MeOH, 5%) gave 22 mg of gummy **5**, ir bands at 3510, 1770, 1730, 1690, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 424 (M^+), 395 (M − CHO), 322 (M − $C_5H_{10}O_2$), 304 (M − $C_5H_{10}O_2$ − H_2O), 293 (M − $C_5H_{10}O_2$ − CHO), 85 (base peak, C_5H_9O), and 57 (C_4H_9).

Anal. Calcd for $C_{22}H_{30}O_8$: mol wt, 424.2097. Found: mol wt, 424.2106 (MS).

Acanthospermal A Epoxide (3). A solution of 0.05 g of **1a** in 5 ml of $CHCl_3$ was stirred with 0.05 g of *m*-chloroperbenzoic acid at room temperature for 48 hr and extracted with $CHCl_3$. The extracted was washed with sodium metabisulfite and water, dried, and evaporated. Purification of the crude product by preparative TLC ($CHCl_3$–MeOH, 8%) yielded **3** as a gum, ir bands at 3500, 1770, 1730, 1690, 1620, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 450 (M^+), 362 (M − $C_4H_8O_2$), 347 (M − $C_4H_7O_3$), 276 (M − C_4H_7O − $C_4H_7O_3$), 260 (M − $C_4H_7O_3$ − $C_4H_7O_2$), 71 (C_4H_7O), 59 and 43 (base peak).

Anal. Calcd for $C_{23}H_{30}O_9$: mol wt, 450.1890. Found: mol wt, 450.1894 (MS).

$NaBH_4$ Reductions of 1a and 4a. A solution of 0.05 g of **1a** and 0.05 g of $NaBH_4$ in 10 ml of MeOH was stirred at 0° for 4 hr, acidified with dilute acetic acid, evaporated at reduced pressure, diluted with water, and extracted with ethyl acetate. The washed and dried extract was evaporated and the residue was purified by preparative TLC ($CHCl_3$–MeOH, 8%) to give **7** as a gum, ir bands at 3540, 3500, 1770, 1740, 1460, 1370, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 438 (M^+), 350 (M − $C_4H_8O_2$), 324 (M − $C_4H_8O_3$), 316 (M − $C_4H_8O_3$ − H_2O), 246 (M − $C_4H_8O_2$ − $C_4H_8O_3$), 228 (base peak, M − $C_4H_8O_2$ − $C_4H_8O_3$ − H_2O), 71, 59, and 43.

Anal. Calcd for $C_{23}H_{34}O_8$: mol wt, 438.2253. Found: mol wt, 438.2257 (MS).

Reduction of 0.1 g of **4a** with 0.1 g of $NaBH_4$ followed by workup in the same way gave, after preparative TLC ($CHCl_3$–MeOH, 8%), **8** as a gum, ir bands at 3540, 3490, 1770, 1760, 1730, 1460, 1230, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 424 (M^+), 322 (M − $C_5H_{10}O_2$), 280 (M − $C_5H_{10}O_2$ − C_2H_2O), 262 (M − $C_5H_{10}O_2$ − $C_2H_4O_2$), 244 (M − $C_5H_{10}O_2$ − $C_2H_4O_2$ − H_2O), 85 (C_5H_9O), 57 (base peak), and 43.

Anal. Calcd for $C_{22}H_{32}O_8$: mol wt, 424.2097. Found: mol wt, 424.2102 (MS).

Oxidation of 4a to 6. A solution of 0.05 g of **4a** in 10 ml of spectral grade $CHCl_3$ was stirred at room temperature with 0.1 g of active MnO_2, the reaction being monitored by TLC. After 24 hr, when the reaction did not appear to proceed further, the mixture was filtered and the precipitate washed repeatedly with $CHCl_3$. The combined filtrate and washings were evaporated and the residue developed as a preparative TLC plate using $CHCl_3$–MeOH (6%) as solvent. The major band yielded 40 mg of starting material. A minor band yielded 6 mg of the dialdehyde **6** as a gum, ir bands at 1770, 1730, 1690, 1680, 1460, 1240, and 1000 cm^{-1}. The mass spectrum exhibited significant bands at *m/e* 360 (M − 2CHO), 258 (360 − $C_5H_{10}O_2$), 85 (C_5H_9O), and 57.

Anal. Calcd for $C_{22}H_{26}O_8$: mol wt, 418.1628. Found: mol wt, 418.1632 (MS).

