is a confusing factor; a bicyclo[2.2.2]octane derivative has also been found with a twist angle of 3°.[28] In any event it is clear that the twist of the quinuclidine containing N(1) in the bis(quinuclidine)bromine(I) cation is very large.

When considering the crystallographic evidence for the ground-state geometry of [2.2.2] ring systems, it is important to determine whether the structures having twist angles very close to 0 are affected by disorder of mirror-related enantiomers, disorder that may be hidden in the anisotropic thermal parameters if the twist angles are small. In such cases, however, analysis of the thermal motion of the atoms of the [2.2.2] ring system with the TLS rigid-body motion model[20] should reveal an abnormally large libration about the (approximate) C_3 axis. The rms value of 5.2-6.2° (depending on the model) found in this study may be used for comparison, since there is no indication that the librational motion is influenced by any kind of double-well potential. This value agrees very well with the corresponding rms value of 5.9 (2)° found for the approximately C_{3v} bicyclo-[2.2.2]octane-1,4-dicarboxylic acid by Ermer and Dunitz,[27] who also concluded that their structure was unaffected by disorder.

Acknowledgment. This research was partially supported by a grant to L.K.B. from The Camille and Henry Dreyfus Foundation.

Registry No. 7, 85282-84-4; **8**, 85282-86-6.

Supplementary Material Available: Anisotropic thermal parameters, calculated hydrogen positional parameters, and observed and calculated structure factor amplitudes (6 pages). Ordering information is given on any current masthead page.

(29) (a) Meyerhöffer, A.; Carlström, D. *Acta Crystallogr., Sect. B* **1969**, *B25*, 1119-1126. (b) Meyerhöffer, A. *Ibid.* **1970**, *B26*, 341-351.

Synthesis of Optically Active Pyrrolizidinediols: (+)-Heliotridine

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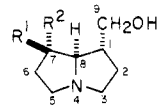
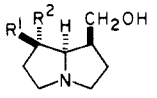
Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received November 29, 1982*

Abstract: A practical synthesis of the unsaturated pyrrolizidinediol (+)-heliotridine (**5**) is reported, starting from the readily available (*S*)-malic acid. The azabicyclo[3.3.0]octane ring system has been constructed via a stereoselective acyliminium ion cyclization directed by an acetoxy substituent. A ketene dithioacetal substituent in the cyclization precursor serves both as an efficient cationic cyclization terminator and later as a means of controlling double bond migration regioselectively into the correct position in the pyrrolizidine skeleton.

The pyrrolizidines are a group of alkaloids that exhibit remarkably diverse types of biological activity. Various members of this family, which have in common the azabicyclo[3.3.0]octane ring system, have been reported to act as antitumor, hypotensive, local anesthetic, antispasmotic, antiinflammatory, carcinogenic, or hepatotoxic agents.[1] Although a number of substitution patterns and oxidation levels of the basic ring system are known, most common are the diols, either saturated (**1**-**4**) or 1,2-unsaturated (**5** and **6**). The bases themselves have been isolated



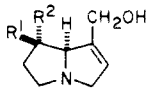
$R^1 = H$, $R^2 = OH$ (+)-Hastanecine, **1**



(-)-Dihydroxheliotridane, **3**

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

(-)-Platynecine, **4**

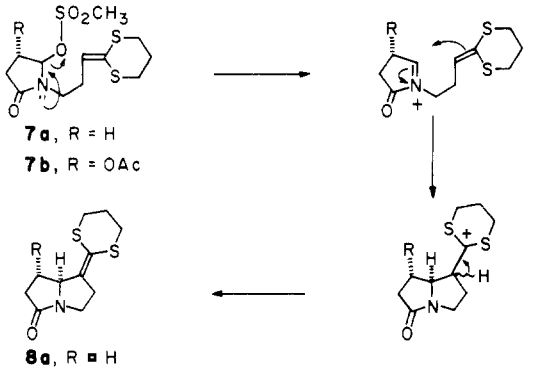


$R^1 = H$, $R^2 = OH$ (+)-Heliotridine, **5**

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

from natural sources, but more often they are present as esters, diesters, or macrocyclic bislactones. An intense interest in their synthesis is evident in the recent profusion of new routes to racemic pyrrolizidines,[2] but a practical total synthesis of optically active

Scheme I



7a, R = H

7b, R = OAc

8a, R = H

8b, R = OAc

derivatives had yet to emerge[3] in spite of the deceptive simplicity of the targets. We therefore sought to develop a strategy for preparing unsaturated pyrrolizidinediols from readily available optically active starting materials, and in this paper we report a

(1) Biological activity: (a) Atal, C. K. *Lloydia* **1978**, *41*, 312. (b) Gelbaum, L. T.; Gordon, M. M.; Miles, M.; Zalkow, L. H. *J. Org. Chem.* **1982**, *47*, 2501. General reviews: (c) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1981**, *41*, 8 and references cited therein. Yearly updates: (d) *Alkaloids (London)* **1971-1980**, *1-11*.

