Acknowledgment. We thank the National Institute on Drug-Abuse (NIDA) for support of this work through Grant DA02357.

Registry No. **5a**, 98689-06-6; **6a**, 98689-07-7; **8a**, 18167-91-4; **8b**, 98689-08-8; **8c**, 93758-01-1; **9a**, 98689-09-9; **9c**, 98689-10-2; **11c**, 98689-12-4; **12c**, 98689-11-3; **12d**, 98689-13-5; **12e**, 98689-15-7; **12f**, 98689-14-6; methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-methyl-4-oxo-3-pyridinecarboxylate, 98689-03-3; methyl 1,4,5,6-tetrahydro-2-methyl-4-oxo-3-pyridinecarboxylate, 68185-61-5; methyl 1,4,5,6-tetrahydro-1-[(benzyloxy)carbonyl]-2-(bromomethyl)-4-oxo-3-pyridinecarboxylate, 98689-04-4; methyl 1,4,5,6-tetrahydro-2-(acetoxymethyl)-1-[(benzyloxy)carbonyl]-4-oxo-3-pyridinecarboxylate, 98689-05-5; vinyl bromide, 593-60-2.

Enantioselective Synthesis of Seven Pyrrolizidine Diols from a Single Precursor

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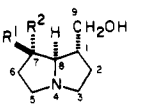
The enantioselective synthesis of seven pyrrolizidine diols has been accomplished from a single, readily available intermediate. The key step of this general scheme involves an acetoxy-directed acyliminium ion–ketene dithioacetal cationic cyclization to give the optically active 1-azabicyclo[3.3.0]octane **14**, from which the pyrrolizidines **1–7** were prepared. The pyrrolizidine diols in the 7*S* series were obtained by adjusting the oxidation level and stereochemistry in the B ring of the key intermediate. Inversion of the C-7 alcohol group, followed by adjustment of oxidation level and stereochemistry in the B ring, afforded the corresponding pyrrolizidines in the 7*R* series.

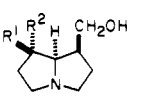
Introduction

The challenging structures and diverse biological activity of pyrrolizidine alkaloids[1] have stimulated a great deal of interest in their synthesis. The ideal general synthetic route to the pyrrolizidines would be stereo- and enantioselective, operationally simple, efficient, and flexible enough to allow different groups and oxidation levels to be introduced at C-1, C-2, C-7, and C-8. Since the first synthesis of (+)-retronecine (**6**) by Geissman and Waiss in 1962,[2a] many new routes to racemic pyrrolizidines have been published,[2] but enantioselective syntheses have been a relatively recent development.[3] Prompted by that fact and by "an obvious deficiency ... of good synthetic routes to 1,2-dehydropyrrolizidines ...",[4] we set out to develop a practical synthesis of either enantiomer of any common pyrrolizidine diol (**1–8**) as part of a larger project directed at macrocyclic bislactones such as monocrotaline (**9**).



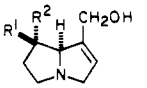
R^1 = H, R^2 = OH (+)-Hastanecine, **1**

R^1 = OH, R^2 = H (−)-Turneforcidine, **2**



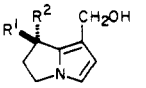
(−)-Dihydroxheliotridane, **3**

(−)-Platynecine, **4**



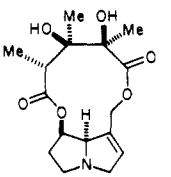
R^1 = H, R^2 = OH (+)-Heliotridine, **5**

R^1 = OH, R^2 = H (+)-Retronecine, **6**



(+)-Dehydroheliotridine, **7**

(−)-Dehydroretronecine, **8**



Monocrotaline, **9**

Preliminary Cyclization Studies

The general plan was to use an optically active alcohol group in an A-ring precursor as a control element to establish the correct absolute stereochemistry at the ring juncture via an acyliminium ion cyclization.[5] Toward that end, we have reported a new cationic cyclization terminator, the ketene dithioacetal group, that efficiently mediates the required five-membered ring formation in this cyclization.

After these model studies verified that the pyrrolizidine skeleton could be constructured in this manner, the synthesis of the more highly oxygenated derivatives **1–8** was undertaken. Of several optically active potential pyrrolizidine diol precursors, the first tested was **13**. This intermediate drew our attention because of its potentially easy accessibility and because the diol protecting group completely blocks one face of the imide ring. Concern about removal of the superfluous oxygen group at C-6 (pyrrolizidine numbering) was deferred until cyclization stereoselectivity was established. Thus, 2,3-*O*-cyclo-

(1) General Review: (a) Robins, D. J. *Fortshr. Chem. Org. Naturst.* **1981**, *41*, 115 and references cited therein. Biological Activity: (b) Atal, C. K. *Lloydia*, **1978**, *41*, 312.

(2) Synthesis of racemic pyrrolizidines: (a) Geissman, T. A.; Waiss, A. C., Jr. *J. Org. Chem.* **1962**, *27*, 139. (b) Viscontini, M.; Gilhof-Schaufelberger, H. *Helv. Chim. Acta* **1971**, *54*, 449; Viscontini, M.; Buzek, H. Ibid. **1972**, *55*, 670. (c) Klose, W.; Nickisch, K.; Bohlmann, F. *Chem. Ber.* **1980**, *113*, 2694; Bohlmann, F.; Klose, W.; Nickisch, K. *Tetrahedron Lett.* **1979**, 3699. (d) Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711. (e) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. (f) Keck, G. E.; Nickel, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (g) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7994. (h) Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 3644.

(3) Enantioselective Synthesis: (a) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Chem. Commun.* **1979**, 1181. (b) Rueger, H.; Benn, M. H. *Heterocycles* **1982**, *19*, 23. (c) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135. (d) Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (e) Rueger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331. (f) Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. (g) Buchanan, J. G.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, *19*, 1299. (h) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235.

(4) Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247.

(5) (a) Speckamp, W. N. "Stereoselective Synthesis of Natural Products—Workshop Conferences Hoechst", Bartman and Winterfeldt, Eds.; Excerpta Medica (Elsevier): Amsterdam, 1979; Vol. 7, p 50. (b) Acyliminium cyclization in alkaloid synthesis has been reviewed: Speckamp, W. N. *Recl. Trav. Chem. Pays-Bas.* **1981**, *100*, 345.

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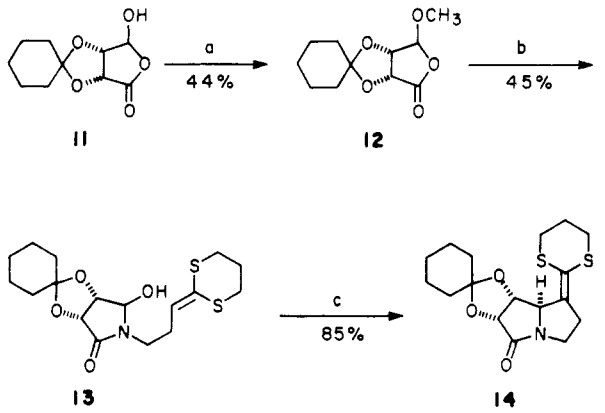
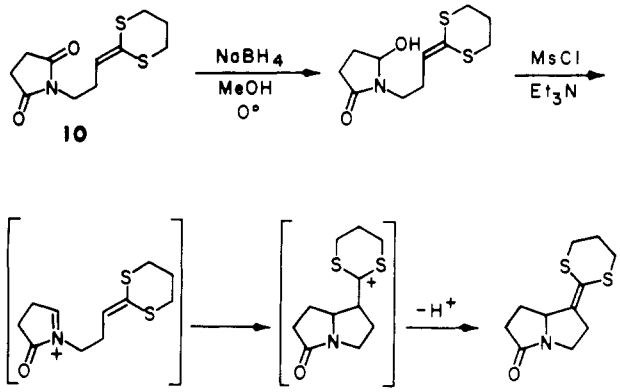
Scheme I[a]



