JOC*Note*

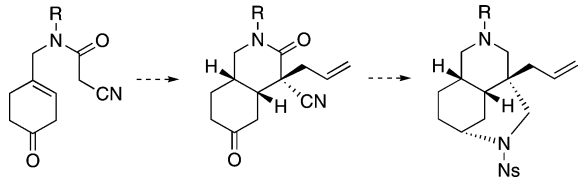
Synthesis of Diazatricyclic Core of Madangamines from *cis*-Perhydroisoquinolines

Josefina Quirante,* Laura Paloma, Faïza Diaba, Xavier Vila, and Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

josep.bonjoch@ub.edu

Received October 30, 2007



Synthesis of the tricyclic core of madangamine alkaloids has been achieved in a 10-step sequence starting from a 4-(aminomethyl)anisole derivative. A Birch reduction and acylation with cyanoacetic acid followed by an intramolecular Michael process renders a polyfunctionalized *cis*-perhydroisoquinoline. A diastereoselective allylation and reduction of amide, nitrile, and ketone groups leads to a bicyclic alcohol, which undergoes aminocyclization through the nosyl derivative to the diazatricyclic ring.

Madangamines are pentacyclic alkaloids with a basic skeleton consisting of a common diazatricyclic core of perhydro-6,4-(iminomethano)isoquinoline and two linear bridges (Figure 1). Madangamines A−E have been isolated from *Xestospongia ingens* sponges collected at Madang in Papua New Guinea (A,[1] B−E[2]), and structural variations in this group of alkaloids occur only in the N(7) to C(9) bridge, which varies both in carbon length (13−15 atoms) and the position and degree of unsaturation. Madangamine F,[3] presenting some new structural trends, has been recently isolated from the Brazilian sponge *Pachychalina alcaloidifera*. Madangamine A is of pharmacological interest as it exhibits in vitro cytotoxicity against murine leukemia P388 cell lines with an IC_{50} value of 1 μg/mL.

Although no madangamine synthesis has been described to date, three synthetic strategies have been developed for the construction of the diazatricyclic core (Scheme 1). In the Weinreb approach,[4] the bridge framework is assembled in the last step by an aminomercuriation process. In contrast, Yamazaki−Kibayashi[5,6] and Marazano[7] have worked with 2-azabicyclo-[3.3.1]nonane intermediates in order to elaborate the hydroisoquinoline unit in the last step. In the work reported here, we have introduced a new synthetic pathway to the diazatricyclic target.

The proposed retrosynthetic analysis, depicted in Scheme 2, involves an initial formation of the fused perhydroisoquinoline ring from a carbocyclic starting material followed by the closure of the bridged ring through an intramolecular alkylation. There are several reported methodologies leading to *cis*-perhydroisoquinolin-6-one derivatives, unsubstituted at C(4a) and C(8a),[8−12]

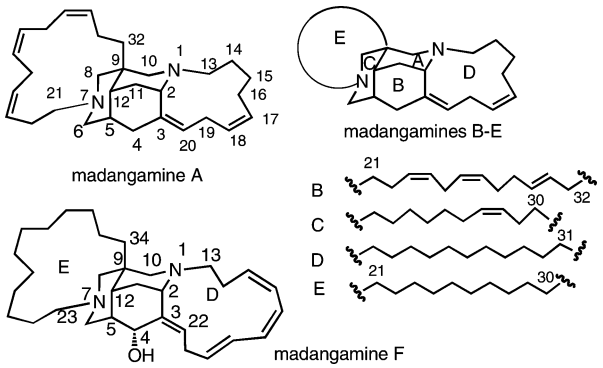
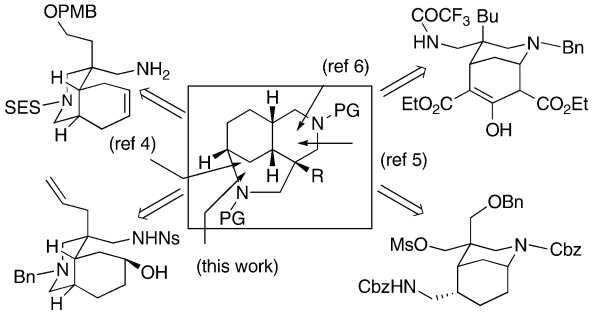
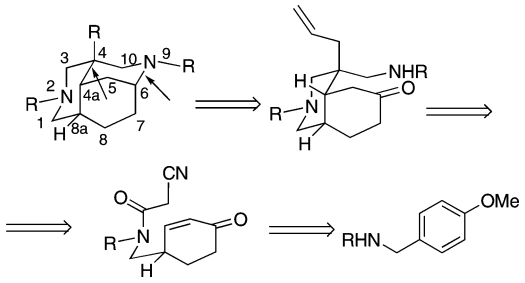


