Chem. Soc., Chem. Commun., 824 (1978).
(18) J. H. van Boom, J. F. M. de Rooy, and C. B. Reese, J. Chem. Soc., Perkin Trans. 1, 2513 (1973).
(19) M. Irie, J. Biochem. (Tokyo), 62, 509 (1967).
(20) (a) F. Sanger, J. E. Donelson, A. R. Coulson, H. Koessel, and D. Fischer, Proc. Natl. Acad. Sci. U.S.A., 70, 1209 (1973); (b) M. Silberklang, A. M. Gillum, and U. L. RajBhandary, Nucleic Acids Res., 4, 4091 (1977).
(21) M. Fujimoto, A. Kuninaka, and H. Yoshino, Agric. Biol. Chem., 38, 777 (1974).
(22) J. H. van Boom, P. M. J. Burgers, P. H. van Deursen, J. F. M. de Rooy, and C. B. Reese, J. Chem. Soc., Chem. Commun., 167 (1976).
(23) J. H. van Boom and P. M. J. Burgers, Recl. Trav. Chim. Pays-Bas, 97, 73 (1978).
(24) C. B. Reese, R. C. Titmas, and L. Yau, Tetrahedron Lett., 2727 (1978).
(25) E. Ohtsuka, M. Ubasawa, S. Morioka, and M. Ikehara, J. Am. Chem. Soc., 95, 4725 (1973).
(26) G. R. Owen, C. B. Reese, H. J. van Boom, and J. D. H. Hersheld, Synthesis, 704 (1974).

Synthesis of the Nontryptamine Moiety of the *Aspidosperma*-Type Indole Alkaloids via Cleavage of a Cyclic α-Diketone Monothioketal. An Efficient Synthesis of (±)-Quebrachamine and a Formal Synthesis of (±)-Tabersonine

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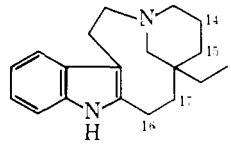
Abstract: The details of an efficient synthesis of (±)-quebrachamine and a formal synthesis of (±)-tabersonine via the cleavage of a cyclic α-diketone monothioketal are described.

Total syntheses of quebrachamine (**1**)[1-5] and tabersonine (**2**),[6] both being the parent bases of the *Aspidosperma* alkaloids and the latter being an in vivo progenitor of the iboga alkaloids,[7,8] have been completed by several groups in interesting manners; however, the overall yields reported are far from practical. Because of the highly efficient synthesis of tryptamine from tryptophan by decarboxylation which has been developed by this group,[9] our present concern lies in constructing the nontryptamine moiety leading to these alkaloids.[10]

As the pivotal synthetic intermediate for quebrachamine (**1**) and tabersonine (**2**), we chose the tetracyclic lactam **12** which possesses a hold for establishing the C-14,15 double bond in the latter as the lactam carbonyl group. Hence a nine-carbon tricarbonyl compound **9** would be required as a nontryptamine moiety in which three carbonyl groups must be differentiated chemically. Since Marshall has reported a cleavage reaction of a cyclic diketone monothioketal easily accessible from the corresponding ketone to give an ω-carboxy thioacetal,[11-14] it became apparent that the reaction would be suitable for the construction of the nine-carbon compound **8** possessing three different carbonyl groups being applied to a cyclic α-diketone monothioketal as **7**.



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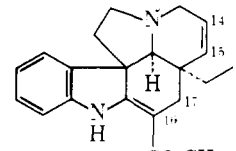

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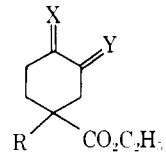
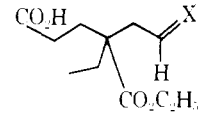
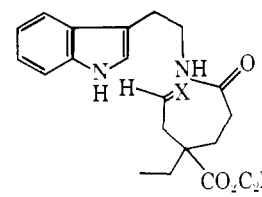


3, R = H, X = O, Y = H_2
4, R = H, X = $-O(CH_2)_2O-$, Y = H_2
5, R = C_2H_5, X = $-O(CH_2)_2O-$, Y = H_2, R = C_2H_5
6, R = C_2H_5, X = O, Y = H_2
7a, R = C_2H_5, X = O, Y = $-S(CH_2)_3S-$
7b, R = C_2H_5, X = O, Y = $(SCH_3)_2$



8a, X = $-S(CH_2)_3S-$
8b, X = $(SCH_3)_2$
9, X = O



10a, X = $-S(CH_2)_3S-$
10b, X = $(SCH_3)_2$
11, X = O

Our initial target, the α-diketone monothioketal **7**, was prepared from the known 4-ethoxycarbonylcyclohexanone ethylene ketal[15] **4** in a satisfactory yield. Thus, **4** was alkylated with ethyl bromide in tetrahydrofuran in the presence of lithium diisopropylamide[16] to produce 4-ethoxycarbonyl-4-ethylcyclohexanone ethylene ketal (**5**) in 92% yield which on hydrolysis with 1 N sulfuric acid in boiling ethanol afforded 4-ethoxycarbonyl-4-ethylcyclohexanone (**6**) in 95% yield. Direct alkylation of the ketoester **3** through a dianion intermediate by using 2 equiv of lithium diisopropylamide, which would save the protection-deprotection sequence, also provided the desired product **6** in a low yield; however, its optimization could not be achieved. Subsequent dithioketalization of **6** was performed to give the α-diketone monothioketal **7a** in 65% yield with trimethylene dithiotosylate through the pyrrolidine enamine intermediate.[17,18] A synthetically equivalent α-diketone monothioketal **7b** was also obtained through the hydroxymethylene ketone intermediate[17,18] with 2 equiv of methyl thiotosylate[19,20] in 57% yield.

Cleavage of the α-diketone monothioketal **7a** proceeded almost quantitatively to give the half-ester **8a** with three different carbonyl groups by treatment with sodium hydride in *tert*-butyl alcohol containing 3 equiv of water. Similarly **7b** afforded **8b** in excellent yield. Marshall reported a more convenient cleavage condition using sodium hydroxide in place of sodium hydride;[13] however, this could not be applied to the present synthesis as concomitant hydrolysis of the ester group occurred to give the dicarboxylic acid **8** (CO_2Et=CO_2H).

With the requisite half-ester **8** in hand, it was now possible to condense it with tryptamine at the specific position of the molecule. Treatment of **8a** with tryptamine in the presence of

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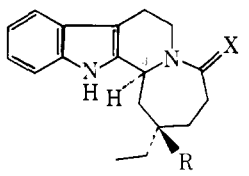
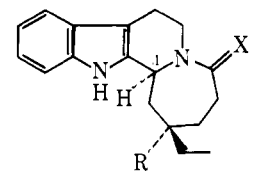
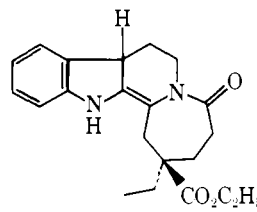
dicyclohexylcarbodiimide in methylene chloride yielded the secondary amide **10a** in overall 60% yield from **7a**. Similarly a synthetically equivalent secondary amide **10b** was obtained in overall 65% yield from **7b**. After conventional methods using mercuric salts,[11,21] Meerwein reagent,[22] or methyl fluorosulfonate[23] as a catalyst had failed to give the aldehyde **11**, it was found that the tetracyclic lactam **12**, regarded as the pivotal intermediate for quebrachamine (**1**) and tabersonine (**2**), was formed in 83% yield as a 1:6 mixture of diastereomers, α-ethyl isomer **12a** and β-ethyl isomer **12b**, by treating **10a** with an excess methyl iodide in aqueous acetonitrile at reflux temperature. Similarly **10b** yielded the lactams, **12a** and **12b**, as a 3:5 mixture of the diastereomers. The condition employed was originally reported by Fetizon and Jurion as a mild method for the hydrolysis of thioketals;[24] however, an acidic byproduct, probably hydriodic acid, could allow further transformation of the initially formed aldehyde **11** into the lactams, **12a** and **12b**, by an intramolecular Pictet-Spengler cyclization. Although a proportion of the diastereomers depended on the