[a] a, MeOH reflux, 3-Å sieves; b, 2-(3-aminopropylidene)-1,3-dithiane,[7] CH_2Cl_2; c, MsCl, Et_3N, CH_2Cl_2.

hexylidene-L-(−)-erythruronic acid, **11** (commercially available from Fluka), was heated at reflux in methanol containing 3-Å molecular sieve to give **12** in 44% unoptimized yield. The ketene dithioacetal amine obtained by treating the imide **10** with hydrazine in refluxing benzene

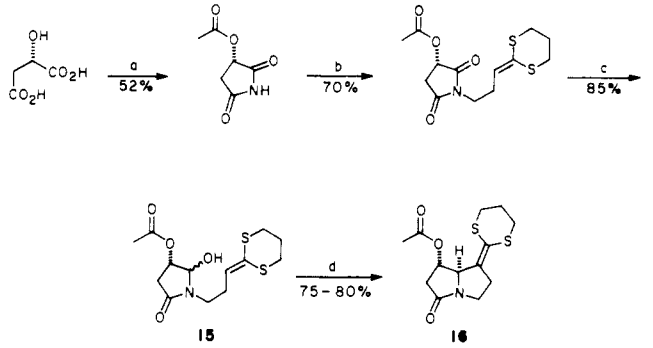


was coupled with **12** in dichloromethane at 0 °C, affording the hydroxy lactam **13** in 45% yield. Cyclization to the pyrrolizidine skeleton was conducted under the nonacidic mesyl chloride conditions described previously.[6] The major product under these conditions was the pyrrolizidine **14**, (see Scheme I) which was isolated in 70% yield after flash chromatography. Interestingly, the reaction time was 2 weeks, in direct contrast to the simple cyclization (starting with **10**), which was complete within a few hours at room temperature.

Subsequently, the cyclization of **13** was monitored by NMR, which revealed that the slow step probably is elimination of methane sulfonate: upon addition of the MsCl/Et_3N to **13** in $CDCl_3$, a new signal corresponding to the methine proton adjacent to the mesylate oxygen appears instantly, the intensity of which gradually decreases over a period of 2 weeks to give another new signal corresponding to the H-8 of the cyclized product **14**. In order to increase the rate of reaction, an equal volume of a more polar solvent (CD_3CN) was added to the reaction mixture after the initial formation of mesylate, affording cyclized product **14** in 85% yield after only 20 h. Presumably, the more polar medium simply accelerates the formation of the acyl iminium salt.

Once the pyrrolizidine ring system had been formed, the next operation attempted was a reductive deoxygenation.

Scheme II[a]



[a] a, AcCl, NH_3, AcCl; b, 2-(3-aminopropylidene)-1,3-dithiane,[7] Ph_3P, DEAD; c, $NaBH_4$, MeOH; d, MsCl, Et_3N.

Treatment of **14** with lithium metal in liquid ammonia afforded a complex mixture of products. In an attempt to avoid this problem, migration of the double bond to the endocyclic position was first undertaken; however, the subsequent deoxygenation reaction also gave a complex mixture of products under a variety of conditions.

Synthesis of 7*S* Diols

The problems encountered in the deoxygenation prompted a search for precursors that would provide an intermediate not requiring this reductive step. The simplest solution to the problem would be simply to omit the offending oxygen substituent entirely (that is, cyclize **15**) (see Scheme II). This strategy introduces two new problems, however: regioselectivity of imide reduction and possible reduced diastereoselectivity of the cyclization. Nonetheless, the precursor **15** required to test the acetoxy-directed cyclization was prepared in anticipation that these potential problems would not be serious ones. Indeed, the conversion of (*S*)-malic acid into the key intermediate **16** proceeds highly selectively and in good yield, as described in detail elsewhere.[7] That same report also describes the conversion of **16** into (+)-heliotridine, and we now wish to disclose that the same key intermediate can easily be converted into six other pyrrolizidine diols, making **1**–**7** available by relatively concise total synthesis. Since (*R*)-malic acid is also commercially available, the enantiomers of **1**–**7** (including **8**) also could be prepared by the routes described.

There are three other 7*S* pyrrolizidine diols (**1**, **3**, and **7**) related to (+)-heliotridine, the synthesis of which requires only adjustment of the oxidation level and stereochemistry in the B ring. Efficient preparation of the saturated C-1 diastereomer **3** requires generating the thermodynamically less stable configuration in which the hydroxymethyl group is approximately eclipsed with the C-7, C-8 bond. One obvious way to obtain **3** is catalytic reduction of heliotridine itself. This reaction is known to be stereoselective in this and several related systems,[8] requiring the use of Raney nickel to avoid hydrogenolysis of the allylic carbon–oxygen bond. Thus, the synthesis of (+)-heliotridine (**5**) also provides a route to (+)-dihydroxyheliotridane (**3**).

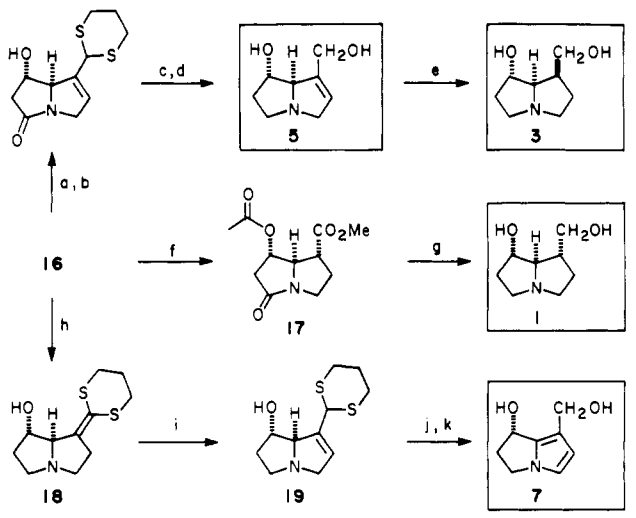
Using methodology first developed in model systems,[6] treatment of the ketene dithioacetal (see Scheme III) with mercuric chloride in acidic alcohol, followed by $LiAlH_4$

(6) Chamberlin, A. R.; Nguyen, H.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682.

(7) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(8) (a) Menshikow, G. P.; Fuzovkov, A. D. *J. General Chem. USSR (Engl. Transl.)* **1949**, *19*, 1702. (b) Warren, F. L.; von Klemperer, M. E. *J. Chem. Soc.* **1958**, 4574.

Scheme III[a]



[a] a, MeONa; b, LDA, MeOH; c, $HgCl_2$, CH_3CN-H_2O, $CaCO_3$; d, $LiAlH_4$; e, Raney nickel; f, HCl-MeOH, $HgCl_2$; g, $LiAlH_4$; h, AlH_3; i, LDA, MeOH; j, $HgCl_2$, CH_3CN-H_2O, $CaCO_3$; k, $NaBH_4$.

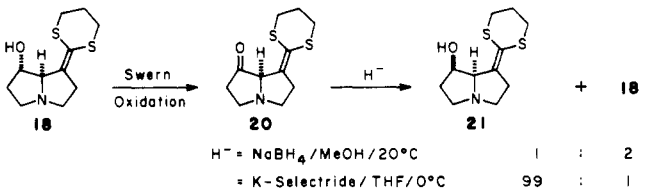
reduction of the resulting lactam diester **17**, gave (+)-hastanecine (43% from **16**). Synthetic **1** was spectrally and chromatographically identical with an authentic sample, and it exhibited an optical rotation ($[\alpha]^{25}_D$ +8.3° (*c* 1.43, EtOH)) comparable to the literature value ($[\alpha]^{18}_D$ +8.5°, $[\alpha]^{20}_D$ +10.0°, EtOH).[9,10] The hydrolysis/transesterification step thus produces the thermodynamically more stable C-1 diastereomer as a result of equilibration of either the product ester diastereomer or the sulfur-stabilized cationic intermediate.

