J|A|C|S
ARTICLES
Published on Web 02/22/2003

Twisted Amide Reduction under Wolff−Kishner Conditions: Synthesis of a Benzo-1-Aza-Adamantane Derivative

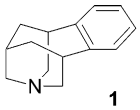
Crystal G. Bashore, Ivan J. Samardjiev, Jon Bordner, and Jotham W. Coe*

Contribution from Pfizer Global Research and Development, Groton Laboratories, Pfizer Inc., Groton, Connecticut 06340

Received August 15, 2002; E-mail: coejw@groton.pfizer.com

Abstract: A synthesis of 4,5-benzo-1-aza-tricyclo[4.3.1.1^{3,8}]undecane (**1**), a benzo-1-aza-adamantane derivative, is described and features a previously unknown application of the Wolff−Kishner reduction of a nonresonance stabilized or "twisted" amide. An intermediate amino ester is converted to a severely "twisted amide", which, when exposed to hydrazine in alcohol, provides the corresponding "twisted" amino hydrazone. Wolff−Kishner conditions (KOH/ethylene glycol, 200 °C) provide the reduced target **1** without hydrolysis to amino acid derivatives. These operations are conveniently performed in a single flask in high yield.

Amino and carboxylate substituted adamantane derivatives have proven to be valuable tools in the service of both physical organic and medicinal chemistry. Indeed, this structural motif is found in numerous medicinal agents and drug candidates.[1] We sought variations of aza-adamantane as novel nicotinic receptor ligands to probe both structural and pharmacological properties. Herein we describe a synthesis of the rigid tricyclic amine, 4,5-benzo-1-aza-tricyclo[4.3.1.1^{3,8}]undecane (**1**), a novel aryl fused aza-adamantane derivative (Figure 1).[2]

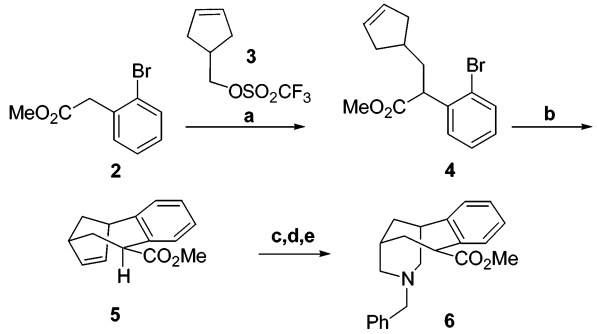


1

Figure 1. Structure of 4,5-benzo-1-aza-tricyclo[4.3.1.1^{3,8}]undecane (**1**).

Our synthesis begins by alkylation of (2-bromo-phenyl)-acetic acid methyl ester (**2**) with cyclopent-3-enylmethyl trifluoromethane sulfonate (**3**).[3,4] The product, cyclopentene **4**, was cyclized under standard Heck conditions[5] to give a single bicyclic olefin **5** in 53% yield (Scheme 1). Benzylic methyne coupling constants (^{1}H NMR, J = 12.5, 3.3 Hz) of **5** are consistent with the indicated pseudoequatorial ester configuration. The *N*-benzyl piperidine was introduced in a three-step,

Scheme 1 [a]



[a] (a) 1 equiv of LDA, THF, −78 °C, 3 h, then **3**, −78 to 20 °C. (b) 2.9 mol % Pd(OAc)$_2$, 5.8 mol % P(*o*-tol)$_3$, 2 equiv of TEA, CH_3CN, 83 °C, 6 h, 53%. (c) $(CH_2)_5NCH_3O{\cdot}H_2O$, 0.5 mol % OsO_4, acetone/H_2O, 100%. (d) 1 equiv of $NaIO_4$, DCE/H_2O. (e) 1.02 equiv of $C_6H_5CH_2NH_2$, 3.6 equiv of NaBH(OAc)$_3$, DCE, 78%.

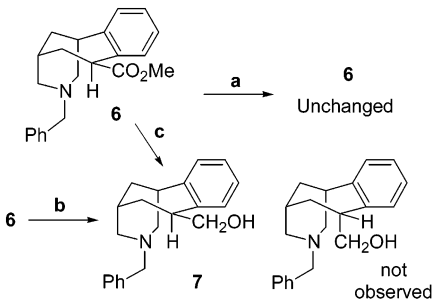
two-pot sequence: dihydroxylation (cat. OsO_4, $(CH_2)_5NCH_3O$),[6] oxidative cleavage ($NaIO_4$),[7] and reductive amination ($PhCH_2NH_2$, NaBH(OAc)$_3$)[8] provided **6** in 78% yield from **5**. Benzylamine **6** contains all of the atoms present in the target structure.

