Addition of a Chiral Boron Enolate to Cyclic *N*-Acyliminium Ions. Stereocontrolled Synthesis of the Pyrrolizidine Ring System

Ronaldo A. Pilli* and Dennis Russowsky

Instituto de Química, Unicamp, Cx. Postal 6154, 13081-970- Campinas, SP Brasil

Received July 19, 1995

The synthesis of the 1-azabicyclo[3.3.0]octane ring system has attracted the interest of synthetic chemists due to the diverse and important biological properties displayed by the corresponding pyrrolizidine alkaloids.[1]

Among the methodologies employed for assembling homochiral pyrrolizidine systems at the different oxidation levels found in Nature,[2] the intramolecular cyclization of derivatives of (*S*)- and (*R*)-malic acid have been successfully explored.[3b,c,4]

As an extension of our studies on the addition of silyl enol ethers and silyl ketene acetals to activated Schiff bases,[5] we envisaged that the substitution pattern present in (+)-hastanecine (**1a**)[3] or (+)-dihydroxyheliotridane (**1b**)[3d] would be readily available through an intermolecular addition of carbon nucleophiles to *N*-acyliminium ion **4** provided that good levels of diastereoselection were achieved (Figure 1). While we reasoned that the stereochemistry at C-8 would be directed by the steric hindrance and/or electronic assistance provided by the acetoxy group,[6,7] the outcome of the stereogenic center at C-1 was not clear from the outset.

During our preliminary studies, racemic succinimide **5** was prepared in 89% yield according to a previously described procedure (Scheme 1).[6] Sodium borohydride reduction took place regioselectively, and after neutralization (10% HCl, rt) and acetylation **6** was obtained as a 1:1 mixture of stereoisomers at C-2. However, when neutralization was carefully carried out with 1% HCl at −23 °C, a 19:1 mixture of **6a**:**6b** was isolated**.** The stereochemistry of the diacetoxy lactams was assigned after analysis of the ^{1}H-NMR spectra: in the major isomer H-5 (δ 6.28) appeared as a doublet ($J_{H_5-H_4}$ = 5.5 Hz) while in the minor one it appeared as a singlet (δ 6.02), the expected pattern for the cis and trans stereochemistry, respectively.[8]

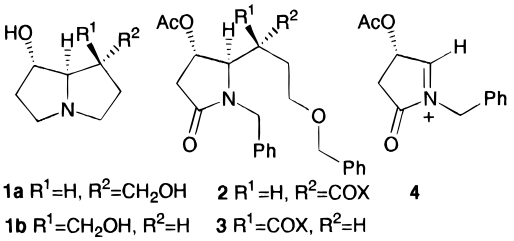
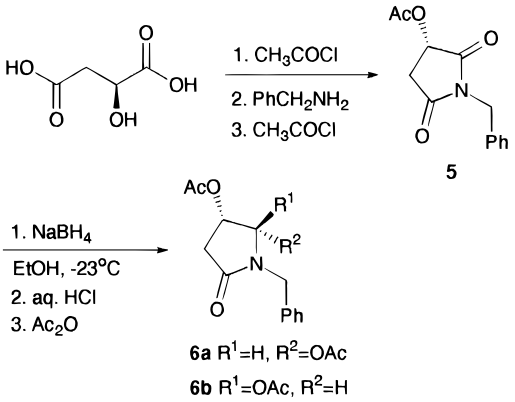
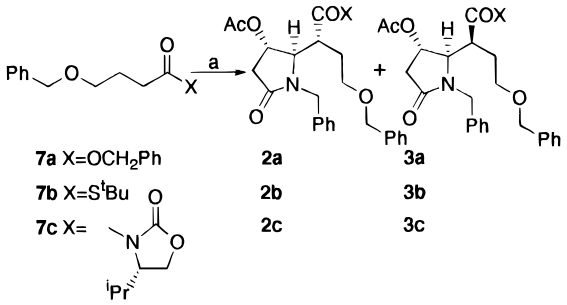


Figure 1.

Scheme 1



Scheme 2



a. for **7a**: i. LDA, THF, -78°C; ii. TMSCl; iii. **6a,b**, TMSOTf (45%); for **7b**: i. LDA, THF, -78°C; then TBDMSCl (62%); ii. **6a,b**, TMSOTf (49%); for **7c**: ^{n}Bu$_2$BOTf, ^{i}Pr$_2$NEt, CH_2Cl_2, 0°C; then **6a,b** (53%).

