A Novel Approach to the Enantioselective Synthesis of Nuphar Alkaloids: First Total Synthesis of (−)-(5*S*,8*R*,9*S*)-5-(3-Furyl)-8-methyloctahydroindolizidine and Total Synthesis of (−)-Nupharamine

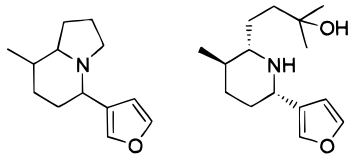
José Barluenga,* Fernando Aznar, Cristina Ribas, and Carlos Valdés

Instituto Universitario de Química Organometálica "Enrique Moles" (Unidad asociada al CSIC), Universidad de Oviedo, Julián Clavería s/n Oviedo, 33071 Asturias, Spain

Received November 24, 1998

Introduction

The asymmetric synthesis of piperidine and indolizidine alkaloids remains a field of great interest, as these types of alkaloids display a very wide range of biological activity and in many cases are scarcely available from natural sources.[1] In particular, sesquiterpenoid and triterpenoid alkaloids incorporating piperidine, indolizidine, and quinolizidine rings, isolated from aquatic plants of the genus *Nuphar*, are known as nuphar alkaloids. Representative members of this family are 5-(3-furyl)-8-methyloctahydroindolizine (**1**) and (−)-nupharamine (**2**).



1 **2**

The structural motif common to nuphar alkaloids is the presence of a trisubstituted piperidine ring with a methyl group attached at C-3 and a 3-furyl substituent at C-6. Some members of this family of alkaloids have shown antibiotic and antifungal activity.[2] Aquatic plants are not the only source of nuphar alkaloids; for example, 5-(3-furyl)-8-methyloctahydroindolizine (**1**) is a minor compound (0.0002%) detected in castoreum, a perfume extract derived from the dried scent glands of the Canadian beaver (*Castor fiber* L.).[3] The structural formula of **1** was determined exclusively by the fragmentation pattern displayed in the mass spectrum, as there was insufficient material for further characterization. Interestingly, indolizidine **1** belongs to the class of 5-substituted octahydroindolizines, compounds with marked biological activity;[4] in particular, 5-arylindolizidines have been identified recently as new antinociceptive agents with analgesic activity.[5] Three of the possible stereoisomers of **1** have been synthesized in racemic form,[6] and to the best of our knowledge, no asymmetric synthesis has been reported.

On the other hand, in the recent years, we have been interested in exploring the synthetic applications of chiral 2-amino-1,3-butadienes in asymmetric Diels−Alder cycloadditions. We have previously shown that chiral 2-aminodiene **3** reacts with aromatic *N*-trimethylsilylaldimines **4** in the presence of $ZnCl_2$ to afford, after mild hydrolysis of the [4 + 2] cycloadduct, 4-piperidones **5** with high to very high enantiomeric excesses (Scheme 1).[7] Piperidones **5** are versatile synthetic intermediates that have been used as precursors of different types of substituted pipecolic acids and that could be employed as a starting point for the preparation of enantiomerically pure piperidine alkaloids. In this paper, we wish to report our initial efforts in this direction; a novel approach to the enantioselective synthesis of nuphar alkaloids. Thus, we describe herein the first enantioselective total synthesis of nuphar indolizidine (−)-(5*S*,8*R*,9*S*)-**1**. Moreover, the generality of our methodology is illustrated by the total synthesis of (−)-nupharamine (**2**).[8]

Results and Discussion

For our study, we chose 4-piperidone **5a**, which can be obtained from the cycloaddition of 2-amino diene **3** with *N*-trimethylsilyl-3-furaldimine with 51% yield and ee >99% (HPLC). Piperidone **5a** is a very convenient starting material for the total synthesis of Nuphar alkaloids, since it already incorporates the methyl and 3-furyl substituents characteristic of nuphar alkaloids and a hydroxymethyl group attached at C2 that can be elabo-

* To whom correspondence should be addressed. E-mail: barluenga@sauron.quimica.uniovi.es.

(1) Some leading references regarding the enantioselective synthesis of piperidine and indolizidine alkaloids: (a) Holmes, A. B.; Smith, L. B.; Williams, S. F. *J. Org. Chem.* **1991**, *56*, 1393−1405. (b) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.*, **1991**, *113*, 6672−6673. (c) Shishido, Y.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1237−1239. (d) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062−9072. (e) Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332−3341. (f) Solladié, G.; Chu, G.-H. *Tetrahedron Lett.* **1996**, *37*, 111−114. (g) Cossy, J.; Cases, M.; Gómez Pardo, D. *Bull Soc. Chim. Fr.* **1997**, *134*, 141−144. (h) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549−8552. (i) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 7469−7470. (j) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182−8187. (k) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633−640. (l) Bardou, A.; Célérier, J.-P.; Llhommet, G. *Tetrahedron Lett.* **1998**, *39*, 5189−5192.