12a, R = $CO_2C_2H_5$, X = O
13a, R = CH_2OH, X = H_2
14a, R = CH_2OMes, X = H_2



12b, R = $CO_2C_2H_5$, X = O
13b, R = CH_2OH, X = H_2
14b, R = CH_2OMes, X = H_2



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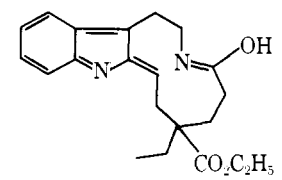

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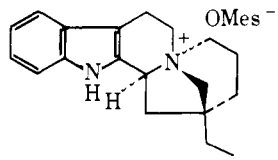
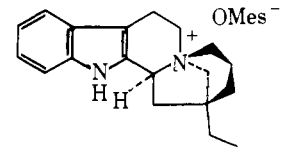
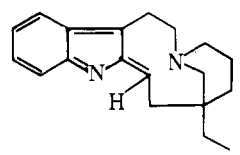


17a



17b



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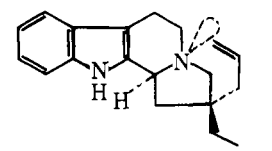
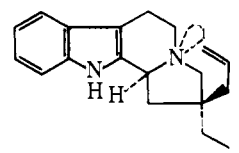


19a



19b

structure of the thioacetals, treatment of the α-ethyl isomer **12a** with a catalytic amount of *p*-toluenesulfonic acid in boiling benzene led to a favorable formation of the β-ethyl isomer **12b** in a 4:1 equilibration presumably via an enamine **15** or a C/D seco intermediate **16**.

Reduction of the lactams, **12a** and **12b**, was accomplished with lithium aluminum hydride in boiling tetrahydrofuran affording the amino alcohols, **13a** and **13b**, in an excellent yield, respectively. Treatment of the alcohols, **13a** and **13b**, with methanesulfonyl chloride in pyridine at 0 °C provided the corresponding mesylates, **14a** and **14b**, which without purification were refluxed in chloroform to give the crystalline quaternary bases,[2] **17a** and **17b**, in quantitative overall yield, respectively.

Table I

compd	$CH_3CH_2C\!\!<$ (ppm)	CH_3CH_2O- (ppm)	CH_3CH_2O- (ppm)	C_3-*H* (ppm)
lactam **12a**	0.91	1.23	4.11	
b	0.83	1.33	4.29	
amino alcohol **13a**	0.90			3.75
b	0.83			3.70
quaternary base **17a**	0.71			
b	1.04			

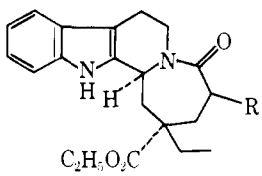
Surprisingly treatment of both isomers **17a** and **17b** with lithium aluminum hydride, which has once been believed to produce dehydroquebrachamine[4] (**1**: 16,17-dehydro), afforded the same product being assigned to the structure represented by **19a**,[6] but the diastereomeric **19b**, which should be expected from the latter, never was isolated. Although formation of **19a** could be explicable to the former **17a** via Hoffmann elimination, a preceding isomerization of the latter **17b** to the former **17a** through a C/D seco intermediate **18** must be involved in the reaction sequence.[25]

By employing the established procedure,[2] both **17a** and **17b** were converted into (±)-quebrachamine (**1**) in excellent yield by treatment with sodium and liquid ammonia, respectively. Overall yield of (±)-quebrachamine (**1**) from the known cyclohexanone ketal **4** was 22% with nine steps.

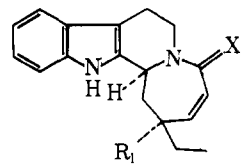
We turn now to a discussion of the stereochemical aspects of the synthetic intermediates. Examination of spectra of the amino alcohols, **13a** and **13b**, established the stereochemistry of C/D ring juncture in each to be the same with trans configuration, since both alcohols showed similar Bohlmann bands in the infrared spectra[26a-e,27] and characteristic C-3 signals at δ 3.75 and 3.70 in the NMR spectra.[26a-e,27] In the NMR spectra of the lactam pair and the alcohol pair, striking but parallel differences of the chemical shifts of the substituents on the quaternary carbon were recognized allowing their stereochemical assignments as shown by taking account of the electronic effect of the indole ring. Moreover, a drastic change of the ethyl signal of the alcohol pair through the intramolecular quaternization was sufficiently instructive. The ethyl group showing higher resonance must be disposed above the plane of the indole ring which is only allowable to **17a** in which more shielding effect from the indole ring could be expected than in its alcohol progenitor **13a**. Whereas, in the other quaternary base **17b**, the ethyl group must be disposed to be far apart from the indole ring as its formation requires, the inversion of the tertiary nitrogen and consequently the stereochemical environment of the ethyl group in its alcohol progenitor **13b** could be drastically changed by the quaternization (Table I).

In the synthesis of tabersonine (**2**) our primary concern in establishing the C-14,15 double bond was efficiently carried out through the pyrolysis of the sulfoxide intermediate **21**.[28] Treatment of the β-ethyl lactam (**12b**), with 2 equiv of lithium diisopropylamide in tetrahydrofuran, followed by 1 equiv of diphenyl disulfide at −78 °C yielded the sulfide **20** in 91% yield. Since the product obtained consisted of one stereoisomer, the reaction proceeded in a stereoselective fashion. Interestingly, the α-ethyl isomer **12a** did not give the corresponding

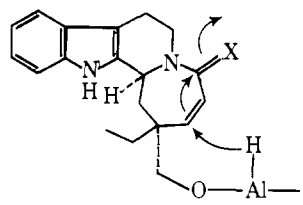
sulfide under the same condition. However, this was not a serious problem from the synthetic point of view, since the α-ethyl lactam **12a** has been shown to be efficiently converted into the β-ethyl counterpart **12b**. Near quantitative oxidation of the sulfide **20** to the corresponding sulfoxide **21** was achieved



20, R = –SPh
21, R = –SPh(=O)



22, R_1 = $CO_2C_2H_5$, X = O
23, R_1 = CH_2OH, X = H_2
25, R_1 = $CO_2C_2H_5$, X = H_2
31, R_1 = CO_2H, X = O
32, R_1 = CH_2OH, X = O
33, R_1 = $CH_2OSi(CH_3)_3$, X = O
34, R_1 = CH_2OMes, X = H_2



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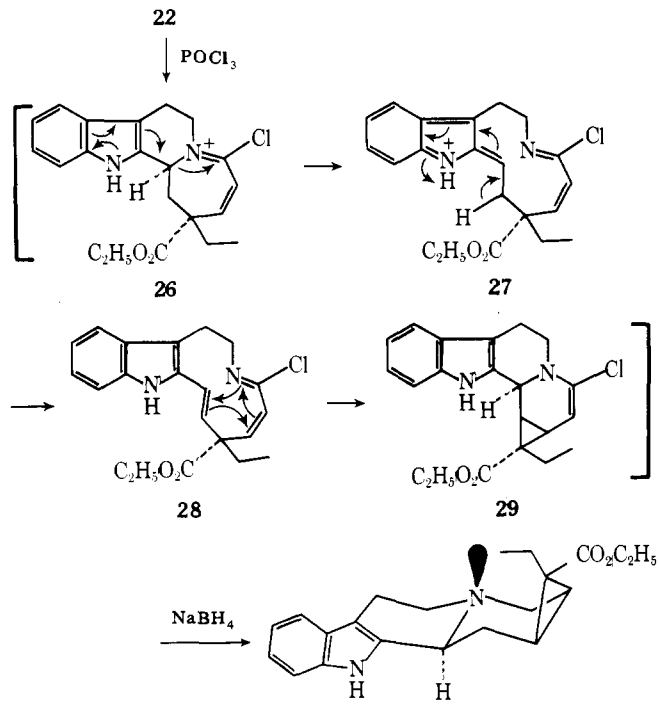
with an equivalent of *m*-chloroperbenzoic acid and the sulfoxide afforded the desired α,β-unsaturated lactam **22** in excellent yield upon pyrolysis in boiling toluene in the presence of calcium carbonate. The NMR spectrum revealed the newly formed vinyl protons appearing as a pair of AB type doublets centered at 6.08 and 6.28 ppm with a coupling constant of 12.0 Hz.

