Synthesis of Tropane Alkaloids via Enantioselective Deprotonation of Tropinone

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · JUNE 1995

Impact Factor: 4.72 · DOI: 10.1021/jo00123a018

Synthesis of Tropane Alkaloids *via* Enantioselective Deprotonation of Tropinone

Marek Majewski* and Ryszard Lazny

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada

Received April 10, 1995[⊗]

Enantioselective deprotonation of tropinone **2** with chiral lithium amides **5a** and **6a**, in the presence of LiCl, gave tropinone lithium enolate in up to 95% ee. The C_2 symmetrical lithium amide **6a** worked best when it was generated *in situ* from the hydrochloride salt of the corresponding amine **6b**. The deprotonation was used as the key step in synthesis of tropane alkaloids: *ent*-anhydroecgonine, *ent*-knightinol, KD-B, chalcostrobamine, *ent*-isobellendine, and *ent*-darlingine. The absolute configuration of natural benzyltropane and pyranotropane alkaloids was established (by correlation with anhydroecgonine) to be 'cocaine-like' i.e., the side chain originates at C-2 of the tropane ring system in all cases.

Introduction

Tropane alkaloids comprise a group of some 200 natural products which mostly occur in plants of *Solanaceae* family.[1] Many of these compounds have interesting biological properties.[1] Chiral tropane alkaloids can be perceived as nonsymmetrically substituted derivatives of 8-methyl-8-azabicyclo[3.2.1]octane (tropane, **1**) having an OH (or functionalized OH) at the 3-position;[2] another OH (free or protected as an ether or an ester) might be present at C-6 or C-7 (or both), and a side chain (usually a carboxyl derivative, hydroxybenzyl group, or benzyl group) is connected to C-2 or C-4 (Figure 1). Absolute configuration of the majority of chiral tropane alkaloids is not known and most of the syntheses of these natural products reported to date were aimed at the racemic modifications.[1] A good synthetic strategy toward tropane alkaloids should be general, i.e., it should allow approaches to several different alkaloids and should be enantioselective with the possibility of synthesizing both enantiomers *via* essentially the same route being a desirable feature.

We are interested in using tropinone (**2**) as the starting material for synthesis of diverse tropane alkaloids. Hydroxyalkylation and carboalkoxylation of tropinone were used in the past as key reactions toward synthesis of several tropane alkaloids by Bick and Lounasmaa.[1,3] These early studies deserve much credit due to their pioneering nature; however, the issues of enantio-, diastereo-, and regioselectivity were not addressed and the yields were, for the most part, low.

Earlier, we,[4] and others,[5] have reported enantioselective deprotonation of tropinone with chiral lithium amide bases. This reaction forms the cornerstone of the work described below.

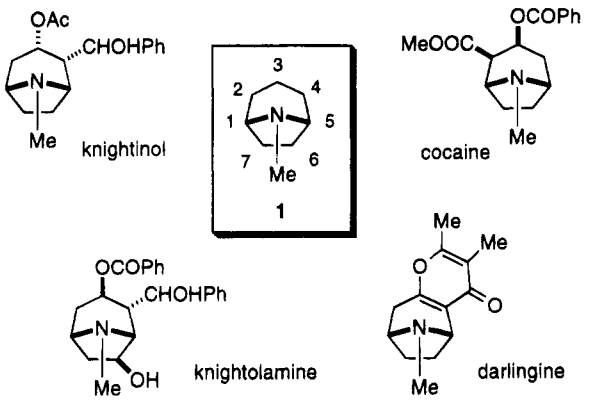


Figure 1. Selected tropane alkaloids. Each structure represents a group of compounds (ref 1).

Results

Enantioselective Deprotonation of Tropinone. We used the aldol addition of tropinone lithium enolate to benzaldehyde to optimize enantioselectivity of deprotonation. This reaction is highly diastereoselective and only the exo-anti diastereoisomer of the aldol **4** is produced (Scheme 1).[4a] Furthermore, the enantiomer ratio of the aldols (+)-**4** and (−)-**4** can be measured by NMR (c.f., the Experimental Section). Earlier studies in our group,[4] involving various lithium amide bases, led to the conclusion that the lithium amide **5a**, derived from the bidentate amine **5b**, was the most promising reagent. After some experimentation, aimed at optimizing the conditions of deprotonation, we observed that the amide **5a** gave the aldol **4** having the highest enantiomeric excess (ee) when 0.5 equiv of LiCl was present in the reaction mixture: (+)-**4** was produced in 95% ee (the absolute configuration of this isomer is shown in Scheme 1, *vide infra*). Another promising base, the C_2 symmetrical lithium amide **6a**, showed much more pro-

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1995.

(1) Reviews: (a) Lounasmaa, M.; Tamminen, T. *Alkaloids* **1993**, *44*, 1. (b) Lounasmaa, M. *Ibid.* **1988**, *33*, 1.

(2) Tropane alkaloid numbering (cf., ref 1) is used throughout the paper except the titles in the Experimental Section. Any two tropanes substituted with the same group at C-2 or C-4 (both α or both β); C-6 or C-7 (both α or both β), but otherwise identical, are enantiomers.

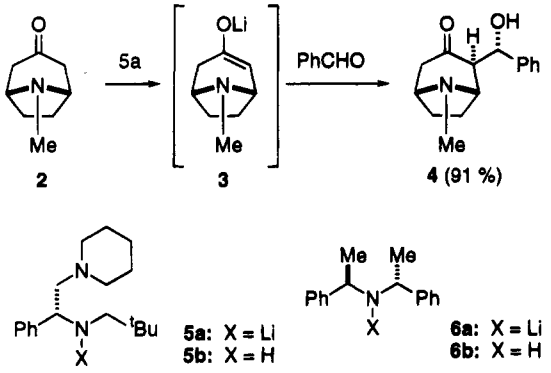
(3) (a) Bick, I. R. C.; Bremmer, J. B.; Gillard, J. W. *Tetrahedron Lett.* **1973**, 5099. (b) Lounasmaa, M.; Johansson, C.-J. *Ibid.* **1974**, 2509. (c) Lounasmaa, M.; Langenskiold, T.; Holmberg, C. *Ibid.* **1981**, *22*, 5179. (d) Lounasmaa, M.; Holmberg, C.; Langenskiold, T. *J. Nat. Prod.* **1983**, *46*, 429. (e) Lounasmaa, M.; Holmberg, C.; Langenskiold, T. *Planta Med.* **1983**, *48*, 56. (f) Kan-Fan, C.; Lounasmaa, M. *Acta Chem. Scand.* **1973**, *27*, 1039.