(2) (a) Wróbel, J. T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, pp 441−465. (b) Cybulski, J.; Wróbel, J. T. In *The Alkaloids*; Brossi, A. Ed.; Academic Press: New York, 1989; Vol. 35, pp 215−257.

(3) Maurer, B.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1169−1185.

(4) Daly, J. W.; Garrafo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 43, pp 185−288.

(5) (a) Carson, J. R.; Carmosin, R. J.; Vaught, J. L.; Gardocki, J. F.; Costanzo, M. J.; Raffa, R. B.; Almond, H. R., Jr. *J. Med. Chem.* **1992**, *35*, 2855−2863. (b) Pearson, W. H.; Gallagher, B. M. *Tetrahedron* **1996**, 12039−12048.

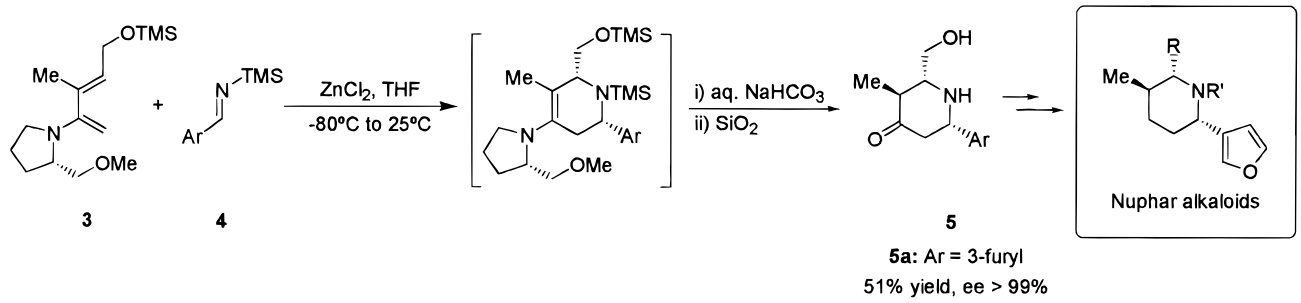
(6) For (±)-(5*S*,8*R*,9*S*)-**1**, see: (a) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664−3671. (b) Tufariello, J. J.; Dyszlewski, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1138−1140. For (±)-(5*R*,8*R*,9*S*)-**1**, see: (c) Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y.; Date, T. *Tetrahedron Lett.* **1983**, *24*, 4249−4252. (d) Kurihara, T.; Matsubara, Y.; Osaki, H.; Harusawa, S.; Yoneda, R. *Heterocycles* **1990**, *30*, 885−896. (e) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976−4977. For (±)-(5*R*,8*R*,9*R*)-**1**, see: ref 3c.

(7) (a) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403−4404. (b) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805−811.

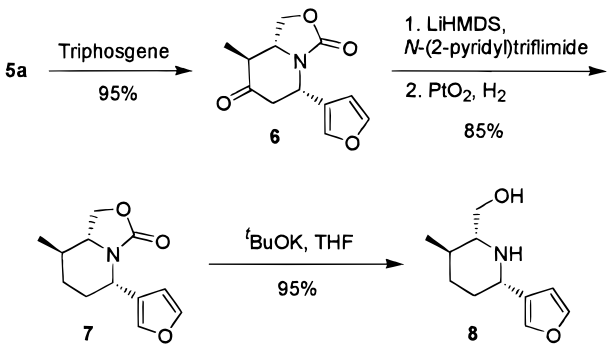
(8) Several asymmetric total syntheses of (−)-nupharamine have been reported: (a) Shimizu, I.; Yamazaki, H. *Chem. Lett.* **1990**, 777−778. (b) Aoyagi, S.; Shishido, Y.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 4325−4328. (c) Honda, T.; Ishikawa, F.; Yamane, S. *J. Chem. Soc., Chem. Commun.* **1994**, 499−500.

10.1021/jo9823240 CCC: $18.00
Published on Web 04/28/1999

Scheme 1



Scheme 2



rated to build each particular compound. Moreover, **5a** features the same absolute and relative stereochemistry of the substituents on the piperidine ring as most of the alkaloids of this family (Scheme 1). Therefore, the transformation of 4-piperidone **5a** into nuphar alkaloids would require two synthetic operations: the transformation of the chain at C2 and the deoxygenation of the ketone functionality.

We decided to carry out the deoxygenation step first, to avoid undesired side reactions due to the ketone, such as epimerization of the C3 atom during the synthesis. First, both the amino and hydroxy functionalities were simultaneously protected as the bicyclic carbamate **6**[9] (Scheme 2) by treatment of 4-piperidone **5a** with triphosgene in the presence of NEt_3. The deoxygenation was then achieved in one step by $NaBH_3CN$ reduction of the in situ generated tosylhydrazone of **6** to obtain compound **7** with a poor 33% yield.[10] Nevertheless, better results were obtained in a two-step procedure by formation of an enoltriflate followed by catalytic hydrogenation in the presence of PtO_2,[11] which afforded bicyclic carbamate **7** in 85% yield (based on 70% conversion of **6**). At this point, hydrolysis of the carbamate moiety of compound **7** employing anhydrous *t*-BuOK in THF afforded the desired piperidine **8**.