(2) For recent syntheses, see: Hart, D. J.; Yang, T. K. *Tetrahedron Lett.* **1982**, *23*, 2761 and references cited therein. Also see ref 5.

(3) (a) An enantioselective synthesis of monohydroxy pyrrolizidines has been reported: Robbins, D. J.; Sakdarat, S. *J. Chem. Soc., Chem. Commun.* **1979**, 1181. (b) The preparation of an optically active pyrrolizidine diol precursor, the Geissman-Waiss lactone, has been reported recently: Rüeger, H.; Benn, M. H. *Heterocycles* **1982**, *19*, 23. (c) After submission of this paper we learned of an enantioselective synthesis of the saturated pyrrolizidine hastanecine (**1**) also starting from malic acid: Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.*, in press. We thank Professor Hart for communicating his results to us prior to publication.

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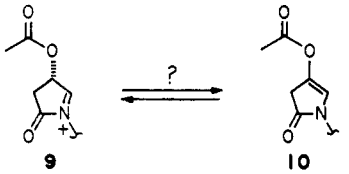
practical method for converting (*S*)-malic acid into (+)-heliotridine (**5**).

Results and Discussion

As a first phase in finding an efficient method of ring formation, an acyliminium ion–ketene dithioacetal cyclization[4] was investigated (Scheme I). In a preliminary published study,[5] the mesylate **7a**, formed from the corresponding hydroxy lactam, undergoes high-yield cyclization to the pyrrolizidine derivative **8a**, presumably via elimination to the acyliminium ion, cationic cyclization, and loss of a proton. However, the necessary extension of this new intramolecular reaction of ketene dithioacetals to the more highly substituted substrate **7b** left a number of questions to be answered. First, what would be the effect of the acetoxy group on the cyclization? Johnson has observed that a pro C-11 alcohol group has a deleterious effect on cationic cyclization to a steroid nucleus, attributed in part to its carbocation-destabilizing inductive effect.[6] On the other hand, an acetoxy group can stabilize adjacent cations via neighboring group participation,[7] so that its effect on cyclization efficacy would be difficult to predict. A second, related question is whether or not the acetoxy group (or any alternative OR) will have a substantial effect on the diastereoselectivity of cyclization; i.e., will it direct the ketene dithoiacetal to attack predominantly one face of the acyliminium ion? To the extent that it does so, of course, the absolute stereochemistry of the pyrrolizidine ring juncture (C-8) is controlled by the configuration of the acetoxy group. Finally, the problem of double bond migration competing with cyclization may arise.

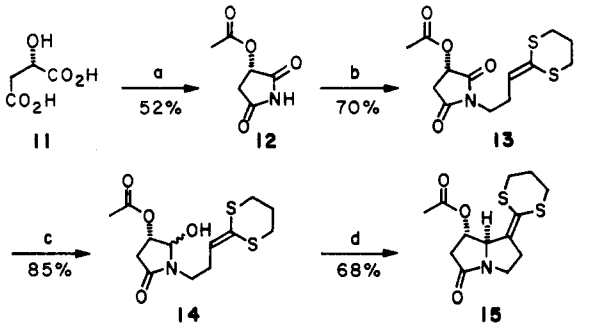


9 **10**

Such a transformation certainly is known for simple acyliminium ions,[9] and it may occur reversibly under the usual acidic conditions employed to form acyliminium ions.[4] In the case at hand (**9** and **10**) such a reaction could lead either to the racemic pyrrolizidine (if it occurred reversibly) or simply to the noncyclized product **10** (if it occurred irreversibly, which is more likely under nonacidic conditions).

