Organic Synthesis Methodology. Preparation and Diastereoselective Birch Reduction−Alkylation of 3-Substituted 2-Methyl-2,3-dihydroisoindol-1-ones

Zihong Guo* and Arthur G. Schultz†

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

guo@3dp.com

Received October 22, 2000

The Birch reduction−alkylation of substituted benzamides derived from L-prolinol has provided a wide range of enantiomerically pure cyclohexane derivatives for utilization in organic synthesis.[1] Asymmetric total syntheses of (−)-longifolene and (+)-apovinamine are two decent examples of the applications by this methodology.[2] We now report a new efficient preparation and Birch reductive alkylation of 3-substituted 2-methyl-2,3-dihydroisoindol-1-ones **2** and **1**. To our knowledge, the Birch reductions of simple aromatic lactams have not been previously reported, although Birch reductions and reductive alkylations of achiral tetralones and related aromatic ketones have received some attention from synthetic chemists.[3] It is expected that the methodology outlined in this note will offer unique opportunities for the enantioselective synthesis of alkaloids and other nitrogen-containing heterocyclic systems when a chiral nonracemic substrate is used.

There is an increasing interest in the development of new synthetic methodologies for the preparation of isoindolinone derivatives because of their importance as key intermediates in organic synthesis and the demonstrated activity as nonnucleosidic HIV-reverse transcriptase inhibitors and vasodilators.[4] Treated with NBS and methylamine, for example, methyl *o*-toluate is transformed in two steps into *N*-methylisoindolinone.[5] A more general one-step conversion of *o*-acylbenzoic acids to isoindolinones is achieved by a reductive amination process.[6] Isoindolinones can also be synthesized by reaction of *o*-bromoanilines with carbon monoxide at 100 °C and 1 atm pressure in the presence of catalytic amounts of $Pd(OAc)_2$, Ph_3P, and n-Bu_3N.[7]

N-Methylphthalimidine **1** was readily prepared in quantitative yield from *N*-methylphthalimide by reduction with zinc in refluxing acetic acid.[8] The crude product was pure, witnessed by its very clean ^{1}H NMR spectrum, and was used directly in the next step without further purification. **1** was lithiated with *t*-BuLi (1.2−1.5 equiv) in THF and quenched with methyl iodide (4 equiv) at −78 °C (Scheme 1).[9] Methylated product **2a** was then isolated, in 69% yield, as an oil, which showed a clear one-proton (benzylic methine) quartet centered at 4.40 ppm and a three-proton (methyl) doublet at 1.45 ppm in the ^{1}H NMR spectrum. CIMS indicated a molecular weight of 161 (M + 1 = 162, 100%). This suggested that methylation occurred selectively at the benzylic position. In fact, this lithiation−methylation process was highly regioselective, and no evidence was suggestive of dimethylation at the C(3) position, O-methylation at the carbonyl oxygen atom, or methylation on the benzene ring. The absence of alkylation on the aromatic ring is noteworthy because amido groups on aryl rings are usually regarded as excellent ortho-metalation substituents. In some cases, a small amount of unreacted **1** could be recovered (<5%), but no attempt to optimize this procedure was made.

Efforts to extend this metalation−alkylation approach to other electrophiles such as ethyl iodide, allyl bromide, benzyl bromide, ethyl bromoacetate, and bromoacetonitrile were made, and the corresponding groups were incorporated into the benzylic C(3) position with moderate to good yields (Scheme 1).

Conversion of **1** to enolate **3** was accomplished by reduction with lithium in ammonia at −78 °C. Alkylation with methyl iodide gave **4a** in 69% yield; alkylations with ethyl iodide, benzyl bromide, *p*-methoxybenzyl bromide, and ethyl bromoacetate provided **4b**−**e** in 49−93% yields, respectively (Scheme 2).

The Birch reduction−alkylations of **2a** occurred to give **5a**−**c** in good yields with high diastereoselectivity under the same reaction conditions (Scheme 3). In these cases, ^{1}H NMR data were obtained before flash chromatographic purification. The ^{1}H NMR spectrum of **5a** showed the presence of two products of C-methylation with a ∼7:1 ratio. No other resonance peaks could be seen. Reductive ethylation of **2a** afforded **5b** in 79% yield. The ^{1}H NMR spectroscopic analyses suggested that the ratio of the two possible diastereoisomers in the reaction mixture might be 10:1. When bulkier benzyl bromide was used in the alkylation step, only a single diastereomer was observed.