Registry No.—**1a,** 56689-33-9; **1b,** 56679-16-4; **2,** 56679-17-5; **3,** 56679-18-6; **4a,** 56679-19-7; **4b,** 56679-20-0; **5,** 56679-21-1; **6,** 56679-22-2; **7,** 56679-23-3; **8,** 56679-24-4.

References and Notes

(1) This work was supported in part by Grant CA-13121 from the U.S. Public Health Service through the National Cancer Institute.
(2) W. Herz and S. V. Bhat, *Phytochemistry*, **11**, 1829 (1972).
(3) In $CDCl_3$ this signal appeared at 6.80 ppm. A similarly large diamagnetic shift on passing from $CDCl_3$ to C_6D_6 was observed earlier for H-2 of frutescin.[2]
(4) Since the results of spin-decoupling experiments on **4a** were similar to those performed on **1a**, they are not discussed in detail.
(5) For references see W. Herz and R. P. Sharma, *J. Org. Chem.*, **40**, 192 (1975).
(6) The proximity of the H-1 signal to H-8 (in $CDCl_3$) and to H-13b (in C_6D_6) interfered with attempts to verify the expected nuclear Overhauser effect between H-1 and H-14.
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(8) Other members of this subgroup are polydalin and uvedalin,[9] enhydrin,[10] maculatin,[11] and frutescin.[2]
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Synthesis of Tabtoxinine-δ-lactam

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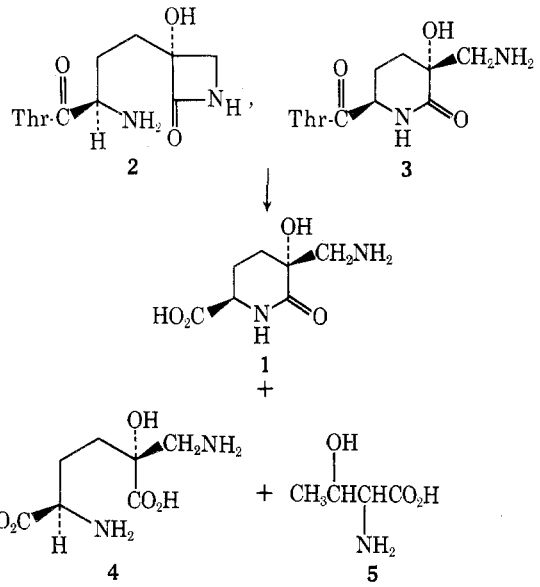
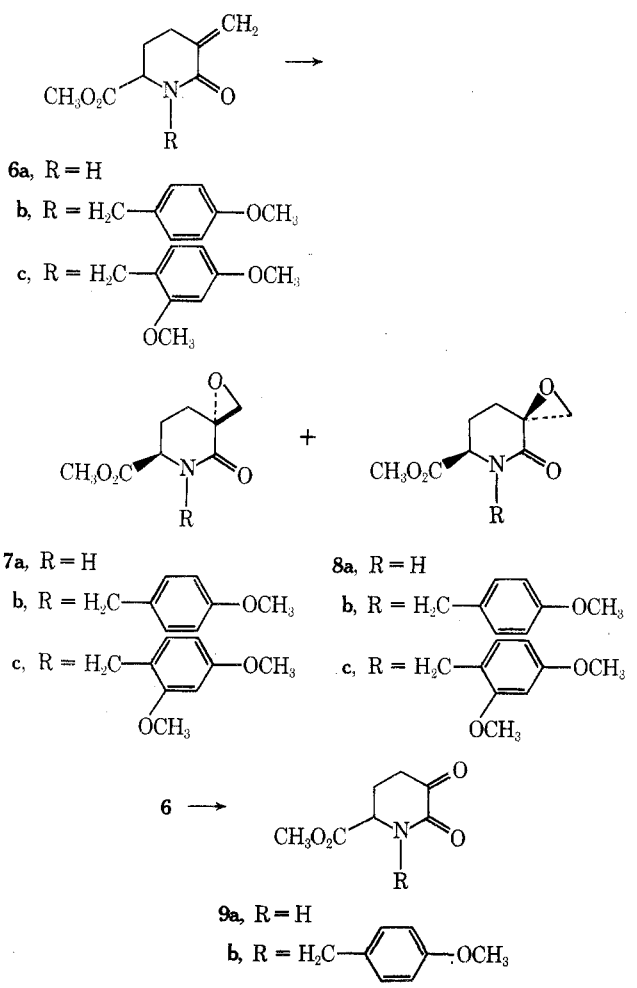
The synthesis is described of tabtoxinine-δ-lactam, an amino acid produced by various Pseudomonad species and also formed on hydrolysis of tabtoxin. The key intermediate in the synthesis is 1-anisyl-6-methoxycarbonyl-3-methylene-2-piperidone, which is easily obtained by application of the α-methylenelactam rearrangement to dimethyl 1-anisyl-2,5-piperidinedicarboxylate. Epoxidation gave a mixture of cis and trans oxides which were individually treated with ammonia. From the trans epoxide, the major isomer, the corresponding 3-aminomethyl-3-hydroxy compound was isolated. Removal of the anisyl protecting group gave the amino acid, *cis*-3-aminomethyl-6-carboxy-3-hydroxy-2-piperidone, identical with tabtoxinine-δ-lactam. This synthesis confirms the structure of, and establishes the aminomethyl and carboxy groups as cis in, the natural amino acid.