The precursor **14** required to test this acetoxy-directed cyclization was prepared in three steps (Scheme II). (*S*)-Malic acid (**11**) was treated sequentially with acetyl chloride, gaseous ammonia, and then acetyl chloride again to give (*S*)-acetoxysuccinimide (**12**) in 52% yield after recrystallization. Attempts to determine the optical purity of this intermediate using chiral ^{1}H NMR shift reagents[10] failed, but its ultimate conversion into the natural product **5** of known optical rotation assures its enantiomeric integrity. Mitsunobu coupling[11] of **12** with 2-(3-hydroxypropylidene)-1,3-dithiane[5] afforded a 70% yield of **13**, which was then reduced with sodium borohydride in methanol (−4 °C, 10 min). Although succinimides are sensitive to overreduction by borohydride,[12] these simple conditions provide an 85% crude yield of white solid that consists of an 11:1 diastereomeric mixture of the hydroxy lactams **14**. Products arising from reduction of the less electrophilic carbonyl group were not detected.[13]

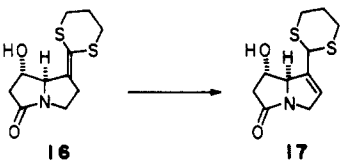
Scheme II. Preparation of the Key Intermediate, **15**[a]



[a] (a) 1, AcCl; 2, NH_3; 3, AcCl. (b) 2-(3-hydroxypropylidene)-1,3-dithiane,[5] Ph_3P, EtO_2CNNCO_2Et. (c) $NaBH_4$, CH_3OH, −4 °C. (d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, −20 → 20 °C.

Cyclization to the pyrrolizidine skeleton was conducted under the nonacidic conditions described previously.[5] Although the diastereomers of **14** could be separated and cyclized individually to the same product, it was more efficacious to simply treat the crude reaction mixture with methanesulfonyl chloride and triethylamine in dichloromethane at −20 °C and then allow it to warm to room temperature. The major product under those conditions is the pyrrolizidine **15**, which is isolated in 68% yield after flash chromatography. HPLC analysis of the crude reaction mixture shows only ~3% of a second product, which is assumed to be the bridgehead diastereomer of **15** based on its ^{1}H NMR. The acetoxy group therefore very effectively blocks the α-face of the acyliminium ion, resulting in efficient relative asymmetric induction during the cyclization step.[14]

Having formed the pyrrolizidine ring system, the next operation undertaken was a migration of the double bond to the desired endocyclic position. Direct formation of the lithiated ketene dithioacetal from **15** followed by protonation α to sulfur[15] clearly is not likely to succeed in this case due to competing β-elimination of the acetoxy group. Instead, the acetate group was first cleaved (K_2CO_3, MeOH) to give a 64% yield of the β-hydroxy lactam **16**, which then does undergo the desired double bond migration via a deprotonation–protonation reaction (excess LDA–HMPT followed by methanol). It is presumed that β-alkoxy enolate



16 **17**

formation[16] under the reaction conditions protects the lactam ring of **16** from various conceivable modes of destruction. The double bond migrated product (**17**), obtained in 80% yield (containing an inseparable 5% of starting material), was then converted into (+)-heliotridine (**5**) in 64% yield by dithiane hydrolysis[17] ($HgCl_2$, CH_3CN, H_2O, $CaCO_3$) followed directly by reduction of both the resulting aldehyde and the lactam carbonyl groups ($LiAlH_4$, THF reflux). The product was spectrally and chromatographically identical with an authentic sample, and it exhibited an optical rotation ($[\alpha]^{20}_D$ +30.3°) comparable to literature values (+30.4° and +31°).[18]

(4) Acyliminium cyclizations in alkaloid synthesis have been reviewed: Speckamp, W. N. *Recl. Trav. Chem. Pays-Bas* **1981**, *100*, 345.
(5) Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619.
(6) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.
(7) Capon, B. *Q. Rev. Chem. Soc.* **1964**, *18*, 45.
(8) (a) Wijnberg, B. P.; Speckamp, W. N.; Oostveen, A. R. C. *Tetrahedron* **1982**, *38*, 209. (b) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, 1987.
(9) (a) Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143. (b) Wijnberg, J. B. P. A.; de Boer, J. J. J.; Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 227.
(10) Kime, K.; Sievers, R. E. *Aldrichimica Acta* **1977**, *10*, 54.
(11) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(12) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.
(13) For a study of the regioselectivity of reduction of substituted succinimides, see: Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179.
(14) One appealing explanation for the high stereoselectivity of cyclization is that the acetoxy group is shielding the α-face of the acyliminium ion not as a simple substituent but rather by bridging to the adjacent cationic center.[7] The resulting intermediate would be a cis 5,5-ring system that should undergo attack by the internal nucleophile mainly from the convex face. We are currently exploring this possibility.
(15) Seebach, D.; Kolb, M. *Liebigs Ann. Chem.* **1977**, 811.
(16) For other examples of β-alkoxy enolates (esters and lactones) see: Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, 3055 and references cited therein.
(17) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357.