We initially planned to accomplish the final ring closure via the epimerized ester of **6**, which after reduction to the corresponding alcohol would provide the requisite geometry for S_N2 closure. We found that while enolization (LHMDS) was possible, acidic quenches (AcOH) produced pseudoequatorial

(1) For a general discussion of adamantane related structures of pharmacological interest, see: Jasys, J. V.; Lombardo, F.; Appleton, T. A.; Bordner, J.; Ziliox, M.; Volkmann, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 466−473.
(2) Preliminary accounts of this work have been presented: 37th National Organic Symposium, June 2001, Bozeman, MT; Poster A65. ACS National Meeting, August 2001, Chicago, IL; Abstr. 61.
(3) This alcohol is readily available as described. See: (a) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928−931; *Org. Synth.* **1997**, *75*, 195−200. For more recent approaches, see: (b) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992−8998. (c) Marínez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963−7966. (d) Briot, A.; Bujard, M.; Gouverneur, V.; Nolanz, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517−1519. For a similar use of this alcohol, see: Coe, J. W. *Org. Lett.* **2000**, *2*, 4205−4208.
(4) (a) Su, T. M.; Sliwinski, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5386−5388. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85−126.
(5) Heck, R. F. *Organic Reactions*; Wiley: New York, 1982; Vol. 27, p 345.
(6) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth., Coll. Vol.* **1988**, *6*, 342−348.
(7) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478−479.
(8) (a) Emerson, W. S. *Organic Reactions*; Wiley: New York, 1982; Vol. 4, Chapter 3. (b) Bols, M.; Persson, M. P.; Butt, W. M.; Jørgensen, M.; Christensen, P.; Hansen, L. T. *Tetrahedron Lett.* **1996**, *37*, 2097−2100. (c) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478−2479. (d) Kawaguchi, M.; Ohashi, J.; Kawakami, Y.; Yamamoto, Y.; Oda, J. *Synthesis* **1985**, 701−703. (e) Fray, A. H.; Augeri, D. J.; Kleinman, E. F. *J. Org. Chem.* **1988**, *53*, 896−899. (f) Wolin, R.; Wang, D.; Kelly, J.; Afonso, A.; James, L.; Kirschmeier, P.; McPhail, A. T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 195−200. (g) Meyers, A. I.; Nguyen, T. H. *Tetrahedron Lett.* **1995**, *36*, 5873−5876. (h) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

10.1021/ja028152c CCC: $25.00 **© 2003 American Chemical Society**

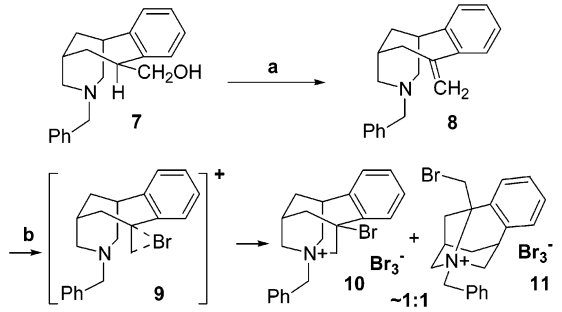
Scheme 2 [a]



[a] (a) 1 equiv of LHMDS, THF, −78 °C, 1 h, then AcOH. (b) 1 equiv of LHMDS, THF, −78 °C, 1 h, camphor sulfonic acid, −78 °C, 15 min, then $LiAlH_4$. (c) $LiAlH_4$, THF, −78 to 0 °C, 100%.

ester **6** exclusively (Scheme 2). An attempt to kinetically quench the preformed enolate with an organic acid at low temperature (camphor sulfonic acid) to generate the epimerized ester followed by low-temperature reduction ($LiAlH_4$, −78 °C) provided amino alcohol **7**. $LiAlH_4$ reduction of **6** also produced **7**. A similar investigation with the olefinic ester **5** (see Scheme 1) failed to provide products resulting from epimerization.

Scheme 3 [a]



[a] (a) CH_3SO_2Cl, TEA, CH_2Cl_2, 0−23 °C, 2 h, 62%. (b) Br_2, CH_2Cl_2, 0 °C, 10 min, 55%.

Closure via bromoamination of the exo-olefin **8** was next explored (Scheme 3). Treatment of **7** with methanesulfonyl chloride/triethylamine[9] produced **8**. These mild conditions facilitated the room temperature E2 elimination of methanesulfonic acid presumably through activation by the proximal tertiary amine.[10] Bromination of **8** offered a potential avenue to the desired ring closure product **10**.[11] Indeed, examination of models revealed that olefin rehybridization from sp^2 to sp^3 in developing bromonium ion **9** would promote ideal alignment for S_N2 displacement at the exo-carbon favoring the formation of **10**. The alternative nonsynchronous S_N1 mediated closure via the tertiary benzylic cation would provide **11**, a strained polycyclic structure.

