Construction of *cis*- and *trans*-Decahydroisoquinolines via Heterogeneous Catalytic Hydrogenation

David I. MaGee,* May Ling Lee, and Andreas Decken

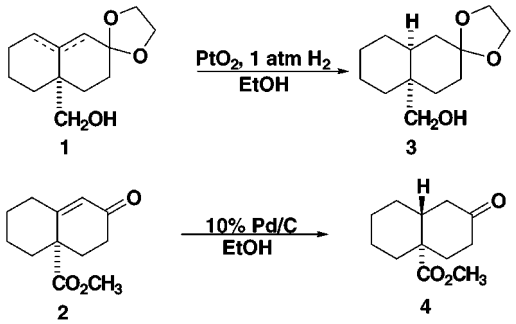
Department of Chemistry, University of New Brunswick, Bag Service #45222, Fredericton, New Brunswick, Canada, E3B 6E2

Received October 12, 1998

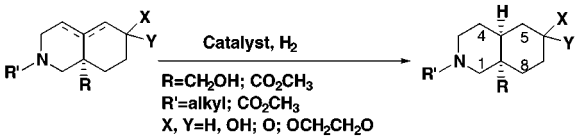
Manzamines are a growing family of marine alkaloids that have been isolated from marine sponges of different genera. The family members are characterized by the presence of a β-carboline pendant, at least one macroazacyclic system and, except manzamine C, a *cis*-hydroisoquinoline as the central core. Due to their challenging structure and potent antileukemia activity, manzamine A and its analogue ircinal A have been targeted for synthesis by several synthetic groups.[1] Not surprisingly, construction of the *cis*-hydroisoquinoline central core is the primary goal in most of these syntheses, since once assembled it will serve as an effective template to introduce most of the remaining stereocenters. Recent strategies can be classified into four categories, namely, intra- and intermolecular Diels−Alder,[2,3] ionic,[4] radical,[5a] and photochemical[5b] cyclization. Herein, we report an alternative approach that makes use of a heterogeneous catalytic hydrogenation to introduce the *cis*-stereochemistry.

It has been known for over four decades that polar groups can influence the stereochemical outcome of olefin hydrogenation over metals,[6] particularly in rigid systems that contain functionalities such as hydroxyl or ester groups, to give high levels of stereochemically enriched products. The stereochemical outcome of these heterogeneous hydrogenations has been rationalized by invoking a haptophilic effect between the polar functionality of the substrate with the surface of the catalyst.[7] Worth noting is the hydrogenation of **1** and **2** in which either *cis*- (**3**) or *trans*-product (**4**) was obtained by a simple change of the angular group,[6] Scheme 1.

Scheme 1



With this in mind, we envisioned that the *cis*-ring juncture required for the hydroisoquinoline portion of the manzamines could be prepared from an analogous substrate by heterogeneous catalytic hydrogenation, eq 1.[8] Surprisingly, what appears to be a simple and straightforward approach to this ring system has, to our knowledge, not been previously investigated.[9,10]



(1)

To study the feasibility of this strategy for the synthesis of the *cis*-fused hydroisoquinolines, dioxolane **9** was synthesized through a series of uncomplicated transformations in good overall yield, Scheme 2. Initially, hydrogenation of **9** in ethanol was attempted using 10% Pd/C as catalyst at room temperature and atmospheric hydrogen pressure. Although the reaction proceeded, it was extremely sluggish, and upon prolonged reaction, the *N*-benzyl group was also hydrogenated. Conversely when PtO_2 was used as the catalyst, hydrogenation proceeded as expected and yielded decahydroisoquinoline **11** in high yield. Dramatic differences in the stereochemical outcome can be obtained when using different catalysts; however, Thompson not only demonstrated that PtO_2 closely parallels Pd/C in its ability to direct hydrogenation in the presence of haptophilic groups,[11] but that with platinum, consistently higher levels of *cis*-product were obtained.

From the above precedent as well as ^{1}H NMR evidence, we tentatively assigned this compound as the *cis*-derivative.[12] To help verify this, it was assumed that subjecting alkene-ester **8** to the same hydrogenation conditions would produce the *trans*-adduct; however, upon hydro-

* Corresponding author. Phone: 506-453-4870, fax: (506)453-4981; e-mail dmagee@unb.ca.

(1) For a review, see: Langlois, Y.; Magnier, E. *Tetrahedron* **1998**, *54*, 6201.

(2) (a) Marko, I. E.; Southern, H. M.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657. (b) Leonard, J.; Fearnley, M.; Finlay, R.; Knight, J. A.; Wong, G. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2359. (c) Pandit, U. K.; Brands, K. M. J.; Meekel, A. A. P. *Tetrahedron* **1991**, *47*, 2005. (d) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691.