Our initial attempts focused on the addition of the silyl ketene acetal and the silyl ketene thioacetal prepared from **7a** and **7b**[9] , respectively, to racemic *N*-acyliminium ion **4** (Scheme 2). As previously described for Schiff bases[5] and α-ethoxypiperidines and pyrrolidines,[10] nucleophilic addition proceeded in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to afford a 1:1 ratio of diastereoisomers **2a,b**/**3a,b**, in 45% and 49% yield, respectively.[11]

The trans relationship between the substituents at C-7 and C-8 (hastanecine numbering system) in both diastereoisomers was apparent from the splitting pattern

(1) Rizk, A. F. M., Ed. *Natural Occurring Pyrrolizidine Alkaloids*; CRC: Boston, 1991.

(2) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672 and references cited therein.

(3) For total synthesis of (+)- and (−)-hastanecine (**1a**), see: (a) Aasen, A. J.; Culvenor, C. C. J.; Smith, L. W. *J. Org. Chem.* **1969**, *34*, 4137. (b) Hart, D. J.; Yang, T-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135. (c) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425. (d) Mulzer, J.; Scharp, M. *Synthesis* **1993**, 615. For total synthesis of (+)-dihydroxyheliotridane (**1b**) see, ref 3d.

(4) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959.

(5) Pilli, R. A.; Russowsky, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1053. (b) Pilli, R. A.; Alves, C. F., unpublished results.

(6) (a) Koot, W.-J., van Ginkel, R., Kranenburg, M., Hiemstra, H., Louwrier, S., Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401. (b) Yoda, H., Kitayama, H., Katagiri, T.; Tanabe, K. *Tetrahedron* **1992**, *48*, 3313.

(7) Bernardi, A., Micheli, F., Potenza, D., Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949.

(8) The regiochemical outcome of the reaction was correlated with LUMO's atomic coefficients at C-2 and C-5 (0.194 and 0.088, respectively) and the transition state corresponding to the approach of the borohydride anion to the re face of the carbonyl at C-2 was shown to be *ca.* 1 kcal mol^{-1} more stable than the one involved in the approach to the si face.

(9) Sudo, R., Kaneda, A.; Itoh, N. *J. Org. Chem.* **1967**, *32*, 1844.

(10) (a) Pilli, R. A., Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, *34*, 2729. (b) Pilli, R. A., Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717.

(11) The composition of the mixture **6a**/**6b** proved to be of no consequence to the stereochemical outcome of the nucleophilic addition. The same product distribution was observed when either a 1:1 or a 19:1 mixture of **6a**/**6b** was employed.

S0022-3263(95)01302-8 CCC: $12.00

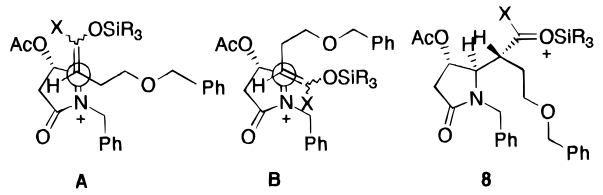


Figure 2.

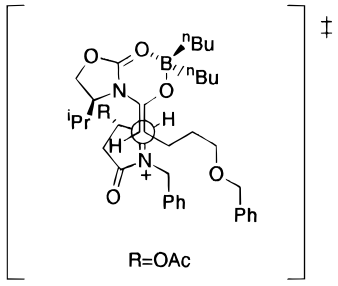


Figure 3.

of H-7 which appeared as a doublet for **2a**, **2b**, and **3a** (J = 6.9, 6.3, and 6.5 Hz, respectively) and as a double doublet for **3b** (J = 6.3 and 1.2 Hz). The stereocontrol exerted by the substituent at C-7 was ascribed both to the steric hindrance and to the electronic stabilization of the *N*-acyliminium ion by the proximal acetoxy group.

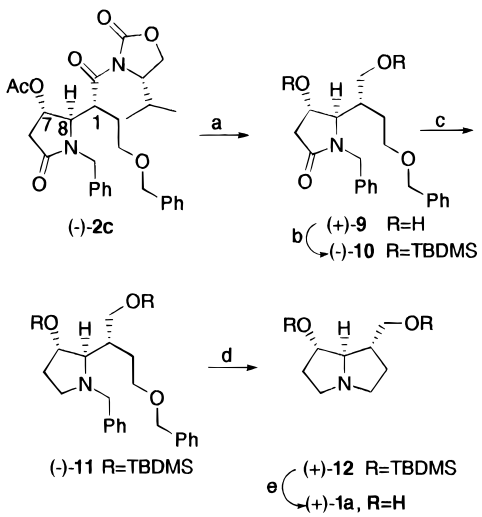
The lack of stereochemical control in the formation of the stereogenic center at C-1 could conceivably arise from the intervention of the equally favored antiperiplanar (A) and synclinal (B) approaches or to a facile enolization involving intermediate **8** (Figure 2).