(4) (a) Majewski, M.; Zheng, G.-Z. *Can. J. Chem.* **1992**, *70*, 2618. (b) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653.

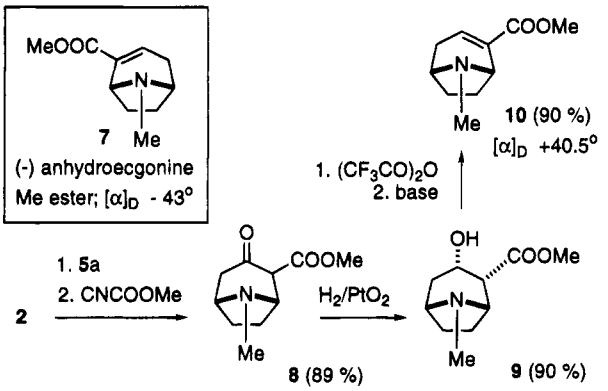
(5) (a) Momose, T.; Toyooka, N.; Seki, S.; Hirai, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2072. (b) Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.* **1990**, 1319. (c) Bunn, B.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3113. (d) A review on enantioselective deprotonation: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

0022-3263/95/1960-5825$09.00/0

Scheme 1



Scheme 2



nounced LiCl effect: in the absence of LiCl the levorotatory aldol (−)-**4** was formed in 36% ee; however, when 1 equiv of LiCl was added to the reaction mixture, the selectivity increased to 90% ee.

The effect of lithium salts on enantioselectivity of deprotonation of ketones has been observed before.[4b,5c,6] The observation that the amide **6a** works best in the presence of 1 equiv of LiCl prompted us to use the HCl salt of the amine **6b** to generate the corresponding lithium amide. When treated with n-BuLi (2 equiv) this salt produced **6a**−LiCl which was used, *in situ*, to deprotonate tropinone. This procedure proved much more convenient than using the free amine; the hydrochloride is easy to purify by crystallization and can be easily stored whereas the free amine **6b** is difficult to distill and readily absorbs moisture and CO_2 from the air.

To establish the absolute stereoselectivity of deprotonation we decided to synthesize an alkaloid of known absolute configuration. The methyl ester of natural anhydroecgonine (**7**) which has the same absolute configuration as cocaine,[7] was chosen for this study. The synthesis of this compound was accomplished *via* deprotonation of tropinone with **5a**, followed by methoxycarbonylation using Mander's reagent under conditions developed earlier in our group,[4a] and by reduction of the β-keto ester **8**, using H_2 over Adams catalyst, followed by dehydration of the resulting alcohol **9** (Scheme 2). The (+)-methyl ester **10** of high optical purity (94% ee; 72% yield from tropinone) was obtained by this sequence of reactions showing that the base **5a** attacks preferentially a hydrogen at C-4 of tropinone (tropane numbering), whereas the base **6a** prefers to abstract the proton from C-2.

Synthesis of Benzyltropanes. This group includes about a dozen alkaloids having the *endo*-benzyl or the *endo*-α-hydroxybenzyl group, which was believed to originate at C-4.[1a] The aldol **4** looked like a good intermediate for synthesis of these tropanes; however, since compound **4** is the *exo*-isomer the epimerization was required. The axial orientation of the side chain in **4** is stabilized by hydrogen bonding between the OH group and the nitrogen.[8] Consequently, all attempts to epimerize compound **4** to its α-isomer using acids or bases were not successful and either the starting material was recovered or retroaldolization occurred. For example treating **4** with Na_2CO_3 in ethanol for 30 min (reflux) led to the complete conversion of the aldol to a mixture of tropinone and benzaldehyde.

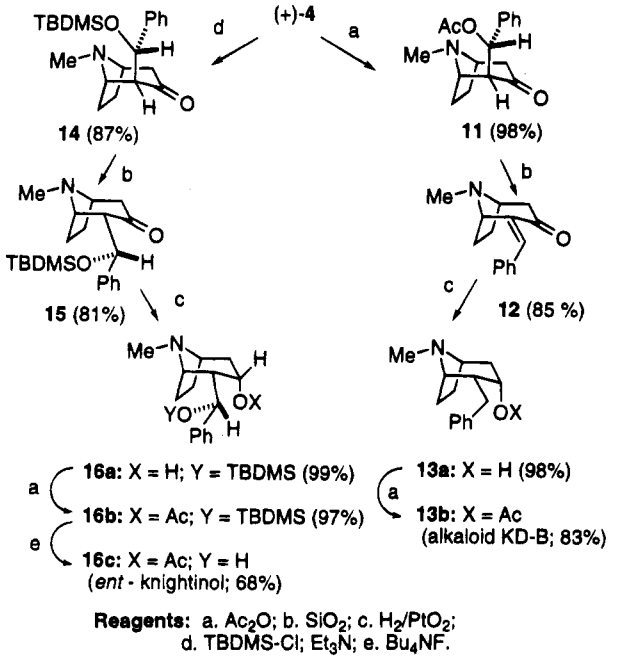
Clearly, the OH group had to be protected to avoid the retro-aldol reaction. Reaction of the (+)-**4** with Ac_2O yielded the acetate (−)-**11** which was unstable and readily underwent elimination to give the enone (−)-**12**. The enone was efficiently hydrogenated and the resulting alcohol **13a** was acetylated to yield alkaloid KD-B (**13b**; absolute stereochemistry as shown).

The TMS enol ether of the aldol (+)-**4** (prepared with TMS-CN) was also unstable and decomposed on a SiO_2 column; however, the TBDMS enol ether (+)-**14** was reasonably stable and could be epimerized cleanly under mildly acidic conditions (SiO_2). Initial attempts at reduction of the ketone group in the resulting compound (−)-**15** with hydride reagents were not successful: reactions with $NaBH_4$ or $LiAlH_4$ proceeded very slowly and the reduction with DIBAL-H, precedented on tropinone,[9a] in our hands was not very clean. Finally, reduction with H_2 over PtO_2 proved clean,[9b] efficient, and highly stereoselective (quantitative yield of **16a**, one isomer), and subsequent acetylation of the reduction product **16a** followed by cleavage of the silyl ether with Bu_4NF yielded (−)-**16c** which had all spectral characteristics identical with the natural product knightinol but was levorotatory (rotation indicated 97% optical purity) (Scheme 3). Since the natural alkaloid is dextrorotatory then compound **16c** must be the *ent*-knightinol, and thus the above synthesis established the absolute configuration of the natural product: the stereogenic center in the side chain of natural knightinol has the *R* configuration (opposite to **16c**) and the side chain must originate at C-2 as is the case in the cocaine group of tropane alkaloids.[1,10]