The other oxidation level of the B ring, the aromatic pyrrole dehydroheliotridine **7**, also is accessible from the intermediate **16**. Aluminum hydride reduction of both the ester and lactam carbonyl groups in **16** (94% yield), followed by double bond migration (LDA; MeOH), afforded the intermediate **19** (80% yield). Treatment of **19** with mercuric chloride combines dithiane hydrolysis and aromatization, resulting in a facile preparation of the dehydro derivative **7** after reduction of the aldehyde group (41% from **16**). The dehydrogenation step presumably occurs via mercuric ion mediated iminium ion formation[11] followed by tautomerization to the pyrrole.

The Problem of C-7 Alcohol Inversion

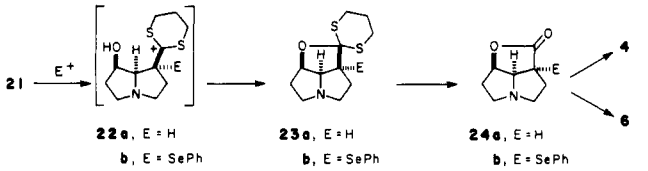
Preparation of the 7*R* derivatives corresponding to the four 7(*S*)-pyrrolizidines could in principle be carried out simply by subjecting each 7*S* derivative (or one of its precursors) to an alcohol inversion sequence. Not surprisingly, the one-step Mitsunobu inversion[12] attempted on several intermediates was unsuccessful, because the nucleophile (carboxylate) is required to attack the C-7 center from the concave face of the ring. Competitive elimination was the major pathway as evidenced by the unsaturated products isolated.

An alternate solution is to conduct an oxidation–reduction sequence that would make use of the cis-5,5-ring system's "cup" shape to control the C-7 stereochemistry. Reduction of related bicyclic ketones from the convex face is well-known in analogous all-carbon ring systems, but there is one precedent to the contrary in the pyrrolizidine literature.[13] This result is puzzling, because it requires that hydride approach from the heavily shielded face of the carbonyl group. We therefore conducted several preliminary reductions of **20**, obtained by Swern oxidation[14]



of **18**, and found that sodium borohydride does indeed preferentially attack from the *concave* face. Fortunately, the use of bulky reducing agents such as K- or L-Selectride allows very selective conversion of **18** into **21** (76% yield after flash chromatography) by attack from the convex face. A retrospective literature search revealed that sodium borohydride reduction from the more congested face of a hindered ketone in a cis-5,5-ring system also has been documented for an all-carbon system.[15] A possible explanation for both examples is that the sodium borohydride reduction involves a late transition state, so that steric factors in the approach of the reducing agent are minimal unless the hydride source is very bulky (as is K-Selectride).

Having **21** in hand allows preparation of the saturated B-ring diastereomer **4**. In this case the thermodynamically less favorable stereochemistry at C-1 should be easily accessible—in direct contrast to the 7*S* derivatives—because the (newly inverted) C-7 oxygen now is ideally located to trap a sulfur-stabilized carbocation **22** having

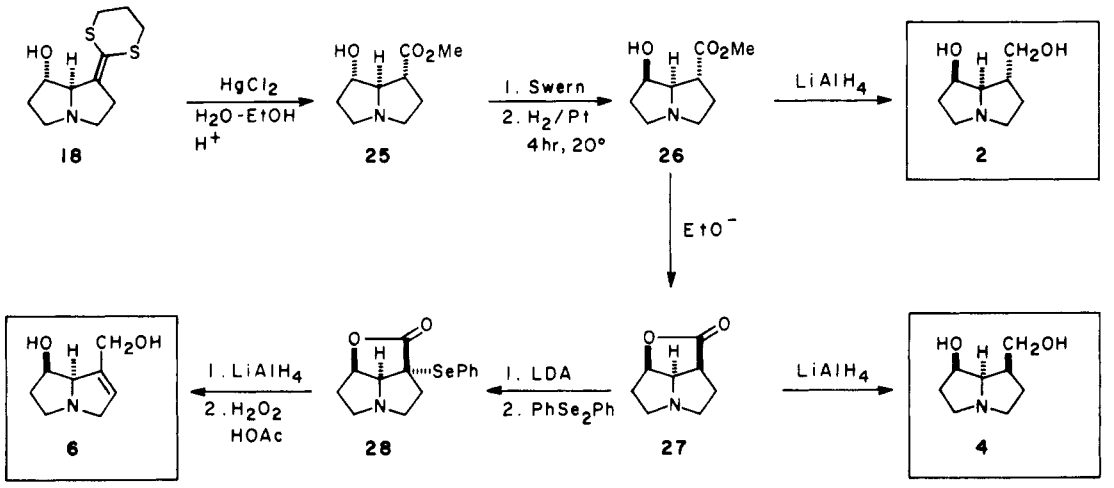


the desired relative stereochemistry at C-1. Indeed, treatment of **21** with trifluoracetic acid in dichloromethane cleanly afforded the protected lactone **23a** (95% yield), which was then converted into platynecine (**4**) in 82% yield by dithiane hydrolysis[16] ($HgCl_2$, $CaCO_3$, CH_3CN, H_2O) followed by reduction of the resulting lactone ($LiAlH_4$, THF).[17,18]

Before the optical rotation of **4** was obtained, the intermediate **21** was also converted into retronecine by a related series of steps. Although conversion of **21** into the unsaturated derivative retronecine (**6**) in the usual way (double bond migration/Hg^{+2} hydrolysis/reduction) is doomed to failure because of the aforementioned B-ring aromatization during the mercuric ion mediated hydrolysis step, the C-7 oxygen can again trap the carbocation gen-

(9) Klasek, A.; Weinbergova, O. "Recent Developments in the Chemistry of Natural Carbon Compounds"; Akademiai Kiado: Budapest, 1975; Vol. 6, p 48.
(10) Aasen, A. J.; Culvenor, C. C. J. *Austral. J. Chem.* **1969**, *34*, 4137.
(11) Mercuric ion oxidation is a known method for forming iminium ions from amines: Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439.
(12) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(13) (a) Aasen, A. J.; Culvenor, C. C. J. *Aust. J. Chem.* **1969**, *34*, 2657. (b) Culvenor, C. C. J.; Edgar, J. A.; Smith, L. W.; Tweeddale, H. J. *Ibid.* **1970**, *213*, 1853.
(14) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(15) Ito, T.; Tomiyoshi, N.; Nakamura, K.; Azuma, S.; Izawa, M.; Maruyama, F.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron* **1984**, *40*, 241.
(16) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829.
(17) (a) Viscontini, M.; Gilhof-Schaufelberger, H. *Helv. Chim. Acta* **1971**, *54*, 449. (b) Viscontini, M.; Buzek, H. *Ibid.* **1972**, *55*, 670.
(18) Niwa, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 125.

Scheme IV



erated from a selenium electrophile[19,20] (rather than a proton) to effect ring closure of **21** to **23b**. This step places a potential leaving group in the appropriate position for alkene formation, and obviates the need to expose a dihydropyrrole to conditions that might cause aromatization. Thus, treatment of **21** with phenylselenium chloride (0 °C, THF, CH_2Cl_2, 2 h) proceeded smoothly to give **23b** in 96% isolated yield. Dithiane hydrolysis[21] ($HgCl_2$, $CaCO_3$, CH_3CN, H_2O) gave the α-selenolactone **24b** (92% yield).