The indolizidine structure was built as depicted in Scheme 3; a one-pot process of Swern oxidation followed by a Wittig olefination reaction over compound **8** led to conjugated ester **9**. Catalytic hydrogenation of the double bond in the presence of Pd/C gave aminoester **10**, which was cyclized to indolizidone **11** in refluxing toluene. Finally, reduction of the lactam with excess of $LiAlH_4$ led to nuphar alkaloid (−)-(5*S*,8*R*,9*S*)-**1**, $[\alpha]^{20}_D = -99.0$ (*c* 1.3, CH_2Cl_2). Synthetic (−)-**1** showed an MS spectrum identical to the natural material[3] and IR and ^{13}C NMR spectra identical to those of previously reported synthetic (±)-**1**.[6a]

Chiral piperidine **8** can be regarded as a key intermediate in the total synthesis of other nuphar alkaloids. The synthetic sequence developed to elaborate the C2 side chain of (−)-nupharamine is summarized in Scheme 3. First, *N*-Cbz-protected hydroxymethylpiperidine **12** was obtained from **8** in 59% yield after a three-step sequence that involves protection of the hydroxy group as a TBDMS ether, formation of the carbamate by treatment with benzyl chloroformate, and deprotection of the silyl ether in acidic media. Then, the same one-pot procedure of Swern oxidation followed by Wittig olefination described above, led to protected conjugated ester **13** with excellent yield. Careful hydrogenation of the double bond of **13** (H_2 (1 atm), Pd/C, EtOH, rt, 3.5 h) gave ester **14**,[12] which was then treated with an excess of MeLi to give tertiary alcohol **15**. Finally, (−)-nupharamine **2** was obtained after deprotection of the benzyl carbamate. Spectroscopic data (IR, MS, and ^{13}C NMR) and optical rotation of synthetic (−)-nupharamine **2** were in accordance with those previously reported.[8]

In summary, we have described a new approach to the enantioselective synthesis of nuphar alkaloids, exemplified by the first enantioselective synthesis of (−)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizine alkaloid and the total synthesis of (−)-nupharamine. Our approach demonstrates that 4-piperidones derived from chiral 2-aminodienes are useful precursors of piperidine alkaloids. It is worth pointing out that the enantiomers of these alkaloids are equally approachable in optically pure form by this synthetic approach by employing the chiral 2-aminodiene derived from (*R*)-2-methoxymethylpyrrolidine. Additionally, derivatives with other aromatic rings instead of the 3-furyl group would also be accessible, and furthermore, the keto group of the starting 4-piperidone will allow for the synthesis 4-substituted derivatives.

Experimental Section

General Methods. The same experimental techniques were used as reported previously; see ref 5b. Compounds **4a** and **6** were prepared as described in refs 5b and 7, respectively.

Synthesis of (−)-(2*S*,5*R*,6*R*)-2-(3-Furyl)-5-methyl-1-aza-8-oxabicyclo[4,3,0]nonan-9-one (7). (a) The Hydrazone Method. To a solution of carbamate **6** (3.40 mmol, 800 mg) in DMF (8.5 mL) were successively added sulfolane (8.5 mL), *p*-toluensulfonylhydrazide (3.97 mmol, 740 mg), and *p*-toluen-

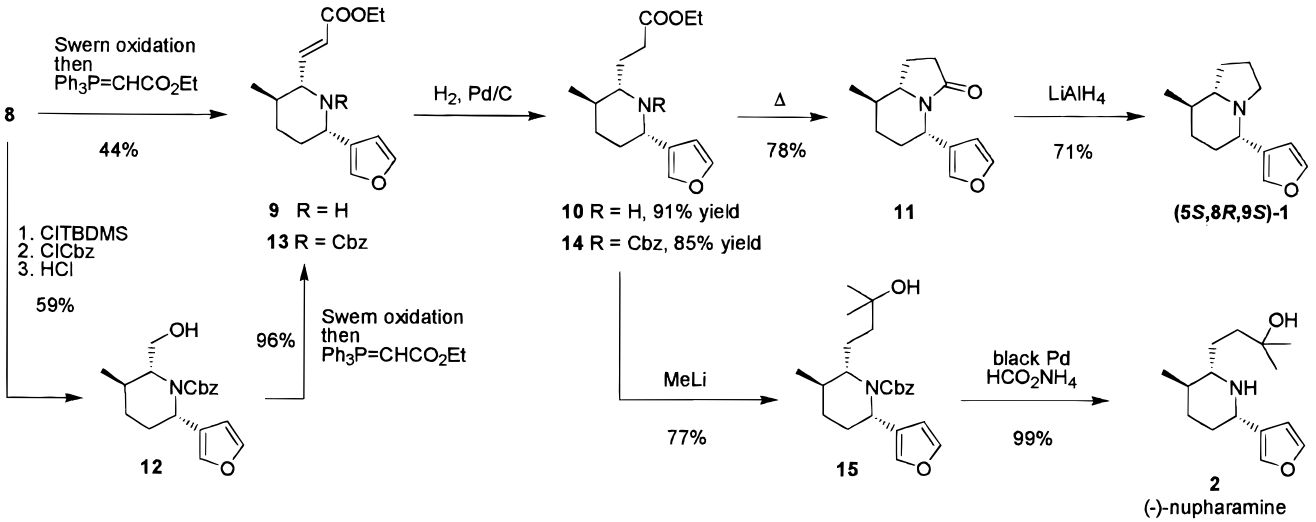
(9) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. *J. Org. Chem.* **1998**, *63*, 3918−3924.