Stereochemical assignments were temporarily made according to conformational analyses and a comparison with the results of a previous study on the Birch reduction−alkylation of dihydroisoquinolione **6b** (Scheme

* To whom correspondence should be addressed: 3-Dimensional Pharmaceuticals, Inc., 665 Stockton Drive, Exton, PA 19341.

† Deceased on January 20, 2000.

(1) (a) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207. (b) Schultz, A. G. *J. Chinese Chem. Soc.* **1994**, *41*, 487.

(2) (a) Schultz, A. G. and Puig, S. *J. Org. Chem.* **1985**, *50*, 915. (b) Schultz, A. G.; Malachowski, W. P.; Pan, Y. *J. Org. Chem.* **1997**, *62*, 1223.

(3) However, Birch reductions and reductive alkylations of pyrrolobenzoazepin-10-ones and pyrrolobenzodiazepine-5,11-diones have been reported; see: (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828. (b) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493.

(4) (a) Allin, S. M.; Vaidya, D. D.; Page, M. I.; Slavwin, A. M.; and Smith, T. *Tetrahedron Lett.* **2000**, *41*, 2219. (b) Mamouni, A.; Daich, A.; and Decroix, B. *Synth. Commun.* **1997**, *27*, 2241. (c) Campbell, J. B.; Dedinas, R. F.; and Trumbower-Walsh, S. A. *J. Org. Chem.* **1996**, *61*, 6205. (d) DeClercq, E. *J. Med. Chem.* **1995**, *38*, 2491. (e) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003. (f) Cho, C. S.; Shim, H. S.; Choi, H. J.; Kim, T, J.; Shim, S. C.; Kim, M. C. *Tetrahedron Lett.* **2000**, *41*, 3891.

(5) Danishefsky, S.; Bryson, T. A.; Puthenpurrayil, J. *J. Org. Chem.* **1975**, *40*, 796.

(6) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Shepard, K. L. *J. Org. Chem.* **1978**, *43*, 3719.

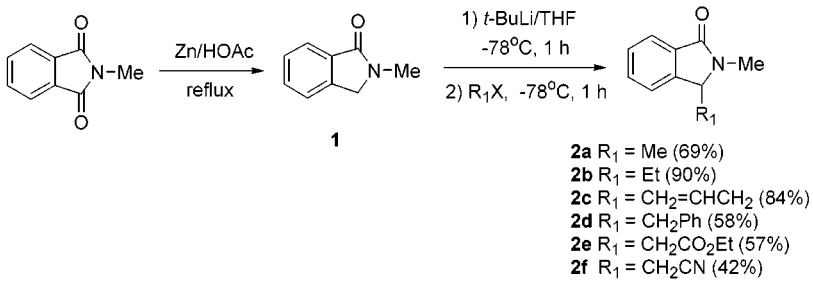
(7) (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684. (b) Campbell, J. B.; Dedinas, R. F.; Walsh, S. A. T. *J. Org. Chem.* **1996**, *61*, 6205. (c) Luzzio, F. A.; Zacherl, D. P. *Tetrahedron Lett.* **1998**, *39*, 2285. (d) For a similar approach, see: Bird, C. W. *J. Organomet. Chem.* **1973**, *47*, 281.

(8) Brewster, J. H.; Fusco, A. M.; Carosino, L. E.; Corman, B. G. *J. Org. Chem.* **1963**, *28*, 498.

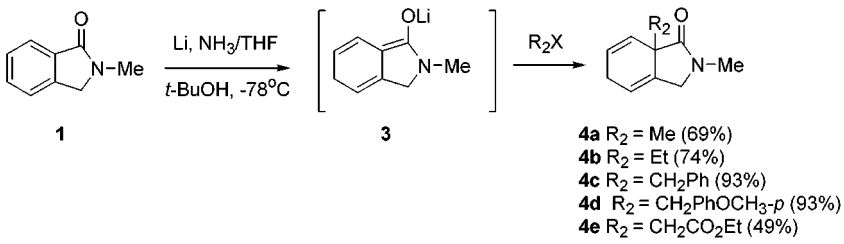
(9) A similar method has appeared recently; see: Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P. *Tetrahedron Lett.* **1998**, *39*, 2319.