Reduction of the unsaturated lactam **22** to the β,γ-unsaturated amine **23** met with unexpected difficulty. Reduction with lithium aluminum hydride under various conditions did not provide the unsaturated amine **23**, efficiently, but the saturated amine **13b** as a major product. Apparently as the saturated amine **13b** could be formed through the participation of a chelate complex such as **24** allowing internal 1,4-hydride addition, a selective reduction of the lactam carbonyl was attempted by employing the newly reported technique. The unsaturated lactam **22** was treated with hot phosphorus oxychloride, followed by reduction with sodium borohydride in anhydrous methanol[29,30] to form **25**. However, the product obtained in 50% yield did not show the characteristics of **25**, but those of the peculiar pentacyclic isomer **30**. It exhibited Bohlmann bands in the infrared spectrum as well as a signal of C_3-*H* at 3.82 ppm as a doublet in the NMR spectrum, indicating the C/D trans configuration. Furthermore the NMR spectrum exhibited appropriate cyclopropane protons at 0.75–1.10 ppm as a multiplet and a highly shielded signal of CH_3CH_2– at 0.50 ppm as a triplet indicating the configuration as shown. This compound may be produced through an intervention of C/D seco intermediates, **27** and **28**, as shown in Scheme I. Reduction by using Meerwein salt[31] also did not give a fruitful result.

Successful conversion of the unsaturated lactam **22** into the unsaturated amine **23** was achieved via a rather circuitous way. Thus, the ester group of **22** was hydrolyzed with potassium hydroxide in boiling methanol to give the carboxylic acid **31** in 95% yield which on condensation with ethyl chloroformate in the presence of triethylamine followed by reduction with sodium borohydride[32] provided the primary alcohol **32** in 93% overall yield. Treatment of **32** with trimethylsilyl chloride in tetrahydrofuran in the presence of triethylamine afforded the

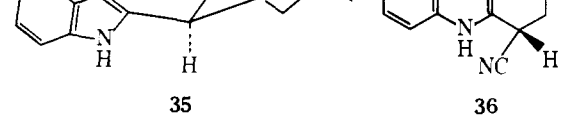
Scheme I



26 **27** **28** **29** **30**

silyl ether **33** which without purification was reduced with lithium aluminum hydride in cold tetrahydrofuran to give the unsaturated amine **23** in 61% overall yield accompanied by a minor amount of the saturated amine **13b**.

Treatment of **23** with methanesulfonyl chloride in pyridine, followed by refluxing **34** in chloroform as the saturated congeners, afforded the crystalline quaternary base **35** in quantitative yield. The observed melting point was not identical with that reported,[6] but its validity was ascertained by the mass spectrum and by the chemical transformations. Presumably our compound consisted of an alternative diastereomer. On treatment with lithium aluminum hydride in boiling tetrahydrofuran **35** provided tetradehydroquebrachamine (**1**; 14,15,16,17-tetradehydro) in 58% yield whose mass spectrum was completely identical with that of the starting material as reported by Ziegler and Bennett.[6] Upon treatment with potassium cyanide in boiling dimethylformamide, **35** afforded 16-cyano-14,15-dehydroquebrachamine (**36**) in 27% yield, whose spectral data (IR, MS) were completely identical with those reported. Since the conversion of **36** into (±)-tabersonine



35 **36**

(**2**) has been accomplished by Ziegler and Bennett,[6] this constitutes a formal synthesis.[35] Overall yield of the tabersonine precursor **33** from the known ethylene ketal **4** was 4%.

The relatively simple sequence described here provides an efficient route to the construction of the nontryptamine moiety of the *Aspidosperma* indole alkaloids with a double bond and a carbomethoxy group in an appropriate position.

Experimental Section

Melting points were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. Infrared absorption spectra were recorded on a Shimadzu IR 400 instrument, and proton magnetic resonance spectra were recorded on Jeol PS 100, PMX 60, and Hitach H-60

spectrometers with tetramethylsilane as an internal reference. Mass spectra were recorded on a Hitachi RMU-7 spectrometer.

4-Ethoxycarbonyl-4-ethylcyclohexanone Ethylene Ketal (5). To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (29.5 mL, 211 mmol) in anhydrous tetrahydrofuran (150 mL) and *n*-butyllithium (2.19 M in hexane, 96.4 mL, 211 mmol) at −78 °C under nitrogen, was added a solution of 4-ethoxycarbonylcyclohexanone ethylene ketal (**4**)[15] (35.0 g, 164 mmol) in anhydrous tetrahydrofuran (150 mL). After stirring at −78 °C for 10 min, ethyl bromide (25.0 mL, 328 mmol) was added dropwise over a period of 10 min. The reaction mixture was stirred at −78 °C for 1 h, allowed to reach room temperature, and stirred at room temperature for an additional 1 h. The reaction was quenched by the addition of saturated NH_4Cl (50.0 mL) and the reaction mixture was extracted thoroughly with ether. The ethereal extract was washed with saturated NaCl and dried over anhydrous K_2CO_3. Removal of the solvent in vacuo afforded an yellow oil which, upon distillation in vacuo, gave **5** (36.4 g, 91.7%) as a clear colorless oil: bp 100–101 °C (1 mm); IR (neat) 1720, 1190, 1108, 1080 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (3 H, t, J = 7.0 Hz), 1.25 (3 H, t, J = 7.0 Hz), 3.80 (4 H, s), 4.10 (2 H, q, J = 7.0 Hz).

Anal. ($C_{13}H_{22}O_4$) C, H, N.

4-Ethoxycarbonyl-4-ethylcyclohexanone (6). A mixture of **5** (36.0 g, 149 mmol) and 1 N H_2SO_4 (180 mL) in ethanol (180 mL) was refluxed for 2 h. Most of the ethanol was removed in vacuo and the residue was extracted thoroughly with ether. The ethereal extract was washed with saturated NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded an yellow oil which, upon distillation in vacuo, gave **6** (28.0 g, 94.9%) as a clear colorless oil: bp 76–81 °C (1 mm); IR (neat) 1720, 1180 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7.0 Hz), 1.30 (3 H, t, J = 7.0 Hz), 1.63 (2 H, q, J = 7.0 Hz), 4.17 (2 H, q, J = 7.0 Hz).

Anal. ($C_{11}H_{18}O_3$) C, H, N.

4-Ethoxycarbonyl-4-ethyl-2,2-(propane-1,3-dithio)cyclohexanone (7a). A mixture of **6** (10.5 g, 53 mmol) and pyrrolidine (4.90 g, 63 mmol) in benzene (50 mL) was refluxed using a Dean-Stark head until no more water was collected (4 h). The excess pyrrolidine and solvent were removed in vacuo to give the enamine (13.3 g) as a pale yellow oil, which was used without further purification.