FIGURE 1. Madangamine structures.

SCHEME 1. Construction of the Diazatricyclic Madangamine Core



SCHEME 2. Retrosynthesis for the Diazatricyclic Madangamine Core



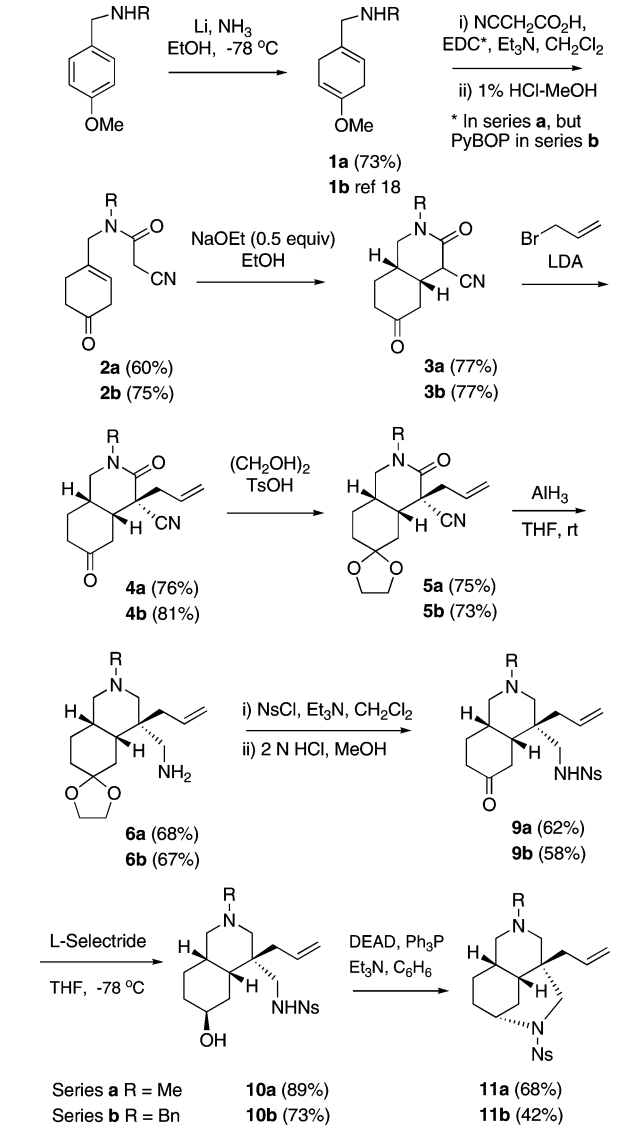
(1) Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007−6008.
(2) Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267−271.
(3) Oliveira, J. H. H. L.; Nascimento, A. M.; Kossuga, M. H.; Cavalcanti, B. C.; Pessoa, C. O.; Moraes, M. O.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E.; Pinheiro, U. S.; Berlinck, R. G. S. *J. Nat. Prod.* **2007**, *70*, 538−543.
(4) Matzanke, N.; Gregg, R. J.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1997**, *62*, 1920−1921.
(5) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509−6512.
(6) For the synthesis of an azatricyclic compound embodying the ACE madangamine skeleton, see: Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489−3492.
(7) Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Bénéchie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437−2440.
(8) Stork, G.; Livingston, D. A. *Chem. Lett.* **1987**, 105−108.