(10) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662−3668.

(11) (a) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182−8187. (b) Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1982**, *23*, 117−120.

(12) Longer reaction times and/or larger quantities of Pd/C led to deprotection of the Cbz group and, ultimately, to the reduction of the furan ring.

Scheme 3



sulfonic acid (0.45 mmol, 86 mg). The resulting solution was heated at 110 °C, and $NaBH_4$ was added in three portions at 1 h intervals. Then, 1 h after the last addition, the reaction mixture was cooled, and H_2O (10 mL) was carefully added, followed by EtOAc (10 mL). The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Sulfolane and DMF were eliminated by Kugelröhr distillation (0.01 mmHg, 90 °C, 6 h). Column chromatography (SiO_2, hexane/EtOAc 2:1) of the residue afforded bicyclic compound **7** (33% yield, 248 mg).

(b) The Enoltriflate Method. To a solution of ketone **6** (200 mg, 0.82 mmol) in 15 mL of dry THF, under nitrogen atmosphere and cooled to −80 °C, was added dropwise 1 mL (1 mmol) of 1 M solution lithium hexamethyldisilylamide in THF. After the reaction was stirred for 90 min at −80 °C, a solution of 500 mg (1.4 mmol) of freshly prepared *N*-(2-pyridyl)triflimide[13] in 2 mL of THF was added, and the stirring was continued at −80 °C for 90 min. The cold bath was removed, and the reaction was quenched with 2 mL of H_2O. The reaction mixture was diluted with 40 mL of Et_2O, dried over Na_2SO_4, and concentrated in vacuo. The reaction crude contained a mixture of the enoltriflate and the starting material **6**, which were separated by column chromatography (SiO_2, hexane/EtOAc 3:1−1:1). The first fraction (R_f = 0.34, SiO_2, hexane/EtOAc 1:1) consisted in the desired enoltriflate (202 mg, 0.55 mmol), and the second fraction (R_f = 0.24, SiO_2, hexane/EtOAc 1:1) afforded the unreacted ketone (0.24 mmol, 60 mg): yield 96% (based on 70% conversion of **6**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m; 1H), 7.41 (m; 1H), 6.42−6.40 (m; 1H), 5.79 (m; 1H), 5.16 (m; 1H), 4.51 (dd, J = 8.2, 7.4 Hz; 1H), 3.99 (dd, J = 10.6, 8.2 Hz; 1H), 3.77 (ddd, J = 10.6, 9.0, 7.4 Hz; 1H), 2.96−2.80 (m; 1H), 1.20 (d, J = 7.1 Hz; 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 148.0, 142.2, 141.2, 121.5, 120.1, 109.1, 66.6, 59.9, 47.1, 37.5, 11.9 ppm. The enoltriflate was hydrogenated according with the following procedure: A flask containing the enoltriflate (90 mg, 0.24 mmol) and 6.8 mg of PtO_2 was capped with a rubber septum, evacuated with a needle, and filled with hydrogen with a balloon. Then, 8 mL of EtOH was added to the flask with a syringe, and the mixture was stirred at room temperature. The reaction was monitored by TLC (SiO_2, hexane/EtOAc/methylene chloride 1:1:1), and the septum was removed when the spot of the starting material disappeared (R_f = 0.37), typically 6−8 h (longer reaction times will result in hydrogenation of the furan ring). The reaction was diluted with diethyl ether, filtered through Celite, and concentrated under reduced pressure to obtain a pale yellow oil. The crude was purified by flash chromatography (SiO_2, hexane/EtOAc 2:1), affording 47 mg of carbamate **7** (yield 89%). Overall yield of the two steps (based on 70% conversion of **6**) 85%: R_f = 0.27 (SiO_2, hexane/EtOAc 1:1); $[\alpha]^{20}_D$ = −69.3 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.39 (m; 2H), 6.44−6.43 (m; 1H), 4.38 (dd, J = 8.6, 7.6 Hz; 1H), 4.12 (dd, J = 10.9, 3.6 Hz; 1H), 3.87 (t, J = 8.6 Hz; 1H), 3.26 (td, J = 9.2, 7.6 Hz; 1H), 1.98−1.47 (m; 4H), 1.35−1.14 (m; 1H), 0.94 (d, J = 6.4 Hz; 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 142.3, 139.2, 123.8, 109.6, 66.2, 62.4, 50.1, 34.5, 33.2, 31.6, 16.6 ppm. Anal. Calcd for $C_{12}H_{15}NO_3$ (221.26): C, 65.14; H, 6.83; N, 6.33. Found: C, 64.76; H, 6.69; N, 6.22.

