The Tandem Cycloaddition Chemistry of Nitroalkenes. A Novel Synthesis of (−)-Hastanecine

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A short and efficient asymmetric synthesis of the pyrrolizidine necine base (−)-hastanecine is described. The key reaction in the synthesis is a sequential inter [4 + 2]/inter [3 + 2] cycloaddition. The Lewis acid promoted [4 + 2] cycloaddition between 2-acyloxy nitroalkene **16** and chiral vinyl ether **17** afforded a nitronate which underwent facile [3 + 2] cycloaddition with dimethyl maleate. The resulting nitroso acetal **19** had all the required stereocenters for (−)-hastanecine. The critical unmasking of the nitroso acetal **19** employed a hydrogenolytic cleavage to give the 1-azabicyclo-[3.3.0]octane skeleton of (−)-hastanecine.

Introduction and Background

Pyrrolizidine alkaloids have a long history for attracting the interest of synthetic chemists due to their diverse physiological properties and their compact structural complexity.[1] The alkaloids have been isolated from numerous plant sources throughout the world of which the main sources are the families Boraginaceae (all genera), Compositae (tribes Senecioneae and Eupatorieae), and Leguminosae (genus *Crotalaria*).[2] Pyrrolizidine alkaloids are composed of two subunits, the necine base and the necic acid. The necine base, a 1-azabicyclo-[3.3.0]octane ring system with various degrees of oxidation, is the common subunit for this class of alkaloids, Figure 1.

(−)-Hastanecine is the necine base of hastacine (**11**) which was isolated from *Cacalia hastata*, family Compositae (tribe Senecioneae), in 1945.[3] The structure and stereochemistry of (−)-hastanecine was determined by Culvenor et al. in 1969 by a synthesis of (+)-hastanecine and comparison to the natural occurring enantiomer.[4] As a vehicle to illustrate new methods of stereocontrol, hastanecine has been the target for synthesis through intramolecular cyclopropanation,[5a] acyliminum ion cyclization,[5b,c] radical cyclization,[5d] and intramolecular S_N2 displacement reactions.[5e]

The hetero Diels–Alder cycloaddition constitutes an important class of reactions for the synthesis of alkaloids

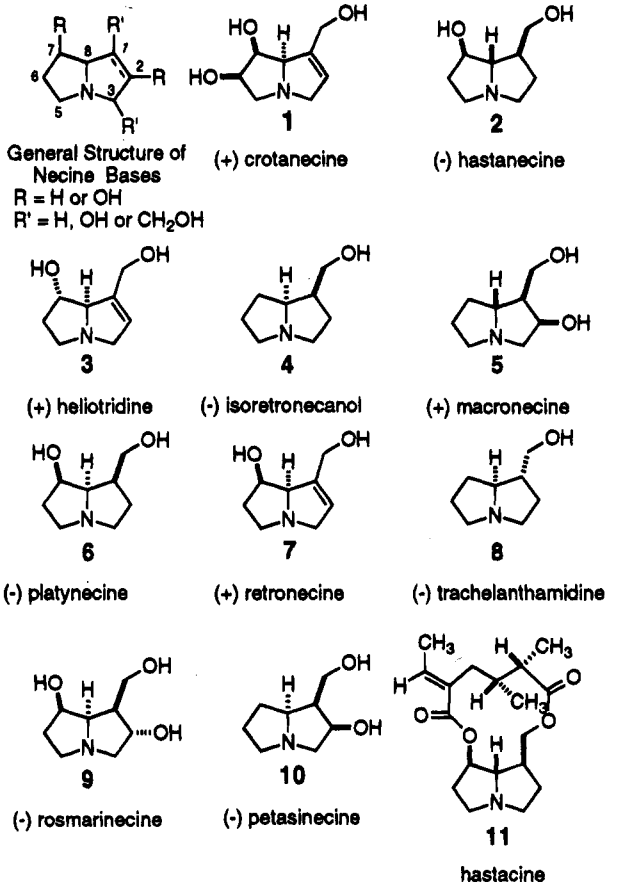

Figure 1. Structure of several necine bases of pyrrolizidine alkaloids.

due to its ability to construct functionalized, heterocyclic rings with up to four contiguous stereogenic centers.[6] Over the past few years we have extensively developed the use of nitroalkenes as heterodienes in [4 + 2] cycloaddition reactions.[7] In the presence of Lewis acid promoters, nitroalkenes of various substitution patterns react as dienes in inverse electron demand cycloadditions. These cycloadditions have been shown to proceed with high diastereoselectivity utilizing chiral vinyl ethers

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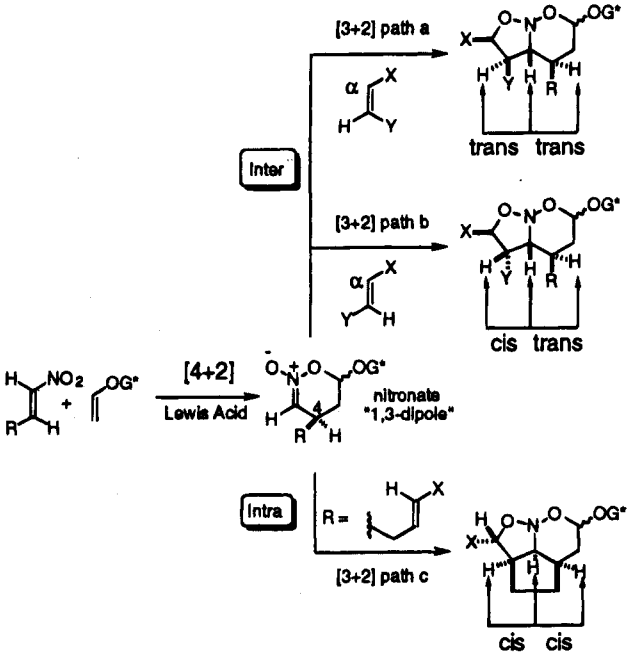
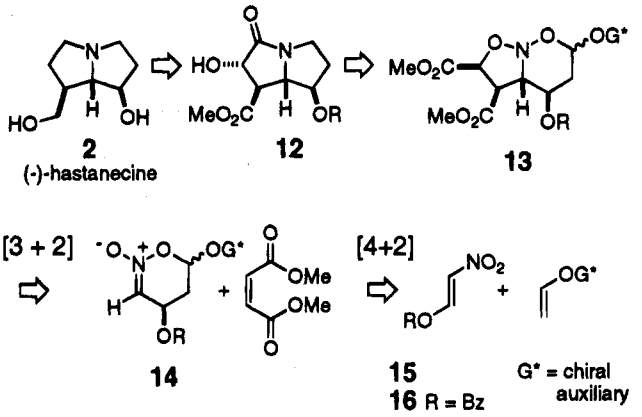
derived from camphor, *trans*-2-phenylcyclohexanol and 2,2-diphenylcyclopentanol as the dienophile.[7f,g,k] The approach of the dienophile to the nitroalkene, endo or exo, can be controlled by the appropriate choice of Lewis acid.[7g] This behavior provides access to either enantiomeric family of the resulting nitronate (as defined by the configuration of the newly created center at C(4)) utilizing a single enantiomer of the chiral vinyl ether. For example, by employing titanium diisopropoxide dichloride, the approach of the vinyl ether to the nitroalkene is preferentially endo while when using the more bulky aluminum-based Lewis acid methylaluminum bis(2,6-diphenylphenoxide) (MAPh) a switch in selectivity to the exo approach is observed. The resulting nitronate can be hydrogenated to a pyrrolidine[7h] or be used as a 1,3-dipole in a [3 + 2] cycloaddition with various dipolarophiles.[8,9] The dipolarophiles examined have been shown to react preferentially in an exo mode for intermolecular cycloadditions.[7k,8] In addition, high facial selectivity has been observed in intermolecular [3 + 2] cycloadditions involving C(4) substituted nitronates.[7k]