10.1021/jo702340w CCC: $40.75
Published on Web 12/21/2007

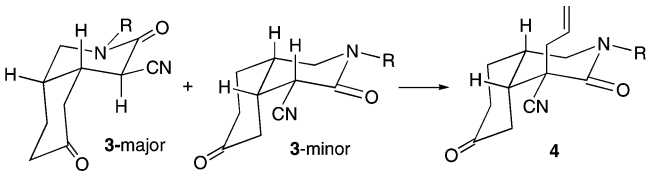
as required for our madangamine diazatricyclic core approach.[13−17] We chose a Michael process since it would allow the N(9) and C(10) atoms[18] to be incorporated in a latent form as a nitrile, using a cyanoacetamide as the Michael donor group.[19] Moreover, this synthetic approach could be extended to the elaboration of the eastern macrocycle if the carbonyl group of the Michael acceptor allowed a functionalization at C(7).

The synthesis began with a Birch reduction of the *N*-methyl-4-methoxybenzylamine.[20] The secondary amine **1a** was coupled with cyanoacetic acid using several coupling agents,[21] the best results being obtained with EDC (Scheme 3). The resulting dihydroanisole (not shown) was submitted to an acid treatment to hydrolyze its enol ether, thus generating the achiral nitrogen-tethered cyanoacetamide and cyclohexenone **2a**, the key precursor of the perhydroisoquinoline ring. Compound **2a** was found to be a mixture of rotamers around the amide bond. Treatment of β,γ-enone **2a** with a substoichiometric quantity of NaOEt induced the isomerization of the double bond and then an intramolecular Michael process to diastereoselectively give the *cis*-perhydroisoquinoline **3a** in 77% overall yield. The mixture

SCHEME 3. Synthesis of the Diazatricyclic Madangamine Core



SCHEME 4. Diastereoselective Allylation of the Epimeric Mixture of 3



of epimers (7:3) at C(4) in compound **3a** is synthetically irrelevant since in the next step both evolve through the same carbanion intermediate to give the stereogenic quaternary center at this carbon. The allylation takes place from the top face under a sterically controlled kinetic reaction to give exclusively **4a** (Scheme 4). The stereochemistry as well as the preferred conformation for **4a** were established unequivocally from NMR data: (i) the ^{1}H NMR coupling pattern for the methylene proton at C-1ax, which appears as dd (J = 13.2 and 10.4 Hz); (ii) the NOESY interaction between the H-8a and the methylene of the allyl substituent at C-4; (iii) the chemical shift of C-7 (δ 36.2),

(9) Godleski, S. A.; Villhauer, E. B. *J. Org. Chem.* **1984**, *49*, 2246−2252.

(10) Hutchinson, D. R.; Khau, V. V.; Martinelli, M. J.; Nayyar, N. K.; Peterson, B. C.; Sullivan, K. A. *Org. Synth.* **1998**, *75*, 223−234.

(11) MaGee, D. I.; Lee. M. L. *Tetrahedron Lett.* **2001**, *42*, 7177−7180.

(12) Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 4661−4664.

(13) For other procedures for the synthesis of functionalized *cis*-perhydroisoquinolines without substituents at the methine ring carbons, see the following references: (a) from an acyclic precursor through an intramolecular Diels−Alder, ref 14; (b) from a nitrogen-containing ring and further elaboration of the carbocyclic ring, ref 15; (c) from a functionalized carbocyclic ring and later piperidine ring formation, ref 16; (d) from a bicyclic carbocyclic derivative and a insertion of the nitrogen atom, ref 17.

(14) (a) Leonard, J.; Appleton, D.; Fearnley, S. P. *Tetrahedron Lett.* **1994**, *35*, 1071−1074. (b) Murray, W. V.; Sun, S.; Turchi, I. J.; Brown, F. K.; Gauthier, A. D. *J. Org. Chem.* **1999**, *64*, 5930−5940. (c) Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. *J. Org. Chem.* **2003**, *68*, 5274−5285. (d) Zeng, Y.; Reddy, D. S.; Hirt, E.; Aubé, J. *Org. Lett.* **2004**, *6*, 4993−4995.