(3) (a) Langlois, Y.; Magnier, E. *Tetrahedron Lett.* **1995**, *36*, 9475. (b) Nakagawa, M.; Torisawa, Y.; Ali, M. A.; Tawet, F.; Kageyama, A.; Aikawa, M.; Fukui, N.; Hino, T. *Heterocycles* **1996**, *42*, 677. (c) Simpkins, N. S.; Imbroisi, D. O. *Tetrahedron Lett.* **1989**, *30*, 4309.

(4) (a) Overman, L. E.; Kamenecka, T. M. *Tetrahedron Lett.* **1994**, *35*, 4279. (b) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519. (c) Yamamura, S.; Li, S.; Hosomi, H.; Ohba, S. *Tetrahedron Lett.* **1998**, *39*, 2601.

(5) (a) Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tetrahedron Lett.* **1993**, *34*, 6509. (b) Hart, D. J.; Campbell, J. A. *Tetrahedron Lett.* **1992**, *33*, 6247.

(6) Minckler, L. S.; Hussey, A. S.; Baker, R. H. *J. Am. Chem. Soc.* **1956**, *78*, 1009.

(7) Thompson, H. W.; Naipawer, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 5, 6379.

(8) The numbering scheme for an isoquinoline system is used throughout this text.

(9) We were unable to find any reports of C-8a-substituted decahydroisoquinolines being synthesized by this strategy; however, for unsubstituted systems see: (a) Marchant, A.; Pinder, A. R. *J. Chem. Soc.* **1956**, 327. (b) McElvain, S. M.; Parker, P. H., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 5312.

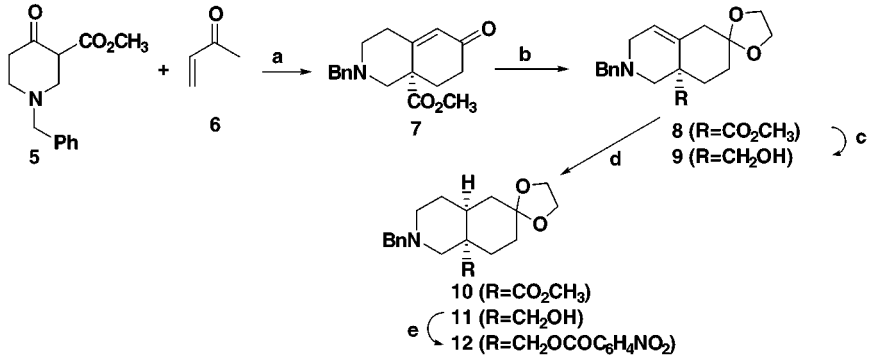
(10) A related example has recently been reported. See: Brands, K. M. J.; DiMichele, L. M. *Tetrahedron Lett.* **1998**, *39*, 1677.

(11) Thompson, H. W.; McPherson, E.; Lences, B. L. *J. Org. Chem.* **1976**, *41*, 2903.

(12) The ^{1}H NMR spectrum showed a 1.5% NOE between H-4a and the 8a-hydroxymethyl hydrogens. There were other NOE's that were supportive of the above structure but the one noted was the most indicative.

10.1021/jo982055d CCC: $18.00
Published on Web 03/16/1999

Scheme 2



Conditions : a) $NaOCH_3$, CH_3OH, reflux, 62%; b) TMSCl, ethylene glycol, 88%; c) $LiAlH_4$, THF, 92%; d) 5 wt% PtO_2, EtOH, 89%; e) p-$NO_2C_6H_4COCl$, NEt_3, 63%.

genation followed by $LiAlH_4$ reduction, alcohol **11** was unexpectedly obtained as the major product, Scheme 2. Consequently, to verify the stereochemistry, the hydroxymethyl group was transformed into *p*-nitrobenzoate **12**, which was a crystalline solid that was amenable to X-ray analysis. The X-ray structure[13] of this compound clearly showed that the reduction yielded the required *cis*-decahydroisoquinoline.

Although hydrogenation of **9** had advanced as anticipated, it was surprising that **8** did not give the opposite stereoisomer. Clearly, for whatever reasons, our system was different from analogous compounds found in the literature. As a result, we decided to carry out a thorough investigation to determine what structural features would be required to produce exclusively either the *cis*- or *trans*-product. To achieve this goal, however, two important things had to be accomplished; first, a variety of substrates needed to be made, and second, a quick and reliable method had to be found to determine the stereoselectivities.