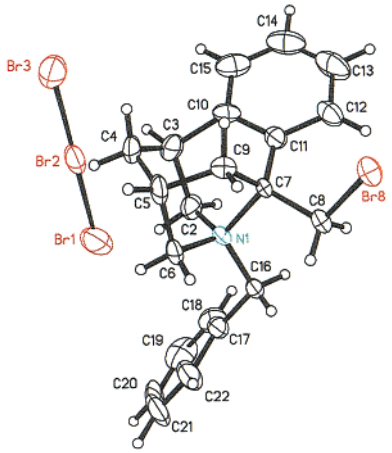


Figure 2. Crystal data and structure refinement for **11**.

Treatment of a solution of **8** in methylene chloride with bromine resulted in the precipitation of a crystalline solid. ^1H NMR and GCMS analysis showed this crude material to be a ~1:1 mixture of two isomers. A material suitable for single crystal X-ray analysis was obtained upon recrystallization from acetonitrile and identified as the quarternized perbromide **11**, the result of closure at the benzylic carbon (Figure 2). Attempts to isolate the second isomer as an X-ray quality crystalline material were unsuccessful, as were our efforts to preparatively isolate homogeneous components by both reverse phase and supercritical fluid HPLC techniques. On the basis of elemental, chromatographic, and NMR analysis, we believe the other component is isomer **10**. We conclude that the geometric considerations that led us to anticipate **10** to be produced under these conditions were partially correct; the competitive benzylic ring opening to produce **11** is not so surprising.

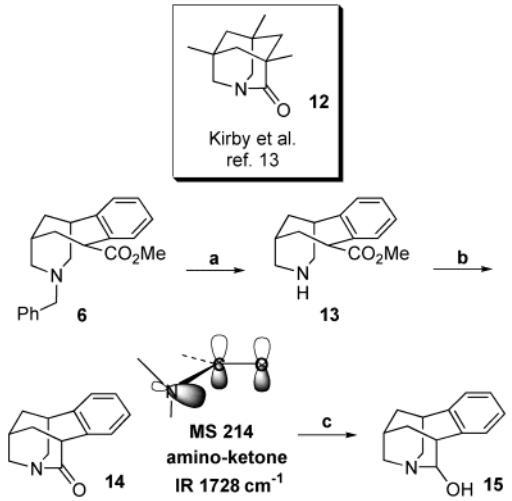
These results led us to an alternative end game strategy. After removal of the benzyl group of **6**, could the resulting amine act to trap the epimerized ester and form a twisted "amide", and, if so, would it be possible to reduce the resulting carbonyl directly? In recent work by Kirby et al., twisted amide **12** was isolated and studied (Scheme 4).[13] The nonepimerizable ring system derived from the Kemp triacid provided an ideal platform to probe the chemistry of the resulting amino ketones. Indeed, they behaved like amines (N-alkylation by Meerwin's reagent) and ketones (ketalization, Wittig chemistry).

Debenzylation of **6** provided amino ester **13**, and base-catalyzed ring closure in hot toluene provided twisted amide **14**. This crude material exhibited a ketone IR stretch (1728 cm^{-1}) similar to Kirby's observation with ketone **12**. Typically **14** was isolated by simple evaporation of the reaction medium; as expected, **14** was found to be unstable under aqueous conditions (see Supporting Information).[13]

With ready access to amino-ketone **14**, we studied various reduction conditions. Formation of the corresponding tosylhy-

(9) O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614−8616.
(10) For literature insights, see: Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485. For a discussion of E2 elimination, see: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 982−1050.
(11) For examples of bromo-amination, see: (a) Stevens C.; Verbeke, A.; De Kimpe, N. *Synlett* **1998**, 180−183. (b) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547−5550. (c) Horning, D. E.; Muchowski, J. M. *Can. J. Chem.* **1974**, *52*, 1321−1330 and references therein. For involvement by amides, see: (d) Sakurai, O.; Takahashi, M.; Ogiku, T.; Hayashi, M.; Horikawa, H.; Iwasaki, T. *Tetrahedron Lett.* **1994**, *35*, 6317−6320. (e) Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600−5602. (f) Balko, T. W.; Brinkmeyer, R. S.; Terando, N. H. *Tetrahedron Lett.* **1989**, *30*, 2045−2048. (g) Knapp, S.; Levorse, A. T.; Potenza, J. A. *J. Org. Chem.* **1988**, *53*, 4773−4779 and references therein.
(12) C−N bond lengths in **11** confirm the additional strain inherent in the bicyclic C−N (benzylic) bond: 1.627 versus 1.515, 1.532 (benzylic), and 1.512 Å; see Supporting Information and compare to an analogous quaternary ammonium salt, **2** in: Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415, Supporting Information. Efforts to equilibrate **10** and **11** via solvolysis with bromide and iodide salts failed to alter the product ratios.
(13) (a) Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785−786. (b) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Am. Chem. Soc.* **1998**, *120*, 7101−7102. (c) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522−529.