(15) (a) Aldol process: McElvain, S. M.; Parker, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 5312−531. McElvain, S. M.; Remy, D. C. *J. Am. Chem. Soc.* **1960**, *82*, 3960−3966. (b) Intermolecular Diels−Alder: Ma, J.; Nakagawa, M.; Torisawa, Y.; Hino, T. *Heterocycles* **1994**, *38*, 1609−1613. Langlois, Y.; Magnier, E. *Tetrahedron Lett.* **1995**, *36*, 9475−9478. (c) Ring-closing metathesis: Amat, M.; Pérez, M.; Minaglia, A. T.; Casamitjana, N.; Bosch, *Org. Lett.* **2005**, *7*, 3653−3656.

(16) (a) Photocyclization: Xu, W.; Zhang, X.-M.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863−8878. Jung, Y. S.; Swartz, W. H.; Xu, W.; Mariano, P. S. *J. Org. Chem.* **1992**, *57*, 6037−6047. (b) Radical cyclization: Stork, G.; Mash, R. *Heterocycles* **1989**, *28*, 723−727. Kaoudi, T.; Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 3125−3127. (c) *N*-Alkylation and related processes: Hansen, M. M.; Bertsch, C. F.; Harkness, A. R.; Huff, B. E.; Hutchinson, D. R.; Khau, V. V.; LeTourneau, M. E.; Martinelli, M. J.; Misner, J. W.; Peterson, B. C.; Rieck, J. A.; Sullivan, K. A.; Wright, I. G. *J. Org. Chem.* **1998**, *63*, 775−785. Hart, D. J.; Ellis, D. A. *Heterocycles* **1998**, *49*, 117−120. Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409−1417.

(17) (a) Aubé, J.; Ghosho, S.; Tanol, M. *J. Am. Chem. Soc*. **1994**, *116*, 9009−9018. (b) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947−950.

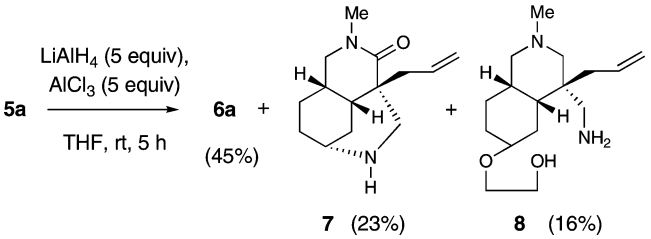
(18) The systematic nomenclature is used throughout this paper (see Scheme 2), while the madangamine numbering has been showed in Figure 1.

(19) For an approach to 3-oxabicyclo[4.4.0]decan-4,8-diones based on an intramolecular Michael process of a cyanoacetate upon enones, see: (a) Grossman, R. B.; Ley, S. V. *Tetrahedron* **1994**, *50*, 11533−11568. (b) de la Puente, M. L.; Grossman, R. B.; Ley, S. V.; Simmonds, M. S. J.; Blaney, W. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1517−1521.

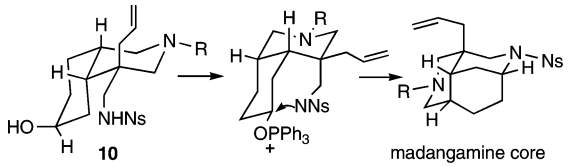
(20) Quirante, J.; Vila, X.; Paloma, L.; Guiu, J. M.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 1372−1379.

(21) For other coupling conditions using cyanoacetic acid, see: Lemaire, S.; Giambastiani, G.; Prestat, G.; Poli, G. *Eur. J. Org. Chem.* **2004**, 2840−2847.