In formulating a synthetic logic for (−)-hastanecine that employs the attributes of the nitroalkene tandem cycloaddition outlined above, we first note that the absolute configuration is established by the [4 + 2] cycloaddition in the creation of the stereogenic center at C(4) of the nitronate (C(7) of (−)-hastanecine), Scheme 1. Second, the 1-azabicyclo[3.3.0]octane skeleton of (−)-hastanecine has a trans/trans relationship between the three contiguous stereocenters at C(1), C(7), and C(8), Figure 1. Outlined in Scheme 1 is the complete analysis of the stereochemical consequences of the [3 + 2] component of the tandem process in both inter- and intramolecular modes using both cis and trans dipolarophiles. In the intermolecular mode, the preferred approach of a dipolarophile to C(4) substituted nitronates is to the face of the nitronate that contains the smaller substituent resulting in a trans relationship between the adjacent stereocenters, Scheme 1, paths a or b.[7k] The C(4) of the nitronate will become C(7) of the necine skeleton giving

Scheme 1



Scheme 2



correct relative stereochemistry of C(7) and C(8) for (−)-hastanecine. Third, the relationship between C(1) and C(8) in (−)-hastanecine is established by the orientation and configuration of the dipolarophile. For intermolecular 1,3-dipolar cycloadditions of nitronates, the regio-directing substituent on the dipolarophile (X) prefers an exo orientation and the α-carbon becomes attached to the oxygen end of the dipole.[8,9] The location of the β-carbon substituent (Y) is then determined by the configuration of the dipolarophile. Therefore, to obtain the trans relationship between C(1) and C(8) required for (−)-hastanecine, the dipolarophile has to be cis disubstituted, path a, Scheme 1.

The retrosynthesis of (−)-hastanecine is summarized in Scheme 2.[10] According to the foregoing analysis, the key nitroso acetal **13** would arise from a [3 + 2] cycloaddition of dimethyl maleate with nitronate **14** which in turn would arise from the [4 + 2] cycloaddition between a chiral vinyl ether and a 2-acyloxy nitroalkene **15**. Hydrogenolytic cleavage of **13** should give rise to α-hydroxy lactam **12** which should afford (−)-hastanecine

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Table 1. Cycloadditions with 16

Lewis acid	Lewis acid equiv	cis nitronate	trans nitronate	unknown nitronate	yield (%)[a]
MAD	1	1[b]	7.6	6.5	71
MAPh	1	1	1.6		57
$Ti(O\text{-}i\text{-}Pr)_2Cl_2$	6	13		1[c]	85

[a] Isolated total yield after chromatography. [b] Contaminated with unknown nitronate. [c] Mixture of diastereomers, not the same as obtained from MAD-promoted reaction.

after a simple deoxygenation and reduction. The choice of appropriate chiral auxiliary for the vinyl ether would be made on the basis of yield and selectivity in reaction with the acyloxy nitroalkenes. The preparation of 2-acyloxy-substituted nitroalkenes has been described.[11] In fact, the 2-benzoyloxy nitroalkene **16** had been prepared and used as a *dienophile* in Diels–Alder reaction for the preparation of amino alcohols.[11a]

The approach described above is quite flexible and would allow for the synthesis of all the necines in Figure 1 by the appropriate choice of 2-acyloxy or 2-acylthio nitroalkene as the diene and appropriate vinyl ether or 2-oxy-substituted enol ether as the dienophile in the cycloaddition. By tethering a dipolarophile by two atoms to the C(4) center of the nitronate, the stereochemistry is dictated to be cis between the three adjacent stereocenters in the resulting nitroso acetal.[7c] Such an all-cis relationship in the necine skeleton is found for example in (−)-rosmarinecine and (−)-platynecine between C(1), C(7), and C(8). Hydrogenolytic cleavage of the nitroso acetal leads to highly functionalized lactams. This reports discloses the successful utilization of the inter [4 + 2]/inter [3 + 2] cycloaddition strategy for the stereoselective construction of (−)-hastanecine.

Results

Synthesis of Hastanecine. The required 2-benzoyloxy nitroalkene **16** was prepared by a modification of a literature procedure.[11a] Addition of benzoyl chloride to a cold suspension of potassium nitroacetaldehyde[12] in nitromethane afforded the highly-crystalline nitroalkene in 85% yield after recrystallization. The 2-acetyloxy and the 2-pivaloyloxy nitroalkenes could be made by the same method using the corresponding acid chlorides, unfortunately those nitroalkenes were oils that could not be purified by chromatography or distillation. The 2-benzoyloxy nitroalkene was employed as a diene in Lewis acid-promoted cycloaddition and to our knowledge is the first example of the use of 2-acyloxy nitroalkenes as a diene in Diels–Alder cycloaddition, Scheme 3. A survey of Lewis acid promoters for the cycloaddition between nitroalkene **16** and (1*S*,2*R*)-2-phenylcyclohexyl vinyl ether (+)-**17**[7g] was performed, Table 1. The use of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) or MAPh as the Lewis acid promoter gave a nonselective cycloaddition in which no preference was observed for endo or exo approach of the dienophile. Fortunately, by using titanium diisopropoxide dichloride the [4 + 2] cycloaddition afforded nitronate (+)-**18a** with high selectivity. The stereostructure of the nitronate was assumed to be cis (β-anomer) on the basis of the well-documented preference of titanium diisopropoxide dichloride to promote endo mode cycloadditions.[7g] The major product (+)-**18a** was formed in a ratio of 13/1 to **18b** that could be separated by chromatography. The minor fraction **18b** was a mixture of two components (by ^1H NMR ca. 2.7/1) that could not be assigned as the diastereomeric nitronates, although combustion analysis provided the same empirical formula. Optimal conditions for the cycloaddition were found to require the addition of 6 equiv of titanium diisopropoxide dichloride to a solution of nitroalkene **16** and 2 equiv of vinyl ether (+)-**17** at −90 °C followed by warming to −78 °C. After workup, nitronate (+)-**18a** was obtained in 71% yield as a crystalline compound.

The nitronate (+)-**18a** was found to be a reactive dipole which combined with dimethyl maleate at room temperature to afford nitroso acetal (−)-**19** in 88% yield as a single diastereomer. The stereostructure was assigned on the basis of the well-documented preference for exo orientation of the dipolarophile to the less hindered face (vide infra).[7k,8]

The critical unmasking procedure required the hydrogenolysis of the nitroso acetal (−)-**19** to reveal the 1-azabicyclo[3.3.0]octane skeleton of (−)-hastanecine. The cleavage of nitroso acetal (−)-**19** with hydrogen over Raney nickel under similar reactions conditions previously employed in these laboratories afforded the α-hydroxy lactam (−)-**20** in only poor to moderate yield.[7g] An extensive survey of reaction conditions (pressure, catalyst, solvent, additive) was therefore performed. Even though Raney nickel is the catalyst of choice for the cleavage of N–O bonds,[13,14] other catalysts were examined as well. Performing the hydrogenolytic cleavage with Pd/C, $Pd(OH)_2$, or PtO_2 at 160 psi of hydrogen resulted in *no product formation* and only starting material was recovered. Returning to the use of Raney nickel as the catalyst, we then examined variation in the catalyst activity and reaction conditions to improve the yield, Table 2. Employing more reactive Raney nickel prepared according to literature procedures[15] did not increase the yield. Using 160 psi of hydrogen pressure with Raney nickel (activity W-2), a solvent effect was observed for the reaction. Methanol was observed to be a superior solvent compared to the less polar solvents such as tetrahydrofuran (THF) and isopropyl alcohol (*i*-PrOH). Furthermore, no improvement was observed when a 15% water solution in methanol was used and neither did the use of slightly acidic conditions. The final variable examined was the hydrogen pressure and indeed, the reaction did show a pressure dependence; performing the reaction at higher pressures resulted in increased yields. Furthermore, the reactions performed at 160 psi or lower were found to be very capricious and attempts to perform the reaction on larger scale resulted in considerably lower yields. Optimal conditions were found to be the use of Raney nickel (W-2) at 260 psi of hydrogen in methanol which afforded the α-hydroxy lactam (−)-**20** in 72% yield (68% after recrystallization)