Deprotection of the Bicyclic Carbamate. Synthesis of (−)-(2*R*,3*R*,6*S*)-6-(3-Furyl)-2-hydroxymethyl-3-methylpiperidine (8). To a solution of carbamate **7** (1.10 mmol, 240 mg) in dry THF (15 mL) cooled at 0 °C was added *t*-BuOK (4.40 mmol, 495 mg). After 30 min of stirring at this temperature, the reaction mixture was poured over an aqueous HCl solution (1 N, 5 mL), and the resulting mixture was made basic by addition of Na_2CO_3. The organics were extracted with EtOAc (5 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Flash column chromatography (Al_2O_3) of the residue afforded piperidine **8** (95% yield, 205 mg): colorless oil; R_f = 0.33 (Al_2O_3, EtOAc); $[\alpha]^{20}_D$ = −22.9 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.37 (m; 2H), 6.43−6.41 (m; 1H), 3.79 (dd, J = 11.0, 3.1 Hz; 1H), 3.64 (dd, J = 10.7, 2.6 Hz; 1H), 3.51 (dd, J = 11.0, 7.6 Hz; 1H), 2.47 (ddd, J = 9.5, 7.6, 3.1 Hz; 1H), 1.93−1.79 (m; 2H), 1.61−1.13 (m; 3H), 0.91 (d, J = 6.1 Hz; 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 138.5, 128.4, 108.9, 63.8, 63.1, 52.5, 33.7, 32.8, 32.2, 17.8 ppm; HRMS (EI) calcd for $C_{11}H_{16}NO_2$ (M^+ − H) 194.1181, found 194.1183.

(−)-(2*R*,3*R*,6*S*)-(*E*)-2-(2-Ethoxycarbonyl-1-ethenyl)-6-(3-furyl)-3-methylpiperidine (9). Dry DMSO (1.31 mmol, 93 mL) was added dropwise to a cooled (−65 °C) solution of $(COCl)_2$ (0.66 mmol, 58 mL) in dry CH_2Cl_2 (10 mL), and stirring was continued at this temperature for 20 min. Then, a solution of alcohol **8** (0.50 mmol, 98 mg) in dry CH_2Cl_2 (7 mL) was added dropwise, and the reaction mixture was stirred at −65 °C for 90 min. Thereafter, NEt_3 (1.97 mmol, 275 mL) was added and the temperature was permitted to reach −15 °C during 90 min. Afterward, $Ph_3P{=}CHCO_2Et$ (0.75 mmol, 260 mg) was added in one portion, and the reaction mixture was warmed to room temperature over 90 additional min. The reaction mixture was poured over brine (10 mL), and the aqueous layer was extracted with CH_2Cl_2; the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. Column chromatography (SiO_2) of the residue afforded conjugated ester **9** (44% yield, 58 mg): yellow oil; R_f = 0.57 (SiO_2, CH_2Cl_2/EtOAc 2:1); $[\alpha]^{18}_D$ = −31.0 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.35 (m; 2H); 6.95 (dd, J = 15.7, 7.9 Hz; 1H), 6.41−6.39 (m; 1H), 5.98 (dd, J = 15.7, 0.9 Hz; 1H), 4.24−4.13 (m; 1H), 4.19 (q, J = 7.0 Hz; 2H), 3.67 (dd, J = 11.0, 2.8 Hz; 1H), 2.99 (ddd, J = 9.1, 7.9, 0.9 Hz; 1H), 1.94−1.18 (m; 4H), 1.28 (t, J = 7.0 Hz; 3H), 0.88 (d, J = 6.4 Hz; 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.3, 149.3, 142.8, 138.4, 128.8, 122.1, 108.9, 65.2, 60.3, 52.6, 35.4, 33.6, 33.3, 18.5, 14.1 ppm.

(13) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1996**, *74*, 77−81.

(−)-(2*S*,3*R*,6*S*)-2-(2-Ethoxycarbonylethyl)-6-(3-furyl)-3-methylpiperidine (10). A suspension of conjugated ester **9** (0.19 mmol, 50 mg), EtOH (8 mL), and Pd/C (50 mg) was degassed through a freezing-vacuum-melting sequence (three turnovers); the flask was finally filled with H_2 with the aid of a balloon (1 atm), and a vigorous stirring was kept for 6 h at room temperature. Then, the reaction mixture was filtered through a Celite pad, the retained solid was washed with EtOH (3 × 3 mL), and the organic solvent was eliminated under vacuum. Flash column chromatography (SiO_2) of the residue afforded ester **10** (91% yield, 46 mg): colorless oil; R_f = 0.40 (SiO_2, CH_2Cl_2/EtOAc 1:1); $[\alpha]^{23}_D$ = −39.3 (*c* 1.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.33 (m; 2H), 6.39 (s; 1H), 4.12 (q, *J* = 7.3 Hz; 2H), 3.58 (dd, *J* = 11.2, 2.2 Hz; 1H), 2.43 (dd, *J* = 8.8, 6.7 Hz; 1H), 2.42 (t, *J* = 7.7 Hz; 1H), 2.31 (td, *J* = 8.4, 3.0 Hz; 1H), 2.07−1.95 (m; 1H), 1.88−1.77 (m; 2H), 1.69−1.62 (m; 4H), 1.25 (t, *J* = 7.3 Hz; 3H), 0.90 (d, *J* = 6.0 Hz; 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 142.7, 138.3, 129.4, 109.1, 62.3, 60.2, 53.2, 35.4, 34.1, 33.8, 30.5, 28.5, 18.3, 14.2 ppm.