SCHEME 5. Aminocyclization of 5 Using AlH_2Cl



SCHEME 6. Stereochemical Course of the Final Cyclization



which is diagnostic for *cis*-perhydroisoquinolin-6-ones with the depicted conformation.[22]

After carbonyl protection of ketone **4a**, we initiated studies for the reduction of amide and cyano groups of **5a** to achieve the required diamino derivative **6a**. Interestingly, when we used an equimolecular mixture of $LiAlH_4$ and $AlCl_3$ at room temperature (AlH_2Cl in the reaction medium) we obtained a mixture of the expected **6a** together with the diazatricyclic compound **7** (23%) and the byproduct **8** (Scheme 5). Attempts to optimize the formation of **7** either from **6a** or **8** using the same reagents but varying the reaction time were unsuccessful. In search of the best conditions to exclusively obtain **6a**, the hydrogenolysis process was minimized by carrying out the reduction using a 3:1 mixture of $LiAlH_4$ and $AlCl_3$ to generate alane. Thus, **6a** was isolated in 68% overall yield (85% yield on 0.3 mmol scale).

For the final ring closure of the bridged subunit, the nosyl group at the exocyclic nitrogen and a hydroxyl group at C-6 were required to attempt an alkylation of amines with alcohol derivatives using the Fukuyama protocol.[23] After nosylation and cleavage of the acetal group, ketone **9a** was isolated. Considering that the conformation of this compound differs from the one needed for the cyclization process (see Scheme 6), we carried out the reduction using L-Selectride to prepare the corresponding axial alcohol. Then, **10a** was treated with Ph_3P, DEAD, and Et_3N, undergoing the corresponding S_N2 substitution through a conformational inversion of the azabicyclic ring to give the target **11a** in 68% yield.

The same sequence (**2** → **11**) was also carried out working with *N*-benzyl-substituted derivatives (series **b**). In this case, the starting compound **2b** was prepared by the Birch reduction of 4-methoxybenzylamine, followed by a reductive amination of the resulting dihydroanisole.[20] The overall synthetic sequence resulted in similar yields to those of series **a**, as depicted in Scheme 3.

In conclusion, we have described a concise 10-step synthesis of the diazatricyclic core of madangamines. Our approach features canonical reactions such as Michael and *N*-alkylation intramolecular processes in the ring-closure steps, which could allow the synthetic process to be extended to more elaborate derivatives en route to the madangamines.

Experimental Section

***N*-Benzyl-2-cyano-*N*-(4-oxocyclohex-1-enylmethyl)acetamide (2b).** To a cooled (0 °C) solution of amine **1b** (3.77 g, 16.74 mmol) in CH_2Cl_2 (55 mL) were added *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC, 8 g, 41.3 mmol), cyanoacetic acid (3.55 g, 41.3 mmol), and DMAP (2 g, 16.4 mmol). The resulting solution was stirred overnight at rt, diluted with CH_2Cl_2, and washed sequentially with 10% aqueous citric acid, saturated $NaHCO_3$, and brine. The organic phase was concentrated to give the crude cyanoacetamide. To a solution of the above enol ether in EtOH (45 mL) was added aqueous 1% HCl (45 mL). After the reaction mixture was stirred 5 h at rt, EtOH was evaporated and the resulting aqueous phase was neutralized with 1 N NaOH and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was purified by chromatography (SiO_2, 1:1 hexane/EtOAc) to give **2b** (3.5 g, 9.4 mmol, 75%) as an orange oil: IR(NaCl) 1714, 1660; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) mixture of rotamers 2.32 and 2.41 (2m, H-6), 2.40−2.60 (m, 2H, H-5), 2.89 and 2.91 (2s, 2H, H-3), 3.53 and 3.57 (2s, 2H, CH_2CN), 3.82 and 4.12 (2s, 2H, NCH_2), 4.51 and 4.61 (2s, 2H, CH_2Ph), 5.57 and 5.62 (2s, 1H, H-2), 7.10−7.50 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 25.0 and 25.2 (CH_2CN), 26.3 and 26.5 (C-6), 37.6 and 37.9 (C-5), 39.0 and 39.3 (C-3), 49.6 and 50.6 (CH_2Ph), 50.9 and 52.1 (NCH_2), 113.8 and 113.9 (CN), 121.1 and 122.2 (C-2), 127.9, 128.0, 128.3, 128.8, 129.4 (Ar), 132.3 and 133.1 (*ipso*-Ar), 134.8 and 136.0 (C-1), 162.4 and 162.6 (NCO), 208.4 and 209.2 (C-4); HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_2$ 283.1441 $[M + H]^+$, found 283.1436.