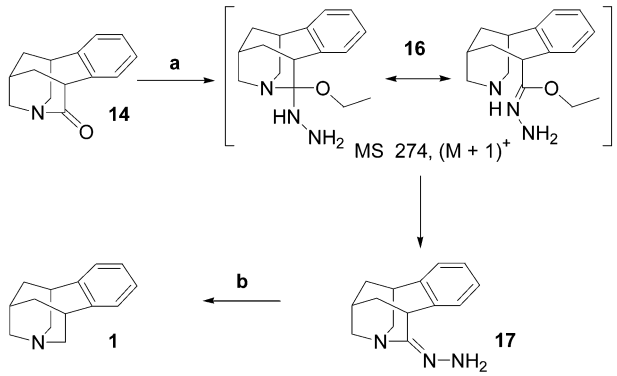
Scheme 4 [a]



[a] (a) H_2, $Pd(OH)_2$, CH_3OH, 84%. (b) 10 mol % *t*-BuOK, toluene ($-CH_3OH$), 110 °C, 49−58%. (c) $LiAlH_4$, THF or $NaBH_4$, EtOH.

drazone ($TsNHNH_2$, EtOH) was observed in low yield, and reduction failed to produce **1** (KBH_4 or $(PhCOO_2)_2BH$).[14] As would be expected for such a structure, treatment of **14** with $NaBH_4$ or $LiAlH_4$ led to formation of a stable hemiaminal **15**; further reduction via iminium intermediates is precluded by geometric constraints.[15]

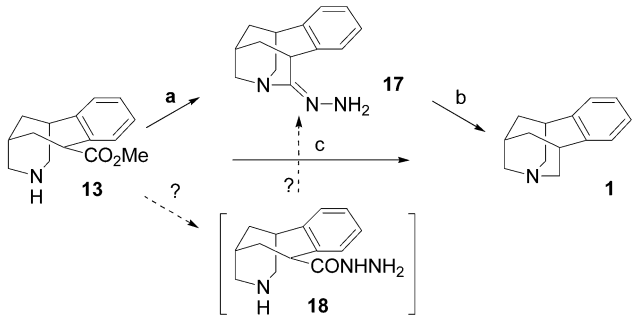
Scheme 5 [a]



[a] (a) NH_2NH_2, EtOH, 1 h, 68 °C. (b) KOH, $(HOCH_2)_2$, 200 °C, 2 h, 68%.

Although early on we had dismissed Wolff−Kishner reduction conditions as too harsh,[16] exposure of ketone **14** to hydrazine in boiling ethanol produced the mixed ethanol-amino-hydrazine intermediate(s) **16** (detectable by APCI MS analysis), which converted to hydrazone **17** after removal of solvent. Gratifyingly, amino hydrazone **17** was readily converted to the desired reduction target **1** in the absence of additional hydrazine in 68% yield (KOH, hot ethylene glycol, 200 °C, 1.5 h, Scheme 5). In retrospect, the stereoelectronic bias that prevents formation

Scheme 6 [a]



[a] (a) 5 equiv of NH_2NH_2, EtOH, 24 h, 68 °C. (b) KOH, $(HOCH_2)_2$, 200 °C, 62%. (c) 4.5 equiv of NH_2NH_2, $(HOCH_2)_2$, 48 h, 90 °C, then KOH, $(HOCH_2)_2$, 200 °C, 7−24 h, 64−85%.

of an intermediate "anti-Bredt" iminium ion[15] in reduction of **14** with $NaBH_4$ or $LiAlH_4$ also favors the ejection of H_2O or alcohol in this hydrazone formation sequence. Furthermore, torsional restriction prevents amide resonance stabilization and insulates the "ketone" and "amino" functionalities during the Wolff−Kishner reduction.[17] Although the behavior of this "ketone" has been anticipated by R. B. Woodward,[18] we are unaware of any example of a Wolff−Kishner reduction of a substrate such as **14** (or amino hydrazone **17**). In fact, the hydrolytic *instability* of a 2-quinuclidone "ketone" to *t*-BuOK/*t*-BuOH observed by Doering and Chanley[18] makes the stability of **14** and **17** under the hydrolytic hydrazine/ethanol and KOH/ethylene glycol Wolff−Kishner conditions all the more surprising. These results highlight the additional degree of structural stabilization in this polycyclic structure. Presumably the additional structural rigidity conferred by the 3,5-bis axially bridged bicyclic piperidine aids the performance of this platform under Wolff−Kishner conditions, insulating against solvolysis as observed under nonaqueous conditions with 2-quinuclidone.