Conversion of the tricyclic lactone **24b** into retronecine was carried out by treatment of the α-selenolactone with lithium aluminum hydride in THF at −20 °C, followed by oxidation and elimination[23] (H_2O_2, HOAc, 20 °C, 1.5 h), affording retronecine (**6**) in a yield of 79% (from **24b**) after recrystallization. *Unfortunately, both retronecine and platynecine prepared from 21 proved to be racemic.* The step was easily traced to the oxidation (or workup) of **18**, so that variations of the Swern procedure were attempted. Unfortunately, the resulting ketone **20** was found to be racemic in all cases. Since the Swern oxidation does not often racemize α-chiral keto compounds,[24] the problem is most likely due to the presence of the β,γ-ketene dithioacetal double bond in **20**, which enhances the acidity of the C-7 methine proton to such extent that deprotonation readily occurs under the reaction conditions or the work up.

Synthesis of 7*R* Diols

In order to avoid racemization, the ketene dithioacetal **18** was converted into the methyl ester **25** (see Scheme IV) ($HgCl_2$, MeOH, 6 M HCl, TFA, reflux, 71% yield), *prior* to Swern oxidation (72% yield). The resulting keto ester exhibited an optical rotation ($[\alpha]^{24}_D$ +67.6° (*c* 2.67, MeOH)) comparable to the published value ($[\alpha]^{20}_D$ +64° (*c* 1.0, MeOH),[13] bearing out our rationale for the racemization of **20**. Hydrogenation of the ketone derived from **25** (H_2, PtO_2, MeOH, 20 °C, 4 h) resulted in selective reduction from the convex face, to give the ester alcohol **26** quantitatively. Further reduction of **26** ($LiAlH_4$, THF) afforded (+)-turneforcidine, **2** (75%), which was spectrally and chromatographically identical with an authentic sample, exhibiting an optical rotation ($[\alpha]^{24}_D$ −11.4°, MeOH) comparable to the literature value ($[\alpha]_D$ −10.5°).[9]

Efficient preparation of the C-1 diastereomer **4** again presents the problem of generating what appears to be the thermodynamically less stable configuration at C-1. As in the case of **21**, however, the 7*R* alcohol group is situated in a position to trap an equilibrating C-1 substituent, in this case as the cyclic lactone (**27**). This lactone should not suffer any further transformation, since it is well precedented that it is unreactive toward various equilibrating conditions.[25] Inversion of the C-7 alcohol group should thus in turn serve as a means of inverting the C-1 ester group of **26**. As predicted, treatment of **26** with a solution of sodium ethoxide in refluxing ethanol effectively inverts the C-1 stereochemistry, giving cleanly the tricyclic lactone **27** (75% yield), which exhibits an optical rotation ($[\alpha]^{22}_D$ +84.4° (*c* 0.71, $CHCl_3$)) comparable to the literature value ($[\alpha]^{21}_D$ +84° (*c* 1.4, $CHCl_3$). Reduction of **27** ($LiAlH_4$, THF) gave (−)-platynecine, **4** (81% yield), which also exhibits an optical rotation ($[\alpha]^{22}_D$ −55.1°, (*c* 2.14, CH_3Cl)) comparable to the literature value ($[\alpha]_D$ −57°, ($CHCl_3$)).[9]

Conversion of **27** into the unsaturated derivative (+)-retronecine (**6**) was accomplished by the procedure reported by Robins[23] and by Yamada[18] for the racemic material: α-selenylation, reduction of the lactone, and oxidation–elimination of the selenoxide. The resulting product was spectrally and chromatographically identical with an authentic sample of (+)-retronecine, exhibiting an optical rotation ($[\alpha]^{26}_D$ +50.4° (*c*, 0.29, EtOH)) comparable to the literature values ($[\alpha]_D$ +50.2°, $[\alpha]^{22}_D$ +52.2° (*c* 0.95, EtOH)).[9] This published three-step sequence suffers from a low percentage conversion of **27** into **28** that is most likely due to unusually slow formation of the enolate of **27**, since the resulting π-bond introduces significant strain into the tricyclic system. Nonetheless, the reaction was a clean one and the starting material could be recovered (71%) for recycling.

Conclusion

The enantioselective synthesis of seven pyrrolizidine diols has been accomplished from a single, readily available intermediate. The key step of this general scheme involves an acetoxy-directed acyliminium ion–ketene dithioacetal

(19) Kozikowski, A. P.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 2236.
(20) For a review of selenium reagents in organic synthesis, see: Clive, D. L. J. *Aldrichimica Acta* **1978**, *11*, 43.
(21) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357.
(22) This lactone previously has been prepared in racemic form by other routes.[18]
(23) Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1734.
(24) See for example: (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Dailey, O. D.; Fuchs, F. L. *J. Org. Chem.* **1980**, *45*, 216. (c) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214.
(25) Specifically, attempted epimerization of the C-1 diastereomer of **26** gave only the lactone **27**.[13a]

cationic cyclization to give the optically active 1-aza-bicyclo[3.3.0]octane system common to all pyrrolizidine alkaloids. The pyrrolizidine diols in the 7-*S* series were obtained by adjusting the oxidation level and stereochemistry in the B ring of the key intermediate. Inversion of the C-7, followed by adjustment of oxidation level and stereochemistry in the B ring of the key intermediate, afforded the pyrrolizidine diols in 7*R* series.

The synthesis is a practical and versatile one, since the key intermediate can be prepared in large quantities in only four steps from (*S*)-malic acid, and subsequently converted to any one of seven pyrrolizidine diols in eight steps or fewer. Since (*R*)-malic acid also is commercially available, all of the corresponding enantiomeric pyrrolizidine diols in the 8*R* series could also be prepared using the same methodology. Work is proceeding on the conversion of some of these diols into macrocyclic bis lactones.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. ^{1}H magnetic resonance spectra were obtained on a Bruker WM 250 (250 MHz) spectrometer unless otherwise stated; a Varian Associates FT80A (80 MHz) was used where specified. Spectra are reported in ppm from internal tetramethylsilane on the scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), and interpretation or integration. Melting points were taken on a Laboratory Devices melting-point apparatus and are reported uncorrected. Mass spectra were recorded on Finnigan 9610 spectrometer at 70 eV. High-pressure liquid chromatography were performed on a Waters analytical instrument with a 30-cm μ-Porasil Column and 254-nm detector. Elemental analyses were performed by Galbraith Laboratories, Inc. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter at the sodium D line in a 1-dm cell at the designated concentration in g per 100 mL.

When necessary, solvents and reagent were dried prior to use. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin-layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel plates (60 F-254). Flash chromatography was performed on silica gel 200–400 mesh (Merck).

2-[3-Aminopropylidene]-1,3-dithiane. A mixture of the succinimide **10** (770 mg, 3.27 mmol) and hydrazine hydrate (0.165 g, 6.54 mmol) in benzene (10 mL) was heated at reflux under a Dean–Stark trap for 24 h and then filtered through K_2CO_3/Celite. The filtrate was evaporated to dryness to give 0.476 g (83%) of the amine as an oil. An analytical sample was prepared by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$ = 60/25/1): bp 125–127 °C (2.5 mmHg); ^{1}H NMR (80 MHz, $CDCl_3$) δ 5.87 (t, *J* = 7.3 Hz, CH=C), 2.6–3.0 (m, 6 H), 2.0–2.5 (m, 4 H), 1.13 (s, NH_2).

2,3-(Cyclohexylidenedioxy)-4-hydroxy-4-methoxybutanoic Acid Lactone (12). A mixture of 2,3-*O*-cyclohexylidene-L(−)-erythruronic acid (**11**) (3.0 g, 14.0 mmol), purchased from Fluka, and activated 3-Å molecular sieve (1.5 g) in methanol (7 mL) was heated at reflux for 5 h. After cooling, the reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (5 × 50 mL). Flash chromatography (ethyl acetate/hexane = 1/3) gave 1.39 g (44%) of **12** as a clear oil: ^{1}H NMR (80 mHz, $CDCl_3$) δ 5.37 (s, OCHO), 4.83 (d, *J* = 5.5 Hz, OCHC=O), 4.56 (d, *J* = 5.5 Hz, $OCHC(O-)_2$), 3.55 (s, CH_3), 1.4–1.7 (m, 10H).