The first task proved to be straightforward because nine different substrates could be synthesized in a rapid fashion by standard functional group manipulation of enone **7**; these are shown in Table 1. These compounds would allow us to probe the effect of all of the functionalities associated with our system, namely, the position of the alkene, the nitrogen protecting group, and the oxygen at C-6.[14] With these in hand, our attention focused on the second problem, identification of the stereoisomers. Fortuitously, it was discovered that oxidation[15] of the crude hydride reduction product from deketalized ester **10** to a keto aldehyde showed two signals in the ^1H NMR region of the aldehyde, one a singlet and the other a much smaller doublet in an 86:14 ratio. We ascribed these two signals to the two stereoisomers; the singlet (δ 9.56) for the *cis*-isomer[16] and the doublet (δ 9.62, d, J = 2.4 Hz) to the *trans*-isomer.[17] The two signals had baseline separation and therefore allowed for easy comparison of their integral ratios.[18] This meant that the assignment of the stereochemical efficiency of the hydrogenation could be simply determined by chemically transforming the hydrogenation products into their corresponding aldehydes and observing their ^1H NMR spectra.[19]

The study was initiated by subjecting the nine substrates to hydrogenation with catalytic PtO_2 for the indicated times. We then transformed these products through standard techniques to their keto-aldehydes. The results are presented in Table 1. It should be pointed out that certain substrates (entries 8, 7, and 17) were not very soluble in ethanol, so a cosolvent (CH_2Cl_2) was added to aid solubilization. It was felt that this may have only a slight deleterious effect on the stereochemical outcome of the hydrogenation since Thompson had shown that use of solvents with high dielectric constants (9.08 for CH_2Cl_2) preferred to give *cis*-product.[11] The most important point illustrated in the table is that high stereochemical levels of either *cis*- or *trans*-product can be obtained by a judicious choice of functionality (entries 1, 9, and 11 vs entry 3). Second, it was found that the position of the alkene with respect to the oxygen substituent at C6 was important. For instance, extremely high levels of *cis*-adduct could only be obtained if the alkene migrated to C4−C4a (entries 1 and 9), whereas if the alkene remained at C4a−C5, either diminished stereoselectivity or no reaction was observed (entries 5, 6, and 7). These differences may be attributed to several factors, including a slight conformational difference in the molecule as a result of the olefin position, an increased haptophilic effect due to the presence of the ketal, and an electronic effect[20] from the oxygen lone pair of the ketal with the olefin. Also deserving attention is that the oxygen functionality at C6 has a profound effect on the hydrogenation (entries 5−8). Thus it seems difficult to justify simply a steric argument since the presence of an axial oxygen should in fact have no bearing on the addition of H_2 *syn* to the hydroxymethyl group. It seems, however, that in these compounds, an allylic axial alkoxy group is exerting a stabilizing electronic effect to the alkene, making it less reactive toward hydrogenation. Although

(13) See the Supporting Information for the crystal structure and related data.

(14) It is well-known that various factors control the stereochemistry of hydrogenation, not the least of which is substrate structure. See: (a) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, 1979; pp 52−55. (b) Dauben, W. G.; Rogan, J. B. *J. Am. Chem. Soc.* **1957**, *79*, 5002.

(15) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(16) The singlet at δ 9.56 was shown to be for the *cis*-compound by taking stereochemically pure **11**, deketalizing it, and then oxidizing the hydroxy ketone to a keto-aldehyde via a Swern oxidation.

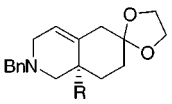
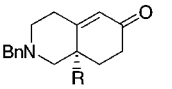
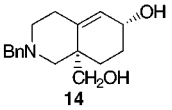
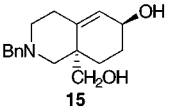
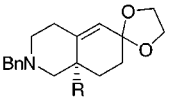
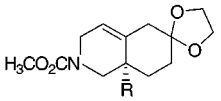
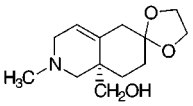
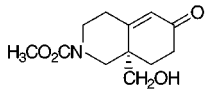
(17) The doublet in the *trans*-isomer is the result of a w-coupling with H-4a. This was shown by COSY and selective proton decoupling spectra.

(18) Although only accurate to within approximately 2−3%, this method proved sufficient for our needs.

(19) It was assumed that the w-coupling observed in the *trans*-product was a result of the rigid bicyclic system and would be seen for all *trans*-compounds. This is what was observed.

(20) Ishiyama, J.; Senda, Y.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 2* **1982**, 71.