In a preferred procedure, ester **13** was treated with hydrazine to prepare the amino hydrazone **17** directly (Scheme 6, hydrazine, 11 equiv, EtOH, 48 h). We do not have evidence that intermediate amino acyl hydrazide **18** is on the path to **17** and suspect that epimerization and "amide" formation precedes hydrazine condensation to generate **17**. This product can then be converted to **1** upon exposure to KOH in ethylene glycol. These operations were most simply performed in situ. An ethylene glycol solution of amino ester **13** was converted to the intermediate **17** upon exposure to excess hydrazine at 70 °C (4.5 equiv). Once the conversion is complete (TLC, 24−48 h), KOH was added (2.1 equiv), and the mixture was heated to 200 °C for 7−24 h. The desired product was formed in 64−85% yield. This approach is operationally simple and completes an efficient preparation of the target structure.

In summary, the synthesis of 4,5-benzo-1-aza-tricyclo-[4.3.1.1^{3,8}]undecane (**1**), a novel aryl fused aza-adamantane analogue, has been described and proceeds in six steps and 22−27% overall yield (Figure 3). The ketone-like character of twisted amide **14** has been used advantageously to generate the corresponding tertiary amine under Wolff−Kishner conditions.

(14) (a) Caglioti, L. *Tetrahedron* **1966**, *22*, 487−493. (b) Kabalka, G. W.; Summers, S. T. *J. Org. Chem.* **1981**, *46*, 1217−1218.
(15) For examples of bridgehead imines, see: Eguchi, S.; Okano, T.; Takeuchi, H. *Heterocycles* **1987**, *26*, 3265−3284. For bridgehead iminium ion chemistry, see: (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280−8281. (b) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013−3015. (c) Brummond, K. M.; Jianliang, L. *Org. Lett.* **2001**, *3*, 1347−1349.
(16) For reviews, see: (a) Todd, D. *Organic Reactions;* Wiley: New York, 1948; Vol. 4, pp 378−422. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 1209−1211. (c) For the mechanism of the Wolff−Kishner reduction, elimination, and isomerization reactions, see: Szmant, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 120−128.
(17) The connectivity of these atoms is identical to that of the "amidrazone", see: Rapaport, H.; Bonner, R. M. *J. Am. Chem. Soc.* **1950**, *72*, 2783−2784. However, **17** is constrained to behave like an "amino hydrazone".
(18) Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586−588. See ref 12 therein.

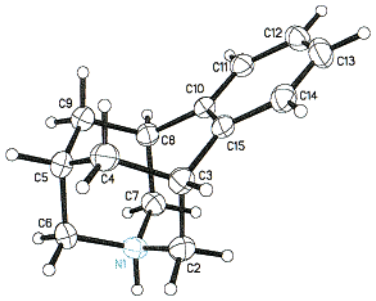


Figure 3. Crystal data and structure refinement for **1** (succinate).

Experimental Procedures

General Methods. Unless otherwise noted, all materials were purchased from commercial sources. Anhydrous solvents were used as provided (in Sure/Seal bottles), and reactions were performed under dry nitrogen atmosphere. Thin-layer chromatography was performed with EM Separations Technology silica gel F_{254}. Silica gel chromatography was carried out with J. T. Baker 40 μm silica gel according to Still's procedure (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923). All glassware was flame dried under dry nitrogen purge before use. ^{1}H NMR spectra were collected at 400 MHz with residual ^{1}H-solvent as internal standard (e.g., $CHCl_3$, 7.26 ppm). Melting points are uncorrected. All spectroscopic data for known compounds were in complete accord with literature values.

2-(Bromo-phenyl)-acetic Acid Methyl Ester (2). 2-(Bromo-phenyl)-acetic acid (76.6 g, 356 mmol) and catalytic concentrated HCl (2 mL) in methanol (500 mL) were heated under reflux for 2.5 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The resulting product was diluted with diethyl ether (250 mL) and then washed with a saturated aqueous $NaHCO_3$ solution (250 mL) and saturated aqueous NaCl solution (250 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 81.3 g (99%) of clear oil.

Trifluoro-methanesulfonic Acid Cyclopent-3-enylmethyl Ester (3). Cyclopent-3-enyl-methanol[2a] (12 g, 122 mmol) and pyridine (23.7 mL, 23.2 g, 293 mmol) were stirred in CH_2Cl_2 (125 mL) in a 0.5 L 3NRB flask equipped with an N_2 inlet and addition funnel at −78 °C. To this solution was added trifluoromethane sulfonic anhydride (24.6 mL, 41.2 g, 146 mmol) dropwise over 30 min via addition funnel. The mixture was stirred and allowed to warm to 0 °C (pink solution, some white ppts).