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Scheme 3

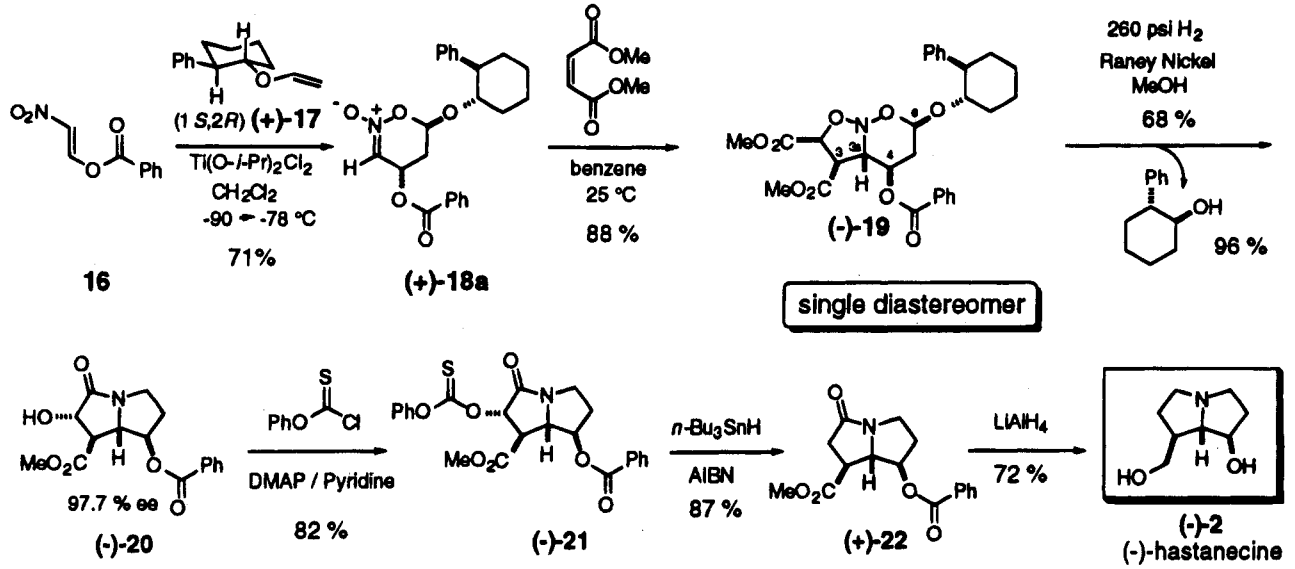

Table 2. Hydrogenolysis of 19[a]

solvent	pressure (psi)	**20**, yield (%)[b]
MeOH	160	46–60
THF	160	20
i-PrOH	160	34
15% H_2O/MeOH	160	61
10% PPTS/MeOH	160	44
15% H_2O/10% TsOH/MeOH	160	20
MeOH[c]	160	50
MeOH	14.6	36
MeOH[d]	14.6	48
MeOH	100	45–60
MeOH	260	72
MeOH	360	68

[a] All reactions employed W-2 Raney nickel at room temperature unless otherwise specified. [b] Yield after chromatography. [c] W-4 Raney nickel. [d] Sonication at 20 °C.

and 97.7% enantiomeric purity as determined by chiral HPLC using a Daicel Chiralpak AD column. In addition to the α-hydroxy lactam, the auxiliary, (1*S*,2*R*)-2-phenylcyclohexanol, was recovered in 96% yield, Scheme 3.

Lactam (−)-**20** contained all of the stereocenters and functionality needed for (−)-hastanecine. In fact, it is over-functionalized for this particular target and the second half of the synthesis involved deoxygenation at C(1) and reduction of the amide and the ester. The Barton–McCombie[16] deoxygenation method was found to be the method of choice.[17] Activation of the alcohol with thiocarbonyl diimidazole resulted in a very unstable product that decomposed under high vacuum after only a few hours at room temperature. Instead, using phenyloxy chlorothionocarbonate with DMAP and pyridine gave the stable, easily handled derivative (−)-**21** in 82% yield.[18] Heating the ester (−)-**21** in refluxing benzene with slow addition of a solution of 2,2′-azobis(isobutyronitrile) (AIBN) and tributyltin hydride in benzene gave the deoxygenated product (+)-**22**, in 87% yield after recrystallization.

The final stages in the synthesis involved (1) reduction of the lactam to a pyrrolidine, (2) reduction of the ester to a primary alcohol, and (3) removal of the benzoate protecting group. This could all be accomplished by lithium aluminum hydride reduction of (+)-**22**. Due to the extreme polarity of (−)-hastanecine, extensive purification was required to obtain an analytically pure sample after reduction. The crude diol was freed from the alumina byproducts resulting from the reduction by filtration. Excessive washing of the filter cake with methanol gave a white solid after evaporation of solvent which was purified by silica gel column chromatography using chloroform, methanol, and ammonium hydroxide (10/5/1) as the solvent system. Repeated recrystallization of the white solid from acetone with hot gravity filtration gave a compound containing incombustible impurities therefore requiring further purification. Chromatography on basic alumina gave, after further recrystallization from acetone, analytically pure (−)-hastanecine in 71% yield. The physical properties are similar to the reported values, mp 111–112 °C and $[\alpha]^{23}_D$ −10.4° (ethanol, *c* = 0.44) (lit.[4a] mp 113–114 °C, $[\alpha]^{20}_D$ −10.0° (ethanol, *c* = 0.44)). Furthermore, a ^{1}H NMR spectrum of synthetic (−)-hastanecine is nearly identical to a spectrum of (+)-hastanecine (synthetic), obtained from Culvenor.[19]

Stereochemical Assignment. A thorough comparison of physical and spectroscopic properties of synthetic (−)-hastanecine was not possible due to the lack of an authentic sample from natural sources. The only reported spectroscopic data for natural hastanecine is a 60 MHz ^{1}H NMR spectrum with very poor resolution. Furthermore no ^{13}C NMR spectra had been reported in the literature at the completion of this synthesis of either synthetic or natural occurring hastanecine.[20] Therefore, to independently confirm that compound **2** was hastanecine, we needed to unambiguously establish the stereostructure of an intermediate that had all the required

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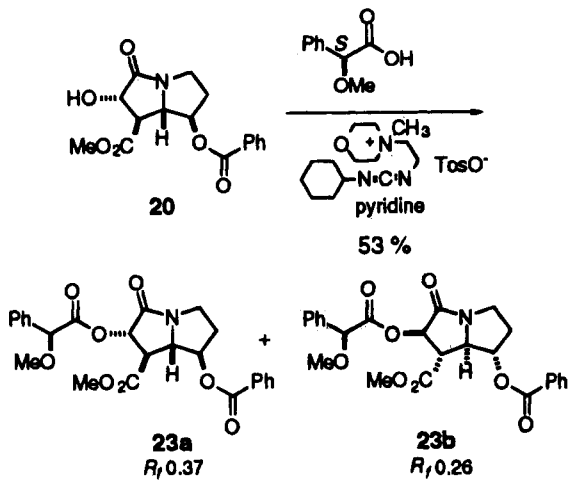
(20) After the completion of this study, the full spectroscopic profile for (−)-hastanecine was reported in ref 5e.

Scheme 4



stereocenters installed and from which further manipulations would not change that stereochemistry. We chose lactam (−)-**20** since it was already highly crystalline and then prepared selected derivatives that would give the absolute as well as the relative configuration.

The lactam (−)-**20** was thus esterified with (*S*)-methoxyphenylacetic acid, Scheme 4. Since relatively large quantities of racemic lactam **20** were available it was used instead of optically active material giving a mixture of diastereomers **23** that could easily be separated and correlated to the esterified, optically active lactam. To prevent racemization it was necessary to use a carbodiimide coupling with 1-hydroxybenzotriazole (HOBt) as an additive in acetonitrile.[21] The diastereomeric esters **23** that were obtained from the carbodiimide coupling with racemic lactam **20** were separated by column chromatography to provide a less polar ester **23a** (R_f 0.37 (hexane/EtOAc, 1/1)) as a solid and a more polar ester **23b** (R_f 0.26 (hexane/EtOAc 1/1)) as an oil. After numerous recrystallizations the less polar diastereomer **23a** finally gave crystals suitable for X-ray analysis grown by diffusion crystallization from acetone/pentane solution. The X-ray crystal structure[22] established two facts. First, the relative configuration of C(1), C(7), and C(8) in **23a** is correct for the structure known as hastanecine. Second, since the absolute configuration of the mandelate derivatizing agent was *S*, the absolute configurations of C(1), C(7), and C(8) in **23a** are also correct for (−)-hastanecine. Esterification of optically active lactam (−)-**20** under the same conditions as above gave a product with identical spectroscopic and chromatographic properties to the less polar diastereomer **23a**. Thus, (−)-**20** is in the correct configurational series for (−)-hastanecine.