Table 1. Reduction of Unsaturated Hydroisoquinolines with PtO_2 Catalyst (entries 1−11) and Na/NH_3 (entry 12)

Entry	Educt	R	Reaction time	cis/trans ratio	Yield (%)
1		**9**, CH_2OH	48 h	99 : 1	89
2		**8**, CO_2CH_3	15 h	86 : 14	83
3		**13**, CH_2OH	15 h	4 : 96	95
4		**7**, CO_2CH_3	15 h	60 : 40	96
5	 **14**		48 h	83 : 7	87
6	 **15**		24 h	nr	nr
7		**16**, CH_2OH	48 h	nr	nr
8		**17**, CO_2CH_3	48 h	nr	nr
9		**18**, CH_2OH	15 h	99 : 1	95
10		**19**, CO_2CH_3	15 h	84 : 16	88
11	 **20**		15 h	99 : 1	86
12	 **21**		20 min	5 : 95	64

there have been reports of this type of hyperconjugative effect,[19] they have not surfaced to the extent that we appear to see in our system. A final item worth noting is that the protecting group, and hence the hybridization, of the nitrogen appears to play no significant role in determining the stereochemical course of the reaction.

In addition to the normal hydrogenation conditions, it was of interest to determine whether other types of reductions, such as the Birch reduction, could be utilized to obtain the *cis*-stereochemistry. This was based on the assumption that protonation of the initially formed radical anion would occur by *syn*-delivery of the proton from the homoallylic alcohol. There was precedent for this type of process;[21] however, when the enone in entry 12 was subjected to the Birch conditions (Na, NH_3, −78 °C) only *trans*-product was observed. This result implies that the carbanion intermediate was either very stable and did not abstract a proton until the methanol quench, which is unlikely, or that protonation from the solvent (NH_3) was more favorable and/or faster, or that protonation occurred intermolecularly.

In conclusion, we have demonstrated that both *cis*- and *trans*-hydroisoquinolines can be exclusively prepared by heterogeneous catalytic hydrogenation. However, of the functionalities we have studied, the presence of a ketal, a migrated olefin, and an angular hydroxymethyl group are crucial for the introduction of *cis*-stereoselectivity in these substrates. This protocol allows for a rapid entry into angularly functionalized decahydroisoquinolines with defined stereochemistry. Extension of this approach to the synthesis of manzamine A is currently under investigation.

(21) Lin, Z.; Chen, J.; Valenta, Z. *Tetrahedron Lett.* **1997**, *38*, 3863.

Experimental Section

All reactions were carried out in a flame-dried or oven-dried (140 °C) glassware under an argon atmosphere. Temperatures indicated refer to external bath temperatures, and all reactions were stirred magnetically. Air-sensitive reagents were transferred through rubber septa via syringes. The phrase "removed under reduced pressure" refers to removal of solvent with a Büchi rotary-evaporator using a water aspirator and a bath temperature of 30 °C. All commercial reagents were purchased from Aldrich Chemicals and were used without further purification. Platinum oxide was purchased from Aldrich Chemicals and had a surface area ≥ 60 m^2/g. Tetrahydrofuran was dried over Na/benzophenone and was

transferred via syringe. Extraction solvents were purchased in bulk and distilled prior to use. Column chromatography was performed on Merck silica gel (230−400 mesh) following the procedure of Still.[22] Reagent grade solvents were used without further purification for chromatographic separations. Melting points are uncorrected.

2-Benzyl-6-oxo-2,3,4,6,7,8-hexahydro-1*H*-isoquinoline-8a-carboxylic Acid Methyl Ester (7). To a solution of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate (**5**) (2.47 g, 10.0 mmol) in anhydrous methanol (20 mL) was added sodium hydride (0.05 g, 2 mmol) in three portions over 10 min. The resulting solution was brought to reflux, and then methyl vinyl ketone **6** (0.84 g, 12.0 mmol) was added dropwise over 30 min. After complete addition, the reaction mixture was kept at reflux for an additional 2 h, at which time it was cooled to room temperature and concentrated by rotary evaporation. The resulting reddish brown oil was diluted with water and extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow solid which was purified by flash chromatography (hexanes/ethyl acetate = 4/1) to give 2.00 g (67%) of a pale yellow solid **7**. An analytical sample was prepared by recrystallization from diethyl ether. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.25 (m, 5H), 5.95 (d, 1H, J = 2), 3.74 (s, 3H), 3.53 (ABq, 2H, J = 13.2, $\Delta\delta$ = 60.0), 3.42 (dd, 1H, J = 2.4, 11.2), 2.99 (m, 1H), 2.86 (m, 1H), 2.39−2.12 (m, 5H), 1.88 (d, 1H, J = 11.6), 1.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 198.3, 173.2, 160.1, 137.9, 128.8, 128.2, 127.2, 126.8, 63.0, 62.1, 53.7, 52.5, 49.8, 34.4, 33.5, 30.9. FT-IR (neat) cm^{-1}: 2936 (m), 1728 (s), 1676 (s), 1632 (m), 1244 (m). HREIMS m^+/z (%): $C_{18}H_{21}NO_3$ (calcd) = 299.1521, $C_{18}H_{21}NO_3$ (found) = 299.1541 (100.0). mp = 105.2−106.0 °C.