(4*RS*,4a*RS*,8a*SR*)- and (4*RS*,4a*SR*,8a*RS*)-2-Benzyl-3,6-dioxodecahydroisoquinoline-4-carbonitrile (3b). To a solution of **2b** (3 g, 10.64 mmol) in EtOH (110 mL) was added NaOEt (1 M solution in EtOH (5.3 mL, 5.3 mmol). After the resulting solution was stirred at rt for 1 h, acetic acid was added (7 mL) and the mixture was concentrated. The obtained residue was taken up in CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ and H_2O. The organic phase was dried, concentrated, and purified by chromatography (SiO_2, 20:80 hexane/EtOAc) to afford **3b** (2.3 g, 8.16 mmol, 77%) as an orange oil and as an epimeric mixture at C-4 (7:3 ratio): IR (NaCl) 1715, 1656; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) major epimer 1.84 (m, 2H, H-8), 2.39 (m, 2H, H-7), 2.50 (dd, J = 15.2, 6.8, 1H, H-5), 2.55 (m, 1H, H-8a), 2.62 (dd, J = 15.2, 5.2, 1H, H-5), 2.84 (m, 1H, H-4a), 3.22 (dd, J = 12.8, 5.2, 1H, H-1), 3.38 (d, J = 9.2, 1H, H-4), 3.50 (dd, J = 12.8, 5.2, 1H, H-1), 4.48 and 4.77 (2d, J = 14.8, 2H, CH_2Ph), 7.20−7.40 (m, 5H, ArH); minor epimer 1.92 (m, 2H, H-8), 2.29−2.35 (m, 3H, H-4, H-5, H-7), 2.43 (m, 1H, H-8a), 2.70 (dq, J = 12 and 5 Hz, 1H, H-4a), 2.76 (m, 1H, H-5), 3.33 (dd, J = 13, 6.8, 1H, H-1), 3.44 (t, J = 12.8 Hz, H-1), 3.90 (d, J = 5.6, 1H, H-4), 4.65 (s, 2H, CH_2Ph), 7.20−7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) major epimer 25.3 (C-8), 30.9 (C-8a), 38.0 (C-4), 38.2 (C-4a), 38.5 (C-7), 43.0 (C-5), 48.8 (C-1), 50.8 (CH_2Ph), 116.7 (CN), 128.1, 128.3 and 129.0 (Ar), 135.6 (*ipso*-Ar), 160.4 (C-3), 206.9 (C-6); minor epimer 25.9 (C-8), 30.2 (C-8a), 36.0 (C-7), 36.3 (C-4a), 39.3 (C-5), 40.0 (C-4), 46.3 (C-1), 51.0 (CH_2Ph), 115.4 (CN), 135.7 (*ipso*-Ar), 161.1 (C-3), 206.7 (C-6); HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_2$ 283.1441 $[M + H]^+$, found 283.1434.

(4*RS*,4a*SR*,8a*RS*)-4-Allyl-2-benzyl-3,6-dioxodecahydroisoquinoline-4-carbonitrile (4b). To a cooled (−78 °C) solution of **3b** (2.36 g, 8.36 mmol) in THF (120 mL) was added LDA (1.5 M in cyclohexane, 4.2 mL, 8.36 mmol), and the reaction mixture was stirred for 1 h. Allyl bromide (0.9 mL, 10.03 mmol) was added, and stirring was continued for 2 h at the same temperature and overnight at rt. After being quenched with saturated NH_4Cl (5 mL), the resulting mixture was stirred, the organic phase was separated,

(22) Bailey, J. M.; Booth, H.; al-Shirayda, H. A. R. Y. *J. Chem. Soc., Perkin Trans. 2* **1984**, 583−587. See also reference 12.