(−)-(2*S*,5*R*,6*S*)-2-(3-Furyl)-5-methyl-1-azabicyclo[4.3.0]-nonan-9-one (11). A solution of amino ester **10** (0.15 mmol, 42 mg) in dry toluene (6 mL) was refluxed for 48 h. Then, the reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under vacuum. The resulting yellow oil was purified by column chromatography (SiO_2) to afford lactam **11** (78% yield, 28 mg): colorless oil; R_f = 0.40 (SiO_2, CH_2Cl_2/EtOAc 3:1); $[\alpha]^{20}_D$ = −74.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36−7.33 (m; 1H), 7.33 (s; 1H), 6.38−6.37 (m; 1H), 4.41 (dd, *J* = 7.6, 4.0 Hz; 1H), 3.12 (td, *J* = 10.1, 6.1 Hz; 1H), 2.39−2.14 (m; 3H), 1.95−1.16 (m; 6H), 0.96 (d, *J* = 6.4 Hz; 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.0, 142.6, 138.7, 126.2, 109.8, 63.4, 49.0, 36.4, 31.4, 31.2, 29.9, 25.1, 17.5 ppm; HRMS (CI) calcd for $C_{13}H_{18}NO_2$ (M + H) 220.1338, found 220.1330.

(−)-(5*S*,8*R*,9*S*)-5-(3-Furyl)-8-methyloctahydroindolizine [(5*S*,8*R*,9*S*)-1]. To a solution of lactam **11** (0.13 mmol, 28 mg) in dry THF (8 mL) cooled to 0 °C was added $LiAlH_4$ (0.52 mmol, 20 mg), and the reaction mixture was then refluxed for 2.5 h. The reaction was allowed to cool to room temperature, and an aqueous saturated solution of Na_2SO_4 was added dropwise until the reaction mixture became clear, with a solid stuck to the walls of the flask. The liquid was decanted, the solid was washed with THF (5 × 2 mL), and the resulting organic solution was concentrated under vacuum. Flash column chromatography (Al_2O_3) of the residue afforded indolizidine (5*S*,8*R*,9*S*)-**1** (71% yield, 19 mg): colorless oil; R_f = 0.48 (Al_2O_3, hexane/EtOAc 10:1); $[\alpha]^{20}_D$ = −99.0 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m; 2H), 6.44 (s; 1H), 2.91 (dd, *J* = 8.4, 5.7 Hz; 1H), 2.88 (td, *J* = 8.8, 2.2 Hz; 1H), 1.98−1.87 (m; 2H), 1.82−1.39 (m; 8H), 1.13−1.02 (m; 1H), 0.90 (d, *J* = 6.6 Hz; 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 139.3, 128.0, 109.6, 71.4, 59.7, 53.1, 36.2, 34.0, 33.8, 28.9, 20.0, 18.8 ppm; MS (EI) *m*/*z* 205 (79), 190 (24), 176 (11), 162 (16) 136 (51), 94 (100); HRMS (EI) calcd for $C_{13}H_{20}NO$ (M^+) 205.1466, found 205.1461; HRMS (FAB) calcd for $C_{13}H_{20}NO$ (M + H) 206.1545, found 206.1536.