***N*-[3-(1,3-Dithian-2-ylidene)propyl]-3(*R*),4(*S*)-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (13).** To a solution of the amine prepared by the above procedure (58 mg, 0.33 mmol) in CH_2Cl_2 (0.8 mL) was added a 1.0 M CH_2Cl_2 solution of methoxy lactone **12** (0.33 μL, 0.33 mmol) at −20 °C. After stirring for 3 h (−20° → 0 °C), the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Flash chromatography (ethyl acetate/hexane = 4/1 + 8% Et_3N) yielded 55 mg (45%) of the hydroxy lactam **13** as a white solid: IR ($CDCl_3$, thin film) 3330, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.87 (t, 7.3 Hz, CH=C), 5.15 (s, NCHO), 4.80 (d, *J* = 5.8 Hz, O=CCH), 4.48 (d, *J* = 5.8 Hz, O=CCH′), 3.54 (dt, *J* = 13.8, 7.0 Hz, NCH′), 3.29 (dt, *J* = 13.6, 6.8 Hz, NCH), 2.88 (m, $(SCH_2)_2$), 2.53 (q, *J* = 7.5 Hz, 2 H), 2.16 (m, $SCCH_2$), 2.4–2.7 (m, 10 H); MS, *m/e* 371 (M^+, 0.5%), 353 ($M^+ - H_2O$, 6%), 255 (42%), 185 (100%), 158 (61%), 145 (40%), 111 (81%); MS (CI, 100 eV), *m/e* 372 (MH^+, 16%), 354 ($MH^+ - H_2O$, 21%), 256 (9%), 158 (100%), 145 (30%), 111 (39%).

5(*S*)-1-Aza-4-[2-(1,3-dithianylidene)]-6(*R*),7(*S*)-(cyclohexylidenedioxy)bicyclo[3.3.0]octan-8-one (14). To a solution of the hydroxy lactam **13** (216 mg, 0.582 mmol) and triethylamine (165 μL, 1.165 mmol) in $CHCl_3$ (3 mL) was added methanesulfonyl chloride (47 μL, 0.60 mmol) dropwise at 0 °C under argon. After stirring for 30 min at +20 °C, dry CH_3CN (3 mL) was added to the reaction mixture and let stand for additional 1 day at 20 °C. Workup with saturated aqueous Na_2CO_3 and brine, and flash chromatography (ethyl acetate/hexane = 1/1) afforded 175 mg (85%) of a homogeneous product (by HPLC) **14** as a white solid: mp 84–86 °C; IR ($CDCl_3$, thin film) 2945, 2870, 1705, 1610 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 7.0, 2.1 Hz, H-6), 4.56 (d, *J* = 7.0 Hz, H-7), 4.45 (br s, H-8), 4.12 (m, H-5), 2.95 (m, 4 H), 2.0–2.7 (m, 4 H), 1.5–1.9 (m, 10 H); ^{13}C NMR (CDCl3) δ 172.4, 136.5, 115.0, 79.9, 78.6, 77.5, 71.1, 42.9, 36.7, 35.3, 34.0, 29.7, 29.4, 25.2, 24.4, 24.2, 23.9; MS, *m/e* 353 (MH^+, 6%), 328 (13%), 255 (39%), 185 (100%).

5(*R*)-1-Aza-4(*R*)-carbomethoxy-6(*S*)-(acetyloxy)bicyclo[3.3.0]octan-8-one (17). A solution of $HgCl_2$ (810 mg, 2.98 mmol) in warm THF (1.0 mL) and 0.3 M HCl (1.33 mL, 0.40 mmol) was added to a stirred solution of ketene thioacetal **16** (425 mg, 1.42 mmol) in methanol (17 mL). The resulting milky mixture was gently heated for 1.5 h, then cooled and filtered through Florisil, and the filter cake was washed with ethyl acetate (35 mL) and methanol (10 mL). The filtrate was treated with $NaBH_4$ (200 mg, 5.26 mmol) to remove excess mercuric salts. After stirring for 10 min at room temperature, the mixture was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give 286 mg (84%) of crude product, which was used directly in the following reaction. A small sample was purified by flash chromatography (ethyl acetate) to give a white solid: mp 95–97 °C; IR ($CDCl_3$) 1740, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.12 (dt, *J* = 8.2, 4.7 Hz, H_7), 4.04 (dd, *J* = 8.8, 4.7 Hz, H_8), 3.74 (s, 3 H), 3.71 (m, 1 H), 3.20 (m, 1 H), 2.86 (dm, *J* = 8.4 Hz, H_6), 2.76 ("q", *J* = 18.6, 8.8 Hz, 1 H), 2.20–2.45 (m, 2 H), 2.08 (s, 3 H); MS, *m/e* (relative intensity) 181 (100%), 168 (23%), 138 (78%), 128 (29%), 100 (14%), 95 (9%); MS (CI, 100 eV), *m/e* (relative intensity) 243 (MH_2^+, 12%), 242 (MH^+, 100%), 180 (9%), 181 (11%).

(+)-Hastanecine (1). A suspension of $LiAlH_4$ (116 mg, 3.06 mmol) in THF (6 mL) was heated at reflux for 0.5 h. To this mixture was added a solution of the crude ester amide **17** (123 mg, 0.51 mmol) in THF (5 mL) dropwise under argon. After heating at reflux for 3 h, the reaction mixture was cooled, diluted with THF (5 mL), quenched with H_2O (0.15 mL), 15% aqueous NaOH (0.15 mL) and H_2O (0.30 mL), and filtered through K_2CO_3/Celite. The filter cake was washed with 10% triethyl amine in THF, and the residue was concentrated in vacuo in vacuo to give 78 mg (97%) of white solid. Flash chromatography ($CHCl_3/CH_3OH/NH_4OH$ = 10/5/1) yielded 40 mg (50%) of (+)-hastanecine, **1**, as a white solid: mp 113–114 °C; $[\alpha]^{25}_D$ +8.2° (*c* 1.43, EtOH) (lit.[57a,60a] mp 113–114 °C; $[\alpha]^{18}_D$ +8.5° (*c* 2.2, EtOH), $[\alpha]^{20}_D$ +10° (EtOH)); MS *m/e* (relative intensity) 157 (M^+, 24%), 113 (32%), 82 (100%). Other spectral data and chromatographic mobility (R_f 0.19, $CHCl_3/CH_3OH/NH_4OH$ = 10/5/1) are identical with an authentic sample of hastanecine.

5(*R*)-1-Aza-4-(1,3-dithian-2-ylidene)-6(*S*)-hydroxybicyclo[3.3.0]octane (18). To a suspension of $LiAlH_4$ (572 mg, 15.03 mmol) in THF (30 mL), which had been heated at reflux for 0.5 h, was added a solution of amide ester **16** (1.50 g, 5.01 mmol) in THF (10 mL) dropwise under argon over 15 min. After heating at reflux for 2 h, the reaction mixture was cooled and quenched with H_2O (0.6 mL), 15% aqueous NaOH (0.6 mL), and H_2O (1.8 mL). After the mixture had stirred for 0.5 h, ~2 g of Na_2SO_4 was added, the resulting mixture was filtered through K_2CO_3/Celite, and the filter cake was washed with 10% triethylamine in THF. Concentration in vacuo gave 1.22 g (100%) of product as a dark green oil. Flash chromatography ($CHCl_3/CH_3OH/NH_4OH$ = 290/10/1 → 140/10/1) yielded 1.00 g (82%) of **18** as a clear oil: $[\alpha]^{23}_D$ −76.4° (*c* 2.58, $CHCl_3$); IR ($CDCl_3$) 3632, 3025,

2983, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$ δ 4.24 (ddd, J = 7.3, 4.1, 3.1 Hz, 1 H), 3.95 (m, 1 H), 3.5 (br s, OH), 3.20 (dt, J = 11.1, 7.0 Hz, 1 H), 2.85–3.05 (m, 5 H), 2.75 (m, 2 H), 2.56 (m, 2 H), 2.04–2.23 (m, 3 H), 2.83 (m, 1 H); ^{13}C NMR ($CDCl_3$) 145.8, 117.2, 77.6, 77.2, 52.3, 52.1, 33.9, 31.6, 29.8, 29.7, 24.6; MS, m/e (relative intensity) 243 (M^+, 7%), 199 (100%), 171 (15%), 158 (10%), 125 (48%).