2-Benzyl-6-oxo-2,3,5,6,7,8-hexahydro-1*H*-isoquinoline-8a-carboxylic Acid Methyl Ester 6-Ethylene Ketal (8). To a suspension of enone **7** (1.00 g, 3.34 mmol) in ethylene glycol (4.15 g, 66.9 mmol) was added TMSCl (2.00 g, 18.4 mmol) slowly by syringe over 10 min. After complete addition, the mixture was stirred at room temperature for 15 h. After the mixture was cooled in an ice bath, it was quenched with saturated $NaHCO_3$ carefully and extracted with ether (4×). The organic layer was successively washed with water and brine. After the organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/ethyl acetate = 2/1) to afford ketal **8** (0.98 g, 85%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (m, 5H), 5.60 (m, 1H), 3.96 (m, 4H), 3.66 (s, 3H), 3.52 (ABq, 2H, J = 13.6, $\Delta\delta$ =16.4), 3.24 (dt, 1H, J = 4.4, 16.0), 3.01 (d, 1H, J = 13.4), 2.81 (dt, 1H, J = 2.0, 14.0), 2.75 (dt, 1H, J = 2.8, 14.4), 2.33 (dd, 1H, J = 2.8, 11.2), 2.09 (d, 1H, J = 11.2), 2.04 (m, 1H), 1.69 (m, 1H), 1.54 (dd, 1H, J = 2.4, 8.8). ^{13}C NMR ($CDCl_3$, 400 MHz): 175.3, 138.3, 133.7, 128.6, 128.1, 127.0, 123.3 108.8, 64.5, 64.4, 61.6, 60.3, 53.3, 52.1, 49.1, 42.1, 31.7, 31.1. FT-IR (neat) cm^{-1}: 2947 (m), 1726 (s), 1679 (w). HREIMS m^+/z (%): $C_{20}H_{25}NO_4$ (calcd) = 343.1783, $C_{20}H_{25}NO_4$ (found) = 343.1770 (100.0). mp = 108.1−109.9 °C.

2-Benzyl 8a-(hydroxymethyl)-2,3,5,6,7,8-hexahydro-1*H*-isoquinolin-6-one Ethylene Ketal (9). To a suspension of lithium aluminum hydride (0.06 g, 1.46 mmol) in 1 mL of THF was added a solution of ketal **8** (0.50 g, 1.46 mmol) in THF (1 mL) dropwise. The resulting mixture was stirred at room temperature for 30 min at which time the mixture was cooled in an ice bath and quenched with 2 drops of water, 2 drops of 10% NaOH, and 6 drops of water again. The resulting suspension was stirred until it turned to milky white and was then filtered through a pad of Celite. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/ethyl acetate = 1/2) to afford **9** as a colorless oil (0.42 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35−7.27 (m, 5H), 5.62 (s, 1H), 4.00−3.91 (m, 4H), 3.57 (ABq, 2H, J = 12.8, $\Delta\delta$ = 24.0), 3.44 (d, 1H, J = 10.0), 3.19 (dt, 1H, J = 3.2, 16.0), 2.92 (dd, 1H, J = 1.2, 11.2), 2.70 (dq, H, J = 2.0, 16.2), 2.53 (dq, 1H, J = 2.8, 14.4), 2.28 (d, 1H, J = 14.4), 2.22 (dd, 1H, J = 2.8, 14.4), 1.66 (m, 2H), 1.39 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 136.8, 134.9, 129.0, 128.5, 127.5, 122.7, 109.0, 68.7, 64.5, 64.4, 63.9, 62.5, 52.7, 40.3, 39.1, 30.6, 30.0. FT-IR (neat) cm^{-1}: 3438 (br), 2936 (s), 1604 (w). HREIMS m^+/z (%): $C_{19}H_{25}NO_3$ (calcd) = 315.1834, $C_{19}H_{25}NO_3$ (found) = 315.1827 (56.6).

