic workup recovers the amide functionality.

(10) For a review of dioxirane chemistry, 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. See also the references cited in ref 1d.

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

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

Scheme 5[a]



[a] Reagents: (i) (a) BH_3·SMe_2, THF, reflux; (b) TMEDA, CH_2Cl_2/Et_2O, ca. 20 °C; (ii) Bu_4NF, THF, ca. 20 °C.

substrates, e.g., the reduction of the amide to an amine. Gratifyingly, our expectations were fulfilled with success because when the macrolactams **3a** and **3b** were treated with the borane−dimethyl sulfide complex both reduction and regioselective [7,6]-transannular cyclization took place to the desired homoprotoberberines. Thus, for derivative **3a**, the 2,3-dimethoxyisoquino[1,2-*b*][3]benzazepine (homoprotoberberine) **2**[6a] was obtained in a 29% yield, while the diastereomer **3b** gave initially the silylated homoprotoberberine **13** in 22% yield, which was easily desilylated to the desired 11,12-dimethoxyisoquino-[1,2-*b*][3]benzazepine **1**.[6a]

Most probably, the initially formed macrocyclic amines have a geometrical disposition that favors the required regioselectivity for the [7,6]-transannular cyclization. Presumably, desilylation of the resulting α-trimethylsilylamine intermediate is easier for the **3a** diastereomer**,** and consequently, the cyclization to **2** takes place directly. For the **3b** diastereomer the *β*-trimethylsilylamine **13** is the primary cyclized product, which requires desilylation to the homoprotoberberine **1**.

To sum up, we have shown that stilbene lactams with 11-membered lactam rings are versatile intermediates for the synthesis of isoquino[1,2-*b*][3]benzazepines (homoprotoberberines). The regioselectivity of the [7,6]-transanular cyclization is ascribed to the geometry of the molecule imposed by the nature of the stilbene double bond. The starting *E* and *Z* stilbene lactams were easily obtained by intramolecular addition of an aryl radical to a trimethylsilylacetylene.

Experimental Section

General Methods. All nonaqueous reactions were conducted under an inert atmosphere of argon gas 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 and triethylamine were distilled from calcium hydride. Slow additions were carried out by using a syringe pump (Harvard 11). Melting points are uncorrected. ^{1}H, ^{13}C, and DEPT NMR spectra were recorded in $CDCl_3$ unless specified; chemical shifts are reported as *δ* values in ppm versus tetramethylsilane (TMS).

***N*-[2-(2-Bromo-4,5-dimethoxy)phenyl]ethyl(2-iodophenyl)acetamide (8). Preparation of 2-Iodophenylacetic Acid.** A stirred solution of 2-iodobenzyl cyanide[13] (2.05 g, 8.42 mmol), prepared in 70% yield from commercial **6**, and NaOH (3.40 g, 84.2 mmol) in 75 mL of EtOH/H_2O (2:1) was refluxed for 6.5 h. The mixture was cooled to room temperature, the ethanol was removed under reduced pressure, and the aqueous solution was acidified with 37% HCl, extracted with CH_2Cl_2, washed with H_2O and saturated brine, dried over anhydrous Na_2SO_4, and concentrated to dryness to afford 1.93 g of 2-iodophenylacetic acid[7] (87%) as colorless plates.

Preparation of 2-Iodophenylacetyl Chloride (7). A solution of 2-iodophenylacetic acid (2.44 g, 9.30 mmol) and $SOCl_2$ (7 mL, 93 mmol) was stirred for 12 h at room temperature. The excess thionyl chloride was evaporated to give crude acyl chloride **7** (2.60 g), which was immediately used without further purification.