Discussion

[4 + 2] Cycloaddition. The 2-benzoyloxy nitroalkene was found to serve admirably as a heterodiene in inverse electron demand Diels–Alder reactions. Indeed, **16** was among the most reactive heterodienes we have examined in cycloadditions with vinyl ethers as it underwent rapid reaction at −78 °C. Furthermore, the benzoyloxy group was stable under the reaction conditions required for the cycloaddition. The only complication was that a very slow addition of MAD was necessary so the BHT group did not add to the nitroalkene displacing the benzoate. The complete lack of diastereoselectivity when MAPh was employed was surprising in view of the highly selective tandem [4 + 2]/[3 + 2] cycloadditions using the same auxiliary.[7g]

The enhanced reactivity observed for **16** can be understood on the basis of both electronic and steric effects. Although these cycloadditions are inverse-electron demand and thus $HOMO_{dienophile} - LUMO_{diene}$ controlled, we have previously shown in a Hammett study of 4-substituted nitrostyrenes that electron-releasing substituents accelerate the reaction.[7i] This effect was interpreted in terms of the enhanced coordination potential of the nitro group. While the benzoyloxy group is normally considered to be electron-withdrawing,[23] the high electron demand of the complexed nitroalkene enhances the resonance contribution.[23b] In addition, we have shown that the rate of cycloaddition is very sensitive to the steric encumbrance at the nitroalkene β-carbon.[7h] The benzoyloxy group is small compared to most carbon subtituents, both aliphatic and aromatic.

The stereochemical course of the cycloaddition can be understood through an endo, s-trans approach of the vinyl ether to the *si*-face of the nitroalkene which is analogous to previous well-documented preference for endo approach of vinyl ethers in titanium dichloride diisopropoxide-promoted cycloadditions.[7g]

[3 + 2] Cycloaddition. 1,3-Dipolar cycloadditions are generally considered to be concerted reactions and depending on the dipole and dipolarophile, under $HOMO_{dipole} - LUMO_{dipolarophile}$ or $HOMO_{dipolarophile} - LUMO_{dipole}$ control.[6c] The analysis of the transition structure for the [3 + 2] cycloaddition of nitronate **18a** with dimethyl maleate requires that two variables be considered: (1) the facial approach of the dipolarophile to the dipole, (2) the exo/endo preference of the dipolarophile. The preference of the dipolarophile for an exo approach to the dipole is well documented and is believed to arise due to mismatched secondary orbital interactions between the nitrogen in the nitronate and the carbonyl carbon in the dipolarophile.[8] The question of diastereofacial control involves the topicity of the approach of the dipolarophile to the nitronate. MOPAC calculations of nitronate **18a** using the PM3 Hamiltonian located two low-energy conformations. The predicted ground state conformation was found to be a twisted chair 3.1 kcal/mol lower in energy than a boat conformation. In the twisted chair conformation, both substituents at C(4) and C(6) are in an axial orientation suggesting that stabilization due to the anomeric effect is considerable, Figure 2. By inspection of the ground state conformation, it is obvious that the benzoate is very effective at shielding the top face of the dipole allowing access by the dipolarophile only from the bottom face. This would explain the high selectivity observed in the cycloaddition which produced only a single diastereomer.

Hydrogenolysis. The hydrogenation of nitroso acetals to lactams is a remarkable transformation worthy

(21) (a) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788. (b) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 2024. (c) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

(22) The ORTEP and fractional corrdinates of **23a** are included in the supplementary material. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(23) (a) Eherenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1. (b) On the σ_R scale, acetoxy is a stronger donor than methyl.

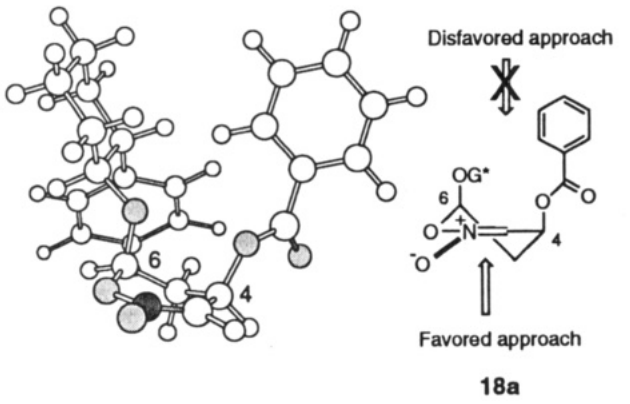
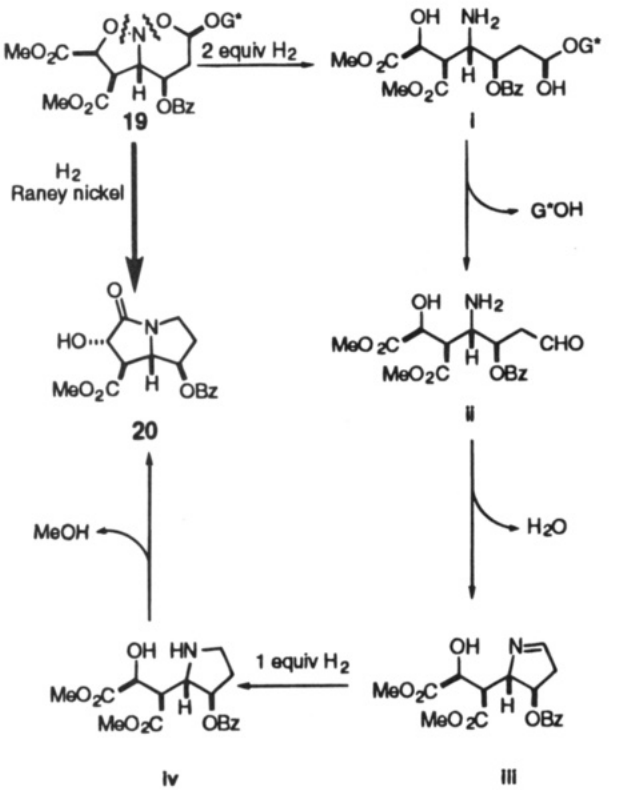


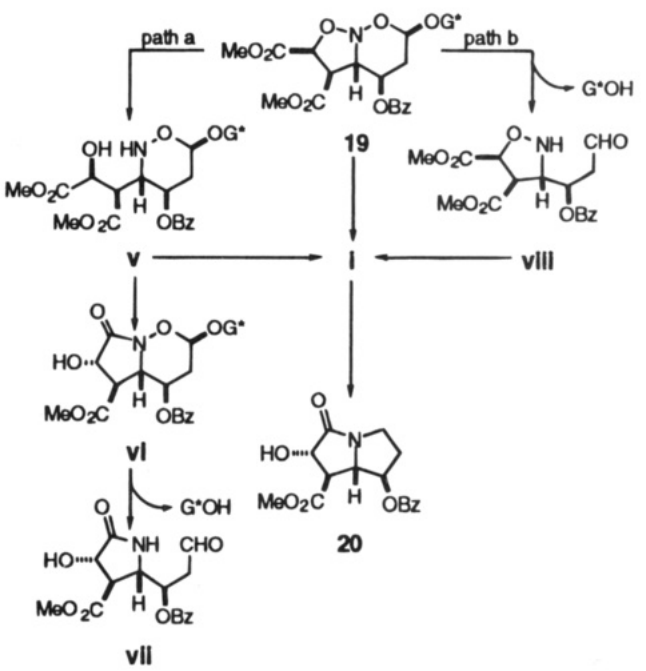
Figure 2. Representation of AM1 ground state conformation for nitronate **18a**.