In order to improve the diastereofacial selectivity of the nucleophile and reduce the Brönsted acidity of H-1 we decided to explore the discriminating ability of chiral boron enolates. Despite their extensive use in enantioselective aldol condensations[12] their role in the preparation of β-amino carbonyl compounds remains to be fully explored.[13,14]

Our rationale to explore the ability of the boron enolate derived from Evans' chiral imide **7c** to control the stereochemistry at C-1 was based on a conceivable antiperiplanar approach of the chelated conformation of the (*Z*)- enolate to (*S*)-**4** which would accommodate the facial preferences of both reagents (Figure 3). This topology resembles the one proposed for the alkylation of metal enolates of chiral oxazolidinones and has also been postulated by Fuentes in his studies on the addition of boron enolates to acylimines.[13]

After some experimentation, we developed a protocol which allowed us to carry out the addition of a boron enolate to an *N*-acyliminium ion formed *in situ* from the corresponding α-acetoxy lactam and $^{n}Bu_2BOTf$:[15] addition

Scheme 3



a. $LiBH_4$, THF (67%); b.TBDMSOTf, 2,6-lutidine, CH_2Cl_2 (64%); c. $BH_3.Me_2S$, THF (73%); d. i. H_2, $Pd(OH)_2$, EtOAc; ii. Ph_3P, Et_3N, CH_3CN (56%); e. HF, CH_3CN (48%).

of **6a**/**6b**, prepared from (−)-**5**, to a CH_2Cl_2 solution of the boron enolate from (+)-**7c** containing a 20 mol % excess of $^{n}Bu_2BOTf$ afforded (−)-**2c**, in 53% yield, as a single stereoisomer.[16] The trans relationship of the substituents at C-7 and C-8 was assigned after analysis of its ^{1}H-NMR spectrum: no coupling was observed between H-7 and H-8 (δ 5.76 and 3.40, respectively) which appeared as doublets (J = 6.6 and 4.8 Hz, respectively). The stereochemistry at C-1 was unambiguously established after its conversion to the corresponding pyrrolizidine, as depicted in Scheme 3.

Reduction of (−)-**2c** with excess of $LiBH_4$ (5.0 equiv) afforded diol (+)-**9** in 67% yield and allowed recovery of the chiral auxiliary in 72% yield after column chromatography. For purification purposes and in order to avoid unwanted reaction at the hydroxyl functionalities in the forthcoming transformations, (+)-**9** was converted to the corresponding silyl ether (−)-**10** in 64% yield after treatment with TBDMSOTf in CH_2Cl_2 and 2,6-lutidine. Lactam reduction with $BH_3{\cdot}Me_2S$ afforded pyrrolidine (−)-**11**, in 73% yield.

Hydrogenolysis with catalysis by $Pd(OH)_2$, followed by treatment of the crude amino alcohol with Ph_3P in CCl_4, afforded the protected pyrrolizidine (+)-**12**, in 56% overall yield. Deprotection (HF/CH_3CN) gave the corresponding

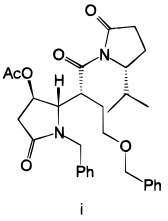
(12) (a) Evans, D. A., Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A., Nelson, J. V., Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

(13) Fuentes, L. M., Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.

(14) (a) Nagao, Y., Kumagai, T., Tamai, S., Abe, T., Kuramoto, Y., Taga, T., Aoyagi, S., Nagase, Y., Ochiai, M., Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Nagao, Y., Dai, W.-M.; Ochiai, M., *Tetrahedron Lett.* **1988**, *29*, 6133. (c) Nagao, Y. Dai, W.-M., Ochiai, M., Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289. (d) Nagao, Y., Dai, W.-M., Ochiai, M., Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148. (e) Nagao, Y., Kumagai, T., Nagase, Y., Tamai, S., Inoue, Y.; Shiro, M. *J. Org. Chem.* **1992**, *57*, 4232. (f) Nagao, Y., Nagase, Y., Kumagai, T., Kuramoto, Y., Kobayashi, S., Inoue, Y., Taga, T.; Ikeda, H. *J. Org. Chem.* **1992**, *57*, 4238.

(15) In our hands, nonreproducible results were obtained with di-n-butylboron triflate in CH_2Cl_2 which is commercially available from Aldrich. $^{n}Bu_2BOTf$ was prepared according to ref 12b and freshly distilled before use.