(−)-(2*R*,3*R*,6*S*)-*N*-Benzyloxycarbonyl-6-(3-furyl)-2-hydroxymethyl-3-methylpiperidine (12). To a solution of piperidine **8** (1.05 mmol, 205 mg) in MeCN (15 mL) were successively added imidazole (2.63 mmol, 179 mg) and *tert*-butyldimethylsilylchlorosilane (2.63 mmol, 397 mg); the mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of H_2O (10 mL) and EtOAc (15 mL), and the aqueous layer was extracted with EtOAc; the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Column chromatography (SiO_2) of the residue afforded (−)-(2*R*,3*R*,6*S*)-2-(*tert*-butyldimethylsilyloxymethyl)-6-(3-furyl)-3-methylpiperidine (220 mg, 67% yield) as a colorless oil: R_f = 0.30 (SiO_2, hexane/Et_2O 3:1); $[\alpha]^{25}_D$ = −47.5 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.37 (m; 2H), 6.40−6.39 (m; 1H), 3.88 (dd, *J* = 9.8, 3.1 Hz; 1H), 3.62 (dd, *J* = 11.0, 2.6 Hz; 1H), 3.49 (dd, *J* = 9.8, 8.9 Hz; 1H), 2.43 (td, *J* = 8.9, 3.1 Hz; 1H), 1.92−1.75 (m; 2H), 1.61−1.10 (m; 3H), 0.92−0.84 (m; 12H), 0.07 (s, 6H) ppm. The silylated derivative obtained was dissolved in MeCN (10 mL). To the stirred solution were successively added aqueous saturated K_2CO_3 (10 mL), and benzylchloroformate (2.10 mmol, 300 μL). The biphasic mixture was vigorously stirred for 4 h, and then the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Column chromatography (SiO_2) of the residue afforded (−)-(2*R*,3*R*,6*S*)-*N*-benzyloxycarbonyl-2-(*tert*-butyldimethylsilyloxymethyl)-6-(3-furyl)-3-methylpiperidine (310 mg, 99% yield) as a colorless oil: R_f = 0.45 (SiO_2, hexane/Et_2O 4:1); $[\alpha]^{20}_D$ = −66.6 (*c* 2.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44−7.25 (m; 7H), 6.26 (s; 1H), 5.36−5.30 (m; 1H), 5.27 (d, *J* = 12.5 Hz; 1H), 5.19 (d, *J* = 12.5 Hz; 1H), 4.11−4.00 (m; 1H), 3.83−3.19 (m; 2H), 2.22−1.79 (m; 4H), 1.40−1.25 (m; 1H), 1.11 (d, *J* = 7.0 Hz; 3H), 0.83 (s; 9H), −0.06 (s; 6H) ppm. The O,N-diprotected piperidine obtained was then dissolved in THF (15 mL), and aqueous HCl (3N, 10 mL) was added. After 30 min of stirring, H_2O (10 mL) and EtOAc (10 mL) were added; the aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Column chromatography (SiO_2) of the residue afforded hydroxypiperidine **12** (88% yield, 203 mg): colorless oil; R_f = 0.23 (SiO_2, hexane/EtOAc 2:1); $[\alpha]^{22}_D$ = −75.6 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46−7.28 (m; 7H), 6.33 (s; 1H), 5.41−5.32 (m; 1H), 5.27 (d, *J* = 12.2 Hz; 1H), 5.18 (d, *J* = 12.2 Hz; 1H), 4.22−4.10 (m; 1H), 3.42 (dd, *J* = 11.3, 7.3 Hz; 1H), 3.36 (dd, *J* = 11.3, 7.9 Hz; 1H), 2.20−1.78 (m; 4H), 1.43−1.23 (m; 1H), 1.12 (d, *J* = 7.0 Hz; 3H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 143.2, 138.7, 136.5, 128.4, 127.9, 127.7, 127.6, 109.7, 67.4, 64.2, 58.8, 45.8, 27.2, 22.2, 22.1, 18.9 ppm. Anal. Calcd for $C_{19}H_{23}NO_4$ (329.40): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.04; H, 7.03; N, 4.25.

(−)-(2*R*,3*R*,6*S*)-(*E*)-*N*-Benzyloxycarbonyl-2-(2-ethoxycarbonyl-1-ethenyl)-6-(3-furyl)-3-methylpiperidine (13). The same experimental procedure described for compound **9** was applied to alcohol **12** (0.50 mmol, 200 mg). Column chromatography (SiO_2) of the resulting residue afforded conjugated ester **13** (96% yield, 165 mg): yellow oil; R_f = 0.38 (SiO_2, hexane/EtOAc 3:1); $[\alpha]^{22}_D$ = −46.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47−7.24 (m; 7H), 6.66 (dd, *J* = 15.9, 7.3 Hz; 1H), 6.26−6.24 (m; 1H), 5.75 (dd, *J* = 15.9, 1.4 Hz; 1H), 5.46−5.38 (m; 1H), 5.25 (d, *J* = 12.4 Hz; 1H), 5.19 (d, *J* = 12.4 Hz; 1H), 4.68−4.59 (m; 1H); 4.12 (q, *J* = 7.0 Hz; 2H), 2.21−1.87 (m; 4H), 1.44−1.36 (m; 1H), 1.25 (t, *J* = 7.0 Hz; 3H), 1.12 (d, *J* = 7.0 Hz; 3H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 156.3, 147.6, 142.9, 139.2, 136.3, 128.3, 127.9, 127.7, 126.9, 121.4, 110.2, 67.4, 60.0, 57.5, 45.7, 30.4, 22.2, 21.9, 18.1, 14.0 ppm; HRMS (EI) calcd for $C_{23}H_{27}NO_5$ 397.1889, found 397.1907.