Scheme 5



of brief discussion. Hydrogenolysis of nitroso acetals, as documented in these laboratories and others, has shown that Raney nickel is the preferred catalyst for the cleavage of the N—O bonds.[7,20] Because of the multitude of reaction steps in this transformation and the lack of identifiable intermediates, many mechanistic interpretations are possible that differ primarily in the sequence of cleavage of the N—O bonds. Further, any proposal should take into account the solvent and pressure dependence of the reaction. One plausible proposal is the rapid cleavage of both N—O bonds to give the corresponding hemiacetal **i** after absorption of 2 equiv of hydrogen, Scheme 5. Subsequent breakdown of the hemiacetal to form the aldehyde **ii**, followed by imine **iii** formation with the loss of water, and the absorption of 1 equiv of hydrogen would form the pyrrolidine **iv**. The pyrrolidine then would lactamize to give the observed product. In less polar solvents THF and *i*-PrOH, the yield of the reaction decreased in comparison to methanol. All the intermediates in this mechanistic proposal are more polar than the starting material or product.

Scheme 6



Thus, a highly polar solvent is needed to remove intermediates from the catalyst surface to prevent overreduction. Furthermore, it is known that acids reduce the activity of the Raney nickel thus explaining the decreased yield under acidic conditions.[15]

The higher yields obtained in the hydrogenation at higher pressures raises the question of the synchronicity of the N—O bond cleavage. The cleavage of the N—O bonds is assumed to be faster under reaction conditions that employ higher pressure. Scheme 6 depicts the plausible consequences of slow, stepwise cleavage of the N—O bonds. If five membered ring N—O bond breaks first (path a), the intermediate 1,2-oxazine **v** can lead either to **i** or to lactam **vi**. If **vi** undergoes another N—O cleavage, the resulting aldehyde **vii** would not be able to form the imine due to the decreased nucleophilicity of the amide nitrogen, and the aldehyde would suffer β-elimination or be reduced to alcohol. If the six-membered ring N—O bond cleaves first (path b), the intermediate isoxazolidine **viii** can still lead to **i**, but again due to the reduced nucleophilicity of the nitrogen, imine formation is retarded and **viii** can suffer the same fate as **vii**. The observation that water had no effect on the yield of (−)-**20** suggests that imine formation is not reversible under these conditions. The decisive factor is the relative rates of the second N—O bond cleavage compared to lactamization of **v** and elimination/overreduction in **viii**. As the rate of the second N—O bond cleavage is increased, the leakage through nonproductive pathways is decreased.

Conclusion. The asymmetric synthesis of (−)-hastanecine has been described in the first example of the sequential inter [4 + 2]/inter [3 + 2] nitroalkene cycloaddition methodology applied toward natural product synthesis. The synthesis was highly efficient, requiring only six steps and resulted in an overall yield of 21%. Also noteworthy is the high stereoselectivity of the [4 + 2] and the [3 + 2] cycloaddition reactions that created the required stereocenters. The synthesis of more complex alkaloids using the tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition approach is under active investigation.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 400 MHz ^1H (100 MHz ^{13}C) in deuterochloroform ($CDCl_3$) or deuteromethanol (CD_3OD) with either tetramethylsilane (TMS) (0.00 ppm ^1H, 0.00 ppm ^{13}C), chloroform (7.26 ppm ^1H, 77.0 ppm ^{13}C), or methanol (3.30 ppm ^1H, 49.00 ppm ^{13}C) as an internal reference unless otherwise stated. Data are reported in the following order: chemical shifts in ppm (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); coupling constants, J, are reported in Hz; integration is provided. Infrared spectra (IR) were obtained in KBr unless otherwise specified. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium 40–66%), w (weak 20–40%), and br (broad). Electron impact (EI) mass spectra were obtained with an ionization voltages of 70 eV. Chemical ionization (CI) mass spectra were obtained with methane as ionization gas. Data are reported in the form *m/e* (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography was performed on silica gel plates with F-254 indicator. Visualization was accomplished by UV light, phosphomolybdic acid, 5% H_2SO_4 in methanol, or *p*-anisaldehyde solution. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: dichloromethane (CH_2Cl_2) and hexane, calcium chloride; ethyl acetate and methyl *tert*-butyl ether (MtBE), potassium carbonate. Chloroform ($CHCl_3$) and methanol (MeOH) were reagent grade. Column chromatography was performed by the method of Still[24] with 32–63 *u*m silica gel or standard grade basic alumina 150 mesh, 58 Å. Melting points (mp) are uncorrected. Analytical high pressure liquid chromatography (HPLC) was performed with flow parameters isocratic at the stated conditions: method A (hexane/EtOH, 2/1, 0.6 mL/min); method B (hexane/EtOAc, 1/1, 1.0 mL/min), (wavelength 254 nm). Columns: (A) Daicel, Chiralpak AD amylose tris(3,5-dimethylphenylcarbamate) (25 cm × 4.6 mm); (B) Supelco LC-Si 5m (250 × 4.5 mm). Solvents for HPLC use were spectrometric grade and filtered prior to use. Optical rotations are reported as $[\alpha]^{\text{temperature}}_{\text{wavelength}}$ (solvent, concentration (c = g/100 mL)). All reactions were performed under a dry nitrogen atmosphere in oven- and/or flame-dried glassware. "Brine" refers to a saturated solution of NaCl.

Semiempirical calculations (MNDO, AM1, PM3) were performed using MOPAC version 6.10 as implemented under the CAChe software version 2.8 running on a Macintosh Quadra 700 with an RP88 coprocessor.

2-(Benzoyloxy)-1-nitroethene (16). To a slurry of potassium nitroacetaldehyde **16**[12] (3.00 g, 23.5 mmol) in nitromethane (84 mL) at −23 °C was added dropwise over 5 min a solution of benzoyl chloride (2.8 mL, 23.5 mmol, 1.0 equiv) in nitromethane (16 mL). The mixture was allowed to stir for 135 min at −23 °C. During this time the color changed to light brown with precipitation of a white solid. Dichloromethane (250 mL) was then added and the resulting solution filtered through Whatman No. 1 filter paper. The filtrate was concentrated by rotary evaporation and the remaining nitromethane was removed under high vacuum with a water bath at room temperature to give crude nitroalkene. The crude product was recrystallized from hexane with hot gravity filtration to afford 3.89 g (85%) of nitroalkene **16** as yellow, crystaline solid. Data for **16**: mp 92–93 °C (hexane); ^1H NMR 9.06 (d, J = 11.0, 1 H), 8.12 (dd, J = 8.2, 0.9, 2 H), 7.70 (tt, J = 7.5, 1.2, 1 H), 7.53 (t, J = 7.8, 2 H), 7.42 (d, J = 11.2, 1 H); ^{13}C NMR 161.47, 148.29, 135.14, 130.56, 129.66, 128.95, 126.34; IR (CCl_4) 1765 (s), 1159 (s); MS (CI, CH_4) 194 (M^+ + H, 0.4). Anal. Calcd for $C_9H_7NO_4$ (193.10): C, 55.96; H, 3.65; N, 7.25. Found: C, 55.94; H, 3.71; N, 7.22.

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

[4*R*,6*R*]-4-(Benzoyloxy)-6-[(1*S*,2*R*)-(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (+)-(18a). To a solution of titanium tetrachloride (1.00 mL, 9.15 mmol, 3.0 equiv) in dichloromethane (30 mL) was added titanium tetraisopropoxide (2.75 mL, 9.19 mmol, 3.0 equiv). The clear solution was stirred at room temperature for 30 min. To a solution of nitroalkene **16** (585 mg, 3.03 mmol) in dichloromethane (9 mL) was added vinyl ether **17**[7g] (1.227 g, 6.06 mmol, 2 equiv). The solution was cooled to −90 °C with the formation of a white precipitate of nitroalkene. A solution of titanium diisopropoxide dichloride (6 equiv) was added over 15 min. The resulting solution was stirred for 10 min at −90 °C, allowed to warm to −78 °C, and stirred for an additional 4.5 h. The reaction was quenched with 1 N NaOH in methanol (25 mL) at −78 °C and then poured directly into dichloromethane (600 mL), washed with water (2 × 200 mL), and back extracted with dichloromethane (2 × 200 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc (6/1, 4/1, 2/1)) to give 950 mg of (+)-**18a** and 74 mg (6%) of an inseparable mixture (^1H NMR ca. 2.7/1) of compounds **18b** with the empirical formula $C_{23}H_{25}NO_5$ from combustion analysis. The residue was recrystallized from hexane/EtOAc to give 855 mg (71%) of (+)-**18a** as highly crystalline light brown solid. Data for (+)-**18a**: mp 122–123 °C (hexane/EtOAc); ^1H NMR 8.07 (d, J = 7.1, 2 H), 7.63 (t, J = 7.3, 1 H), 7.51 (t, J = 7.7, 2 H), 7.26–7.16 (m, 5 H), 6.53 (d, J = 3.9, 1 H), 5.51 (ddd, J = 2.1, 4.2, 8.6, 1 H), 4.64 (m, 1 H), 3.72 (dt, J_d = 4.3, J_t = 10.2, 1 H), 2.56–2.50 (m, 1 H), 2.28–2.26 (m, 1 H), 1.99–1.76 (m, 5 H), 1.68–1.58 (m, 1 H), 1.55–1.42 (m, 2 H), 1.40–1.25 (m, 1 H); ^{13}C NMR 165.51, 143.52, 133.49, 129.74, 129.40, 128.48, 128.27, 127.74, 126.59, 109.77, 101.92, 84.38, 61.52, 51.39, 34.26, 32.30, 29.42, 25.56, 24.96; IR (KBr) 2930 (s), 1718 (s), 1622 (s), 1446 (s); MS (EI, 70 eV) 395 (M^+, 0.1); $[\alpha]^{25}_D$ +144.2° (CH_2Cl_2, c = 1.00); TLC R_f 0.36 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{23}H_{25}NO_5$ (395.45): C, 69.85; H, 6.37; N, 3.54. Found: C, 69.85; H, 6.37; N, 3.53.