This preparation of (+)-heliotridine is relatively concise and can provide workable quantities of the pure product within a week's time. The synthesis illustrates an interesting regioselective imide reduction as well as a useful example of stereochemical control in an acyliminium ion cyclization. A key element is the dual use of a ketene dithioacetal group, first as an efficient cationic cyclization terminator and later as a means of attaining regioselective double bond migration. We are currently investigating other transformations of **15** with the intention of developing routes to all common pyrollizidinediols (**1–6**) via this single intermediate, which is available in multigram quantities.

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 trimethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), and integration. Melting points were taken on a Laboratory Devices melting-point apparatus and are reported uncorrected. Mass spectra were recorded on a Finnigan 9610 spectrometer at 70 eV. High-pressure liquid chromatography was performed on a Waters analytical instrument using 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 10-cm cell at the designated concentration in g per 100 mL.

When necessary, solvents and reagents 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).

3(*S*)-(Acetyloxy)-2,5-pyrrolidinedione (12). A suspension of (*S*)-malic acid (8.00 g, 59.6 mmol) in acetyl chloride (30 mL) was heated at reflux for 1.5 h. The resulting solution was evaporated to dryness in vacuo to give a yellow oil (IR (thin film) 1874, 1793, and 1744 cm^{-1}), which was diluted with tetrahydrofuran (50 mL) and treated with a stream of gaseous ammonia over a 30-min period. The resulting mixture was evaporated to dryness in vacuo to give a white solid. Enough acetyl chloride ($\sim$30 mL) was added to cover the solid, and the resulting mixture was heated at reflux for 2 h, during which time the solution turned dark purple. The mixture was concentrated and chromatographed on 100 g of silica gel (70–230 mesh, ether). Recrystallization (chloroform/hexane) gave 4.91 g (52%) of **12** as large prisms: mp 112–114 °C; $[\alpha]^{25}_D$ −48.0° (*c* 2.2, MeOH); IR ($CDCl_3$) 1803, 1751, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.73 (AB q, *J* = 18.4, 5.2 Hz, 1 H), 3.20 (AB q, *J* = 18.4, 8.8 Hz, 1 H), 5.47 (AB q, J = 8.8, 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.6, 173.1, 170.0, 68.6, 37.0, 20.6; MS, *m/e* (relative intensity) 157 (M^+, 4), 114 ($M^+ - C_2H_3O$, 41), 86 ($M^+ - C_2HNO_2$, 100).

Anal. Calcd for $C_6H_7NO_4$: C, 45.87; H, 4.49; N, 8.91. Found: C, 45.64; H, 4.58; N, 8.87.

3(*S*)-(Acetyloxy)-*N*-[3-(1,3-dithian-2-ylidene)propyl]-2,5-pyrrolidinedione (13). A solution of diethyl azodicarboxylate[11] (3.4 mL, 20 mmol) in tetrahydrofuran (8 mL) was added dropwise to a solution of 2-(3-hydroxypropylidene)-1,3-dithiane[5] (4.0 g crude, 20 mmol), the succinimide **12** (3.14 g, 20 mmol), and triphenylphosphine (5.30 g, 20.0 mmol) in tetrahydrofuran (20 mL) at room temperature. After the solution was stirred overnight, the solvent was removed in vacuo and ethyl acetate/ether (50 mL, 1:1) was added to the residue to precipitate triphenylphosphine oxide. After standing for 1 h, the solids were removed by filtration and the filtrate was concentrated and chromatographed on silica (ethyl acetate:hexane = 4:5) to yield 4.44 g (70%) of yellowish viscous oil: IR (thin film) 1790, 1750, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.15 (m, 2 H), 2.53 ("q", 2 H), 2.64 (AB q, *J* = 18.3, 4.8 Hz, 1 H), 2.85 (m, 4 H), 3.17 (ABq, *J* = 18.3, 8.7 Hz, 1 H), 3.62 (t, *J* = 6.9 Hz, 2 H), 5.45 (AB q, *J* = 8.6, 4.8 Hz, 1 H), 5.83 (t, *J* = 7.1 Hz, 1 H); MS, *m/e* (relative intensity) 315 (M^+, 13), 158 ($M^+ - C_6H_7NO_4$, 47), 145 (100), 111 (58).