Preparation of the Acetamide 8. A solution of acyl chloride **7** (2.60 g, 9.30 mmol) in THF (20 mL) was added by means of a cannula to a cold (0 °C), stirred solution of **5**[1d] (2.28 g, 8.78 mmol) and triethylamine (1.84 mL, 13.18 mmol) in THF (30 mL). Once the addition was finished, the stirring was continued for 12 h at room temperature. The residue obtained by removal of the volatiles under reduced pressure was dissolved in CH_2Cl_2, washed with 5% aqueous HCl, dried over anhydrous Na_2SO_4, concentrated to dryness, and recrystallized from MeOH/EtOAc to afford **8** (4.04 g, 91%) as colorless needles: mp 159−161 °C (MeOH/EtOAc); IR (KBr) *ν* 1646 cm^{-1}; ^{1}H NMR *δ* 2.87 (t, J = 7.0 Hz, 2H), 3.45−3.54, (m, 2H), 3.69 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 5.49 (br s, 1H), 6.67 (s, 1H), 6.94−7.01 (m, 1H), 6.95 (s, 1H), 7.30−7.33 (m, 2H), 7.83 (d, J = 7.9 Hz, 1H); ^{13}C NMR *δ* 34.7 (CH_2), 39.2 (CH_2), 47.9 (CH_2), 55.7 (2 × OCH_3), 110.8 (C), 112.9 (CH), 113.7 (C), 115.0 (CH), 128.3 (CH), 128.6 (CH), 129.7 (C), 130.3 (CH), 138.0 (C), 139.2 (CH), 147.7 (C), 147.9 (C) 169.4 (C=O); MS *m*/*z* (relative intensity) 505 (M^+, 3), 503 (M^+, 3), 242 (100). Anal. Calcd for $C_{18}H_{19}BrINO_3$: C, 42.89; H, 3.80; N, 2.78. Found: C, 42.71; H, 4.09; N, 2.83.

***N*-[2-(2-Bromo-4,5-dimethoxy)phenyl]ethyl[2-(trimethylsilylethynyl)phenyl]acetamide (9).** A mixture of **8** (4.04 g, 8.01 mmol), $(Ph_3P)_2PdCl_2$ (0.28 g, 0.40 mmol), CuI (76 mg, 0.40 mmol), and (trimethylsilyl)acetylene (1.7 mL, 12.02 mmol) in 50 mL of Et_3N and 30 mL of THF was stirred for 6 h at room temperature and passed through a pad of Celite to remove the solids. The filtrate was concentrated and the residue dissolved in CH_2Cl_2. The resulting solution was washed with 5% aqueous HCl and saturated brine, dried over Na_2SO_4, and concentrated to dryness. Purification of the residue by flash chromatography on silica gel (1:2 EtOAc/hexane) afforded **9** (3.26 g, 86%), which was crystallized from diethyl ether as colorless plates: mp 100−102 °C (Et_2O); IR (KBr) *ν* 2154, 1653 cm^{-1}; ^{1}H NMR *δ* 0.24 (s, 9H), 2.82 (t, J = 7.2 Hz, 2H), 3.41−3.49 (m, 2H), 3.73 (s, 2H), 3.78 (s, 3H), 3.84 (s, 3H), 5.79 (br s, 1H), 6.63 (s, 1H), 6.94 (s, 1H), 7.19−7.31 (m, 3H), 7.47 (d, J = 7.3 Hz, 1H); ^{13}C NMR *δ* −0.1 (CH_3), 35.4 (CH_2), 39.5 (CH_2), 42.7 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 99.4 (C), 103.3 (C), 113.2 (CH), 114.0 (C), 115.4 (CH), 122.8 (C), 127.2 (CH), 129.2 (CH), 129.8 (CH), 129.9 (C), 132.6 (CH), 137.3 (C), 148.1 (C) 148.3 (C), 170.4 (C=O); MS *m*/*z* (relative intensity) 475 (M^+, 2), 473 (M^+, 3), 242 (100). Anal. Calcd for $C_{23}H_{28}BrNO_3Si$: C, 58.22; H, 5.95; N, 2.95. Found: C, 58.13; H, 6.17; N, 3.09.

11,12-Dimethoxy-14-trimethylsilyl-6,7,8,9-tetrahydro-5*H*-dibenzo[*d*,*h*]azacycloundecin-6-one (3). A solution of *n*-Bu_3SnH (0.30 mL, 1.13 mmol) and AIBN (54 mg, 20 wt % of **9**) in benzene (30 mL) was added over 5 h by means of a syringe pump to a solution of **9** (0.27 g, 0.56 mmol) in dry, degassed benzene (80 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. This solution was washed with hexane and then concentrated