(16) Reaction of the boron enolate from (+)-**7c** and racemic **4** was carried out under the same conditions described above to afford a 1:1 mixture of two stereoisomers: **2c** as the slow eluting isomer, and a fast eluting isomer to which structure ***i*** was tentatively assigned.



i

diol ($[\alpha]^{25}_{546} = +8.5$ (*c* 0.6, EtOH) in 48% yield, which proved to be identical by ^{1}H- and ^{13}C-NMR with published data for hastanecine (**1a**)[2,3d,4] and clearly different from those expected for dihydroxyheliotridane (**1b**),[3d] the pyrrolizidine which might be obtained from lactam **3c.** In particular, C-7 and C-8 appeared downfield both in $CDCl_3$ (δ 76.80 and 77.23, respectively) and in CD_3OD (δ 75.91 and 78.32, respectively) when compared with the corresponding carbons (δ 71.8 and 73.2, in CD_3OD) in dihydroxyheliotridane (**1b**)[3d] and in close agreement with the reported values by Denmark[2] (δ 76.50 and 76.78, in $CDCl_3$) and Mulzer[3d] (δ 76.8 and 77.8, in CD_3OD) for (−)-hastanecine (**1a**).

The results described herein demonstrate the feasibility of ^{n}Bu$_2$BOTf promoted addition of boron enolates to α-acetoxy lactams through participation of an intramolecularly chelated conformation of the nucleophile broadening the scope of these synthetically useful species.

Experimental Section[17]

^{n}Bu$_2$BOTf was prepared according to ref 12b and distilled immediately prior to use. (*S*)-Acetoxysuccinimide (**5**)[6] and γ-(benzyloxy)butyric acid[9] were prepared according to the published procedures. Ester **2a**, thioester **2b**, and oxazolidinone **2c** were prepared from γ-(benzyloxy)butyric acid using the procedure developed by Steglich[18] and silyl ketene acetal **2b** according to the procedure described by Gennari.[19]

(4*S*, 5*S*)-*N*-Benzyl-2,3-diacetoxybutyrolactam (6a). To a stirred solution of (*S*)-*N*-benzyl-3-acetoxysuccinimide (**5**)[6] (6.63 g, 26.8 mmol) in ethanol (100 mL) at −23 °C was added sodium borohydride (2.04 g, 53.7 mmol) portionwise. After the addition was completed (5 min), the reaction was kept at −23 °C for 20 min when it was acidified with 1% HCl until pH 2−3, followed by neutralization with saturated $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, and filtered, and the solvent was evaporated.

The residue (5.87 g) was dissolved in CH_2Cl_2 and cooled to 0 °C, and Et_3N (3.51 mL, 25.0 mmol), acetic anhydride (4.44 mL, 35.3 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.20 g, 2.3 mmol) were added. The reaction was allowed to warm up to room temperature, and after 1 h it was diluted with CH_2Cl_2 (20 mL) and washed with 10% HCl (20 mL), saturated $NaHCO_3$ (20 mL) and water (2 × 30 mL).

The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (230−400 mesh, 35% ethyl acetate in hexanes) to afford **6a** (6.87 g, 23.6 mmol) in 88% yield. $[\alpha]^{25}_{546} = -76°$ (*c* 1.0, EtOH); mp 136.5−138 °C; IR (KBr) 1745, 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.03 (s, 3H), 2.67 (dd, *J* = 15.0 and 9.0 Hz, 1H), 2.80 (dd, *J* = 15.0 and 8.4 Hz, 1H), 4.26 (d, *J* = 15.0 Hz, 1H), 4.69 (d, *J* = 15.0 Hz, 1H), 5.28 (dt, *J* = 8.7 and 5.4 Hz, 1H), 6.28 (d, *J* = 5.4 Hz, 1H), 7.23−7.35 (m, 5H). ^{13}C-NMR ($CDCl_3$): δ 20.5, 33.9, 44.8, 66.1, 81.6, 128.1, 128.6, 129.0, 136.1, 170.1, 170.3, 171.7; MS *m*/*z*: 230 (14%), 229 (27%), 170 (23%), 90 (100%).

(4*S*,5*R*)-*N*-Benzyl-2-oxo-4-acetoxy-5-[1-(carbobenzyloxy)-3-(benzyloxy)propyl]pyrrolidine (2a and 3a). To a 0.5 M solution of LDA (4.2 mL, 2.1 mmol) in THF/hexanes at −78 °C was added dropwise benzyl 3-(benzyloxy)butanoate (0.51 g, 1.8 mmol),[16] and the reaction mixture was stirred at −78 °C for 1 h when chlorotrimethylsilane (0.354 g, 3.0 mmol) was added. The reaction mixture was allowed to warm up to rt when a white solid precipitated, and after 1 h it was filtered under nitrogen and concentrated under reduced pressure.

The residue was taken up in CH_2Cl_2 (3.0 mL), and a solution of **6a**/**6b** (0.35 g, 1.2 mmol) in CH_2Cl_2 (1.5 mL) followed by freshly distilled TMSOTf (0.17 mL, 0.90 mmol) were added dropwise at 0 °C. The reaction mixture was kept at 0 °C for 2 h and 4 h at rt when it was quenched by addition of saturated $NaHCO_3$ (5 mL). It was extracted with CH_2Cl_2 (2 × 10 mL), the organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel (25% ethyl acetate in hexanes) afforded 0.26 g (0.54 mmol) of a 1:1 mixture of **2a**/**3a**, in 45% yield. Analytically pure samples were obtained by preparative TLC (10% ethyl acetate in hexanes).