***N*-[3-(1,3-Dithian-2-ylidene)propyl]-4(*S*)-(acetyloxy)-5-hydroxy-2-pyrrolidinone (14).** To a suspension of the imide **13** (1.73 g, 5.49 mmol) in methanol (180 mL) was added sodium borohydride (1.1 g, 29.0 mmol) in one portion at −4 °C. After stirring for 10 min (a longer time leads to overreduced products), the mixture was poured into a stirred mixture of saturated aqueous $NaHCO_3$ (150 mL) and dichloromethane (150 mL). The layers were separated and the aqueous phase was extracted with more CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with brine, filtered through $MgSO_4$/Florisil, and concentrated in vacuo to give 1.48 g (85%) of white solid (**14**), which was used in the following reaction without further purification.

^{1}H NMR and TLC indicate an approximately 11:1 mixture of two products, which in one run were separated by flash chromatography. Minor isomer: mp 147–149 °C; R_f 0.47 (ethyl acetate:hexane = 5:1). Major isomer: mp 153–155 °C; R_f 0.41 (ethyl acetate:hexane = 5:1); IR ($CDCl_3$) 3350, 1740, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 2.16 (m, 2 H), 2.45–2.80 (m, 4 H), 2.87 (m, 4 H), 3.38 (m, 1 H), 3.58 (m, 1 H), 5.21 (m, 1 H), 5.34 (br t, 1 H), 5.88 (t, *J* = 7.5 Hz, 1 H); MS (CI, 100 eV), *m/e* (relative intensity) 318 (($M + 1)^+$, 79), 300 (($M + 1)^+ - H_2O$, 38), 258 (($M + 1)^+ - C_2H_4O_2$, 100).

The separated isomers when subjected to the cyclization conditions described next gave the *same* product (**15**), showing that the two are C-5 OH diastereomers of **14**. The regioisomer resulting from reduction of the other imide carbonyl group was not detected.

1-Aza-4-(1,3-dithian-2-ylidene)-6(*S*)-(acetyloxy)bicyclo[3.3.0]octan-8-one (15). To the hydroxy lactam **14** (1.48 g, 4.66 mmol) and 2.2 equiv of Et_3N (1.42 mL, 10.2 mmol) in dichloromethane (45 mL) was added 1.1 equiv of methanesulfonyl chloride (0.40 mL, 5.13 mmol) dropwise at −20 °C under argon. The reaction mixture was allowed to warm to room temperature over several hours, stirred overnight, quenched with saturated aqueous $NaHCO_3$, extracted (3×) with CH_2Cl_2, filtered through $MgSO_4$/Florisil, and concentrated to give 1.20 g of crude product. Flash chromatography (ethyl acetate:hexane = 2:1) yielded 0.95 g (68%) of **15** containing $\leq$3% (by HPLC) of an impurity assumed to be the bridgehead diastereomer: mp 134–135 °C; $[\alpha]^{24}_D$ −159.2° (*c* 1.93, $CHCl_3$); IR ($CDCl_3$) 1742, 1696, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 2.12 (m, 2 H), 2.4–3.0 (m, 9 H), 4.12 (br t, 1 H), 4.60 (dd, *J* = 5.6, 2.0 Hz, 1 H), 5.23 (dt, *J* = 8.2, 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.2, 24.2, 29.5, 29.7, 33.4, 40.3, 42.4, 67.9, 73.0, 123.0, 137.8, 170.3, 173.2; MS, *m/e* (relative intensity) 299 (M^+, 0.4), 239 ($M^+ - C_2H_5O_2$, 100), 228 (23), 211 (42), 186 (51), 112 (54).

Anal. Calcd for $C_{13}H_{17}NO_3S_2$: C, 52.15; H, 5.72; N, 4.68. Found: C, 51.88; H, 5.75; N, 4.59.

This reaction has been conducted on a larger scale ($\sim$5 g of product) with no loss of efficiency.