(+)-Dehydroheliotridine (7). To a stirred suspension of dithiane **19** (90 mg, 0.37 mmol) and $CaCO_3$ (296 mg, 2.96 mmol) in 80% aqueous CH_3CN (5 mL) was added $HgCl_2$ (402 mg, 1.48 mmol) at room temperature. After heating at 50 °C overnight, the solvents were evaporated and the residue was taken up in methanol (25 mL), to which $NaBH_4$ (100 mg, 2.63 mmol) then was added. After stirring for 20 min, the reaction mixture was quenched with several mL of saturated aqueous $NaHCO_3$ solution, filtered through Celite, concentrated, and flash chromatographed ($CHCl_3/CH_3OH/NH_4OH$ = 90/10/1) to give 23 mg (41%) of **7**: mp 90–92 °C (benzene), lit.[13b] mp 91–93.5 °C); $[\alpha]^{24}_D$ +33.0° (c 1.0, EtOH), lit.[13b] $[\alpha]^{22}_D$ + 35° (c 1.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 6.55 (d, J = 2.6 Hz, 1 H), 6.17 (d, J = 2.6 Hz, 1 H), 5.25 (dd, J = 6.7, 2.8 Hz, 1 H), 4.63 (AB q $\Delta\nu$ = 33.0 Hz, J = 12.1 Hz, 2 H), 4.15 (dt, J = 10.3, 7.3 Hz, 1 H), 3.92 (m, 1 H), 2.35–2.90 (m, 4 H); MS, m/e (relative intensity) 153 (M^+, 20%), 136 (16%), 117 (100%), 104 (14%), 90 (54%), 89 (47%).

Swern Oxidation of 18: Racemic 5(R)-1-Aza-4-(1,3-dithian-2-ylidene)bicyclo[3.3.0]octan-6-one (20). Trifluoroacetic anhydride (1.58 g, 7.52 mmol) was added under argon to a stirring solution of Me_2SO (0.783 g, 10.02 mmol) in CH_2Cl_2 (12 mL) at −78 °C. This cold solution was stirred under argon for 20 min. Alcohol **18** (1.22 g, 5.01 mmol) in CH_2Cl_2 (22 mL) was then added dropwise. Stirring at −70 °C under argon was continued for 1 h, and the reaction mixture was quenched with triethylamine (0.798 mg, 7.89 mmol) at −60 °C. After the mixture had been stirred for 10 min, the dry ice bath was removed and the mixture stirred for additional 15 min, then Na_2SO_4 (20 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were filtered through Na_2SO_4/Florisil. Flash chromatography ($CHCl_3/CH_3OH/NH_4OH$ = 590/10/1 → 190/10/1) yielded 0.30 g (24%) of starting material and 0.85 g (70%) of the ketone as a solid (unstable). It was used immediately in the subsequent step): IR ($CDCl_3$) 2920, 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.11 (s, 1 H), 3.34 (dt, J = 12.2, 8.2 Hz, 1 H), 2.05–3.20 (m, 12 H); ^{13}C NMR ($CDCl_3$) 214.6, 136.9, 122.5, 52.5, 47.5, 34.0, 31.5, 29.8, 29.5, 24.6; MS (CI, 100 eV), m/e (relative intensity) 242 (MH^+, 58%), 107 (100%), 71 (29%).

Racemic 5(R)-1-Aza-4-(1,3-dithian-2-ylidene)-6(R)-hydroxybicyclo[3.3.0]octane (21). To a solution of ketone from the above reaction (800 mg, 3.31 mmol) in THF (35 mL) cooled to −78 °C was added L-Selectride (5.0 ml of 1.0 M solution in THF, 5.0 mmol) in one portion under argon. After stirring for 1 h, the reaction mixture was quenched with 10% NH_4OH (35 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 35 mL), and the combined organic layers were dried (Na_2SO_4). Flash chromatograhy ($CHCl_3/CH_3OH/NH_4OH$ = 190/10/1) yielded 611 mg (76%) of **21** as a white solid: mp 169–171 °C; ^{1}H NMR ($CDCl_3$) δ 4.52 ("q", J = 4.1 Hz, 1 H), 4.15 (d, J = 4.1 Hz, 1 H), 3.13 (m, 2 H), 2.92 (m, 6 H), 2.63 (m, 2 H), 2.18 (quintet, J = 6.1 Hz, 2 H), 2.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 142.3, 117.9, 74.7, 72.5, 54.1, 54.0, 52.7, 35.5, 33.4, 29.9, 24.9; MS, m/e (relative intensity) 243 (M^+, 9%), 242 (11%), 199 (100%), 171 (15%), 158 (11%0, 125 (49%), 97 (12%); MS (CI, 100 eV), m/e (relative intensity) 244 (MH^+, 49%), 226 (16%), 199 (9%), 186 (30%), 154 (24%), 123 (22%), 107 (100%), 71 (19%).

HPLC analysis of the crude reaction mixture showed a 99:1 mixture of the alcohols **21**:**18**. Sodium borohydride reduction in methanol (0 °C) gave the same two products in a ratio of 1:2.

Trifluoroacetic Acid Induced Ring Closure of 21 to 23a. To a solution of ketene dithioacetal **21** (55 mg, 0.225 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (31 mg, 0.27 mmol) at room temperature. After stirring for 3 h, the solvent was evaporated and residue was taken up with methanol (5 mL) and K_2CO_3 (~200 mg) was added. After stirring for 10 min, the purple soltion turned yellow and the mixture was filtered through a plug of Al_2O_3 in a pipette to give 52 mg (95%) of yellowish solid after drying in vacuo. IR ($CDCl_3$) 2940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.67 ("t", J = 4.7 Hz, H_7), 4.14 (dd, J = 7.9, 5.0 Hz, H_8), 2.55–3.50 (m, 8 H), 1.70–2.4 (m, 7 H); MS, m/e (relative intensity) 243 (M^+, 18%), 168 (67%), 137 (70%), 109 (80%), 82 (100%).

Racemic 5(R)-1-Aza-4(S)-carboxy-6(R)-hydroxybicyclo-[3.3.0]octane Lactone (24a). To a solution of the dithiane **23a** (8.0 mg, 0.33 mmol) in 80% aqueous CH_3CN (1 mL) was added a mixture of $HgCl_2$ (22.4 mg, 0.0825 mmol) and $CaCO_3$ (165 mg, 0.165 mmol) at room temperature. After stirring for 0.5 h, the reaction mixture was diluted with CH_3CN and filtered, and the filter cake was washed with more CH_3CN. The combined filtrate was concentrated and the residue was taken up with $CHCl_3$, then treated with Na_2S. After stirring for several hours, the solution was filtered through Na_2SO_4/Florisil to yield 4.6 mg (90%) of **24a** as an oil: IR ($CDCl_3$) 2985, 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.02 (dt, J = 5.1, 1.5 Hz, H_7), 4.15 (dd, J = 7.5, 5.4 Hz, H_8), 3.00–3.20 (m, 3 H), 2.81 (dt, J = 11.3, 6.7 Hz, 1 H), 2.05–2.45 (m, 4 H); MS, m/e (relative intensity) 153 (M^+, 36%), 152 (44%), 82 (100%).