10.1021/jo005693g CCC: $20.00
Published on Web 02/07/2001

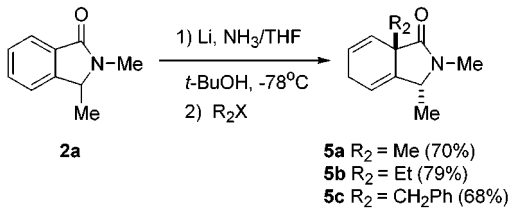
Scheme 1



Scheme 2



Scheme 3



4).[10,11] The Birch reductive alkylation of **6b** provided **7b** with the trans-diastereomer as a major product. The diastereomeric ratios were determined by HPLC before chromatographic separation. The stereochemical structure of **7b** was assigned with a high degree of confidence by comparison of experimentally determined coupling constants for protons at C(3) and C(4) with those determined by utilization of MacroModel, Version 3 (MM2).

Latest studies on the chemistry of the bridged cyclohexene analogues **8a**−**c**, which were obtained from **7** (R_2 = CH_2Ar) by Grewe cyclization, have provided more useful stereochemical information (Scheme 4)[12] and can help further understand the effects of the C(3) methyl substituent (in both isoqunolinone and isoindolinone numbering) on the stereoselectivity of the Birch reductive alkylation of **7** and **2a**. For example, allylic oxidation of bridgehead olefin **8c** provided keto lactam (+)-**8d** (shown in Scheme 5 is its enantiomer (−)-**8d**).[12] The product (**8e**) with cis ring fusion is obtained by hydrogenation (H_2, 5%, Pd/C, EtOAc, 79 psi) of the enone double bond in (−)-**8d**, while the trans ring junction isomer **8f** is available by Birch reduction (Li, NH_3/THF, −78 °C) in the presence of 1 equiv of *t*-BuOH (Scheme 5). The axial methyl substituent is responsible for the observed stereoselectivity, because, in the absence of the axial methyl group (such as in **8a**), hydrogenation of the corresponding bridgehead olefin provided the trans ring junction product.[10,11]

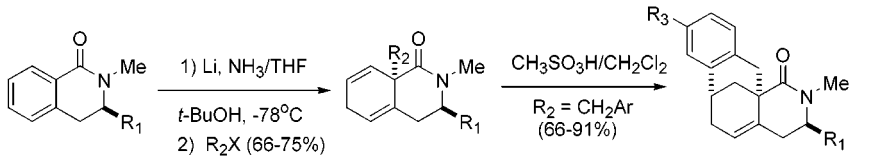
It is believed that the stereoselectivity of the methylation of the enolate generated from **2a** was kinetically controlled by the methyl substituent at C(3) by an early transition-state model resembling the enolate (steric approach control). Calculations by MM2 indicated that both cis and trans isomers of **5a** have similar minimized energy (10.3 vs 10.5 kcal/mol). If thermodynamic factors (product development control) played a role in the alkylation both isomers should have been obtained in approximately equal amounts. Shown in Figure 1 is the lowest energy enolate structure obtained by MM2 calculations. Because the five-membered ring is planar, the proton and the methyl substituent associated with C(3) have equivalent positions with respect to the ring plane. However, the differences in size and bond length between a proton and a methyl group differentiate each side of the ring plane. As a result, the C(3) methyl substituent provides unusually effective shielding of the bottom face of the enolate and blocks the approach of an incoming electrophile very efficiently.

The less steric hindrance double bond of the two in **5** can be regioselectively reduced with diimide, which is formed in situ from heating excess *p*-toluenesulfonyl hydrazide (PTSH) and catalytic sodium acetate, to furnish **9**. For example, the selective saturation of **5a** and **5b** by the diimide method provided **9a** and **9b** in good yields (Scheme 6). No other products were isolated from the reactions.

Cyclization of **4c** and **4d** with trifluoromethanesulfonic acid in CH_2Cl_2 at 0 °C gave the bridged olefin **10a**,**b** in 61−81% isolated yields (Scheme 6). A potential application of **10b** will be the synthesis of the analogues of levorphanol **11**, the levo isomer of *N*-methylmorphinan, which is four times as potent as morphine.[13] Racemic **12a** is synthesized as a lead structure from **8a** in a three-step reaction sequence:[10] (1) $LiAlH_4$/THF; (2) H_2, PtO_2; and (3) DIBAL/$PhCH_3$ and shows modest affinity for the μ-receptor. Structural modifications have been made to enhance opiate receptor affinity and selectivity. Among the modified structures, analogue (−)-**12b** is found to be

(10) Schultz, A. G.; Kirincich, S. J.; Rahm, R. *Tetrahedron Lett.* **1995**, *36*, 4551.
(11) Kirincich, S. J. Ph.D. Thesis, Rensselaer Polytechnic Institute, Troy, NY, 1996.
(12) Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakkar, K.; Bidlack, J. M. *J. Org. Chem.* **1998**, *63*, 7795.
(13) Benson, W. M.; Stefko, P. L.; Randall, L. O. *J. Pharmacol. Exp. Ther.* **1953**, *109*, 189.