A mixture of enamine (13.3 g), trimethylene dithiotosylate[17,18] (22.0 g, 53 mmol), and triethylamine (25 mL) in acetonitrile (380 mL) was refluxed for 3 h. The mixture was concentrated in vacuo and the residue was extracted thoroughly with ether. The ethereal extract was washed with water, 5% HCl, water, saturated $NaHCO_3$, and finally saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (15.3 g), a dark yellow oil, was extracted several times with hot petroleum ether and the extract was concentrated in vacuo to leave an yellow solid which, upon recrystallization from ethanol, gave **7a** (5.3 g) as colorless prisms and additional **7a** (5.1 g) was obtained from the petroleum ether insoluble residue by column chromatography on silica gel (100 g) eluting with methylene chloride, followed by a recrystallization from ethanol (total yield 10.4 g, 65.0%): mp 76–78 °C; IR (Nujol) 1710, 1685, 1208, 1100 cm^{-1} NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 7.5 Hz), 1.30 (3 H, t, J = 7.0 Hz), 1.50–2.30 (6 H, m), 2.30–2.90 (5 H, m), 3.00–3.90 (3 H, m), 4.19 (2 H, q, J = 7.0 Hz); MS *m/e* 302 (M^+), 201, 170, 142, 127, 113.

Anal. ($C_{14}H_{22}O_3S_2$) C, H, S.

4-Ethoxycarbonyl-4-ethyl-2,2-dimethylthiocyclohexanone (7b). To a stirred solution of sodium ethoxide, prepared by dissolving sodium metal (2.50 g, 0.11 g-atm) in absolute ethanol (50.0 mL), with cooling in an ice bath under nitrogen was added dropwise, over a period of 10 min, a mixture of **6** (14.4 g, 73 mmol) and ethyl formate (10.8 g, 146 mmol) in absolute ethanol (100 mL). After stirring at room temperature for 15 h, the reaction mixture was diluted with cold water and washed several times with ether. The aqueous layer was extracted thoroughly with ether after acidification with concentrated HCl. The ethereal extract was washed with saturated NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the hydroxymethylene ketone (17.5 g) as a pale yellow oil, which was used without further purification.

A mixture of crude hydroxymethylene ketone (17.5 g), methyl thiotosylate[19,20] (29.5 g, 146 mmol), and freshly fused potassium acetate (35.8 g, 365 mmol) in absolute ethanol (450 mL) was refluxed under nitrogen for 10 h. Most of the ethanol was removed in vacuo and residue was extracted thoroughly with ether. The ethereal extract was washed with water, saturated $NaHCO_3$, and finally saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (28.4 g), a dark yellow oil, was purified by column chromatography on silica gel (500 g). Elution with methylene chloride afforded a pale yellow solid (23.3 g) which was recrystallized from ethanol to give **7b** (12.1 g, 57.2%) as colorless prisms: mp 56–56.5 °C; IR (Nujol) 1720, 1700, 1260, 1100 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3 H, t, J = 7.0 Hz), 1.31 (3 H, t, J = 7.0 Hz), 1.89 (3 H, s), 2.05 (3 H, s), 4.22 (2 H, q, J = 7.0 Hz); MS *m/e* 290 (M^+), 243, 215, 197, 170, 169, 167.

Anal. ($C_{13}H_{22}O_3S_2$), C, H, S.

N-[2-(3-Indolyl)ethyl]-4-ethoxycarbonyl-4-ethyl-6,6-(propane-1,3-dithio)hexanamide (10a). To a vigorously stirred suspension of 50% sodium hydride oil dispersion (9.60 g, 200 mmol) in ether (350 mL) was added *tert*-butyl alcohol (19.0 mL, 200 mmol), followed by water (1.10 mL, 60 mmol) with cooling in an ice bath. After hydrogen evolution had ceased, **7a** (6.04 g, 20 mmol) was added to the mixture and the stirring was continued for 6 h. Water was added carefully to the reaction mixture with cooling in an ice bath and the aqueous layer was separated. The aqueous layer was washed several times with ether and extracted thoroughly with ether after acidification with concentrated HCl. The ethereal extract was washed with saturated NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded the half-ester **8a** (6.32 g) as an yellow viscous oil, which was used without further purification: IR (neat) 3360–2400, 1712 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3 H, t, J = 7.2 Hz), 1.28 (3 H, t, J = 7.0 Hz), 3.96 (1 H, t, J = 7.0 Hz), 4.14 (2 H, q, J = 7.0 Hz), 10.20 (1 H, br s, disapp. with D_2O); MS *m/e* 320 (M^+), 276, 217, 201, 188, 170, 142, 133, 119, 114, 113.

To a solution of crude **8a** (6.32 g, 19.7 mmol) in methylene chloride (150 mL) with cooling in an ice bath was added dicyclohexylcarbodiimide (4.05 g, 19.7 mmol). After stirring for 1 h, tryptamine (4.41 g, 19.7 mmol) was added to the mixture and the stirring was continued at room temperature for 15 h. The precipitated dicyclohexylurea was removed by filtration and the filtrate was washed with 5% HCl, water, saturated $NaHCO_3$, and finally saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (9.30 g), an yellow viscous oil, was purified by column chromatography on silica gel (200 g). Elution with chloroform gave **10a** (5.50 g, 60.4% from **7a**) as a pale yellow viscous oil, which could not be crystallized: IR (neat) 3200, 1700, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (3 H, t, J = 7.5 Hz), 1.23 (3 H, t, J = 7.0 Hz), 3.87 (1 H, t, J = 6.5 Hz), 4.10 (2 H, q, J = 7.0 Hz), 5.79 (1 H, br s, disapp. with D_2O), 6.90–7.70 (5 H, m), 8.70 (1 H, br s, disapp. with D_2O); MS *m/e* 462 (M^+), 330, 284, 256, 202, 187, 184, 171, 170, 155, 144, 143, 131, 130.

Anal. ($C_{24}H_{34}N_2O_3S_2 \cdot 0.20\ H_2O$) C, H, N, S.

N-[2-(3-Indolyl)ethyl]-4-ethoxycarbonyl-4-ethyl-6,6-dimethylthiohexanamide (10b). The procedure described for the preparation of the half-ester **8a** was followed using a mixture of **7b** (8.40 g, 29.0 mmol), 50% sodium hydride oil dispersion (9.60 g, 200 mmol), *tert*-butyl alcohol (27.5 mL, 290 mmol), and water (1.57 mL, 87 mmol) in ether (500 mL). The workup afforded the half-ester **8b** (8.70 g) as a yellow viscous oil, which was used without further purification: IR (neat) 3400–2400, 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7.0 Hz), 1.28 (3 H, t, J = 7.0 Hz), 2.09 (6 H, s), 3.67 (1 H, t, J = 6.5 Hz), 4.18 (2 H, q, J = 7.0 Hz), 10.63 (1 H, br s, disapp. with D_2O); MS *m/e* 308 (M^+), 261, 215, 187, 169, 121, 93.

Crude **8a** (8.50 g, 27.6 mmol), tryptamine (4.41 g, 27.6 mmol), and dicyclohexylcarbodiimide (5.68 g, 27.6 mmol) was allowed to react in methylene chloride (250 mL) under the same conditions described for the preparation of the amide **10a**. The workup afforded the crude reaction product (11.70 g) as an yellow viscous oil, which was crystallized by triturating with *n*-hexane and recrystallized from ethanol–*n*-hexane to give **10b** (7.70 g, 64.5% from **7b**) as colorless needles: mp 104–105 °C; IR (Nujol) 3300, 3200, 1698, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7.0 Hz), 1.23 (3 H, t, J = 7.0 Hz), 2.03 (6 H, s), 2.95 (2 H, t, J = 6.5 Hz), 3.56 (3 H, m), 4.11 (2 H, q, J = 7.0 Hz), 5.78 (1 H, br s, disapp. with D_2O), 6.90–7.72 (5 H, m), 8.70 (1 H, br s, disapp. with D_2O); MS *m/e* 450 (M^+), 402, 356, 330, 309, 284, 277, 260, 243, 215, 199, 184, 171, 170, 169, 155, 144, 143, 131, 130, 123, 115, 104.