(±)-Platynecine (4). To a suspension of $LiAlH_4$ (1.7 mL of 1.5 M in THF solution, 2.55 mmol) in THF (3.3 mL), which had been refluxed for 0.5 h, was added a solution of the tricyclic lactone **24a** (13 mg, 0.085 mmol) in THF (3 mL) dropwise under argon. After heating at reflux for 4 h, the reaction mixture was cooled and quenched with H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL), and H_2O (0.3 mL) sequentially, dried (Na_2SO_4), then filtered through K_2CO_3/Celite. The filtrate was evaporated to dryness to give 11 mg (82%) of platynecine **4** as a white solid: mp 126–128 °C ($CHCl_3$/acetone), (lit.[17b] mp 128.5 °C); other spectral data[17b] and chromatographic mobility (R_f 0.10, $CHCl_3/CH_3OH/NH_4OH$ = 10/4/1) are identical with an authentic sample of platynecine.

Phenylselenenyl Chloride Induced Ring Closure of 21 to 23b. To a flame-dried round bottom flask containing a solution of the ketene thiacetal **21** (10.2 mg, 0.042 mmol) in THF (1 mL) was added a solution of phenylselenium chloride (12.1 mg, 0.063 mmol) in THF (0.5 mL) at 0 °C under argon. A precipitate appeared immediately. After the mixture had been stirred for 5 min, CH_2Cl_2 (1 mL) was added (reaction mixture became clear). After the mixture had been stirred for 2 h at 0 °C, the solvents were removed, and the residue was subjected to flash chromatography ($CHCl_3/CH_3OH/NH_4OH$ = 350/10/1) to give 16 mg (96%) of product **23b** as a solid: ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2 H), 7.35 (m, 3 H), 4.64 (t, J = 4.6 Hz, H_7), 3.91 (d, J = 4.8 Hz, H_8), 3.40–1.75 (m, 14 H); *MS*, m/e (relative intensity) 399 (M^+, 0.54%), 325 (0.85%), 242 (100%), 168 (15%), 136 (21%), 108 (12%), 82 (41%); MS (CI, 100 eV), m/e (relative intensity) 400 (MH^+, 100%), 244 (87%), 170 (22%), 107 (23%).

Racemic 5(R)-1-Aza-4(R)-carboxy-6(R)-hydroxy-4(R)-(phenylseleno)bicyclo[3.3.0]octane Lactone (24b). Some procedure as for preparation of **24a**, except the starting material is **23b**. Yield = 92%. IR ($CDCl_3$) 3080, 2980, 1770 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2 H), 7.40 (m, 3 H), 4.30 (d, J = 5.0 Hz, H_8), 4.19 (br t, J = 4.5 Hz, H_7), 3.42–3.20 (m, 2 H), 2.58–2.90 (m, 3 H), 2.45 (m, 1 H), 1.90–2.20 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.7, 137.3, 129.9, 129.5, 125.6, 81.0, 78.3, 54.0, 52.6, 52.0, 38.8, 33.7; MS, m/e (relative intensity) 309 (M^+, 11%), 152 (100%).

Reduction of α-Selenolactone 24b to 1-(Phenylseleno)-platynecine. To a solution of the α-selenolactone **24b** (78 mg, 0.253 mmol) in THF (4 mL) was added 2.0 mL of a 1.0 M $LiAlH_4$ solution in THF (2.0 mmol) in one portion under argon at −35 °C. After stirring for 3 h as it warmed to −10 °C, the reaction was quenched with H_2O (0.1 mL) in THF (2 mL), 15% NaOH (0.1 mL), H_2O (0.3 mL) in THF (2 mL), and Na_2SO_4·10 H_2O (~1 g). Filtration through Na_2SO_4/K_2CO_3/Celite and concentration gave 78 mg of crude product. Chromatography on alumina (Activity II, $CHCl_3/MeOH/NH_4OH$ = 200/20/0.5) afforded 73 mg (92%) of an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 2 H), 7.31 (m, 3 H), 4.23 (m, 1 H), 3.97 (br s, 2 H), 3.55 (dt, J = 9.7, 6.8 Hz, 1 H), 3.27 (m, 1 H), 3.13 (d, J = 2.7 Hz, 1 H), 2.75–3.05 (m, 3 H), 2.27 (dt, J = 13.4, 9.0 Hz, 1 H), 1.85–2.05 (m, 3 H), 1.30 (m, 1 H); MS (CI, 100 eV), m/e (relative intensity) 314 (MH^+, 100%), 312 (52%), 310 (20%), 296 ($MH^+ - H_2O$, 16%), 156 (MH^+ − PhSeH, 21%), 138 (11%), 112 (16%).

(±)-Retronecine (6). To a solution of the seleno compound from the above procedure (72 mg, 0.23 mmol) in acetic acid (2.5 mL) was added 30% H_2O_2 (72 μL, 0.69 mmol) at room temperature. After stirring for 1.5 h, ~0.2 mL of Me_2S was added and allowed to stir for 30 min. The yellowish solution was then basified with saturated aqueous K_2CO_3 solution (2 mL) and solid K_2CO_3

(added until no more fizzling). The mixture was then evaporated to dryness in vacuo under a steam bath. The residue was triturated with $CHCl_3$ (3 × 50 mL), and the combined organic solvents were filtered through Na_2SO_4. Chromatography on alumina ($CHCl_3$/MeOH/NH_4OH = 1/0/0 → 200/20/0.5) and followed by recrystallization (acetone) afforded 30.5 mg (86%) of **6**: mp 129–130 °C (lit.[14] mp 130–131 °C); other spectral data and chromatographic mobility (R_f 0.23, $CHCl_3$/MeOH/NH_4OH = 10/4/1) are identical with an authentic sample, except the optical rotation is zero.

Hydrolysis of 18 to 25. To a solution of **18** (1.46 g, 6.0 mmol) in MeOH (60 mL) was added successively 6.0 M HCl (2.5 mL, 15.0 mmol), $HgCl_2$ (3.42, 12.6 mmol), and trifluoroacetic acid (1.16 mL, 15.0 mmol). After heating gently for 8 h, the milky mixture was filtered through Celite and the filter cake was washed with more MeOH. The filtrate was then treated carefully with $NaBH_4$ (114 mg, 3.0 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was filtered through Celite, concentrated, and chromatographed on alumina ($CHCl_3$/MeOH/NH_4OH = 1/0/90 → 100/20/1) to yield 783 mg (71%) of **25** as a clear oil: IR ($CDCl_3$) 3350, 2950, 1730 cm^{-1}; $[\alpha]^{22}_D$ −15.5° (*c* 9.67, EtOH), (lit.[13a] $[\alpha]^{20}_D$ −18.5° (*c* 2.1, EtOH)); ^1H NMR ($CDCl_3$) δ 5.05 (br s, OH), 4.13 (m, 1 H), 3.68 (s, 3 H), 3.40 ("dd", *J* = 8.1, 2.5 Hz, 1 H), 3.25 (m, 2 H), 2.55 (m, 3 H), 2.05 (m, 3 H), 2.79 (m, 1 H); ^{13}C NMR $CDCl_3$) δ 174.0, 76.3, 75.7, 54.5, 51.8, 47.9, 33.5, 29.6; MS, *m/e* (relative intensity) 185 (M^+, 2%), 167 ($M^+ - H_2O$, 16%), 254 (8%), 141 ($M^+ - C_2H_4O$, 21%), 82 (100%); MS (CI, 100 eV), *m/e* (relative intensity) 186 (MH^+, 100%).