Scheme 4



6a R_1 = H
6b R_1 = Me

7a R_1 = H
7b R_1 = Me

8a R_1 = H, R_3 = OMe
8b R_1 = Me, R_3 = H
8c R_1 = Me, R_3 = OMe

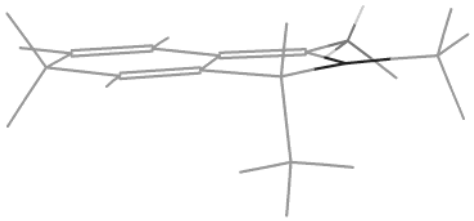
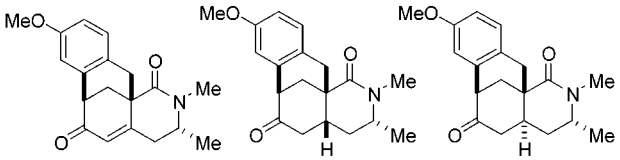


Figure 1. Most stable conformation of the enolate generated from **2a**.

Scheme 5



(-)-**8d** **8e** **8f**

10-fold greater potent than that of determined for the lead structure **12a** (Scheme 7).[12]

Experimental Section

IR spectra were recorded on a Perkin-Packard model spectrometer in $CHCl_3$ solution or in liquid film. ^{1}H NMR and ^{13}C NMR were measured with a 500 HMz spectrometer and in $CDCl_3$ solution using TMS as an internal standard. Extracts were dried over anhydrous $MgSO_4$ before evaporation of solvents on a rotary evaporator under reduced pressure. Dry THF and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. Dry dichloromethane was distilled from CaH_2 prior to use.

General Procedure for the Preparation of 3-Substituted 2-Methyl-2,3-dihydroisoindol-1-ones. 2,3-Dimethyl-2,3-dihydro-isoindol-1-one (2a). To a solution of **1** (1.12 g, 7.6 mmol) in THF (90 mL) at −78 °C was added *t*-BuLi (5.4 mL, 1.2 equiv, 1.7 M in pentane). After the resulting solution was stirred at −78 °C for 1 h, MeI (1.9 mL, 4.0 equiv) was added to the solution. Stirring was continued for 1 h, and the reaction mixture was allowed to warm to room temperature and quenched with water. Removal of solvent in vacuo and chromatography of the resulting residue on silica gel (hexane/ethyl acetate 1:1) gave **2a** (0.85 g, 69%): ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3 H), 3.09 (s, 3 H), 4.40 (q, 1 H), 7.35−7.60 (m, 3 H), 7.80 (d, 1 H); IR (film) 1660, 1460, 1380 cm^{-1}; CIMS *m*/*z* (rel intensity) 162 (M^+ + 1, 100). Analytical data are consistent with literature values.[5]

3-Ethyl-2-methyl-2,3-dihydroisoindol-1-one (2b). Isolated as an oil in 56% yield: ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 3 H), 1.95 (m, 2 H), 3.00 (s, 3 H), 4.40 (t, 1 H), 7.32 (d, 1 H), 7.41 (q, 2 H), 7.72 (d, 1 H); IR (film) 2960, 2920, 2870, 1655, 1450, 1415, 1385 cm^{-1}; CIMS *m*/*z* (rel intensity) 176 (M^+ + 1, 100). Analytical data are consistent with literature values.[5]

3-Allyl-2-methyl-2,3-dihydro-isoindol-1-one (2c). Isolated as an oil in 47% yield: ^{1}H NMR ($CDCl_3$) δ 2.70 (m, 2 H), 3.08 (s, 3 H), 4.45 (t, 1 H), 4.98 (t, 3 H), 5.30 (m, 1 H), 7.35−7.50 (m, 3 H), 7.77 (d, 1 H); IR (film) 2890, 1655, 1455, 1405, 1377 cm^{-1}; CIMS *m*/*z* (rel intensity) 188 (M^+ + 1, 100).