Anal. ($C_{23}H_{34}N_2O_3S_2$) C, H, N, S.

Cyclization of ω-Propane-1,3-dithianyl Amide 10a. A mixture of **10a** (5.00 g, 10.8 mmol), methyl iodide (6.8 mL, 108 mmol), and water (1.4 mL, 77.8 mmol) in acetonitrile (70 mL) was refluxed under nitrogen for 15 h. Most of the excess methyl iodide and the solvent were removed in vacuo and the residue was extracted with methylene

chloride. The extract was washed with water, 1% $Na_2S_2O_3$, and finally saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (5.60 g), an yellow viscous oil, was chromatographed on silica gel (250 g). Elution with methylene chloride afforded pale yellow crystals which were recrystallized from ethanol to give β-ethyl lactam **12b** (2.72 g, 71.2%) as colorless needles: mp 172–173 °C; IR (Nujol) 3370, 1728, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7.8 Hz), 1.33 (3 H, t, J = 7.0 Hz), 1.40–1.90 (5 H, m), 2.40–2.90 (6 H, m), 4.29 (2 H, q, J = 7.0 Hz), 4.75–5.08 (2 H, m), 7.00–7.59 (4 H, m), 8.27 (1 H, br s, disapp. with D_2O); MS m/e 354 (M^+), 298, 297, 224, 197, 184, 171, 169, 168, 156, 155, 149, 143, 141.

Anal. ($C_{21}H_{26}N_2O_3$), C, H, N.

Further elution with chloroform afforded pale yellow crystals which was recrystallized from ethanol to give α-ethyl lactam **12a** (0.44 g, 11.5%) as colorless needles: mp 247–249 °C; IR (Nujol) 3180, 1728, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.0 Hz), 1.23 (3 H, t, J = 7.5 Hz), 1.60–3.14 (11 H, m), 4.11 (2 H, q, J = 7.5 Hz), 4.60–5.10 (2 H, m), 7.00–7.55 (4 H, m), 8.25 (1 H, br s, disapp. with D_2O); the mass spectrum was similar to that displayed by β-ethyl lactam **12b**.

Anal. ($C_{21}H_{26}N_2O_3$), C, H, N.

Cyclization of ω-Dimethylthioacetal Amide 10b. A mixture of **10b** (11.1 g, 24.6 mmol), methyl iodide (15.4 mL, 246 mmol), and water (3.0 mL, 167 mmol) in acetonitrile (160 mL) was refluxed under nitrogen for 15 h. The workup as described above afforded a yellow viscous oil (9.70 g) which, upon purification by column chromatography on silica gel (250 g) and recrystallization, gave β-ethyl lactam **12b** (4.30 g, 49.3%) and α-ethyl lactam **12a** (2.70 g, 31.4%).

Isomerization of α-Ethyl Lactam 12a to β-Ethyl Lactam 12b. A mixture of **12a** (177 mg, 0.55 mmol) and p-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in benzene (15 mL) was refluxed under nitrogen for 30 h. The reaction mixture was washed with 5% NaOH, water, and saturated NaCl, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded a pale yellow viscous oil (180 mg). Preparative thin-layer chromatography on silica gel developed with 5% methanol–chloroform gave β-ethyl lactam **12b** (120 mg, 67.8%) and α-ethyl lactam **12a** (30 mg, 16.9%) each as colorless crystals.

α-Ethyl Amino Alcohol 13a. To an ice-cooled solution of **12a** (500 mg, 1.41 mmol) in anhydrous tetrahydrofuran (10 mL) under nitrogen was added a solution of lithium aluminum hydride in tetrahydrofuran (0.52 M, 25 mL, 13 mmol). After refluxing for 3 h, the reaction mixture was cooled in an ice bath and treated carefully with 10% NH_4OH. The resulting sludge was filtered through a bed of Celite and washed thoroughly with methylene chloride. The combined filtrate was washed with saturated NaCl and dried over anhydrous K_2CO_3. Removal of the solvent in vacuo afforded a colorless crystalline residue (460 mg), which was recrystallized from methanol to give **13a** (400 mg, 95.1%) as colorless needles: mp 232.5–235 °C; IR (Nujol) 3260, 2790, 1040 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.90 (3 H, t, J = 7.0 Hz), 3.75 (1 H, m), 6.85–7.45 (4 H, m), 10.20 (1 H, br s, disapp. with D_2O); MS m/e 298 (M^+), 297, 277, 224, 211, 208, 197, 184, 171, 170, 169, 156, 143, 127, 125, 110.

Anal. ($C_{19}H_{26}N_2O$) C, H, N.

β-Ethyl Amino Alcohol 13b. β-Ethyl lactam **12b** (885 mg, 2.5 mmol) was reduced in the same manner as α-ethyl lactam **12a.** The workup afforded a colorless crystalline residue (800 mg), which was recrystallized from methanol to give **13b** (732 mg, 98.2%) as colorless needles: mp 219–221 °C; IR (Nujol) 3320, 2800–2600, 1037 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.83 (3 H, t, J = 7.0 Hz), 3.70 (1 H, m), 6.88–7.50 (4 H, m), 9.70 (1 H, br s, disapp. with D_2O); the mass spectrum was similar to that displayed by α-ethyl amino alcohol **13a**.

Anal. ($C_{19}H_{26}N_2O$) C, H, N.

Quaternary Salt 17a. To an ice-cooled solution of **13a** (500 mg, 1.67 mmol) in dry pyridine (10 mL) under nitrogen was added ice-cold methanesulfonyl chloride (0.96 mL, 12.4 mmol), and the mixture was stirred with cooling in an ice bath for 3 h. Most of the excess methanesulfonyl chloride and pyridine were removed on an oil pump at room temperature. The residue was washed twice with anhydrous ether, treated with water (2.0 mL) and 10% NH_4OH (4 mL) with cooling in an ice bath, and extracted thoroughly with chloroform. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo below 40 °C. The gummy residue was dissolved in chloroform (20 mL) and the solution was refluxed under nitrogen for 3 h. Removal of the solvent in vacuo afforded practically pure **17a** (638 mg) quantitatively as an yellow hygroscopic amorphous compound, which was used without further purification: NMR (D_2O) δ 0.71 (3 H, t, J = 6.5 Hz), 1.13 (2H, q, J = 6.5 Hz), 2.93 (3 H, s), 7.10–7.70 (4 H, m).

Quaternary Salt 17b. β-Ethyl amino alcohol **13b** (1.35 g, 4.53 mmol) was mesylated in the same manner as α-ethyl amino alcohol **13a.** The workup afforded practically pure **17b** (1.90 g) quantitatively as pale yellow hygroscopic crystals, which was used without further purification: mp 206–208 °C (dec); NMR (D_2O) δ 1.04 (3 H, t, J = 6.8 Hz), 2.90 (3 H, s), 7.20–7.80 (4 H, m).