2a (more polar): colorless oil, ^{1}H-NMR: δ 1.70−1.80 (m, 1H), 1.93 (s, 3H), 2.10−2.25 (m, 1H), 2.34 (dd, *J* = 18.0 and 1.2, 1H), 2.80 (ddd, *J* = 18.0, 6.9 and 1.2, 1H), 3.13 (qt, *J* = 4.5, 1H), 3.32−3.44 (m, 2H), 3.47 (d, *J* = 4.5, 1H), 3.92 (d, *J* = 15.6, 1H), 4.35 (s, 2H), 4.97 (d, *J* = 12.0, 1H), 5.04 (d, *J* = 12.0, 1H), 5.13 (d, *J* = 15.6, 1H), 5.46 (d, *J* = 6.9, 1H), 7.2--7.40 (m, 15H); ^{13}C-NMR: δ 21.0, 28.6, 37.4, 42.3, 44.1, 65.4, 67.3, 67.77, 68.6, 73.1, 127.8, 127.9, 128.0, 128.9, 128.4, 128.6, 128.8, 128.9, 128.9, 135.4, 135.8, 138.3, 170.2, 172.6, 173.1.

3a (less polar): colorless oil, ^{1}H-NMR: δ 1.50−1.70 (m, 1H), 1.87 (s, 3H), 1.90−2.05 (m, 1H), 2.21 (dd, *J* = 18.6 and 2.0, 1H), 2.80 (dd, *J* = 18.6 and 6.6, 1H), 2.98 (ddd, *J* = 11.2, 4.5 and 2.4, 1H), 3.28 (dt, *J* = 8.7 and 4.5, 1H), 3.36−3.44 (m, 1H), 3.70 (d, *J* = 4.5, 1H), 3.88 (d, *J* = 15.3, 1H), 4.39 (s, 2H), 5.01 (d, *J* = 15,3, 1H), 5.07 (s, 2H), 5.13 (d, *J* = 6.6, 1H), 7.20-7.40 (m, 15H). ^{13}C-NMR: δ 20.7, 26.2, 37.5, 42.3, 44.5, 64,8, 67.0, 67.8, 69.4, 73.1, 127.8, 127.9, 128.4, 128.5, 128.5, 128.6, 128.7, 128.9, 135.7, 135.8, 138.4, 170.2, 172.2, 172.7. Anal. Calcd for $C_{28}H_{33}NO_6$: C-70.15, H-6.89, N-2.92. Found: C-70.34, H-7.12, N-3.35.

(4*S*,5*R*)-*N*-Benzyl-2-oxo-4-acetoxy-5-[1-[(*tert*-butylthio)-carbonyl]-3-(benzyloxy)propyl]pyrrolidine (2b and 3b). To a solution of **6a**/**6b** (0.15 g, 0.51 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added dropwise the silyl ketene thioacetal prepared from **7b**[19] (0.27 g, 0.80 mmol) followed by TMSOTf (0.10 mL, 0.55 mmol). The reaction was kept 15 min at 0 °C and 4 h at rt when it was quenched with saturated $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), the organic phases were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography on silica gel (10% ethyl acetate in hexanes) afforded 0.12 g (0.25 mmol) of a 1:1 mixture of **2b**/**3b**, in 49% yield. Analytically pure samples were obtained after preparative TLC (5% ethyl acetate in hexanes).

2b (more polar): colorless oil, IR (film) 1741, 1700, 1670 cm^{-1}; ^{1}H-NMR: δ 1.42 (s, 9H), 1.70 (m, 1H), 1.92 (s, 3H), 2.15 (m, 1H), 2.36 (d, *J* = 18.0, 1H), 2.83 (ddd, *J* = 18.0, 6.6 and 1.2, 1H), 3.25 (qt, *J* = 4.8, 1H), 3.34 (d, *J* = 4.2, 1H), 3.37−3.42 (m, 2H), 3.97 (d, *J* = 15.6, 1H), 4.42 (s, 2H), 5.27 (d, *J* = 15.6, 1H), 5.51 (d, *J* = 6.3, 1H), 7.20−7.40 (m, 10H). ^{13}C-NMR: δ 21.0, 29.2, 29.5, 37.4, 44.3, 49.2, 49.6, 65.99, 67.2, 68.7, 73.2, 127.9, 127.9, 128.0, 128.2, 128.6, 129.0, 135.7, 138.4, 170.3, 172.8, 201.9.