2-Benzyl-6-oxo-8a-(hydroxymethyl)-*cis*-octahydroisoquinoline *p*-Nitrobenzoate Ester 6-Ethylene Ketal (12). A mixture of alcohol **11** (0.45 g, 1.42 mmol) and *p*-nitrobenzoyl chloride (0.40 g, 2.13 mmol) in a mixture of methylene chloride and pyridine (5 mL, 1:1) was stirred for 15 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (10 mL), and the organic layer was separated, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/ethyl acetate = 3/1) to give 0.43 g of a white crystalline solid in 65% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 2H, J = 9.2), 7.99 (d, 2H, J = 9.2), 7.27 (d, 2H, J = 7.2), 7.14 (t, 2H, J = 7.2), 7.07 (t, 1H, J = 7.2), 4.71 (d, 1H, J = 10.0), 4.35 (d, 1H, J = 10.8), 3.95 (m, 4H), 3.13 (ABq, 2H, J = 13.2, $\Delta\delta$ = 124), 2.65 (broad, 1H), 2.38−2.29 (m, 3H), 2.09−1.99 (m, 3H), 1.70−1.35 (m, 6H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.5, 150.3, 138.9, 135.8, 128.7, 128.1, 126.7, 123.4, 109.0, 76.0, 71.3, 64.2, 63.1, 52.5, 49.8, 36.5, 35.3, 32.5, 30.3, 29.9, 27.4. FT-IR (neat) cm^{-1}: 2936 (s), 1728 (s), 1604 (m), 1530 (s). HREIMS m^+/z (%): $C_{26}H_{30}N_2O_6$ (calcd) = 466.2104, $C_{26}H_{30}N_2O_6$ (found) = 466.2102 (100.0). mp = 138.2−138.6 °C.

General Procedure for Catalytic Hydrogenation of Various Unsaturated Hydroisoquinolines. A round-bottomed flask containing a 0.1 M solution of alkene in anhydrous ethanol, unless stated otherwise, and 7 mol % of PtO_2 was alternately evacuated by water aspirator and filled with hydrogen three times to remove air. The final charge of hydrogen was adjusted to 1 atm with a mercury leveling bulb, and stirring was begun. When at least the theoretical amount of hydrogen was absorbed and uptake ceased, see Table 1 for the stated time, the product was isolated by suction filtration through a pad of Celite followed by removal of all solvent by rotary evaporation.

2-Benzyl-6-oxo-*cis*-octahydroisoquinoline-8a-carboxylic Acid Methyl Ester 6-Ethylene Ketal (10). Following the above procedure with 10% CH_2Cl_2 in ethanol as solvent, cis- and trans-isomers were obtained as an inseparable mixture in 83% yield (86:14 ratio) as a colorless oil from **8** following purification by flash chromatography (hexanes/ethyl acetate = 2:1). ^{1}H NMR

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

($CDCl_3$, 400 MHz): δ 7.26 (m, 5H), 3.95−3.90 (m, 4H), 3.66 (s, 3H), 3.45 (ABq, 2H, J = 13.4, $\Delta\delta$ = 40.0), 2.35 (m, 5H), 1.83−1.9 (m, 8H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 176.5, 138.7, 128.7, 128.0, 126.8, 108.6, 64.3, 64.0, 63.0, 62.5, 60.3, 51.7, 46.1, 35.5, 32.4, 31.3, 28.0. FT-IR (neat) cm^{-1}: 2979 (s), 2811 (s), 1735 (s), 1603 (w), 1449 (m). HREIMS m^+/z (%): $C_{20}H_{27}NO_4$ (calcd) = 345.1940, $C_{20}H_{27}NO_4$ (found) = 345.1943 (100.0).

2-Benzyl-6-oxo-8a-(hydroxymethyl)-*cis*-octahydroisoquinoline 6-Ethylene Ketal (11). Obtained in 89% yield, as a colorless oil, following the above procedure from **9** and purification by flash chromatography (hexanes/ethyl acetate = 1/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.24 (m, 5H), 3.95−3.90 (m, 4H), 3.57 (ABq, 2H, J = 10.4, $\Delta\delta$ = 24.0), 3.46 (s, 2H), 2.68 (d, 1H, J = 10.4), 2.52 (q, 2H, J = 11.6), 2.51 (m, 1H), 2.17 (t, 1H, J = 11.6), 1.97 (m, 1H), 1.90 (t, 1H, J = 13.2), 1.55−1.51 (m, 2H), 1.40−1.21 (m, 4H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 137.4, 128.9, 128.4, 127.3, 109.1, 76.2, 64.2, 64.1, 63.3, 56.1, 48.2, 35.7, 35.5, 35.4, 30.6, 30.3, 28.4. FT-IR (neat) cm^{-1}: 3416 (br), 2841 (s), 1460 (m). HREIMS m^+/z (%): $C_{19}H_{25}NO_3$ (calcd) = 317.1992, $C_{19}H_{25}NO_3$ (found) = 317.1992 (12.2).