(23) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891−1893 and references therein.

and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried, concentrated, and purified by chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to give **4b** (2.2 g, 6.85 mmol, 81%) as an orange oil: IR (NaCl) 1714, 1652; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY, NOESY) 1.84 (m, H-8ax), 1.97 (m, H-8eq), 2.30 (dtd, J = 16.5, 5.5, 1.5 Hz, 1H, H-7eq), 2.31−2.53 (m, 2H, H-7ax and H-5), 2.45−2.53 (m, 2H, H-4a, H-8a), 2.77 (m, 1H, CH_2), 2.92 (ddt, J = 14.2, 6, 1.2 Hz, 1H, CH_2), 3.30 (dd, J = 13.2, 3.3 Hz, 1H, H-1eq), 3.49 (dd, J = 13.2, 10.4 Hz, 1H, H-1ax), 4.53 and 4.74 (2d, J = 14.4 Hz, 1H each, CH_2Ph), 5.25 (dq, J = 16.8, 1.2 Hz, 1H, =CH_2), 5.30 (d, J = 10.4 Hz, 1H, =CH_2), 5.89 (dddd, J = 16.8, 10.4, 8, 6.4 Hz, 1H, =CH), 7.25−7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 25.8 (C-8), 27.0 (C-8a), 36.2 (C-7), 38.4 (C-4a), 40.4 (C-5), 40.9 (CH_2), 46.3 (C-1), 49.1 (C-4), 51.1 (CH_2Ar), 117.7 (CN), 121.3 (=CH_2), 128.1, 128.2, 129.0 (Ar), 130.8 (=CH), 135.9 (*ipso*-Ar), 164.1 (C-3), 206.9 (C-6); HRMS (ESI-TOF) calcd for $C_{20}H_{23}N_2O_2$ 323.1754 $[M + H]^+$, found 323.1751.

(4*RS*,4a*SR*,8a*RS*)-4-Allyl-4-(aminomethyl)-2-benzyloctahydroisoquinolin-6(2*H*)-one Ethylene Acetal (6b). A solution of $AlCl_3$ (350 mg, 2.62 mmol) in THF (12 mL) was added to $LiAlH_4$ (1 M in THF, 7.9 mL). The mixture was stirred for 15 min, and **5b** (1 g, 2.62 mmol) in THF (10 mL) was added dropwise. After being stirred overnight at rt, the mixture was cooled to 0 °C and quenched with aqueous 30% KOH. The reaction mixture was extracted sequentially with CH_2Cl_2, $CHCl_3$, and $CHCl_3$/*i*-PrOH (4:1). The dried organic extracts were concentrated and purified by chromatography (Al_2O_3, CH_2Cl_2/MeOH, 99:1) to yield diamine **6b** (0.65 g, 1.76 mmol, 67%): IR (NaCl) 3382, 3027, 2931, 2803, 1451; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.48 (m, 2H, H-5 and H-8), 1.48−1.56 (m, 2H, H-7), 1.68−1.74 (m, 2H, H-5 and H-8), 1.73 (d, J = 12.8 Hz, 1H, H-3), 1.87 (dm, J = 13.2 Hz, 1H, H-4a), 2.24 (m, 2H, H-1 and H-8a), 2.26−2.32 (m, 2H, H-3 and CH_2), 2.32 and 2.38 (2d, J = 7.2 Hz, 1H each, CH_2NH_2), 2.45 (m, 1H, H-1), 2.73 (dd, J = 13.8, 7.2 Hz, 1H, CH_2), 3.41 and 3.48 (2d, J = 13.2 Hz, 1H each, CH_2Ar), 3.88−3.98 (m, 4H, OCH_2), 5.01 (dd, J = 10.4, 2 Hz, 1H, =CH), 5.08 (dm, J = 17.2 Hz, 1H, =CH_2), 5.73 (dddd, 1H, 17, 10, 9, 7.2 Hz, =CH), 7.20−7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 26.8 (C-8), 29.2 (C-8a), 30.0 (C-7), 30.9 (C-5), 36.9 (C-4a), 37.5 (CH_2), 40.5 (C-4), 44.5 (CH_2N), 53.2 (C-1), 54.9 (C-3), 63.2 (CH_2Ar), 64.1, 64.3 (CH_2O), 109.7 (C-6), 117.1 (=CH_2), 126.9, 128.1 and 128.8 (Ar), 135.2 (=CH), 139.1 (*ipso*-Ar); HRMS (ESI-TOF) calcd for $C_{22}H_{33}N_2O_2$ 357.2536 $[M + H]^+$, found 357.2535.