3-Benzyl-2-methyl-2,3-dihydro-isoindol-1-one (2d). Isolated in 58% yield: ^{1}H NMR ($CDCl_3$) δ 2.90 (dd, 1 H), 3.12 (s, 2 H), 3.35 (dd, 1 H), 4.63 (dd, 1 H), 6.95 (m, 1 H), 7.05 (m, 2 H), 7.23 (m, 3 H), 7.37 (m, 2 H), 7.74 (m, 1 H); IR (film) 3000, 2995, 1655, 1405, 1375 cm^{-1}; CIMS *m*/*z* (rel intensity) 238 (M^+ + 1, 100).

(2-Methyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)acetic Acid Ethyl Ester (2e). Isolated in 57% yield: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H), 2.75 (dq, 2 H), 3.08 (s, 3 H), 4.13 (q, 2 H), 4.81 (t, 1 H), 7.38−7.53 (m, 3 H), 7.78 (d, 1 H); IR (film) 1650, 1375 cm^{-1}; CIMS *m*/*z* (rel intensity) 234 (M^+ + 1, 100).

(2-Methyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)acetonitrile (2f). Isolated in 42% yield: ^{1}H NMR ($CDCl_3$) δ 2.90 (dq, 2 H), 3.16 (s, 3 H), 4.62 (dd, 1 H), 7.47−7.60 (m, 3 H), 7.84 (d, 1 H); IR ($CDCl_3$) 1660, 1455, 1410, 1375 cm^{-1}; CIMS *m*/*z* (rel intensity) 187 (M^+ + 1, 100).

General Procedure for the Birch Reductive Alkylation. A solution of **1** (**2a** or **6**)(1.82 g, 12.4 mmol) and *tert*-butyl alcohol (1.16 mL, 1.0 equiv) in THF (50 mL) was cooled to −78 °C, and ammonia (∼700 mL) was added. Lithium (0.38 g, 3 equiv) was added in small pieces, and after 15 min, excess metal was consumed by the addition of 1,3-pentadiene (0.8 mL). Methyl iodide (0.38 mL, 4 equiv) in THF (3 mL) was added, and the reaction mixture was stirred at −78 °C for 1 h. Ammonia was allowed to evaporate, water was added, and the mixture was extracted with methylene chloride (3 × 150 mL). The combined organic layers were washed with 10% sodium thiosulfate, dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography on silica gel (hexane/ethyl acetate 2:1) to afford pure samples.

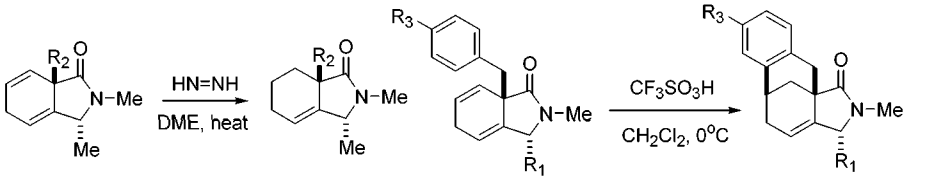
(+)-(3*S*,8a*R*)-3,4,6,8a-Tetrahydro-2,3,8a-trimethyl-1(*2H*)-isoquinolinone [7b (R_2 = Me)]: 72% isolated yield; IR ($CHCl_3$) 1610 cm^{-1}; ^{1}H NMR δ (500 MHz, $CDCl_3$) 6.17 (dt, *J* = 10.0, 1.5 Hz, 1 H), 5.76−5.72 (m, 1 H), 5.55−5.53 (m, 1 H), 3.48 (m, *J* = 6.0, 1.6, 6.6 Hz, 1 H), 2.98−2.94 (m, 1 H), 2.90 (s, 3 H), 2.68−2.66 (m, 2 H), 2.06 (dd, *J* = 13.2, 1.6 Hz, 1 H), 1.38 (s, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ (125.7 MHz, $CDCl_3$) 173.1, 133.2, 130.7, 123.0, 120.9, 53.7, 43.5, 35.1, 34.0, 28.4, 26.1, 18.1; $[\alpha]^{21}_D$ +170 (*c* 0.80, $CHCl_3$); CIMS *m*/*z* (rel intensity) 192 (M + 1, 100). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.36; H, 8.96; N, 7.32. Found: C, 74.24; H, 8.99; N, 7.23.[12]

2,7a-Dimethyl-2,3,5,7a-tetrahydroisoindol-1-one (4a). Isolated as a light yellow oil in 69% isolated yield (1.26 g): ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 2.62 (q, 2 H), 2.81 (s, 3 H), 3.69 (d, *J* = 12.2 Hz, 1 H), 4.02 (d, *J* = 12.5 Hz, 1 H), 5.67 (br, 1 H), 5.78 (m, 1 H), 6.04 (dd, *J* = 9.3, 1.2 Hz, 1 H); IR (film) 2900, 1650, 1415, 1385 cm^{-1}; CIMS *m*/*z* (rel intensity) 164 (M^+ + 1, 100).