(−)-(2*S*,3*R*,6*S*)-*N*-Benzyloxycarbonyl-2-(2-ethoxycarbonylethyl)-6-(3-furyl)-3-methylpiperidine (14). An adaptation of the experimental procedure described for compound **10** was applied to alcohol **13** (0.32 mmol, 127 mg), carrying out the hydrogenation for 3.5 h with a smaller ammount of Pd/C (10 mg). Flash column chromatography (SiO_2) of the resulting residue afforded ester **14** (85% yield, 110 mg): colorless oil; R_f = 0.39 (SiO_2, hexane/EtOAc 4:1); $[\alpha]^{23}_D$ = −79.1 (*c* 2.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m; 7H), 6.33 (s, br; 1H), 5.39 (s, br; 1H), 5.26 (d, *J* = 12.5 Hz; 1H), 5.11 (d, *J* = 12.5 Hz; 1H), 4.08−3.98 (m; 1H), 3.99 (q, *J* = 7.3 Hz; 2H), 2.22−1.99 (m; 4H), 1.91−1.64 (m; 2H), 1.55 (quint, *J* = 7.1 Hz; 1H), 1.37−1.18 (m; 2H), 1.16 (t, *J* = 7.3 Hz; 3H), 1.05 (d, *J* = 7.1 Hz; 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 156.8, 142.8, 138.6, 136.5, 128.3, 127.8, 127.6, 127.5, 110.1, 67.1, 59.9, 56.4, 45.1, 31.3, 31.0, 29.3, 21.9, 21.4, 18.5, 14.0 ppm; HRMS (EI) calcd for $C_{23}H_{29}NO_5$ 399.2046, found 399.2057.

(−)-(2*S*,3*R*,6*S*)-*N*-Benzyloxycarbonylnupharamine (15). To a solution of ester **14** (0.24 mmol, 96 mg) in dry THF (15 mL) cooled to −70 °C was added dropwise MeLi (1.6M in Et_2O, 1.15 mmol, 720 mL), and the mixture was stirred at this temperature for 15 min. Then, the reaction was quenched by the slow addition of H_2O (5 mL), and the cooling bath was removed. The reaction was allowed to reach rt and then extracted with EtOAc; the combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was eliminated under vacuum. Column chromatography (SiO_2) of the residue afforded compound **15** (77% yield, 72 mg): colorless oil; R_f = 0.25 (SiO_2, hexane/EtOAc 2:1); $[\alpha]^{24}_D$ = −82.5 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.31 (m; 7H), 6.37 (s; 1H), 5.39 (s, br; 1H), 5.22 (s; 2H), 4.08−3.94 (m; 1H), 2.17−1.23 (m; 9H), 1.07 (d, *J* = 7.0 Hz; 3H), 0.99 (s; 3H), 0.96 (s; 3H) ppm; ^{13}C NMR (50 MHz,

$CDCl_3$) δ 157.0, 142.5, 138.9, 136.7, 128.4, 128.1, 127.9 (×2), 110.7, 70.4, 67.1, 57.5, 45.1, 40.5, 31.3, 29.3, 29.0, 28.6, 22.0, 21.6, 18.7 ppm; HRMS (EI) calcd for $C_{23}H_{31}NO_4$ 385.2253, found 385.2249.

(−)-Nupharamine (2). To a solution of piperidine **15** (0.16 mmol, 62 mg) in MeOH (10 mL) were added black Pd (10 mg) and HCO_2NH_4 (0.80 mmol, 50 mg), and the mixture was vigorously stirred at room temperature for 14 h. Afterward, the solvent was removed under vacuum, and the residue obtained was dissolved in EtOAc (6 mL), aqueous saturated $NaHCO_3$ (3 mL), and brine (3 mL). The aqueous layer was extracted with EtOAc; the combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was eliminated under vacuum. Flash column chromatography (Al_2O_3) of the residue afforded alkaloid **2** (99% yield, 40 mg): colorless oil; R_f = 0.37 (Al_2O_3, CH_2Cl_2/EtOAc 3:1); $[\alpha]^{20}_D$ = −29.5 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s; 2H), 6.41 (s; 1H), 3.61 (dd, *J* = 11.2, 2.1 Hz; 1H), 2.43−2.33 (m; 1H), 1.90−1.64 (m; 4H); 1.61−1.39 (m; 4H), 1.28−1.12 (m; 2H); 1.19 (s; 3H), 1.17 (s; 3H), 0.89 (d, *J* = 6.4 Hz; 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 138.3, 128.7, 109.1, 68.7, 62.8, 52.9, 39.5, 34.0, 33.7, 33.4, 30.1, 29.1, 28.3, 18.4 ppm; MS (EI) *m*/*z* 251 (2), 236 (8), 164 (100), 107 (33) 94 (36). HRMS (EI) calcd for $C_{15}H_{25}NO_2$ 251.1885, found 251.1879.

Acknowledgment. We acknowledge financial support of this work by the Comisión Asesora de Investigación Científica y Técnica DGICYT of Spain (PB-92 1005). A FICYT predoctoral fellowship to C.R. from the Regional Government of the Principado de Asturias is gratefully acknowledged.

Supporting Information Available: Copies of ^{13}C NMR and DEPT 3 NMR spectra of all the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9823240