Data for **18b**: mp 56–58 °C; ^1H NMR 8.07–8.03 (m, 1.4 H), 7.88–7.86 (m, 0.6 H), 7.63–7.55 (m, 1 H), 7.49–7.41 (m, 2 H), 7.29–7.04 (m, 5 H), 6.02 (d, J = 4.4, 0.3 H), 5.66–5.61 (m, 1 H), 5.38–5.37 (m, 0.3 H), 4.85 (dd, J = 5.5, 1.8, 0.5 H), 4.21–4.10 (m, 0.5 H), 3.76–3.69 (m, 1 H), 2.61–2.09 (m, 4 H), 1.93–1.18 (m 9 H); ^{13}C NMR 165.42, 156.25, 143.55, 143.51, 133.34, 133.27, 129.95, 129.89, 128.31, 128.23, 127.84, 127.32, 126.51, 125.86, 109.00, 106.83, 95.46, 83.78, 76.68, 69.09, 61.25, 51.10, 50.48, 37.01, 34.76, 34.30, 32.41, 29.86, 29.56, 25.97, 25.92, 25.56, 24.99, 24.48; IR (KBr) 3028 (w), 2930 (m), 2856 (w), 1770 (m), 1601 (w), 1493 (w); TLC R_f = 0.19 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{23}H_{25}NO_5$ (395.45): C, 69.85; H, 6.37; N, 3.54. Found: C, 69.65; H, 6.40; N, 3.52.

(2*S*,3a*S*,3*R*,4*R*,6*R*)-3-Carbomethoxy-4-(benzoyloxy)-6-[(1*S*,2*R*)-2-phenyl-cyclohexyloxy]hexahydroisoxazolo-[1,7-*b*] [1,2]oxazine-2-carboxylic Acid Methyl Ester (−)-(19). To a solution of nitronate (+)-**18a** (770 mg, 1.94 mmol) in benzene (50 mL) was added dimethyl maleate (0.96 mL, 7.76 mmol, 4 equiv) and the solution was stirred at room temperature for 10.5 h. The solution was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc (8/1, 4/1, 2/1)) to give 973 mg of nitroso acetal (−)-**19**. The crude product was recrystallized from hexane/EtOAc to give 929 mg (88%) of (−)-**19** as a white amorphous solid. Data for (−)-**19**: mp 151–151.5 °C (hexane/EtOAc); ^1H NMR 8.01 (d, J = 7.6, 2 H), 7.57 (t, J = 7.2, 1 H), 7.44 (t, J = 7.6, 2 H), 7.26–7.17 (m, 5 H), 5.21 (d, J = 9.7, 1 H), 5.08 (dt, J_d = 9.0, J_t = 4.4, 1 H), 4.13 (t, J = 5.8, 1 H), 4.08 (dd, J = 4.0, 9.6, 1 H), 3.77–3.72 (m, 4 H), 3.67–3.54 (m, 4 H), 2.54–2.47 (m, 1 H), 2.38–2.35 (m, 1 H), 1.91–1.84 (m, 3 H), 1.77–1.71 (m, 2 H), 1.66–1.25 (m, 4 H); ^{13}C NMR 169.29, 168.09, 165.51, 143.96, 133.28, 129.65, 129.33, 128.32, 128.03, 127.76, 126.27, 98.75, 82.09, 75.40, 68.51, 52.61, 52.58, 51.14, 51.09, 34.42, 32.40, 29.83, 25.69, 25.13; IR (KBr) 2924 (m), 1755 (s), 1738 (s), 1714 (s), 1448 (s); $[\alpha]^{25}_D$ −18.7° (CH_2Cl_2, c = 1.10); TLC R_f 0.28 (pentane/MtBE, 2/1). Anal. Calcd for $C_{29}H_{33}NO_9$ (539.58) C, 64.55; H, 6.16; N, 2.59. Found: C, 64.66; H, 6.22; N, 2.54.

[1*S*,6*R*,6a*S*,7*R*]-6-(Benzoyloxy)-7-carbomethoxy-1-hydroxyhexahydro-1*H*-pyrrolizin-2-one (−)-(20). To a solution of nitroso acetal (−)-**19** (618 mg, 1.14 mmol) in methanol (90 mL) was added a catalytic amount of methanol-washed W-2 Raney nickel. The suspension was stirred in a 125 mL Erlenmeyer flask in a steel autoclave for 14 h under 260 psi atmosphere of H_2 at room temperature. The catalyst was filtered off, washed with methanol (150 mL) and the solution concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc (8/1, 1/1, 0/1)) to afford 264 mg of α-hydroxy lactam (−)-**20** and 194 mg (96%) of (1*S*,2*R*)-*trans*-2-phenylcyclohexanol. The α-hydroxy lactam was recrystallized from hexane/EtOAc to give 249 mg of (−)-**20** (68%) as a white amorphous solid. The α-hydroxy lactam (−)-**20** was determined to be 97.7% ee by HPLC analysis. Data for (−)-**20**: mp 142−143.5 °C (hexane/EtOAc); ^{1}H NMR 7.99 (d, J = 7.3, 2 H), 7.57 (t, J = 7.3, 1 H), 7.43 (t, J = 7.7, 2 H), 5.21 (dt, J_d = 7.0, J_t = 4.8, 1 H), 4.79 (d, J = 9.6, 1 H), 4.50 (br, d, J = 2.5, 1 H), 4.01 (dd, J = 4.5, 8.7, 1 H), 3.93−3.87 (m, 1 H), 3.75 (s, 3 H), 3.25 (dt, J_d = 11.7, J_t = 7.7, 1 H), 3.15 (t, J = 9.2, 1 H), 2.45−2.37 (m, 1 H), 2.26−2.23 (m, 1 H); ^{13}C NMR 173.09, 171.34, 165.95, 133.40, 129.57, 129.15, 128.41, 76.80, 74.95, 63.80, 54.41, 52.59, 40.93, 31.50; IR (KBr) 3321 (m), 2993 (m), 2949 (m), 2897 (m), 1728 (s), 1707 (s), 1684 (s); $[\alpha]^{25}_D$ −67.8° (CH_3OH, c = 0.97); TLC R_f 0.48 (EtOAc); HPLC t_R (1*R*,6*S*,6a*R*,7*S*)-(+)-**20**, 22.4 min (1.1%); t_R (1*S*,6*R*,-6a*S*,7*S*)-(−)-**20**, 25.4 min (98.8%) (column A; method A). Anal. Calcd for $C_{16}H_{17}NO_6$ (319.31): C, 60.18; H, 5.36; N, 4.38. Found: C, 60.19; H, 5.40; N, 4.39.