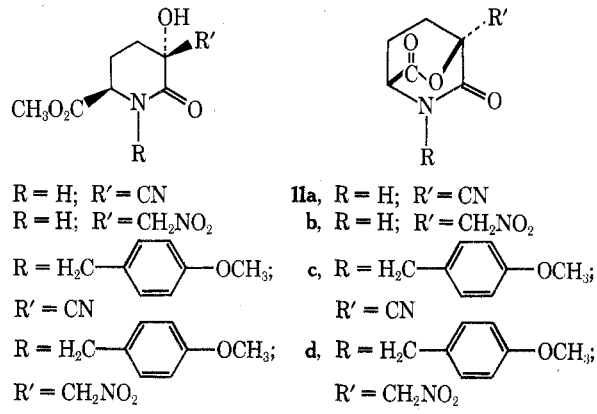
Tabtoxinine-δ-lactam (**1**) is an amino acid produced by various Pseudomonad species and is one of the compounds found in the hydrolysis of tabtoxin (**2**) or isotabtoxin (**3**).[1,2] The other hydrolysis products are tabtoxinine (**4**) and threonine (**5**).[1-3] Tabtoxin (**2**), the chlorosis-inducing exotoxin produced by *Pseudomonas tabaci, P. coronafaciens,* and other phytopathogenic *Pseudomonas,* is the component responsible for the toxicity of these bacteria to various plants (e.g., tobacco, soybean, oat, timothy). Tabtoxin (**2**) is relatively unstable, and at room temperature and pH 7 the biological activity of toxic solutions decreases with a half-life of about 1 day[3] as ready translactamization occurs to the more stable and nontoxic δ-lactam isomer, isotabtoxin (**3**).[1,3] Presented here is the total synthesis of (±)-tabtoxinine-δ-lactam (**1**) which further confirms the structure assigned to isotabtoxin (**3**) and to tabtoxin (**2**), and establishes the relative stereochemistry as shown in structures **1, 2, 3,** and **4.**



Results and Discussion

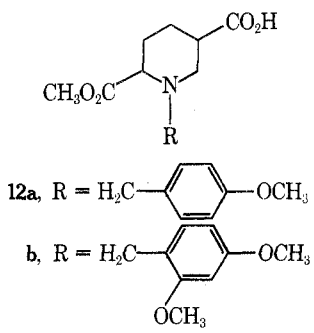
A key intermediate for the synthesis of tabtoxinine-δ-lactam (1) appeared to be an α-methylenelactam of the general type 6. Epoxidation of these α-methylenelactams for which there was precedent[4,5] would then yield the epoxides 7 and 8. Opening of these epoxides by attack at the least substituted carbon with ammonia or an amine would afford the desired lactam 1 or some derivative of it. Alternately, these α-methylenelactams 6 can be ozonolyzed to the corresponding α-ketolactams 9,[4] which potentially can





be elaborated with hydrogen cyanide or nitromethane to yield the adducts 10 and/or 11. Reduction of the adducts 10 would then yield the α-hydroxy-α-aminomethyllactam 1 or some derivative of it. Also, the α-ketolactams could be treated with dimethyloxosulfonium methylide to produce the epoxides 7 and/or 8.