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and the residue chromatographed on silica gel (1:1 EtOAc/hexane). Macrolactams *E*, **3a** (0.11 g, 50%, $R_f = 0.25$), and *Z*, **3b** (56 mg, 25%, $R_f = 0.12$), were obtained as colorless needles after crystallization from EtOAc/hexane. Macrolactam *E*, **3a**: mp 162−164 °C (EtOAc/hexane); IR (film) ν 1672 cm^{-1}; ^1H NMR δ 0.12 (s, 9H), 2.34−2.39 (m, 1H), 2.46−2.57 (m, 1H), 2.72 (dt, $J = 3.1$, 12.7 Hz, 1H), 3.43 (d, $J = 17.3$ Hz, 1H), 3.72 (d, $J = 17.3$ Hz, 1H), 3.80 (s, 3H), 3.92 (s, 3H), 4.00−4.12 (m, 1H), 5.14−5.16 (m, 1H), 6.52 (s, 1H), 6.59 (s, 1H), 7.00 (s, 1H), 7.08−7.17 (m, 3H), 7.23−7.29 (m, 1H); ^{13}C NMR δ −1.4 (CH_3), 33.4 (CH_2), 41.3 (CH_2), 42.7 (CH_2), 55.7 (OCH_3), 56.1 (OCH_3), 112.8 (CH), 114.2 (CH), 127.1 (CH), 127.7 (CH), 128.9 (C), 130.5 (CH), 131.3 (CH), 132.4 (C), 133.3 (C), 138.9 (CH), 139.6 (C), 146.2 (C), 147.5 (C) 150.6 (C), 171.8 (C═O); MS *m*/*z* (relative intensity) 395 (M^+, 83), 73 (100). Anal. Calcd for $C_{23}H_{29}NO_3Si$: C, 69.84; H, 7.40; N, 3.54. Found: C, 69.70; H, 7.40; N, 3.67. Macrolactam *Z*, **3b**: mp 200−202 °C (EtOAc/hexane); IR (KBr) ν 1646 cm^{-1}; ^1H NMR δ −0.09 (s, 9H), 2.32−2.38 (m, 1H), 2.79−2.91 (m, 1H), 3.00−3.15 (m, 1H), 3.40 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 4.00−4.13 (m, 1H), 5.85−5.88 (m, 1H), 6.57 (s, 1H), 6.69 (s, 1H), 7.05 (s, 1H), 7.20−7.38 (m, 3H), 7.50−7.71 (m, 1H); ^{13}C NMR δ −0.1 (CH_3), 31.4 (CH_2), 42.6 (CH_2), 43.6 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 110.3 (CH), 112.8 (CH), 126.5 (CH), 127.6 (CH), 127.7 (CH), 129.6 (C), 131.0 (CH), 135.1 (C), 138.5 (C), 139.6 (C), 144.4 (CH), 146.9 (C), 147.3 (C) 147.8 (C), 171.3 (C═O); MS *m*/*z* (relative intensity) 395 (M^+, 91), 83 (100); HRMS calcd for $C_{23}H_{29}NO_3Si$ 395.19167, found 395.19157.

***cis*-11,12-Dimethoxy-6,7,8,9-tetrahydro-5*H*-dibenzo-[*d*,*h*]azacycloundecin-6-one (10).** A suspension of **3a** (35.0 mg, 0.09 mmol) and NaH (2.0 mg, 0.09 mmol) in DMF (1 mL) was stirred under argon at room temperature for 12 h. The reaction mixture was poured into CH_2Cl_2, washed with water and saturated brine, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by preparative TLC on silica gel (1:2 EtOAc/hexane) to afford **10** (10.0 mg, 36%) as a yellow oil: IR (KBr) ν 1665 cm^{-1}; ^1H NMR δ 2.43−2.48 (m, 1H), 2.51−2.59 (m, 1H), 2.97, (dt, $J = 3.7$, 12.8 Hz, 1H), 3.43 (d, $J = 17.2$ Hz, 1H), 3.69 (d, $J = 17.2$ Hz), 3.80 (s, 3H), 3.89 (s, 3H), 4.08−4.19 (m, 1H), 5.16−7.19 (m, 1H), 6.54 (s, 1H), 6.80 (d, $J = 12.2$ Hz, 1H), 6.83 (s, 1H), 6.91 (d, $J = 12.2$ Hz, 1H), 7.08−7.24 (m, 3H), 7.40 (m, 1H); ^{13}C NMR δ 32.4 (CH_2), 41.2 (CH_2), 43.1 (CH_2), 55.8 (OCH_3), 56.1 (OCH_3), 112.3 (CH), 115.1 (CH), 126.9 (CH), 127.8 (CH), 128.7 (C), 130.4 (C), 130.7 (CH), 131.2 (CH), 131.4 (CH), 133.0 (C), 134.4 (CH), 137.6 (C), 146.3 (C) 148.5 (C), 171.6 (C═O); MS *m*/*z* (relative intensity) 323 (M^+, 66), 178 (100).