7a-Ethyl-2-methyl-2,3,5,7a-tetrahydroisoindol-1-one (4b). Isolated as an oil (74%): ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3 H), 1.60 (m, 2 H), 2.65 (m, 2 H), 2.87 (s, 3 H), 3.73 (d, 1 H), 4.05 (d, 1 H), 5.82 (m, 1 H), 5.95 (m, 1 H), 5.99 (d, 1 H); CIMS *m*/*z* (rel intensity) 178 (M^+ + 1, 100).

(+)-(3*S*,8a*R*)-3,4,6,8a-Tetrahydro-2,3-dimethyl-8a-(phenylmethyl)-1(*2H*)-isoquinolinone [7b (R_2 = CH_2Ph)]. Isolated in 68% isolated yield: IR ($CHCl_3$) 1620 cm^{-1}; ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.18−7.14 (m, 3 H), 7.09−7.06 (m, 2 H), 6.13 (dd, *J* = 9.8, 2.5 Hz, 1H), 5.74−5.70 (m, 1 H), 5.49 (dt, *J* = 3.1, 1.6 Hz, 1 H), 3.46 (dd, *J* = 6.0, 1.6 Hz, 1 H), 3.10 (d, *J* = 12.5 Hz, 1 H), 2.95 (s, 3 H), 2.94 (d, *J* = 12.5 Hz, 1 H), 2.86−2.81 (m, 1 H), 2.28 (dt, *J* = 22.2, 4.8 Hz, 1 H), 2.04 (dd, *J* = 13.1, 1.3 Hz, 1 H), 1.66 (m, 1 H), 1.12 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR δ (125.7 MHz, $CDCl_3$) 172.4, 137.0, 130.8, 130.2, 128.5, 127.0, 126.3, 126.0, 124.5, 54.0, 50.0, 45.0, 35.7, 34.4, 26.2, 18.5; $[\alpha]^{24}_D$ −150

Scheme 6



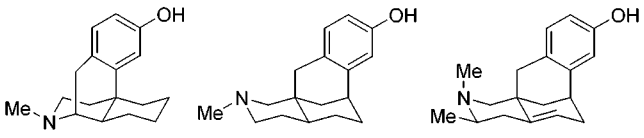
5a R_2 = Me
5b R_2 =Et

9a R_2 = Me
9b R_2 = Et

4c R_1 = R_3 = H
4d R_1 = H, R_3 = OMe

10a R_1 = R_3 = H
10b R_1 = H, R_3 = OMe

Scheme 7



11 **12a** (-)-**12b**

(*c* 1.0, $CHCl_3$); CIMS *m*/*z* (rel intensity) 268 (M + 1, 100); HRMS calcd for $C_{18}H_{21}NO$ (M + H) 268.1701, found 268.1704.[12]

7a-Benzyl-2-methyl-2,3,5,7a-tetrahydroisoindol-1-one (4c). Isolated in 93% yield. Benzyl bromide (1.5 equiv) was used in the alkylation step: ^{1}H NMR ($CDCl_3$) δ 2.17 (d, 1 H), 2.59 (d, 1 H), 2.65 (s, 3 H), 2.94 (d, 1 H), 3.13 (m, 1 H), 3.45 (d, 1 H), 5.74 (d, 1 H), 5.84 (m, 1 H), 6.13 (dd, 1 H), 7.09 (m, 2 H), 7.18 (m, 3 H).

7a-(*p*-Methoxybenzyl)-2-methyl-2,3,5,7a-tetrahydro-1*H*-isoindol-1-one (4d). Isolated in 93% yield. Methoxybenzyl chloride (1.2 equiv) was used: ^{1}H NMR ($CDCl_3$) δ 2.22 (d, 1 H), 2.53 (d, 2 H), 2.68 (s, 3 H), 2.88 (d, 1 H), 3.18 (d, 1 H), 3.47 (d, 1 H), 3.76 (s, 3 H), 5.76 (d, 1 H), 5.86 (q, 1 H), 6.12 (dd, 1 H), 6.72 (q, 2 H), 6.99 (dd, 2 H); CIMS *m*/*z* (rel intensity) 270 (M^+ + 1, 100).