Oxidation of 25. To a solution of Me_2SO (0.521 mL, 7.34 mmol) in CH_2Cl_2 (7.5 mL) cooled to −70 °C was added trifluoroacetic anhydride (0.831 mL, 5.88 mmol) dropwise under argon. After the mixture had been stirred for 10 min at this temperature, a solution of **25** (676 mg, 3.65 mmol) in CH_2Cl_2 (7.5 mL) cooled to −70 °C was added. The resulting mixture was allowed to stir at −65 °C for 1 h, then Et_3N (1.02 mL, 7.34 mmol) was added slowly to the reaction flask. After the mixture had been stirred for 20 min, the cold bath was removed and stirring was continued for an additional 20 min. The reaction was quenched with H_2O (6 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with saturated aqueous K_2CO_3 (3 mL) and extracted with $CHCl_3$ (5 × 10 mL). Filtration through Na_2SO_4 and flash chromatography ($CHCl_3$/MeOH/NH_4OH = 390/10/1 → 190/10/1) gave 495 mg (74%) of a solid: Recrystallization from acetone–pentane gave 481 mg (72%) of white needles: mp 101–102 °C (lit.[13a] 101–102 °C); $[\alpha]^{24}_D$ +67.6° (*c* 2.67, MeOH) (lit.[13a] $[\alpha]^{20}_D$ +64° (*c* 1.09; MeOH)); IR ($CDCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (d, *J* = 4.1 Hz, 1 H), 3.73 (s, 3 H), 3.42 (dt, *J* = 11.7, 7.5 hz, 1 H), 3.20 (m, 1 H), 3.02 (m, 2 H), 2.70 (m, 1 H), 2.45 (t, *J* = 7.4 Hz, 2 H), 2.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 217.2, 173.8, 71.6, 53.7, 52.3, 47.9, 45.5, 35.2, 29.6; MS (CI, 100 eV), *m/e* (relative intensity) 184 (MH^+, 100%).

Hydrogenation to 26. A mixture of the ketone from the above reaction (30 mg, 0.164 mmol) and PtO_2 (23 mg) in MeOH (3.5 mL) was hydrogenated at room temperature and pressure for 1.5 h. The mixture was filtered through glass wool and concentrated to give 29.5 mg (97%) of **26** as a clear oil: $[\alpha]^{21}_D$ −48.2° (*c* 2.33, MeOH); IR ($CDCl_3$) 3620, 3000, 1730 cm^{-1}; ^1H NMR ($CDCl_3$ δ 4.40 (br s, OH), 4.13 (m, 1 H), 3.60 (s, 3 H), 3.57 (dd, *J* = 7.4, 4.5, Hz, 1 H), 3.18 (m, 1 H), 2.94–3.10 (m, 2 H), 2.52 (m, 2 H), 2.00–2.20 (m, 2 H), 1.80–2.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.0, 72.1, 70.5, 55.4, 52.2, 51.9, 41.9, 37.0, 31.8; MS, *m/e* (relative intensity) 185 (M^+, 3%), 167 ($M^+ - H_2O$, 11%), 14. (7%), 141 (21%), 82 (100%).

(+)-5(*R*)-1-Aza-4(*S*)-carboxy-6(*R*)-hydroxybicyclo[3.3.0]octane. To a solution of **26** (130 mg, 0.75 mmol) in dry ethanol (distilled from Na and stored over activated powdered 3-Å molecular sieve, 7.5 mL) was added a solution of EtONa (prepared from 18 mg, 0.77 mmol of Na and 3 mL of dry EtOH) in ethanol under argon. The resulting mixture was heated gently for 2.5 h, cooled, and quenched with concentrated H_2SO_4 (61 μL, 1.05 mmol). The mixture was diluted with MeOH (5 mL), basified with solid K_2CO_3 and NH_4OH (5 drops), filtered through Al_2O_3/Na_2SO_4 (washed the filter cake with 10–20% MeOH in $CHCl_3$), and then subjected to flash chromatography ($CHCl_3$/MeOH/NH_4OH = 490/10/1 → 190/10/1) to give 86 mg (75%) of **27** as a clear oil: IR ($CDCl_3$) 2985, 1770 cm^{-1}; $[\alpha]^{22}_D$ +84.4° (*c* 0.71, $CHCl_3$) (lit.[23] $[\alpha]^{21}_D$ +84° (*c* 1.4, $CHCl_3$)); ^1H NMR ($CDCl_3$) δ 5.00 (ddd, *J* = 5.1, 5.1, 3.6 Hz, 1 H), 4.14 (dd, *J* = 7.5, 5.4 Hz, 1 H), 3.10 (m, 3 H), 2.80 (dt, *J* = 11.3, 6.8 Hz, 1 H), 2.66 (dt, *J* = 10.1, 6.1 Hz, 1 H), 2.05–2.40 (m, 4 H); MS, *m/e* (relative intensity) 153 (M^+, 36%), 152 (44%), 82 (100%).

Phenylselenylation of Lactone 27 to 28. To a solution of lithium diisopropyl amide (prepared from 0.24 mL of diisopropyl amine and 0.70 mL of 2.42 M *n*-BuLi in hexane under argon) in THF (1.5 mL) was added dropwise a solution of **27** (52 mg, 0.34 mmol) in THF (2.0 mL) in 1–2 min at −78 °C. The reaction mixture was stirred for 1 h at −70 °C for 1.5 h, then a solution of phenyl diselenide (531 mg, 1.70 mmol) in THF (1 mL) containing hexamethylphosphoramide (0.3 mL, 1.70 mmol) was rapidly added at −78 °C. The reaction mixture was stirred for 1 h at −70 °C and 1.5 h at −40 °C and then quenched with 1.5 M HCl (4.5 mL). The mixture was diluted with ether (30 mL) and separated, and then the organic layer was extracted with 1.5 M HCl (2 × 4.5 mL) and H_2O (1 × 4.5 mL). The combined aqueous layers were concentrated and basified with NH_4OH (2 mL) and solid K_2CO_3. Extraction with $CHCl_3$ (5 × 10 mL), filtration through Na_2SO_4, and flesh chromatography ($CHCl_3$/MeOH/NH_4OH = 690/10/1 → 140/10/1) afforded 37 mg (71%) of starting lactone and 26 mg (25%) of **28** as an oil. IR, ^1H NMR, ^{13}C NMR, and mass spectra were identical with those reported to racemic **28**.[18,23]

(+)-Retronecine (6). Conversion of **28** to (+)-retronecine (**6**) was accomplished by published procedures for racemic **6**.[18,23] The overall yield for the two steps was 79%: mp 120–121 °C (lit.[9,22e] 121–122°, 119–121 °C); $[\alpha]^{26}_D$ +50.4° (*c* 0.29, EtOH) (lit.[9,22e] $[\alpha]_D$ +50.2°, $[\alpha]^{22}_D$ +52.2°, EtOH). Other spectral data and chromatographic mobility (R_f 0.23, $CHCl_3$/MeOH/NH_4OH = 10/4/1) are identical with those of an authentic sample.

(−)-Platynecine (4). Reduction of **27** to (−)-platynecine was accomplished by the procedure described above for the conversion of **24a** into (±)-platynecine. The yield was 81%: mp 151–152 °C, (lit.[9] 151–152 °C); $[\alpha]^{22}_D$ −55.1° (*c* 2.14, $CHCl_3$), (lit.[9] $[\alpha]_D$ −57.0°, $CHCl_3$). Other spectral data[10] and chromatographic mobility (R_f 0.17, $CHCl_3$/MeOH/NH_4OH = 5/5/1) are identical with those of an authentic sample.

(−)-Turneforcidine (2). Reduction of **26** to (−)-turneforcidine was accomplished using the procedure described above for the conversion of **24a** into **4**. The yield was 75%: mp 118–120 °C, (lit.[9] mp 118.5–120 °C); $[\alpha]^{24}_D$ −11.4°, (*c* 1.2, MeOH), (lit.[9] $[\alpha]_D$ −10.5°, MeOH). Other spectral data[10] and chromatographic mobility (R_f 0.22, $CHCl_3$/MeOH/NH_4OH = 5/5/1) are identical with those of an authentic sample.

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