Synthesis of Pyranotropanes. The nonracemic tropinone lithium enolate **3**, generated *via* deprotonation of tropinone with the chiral lithium amide **5a**, has three nucleophilic centers (oxygen, carbon, and nitrogen) and can react at either of these depending on the electrophile used.[4a] It is well known that acyl cyanides give less O-acylation and are generally better acylating agents than acyl halides or carbonates.[11] Acylation of tropinone with acyl cyanide reagents under thermodynamic conditions was used in synthesis of racemic tropane alkaloids by Lounasmaa.[3d,e] Under kinetic conditions, necessary

(6) Majewski, M.; Gleave, D. M. *J. Org. Chem.* **1992**, *57*, 3599.
(7) (a) Campbell, H. F.; Edwards, E. O.; Kolt, R. *Can. J. Chem.* **1977**, *55*, 1372. (b) Hardegger, E.; Ott, H. *Helv. Chim. Acta* **1955**, *38*, 312.
(8) Li, J.; Quail, J. W.; Zheng, G.-Z.; Majewski, M. *Acta Crystallogr.* **1993**, *C49*, 1410.
(9) (a) Hayakawa, Y.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2617. (b) Keagle, L. C.; Hartung, W. H. *J. Am. Chem. Soc.* **1946**, *68*, 1608.
(10) Absolute stereochemistry of benzyltropanes and pyranotropanes has not been, to the best of our knowledge, conclusively established by either correlation of by X-ray studies. However, structures, presumably drawn in an arbitrary fashion, having the side chain originating at C-4 were published (e.g., ref 1b, p 52) which might lead to confusion.
(11) Mander, L., N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

Scheme 3



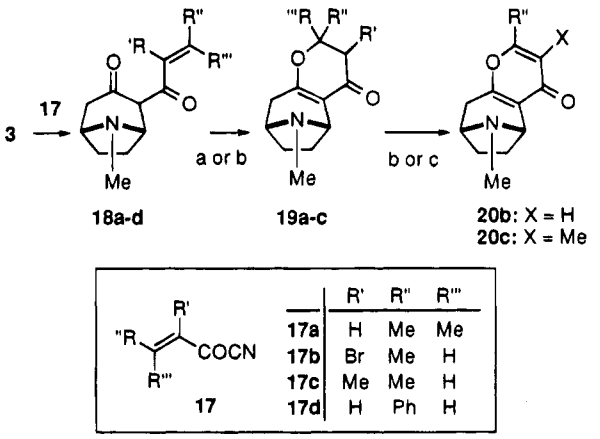
Reagents: a. Ac_2O; b. SiO_2; c. H_2/PtO_2; d. TBDMS-Cl; Et_3N; e. Bu_4NF.

for enantioselective deprotonation, most acyl cyanides afforded the corresponding C-acylation products in good yield which served as a convenient entry into pyranotropanes (Scheme 4).

To generalize and optimize the conditions we tried several acyl cyanides of general structure **17**. Senecioyl cyanide (**17a**) reacted with the enolate **3** to give compound **18a** (90% yield) which could be purified by chromatography but was usually submitted to cyclization (Na_2CO_3, EtOH) in the crude form. The cyclization was efficient and gave the product **19a** in 90% yield (from tropinone) and in 93% ee (by HPLC). Cinnamoyl cyanide (**17d**) readily afforded the levorotatory isomer of 4-cinnamoyltropinone [(−)-**18d**], spectral data of which were identical with those reported for the natural product chalcostrobamine. The dextrarotatory isomer of chalcostrobamine [(+)-**18d**] was synthesized in 92% ee via an identical route but using the base **6a**, generated *in situ* from the hydrochloride of the amine **6b**, for initial deprotonation.

The reaction of tropinone enolate with crotonyl cyanide was not very efficient, and purification of the cyclized product was complicated due to a mixture of diastereoisomers being formed. This prompted us to look for a different reagent which would allow synthesis of isobellendine (**20b**). 2-Bromocrotonyl cyanide (**17b**) was synthesized from crotonyl cyanide and proved to be a good acylating agent, yielding **18b** which, without purification, was subjected to cyclization. The ring closure proceeded with concomitant elimination of HBr to give (−)-**20b** (*ent*-isobellendine) in 45% yield (from tropinone). Tigloyl cyanide (**17c**) was used to synthesize *ent*-darlingine [(−)-**20c**] in a four step sequence: acylation was followed by cyclization (Na_2CO_3/EtOH), bromination (with $CuBr_2$), and elimination (with Et_3N) which finally yielded (−)-**20c** in 53% overall yield from tropinone. It is noteworthy that the syntheses described above established the absolute configuration of pyranotropanes and proved that these natural products have the acyl side chain originating at C-2, analogously to the cocaine series.

Scheme 4



	R'	R"	R'"
17a	H	Me	Me
17b	Br	Me	H
17c	Me	Me	H
17d	H	Ph	H

Reagents: a. Na_2CO_3 / EtOH; b. Et_3N; c. (i) $CuBr_2$, (ii) NH_3
[**18b**: *ent*-chalcostrobamine; **20b**: *ent*-isobellendine; **20c**: *ent*-darlingine]

Conclusions

Enantioselective deprotonation of tropinone was used for synthesis of benzyltropane and pyranotropane alkaloids. Two chiral lithium amide bases **5a** and **6a**, used in the presence of LiCl, deprotonate tropinone with high enantioselectivity and give the opposite enantiomers of the enolate. An efficient procedure for generating a lithium amide–LiCl complex from the hydrochloride of the amide **6a** was developed. Although the *ent*-forms of the natural products were mostly produced in our study, the use of the optical antipode of the chiral base **5a**, or the use of the base **6a**, permits the synthesis of the natural enantiomers (as demonstrated by the synthesis of dextrorotatory chalcostrobamine). The synthetic methodology described above also allowed the assignment of absolute configuration of tropane alkaloids.

Experimental Section

General. All air sensitive reactions were carried out under Ar. THF was distilled under nitrogen from sodium/benzophenone. Diisopropylamine was distilled from CaH_2 and was stored over 4 Å molecular sieves. LiCl was dried at 150 °C and then dissolved in THF, and the solution was stored under Ar. BuLi was periodically titrated using 2,5-dimethoxybenzyl alcohol as the indicator. Flash chromatography[12] was carried out using Merck Kieselgel 60 (230–400 mesh), and TLC was performed on precoated plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), the Dragendorff reagent, or a developing solution made of phosphomolybdic acid and ceric sulfate followed by charring on a hot plate. Optical rotation was measured on Perkin Elmer 241 polarimeter, all concentrations are given in g/100 mL. Mass spectra are reported as *m*/*z* ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV. Infrared (IR) spectra were recorded on a Fourier Transform interferometer with a diffuse reflectance cell. Only diagnostic peaks are reported. Magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts are reported in ppm downfield of TMS (δ).