7a-Ethoxycarbonylmethyl-2-methyl-2,3,5,7a-tetrahydro-1*H*-isoindol-1-one (4e). Isolated in 49% yield: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H), 2.50 (q, 2 H), 2.65 (br, 2 H), 2.87 (s, 3 H), 3.70 (d, 1 H), 4.01 (t, 2 H), 4.14 (m, 2 H), 5.90 (m, 1 H), 5.97 (m, 1 H), 6.10 (dt, 1 H); CIMS *m*/*z* (rel intensity) 236 (M^+ + 1, 100).

2,3,7a-Trimethyl-2,3,5,7a-tetrahydro-1*H*-isoindol-1-one (5a). Isolated in 70% yield: ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3 H), 1.32 (d, J = 6.4 Hz, 3 H), 2.70 (m, 2 H), 2.82 (s, 3 H), 4.15 (m, 1 H), 5.71 (d, J = 1.7 Hz, 1 H), 5.83 (m, 1 H), 6.13 (d, J = 8.3 Hz, 1 H); CIMS *m*/*z* (rel intensity) 178 (M^+ + 1, 100). Ratio of the two isomers: ~7:1.

2,3-Dimethyl-7a-ethyl-2,3,5,7a-tetrahydro-1*H*-isoindol-1-one (5b). Isolated in 79% yield as an oil: ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.4 Hz, 3 H), 1.30 (d, J = 6.4 Hz, 3 H), 1.57 (m, 2 H), 2.67 (m, 2 H), 2.81 (s, 3 H), 4.10 (m, 1 H), 5.78 (d, J = 1.9 Hz, 1 H), 5.95 (m, 1 H), 6.00 (d, J = 1.5 Hz, 1 H); IR (film) 3000, 1660, 1405, 1380 cm^{-1}; CIMS *m*/*z* (rel intensity) 192 (M^+ + 1, 100). Ratio of the two isomers: ~10:1.

2,3-Dimethyl-7a-benzyl-2,3,5,7a-tetrahydro-1*H*-isoindol-1-one (5c). Isolated in 68% yield: ^{1}H NMR ($CDCl_3$) δ 1.14 (dd, J = 6.4, 6.3 Hz, 3 H), 2.20 (d, J = 10.4 Hz, 1 H), 2.56 (t, J = 5.8, 5.4 Hz, 1 H), 2.59 (d, J = 12.7 Hz, 1 H), 2.62 (d, J = 1.0 Hz, 3 H), 2.96 (d, J = 12.7 Hz, 1 H), 3.23 (m, 1 H), 5.75 (d, J = 6.1 Hz, 1 H), 5.86 (m, 1 H), 6.18 (dd, J = 9.5 and 3.2 Hz, 1 H), 7.09 (m, 2 H), 7.19 (m, 3 H); CIMS *m*/*z* (rel intensity) 254 (M^+ + 1, 100).

General Procedure for the Selective Reduction of the Double Bond: 2,3,7a-Trimethyl-2,3,5,6,7,7a-hexahydro-1*H*-isoindol-1-one (9a). To a solution of **5a** (177 mg, 1.0 mmol) and PTSH (1.80 g, 9.6 mmol) in DME (30 mL) warmed under reflux was added a solution of NaOAc (1.60 g, 19 mmol) in water (30 mL) within 2 h. After being heated overnight, the reaction mixture was cooled to room temperature, poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (hexane/ethyl acetate 2:1) afforded **9a** as a yellowish oil (90 mg, 50%): ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.72 (m, 2 H), 1.83 (dt, J = 12.7, 4.4 Hz, 1 H), 2.11 (m, 1 H), 2.79 (s, 3 H), 4.07 (m, 1 H), 5.50 (t, J = 3.4, 2.2 Hz, 1 H); IR (film) 2400, 2830, 1645, 1405, 1375 cm^{-1}; CIMS *m*/*z* (rel intensity) 180 (M^+ + 1, 100).