Methyl 2-[8-Trimethylsilyl-6-[(*Z*)-1-(methyloxycarbonyl)methylidene]-2-oxo-2,3,4,5,6,7-hexahydro-1*H*-benzazacycloundecin-7-yliden]acetate (11). A cold solution of methyl(trifluoromethyl)dioxirane[1d,11] (0.51 M in 1,1,1-trifluoro-2-propanone, 0.14 mL, 0.071 mmol) was added to a solution of **3a** (27.0 mg, 0.068 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 4 h, another 0.10 mL of TFD (0.051 mmol) was added, and TLC monitoring showed that the starting material had been consumed after 12 h. Removal of the solvent (20 °C, 740 Torr), followed by preparative TLC on silica gel (1:2 EtOAc/hexane), afforded 34.0 mg (83%) of **11** as a pale solid: IR (film) ν 1727, 1681 cm^{-1}; ^1H NMR δ 0.28 (s, 9H), 2.25−2.32 (m, 1H), 2.38−2.52 (m, 1H), 2.79−2.94 (m, 1H), 3.50−3.66 (m, 2H), 3.54 (s, 3H), 3.66 (s, 3H), 3.83−3.95 (m, 1H), 5.08−5.13 (m, 1H), 5.42 (d, $J = 2.1$ Hz, 1H), 6.02 (s, 1H), 6.98 (s, 1H), 7.04−7.28 (m, 4H); ^{13}C NMR δ 0.4 (CH_3), 33.6 (CH_2), 36.2 (CH_2), 43.2 (CH_2), 50.9 (OCH_3), 51.3 (OCH_3), 116.9 (CH), 122.3 (CH), 127.3 (CH), 128.4 (CH), 129.9 (CH), 130.8 (CH), 133.5 (C), 138.9 (C), 142.6 (CH), 145.0 (C), 150.7 (C), 151.9 (C), 164.6 (C═O), 165.8 (C═O), 170.8 (C═O); MS *m*/*z* (relative intensity) 427 (M^+, 4), 368 (100).

Methyl 2-[1a-Trimethylsilyl-2-[(*E*)-1-(methyloxycarbonyl)methylidene]-7-oxo -2,3,4,5,6,7,8,12b-octahydro-1a*H*-benzo[*d*]oxireno[2,3-*f*]azacycloundecin-3- yliden]acetate (12). A cooled (−78 °C) solution (7.2 mL) of 0.09 M DMD[1d] (0.64 mmol) in acetone was added in doses at room temperature to a stirred solution of **3b** (32.0 mg, 0.081 mmol) in acetone (1 mL) over 5 d. Removal of the solvent (20 °C, 740 Torr), followed by preparative TLC of the residue on silica gel (1:2 EtOAc/hexane), afforded 15.0 mg (42%) of crude **12**: ^1H NMR δ −0.15 (s, 9H), 2.24−2.36 (m, 1H), 2.84−2.95 (m, 1H), 3.24−3.56 (m, 1H), 3.60−3.68 (m, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 3.98 (s, 1H), 4.02−4.18 (m, 1H), 5.95−5.98 (m, 1H), 6.03 (s, 1H), 6.12 (s, 1H), 7.34−7.58 (m, 4H).