Preparation of the α-methylenelactams 6 appeared to offer an ideal application of the α-methylenelactam rearrangement, i.e., 12 → 6.[6] Since the rearrangement occurs

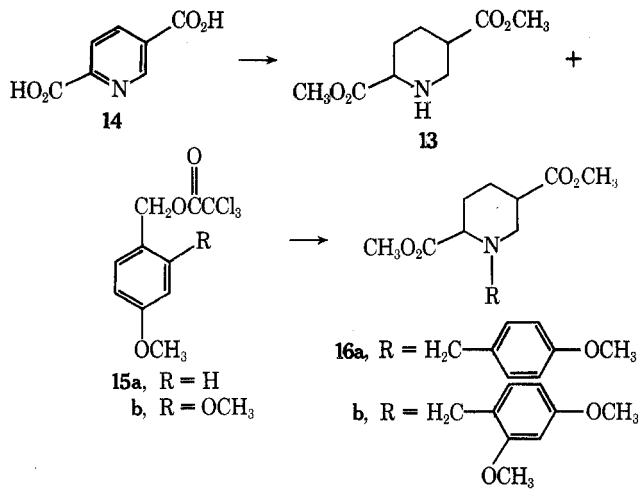


only when the amino group in the starting cyclic β-amino acid is tertiary, the preparation of the N-substituted amino acids 12a and 12b was undertaken. The anisyl group (An) and the 2,4-dimethoxybenzyl group (Dmb) were chosen as the nitrogen protecting groups because they did not interfere with the rearrangement[6] and they are easily removable at the lactam stage[7] to afford the desired NH lactams.

Preparation of these cyclic β-amino acids 12 was accomplished by first reducing isocinchomeronic acid (14) and esterifying the piperidine-2,5-dicarboxylic acid. Alkylation with anisyl chloride or 2,4-dimethoxybenzyl chloride afforded the *N*-benzyl derivatives 16a and 16b in very poor yields owing to the extreme ease with which these benzyl chlorides polymerize. To circumvent this problem, the trichloroacetates, which would be less prone to SN1 type dissociation, of anisyl alcohol 15a or 2,4-dimethoxybenzyl alcohol 15b were employed to give the corresponding benzyl derivatives 16a and 16b, now in respectable yields. Selective alkaline hydrolysis of the less hindered β ester then yielded the β amino acids 12a and 12b.

Rearrangement of the acid 12a and 12b to the respective α-methylenelactams 6b and 6c was readily accomplished in refluxing acetic anhydride. Debenzylation of either lactam 6b or 6c to afford 6a was effected in comparable yield by heating the benzyllactams in trifluoroacetic acid at reflux in the presence of anisole.[7]

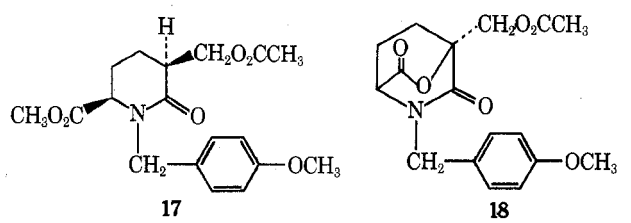
Reaction of the α-methylenelactam 6a with *m*-chloroperbenzoic acid (MCPBA) failed to yield the epoxides 7a or 8a in good yield. This is surprising since the corresponding demethoxycarbonyl compound (3-methylene-2-piperidone) is convertible to epoxide. Evidently overoxidation of the lactam 6a readily occurs because there is continued peracid



consumption beyond 100 mol %. The NMR spectrum of the crude reaction mixture revealed many new absorptions in the olefinic region, indicative of pyridone formation and perhaps initiated at the labile α-H at C-6.

Oxidation of α-methylenelactam **6b** with MCPBA proceeded smoothly to yield the trans and cis epoxides, **7b** and **8b**, in a ratio of 8:1, respectively. The epoxides could be separated via column chromatography (silica gel) with significant loss of material owing to the sensitivity of these epoxides to silica gel. Efforts to alter the epoxide ratio by varying the solvent (ether, ethyl acetate, and carbon tetrachloride) or by employing benzonitrile–hydrogen peroxide had little or no effect.