1-Aza-4-(1,3-dithian-2-ylidene)-6(*S*)-hydroxybicyclo[3.3.0]octan-8-one (16). To the acetate **15** (1.17 g, 3.90 mmol) in methanol (100 mL) was added a solution of saturated K_2CO_3 in methanol (50 mL) dropwise over a 1-h period at −35 °C. After the mixture was stirred for 2 h, it was warmed to −10 °C and then maintained at that temperature for an additional 2 h. The solution was then neutralized by the addition of dry ice, filtered through Na_2SO_4/Florisil, and preadsorbed onto silica gel (230–400 mesh). Flash chromatography (ethyl acetate) yielded 0.64 g (64%) of crystalline **16**: mp 139–140 °C; IR ($CDCl_3$) 3330, 1680, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.21 ("quintet", *J* = 6.0 Hz, 2 H), 2.53 (m, 1 H), 2.7–2.8 (m, 3 H), 2.9–3.0 (m, 5 H), 3.46 (d, *J* = 1.9 Hz, OH), 4.06 (m, 1 H), 4.30–4.45 (m, 2 H); MS, *m/e* (relative intensity) 257 (M^+, 95), 228 (100), 185 (65); MS (CI, 100 eV), *m/e* (relative intensity) 258 (($M + 1)^+$, 100), 240 (($M + 1)^+ - H_2O$, 3). A less polar product (0.20 g, 20%), presumed to arise by β-elimination, was also isolated: ^{1}H NMR ($CDCl_3$) δ 7.64 (d, *J* = 5.7 Hz, 1 H), 6.00 (d, *J* = 5.8 Hz, 1 H), 3.96 (m, 1 H), 3.32 (m, 1 H), 2.75–3.15 (m, 6 H), 2.55–2.75 (m, 1 H), 2.16 ("quintet", 2 H).

1-Aza-4-(1,3-dithian-2-yl)-6(*S*)-hydroxybicyclo[3.3.0]oct-3-en-8-one (17). To the ketene dithioacetal **16** (600 mg, 2.35 mmol) and hexamethylphosphoramide (2.45 mL, 14.1 mmol) stirred in tetrahydrofuran (4.7 mL) was added a solution of lithium diisopropylamide (14.1 mmol in 20 mL of THF) at −78 °C. After 15 min, the −78 °C bath was replaced with a −30 °C bath for an additional 3 h. The dark red solution was cooled to −78 °C and an excess of methanol (1 mL) was added. After several minutes the solution was warmed to room temperature, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Flash chromatography (ethyl acetate) gave 480 mg (80%) of **17** containing 5% starting material (by ^{1}H NMR integration): mp 183–185 °C; IR ($CDCl_3$) 3350, 1695, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.8–2.0 (m, 1 H), 2.13–2.25 (m, 1 H), 2.65 (AB q, *J* = 15.5, 7.4 Hz, 1 H), 2.75–2.90 (m, 1 H), 2.90–3.01 (m, 4 H), 3.23 (d, *J* = 2.7 Hz, OH), 3.74 (br d, 1 H), 4.35–4.65 (m, 3 H), 4.99 (s, 1 H), 5.96 (s, 1 H); MS, *m/e* (relative intensity) 257 (M^+, 25), 239 ($M^+ - H_2O$, 86), 206 (23), 151 (50), 119 (65), 111 (100); MS (CI, 100 eV), *m/e* (relative intensity) 258 (($M + 1)^+$, 100), 239 (5), 150 (3).

(+)-Heliotridine (5). Mercury(II) chloride (1.9 g, 7.0 mmol) was added to a stirred mixture of the dithiane **17** (450 mg, 1.75 mmol) and