(±)-Quebrachamine (1) through Reductive Cleavage of Quaternary Salts. (a) Using Sodium in Liquid Ammonia. A solution of crude quaternary salt **17a** (300 mg, 0.8 mmol) in absolute ethanol (10 mL) was transferred to a three-necked flask fitted with a dry ice condenser and an ammonia outlet. After condensing liquid ammonia (100 mL) into the flask, freshly cut sodium metal was added in small pieces until the blue color persisted for 20 min. The reaction was quenched by the addition of NH_4Cl and the ammonia was allowed to evaporate. The residue was treated with water and extracted with methylene chloride. The extract was washed with water and saturated NaCl and dried over anhydrous K_2CO_3. Removal of the solvent in vacuo afforded a deep red gum (254 mg). Preparative thin-layer chromatography on silica gel developed with 15% methanol–chloroform afforded a crystalline residue, which was recrystallized from methanol to give (±)-quebrachamine (**1**) (190 mg, 84.2% from **13a**) as colorless needles: mp 112.5–114 °C (lit.[1] mp 113–116 °C); IR (Nujol) 3255, 2800–2700 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, unsym t, J = 6.0 Hz), 6.83–7.60 (4 H, m), 7.65 (1 H, br s, disapp. with D_2O); MS m/e 282 (M^+), 267, 253, 157, 138, 125, 124, 110, 96. The mass spectrum of this material was identical with that of (−)-quebrachamine.[33]

Similarly the crude quaternary salt **17b** (1.28 g, 3.4 mmol) was also converted to (±)-quebrachamine (**1**) (750 mg, 78.2% from **13b**) in the manner described for quaternary salt **17a**.

(b) Using Lithium Aluminum Hydride. To a suspension of crude quaternary salt **17b** (500 mg, 1.33 mmol) in anhydrous tetrahydrofuran (30 mL) under nitrogen was added lithium aluminum hydride (0.52 M in tetrahydrofuran, 30 mL, 15.6 mmol). After refluxing for 3 h, the reaction mixture was cooled in an ice bath and treated carefully with 10% NH_4OH. The resulting sludge was filtered through a bed of Celite and washed thoroughly with methylene chloride. The combined filtrate was washed with saturated NaCl and dried over anhydrous K_2CO_3. Removal of the solvent in vacuo afforded a yellow gum (360 mg). Preparative thin-layer chromatography on silica gel developed with 15% methanol–chloroform gave (±)-quebrachamine (**1**) (66 mg, 16.0% from **13b**) and the allylamine **19** (150 mg, 40.1% from **13b**).

Allylamine **19**, colorless needles, mp 108–109 °C (lit.[4] mp 107–108 °C) (recrystallized from methanol), showed the following characteristics: IR (Nujol) 3300, 3050 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (3 H, t, J = 6.5 Hz), 4.18 (1 H, br t, J = 7.5 Hz), 4.90–5.28 (2 H, m), 5.51–6.20 (1 H, m), 6.90–7.60 (4 H, m), 7.85 (1 H, br s, disapp. with D_2O); MS m/e 280 (M^+), 279, 251, 239, 238, 237, 223, 209, 208, 184, 169, 156.

When the isomeric quaternary salt **17a** was treated under the same condition, it gave (±)-quebrachamine (**1**) and the allylamine **19** in yields of 13.7 and 54.7%, respectively.

α-Sulfenyl Lactam 20. To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (1.30 mL, 9.31 mmol) in anhydrous tetrahydrofuran (100 mL) and n-butyllithium (2.19 M in hexane, 4.25 mL, 9.31 mmol) at −78 °C under nitrogen, was added **12b** (1.50 g, 4.23 mmol). The reaction temperature was allowed to rise to room temperature over a period of 20 min after which time the solution became clear. The solution was cooled to −78 °C and diphenyl disulfide[34] (1.01 g, 4.65 mmol) was added. After stirring at −78 °C for 1.5 h, the reaction was quenched by the addition of saturated NH_4Cl (15.0 mL). The reaction mixture separated into two layers and the aqueous layer was separated and extracted with methylene chloride. The organic layers were washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (2.53 g), a pale yellow viscous oil, was crystallized by triturating with ethanol and recrystallized from ethanol to give **20** (1.20 g, 94.6%) as colorless needles: mp 167–168 °C; IR (Nujol) 3280, 1720, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 7.0 Hz), 1.33 (3 H, t, J = 7.0 Hz), 4.00–4.90 (4 H, m), 6.00 (1 H, d, J = 8.3 Hz), 7.00–7.65 (4 H, m), 8.50 (1 H, br s, disapp. with D_2O); MS m/e 462 (M^+), 353, 323, 298, 184, 171, 170, 169, 156, 144.

Anal. ($C_{27}H_{30}N_2O_3S$) C, H, N, S.

α,β-Unsaturated Lactam Ester 22. To an ice-cooled suspension of **20** (1.66 g, 3.60 mmol) and $NaHCO_3$ (910 mg, 10.8 mmol) in methylene chloride (40 mL) under nitrogen was added *m*-chloroperbenzoic acid (70% purity, 986 mg, 4.00 mmol). After stirring for 30 min, the reaction mixture was washed with water and saturated NaCl and dried over anhydrous K_2CO_3. Removal of the solvent in vacuo afforded the practically pure sulfoxide **21** (1.77 g) as a pale yellow powder, which was used without further purification.

A mixture of crude **21** (1.77 g) and $CaCO_3$ (1.08 g, 10.8 mmol) in toluene (50 mL) was refluxed under nitrogen for 30 min. The reaction mixture was filtered and the filtrate was washed with water. The aqueous layer was extracted with methylene chloride. The extract and filtrate were washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (1.71 g), a yellow viscous oil, was crystallized by triturating with ethanol and recrystallized from ethanol to give **22** (1.20 g, 94.6%) as colorless plates: mp 167–168 °C; IR (Nujol) 3260, 1720, 1648, 1598 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (3 H, t, *J* = 7.6 Hz), 1.39 (3 H, t, *J* = 7.1 Hz), 1.52–2.08 (4 H, m), 2.60–3.40 (4 H, m), 4.32 (2 H, q, *J* = 7.1 Hz), 4.60–4.90 (2 H, m), 6.08 (1 H, d, *J* = 12.0 Hz), 6.28 (1 H, dd, *J* = 12.0 Hz and 2.0 Hz), 6.90–7.56 (4 H, m), 8.68 (1 H, br s, disapp. with D_2O); MS *m/e* 352 (M^+, 323, 279, 251, 224, 184, 171, 170, 169, 156, 155, 154, 144, 143, 142.

Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

Formation of the Pentacyclic Compound 30 from α,β-Unsaturated Lactam Ester 22. A solution of **22** (100 mg, 0.28 mmol) in phosphorus oxychloride (1.5 mL) was gently refluxed under nitrogen for 30 min. Most of the phosphorus oxychloride was removed in vacuo. The residue was dissolved in absolute methanol (5.0 mL) and sodium borohydride (113 mg, 3.0 mmol) was added to the solution with cooling in an ice bath. After stirring at 0 °C for 1 h, most of the methanol was removed in vacuo, and the residue was treated with water and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a dark red viscous oil (95 mg). Preparative thin-layer chromatography on silica gel developed with 2.5% methanol–chloroform gave **30** (48 mg, 50.7%) as a pale yellow semisolid: IR (Nujol) 3325, 1686 cm^{-1}; NMR ($CDCl_3$) δ 0.50 (3 H, t, *J* = 7.0 Hz), 0.75–1.10 (2 H, m), 1.28 (3 H, t, *J* = 7.0 Hz), 1.90–3.30 (10 H, m), 3.82 (1 H, br d), 4.10 (2 H, q, *J* = 7.0 Hz), 7.00–7.70 (4 H, m), 8.23 (1 H, br s, disapp. with D_2O); MS *m/e* 338 (M^+), 324, 323, 308, 293, 265, 249, 223, 197, 184, 171, 169, 156, 141.