2-Benzyl-6-hydroxy-*trans*-octahydroisoquinoline-8a-carboxylic Acid Methyl Ester. Obtained in 95% yield, as a colorless oil, following the above procedure from **7** with 10% CH_2Cl_2 in ethanol as solvent, and purification by flash chromatography (hexanes/ethyl acetate = 2/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−7.21 (m, 5H), 3.71 (q, 1H, J = 7.0), 3.63 (s, 3H), 3.43 (ABq, 2H, J = 13.5, $\Delta\delta$ = 100), 3.14 (d, 1H, J = 10.8), 2.94 (d, 1H, J = 10.8), 2.21 (dq, 1H, J = 4.6, 12.6), 2.09−1.61 (m, 5H), 1.62 (d, 1H, J = 5.5), 1.38 (dd, 1H, J = 2.4, 13.0), 1.26−1.13 (m, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 174.5, 138.7, 128.6, 127.9, 126.8, 70.8, 63.2, 62.6, 54.9, 51.1, 47.7, 42.0, 37.7, 32.4, 32.3, 28.8. FT-IR (neat) cm^{-1}: 3398 (br), 2935−2805 (m), 1738 (s), 1596 (w), 1453 (m). HREIMS m^+/z (%): $C_{18}H_{25}NO_3$ (calcd) = 303.1829, $C_{18}H_{25}NO_3$ (found) = 303.1834 (100.0).

6-Oxo-8a-(hydroxymethyl)-*cis*-octahydroisoquinoline-2-carboxylic Acid Methyl Ester 6-Ethylene Ketal. Obtained in 95% yield, as a colorless oil, following the above procedure from **18** and purification by flash chromatography (hexanes/ethyl acetate = 1/2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00−3.10 (m, 4H), 3.82−3.69 (m, 7H), 3.13 (broad, 3H), 1.94−1.76 (m, 4H), 1.67−1.50 (m, 4H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 157.3, 108.8, 67.4, 64.3, 64.2, 53.0, 43.2, 40.2, 37.6, 35.3, 32.6, 30.3, 29.5, 26.7. FT-IR (neat) cm^{-1}: 3460 (br), 2936 (m), 1698 (s), 1684 (s), 1478 (m), 1456 (m). HREIMS m^+/z (%): $C_{14}H_{23}NO_5$ (calcd) = 285.1576, $C_{14}H_{23}NO_5$ (found) = 285.1563 (100.0).

6-Oxo-*cis*-octahydroisoquinoline-2,8a-dicarboxylic Acid Methyl Ester 6-Ethylene Ketal. Obtained in 88% yield, as a colorless oil, following the above procedure from **19** and purification by flash chromatography (hexanes/ethyl acetate = 2/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.97−3.88 (m, 4H), 3.71 (s, 3H), 3.69 (s, 3H), 3.61−3.52 (m, 3H), 3.40−3.14 (broad, 1H), 2.54 (m, 1H), 1.97−1.54 (m, 8H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 175.4, 156.0, 108.0, 64.3, 63.9, 52.5, 52.1, 47.3, 41.4, 35.7, 33.7, 31.2, 27.9, 27.0. FT-IR (neat) cm^{-1}: 2937 (s), 1735 (s), 1698 (s). HREIMS m^+/z (%): $C_{15}H_{23}NO_6$ (calcd) = 313.1525, $C_{15}H_{23}NO_6$ (found) = 313.1502 (82.8).

2-Methyl-6-oxo-8a-(hydroxymethyl)-*cis*-octahydroisoquinoline 6-Ethylene Ketal. Obtained in 86% yield, as a colorless oil, following the above procedure from **20**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (m, 4H), 3.60 (d, 2H, J = 2.4), 2.66 (d, 1H, J = 8.4), 2.51 (m, 3H), 2.56 (s, 3H), 2.17 (t, 1H, J = 11.6), 1.93 (m, 1H), 1.88 (t, 1H, J = 13.2), 1.55 (m, 2H), 1.42−1.26 (m, 4H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 109.1, 64.3, 64.2, 57.9, 54.8, 50.2, 46.1, 37.0, 35.7, 34.8, 30.7, 30.4, 28.3. FT-IR (neat) cm^{-1}: 3429 (br), 2947−2884 (m), 1475 (m), 1446 (m), 1104 (s). HREIMS m^+/z (%): $C_{13}H_{23}NO_3$ (calcd) = 241.1678, $C_{13}H_{23}NO_3$ (found) = 241.1662 (100.0).

2-Benzyl-6-oxo-*cis*-octahydroisoquinoline-8a-carbaldehyde. Obtained from the following procedure: 0.42 g of **11** (1.41 mmol) was stirred with 3 equiv of pTsOH in wet acetone (15 mL) for 15 h at room temperature. After neutralization with $NaHCO_3$ and extraction with Et_2O (3×), the crude product was then subjected to Swern oxidation which provided 0.28 g of a clear oil in 75% yield after SiO_2 chromatography (hexanes/ethyl acetate = 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.56 (s, 1H), 7.30 (m, 5H), 3.54 (d, 1H, J = 13.2), 3.47 (s, 1H, J = 13.2), 2.73 (m, 1H), 2.59 (dd, 1H, J = 0.8, 11.4), 2.51−2.19 (m, 8H), 1.95 (m, 1H), 1.70 (m, 1H), 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 210.0, 204.4, 138.0, 128.6, 128.3, 128.2, 127.9, 127.2, 62.7, 55.3, 52.1, 49.6, 43.3, 37.7, 35.1, 27.8, 26.5. FT-IR (neat) cm^{-1}: 2937 (m), 2711 (m), 1720 (s), 1603 (w), 1493 (m). HREIMS m^+/z (%): $C_{16}H_{21}NO_2$ − H (calcd) = 270.1521, $C_{16}H_{21}NO_2$ − H (found) = 270.1527 (32.2).