Chromatographic analyses of enantiomeric purity were done on an HPLC system with a ChiraDex 250-4 column (Merck) and an UV detector (at 254 nm) in 50% MeOH/phosphate buffer (pH = 6.8, *c* = 0.025 M). Errors were estimated to be ±1%. In order to maximize the signal to noise ratio all spectra for ^1H-NMR analysis of enantiomeric excess values (% ee) were recorded on fairly concentrated samples (0.10–0.15 M) in the presence of ca. 15 mg of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthranyl)-ethanol [(*S*)-(+)-TFAE]; errors were estimated statistically as ±2%. The following reagents were prepared as described in

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1979**, *43*, 2923.

the literature: chiral amines **5b**[13] and **6b**,[14] crotonyl cyanide and acyl cyanides **17a,c,d**.[15]

Procedure for Generation of Nonracemic Tropinone Lithium Enolate [(1*S*)-3]. A solution of n-BuLi in hexane (2.0 M, 0.60 mL, 1.2 mmol) was added to a solution of **5b** (0.329 g, 1.2 mmol) in THF (3.5 mL) at 0 °C, and the mixture was stirred for 45 min. LiCl in THF (0.5 molar equivalents per **5b**, 0.50 M, 0.96 mL, 0.48 mmol) was added, and the solution was stirred for 15 min. After cooling to −78 °C, tropinone (0.139 g, 1 mmol) in THF (1 mL) was added dropwise and the resulting solution was stirred for 2.5 h at −78 °C prior to addition of the electrophile.

Procedure for Generation of Nonracemic Tropinone Lithium Enolate [(1*R*)-3] Using Chiral Amine Hydrochloride. A solution of n-BuLi in hexane (2.5 M, 0.92 mL, 2.3 mmol) was added to a solution of the hydrochloride of amine **6b** (0.300 g, 1.15 mmol) in THF (4.0 mL) at 0 °C. The mixture was stirred at 0 °C for 60 min and then was cooled to −78 °C. Tropinone **2** (0.139 g, 1 mmol) in THF (0.5 mL) was then added, and the resulting solution was stirred for 2.5 h at −78 °C prior to addition of the electrophile.

(+)-(1*S*,2*R*,1′*S*)-2-(1′-Hydroxybenzyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (4).[4a] Benzaldehyde (0.13 mL, 0.136 g, 1.28 mmol) was added to nonracemic (1*S*)-**3** (1.0 mmol, cf. above), and the mixture was stirred at −78 °C for 15 min followed by quenching with saturated aqueous NH_4Cl (4 mL). The reaction mixture was warmed up to rt and was extracted with Et_2O (4 × 10 mL). The combined extracts were dried ($MgSO_4$), the solvents were removed, the residue was dissolved in CH_2Cl_2 (1 mL), and the solution was diluted with hexane (20 mL), which caused the product to precipitate. The product was washed with hexane (2 × 10 mL) and dried under vacuum overnight. Compound **4** was obtained as a white crystalline solid (0.225 g, 91%; 95% ee by ^{1}H NMR with (*S*)-(+)-TFAE). Mp 128−130 °C (Et_2O); $[\alpha]^{25}_D$ +19.7° (*c* = 1.20, MeOH), (literature data:[4a] mp 132−133 °C; $[\alpha]^{20}_D$ +23°; *c* = 0.0173, $CHCl_3$).

(−)-(Methoxycarbonyl)tropinone (8).[16a,b] Modified literature procedure:[4a] Methyl cyanoformate (0.12 mL, 0.129 g, 1.5 mmol) was added quickly to the nonracemic enolate (1*S*)-**3** (1.0 mmol), and the mixture was stirred at −78 °C for 30 min followed by quenching with solution of $AgNO_3$ (0.17 g, 1 mmol) in THF (1 mL), water (0.25 mL), and AcOH (0.25 mL). Immediately after warming to rt the mixture was treated with NH_3/H_2O (to dissolve the Ag salts), diluted with water, and extracted with $CHCl_3$ (4 × 10 mL). The combined extracts were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was purified by chromatography (SiO_2 deactivated with Et_3N; 50% AcOEt in hexane followed by 10% MeOH in CH_2Cl_2) which afforded **8** as white crystals (0.175 g, 89%). Mp 102−104 °C (sublimed; lit.[16a] mp 104−105 °C); $[\alpha]^{25}_D$ −16.4° (*c* = 1.06, MeOH; lit.[16b] $[\alpha]^{18}_D$ −20.2°; *c* = 1, MeOH); 92% ee by ^{1}H NMR with (*S*)-(+)-TFAE.

(+)-(Methoxycarbonyl)tropine (9).[16a] (−)-(Methoxycarbonyl)tropinone (0.197 g, 1 mmol) was dissolved in absolute EtOH (12 mL) and hydrogenated over PtO_2 catalyst (8 mg) at 50 psi for 4 days. When TLC (10% MeOH-CH_2Cl_2) showed almost complete conversion the catalyst was filtered off using Celite and the solvent was removed under vacuum. The residue was 94% pure **9** by NMR. Further purification by chromatography (10% MeOH in CH_2Cl_2 followed by MeOH:$CHCl_3$ 1:1) gave **9** as a colorless oil (0.179 g, 90%). Mp 73−75 °C (hexane; lit.[16a] mp 79−80 °C); $[\alpha]^{25}_D$ +39.3° (*c* = 0.47, $CHCl_3$; lit.[16a] $[\alpha]^{20}_D$ +37.7°; *c* = 1, $CHCl_3$). ^{1}H-NMR 4.29 (t, *J* = 4.5, 1H), 3.76 (s, 3H), 3.50−3.43 (m, 1H), 3.17−3.10 (m, 1H), 2.95 (t, *J* = 3.5, 1H), 2.33 (s, 3H), 2.16−1.94 (m, 5H), 1.85−1.75 (m, 1H).