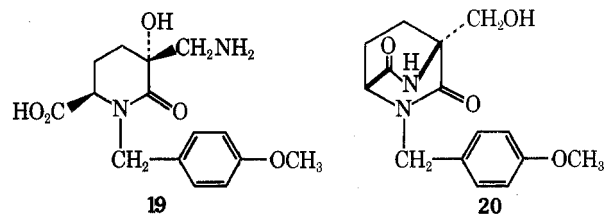
The stereochemistry of epoxides **7b** and **8b** was established by heating them in acetic acid. Trans epoxide **7b** exclusively afforded acetate **17**, and cis epoxide **8b** gave as the sole product the lactone acetate **18**.



Reaction of the *N*-2,4-dimethoxybenzyl α-methylenelactam **6c** with MCPBA also failed to produce any epoxide. Examination of the reaction mixture revealed almost complete disappearance of the aryl methoxy groups and the appearance of numerous new absorptions in the vinyl region. This evidence was suggestive of oxidation of the electron-rich dimethoxyphenyl nucleus to quinoid-type intermediates.

Ozonolysis of the α-methylenelactams **6a** and **6b** produced the respective α-ketolactams **9a** and **9b** in high yield. Reaction of the α-ketolactam **9b** with dimethyloxosulfonium methylide afforded the epoxides **7b** and **8b** in a ratio of 4:1; however, since other products were present, purification was difficult and this method for epoxide formation was not explored further. Treatment of the α-ketolactam **9b** with nitromethane and sodium methoxide afforded a nitro adduct which by NMR appeared to be the nitrolactone **11d** (appearance of a two-proton multiplet at δ 4.5–5.3 for the $-CH_2NO_2$ group and the clean disappearance of the methyl ester); however, the mass spectrum of this adduct was not commensurate with this structure. Treatment of the α-ketolactam **9b** with hydrogen cyanide produced what appeared to be the cyanohydrin **10c** but subsequent attempts to reduce it to the amine failed. Treatment of the α-ketolactam **9a** with dimethyloxosulfonium methylide failed to produce any epoxide, and reaction with nitromethane and sodium methoxide also failed to yield a nitro adduct.

As a result of these failures to obtain synthetically useful products from the α-ketolactams, we focused our efforts on the epoxide **7b**. Opening of the epoxide **7b** with ammonium hydroxide occurred at both carbons of the epoxide and provided the aminol acid **19** (with retention) and the diketopiperazine **20** (with inversion) in a ratio of 2:1, respectively.



An alternative explanation for the formation of diketopiperazine **20** would be initial formation of the amide from ester **7b** and intramolecular attack of the amide nitrogen to open the epoxide. This path is less likely since none of the corresponding amide of **19** was formed. Heating the aminol acid **19** in trifluoroacetic acid at reflux in the presence of anisole afforded tabtoxinine-δ-lactam (**1**).

The characterization of the synthetic material was totally consistent with its proposed structure. Most notable in its NMR spectrum is a set of doublets at δ 3.2 with a coupling constant of J = 13 Hz which is shown by the natural compound and is characteristic of these α-hydroxy-α-aminomethylcarbonyl systems.[1,3] Its mass spectra exhibited major peaks at $M^+ - H_2O$ and $M^+ - (CH_2{=}NH)$ as does the natural product and is also characteristic of these α-hydroxy-α-aminomethylcarbonyl systems.[1,3] Finally, our synthetic (±)-tabtoxinine-δ-lactam showed the same R_f values as the natural amino acid in three different systems.

Experimental Section[8]

Dimethyl 2,5-Piperidinedicarboxylate (13). A mixture of 2,5-pyridinedicarboxylic acid monohydrate (**14**, 37 g, 0.2 mol), concentrated ammonium hydroxide (20 ml), water (200 ml), and rhodium on alumina (10 g of 5%) was hydrogenated at 1–3 atm for 25 hr. The mixture was filtered through super-cel, the filtrate was evaporated to dryness, water (100 ml) was added to the residue, and the solution was again evaporated to dryness. To the residue was added methanol (500 ml) and concentrated sulfuric acid (30 ml), and this solution was heated to reflux for 16 hr. The solution was cooled and then poured into 400 ml of a cooled potassium carbonate solution. After the basic aqueous solution was extracted with chloroform (3 × 400 ml), the combined chloroform extracts were dried ($MgSO_4$) and then evaporated to an oily residue which was distilled to produce 32 g (80%) of the dimethyl ester **13**, bp 87–90° (0.1 mm) [lit.[9] bp 104–106° (0.4 mm)].