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calcium carbonate (1.4 g, 14 mmol) in aqueous acetonitrile (18 mL, 20% H_2O). The mixture was stirred at room temperature for 4 h, and the solvent was removed in vacuo. A small sample purified by flash chromatography (ethyl acetate + 5% Et_3N) gave the pure α,β-unsaturated aldehyde: ^1H NMR ($CDCl_3$) δ 9.85 (s, H_9), 6.95 (d, J = 1.7 Hz, H_2), 4.70 (dm, J = 19 Hz, H_3), 4.61 (m, H_8), 4.30 (dt, J = 10.4, 7.4 Hz, H_7), 3.98 (dm, J = 19 Hz, H_3'), 3.31 (br s, OH), 2.86 (AB q, J = 15.6, 10.9 Hz, H_6), 2.07 (ABq, J = 15.6, 8.0 Hz, H_6'). The remaining crude hydrolysis product was suspended in tetrahydrofuran (18 mL), to which lithium aluminum hydride solution (10 mL, 2.5 M in THF) was added dropwise under argon. The reaction mixture was heated at reflux for 18 h and then after cooling to room temperature quenched by the slow addition of water and sodium sulfate dodecahydrate. The precipitate was removed by filtration through Celite/K_2CO_3, and the filter cake was washed with tetrahydrofuran containing 10% triethylamine. Concentration and flash chromatography ($CHCl_3$:MeOH:NH_4OH = 10:4:1) afforded 174 mg (64%) of (+)-heliotridine: mp 115-117 °C [lit.[1c] mp 116-118 °C]; $[\alpha]^{25}_D$ +30.3° (c 1.6, MeOH) [lit.[18b] $[\alpha]^{20}_D$ + 31° (10% in MeOH); lit.[18a] $[\alpha]_D$ +30.4° (EtOH)]; ^{13}C NMR ($CDCl_3$) 141.6, 123.0, 80.3, 75.0, 62.4, 59.6, 54.4, 33.8; MS, m/e (relative intensity) 155 (M^+, 16), 111 (58), 94 (15), 80 (100).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.02; H, 8.39; N, 8.94.

Other spectral data and chromatographic mobility (R_f 0.23, $CHCl_3$:CH_3OH:NH_4OH = 10:4:1) are identical with an authentic sample of heliotridine.

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Registry No. 5, 520-63-8; **12**, 85319-59-1; **13**, 85319-60-4; **14** (isomer 1), 85319-61-5; **14** (isomer 2), 85319-65-9; **15**, 85319-62-6; **16**, 85319-63-7; **17**, 85335-11-1; **11** acetate, 85319-64-8; malic acid, 6915-15-7; acetyl chloride, 75-36-5; 2-(3-hydroxypropylidene)-1,3-dithiane, 83177-74-6.

Total Synthesis of Leukotriene E_4, a Member of the SRS-A Family

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Abstract: Leukotriene E_4 and two analogues homo-LTE_4 and nor-LTE_4 have been prepared via the intermediate epoxides. The epoxides were formed by the coupling of a polyenyne sulfonium salt with the required aldehyde–ester in a biphasic reaction system employing aqueous sodium hydroxide as the base for the generation of the ylide. Reduction of the acetylene bonds yielded the desired polyene epoxides which on treatment with L-cysteine methyl ester gave a 1:1 mixture of diastereomers from which the 5*S*,6*R* isomers were separated.

The slow-reacting substance of anaphylaxis (SRS-A), once thought to be a single entity, is a family of compounds belonging to a group of chemical mediators involved in the phenomenon of immediate-type hypersensitivity. These materials are apparently synthesized de novo by several cell types on antigen challenge and have been something of a mystery for the past 50 years.[1]

Samuelsson et al.[2] was the first to propose a gross structure for one of the members of the SRS family. Based on his pioneering work in the area of arachidonic acid metabolism, and skilfully using the clues left by past investigators, Samuelsson showed that SRS-A was a lipoxygenase-derived metabolite of arachidonic acid.

After this disclosure, other work showed[3] that SRS was a family of related compounds derived from the primary addition product **3** of glutathione and the polyene epoxide **1** (Figure 1). Subsequent enzymatic degradation of this primary adduct then yields the cysteinylglycine and cysteine derivatives **4** and **5**, respectively.[4] These SRS's were named leukotrienes because they contain the characteristic conjugated triene chromophore and were originally isolated from leukocytes.[5] Thus, the primary glutathione adduct **3** is called leukotriene C_4 (LTC_4), while the cysteinylglycine and cysteine derivatives are LTD_4 and LTE_4, respectively. All three products are potent bronchoconstrictive agents; LTD_4 and LTE_4 also have the ability to increase vascular permeability. Both of these features suggests that these mediators may play an important role in asthma and other diseases of the respiratory system. As in the case of the prostaglandins, the leukotrienes are found widely distributed in the body and comprise another important branch of the arachidonic acid cascade. The actual role of these materials in inflammation and asthma will have to await further studies.

As part of a program in the bronchopulmonary area, we have devised a synthesis of LTE_4 for the purpose of developing meaningful animal test systems to detect SRS antagonists of potential use in asthma therapy. While LTE_4 is not the principal SRS formed in human lung, it has a very similar activity profile in the established animal tests to date.[6]

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