(+)-*ent*-Anhydroecgonine Methyl Ester (10).[7] A solution of compound **9** (0.30 g, 1.5 mmol), DMAP (0.003 g), and Et_3N (0.6 mL) in CH_2Cl_2 (2 mL) was cooled to 0 °C. Trifluoroacetic anhydride (0.27 mL, 0.40 g, 1.9 mmol) was added, and the reaction mixture was stirred for 40 h at rt. Quenching with a K_2CO_3 solution, followed by extraction with $CHCl_3$, drying ($MgSO_4$), and concentration under vacuum, yielded a yellow oil of crude **10** (0.271 g). Purification by chromatography (SiO_2; 10% MeOH in CH_2Cl_2) gave a colorless oil of pure **10** (0.244 g, 90%; 93% ee by ^{1}H NMR with (*S*)-(+)-TFAE). $[\alpha]^{25}_D$ +40.5° (*c* = 1.50, MeOH; lit.[7] $[\alpha]_D$ +43°; *c* = 1.5, MeOH). ^{1}H-NMR 6.85 (t, *J* = 3 Hz, 1H), 3.95 (d, *J* = 5 Hz, 1H), 3.76 (s, 3H), 3.50−3.28 (m, 1H), 2.73 (d br, *J* = 20 Hz, 1H), 2.45 (s, 3H), 2.45−2.20 (m, 2H), 2.00−1.88 (m, 2H), 1.65−1.50 (m, 1H).

(−)-(1*S*,2*R*,1′*S*)-2-[(Acetyloxy)benzyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-one (11). Aldol (+)-**4** (0.123 g, 0.50 mmol) was dissolved in Et_3N (0.3 mL), and Ac_2O (0.07 mL, 0.076 g, 0.75 mmol) was added. After standing at rt for 15 h the reaction mixture was shaken with aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried, and the solvent was removed under vacuum to yield pure **11** (0.141 g, 98%) which slowly decomposed on standing. $[\alpha]^{25}_D$ −22.7° (*c* = 1.00, MeOH). ^{1}H-NMR 7.50−7.30 (m, 5H), 6.45 (d, *J* = 10.5 Hz, 1H), 3.41 (m, 1H), 3.03 (dd, J_1 = 14.5 Hz, J_2 = 6 Hz, 1H), 2.68 (d, *J* = 5 Hz, 1H), 2.50 (d, *J* = 10.5,1H), 2.23 (s, 3H), 1.99 (s, 3H), 2.18−1.95 (m, 3H), 1.65−1.25 (m, 2H). ^{13}C-NMR 209.9, 169.9, 138.3, 128.5, 128.4, 127.5, 75.4, 65.0, 63.4, 62.7, 48.8, 41.0, 25.9, 25.8, 20.9. IR (neat) 1710 (C=O), 1735 (C=O). MS (CI-NH_3) 289 (27), 288 (100), 229 (15), 228 (71), 147 (16), 144 (16), 140 (13), 82 (59).

(−)-(1*S*,2*E*)-2-Benzylidene-8-methyl-8-azabicyclo[3.2.1]-octan-3-one (12).[3b] Attempted purification of the acetate **11** (0.141 g, 0.49 mmol) on a SiO_2 column resulted in complete elimination to give **12**. The product was taken in CH_2Cl_2 and washed with Na_2CO_3. The organic layer was dried ($MgSO_4$), the solvent was removed under vacuum, and the residue was purified by chromatography (AcOEt:hexane, 1:1 followed by 3% MeOH in CH_2Cl_2) which afforded an oil comprising a mixture (20:1) of two diastereoisomers of **12** (0.095 g, 85%). $[\alpha]^{25}_D$ −390° (*c* = 1.03, MeOH); ^{1}H-NMR 7.60 (s, 1H), 7.45−7.30 (m, 5H), 4.45 (d, *J* = 7 Hz, 1H), 3.65 (t, *J* = 6 Hz, 1H), 2.95 (ddd, J_1= 19 Hz, J_2 = 5.5 Hz, J_3 = 2 Hz, 1H), 2.46 (s, 3H), 2.60−2.30 (m, 3H), 2.05−1.90 (m, 1H), 1.85−1.70 (m, 1H).

Alkaloid KD-B (13b).[3b] Compound **12** (0.125 g, 0.55 mmol) dissolved in EtOH (absolute, 6 mL) was hydrogenated for 48 h at 55 psi with PtO_2 (6 mg) catalyst. After filtering the catalyst off (Celite) and removal of the solvent, a white solid of the alcohol **13a** was obtained (0.125 g, 98%). Mp 137−138 °C (hexane; lit.[3b] mp of the racemate 123−124 °C); $[\alpha]^{25}_D$ −19.7° (*c* = 1.22, MeOH). ^{1}H-NMR 7.31−7.15 (m, 5H), 3.76 (7, *J* = 4.5 Hz, 1H), 3.13 (br s, 1H), 2.87 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 2.80 (dd, J_1 = 13.5 Hz, J_2 = 8.5 Hz, 1H), 2.67 (dd, J_1 = 13.5 Hz, J_2 = 7.5 Hz, 1H), 2.35−2.22 (m, 1H), 2.27 (s, 1H), 2.14−1.78 (m, 5H), 1.69 (br d, *J* = 14 Hz, 1H). ^{13}C-NMR 140.0, 128.9, 128.2, 125.7, 65.6, 64.0, 60.2, 46.1, 40.2, 39.7, 35.3, 25.2, 21.7.

A mixture of compound **13a** (0.054 g, 0.53 mmol), triethylamine (0.5 mL), DMAP (5 mg), acetic anhydride (0.05 mL), and $CHCl_3$ (a few drops) was kept at rt for 48 h. The solvents were removed under vacuum, and the residue was diluted with aqueous Na_2CO_3 and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated (rotovap), and the product was purified by chromatography (3−10% MeOH in CH_2Cl_2) which yielded the alkaloid **13b** as an oil (0.061 g, 85%; 94% ee by ^{1}H NMR with (*S*)-(+)-TFAE). $[\alpha]^{25}_D$ +1.40° (*c* = 1.78, MeOH); $[\alpha]^{25}_D$ −13.6° (*c* = 1.0, $CHCl_3$); lit.[3f] $[\alpha]_D$ 0° (no solvent or temperature given). ^{1}H-NMR 7.35−7.10 (m, 5H), 4.90 (t, *J* = 4.5 Hz, 1H), 3.20−3.13 (m, 1H), 2.95−2.85 (m, 1H), 2.73−2.53 (m, 2H), 2.30 (s, 3H), 2.50−2.00 (m, 3H), 2.12 (s, 3H), 2.20−1.80 (m, 2H), 1.75 (d, *J* = 15 Hz, 1H). ^{13}C-NMR 170.1, 139.1, 128.8, 128.3, 126.0, 69.1, 63.4, 69.9, 45.2, 40.3, 36.8, 35.0, 25.2, 21.5, 21.2.

(13) Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690.
(14) Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am.Chem. Soc.* **1961**, *83*, 1374.
(15) (a) Hoffmann, H. M. R.; Haase, K.; Ismail, Z. M.; Preftitsi, S.; Weber, A. *Chem. Ber.* **1982**, *115*, 3880. (b) Normant, J. F.; Piechucki, C. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2402.
(16) (a) Carroll, F. I.; Lewin A. H.; Abraham, P.; Parham, K.; Boja, J.; W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883. (b) Lewin A. H.; Naseree T.; Carroll F. I. *J. Heterocycl. Chem.* **1987**, *24*, 19.