***p*-Methoxybenzyl Trichloroacetate (15a).** To a solution of anisyl alcohol (13.8 g, 0.1 mol) and *N,N*-dimethylaniline (12.1 g, 0.1 mol) in 150 ml of toluene at 0° was added trichloroacetyl chloride (18.2 g, 0.1 mol) in 50 ml of toluene over a period of 30 min. After stirring for an additional 1 hr at room temperature, the reaction mixture was poured into 200 ml of ice–water and the organic layer was washed sequentially with 10% sulfuric acid and aqueous sodium bicarbonate. After drying ($MgSO_4$), the toluene solution was evaporated to afford a quantitative yield of the trichloroacetate **15a**: NMR δ 3.80 (s, 3 H), 5.32 (s, 2 H), 6.86 (d, 2 H, J = 9 Hz), 7.28 (d, 2 H, J = 9 Hz). This crude acetate was used without further purification in the alkylation reaction; an analytical sample was obtained by column chromatography (silica gel, 1:1 hexane–ether, R_f 0.73).

Anal. Calcd for $C_{10}H_9O_3Cl_3$: C, 42.4; H, 3.2. Found: C, 42.4; H, 3.0.

2,4-Dimethoxybenzyl Trichloroacetate (15b). The acetate **15b** was prepared in a manner analogous to the procedure described above using 2,4-dimethoxybenzyl alcohol in place of anisyl alcohol. This acetate is relatively unstable and exhibits a high propensity to polymerize when not in solution. Thus it must be used

immediately or stored in the cold as a solution: NMR (CCl_4) δ 4.64 (s, 3 H), 4.70 (s, 3 H), 5.25 (s, 2 H), 6.25–6.46 (m, 2 H), 7.10–7.30 (m, 1 H); ir (neat) 1760 cm^{-1}.

Dimethyl 1-(*p*-Methoxybenzyl)-2,5-piperidinedicarboxylate (16a). A mixture of the diester **13** (15 g, 75 mmol), potassium carbonate (13.8 g, 0.1 mol), the trichloroacetate **15a** (29 g, 0.1 mol), and 400 ml of toluene was heated at reflux under nitrogen for 70 hr. The reaction mixture was cooled, the toluene was removed in vacuo, the residue was dissolved in chloroform (200 ml), and the chloroform solution was washed first with 200 ml of a potassium carbonate solution and then with 200 ml of 10% HCl. Evaporation of the chloroform solution produced 15.6 g of the crude piperidine hydrochloride as a yellow solid. Boiling this crude precipitate in hexane furnished white crystals which on recrystallization from 150 ml of ethanol afforded 12.5 g (52%) of analytically pure **16a** hydrochloride: mp 168–170°; NMR δ 1.3–2.8 (m, 5 H), 3.3–3.9 (m, 4 H), 3.64 (s, 3 H), 3.74 (s, 6 H), 4.23–4.44 (m, 2 H), 6.70 (d, 2 H, J = 9 Hz), 7.50 (d, 2 H, J = 9 Hz); mass spectrum m/e 321 (M^+ – HCl).

Anal. Calcd for $C_{17}H_{24}NO_5Cl$: C, 57.1; H, 6.8; N, 3.9. Found: C, 57.3; H, 6.8; N, 3.9.

An analytical sample of the free amine, obtained by treatment of the hydrochloride with K_2CO_3, was obtained by GC (glass column 10 ft 3% OV-17, 240°C, flow rate 50 ml/min, retention time 5.7 min): NMR δ 1.4–3.5 (m, 8 H), 3.56 (s, 3 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 3.57–3.69 (m, 2 H), 6.75 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.2; N, 4.4. Found: C, 63.7; H, 7.3; N, 4.4.

Dimethyl 1-(2,4-Dimethoxybenzyl)-2,5-piperidinedicarboxylate (16b). A mixture of the amino ester **13** (32 g, 0.16 mol), the trichloroacetate **15b** (62 g, 0.2 mol), potassium carbonate (28 g, 0.2 mol), and 400 ml of toluene was heated at reflux under nitrogen for 4 hr. The reaction mixture was cooled, washed with 200 ml of an aqueous potassium carbonate solution, dried ($MgSO_4$), and evaporated in vacuo to furnish an oily residue. Chromatography of the residue on 1600 g of silica gel employing 4% methanol–chloroform as the eluent produced 44 g (64%) of the alkylated amine **16b:** TLC (2% CH_3OH–$CHCl_3$) R_f 0.4; NMR (CCl_4) δ 1.42–3.8 (m, 8 H), 3.55 (s, 2 H), 3.61 (s, 3 H), 3.69 (s, 9 H), 6.20–6.42 (m, 2 H), 6.92–7.24 (m, 1 H); ir (neat) 1730, 1625, 1600 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.5; H, 7.2; N, 4.0. Found: C, 61.6; H, 7.2; N, 4.1.