α,β-Unsaturated Lactam Carboxylic Acid 31. **22** (352 mg, 10 mmol) was dissolved in 10% methanolic KOH solution (20 mL) and the mixture was refluxed under nitrogen for 2 h. Most of the methanol was removed in vacuo and the residue was extracted with water. The aqueous extract was washed with methylene chloride and extracted thoroughly with ethyl acetate after acidification with concentrated HCl. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a colorless crystalline residue (330 mg) which, upon recrystallization from ethanol, gave **31** (308 mg, 95.3%) as colorless needles: mp 179.5–180 °C; IR (Nujol) 3400, 3050–2300, 1690, 1620, 1563 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.85 (3 H, t, *J* = 7.5 Hz), 1.50–2.20 (3 H, m), 2.48–3.75 (4 H, m), 4.50–5.10 (2 H, m), 6.00 (1 H, d, *J* = 12.5 Hz), 6.48 (1 H, d, *J* = 12.5 Hz), 6,90–7.50 (4 H, m), 7.85 (1 H, br s, disapp. with D_2O), 9.70 (1 H, br s, disapp. with D_2O); MS *m/e* 324 (M^+), 280, 265, 251, 197, 171, 170, 169, 143, 115.

Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

α,β-Unsaturated Lactam Alcohol 32. To an ice-cooled solution of **31** (275 mg, 0.85 mmol) in anhydrous tetrahydrofuran (25 mL) under nitrogen were added triethylamine (0.18 mL, 1.27 mmol) and ethyl chloroformate (0.12 mL, 1.27 mmol) in that order. After stirring at 0 °C for 3 h, the precipitated triethylamine hydrochloride was filtered and washed with anhydrous tetrahydrofuran (5.0 mL). The combined filtrate was added dropwise, over a period of 30 min, to aqueous sodium borohydride (2.5 M, 5.0 mL, 12.5 mmol) with cooling in an ice bath. After addition was complete, the reaction mixture was stirred at room temperature for 1.5 h and then made acidic with concentrated HCl. The reaction mixture was separated and the aqueous layer was extracted with methylene chloride. The organic layers were washed with 5% NaOH and saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction product (270 mg), a pale yellow crystalline residue, was recrystallized from ethanol to give **32** (254 mg, 93.1%) as colorless needles: mp 233–234 °C; IR (Nujol) 3350, 3240, 1630, 1579, 1060 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.80 (3 H, t, *J* = 7.0 Hz), 1.38 (2 H, q, *J* = 7.0 Hz), 2.00–4.00 (8 H, m), 4.62 (3 H, m, 1 H disapp. with D_2O), 5.88 (1 H, d, *J* = 10.5 Hz), 6.15 (1 H, d, *J* = 10.5 Hz), 6.95–7.70 (4 H, m), 10.19 (1 H, br s, disapp. with D_2O); MS *m/e* 310 (M^+), 279, 224, 184, 171, 170, 169, 156, 144, 143.

Anal. ($C_{19}H_{22}N_2O_2$) C, H, N.

Unsaturated Amino Alcohol 23. (a) From α,β-Unsaturated Lactam Alcohol 32. To an ice-cooled solution of **32** (250 mg, 0.80 mmol) and triethylamine (1.1 mL, 8.0 mmol) in anhydrous tetrahydrofuran (25 mL) under nitrogen was added trimethylsilyl chloride (1.0 mL, 8.0 mmol). After stirring at 0 °C for 6 h, the excess trimethylsilyl chloride and triethylamine and solvent were removed in vacuo. The residue was dissolved in anhydrous tetrahydrofuran (5.0 mL) and the solution was added to a solution of lithium aluminum hydride in tetrahydrofuran (1.6 M, 5.0 mL, 8.0 mmol) under nitrogen. After stirring at 0 °C for 2.5 h, the reaction mixture was treated carefully with 10% NH_4OH. The resulting sludge was filtered through a bed of Celite and washed thoroughly with methylene chloride. The combined filtrate was washed with saturated NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo to afford a pale yellow crystalline residue (250 mg). Preparative thin-layer chromatography on silica gel developed with 10% methanol–chloroform gave the unsaturated amino alcohol **23** (145 mg, 61.2%) and β-ethyl amino alcohol **13b** (70 mg, 29.3%).

Unsaturated amino alcohol **23**, colorless prisms, mp 201–203.5 °C (recrystallized from ethanol), showed the following characteristics: IR (Nujol) 3400–3100, 1080 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (3 H, t, *J* = 7.0 Hz), 1.12–1.60 (3 H, m), 2.00 (2 H, d, *J* = 9.0 Hz), 2.43–3.36 (4 H, m), 3.40–3.80 (1 H, m), 3.48 (1 H, d, *J* = 11.0 Hz), 3.74 (1 H, d, *J* = 11.0 Hz), 4.55 (1 H, t, *J* = 9.0 Hz), 5.50 (1 H, br s, disapp. with D_2O), 5.50 (1 H, dd, *J* = 11.0 Hz and 2.8 Hz), 5.96 (1 H, ddd, *J* = 11.0 Hz, 6.0 Hz, and 3.0 Hz), 7.08–7.60 (4 H, m), 8.24 (1 H, br s, disapp. with D_2O); MS *m/e* 296 (M^+), 295, 279, 265, 223, 209, 184, 171, 170, 169, 156, 155, 154, 144, 143.

Anal. ($C_{19}H_{24}N_2O$) C, H, N.

(b) From α,β-Unsaturated Lactam Ester 22. To an ice-cooled solution of **22** (300 mg, 0.85 mmol) in anhydrous tetrahydrofuran (10 mL) under nitrogen was added lithium aluminum hydride (162 mg, 4.25 mmol). After refluxing for 1.5 h, the reaction mixture was worked up in the manner described above to afford a pale yellow crystalline residue (300 mg). Preparative thin-layer chromatography developed with 10% methanol–chloroform gave the unsaturated amino alcohol **23** (12 mg, 4.8%) and β-ethyl amino alcohol **13b** (220 mg, 86.8%) each as colorless crystals.

Quaternary Salt 35. Unsaturated amino alcohol **23** (140 mg, 0.47 mmol) was mesylated in the manner described for the preparation of the quaternary salt **17b**. The workup afforded a yellow powder (190 mg), which was recrystallized from methanol–acetone to give **35** (170 mg, 96.6%) as colorless hygroscopic needles: mp 261 °C (dec); NMR (D_2O) δ 1.06 (3 H, t, *J* = 7.0 Hz), 1.83 (2 H, q, *J* = 7.0 Hz), 2.22 (2 H, m), 2.85 (3 H, s), 2.96–4.50 (9 H, m), 6.34 (1 H, d, *J* = 10.0 Hz), 7.14–7.80 (5 H, m); MS *m/e* 278 ($M^+ - MeSO_3H$), 249, 208, 206, 194, 184, 171, 170, 169, 168, 167, 155, 154.

Anal. ($C_{20}H_{26}N_2O_3S$) C, H, N, S.