The reaction was quenched at 0 °C by addition of cold aqueous HCl solution (25 mL of concentrated HCl, 0.3 mol, and H_2O, 150 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with cold 50% saturated aqueous $NaHCO_3$ solution (100 mL), cold H_2O (2 × 100 mL), and cold saturated aqueous NaCl solution (100 mL). The organic layer was dried through a cotton plug and concentrated in vacuo with a room temperature bath to a dark red liquid (>25 g, 89.9% of theory (28.1 g), MW 230.21). This material was taken on directly in the next step (TLC 20% EtOAc/hexanes R_f 0.67).

2-(2-Bromo-phenyl)-3-cyclopent-3-enyl-propionic Acid Methyl Ester (4). 2-(Bromo-phenyl)-acetic acid methyl ester (**3**, 23.6 g, 103 mmol) was stirred in THF (100 mL) and cooled to −78 °C and then treated with 2.0 M lithium diisopropylamide in THF (54 mL, 108 mmol) dropwise via an addition funnel over 30 min. A yellow slurry forms. After 3 h at −78 °C, freshly prepared trifluoro-methanesulfonic acid cyclopent-3-enylmethyl ester (23.7 g, 103 mmol) in THF (50 mL) was added via cannula, while the reaction mixture was maintained at −78 °C. The reaction mixture was allowed to warm slowly to ambient temperature overnight. The resulting red solution was concentrated in vacuo, quenched with a saturated aqueous NH_4Cl solution (150 mL), extracted with EtOAc (4 × 100 mL), and washed with H_2O (2 × 100 mL) and saturated aqueous NaCl solution (1 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting red oil was filtered through silica gel pad eluting with 5% EtOAc/hexanes to yield an oil (37.9 g, 100%).

Data for **4**: (TLC 20% EtOAc/hexanes R_f 0.60); ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, J = 7.2, 1.2 Hz, 1H), 7.38 (dd, J = 7.8, 1.6 Hz, 1H), 7.26 (m, 1H), 7.08 (m, 1H), 5.61 (br s, 2H), 4.21 (t, J = 7.0 Hz), 3.65 (s, 3H), 2.52−1.82 (7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 139.0, 133.2, 129.9, 129.1, 128.8, 127.7, 124.9, 52.1, 49.0, 40.1, 39.1, 35.8; GCMS m/z 308, 310 $(M)^+$.

Tricyclo[8.2.1.0^{2,7}]trideca-2(7),3,5,11-tetraene-8-carboxylic Acid Methyl Ester (5). 2-(2-Bromo-phenyl)-3-cyclopent-3-enyl-propionic acid methyl ester (**3**, 53.0 g, 171 mmol) and tri-*o*-tolylphosphine (3.12 g, 10 mmol) were dissolved in anhydrous CH_3CN (1.1 L) and degassed (three vacuum (10 mm)/nitrogen purge cycles). This solution was treated with freshly distilled triethylamine (47.6 mL, 343 mmol) and palladium-(II) acetate (1.12 g, 5.0 mmol). The resulting mixture was warmed under reflux and stirred until judged complete (6 h). The reaction solution was concentrated in vacuo, cooled, and treated with saturated aqueous NH_4Cl solution (150 mL). The organics were extracted with CH_2Cl_2 (3 × 100 mL) and washed with saturated aqueous NaCl solution (1 × 100 mL). The organic layer was dried through a cotton filter and concentrated to an oil (45 g) that was purified by chromatography through silica gel to yield an oil (20.7 g, 53%). (TLC 20% EtOAc/hexanes R_f 0.55); ^{1}H NMR ($CDCl_3$) δ 7.16−7.07 (m, 3H), 6.85 (d, J = 7.5 Hz, 1H), 6.05 (dd, J = 5.5, 2.8 Hz, 1H), 5.88 (dd, J = 5.5, 3.1 Hz, 1H), 4.13 (dd, J = 12.5, 3.3 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, J = 7.6, 3.3 Hz, 1H), 2.98 (m, 1H), 2.27 (m, 1H), 2.17 (m, 1H), 2.04 (m, 1H), 1.57 (d, J = 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 143.7, 138.2, 135.2, 130.8, 129.6, 128.6, 127.1, 126.3, 52.7, 51.9, 47.7, 42.8, 42.7, 38.0; GCMS m/z 228 $(M)^+$; Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.33; H, 7.21. Anal. Calcd for $C_{15}H_{16}O_2 \cdot 1/8H_2O$: C, 78.15; H, 7.10.