Synthesis of Knightinol (16c). Compound 14. Aldol (+)-**4** (0.346 g, 1.41 mmol) was dissolved in dry CH_2Cl_2 (4 mL), and DMAP (0.020 g, 0.16 mmol) and dry Et_3N (2mL) were added followed by addition of TBDMS-Cl (0.420 g, 2.78 mmol). After standing at rt for 16 h the resulting solution was diluted with CH_2Cl_2, shaken with a Na_2CO_3 solution, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was removed under vacuum, and the residue was purified by chromatography (hexane:AcOEt, 9:1) which gave the product **14** (0.442 g, 87%). Mp 77–79 °C, $[\alpha]^{25}_D$ + 20.2° (*c* = 1.10, MeOH). ^{1}H-NMR 7.50–7.20 (m, 5H), 5.30 (d, *J* = 10 Hz, 1H), 3.50–3.45 (m, 1H), 2.95–2.80 (m, 1H), 2.70–2.60 (m, 1H), 2.36 (d, *J* = 10 Hz, 1H), 2.25 (s, 3H), 2.00–1.88 (m, 3H), 1.65–1.52 (m, 1H), 1.42–1.30 (m, 1H), 0.80 (s, 9H), −0.05 (s, 3H), −0.30 (s,3H). ^{13}C-NMR 208.9, 143.0, 127.9, 127.4, 126.8, 75.0, 68.4, 63.4, 62.8, 48.8, 40.8, 25.5, 25.4, 25.3, 17.7, −4.8, −5.4. IR (neat) 1715 (C=O). MS (CI-NH_3) 362 (6), 361 (27), 360 (100), 302 (15), 228 (18), 97 (13), 83 (13), 82 (34). Anal. Calcd for $C_{21}H_{33}O_2NSi$: C, 70.15; H, 9.25; N, 3.90. Found: C, 69.89; H, 9.19; N, 3.75. (Note: traces of compound **15** were also isolated during column chromatography of **14** in some experiments).

Compound 15. The silyl ether **14** (0.420 g, 1.16 mmol) was applied on a SiO_2 column (10 × 4.5 cm; hexane:AcOEt 9:1) and left for 18 h. A hexane–ethyl acetate mixture (1:1) was used to remove the unreacted starting material (0.060 g, 14%). A CH_2Cl_2–MeOH mixture (9:1) was then used to collect the product **15** (0.340 g, 81%). Mp 52–54 °C (racemate; the nonracemic compound was an oil); $[\alpha]^{25}_D$ −88.5° (*c* = 1.13, MeOH). ^{1}H-NMR 7.50–7.20 (m, 5H), 5.12 (d, *J* = 7.5 Hz, 1H), 3.82–3.73 (m, 1H), 3.52–3.43 (m, 1H), 3.12–3.01 (m, 1H), 2.75–2.60 (m, 1H), 2.53 (s, 3H), 2.20–1.18 (m, 4H), 1.68–1.58 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), −0.28 (s,3H). ^{13}C-NMR 208.0, 144.4, 127.7, 127.2, 127.0, 71.3, 62.9, 61.9, 61.3, 47.6, 37.9, 27.6, 25.7, 24.3, 18.0, −4.7, −5.3. IR (neat) 1710 (C=O). MS (CI-NH_3) 361 (32), 360 (100), 359 (22), 302 (25), 228 (51), 97 (75), 83 (33), 82 (54). Anal. Calcd for $C_{21}H_{33}O_2NSi$: C, 70.15; H, 9.25; N, 3.90. Found: C, 70.23; H, 9.25; N, 3.95.

Compound 16a. A solution of **15** (0.065 g, 0.18 mmol) was hydrogenated in EtOH with PtO_2 (10 mg) at 60 psi for 48 h. The catalyst was filtered off on Celite, and the solvent was removed under vacuum. A white solid of **16a** was obtained (0.066 g, 99%). Mp 171–172 °C (EtOH). (Note: racemic **16a** had mp 141–142 °C). $[\alpha]^{25}_D$ −36.0° (*c* = 1.00, MeOH). ^{1}H-NMR 7.45–7.20 (m, 5H), 4.79 (d, *J* = 10 Hz, 1H), 3.55–3.48 (m, 1H), 3.37–3.30 (m, 1H), 3.13–3.05 (m, 1H), 2.36 (s, 3H), 2.20–1.87 (m, 5H), 1.58–1.47 (m, 2H), 0.86 (s, 9H), 0.04 (s, 3H), −0.30 (s, 3H). ^{13}C-NMR 143.9, 128.0, 127.3, 127.2, 74.3, 65.3, 61.5, 60.2, 53.2, 40.8, 40.4, 25.8, 25.6, 22.4, 18.1, −4.5, −5.1. MS CI-isobutane 362 (58), 361 (36), 230 (38), 140 (66), 96 (30), 83 (100), 82 (42), 29 (35). Anal. Calcd for $C_{21}H_{35}O_2NSi$: C, 69.75; H, 9.76; N, 3.87. Found: C, 69.61; H, 9.71; N, 3.78.

Compound 16b. DMAP (0.015 g, 0.12 mmol) and acetic anhydride (0.15 mL, 0.208 g, 2 mmol) were added to the solution of **16a** (0.145 g, 0.40 mmol) in Et_3N (1 mL). After stirring for 60 h at rt the solution was treated with aqueous K_2CO_3 and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum, and the residue was purified by chromatography (3% MeOH in CH_2Cl_2, followed by 6% MeOH in CH_2Cl_2) which gave **16b** (0.156 g, 97%). Mp 178 °C dec; $[\alpha]^{25}_D$ −20.9° (*c* = 1.00, MeOH). ^{1}H-NMR 7.32–7.13 (m, 5H), 4.57 (d, *J* = 10 Hz, 1H), 4.19 (t, *J* = 4.5 Hz, 1H), 3.68–3.58 (m, 1H), 3.17–3.08 (m, 1H), 2.40 (s, 3H), 2.30–2.10 (m, 2H), 2.12–1.94 (m, 3H), 2.08 (s, 3H) 1.80–1.55 (m, 2H) 0.85 (s, 9H), 0.03 (s, 3H), −0.30 (s, 3H). ^{13}C-NMR 169.5, 142.2, 128.1, 127.7, 126.8, 73.7, 68.3, 61.5, 59.8, 51.6, 40.5, 36.5, 25.6, 25.5, 21.9, 21.4, 18.0, −4.6, −5.2. IR (neat) 1739 (C=O). MS (CI-isobutane) 404 (14), 403 (16), 344 (32), 55 (23), 44 (53), 40 (50), 29 (100), 28 (31). Anal. Calcd for $C_{23}H_{37}O_3NSi$: C, 68.44; H, 9.24; N, 3.47. Found: C, 68.14; H, 9.31; N, 3.24.