5,6,8,9,14,14a-Hexahydro-2,3-dimethoxyisoquino[1,2-*b*]-[3]benzazepine (2). To a solution of **3a** (0.16 g, 0.41 mmol) in THF (7 mL) was added $BH_3{\cdot}SMe_2$ (10.0 M, 0.20 mL, 2.0 mmol). After the reaction mixture was refluxed for 12 h, the solvent was evaporated and the residue was dissolved in a mixture of CH_2Cl_2 (2 mL) and Et_2O (2 mL). TMEDA (0.61 mL, 4.10 mmol) was added, and stirring was continued for 24 h at room temperature. Removal of the solvent followed by preparative TLC on silica gel (MeOH) afforded **2**[6a] (36.0 mg, 29%) as colorless plates: ^1H NMR δ 2.61−2.99 (m, 6H), 3.20−3.62 (m, 4H), 3.85−3.89 (m, 1H), 3.85 (s, 3H), 3.89 (s, 3H), 6.57 (s, 1H), 6.71 (s, 1H), 7.12−7.25 (m, 4H); ^1H NMR (Py-d_5) δ 2.63−3.38 (m, 9H), 3.65−3.75 (m, 1H), 3.84 (s, 3H), 3.84−4.00 (m, 1H), 3.93 (s, 3H), 6.79 (s, 1H), 7.08 (s, 1H), 7.22−7.36 (m, 3H), 7.42−7.45 (m, 1H); ^{13}C NMR δ 29.0 (CH_2), 34.5 (CH_2), 43.0 (CH_2), 48.3 (CH_2), 55.8 (OCH_3), 56.1 (OCH_3), 56.8 (CH_2), 62.7 (CH), 110.3 (CH), 111.1 (CH), 126.2 (CH), 126.4 (CH), 126.9 (C), 129.0 (CH), 129.3 (CH), 131.0 (C), 141.0 (C), 142.2 (C), 147.3 (C), 147.5 (C); ^{13}C NMR (Py-d_5) δ 30.2 (CH_2), 35.9 (CH_2), 44.6 (CH_2), 50.0 (CH_2), 56.4 (CH_3), 56.9 (CH_3), 58.0 (CH_2), 64.1 (CH), 112.7 (CH), 113.1 (CH), 127.1 (CH), 127.2 (CH), 128.6 (C), 129.8 (CH), 130.4 (CH), 132.6 (C), 142.3 (C), 143.3 (C), 148.9 (C), 149.1 (C); MS *m*/*z* (relative intensity) 309 (M^+, 52), 308 (100).

5,6,8,9,14,14a-Hexahydro-11,12-dimethoxyisoquino[1,2-*b*][3]benzazepine (1). To a solution of **3b** (44 mg, 0.11 mmol) in THF (4 mL) was added $BH_3{\cdot}SMe_2$ (10.0 M, 56 μL, 0.56 mmol). After the reaction mixture was refluxed for 12 h, the solvent was evaporated and the residue was dissolved in a mixture of CH_2Cl_2 (2 mL) and Et_2O (2 mL). TMEDA (0.20 mL, 1.34 mmol) was added to the solution, and stirring was continued for 24 h at room temperature. Removal of the solvent followed by preparative TLC on silica gel (48:48:4 EtOAc/hexane/MeOH) afforded silylated homoprotoberberine **13** (9.0 mg, 22%): ^1H NMR δ 0.05 (br s, 9H), 2.60−3.79 (m, 9H), 3.84 (br s, 7H), 6.51 (s, 1H), 6.61 (br s, 1H), 7.11−7.23 (m, 3H), 7.39 (br s, 1H); MS *m*/*z* (relative intensity) 381 (M^+, 70), 366 (50), 308 (46), 280 (59), 223 (71), 216 (69), 192 (73), 165 (100), 73 (85).

Tetrabutylammonium fluoride (7.0 mg, 2.83 mmol, 1 M in THF) was added to a solution of **13** (9.0 mg, 0.84 mmol) in THF (1 mL), and the resulting mixture was stirred at room temperature for 15 min. After solvent concentration, the residue was purified by preparative TLC on silica gel (48:48:4 EtOAc/hexane/MeOH) to afford homoprotoberberine **1**[6a] (6.0 mg, 86%) as colorless plates: ^1H NMR δ 2.57−3.37 (m, 10H), 3.88 (br s, 7H), 6.63 (s, 1H), 6.82 (s, 1H), 7.16−7.35 (m, 4H); MS *m*/*z* (relative intensity) 309 (M^+, 17), 165 (100).

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Supporting Information Available: Copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds and the whole data list of IR and MS of compounds **8**, **9**, **3a**,**b**, **10**, **11**, **2,** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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