11,12-Dihydroxy-tricyclo[8.2.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxylic Acid Methyl Ester. Tricyclo[8.2.1.0^{2,7}]trideca-2(7),3,5,11-tetraene-8-carboxylic acid methyl ester (**5**, 42.3 g, 185 mmol) in acetone (900 mL) and H_2O (50 mL) was treated with *N*-methylmorpholine-*N*-oxide hydrate (27.5 g, 204 mmol) and OsO_4 (9.4 mL of a 2.5 wt % solution in *t*-BuOH, 0.93 mmol, 0.5 mol %). After being stirred for 24 h, the solution was quenched with 25 g of florisil and saturated aqueous $NaHSO_3$ solution (300 mL). After 1 h, the dispersion was filtered through a Celite pad and concentrated to remove organic solvent. The aqueous mixture was extracted with CH_2Cl_2 (6 × 75 mL), and the resulting organic layer was washed with H_2O (2 × 100 mL) and saturated aqueous NaCl solution (1 × 100 mL). The organic layer was dried through a cotton filter, concentrated, and filtered through a silica gel pad (3 × 5 in.) eluting with 50% EtOAc/hexanes and concentrated to yield an oil (48.5 g, 100%). (TLC EtOAc, R_f 0.62); ^{1}H NMR ($CDCl_3$) δ 7.15−7.06 (m, 3H), 6.86 (d, J = 7.0 Hz, 1H), 4.44 (m, 1H), 4.21 (m, 1H), 3.78 (s, 3H), 3.65 (dd, J = 11.9, 2.7 Hz, 1H), 3.10 (d, J = 8.3 Hz, 1H), 2.87 (m, 2-O*H*), 2.60 (m, 1H), 2.44 (m, 1H), 2.07 (br dd, J = 14.4, 11.9 Hz, 1H), 1.93 (br d, J = 14.4 Hz, 1H), 1.39 (d, J = 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 145.3, 136.0, 130.2, 128.7, 127.2, 126.4, 78.4, 77.0, 57.0, 52.2, 48.9, 46.5, 35.5, 33.2; GCMS m/z 262 $(M)^+$; Anal. Calcd for $C_{15}H_{16}O_4$: C, 68.69; H, 6.92. Found: C, 69.57; H, 6.95.

12-Benzyl-12-aza-tricyclo[8.3.1.0^{2,7}]tetradeca-2(7),3,5-triene-8-carboxylic Acid Methyl Ester (6). 11,12-Dihydroxy-tricyclo[8.2.1.0^{2,7}]-trideca-2(7),3,5-triene-8-carboxylic acid methyl ester (48.5 g, 185 mmol) was vigorously stirred in H_2O (570 mL) and 1,2-dichloroethane (DCE) (350 mL) under nitrogen in a cool water bath (~10 °C) and treated with sodium periodate ($NaIO_4$) (39.6 g, 185 mmol). After 30 min, the layers were separated, and the aqueous layer was extracted with DCE (2 × 80 mL). The organic layer was washed with H_2O (4 × 200 mL, until no reaction to starch iodide is observed in the aqueous wash) and then dried through a cotton plug. To this was added benzylamine (20.8 g, 194 mmol), and this mixture was stirred for 10 min and then

transferred via filtration through a cotton plug into an addition funnel. This mixture was added over 30 min to a magnetically stirred slurry of $NaBH(OAc)_3$ (126 g, 592 mmol) in DCE (400 mL). After it was stirred for 18 h, the reaction was quenched with saturated aqueous Na_2CO_3 solution (~200 mL) carefully at first, and the mixture was stirred for 1 h (pH 9). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, and evaporated to an oil (48.5 g, 78%). (TLC CH_2Cl_2 R_f 0.30); ^{1}H NMR ($CDCl_3$) δ 7.31−7.06 (m, 8H), 6.96 (m, 1H), 5.35 (dd, J = 8.3, 2.5 Hz, 1H), 3.56 (s, 3H), 3.49 (AB d, J = 13.3 Hz, 1H), 3.30 (AB d, J = 13.3 Hz, 1H), 3.11 (dd, J = 11.2, 1.7 Hz, 1H), 3.05 (br s, 1H), 2.79 (br d, J = 10.8 Hz, 1H), 2.40 (dd, J = 11.2, 4.0 Hz, 1H), 2.27−2.15 (m, 4H), 1.91 (br d, J = 11.9 Hz, 1H), 1.79 (br d, J = 11.9 Hz, 1H); GCMS m/z 335 $(M)^+$; Anal. Calcd for $C_{22}H_{25}NO_2 \cdot 1/4H_2O$: C, 77.73; H, 7.56; N, 4.12. Found: C, 77.88; H, 7.40; N, 3.94.