(17) Bick, I. R. C.; Gillard, J. W.; Leow, H. *Aust. J. Chem.* **1979**, *32*, 1827 and 2523.

***ent*-Knightinol (16c).**[19] Compound **16b** (0.085 g, 0.21 mmol) was dissolved in 1 M TBAF solution in THF (0.5 mL, 0.5 mmol). After standing at rt for 1.5 h the solution was treated with aqueous K_2CO_3 and extracted with $CHCl_3$ (4 × 5 mL). The combined extracts were dried ($MgSO_4$), concentrated under vacuum, and purified on a short silica column (10% MeOH in CH_2Cl_2, followed by 1% Et_3N–10% MeOH in CH_2Cl_2). White solid of **16c** was obtained (0.042 g, 68%; 97% ee by ^{1}H NMR with (*S*)-(+)-TFAE). Mp 149–151 °C (hexane–acetone; lit.[19] mp 153–154 °C); $[\alpha]^{25}_D$ −13.0° (*c* = 1.00, $CHCl_3$), natural knightinol[17b] $[\alpha]^{25}_D$ +13.5° (*c* = 1.00, $CHCl_3$). ^{1}H-NMR 7.37–7.23 (m, 5H), 4.65 (d, *J* = 10 Hz, 1H), 4.32 (t, *J* = 4.5 Hz, 1H), 3.94–3.75 (m, 1H), 3.16–3.10 (m, 1H), 2.55–2.45 (m, 1H), 2.36 (s, 3H), 2.40–2.25 (m, 1H), 2.12–1.94 (m, 3H), 2.00 (s, 3H) 1.80–1.60 (m, 2H). ^{13}C-NMR 169.5, 142.0, 128.7, 128.3, 126.7, 73.2, 68.4, 61.2, 59.7, 50.4, 40.6, 36.7, 25.6, 21.9, 21.3.

General Procedure for Acylation with Acyl Cyanides. Acyl cyanide **17** (1–2.5 mmol) in THF (0.5 mL) was added fast to the preformed nonracemic tropinone lithium enolate (1*S*)-**3** (1 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min followed by quenching with 40% K_2CO_3 (4 mL). After warming to rt the reaction mixture was extracted with Et_2O or $CHCl_3$ (3 × 10 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed under vacuum to give a crude product which was purified by chromatography.

3-Bromo-2-oxo-3-pentenenitrile (17b). Bromine (5.0 mL, 15 g, 94 mmol) was added to crotonyl cyanide (9.0 g, 95 mmol) dissolved in $CHCl_3$ (3 mL) at 0 °C. The mixture was stirred for 1 min. The solvent was then removed under vacuum, and SiO_2 (1 g) was added to the residue. The resulting mixture was refluxed for 30 min under reduced pressure at 140 °C (water aspirator with bleed). Distillation of the resulting material under vacuum gave **17b** (12.4 g, 75%). Bp 75–80 °C at 20 mmHg; NMR 7.93 (q, *J* = 8 Hz, 1H), 2.25 (d, *J* = 8 Hz, 3H). IR (neat) 2225 (CN), 1680 (C=O), 1620 (C=C).

(±)-2-Senecioyltropinone (18a). Reaction of senecioyl cyanide (**17a**) (0.20 mL, 0.28 g, 2.6 mmol) with racemic tropinone lithium enolate (1 mmol; generated as above but using LDA and without LiCl) gave, after chromatography (3% MeOH in CH_2Cl_2), the product **18a** as a yellowish oil (0.199 g, 90%). ^{1}H-NMR 17.25 (br s, 1H, enol form), 5.93 (s, 1H), 3.85 (d, *J* = 5 Hz, 1H), 3.38 (t, *J* = 5 Hz, 1H), 2.82 (dd, *J* = 5 Hz, *J* = 18.5 Hz, 1H), 2.40 (s, 3H), 2.23–2.20 (m, 2H), 2.17(s, 3H), 2.05 (d, *J* = 18.5 Hz, 1H), 1.95 (s, 3H), 1.75 (t, *J* = 10 Hz, 1H), 1.60 (t, *J* = 10 Hz, 1H). ^{13}C-NMR 189.6, 181.1, 154.1, 116.8, 111.9, 58.4, 57.2, 38.7, 36.6, 33.1, 28.7, 28.1, 20.8. IR (neat) 1650 (C=C), 1591 (C=O), 1569 (C=O). MS 221 (27), 194 (6), 193 (50), 192 (100), 191 (6), 137 (24), 136 (37), 110 (8). Anal. Calcd for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.33; H, 8.69; N, 6.21.

(±)-11,11-Dimethyl-10,11-dihydropyranotropan-3-one (19a). 2-Senecioyltropinone (**18a**) (0.199 g, 0.90 mmol) was dissolved in EtOH (8 mL), anhydrous Na_2CO_3 (0.2 g) was added, and the resulting suspension was refluxed for 1 h. The solvent was removed under vacuum, and the residue was taken in Et_2O and filtered through Celite. Removal of Et_2O gave pure product **19a** (0.197 g, 99%). ^{1}H-NMR 4.03 (d, *J* = 5 Hz, 1H), 3.39 (t, *J* = 5 Hz, 1H), 2.71 (dd, 5Hz, 12Hz, 1H), 2.50 (q, *J* = 18.5 Hz, 2H), 2.34 (s, 3H), 2.20–2.15 (m, 2H), 1.88 (d, 18.5 Hz, 1H), 1.77–1.68 (m, 1H), 1.57–1.51 (m, 1H), 1.44 (s, 3H), 1.41(s, 3H). ^{13}C-NMR 189.6, 166.4, 114.1, 80.0, 57.6, 54.9, 47.0, 36.6, 34.7, 33.0, 28.7, 27.0, 25.0. IR (neat) 1659 (C=C), 1609 (C=O). MS 221 (18), 193 (29), 192 (100), 136 (24), 135 (20), 81 (18), 56 (10). Anal. Calcd for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.39; H, 8.68; N, 6.17.