3b (less polar): colorless oil; IR (film) 1744, 1700, 1667 cm^{-1}; ^{1}H-NMR: δ 1.43 (s, 9H), 1.60−1.70 (m, 1H), 1.89 (s, 3H), 2.00−2.15 (m, 1H), 2.38 (dd, *J* = 18.0 and 1.5, 1H), 2.85 (ddd, *J* = 18.0, 5.4 and 1.5, 1H), 2.98 (m, 1H), 3.30 (dt, *J* = 9.4 and 4.5, 1H), 3.40 (m, 1H), 3.60 (dd, *J* = 6.0 and 1.2, 1H), 3.87 (d, *J* = 15.0, 1H), 4.44 (d, *J* = 9,3, 1H), 4.47 (d, *J* = 9.3, 1H), 5.11 (d, *J* = 15.0, 1H), 5.17 (dd, *J* = 6.3 and 1.2, 1H), 7.20−7.40 (m, 10H). ^{13}C-NMR: δ 20.8, 27.7, 29.6, 37.3, 44.9, 48.9, 51.7, 64.6, 67.2, 69.7, 73.2, 127.9, 128.0, 128.0, 128.6, 128.6, 128.9, 135.9, 128.3, 170.1, 172.8, 200.3. Anal. Calcd for $C_{26}H_{35}NO_5S$: C-67.59, H-7.01, N-2.81. Found: C-67.35, H-6.70, N-2.65.

(4*S*)-4-Isopropyl-3-[(2*R*)-2-[(4*S*,5*R*)-*N*-Benzyl-2-oxo-4-acetoxy-5-pyrrolidinyl]-4-(benzyloxy)butanoyl]-2-oxazolidinone (2c). To a solution of **7c** (0.091 g, 0.30 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added ^{n}Bu$_2$BOTf (0.10 g, 0.37 mmol) followed by diisopropylethylamine (0.064 g, 0.50 mmol). The reaction mixture was kept 45 min at 0 °C when a solution of **6a**/**6b** (0.087 g, 0.30 mmol) in CH_2Cl_2 (1.0 mL) was added. After 15 min at 0 °C the reaction mixture was stirred 4 h at rt when it was quenched with saturated $NaHCO_3$ (5 mL). The mixture was diluted with CH_2Cl_2 (10 mL), and the organic phase was washed with 10% HCl (5 mL) and saturated $NaHCO_3$ (5 mL) and dried over $MgSO_4$. Evaporation under reduced pressure, followed by column chromatography on silica gel (25% ethyl acetate in hexanes) afforded 0.084 g (0.16 mmol) of **2c** as a colorless oil, in 53% yield. $[\alpha]^{25}_{546} = -16.6$ (*c* 3.4, CH_2Cl_2); IR (film) 1773, 1740, 1697 cm^{-1}; ^{1}H-NMR: δ 0.74 (d, *J* = 3.4, 3H), 0.76 (d, *J* = 3.4, 3H), 1.72 (m, 1H), 1.93 (s, 3H), 2.05 (m, 1H), 2.36 (d, *J* = 18.0, 1H), 2.45 (m, 1H), 3.00 (dd, *J* = 18.0 and 6.6,

(17) For a general experimental information see ref 10b.

(18) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(19) Gennari, C., Beretta, M. G., Bernardi, A., Moro, G., Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

1H), 3.05 (t, J = 9.0, 1H), 3.40 (d, J = 4.8, 1H), 3.60 (m, 2H), 3.80 (dd, J = 9.0 and 3.3, 1H), 3.99 (m, 2H), 4.31 (d, J = 11.1, 1H), 4.43 (d, J = 11.1, 1H), 4.86 (m, 1H), 5.23 (d, J = 15.7, 1H), 5.76 (d, J = 6.6, 1H), 7.26−7.36 (m, 10H). ^{13}C-NMR: δ 14.3, 17.8, 21.0, 28.7, 30.4, 37.5, 40.4, 43.6, 58.5, 62.5, 66.9, 68.8, 69.6, 72.9, 127.5, 127.7, 128.0, 128.3, 128.7, 135.4, 138.3, 154.5, 170.0, 172.6, 174.4. Anal. Calcd for $C_{30}H_{36}N_2O_7$: C-67.16, H-6.71, N-5.22. Found: C-66.89, H-6.68, N-5.09.