2-Benzyl-6-oxo-*trans*-octahydroisoquinoline-8a-carbaldehyde. Obtained by the following procedure: 0.52 g of the product obtained from hydrogenation of **7** (1.82 mmol) was reduced with 1.5 equiv of $LiAlH_4$ in THF at 0 °C for 30 min. Workup following the procedure given for **9**, followed by Swern oxidation, gave 0.32 g of a clear oil in 71% overall yield after SiO_2 chromatography (hexanes/ethyl acetate = 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.62 (d, 1H, J = 2.4), 7.34−7.26 (m, 5H), 3.61 (d, 1H, J = 13.2), 3.41 (d, 1H, J = 13.2), 3.10 (dd, 1H, J = 2.0, 11.6), 3.03 (m, 1H), 2.96 (d, 1H, J = 14.0), 2.33−2.25 (m, 3H), 2.23 (dt, 1H, J = 3.2, 12.4), 1.99−1.93 (m, 2H), 1.82 (d, 1H, J = 11.2), 1.71 (m, 1H), 1.54−1.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 210.0, 204.7, 138.1, 128.7, 128.3, 127.2, 62.7, 61.1, 53.9, 48.8, 44.2, 42.1, 37.8, 29.4, 28.7. FT-IR (neat) cm^{-1}: 2937 (m), 2811 (m), 1713 (s), 1603 (w), 1493 (m), 1449 (m). HREIMS m^+/z (%): $C_{16}H_{21}NO_2$ + H (calcd) = 272.1676, $C_{16}H_{21}NO_2$ + H (found) = 272.1670 (38.4).

8a-Formyl-6-oxo-*trans*-octahydroisoquinoline-2-carboxylic Acid Methyl Ester. To 5 mL of THF at −78 °C was condensed 5 mL of ammonia, followed by addition of 0.30 g (13.0 mmol) of sodium. After stirring for 30 min, hydroxy-enone **21** (0.21 mg, 0.88 mmol) in 1 mL of THF was added. The reaction mixture was stirred at −78 °C for 20 min and then quenched with saturated NH_4Cl until the blue color disappeared. The mixture was then warmed to room temperature and extracted with ether (3×). The combined organic phase was washed with brine, dried over K_2CO_3, and concentrated under reduced pressure. The crude was subjected to oxidation without purification. To the stirred solution of oxalyl chloride (0.22 g, 1.76 mmol) in 1.0 mL of THF at −78 °C was added dimethyl sulfoxide (0.28 g, 3.52 mmol) in 1 mL of THF. The solution was stirred at −78 °C for 30 min at which time a solution of crude alcohol (about 0.88 mmol) in 1 mL of THF was added. The resulting solution was warmed to −40 °C and after 15 min was treated with

0.61 mL of triethylamine (4.5 mmol). The reaction mixture was warmed briefly to room temperature and quenched with saturated $NaHCO_3$ and extracted with ether (3×). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes/ethyl acetate = 3/1) to give 0.14 g of a colorless oil (64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.71 (s, 1H), 4.65 (broad, 1H), 4.24 (broad, 1H), 3.71 (s, 3H), 2.84 (m, 2H), 2.57 (m, 1H), 2.44 (m, 1H), 2.31 (m, 2H), 2.18 (m, 1H), 1.97 (dq, 1H, J = 4.8, 12.6), 1.85 (dt, 1H, J = 2.8, 13.2), 1.61−1.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.7, 203.4, 156.2, 53.0, 50.8, 44.1, 44.0, 43.8, 42.0, 37.9, 29.5, 28.0. FT-IR (neat) cm^{-1}: 2958 (m), 1727 (s), 1698 (s). HREIMS m^+/z (%): $C_{12}H_{17}NO_4$ (calcd) = 239.1153, $C_{12}H_{17}NO_4$ (found) = 239.1143 (13.5).

Acknowledgment. We gratefully thank NSERC Canada (operating grant for DM and a PGS-B for M.L.L.) and the University of New Brunswick for financial support, Dr. Larry Calhoun for NMR assistance, and Dan Drummond for mass spectral service.

Supporting Information Available: Copies of ^{1}H NMR spectra for selected compounds and X-ray crystallographic parameters for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982055D