(−)-11,11-Dimethyl-10,11-dihydropyranotropan-3-one (19a). Reaction of senecioyl cyanide (**17a**) (0.20 mL, 0.28 g, 2.6 mmol) with nonracemic enolate (1*S*)-**3** (1 mmol) gave the crude product **18a** which was dissolved in EtOH (2 mL), anhydrous Na_2CO_3 (0.2 g) was added, and the mixture was

(18) (a) A sample of natural darlingine was kindly provided by Professor Bick. (b) A sample of knightinol was kindly provided by Professor Lounasmaa.

(19) Lounasmaa, M.; Pusset, J.; Sevenet, T. *Phytochemistry* **1980**, *19*, 953 and 949.

refluxed for 1 h. After the solvent was removed, the crude **19a** was dissolved in Et_2O, filtered, and purified by chromatography (SiO_2 deactivated with Et_3N; 50% AcOEt in hexane followed by 10% MeOH in CH_2Cl_2) which gave the chiral amine **5b** (0.312 g, 95% recovery) and the product **19a** as a yellowish oil (0.199 g, 90%); $[\alpha]^{25}_D$ −35.1° (c = 1.02, MeOH), 93% ee by HPLC.

(−)-*ent*-Isobellendine (20b).[17] 2-Bromo-2-butenoyl cyanide (**17b**) (0.044 g, 0.25 mmol) in THF (0.25) and nonracemic enolate (1*S*)-**3** (1 mmol) gave a crude product which was dissolved in Et_3N (1.5 mL) and refluxed for 3 h. Et_3N was removed under vacuum, and the residue was made basic with 40% K_2CO_3 and was extracted with Et_2O (3 × 10 mL). Chromatography (SiO_2; Et_3N; 50% AcOEt in hexane followed by 10% MeOH in CH_2Cl_2) gave **20b** as an oil which crystallized on standing (0.023 g, 45%). Mp 100−101 °C (hexane), $[\alpha]^{25}_D$ −47.4° (c = 1.01, MeOH); (lit.[17] mp 114−116 °C, Et_2O; $[\alpha]^{19}_D$ +143° in $CHCl_3$); 92% ee by ^1H NMR with (*S*)-(+)-TFAE. ^1H-NMR 6.06 (s, 1H), 4.18 (d, J = 5 Hz, 1H), 3.58 (m, 1H), 3.12 (dd, J = 17 Hz, J = 5 Hz, 1H), 2.41 (s, 3H), 2.35−2.12 (m, 2H), 2.23 (s, 3H), 1.91−1.80 (m, 1H), 1.65-1.51 (m, 1H), 1.48−1.35 (m, 1H).

(−)-*ent*-Darlingine (20c).[17] Reaction of tigloyl cyanide (**17c**) (0.050 g, 0.46 mmol) with nonracemic enolate (1*S*)-**3** (1 mmol) gave a crude product containing the chiral amine **5b**. The crude product was dissolved in EtOH (2 mL), Na_2CO_3 was added (0.05 g), and the mixture was refluxed for 1 h. Removal of EtOH, followed by chromatography (SiO_2 deactivated with Et_3N; 50% AcOEt in hexane followed by 10% MeOH in CH_2Cl_2), gave a mixture of diastereomers of dihydrodarlingine (**19c**) (0.044 g, 80%). The mixture was dissolved in AcOEt (7 mL) and refluxed with $CuBr_2$ (0.096 g, 0.42 mmol) for 30 h. Et_3N (2 mL) was then added, and the mixture was refluxed for 15 min. After the solvents were removed the residue was treated with 20% aqueous NH_3 (4 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude product which was dissolved in $CHCl_3$ and passed through a short silica gel column. The resulting oil of **20c** crystallized on drying under vacuum (0.030 g, 53%; 91% optical purity). Mp 110−111 °C; $[\alpha]^{25}_D$ −45.8° (c = 1.02, MeOH; natural darlingine:[18a] mp 112−113 °C, $[\alpha]^{25}_D$ +50.5° c = 1.02, MeOH). ^1H-NMR 4.18 (d, J = 5 Hz, 1H), 3.48 (m, 1H), 3.02 (dd, J = 17.5 Hz, J = 5 Hz, 1H), 2.37 (s, 3H), 2.28−2.20 (m, 2H), 2.26 (s, 3H), 1.94 (s, 3H), 2.13 (dd, J = 17.5 Hz, J = 1 Hz, 1H), 1.88−1.78 (m, 1H), 1.59−1.50 (m, 1H).

(−)-*ent*-Chalcostrobamine (18d).[19] Reaction of cinnamoyl cyanide (**17d**) (0.080 g, 0.51 mmol) with enolate (1*S*)-**3** (0.5 mmol) gave, after purification by chromatography (SiO_2 deactivated with Et_3N; 50% AcOEt in hexane followed by 10% MeOH in CH_2Cl_2) **18d** as a yellow oil (0.050 g, 75%). $[\alpha]^{25}_D$ −110.9° (c = 1.05, MeOH); −179.0° (c = 1.04, $CHCl_3$); 95% ee by ^1H NMR with (*S*)-(+)-TFAE. ^1H-NMR 7.67 (d, J = 15.5 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 7.33 (m, 2H), 6.81 (d, J = 15.5 Hz, 1H), 4.03 (d, J = 5 Hz, 1H), 3.40 (t, J = 5 Hz, 1H), 2.84 (dd, J = 19 Hz, J = 3 Hz, 1H), 2.41 (s, 3H), 2.34−2.20 (m, 2H), 2.11 (d, J = 19, 1H), 1.84−1.75 (m, 1H), 1.65−1.55 (m, 1H).

(+)-Chalcostrobamine.[19] Cinnamoyl cyanide (0.188 g, 1.2 mmol) in THF (0.8 mL) was added to a solution of nonracemic enolate (1*R*)-**3** (1 mmol, from hydrochloride of amine **6b**) at −78 °C. The mixture was stirred for 30 min, quenched with 40% K_2CO_3 (4 mL), and extracted with $CHCl_3$ (3 × 20 mL). The extracts were dried ($MgSO_4$), the solvent was removed, and the crude product was purified by chromatography (AcOEt:hexane, 9:1 and then 10% MeOH in CH_2Cl_2) which yielded the chiral amine **6b** (0.259 g, 99% recovery) and (+)-chalcostrobamine as a yellow oil (0.209 g, 78%) having $[\alpha]^{24}_D$ +165° (c = 1.10, $CHCl_3$; lit.[19] $[\alpha]^{20}_D$ +12°, $CHCl_3$); 92% ee by NMR with (*S*)-(+)-TFAE.

Acknowledgment. We thank Natural Sciences and Engineering Research Council of Canada and the University of Saskatchewan for financial support. We are grateful to Professor Bick for providing original samples of darlingine and isobellendine, and to Professor Lounasmaa for samples of knightinol and acetylknightinol.

JO9506802