(4*S*,5*R*,1′*R*)-*N*-Benzyl-2-oxo-4-hydroxy-5-[1′-(hydroxymethyl)-3′-benzyloxy)propyl]pyrrolidine (9). To a solution of **2c** (0.23 g, 0.43 mmol) in THF (1.0 mL) at 0 °C was added $LiBH_4$ (0.037 g, 1.7 mmol). After 5 min the reaction was allowed to warm up and stirred 4 h at rt. The reaction was quenched by dropwise addition of methanol (2 mL), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford (*S*)-4-isopropyloxazolidinone (0.040 g, 0.31 mmol, 72% recovery) after elution with 50% ethyl acetate in hexanes and (+)-**9** (0.10 g, 0.29 mmol, 67% yield) as a colorless oil upon elution with 1% methanol in ethyl acetate. $[\alpha]^{25}_{546}$ = +6.8 (*c* 10.0, CH_2Cl_2); IR (film) 3396, 3030, 1666 cm^{-1}; ^{1}H-NMR: δ 1.65 (m, 1H), 1.75−2.00 (m, 2H), 2.31 (dd, J = 17.7 and 1.5, 1H), 2.70−2.90 (m, 2H), 3.30−3.60 (m, 6H), 3.90 (d, J = 15.0, 1H), 4.35 (d, J = 11.7, 1H), 4.38 (s, br, 1H), 4.40 (d, J = 11.7, 1H), 5.03 (d, J = 15.0, 1H), 7.20−7.40 (m, 10H). ^{13}C-NMR: δ 28.5, 38.8, 40.4, 44.2, 60.5, 65.8, 69.0, 69.3, 73.6, 127.8, 128.2, 128.3, 128.8, 129.0, 136.3, 137.6, 174.2.

(4*S*,5*R*,1′*R*)-*N*-Benzyl-2-oxo-4-[(*tert*-butyldimethylsilyl)oxy]-5-[1′-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3′-(benzyloxy)propyl]pyrrolidine (10). To a solution of (+)-**9** (0.30 g, 0.81 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C was added 2,6-lutidine (0.51 mL, 4.5 mmol) followed by TBDMSOTf (0.78 mL, 3.3 mmol). The reaction mixture was stirred 3 h at 0 °C when it was diluted with CH_2Cl_2 (20 mL) and washed with 10% HCl (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford 0.32 g (0.54 mmol, 64% yield) of (−)-**10**. $[\alpha]^{25}_{546}$ = −1.1 (*c* 3.4, CH_2Cl_2); IR (film) 1692 cm^{-1}; ^{1}H-NMR: δ -0.04 (s, 3H), −0.02 (s, 3H), 0.00 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 0.86 (s, 9H), 1.57 (m, 1H), 1.74−1.90 (m, 1H), 1.93−2.20 (s, br, 1H), 2.25 (d, J = 17.1, 1H), 2.85 (dd, J = 17.1 and 5.4, 1H), 3.36−3.52 (m, 5H), 3.84 (d, J = 15.6, 1H), 4.37 (d, J = 12.0, 1H), 4.43 (d, J = 12.0, 1H), 4.48 (d, J = 5.4, 1H), 5.12 (d, J = 15.6, 1H), 7.22−7.33 (m, 10H). ^{13}C-NMR: δ -5.8, −5.6, −4.9, −4.6, 17.7, 18.1, 25.6, 25.9, 27.8, 35.9, 41.2, 43.9, 58.9, 67.1, 67.6, 69.8, 73.1, 127.5, 127.8, 127.9, 128.6, 128.7, 128.9, 136.4, 138.5, 174.5.

(2*R*,3*S*,1′*R*)-*N*-Benzyl-2-[1′-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-3′-(benzyloxy)propyl]-3-[(*tert*-butyldimethylsilyl)-oxy]pyrrolidine (11). To a solution of (−)-**10** (0.30 g, 0.52 mmol) in THF (8.0 mL) at 0 °C was added BH_3·Me_2S (10 M solution in THF, 0.56 mL, 5.6 mmol). The reaction was stirred 16 h at rt, quenched at 0 °C with ethanol (20 mL), and the resulting mixture was refluxed during 2 h. The solvent was removed under vacuum, and the residue was chromatographed on silica gel (5% ethyl acetate in hexanes) to afford (−)-**11** (0.21 g, 0.38 mmol), in 73% yield.

$[\alpha]^{25}_{546}$ = −31.5 (*c* 2.9, CH_2Cl_2); ^{1}H-NMR: δ 0.029 (s, 3H), 0.045 (s, 6H), 0.064 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.53 (dd, J = 12.5 and 5.6, 1H), 1.70−1.98 (m, 4H), 2.42 (ddd, J = 11.7, 8.4 and 5.7, 1H), 2.60 (s, br, 1H), 2.82 (t, J = 7.6, 1H), 3.36 (d, J = 13.4, 1H), 3.58−3.67 (m, 3H), 3.84 (dd, J = 9.9 and 3.9, 1H), 4.00 (d, J = 13.4, 1H), 4.38 (d, J = 5.4, 1H), 4.53 (s, 2H), 7.20−7.36 (m, 10H). ^{13}C-NMR: δ -5.6, −5.5, −4.6, −4.3, 17.8, 18.2, 25.8, 25.9, 28.7, 34.5, 38.3, 51.6, 59.8, 62.3, 68.9, 72.8, 74.2, 75.5, 126.5, 127.4, 127.7, 128.1, 128.3, 128.5, 138.7, 140.6. Anal. Calcd for: $C_{34}H_{57}NO_3Si_2$: C-69.98, H-9.78, N-2.40. Found: C-70.14, H-9.66, N-2.56.