(±)-14,15,16,17-Tetradehydroquebrachamine (1, 14,15,16,17-Tetradehydro). To an ice-cooled suspension of **35** (80 mg, 0.21 mmol) in anhydrous tetrahydrofuran (5.0 mL) under nitrogen was added lithium aluminum hydride (1.3 M in tetrahydrofuran, 1.0 mL, 1.3 mmol). After refluxing for 7 h, the reaction mixture was treated carefully with 10% NH_4OH with cooling in an ice bath and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo. Preparative thin-layer chromatography on silica gel developed with 10% methanol–chloroform afforded a crystalline residue, which was recrystallized from ethanol–*n*-hexane to give (±)-14,15,16,17-tetradehydroquebrachamine (**1**, 14,15,16,17-tetradehydro) (34 mg, 58.2%) as colorless needles: mp 153–154 °C (lit.[6] mp 151–152 °C); IR (Nujol) 3150, 3025 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3 H, t, *J* = 7.0 Hz), 5.67 (1 H, br d, *J* = 10.0 Hz), 5.95 (1 H, d, *J* = 10.0 Hz), 6.93–7.30 (6 H, m), 7.87 (1 H, br s, disapp. with D_2O); MS *m/e* 278 (M^+), 277, 263, 250, 249, 248, 237, 234, 208, 207, 206, 205, 204, 184, 155, 154, 153. The IR, NMR, and mass spectra of this material were identical with the reported data.[6]

(±)-16-Cyano-14,15-didehydroquebrachamine (36). To a solution of **35** (90 mg, 0.24 mmol) in dimethylformamide (5.0 mL) under ni-

trogen was added pulverized potassium cyanide (78 mg, 1.20 mmol) and the mixture was refluxed gently for 3 h. After removal of the solvent in vacuo, the residue was treated with saturated $NaHCO_3$ and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo to afford a dark red oil (153 mg). Preparative thin-layer chromatography on silica gel developed with 5% methanol-chloroform gave (±)-16-cyano-14,15-didehydroquebrachamine (**36**; 20 mg, 27.4%) as a clear viscous oil: IR (neat) 3320, 2225; NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 6.0 Hz), 3.52 (1 H, dd, J = 7.0 Hz and 4.0 Hz), 5.30–6.2 (2 H, m), 6.90–7.70 (4 H, m), 8.20 (1 H, br s, disapp. with D_2O); MS *m/e* 305 (M^+), 278, 249, 223, 210, 208, 205, 194, 181, 168, 123, 121, 119, 117, 108. The mass spectrum of this material was identical with the reported data.[6]

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References and Notes

(1) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.
(2) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727.
(3) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Leutwiler, A.; Nelson, V. R.; de Souza, J. P. *Helv. Chim. Acta* **1975**, *58*, 1648.
(4) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.*, **1969**, *91*, 2342.
(5) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084.
(6) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1971**, *93*, 5930; *Ibid.* **1973**, *95*, 7458.
(7) Cf. Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151.
(8) Cf. Scott, A. I. "Applications of Biochemical Systems in Organic Chemistry", Weissberger, A., Ed.; Wiley: New York, 1976; p 555.
(9) Takano, S.; Nishimura, T.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1167.
(10) Preliminary form: Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 3022.
(11) Marshall, J. A.; Roebke, H. *Tetrahedron Lett.* **1970**, 1555.
(12) Marshall, J. A.; Buse, C. T.; Seltz, D. E. *Synth. Commun.* **1973**, *3*, 85.
(13) Marshall, J. A.; Seltz, D. E. *J. Org. Chem.* **1974**, *39*, 1814.
(14) Cf. Takano, S.; Ogasawara, K. *J. Synth. Org. Chem. Soc., Jpn.* **1977**, *35*, 795.
(15) Musso, H.; Naumann, K.; Grychtol, K. *Chem. Ber.* **1967**, *100*, 3616.
(16) Cf. Watt, D. S. *Tetrahedron Lett.* **1974**, 707.
(17) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *J. Org. Chem.* **1971**, *36*, 1137.
(18) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *Org. Synth.* **1974**, *54*, 37.
(19) Autrey, R. L.; Scullard, P. W. *J. Am. Chem. Soc.* **1968**, *90*, 4917.
(20) Autrey, R. L.; Scullard, P. W. *J. Am. Chem. Soc.* **1968**, *90*, 4924.
(21) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.
(22) Oishi, T.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1972**, 1085.
(23) Ho, T.-L.; Wong, C. M. *Synthesis* **1972**, 561.
(24) Fetizon, M.; Jurion, M. *Chem. Commun.* **1972**, 382.
(25) Takano, S.; Sato, M.; Hatakeyama, S.; Hirama, M.; Ogasawara, K. *Heterocycles* **1976**, *5*, 221.
(26) Cf. (a) Rosen, W. E.; Shoolery, J. N. *J. Am. Chem. Soc.* **1961**, *83*, 4816; (b) Wenkert, E.; Wickberg, B.; Leicht, C. L. *Ibid.* **1961**, *83*, 5037; (c) Wenkert, E.; Wickberg, B. *Ibid.* **1965**, *87*, 1580; (d) Kutney, J. P.; Cretney, W. J.; Le Quesne, P.; McKagne, B.; Piers, E. *Ibid.* **1966**, *88*, 4756; (e) Trager, W. F.; Lee, C. M.; Beckett, A. H. *Tetrahedron* **1967**, *23*, 365.
(27) Kutney, J. P.; Cretney, W. J.; Le Quesne, P.; McKague, B.; Piers, E. *J. Am. Chem. Soc.* **1970**, *92*, 1712.
(28) Trost, B. M.; Saltzman, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840.
(29) Kametani, T.; Hirai, Y.; Kajiwara, M.; Takahashi, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1975**, *23*, 2637.
(30) Rahman, A.-ur.; Basha, A.; Waheed, N.; Ahmed, S. *Tetrahedron Lett.* **1976**, 219.
(31) Borch, R. F. *Tetrahedron Lett.* **1968**, 61.
(32) Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1968**, *16*, 492.
(33) Biemann, K.; Spiteller, G. *Tetrahedron Lett.* **1961**, 299.
(34) Wallace, T. J. *J. Am. Chem. Soc.* **1964**, *86*, 2018.
(35) Recently another synthesis of tabersonine has been reported. Lévy, J.; Laronze, J.-Y.; Laronze, J.; LeMen, J. *Tetrahedron Lett.* **1978**, 1579.

Lactone Annulation of β-Keto Esters with β-Vinylbutenolide and the Total Synthesis of Racemic Frullanolide[1]

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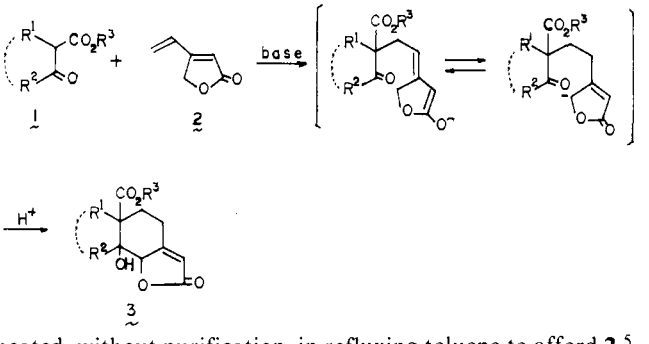
Abstract: A new annulation reaction, in which sodium enolates of β-keto esters **6–11** and β-vinylbutenolide (**2**) yield lactone annulated products **12–17** in one step, is described. Racemic frullanolide (**30**) has been synthesized from one of these annulation products, **14a**.

In the preliminary communication we reported the reactions of 2-methylcyclohexane-1,3-dione and 2-ethoxycarbonylcyclohexanone with β-vinylbutenolide (**2**) affording lactone annulated products.[1a,2] Recently we have extended this annulation reaction to some β-keto esters for the exploration of a new synthetic approach to eudesmanolides.

The reaction is shown by the following general equation, i.e., 1,6-conjugate addition of keto esters **1** to **2** and concomitant intramolecular cyclization yielding lactone annulated products **3**.



The reagent, β-vinylbutenolide (**2**), was expediently prepared from β-vinylbutyrolactone (**4**), easily accessible from (*E*)-2-butene-1,4-diol and ethyl orthoacetate in good yield,[3] as follows: the lithium enolate of the latter lactone was sulfenylated with diphenyl disulfide[4] yielding thiophenoxylactone **5** (Chart I). The product was oxidized with *m*-chloroperbenzoic acid to the corresponding sulfoxide, which was then heated, without purification, in refluxing toluene to afford **2**.[5] This compound is unstable, slowly changing into a polymeric substance even on refrigeration, while **5** is much more stable in storage. In the reaction we usually employed **2** freshly prepared from **5**.

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