(4*RS*,4a*RS*,6*RS*,8a*SR*)-4-Allyl-3-benzyl-9-(2-nitrophenylsulfonyl)perhydro-6,4-(iminomethano)isoquinoline (11b). To a stirred solution of 2-nitrobenzenesulfonamide **10b** (365 mg, 0.71 mmol) and PPh_3 (413 mg, 1.77 mmol) in benzene (7 mL) was slowly added DEAD (0.28 mL, 1.77 mmol) at rt. After being stirred for 2 days, the reaction mixture was concentrated and purified by chromatography (Al_2O_3, hexane to hexane/EtOAc, 80:20) to give **11b** (0.15 g, 0.3 mmol, 42%) as a yellow oil: IR (NaCl) 3077, 2929, 2801, 1543, 1368; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.40 (dt, J = 13.2, 3 Hz, 1H, H-5), 1.44−1.54 (m, 2H, H-4a, and H-7), 1.58−1.72 (m, 1H, H-8), 1.80 (m, 1H, H-8a), 1.86−1.97 (m, 2H, H-1 and H-8), 1.97−2.06 (m, 3H, H-3, CH_2), 2.18 (dm, J = 12.2 Hz, 1H, H-5), 2.28 (m, 1H, H-7), 2.27 (tt, J = 13.2, 6.6 Hz, 1H, H-7), 2.43 (dd, J = 11.6, 1.2 Hz, 1H, H-1), 2.58 (d, J = 11.2 Hz, 1H, H-3), 3.16 (d, J = 13.6 Hz, 1H, H-10), 3.39 and 3.50 (2d, J = 13.4 Hz, 1H each, CH_2Ar), 3.99 (d, J = 12.8 Hz, 1H, H-10), 4.13 (m, $W_{1/2}$ = 9 Hz, 1H, H-6), 4.68 (dd, J = 15, 2 Hz, 1H, =CH_2), 4.89 (dd, J = 10, 2 Hz, 1H, =CH_2), 5.55 (m, 1H, =CH), 7.20−7.35 (m, 5H, ArH), 7.67 and 8.08 (2 m, 4H, H-Ns); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 24.8 (C-7), 28.7 (C-5), 30.6 (C-8), 34.6 (C-8a), 35.0 (C-4a), 36.0 (C-4), 40.9 (CH_2), 47.4 (C-6), 49.5 (C-10), 58.8 (C-3), 61.4 (C-1), 62.8 (CH_2Ar), 118.4 (=CH_2), 124.2, 126.9, 128.2, 128.6, 131.3, and 131.4 (Ar), 133.0 (=CH), 133.2, 133.6, 138.9, and 147.9 (Ar); HRMS (ESI-TOF) calcd for $C_{26}H_{32}N_3O_4S$ 482.2103 $[M + H]^+$, found 482.2108.

Acknowledgment. This research was supported by the MEC (Spain)-FEDER through project CTQ2004-04701/BQU. Thanks are also due to the DURSI (Catalonia) for Grant No. 2005SGR-00442.

Supporting Information Available: Experimental and NMR data for all compounds reported. Copies of ^{1}H and ^{13}C NMR spectra of all compounds as well as COSY and HSQC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702340W