(+)-Bis[(*tert*-butyldimethylsilyl)oxy]hastanecine (12). To a solution of (−)-**11** (0.20 g, 0.32 mmol) dissolved in ethyl acetate (8 mL) was added $Pd(OH)_2$ (5 mg), and the mixture was stirred 8 h under a hydrogen atmosphere (40 psi) in a Parr apparatus. The reaction mixture was filtered over Celite, and the solvent was removed under vacuum. The residue was dissolved in CH_3CN (4.0 mL) and Et_3N (0.12 mL, 0.80 mmol), and carbon tetrachloride (0.12 mL, 0.8 mmol) and triphenylphosphine (0.20 g, 0.76 mmol) were added. The reaction mixture was stirred 48 h at rt, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ethyl acetate:methanol:NH_4OH = 95:4:1) to afford (+)-**12** (0.068 g, 0.18 mmol), in 56% overall yield. $[\alpha]^{25}_{546}$ = +7.4 (*c* 2.6, MeOH). ^{1}H-NMR: δ 0.05 (s, 12H), 0.87 (s, 9H), 0.90 (s, 9H), 1.56−1.72 (m, 2H), 1.74−1.98 (m, 3H), 2.46 (dt, J = 9.7 and 6.0, 1H), 2.62 (ddd, J = 11.0, 6.7 and 4.8, 1H), 3.08 (dd, J = 10.0 and 7.0, 1H), 3.10−3.24 (m, 2H), 3.55 (dd, J = 10.0 and 7.0, 1H), 3.71 (dd, J = 10.0 and 5.4, 1H), 4.02 (dd, J = 7.8 and 3.9, 1H). ^{13}C-NMR: δ -5.3, −4.7, −4.5, 18.0, 18.4, 25.8, 26.0, 30.3, 33.9, 46.9, 52.6, 55.0, 65.4, 75.2, 78.0; MS *m*/*z*: 385 (M$^+$, 2%), 227 (16%), 106 (13%), 82 (100%).

(+)-Hastanecine (1a). To a solution of (+)-**12** (0.060 g, 0.15 mmol) in CH_3CN (3.0 mL) was added 40% HF (2.0 mL), and the mixture was stirred 48 h at rt. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and lyophilized, and the resulting solid was chromatographed on silica gel ($CHCl_3$:MeOH:NH_4OH = 6:3:1) to afford (+)-**1a**, (0.006 g, 0.07 mmol, 48% yield) as a white solid: mp 110 °C, $[\alpha]^{25}_{546}$ = +8.5 (*c* 0.6, EtOH) (lit.[3d] mp 111 °C, $[\alpha]^{25}_{D}$ = +9.0 (*c* 0.49, EtOH). ^{1}H-NMR ($CDCl_3$): δ 1.60−1.76 (m, 1H), 1.84−2.02 (m, 3H), 2.09 (m, 1H), 2.50−2.61 (m, 1H), 2.64−2.76 (m, 1H), 3.10 (s, br, 2H), 3.21−3.40 (m, 3H), 3.56 (dd, J = 10.6 and 7.5, 1H), 3.82 (dd, J = 10.6 and 4.0, 1H), 4.14 (dd, J = 8.5 and 5.0, 1H). ^{1}H-NMR (CD_3OD): δ 1.05−1.71 (m, 1H), 1.78−1.88 (m, 1H), 1.90−2.20 (m, 3H), 2.80 (dt, J = 10.8 and 5.6, 1H), 2.98 (ddd, J = 10.8, 7.4 and 2.7, 1H), 3.30−3.48 (m, 3H), 3.55 (m, 2H), 4.16 (s, br, 1H), 4.69 (s, br, 2H). ^{13}C-NMR ($CDCl_3$): δ 29.7, 33.8, 46.3, 52.7, 54.9, 64.3, 76.8, 77.2. ^{13}C-NMR (CD_3OD): δ 29.9, 33.0, 46.5, 53.4, 55.8, 63.7, 75.9, 78.3.

Acknowledgment. Financial support from FINEP, FAPESP, CNPq, SAE-Unicamp, and International Foundation for Science (Sweden) is gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H- and ^{13}C-NMR for (−)-**2c**, (+)-**12**, and **1a** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9513020