[1*S*,6*R*,6a*S*,7*R*]-6-(Benzoyloxy)-7-carbomethoxy-1-[(phenoxythiocarbonyl)oxy]hexahydro-1*H*-pyrrolizin-2-one (−)-(21). To a solution of α-hydroxy lactam (−)-**20** (250 mg, 0.78 mmol) in dichloromethane (10 mL) was added DMAP (48 mg, 0.39 mmol, 0.5 equiv), pyridine (127 μL, 1.56 mmol, 2.0 equiv), and phenyloxy chlorothionoformate (217 μL, 1.56 mmol, 2.0 equiv). The resulting yellow solution was stirred for 3 h at room temperature. The solution was concentrated *in vacuo* and the crude product was then purified by silica gel column chromatography (EtOAc/hexane (1/1, 2/1, 1/0)) to afford 317 mg of (−)-**21**, which was recrystallized from hexane/EtOAc to give 291 mg (82%) of (−)-**21** as a white crystalline solid. Data for (−)-**21**: mp 168 °C (hexane/EtOAc); ^{1}H NMR 8.01 (dd, J = 8.2, 1.2, 2 H), 7.59 (dt, J_d = 1.2, J_t = 7.4, 1 H), 7.47−7.40 (m, 4 H), 7.30 (t, J = 7.5, 1 H), 7.17−7.14 (m, 2 H), 6.48 (d, J = 9.7, 1 H), 5.20 (dt, J_d = 7.6, J_t = 5.2, 1 H), 4.11 (dd, J = 5.1, 8.0, 1 H), 4.02−3.96 (m, 1 H), 3.74 (s, 3 H), 3.51 (dd, J = 8.3, 9.5, 1 H), 3.37−3.30 (m, 1 H), 2.48−2.40 (m, 1 H), 2.36−2.29 (m, 1 H); ^{13}C NMR 194.20, 170.27, 166.64, 166.09, 153.44, 133.54, 129.61, 129.53, 128.94, 128.47, 126.71, 121.67, 82.07, 76.81, 63.86, 52.82, 51.63, 41.07, 31.32; IR (KBr) 3063 (m), 2957 (m), 2926 (m), 2893 (w), 1749 (s), 1720 (s); MS (EI, 70 eV) 456 (M^+ + 1, 0.01), 455 (M^+, 0.01); $[\alpha]^{25}_D$ −68.7° (CH_2Cl_2, c = 1.02); TLC: R_f 0.47 (hexane EtOAc, 1/1). Anal. Calcd for $C_{23}H_{21}NO_7$ (455.48): C, 60.65; H, 4.64; N, 3.07. Found: C, 60.61; H, 4.62; N, 3.05.

[6*R*,6a*S*,7*S*]-6-(Benzoyloxy)-7-carbomethoxyhexahydro-1*H*-pyrrolizin-2-one (+)-(22). To a refluxing solution of (−)-**21** (271 mg, 0.59 mmol) in benzene (62 mL) was added dropwise a solution of tributyltin hydride (278 μL, 0.77 mmol, 1.3 equiv) and AIBN (19.5 mg, 0.11 mmol, 0.2 equiv) in benzene (8 mL) over 50 min. The resulting solution was stirred at reflux for an additional 2.5 h, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography fitted with a plug on top of potassium flouride (EtOAc/hexane (1/1, 2/1, 1/0)) to afford 167 mg of (+)-**22** which was recrystallized from hexane/EtOAc to give 157 mg (87%) of lactam (+)-**22** as a white, crystalline solid. Data for (+)-**22**: mp 104−105 °C (hexane/EtOAc); ^{1}H NMR 7.97 (d, J = 7.3, 2 H), 7.55 (t, J = 7.4, 1 H), 7.41 (t, J = 7.7, 2 H), 5.11 (dd, J = 5.4, 12.7, 1 H), 4.17 (dd, J = 5.3, 7.7, 1 H), 3.83−3.77 (m, 1 H), 3.66 (s, 3 H), 3.30−3.18 (m, 2 H), 2.91 (dd, J = 11.1, 16.5, 1 H), 2.66 (dd, J = 9.3, 16.6, 1 H), 2.42−2.32 (m, 1 H), 2.21−2.18 (m, 1 H); ^{13}C NMR 172.47, 172.05, 165.97, 133.27, 129.47, 129.16, 128.32, 76.65, 67.74, 52.30, 44.23, 40.29, 37.53, 32.16; IR (KBr) 2949 (m), 1732 (s), 1707 (s), 1676 (s); MS (EI, 70 eV) 304 (M^+ + 1, 0.01); $[\alpha]^{25}_D$ +13.4° (CH_2Cl_2, c = 1.01); TLC R_f 0.24 (EtOAc/hexane, 2/1). Anal. Calcd for $C_{16}H_{17}NO_5$ (303.31): C, 63.35; H, 5.64; N, 4.61. Found: C, 63.31; H, 5.63; N, 4.62.

(−)-Hastanecine (2). To a refluxing solution of lithium aluminum hydride (120 mg, 3.18 mmol, 6 equiv) in THF (8.7 mL) was added a solution of lactam (+)-**22** (161 mg, 0.53 mmol) in THF (8.7 mL). The resulting solution was stirred at reflux an additional 3.5 h, cooled to room temperature, and quenched with water (0.32 mL), 10% NaOH (0.32 mL), and water (0.62 mL). The mixture was diluted with THF (10 mL) and stirred for 20 min and with time the solution turned light gray. The mixture was filtered through a sintered glass funnel, and the cake was washed with MeOH (50 mL) and concentrated *in vacuo* to give 233 mg of a white solid. The crude product was purified by silica gel chromatography. The silica gel column was prepared by having a large Celite plug (1/2 the height of the silica gel) at the bottom of the column ($CHCl_3$/MeOH/NH_4OH, 10/5/1) to give 77 mg of a white crystaline solid. The solid required further purification by chromatography on basic alumina activity II ($CHCl_3$/MeOH 6/1, 4/1, 2/1). Which was followed by passing it through a plug of basic alumina activity IV ($CHCl_3$/MeOH 6/1, 4/1, 2/1) to give 67 mg of white solid which was recrystallized from acetone to give 59 mg (71%) of (−)-hastanecine as a highly crystalline white solid. Data for (−)-**2**: mp 111−112 °C (acetone); ^{1}H NMR (CD_3OD) 4.93 (s, 2 H), 4.06 (dt, J_d = 4.9, J_t = 2.7, 1 H), 3.63−3.54 (m, 2 H), 3.30−3.04 (m, 2 H), 2.96 (dd, J = 2.1, 7.5, 1 H), 2.70 (ddd, J = 4.2, 6.9, 11.2, 1 H), 2.53 (dt, J_d = 5.5, J_t = 10.2, 1 H), 2.06−1.87 (m, 3 H), 1.73−1.67 (m, 1 H), 1.58−1.50 (m, 1 H); ^{13}C NMR (CD_3OD) 77.82, 76.79, 65.27, 55.36, 53.00, 47.77, 33.50, 30.87; ^{1}H NMR 4.90 (s, very broad, 2 H), 4.06 (dd, J = 5.3, 8.8, 1 H), 3.78 (dd, J = 4.3, 10.6, 1 H), 3.51 (dd, J = 7.8, 10.5, 1 H), 3.19−3.10 (m, 3 H), 2.62 (dt, J_d = 10.7, J_t = 6.2, 1 H), 2.48 (dt, J_d = 5.5, J_t = 10.0, 1 H), 2.04 (dt, J_d = 18.8, J_t = 6.3, 1 H), 1.95−1.78 (m, 3 H), 1.65−1.57 (m, 1 H); ^{13}C NMR 76.78, 76.50, 64.45, 54.88, 52.64, 46.64, 33.90, 29.86; IR (KBr) 3318 (s), 2982 (s), 2910 (s), 2856 (s), 2573 (m); MS (EI, 70 eV) 157 (M^+, 6), 113 (17), 82 (100); $[\alpha]^{23}_D$ −10.4° (ethanol, c = 0.44); TLC R_f 0.13 (chloroform/methanol/ammonium hydroxide (10/5/1)). Anal. Calcd for $C_8H_{15}NO_2$ (157.21): C, 61.12; H, 9.61; N, 8.91. Found: C, 61.13; H, 9.62; N, 8.90.