12-Aza-tricyclo[8.3.1.0^{2,7}]tetradeca-2(7),3,5-triene-8-carboxylic Acid Methyl Ester (13). 12-Benzyl-12-aza-tricyclo[8.3.1.0^{2,7}]tetradeca-2(7),3,5-triene-8-carboxylic acid methyl ester (**6**, 48.5 g, 145 mmol) was stirred in CH_3OH (200 mL) and treated with 3 N HCl EtOAc (70 mL). After 5 min, the solution was concentrated to a yellow oil. This was dissolved in CH_3OH (1.0 L), treated with ammonium formate (183 g, 2.89 mol) and $Pd(OH)_2$ (9.6 g of 20 wt %/C), and then warmed under reflux temperature. After 20 min, the conversion was deemed complete (TLC), and the reaction mixture was cooled, filtered through a Celite pad, and concentrated. The residues were dissolved in $CHCl_3$ (200 mL) and washed with saturated aqueous Na_2CO_3 solution (200 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, and evaporated to an oil (29.9 g, 84%). (TLC 10% CH_3OH/CH_2Cl_2 R_f 0.20); ^{1}H NMR ($CDCl_3$) δ 7.31−7.02 (m, 8H), 4.30 (dd, J = 6.2, 3.1 Hz, 1H), 3.68 (s, 3H), 3.18 (d, J = 12.5 Hz, 1H), 3.09 (dd, J = 12.5, 4.0 Hz, 1H), 3.00 (br s, 1H), 2.90 (dd, J = 12.2, 3.0 Hz, 1H), 2.78 (d, J = 12.2 Hz, 1H), 2.59 (m, 1H), 2.18 (m, 1H), 2.08−2.00 (m, 2H), 1.83 (ddd, J = 14.5, 4.5, 4.5 Hz, 1H); APCI MS m/z 246 $(M + 1)^+$; Anal. Calcd for $C_{15}H_{19}NO_2 \cdot H_2O$: C, 68.42; H, 8.04; N, 5.32. Found: C, 67.98; H, 7.47; N, 5.12.

4,5-Benzo-1-aza-tricyclo[4.3.1.1^{3,8}]undecane (1). 12-Aza-tricyclo-[8.3.1.0^{2,7}]tetradeca-2(7),3,5-triene-8-carboxylic acid methyl ester (**13**, 23.3 g, 95 mmol) was stirred in ethylene glycol (100 mL) and treated with hydrazine (8.9 mL, 285 mmol) and then warmed to 90 °C for 24 h. Additional hydrazine was added (4.5 mL, 142 mmol), and the reaction solution was maintained at 90 °C for an additional 24 h, at which time complete consumption of starting material was observed (TLC). To this solution was added KOH (13.3 g, 202 mmol based on 85% KOH content), and the reaction solution was warmed to 200 °C for 24 h. (In other experiments, this conversion was monitored (APCI MS and TLC) and deemed complete after 7 h.) After being cooled to ambient temperature, the mixture was treated with 1 N HCl (1.0 L) and extracted with Et_2O (3 × 150 mL). Saturated aqueous Na_2CO_3 solution was added to the aqueous mixture to achieve pH 9, and this solution was extracted with $CHCl_3$ (6 × 150 mL). This organic solution was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, and evaporated to a white solid (12.2 g, 64%). (On a 3.28 g scale, a yield of 2.26 g or 85% was recovered.) (TLC 1% NH_4OH in 10% CH_3OH/CH_2Cl_2 R_f 0.35); ^{1}H NMR ($CDCl_3$) δ 7.19−7.00 (m, 4H), 3.36 (dd, J = 13.3, 5.0 Hz, 2H), 3.25 (d, J = 13.7 Hz, 2H), 3.18 (s, 2H), 2.64 (m, 2H), 2.20 (br d, J = 13.3 Hz, 2H), 2.00 (br d, J = 13.7 Hz, 2H), 1.21 (br s, 1H); ^{13}C NMR (free base, $CDCl_3$, 100 MHz) δ 146.53, 128.15 (CH), 126.50 (CH), 56.19 (CH_2), 55.38 (CH_2), 41.20 (CH), 33.88 (CH), 25.99 (CH); GC MS m/z 199 $(M)^+$. A sample of this material was converted to the HCl salt (excess 3 N HCl, EtOAc in EtOAc), stripped to dryness, and analyzed. Anal. Calcd for $C_{14}H_{17}N \cdot HCl \cdot 1/3H_2O$: C, 69.55; H, 7.78; N, 5.79. Found: C, 69.49; H, 7.48; N, 5.93.

Acknowledgment. We thank David A. Koss and Thomas N. O'Connell for their commitment and efforts to separate perbromide salts **10** and **11**, Diane M. Rescek for NMR expertise, and Michael P. DeNinno, Michael A. Brodney, Stanton McHardy, Brian T. O'Neill, David A. Clark, Daniel S. Kemp, and E. J. Corey for their kind and thoughtful assistance reviewing the manuscript.

Supporting Information Available: Full experimental conditions and characterization for **7**, **8**, **10**, **11**, **14**, and **17**, stereoview X-ray structures for **1** and **11**, and X-ray data tables for structures **1** and **11** (PDF and TXT). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028152C