7a-Ethyl-2,3-dimethyl-2,3,5,6,7,7a-hexahydro-1*H*-isoindol-1-one (9b). Isolated in 75% yield as an oil: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.6 Hz, 3 H), 1.24 (d, J = 6.0 Hz, 3 H), 1.63 (m, 3 H), 1.95 (dt, J = 13.5, 3.5 Hz, 1 H), 2.04−2.13 (m, 2 H), 2.80 (s, 3 H), 4.04 (q, J = 6.0 Hz, 1 H), 5.55 (q, J = 2.6 Hz, 1 H); IR (film) 2910, 2850, 1650, 1405, 1375 cm^{-1}; CIMS *m*/*z* (rel intensity) 194 (M^+ + 1, 100).

General Procedure for the Cyclization: 10-Aza-10-methyl-9-oxo-5,6-benzotricyclo-1-dodecene (10a). A mixture of **4c** (460 mg, 1.92 mmol) and CF_3SO_3H (1.5 mL) in CH_2Cl_2 (35 mL) was stirred at 0 °C for 15 min, allowed to warm to room temperature, and stirred overnight. Reaction solution was poured into aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent and chromatography of the residue on silica gel (hexane/ethyl acetate 4:1) gave **10a** (370 mg, 81%): ^{1}H NMR ($CDCl_3$) δ 1.69 (dt, J = 12.0, 2.2 Hz, 1 H), 2.14 (d, J = 18.1 Hz, 1 H), 2.18 (dd, J = 12.0, 3.8 Hz, 1 H), 2.60 (dd, J = 8.1, 2.9 Hz, 1 H), 2.73 (d, J = 16.6 Hz, 1 H), 2.93 (s, 3 H), 3.13 (d, J = 16.6 Hz, 1 H), 3.30 (m, 1 H), 3.73 (d, J = 12.3 Hz, 1 H), 4.06 (d, J = 12.4 Hz, 1 H), 5.51 (s, 1 H), 7.03 (m, 2 H), 7.14 (m, 2 H); IR (film) 3000, 2880, 1650 cm^{-1}; CIMS *m*/*z* (rel intensity) 240 (M^+ + 1, 100).

10-Aza-10-methyl-5,6-(2′-methoxybenzo)tricyclo-9-oxodocec-1-ene (10b). Isolated in 61% yield: ^{1}H NMR ($CDCl_3$) δ 1.68 (dt, J = 12.2, 2.2 Hz, 2 H), 2.18 (m, 2 H), 2.57 (m 1 H), 2.67 (dd, J = 16.1, 1.7 Hz, 1 H), 2.94 (s, 3 H), 3.04 (d, J = 16.1 Hz, 1 H), 3.26 (d, J = 1.7 Hz, 1 H), 3.72−3.80 (m, 4 H), 4.05 (dd, J = 12.4 Hz, 2.2 Hz, 1 H), 5.52 (d, J = 1.3 Hz, 1 H), 6.71 (m, 2 H), 6.96 (d, J = 8.3 Hz, 1 H); CIMS *m*/*z* (rel intensity) 270 (M^+ + 1, 100).

8b. Isolated as a colorless solid in 86% yield: mp 113−115 °C; IR ($CHCl_3$) 1610 cm^{-1}; ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.14−7.09 (m, 3 H), 7.02 (d, J = 6.6 Hz, 1 H), 5.38 (m, 1 H), 3.49 (m, 1 H), 3.40 (d, J = 16.5 Hz, 1 H), 3.25−3.23 (m, 1 H), 2.97 (s, 3 H), 2.84 (dd, J = 16.5, 2.2 Hz, 1 H), 2.79−2.75 (m, 1 H), 2.60−2.55 (m, 1 H), 2.43 (ddd, J = 12.5, 4.0, 1.5 Hz, 1 H), 2.03 (m, 1 H), 2.00 (dd, J = 13.4 Hz, 1 H), 1.74 (dt, J = 12.5, 2.2 Hz, 1 H), 1.17 (d, J) 6.6 Hz, 3 H); ^{13}C NMR δ (125.7 MHz, $CDCl_3$) 173.9, 140.2, 134.5, 132.9, 128.6, 128.5, 126.0, 125.8, 122.4, 53.9, 42.3, 38.9, 35.7, 35.5, 34.2, 33.0, 32.2, 18.6; $[\alpha]^{23}_D$ −150 (*c* 1.0, $CHCl_3$); CIMS *m*/*z* (rel intensity) 268 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.46; H, 8.10.[12]

Acknowledgment. Financial support of this research from the National Institutes of Health (GM 26568) and an ICSC World Laboratories Scholarship to Z.G. are gratefully acknowledged. Z.G. thanks Dr. Bruce Tomczuk and Dr. Tianbo Lu for their helpful discussions.

JO005693G