[1*S*,6*R*,6a*S*,7*R*]-1-[(*S*)-(methoxyphenylacetyl)oxy]-6-(benzoyloxy)-7-carbomethoxyhexahydro-1*H*-pyrrolizin-2-one (23a) and [1*R*,6*S*,6a*R*,7*S*]-1-[(*S*)-(methoxyphenylacetyl)oxy]-6-(benzoyloxy)-7-carbomethoxyhexahydro-1*H*-pyrrolizin-2-one (23b). To a solution of α-hydroxy lactam (±)-**20** (104 mg, 0.31 mmol) in acetonitrile (1 mL) was added 1-hydroxybenzotriazole (47.8 mg, 0.35 mmol, 1.1 equiv) and *N*-cyclohexyl-*N*′-[(*N*″-methyl-2-morpholinio)ethyl]carbodiimide 4-toluenesulfonate (178.9 mg, 0.42 mmol, 1.3 equiv). To the solution was added a solution of (*S*)-methoxyphenylacetic acid (59.5 mg, 0.35 mmol, 1.1 equiv) in acetonitrile (4.2 mL) and a solution of pyridine (27 mg, 0.35 mmol, 1.1 equiv) in acetonitrile (1.0 mL). The clear solution was stirred at room temperature, after 30 min the formation of white precipitate was observed. The solution was stirred an additional 68 h and then diluted with EtOAc (200 mL) and washed with water (40 mL) followed by saturated aqueous Na_2CO_3 solution (40 mL). The aqueous layer was back extracted with EtOAc (40 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc (4/1, 2/1, 1/1, 1/2)) to give 36 mg (23%) of the less polar diastereomer **23a** (R_f 0.37), 46 mg of the more polar diastereomer **23b** (R_f 0.26), and 32 mg (30%) of recovered α-hydroxy lactam **20**. Crystals of the less polar diastereomer **23a** suitable for X-ray analysis were obtained by diffusion crystallization from acetone/pentane. The more polar diastereomer **23b** was repurified by silica gel column chromatography (hexane/EtOAc, 1/1) to give 40 mg (26%) as a gum which could not be separated from an unidentified impurity. Data for **23a**: ^{1}H NMR 7.98 (d, J = 7.0, 2 H), 7.58 (t, J = 7.4, 1 H), 7.49−7.42 (m, 4 H), 7.40−7.32 (m, 3 H), 5.72 (d, J = 9.8, 1 H), 5.15 (dt, J_d = 7.6, J_t = 5.4, 1 H), 4.90 (s, 1 H), 4.06 (dd, J = 5.0, 7.9, 1 H), 3.95−3.89 (m, 1 H), 3.56 (s, 3 H), 3.48 (s, 3 H), 3.38 (dd, J = 8.1, 9.6, 1 H), 3.31−3.25 (m, 1 H), 2.47−2.40 (m, 1 H), 2.32−2.25 (m, 1 H);

^{13}C NMR 170.42, 169.82, 167.35, 166.14, 135.47, 133.49, 129.63, 129.03, 128.84, 128.59, 128.46, 127.21, 82.34, 76.94, 75.50, 63.67, 57.64, 52.55, 51.10, 40.98, 31.31; IR (KBr) 2953 (m), 1761 (s), 1734 (s), 1714 (s), 1599 (m); TLC R_f 0.37 (hexane/EtOAc, 1/1); HPLC t_R **23a**, 8.9 min (column B; method B). Data for **23b**: ^{1}H NMR 7.97–7.95 (m, 2 H), 7.58 (t, J = 7.5, 1 H), 7.47–7.43 (m, 4 H), 7.41–7.35 (m, 3 H), 5.81 (d, J = 10.0, 1 H), 5.08 (dt, J_d = 7.5, J_t = 5.3, 1 H), 4.90 (s, 1 H), 4.06 (dd, J = 5.1, 8.3, 1 H), 3.91 (ddd, J = 5.3, 8.1, 12.1, 1 H), 3.53 (s, 3 H), 3.45 (s, 3 H), 3.29 (dt, J_d = 12.0, J_t = 7.6, 1 H), 3.11 (dd, J = 8.3, 9.7, 1 H), 2.47–2.38 (m, 1 H), 2.31–2.23 (m, 1 H); ^{13}C NMR 170.22, 169.58, 167.40, 166.13, 135.52, 133.52, 129.62, 128.98, 128.91, 128.62, 128.46, 127.43, 81.96, 76.80, 75.11, 63.54, 57.51, 52.53, 51.55, 40.92, 31.35; IR (CCl_4) 2953 (m), 1730 (s), 1603 (w); MS (EI, 70 eV) 467 (M^+, 0.004); TLC R_f 0.26 (hexane/EtOAc 1/1); HPLC t_R **23b**, 15.0 min (column B; method B); HRMS calcd for $C_{25}H_{25}NO_8$ (467.15801), found 467.15841.

[1*S*,6*R*,6a*S*,7*R*]-1-[(*S*)-(methoxyphenylacetyl)oxy]-6-(benzoyloxy)-7-carbomethoxyhexahydro-1*H*-pyrrolizin-2-one (23a). To a solution of α-hydroxy lactam (−)-**20** (50 mg, 0.15 mmol) in acetonitrile (0.5 mL) was added 1-hydroxybenzotriazole (23 mg, 0.17 mmol, 1.1 equiv) and *N*-cyclohexyl-*N*′-[(*N*″-methyl-2-morpholinio)ethyl]carbodiimide *p*-toluenesulfonate (86 mg, 0.20 mmol, 1.3 equiv). To the solution was added a solution of (*S*)-methoxyphenylacetic acid (28.6 mg, 0.17 mmol, 1.1 equiv) in acetonitrile (2.0 mL) and a solution of pyridine (13 mg, 0.17 mmol, 1.1 equiv) in acetonitrile (0.5 mL). The clear solution was stirred at room temperature. After 15 min the formation of white precipitate was observed. The solution was stirred an additional 56 h and then diluted with EtOAc (100 mL) and washed with water (20 mL) followed by saturated aqueous Na_2CO_3 (20 mL). The aqueous layer was back extracted with EtOAc (20 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc (4/1, 2/1, 1/1, 1/2, 0/1)) to give 43 mg (58%) of the less polar diastereomer **23a** (R_f 0.33) as a white solid and 20 mg (40%) of recovered α-hydroxy lactam. An analytical sample of lactam **23a** was obtained by recrystallization from hexane/EtOAc. Data for **23a**: mp 183–185 °C (hexane/EtOAc); ^{1}H NMR 7.98 (d, J = 7.3, 2 H), 7.58 (t, J = 7.3, 1 H), 7.49–7.42 (m, 4 H), 7.40–7.32 (m, 3 H), 5.72 (d, J = 9.8, 1 H), 5.15 (dt, J_d = 7.3, J_t = 5.4, 1 H), 4.90 (s, 1 H), 4.06 (dd, J = 5.1, 8.1, 1 H), 3.95–3.89 (m, 1 H), 3.56 (s, 3 H), 3.48 (s, 3 H), 3.38 (dd, J = 8.2, 9.6, 1 H), 3.31–3.25 (m, 1 H), 2.47–2.40 (m, 1 H), 2.32–2.25 (m, 1 H); ^{13}C NMR 170.41, 169.82, 167.35, 166.14, 135.47, 133.49, 129.61, 129.03, 128.83, 128.59, 128.45, 127.20, 82.33, 76.93, 75.49, 63.66, 57.64, 52.55, 51.09, 40.97, 31.31; IR (KBr) 2953 (m), 1759 (s), 1734 (s), 1714 (s), 1599 (w); MS (EI, 70 eV) 467 (M^+, 0.01); TLC R_f 0.33 (hexane/EtOAc, 1/1); HPLC t_R **23a**, 8.8 min (column B; method B). Anal. Calcd for $C_{25}H_{25}NO_8$ (467.47): C, 64.23; H, 5.39; N, 2.99. Found: C, 64.35; H, 5.27; N, 3.00.

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Supplementary Material Available: ORTEP plot and fractional coordinates for the X-ray crystal structure of **23a** along with a complete listing of ^{1}H NMR and ^{13}C NMR with assignments, infrared absorbances, and mass spectral fragments for all compounds described, ^{1}H NMR and ^{13}C NMR spectra of compounds **23b** and (−)-**2** along with comparison spectra of synthetic (−)-**2** and (+)-**2** are provided (18 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.