1-Anisyl-6-methoxycarbonyl-3-methylene-2-piperidone (6b). A solution of the piperidine hydrochloride **16a** (3.47 g, 9.65 mmol), sodium hydroxide (0.80 g, 20 mmol), methanol (100 ml), and water (5 ml) was stirred at room temperature for 20 hr. The solution was evaporated to dryness in vacuo, and the residue along with triethylamine (10 g, 0.1 mol) and acetic anhydride (100 ml) was heated at reflux under nitrogen for 4 hr. The acetic anhydride and triethylamine were removed in vacuo, the residue was dissolved in chloroform and washed with water, and the oil obtained after evaporation of the chloroform was chromatographed on 80 g of silica gel employing 1:1 hexane–ethyl acetate as the eluent, yield 2.2 g (79%) of lactam **6b:** TLC (1:1 hexane–ethyl acetate) R_f 0.43; NMR δ 1.6–2.2 (m, 2 H), 2.22–2.6 (m, 2 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 3.86–4.06 (m, 2 H), 5.13–5.34 (m, 1.5 H), 5.40 (s, 0.5 H), 6.30–6.45 (m, 1 H), 6.69 (d, 2 H, J = 9 Hz), 7.03 (d, 2 H, J = 9 Hz). An analytical sample was obtained by GC (glass column, 10 ft, 3% OV-17, 240°, flow rate 50 ml per min, retention time 6.2 min).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.2; H, 6.8; N, 4.9.

Methoxycarbonyl-3-methylene-2-piperidone (6a). A solution of the α-methylenelactam **6b** (4.8 g, 16.5 mmol), anisole (4.3 g, 40 mmol), and trifluoroacetic acid (100 g) was heated at reflux under nitrogen for 48 hr. After the trifluoroacetic acid and anisole were removed in vacuo, the residue thus obtained was chromatographed on 300 g of silica gel using ethyl acetate as the eluent to produce 2.1 g (75% yield) of the α-methylenelactam **6a:** TLC (ethyl ether) R_f 0.24; NMR (CCl_4) δ 1.84–2.3 (m, 2 H), 2.31–2.7 (m, 2 H), 3.67 (s, 3 H), 4.0–4.25 (m, 1 H), 5.1–5.26 (m, 1 H), 5.95–6.15 (m, 1 H), 7.57–7.58 (s, 1 H); ir (neat) 1730, 1660, 1610 cm^{-1}. An analytical sample was obtained by GC (glass column, 10 ft, 3% OV-17, 190°, flow rate 50 ml/min, retention time 6.0 min).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.6; H, 6.4; N, 8.2.

1-Anisyl-3-keto-6-methoxycarbonyl-2-piperidone (9b). Into a solution of the α-methylenelactam **6b** (0.90 g, 3 mmol) and methanol (50 ml) at −78° was passed a stream of ozone for 40 min (O_3 content, 0.1 mmol/min). Dimethyl sulfide (1 ml) was added to the solution, which was left standing for 22 hr at −78° under nitrogen. After warming to room temperature, the methanol and excess dimethyl sulfide were evaporated, the residue was dissolved in 100 ml of ether, and the ethereal solution was washed with water (3 × 50 ml). Evaporation of the ethereal solution after drying ($MgSO_4$) and chromatography of the crude material on 50 g of silica gel employing 5% methanol–ethyl acetate as the eluent gave 0.42 g of purified α-ketolactam which crystallized on standing. Recrystallization from methylene chloride–ethyl ether afforded analytically pure α-ketolactam **9b:** mp 81–83°; mass spectrum m/e 291 (M^+); NMR δ 2.0–2.66 (m, 4 H), 3.50 (s, 3 H), 3.60 (s, 3 H), 3.5–4.3 (m, 2 H), 4.84 (d, 1 H, J = 15 Hz), 6.55 (d, 2 H, J = 8 Hz), 6.95 (d, 2 H, J = 8 Hz); ir (Nujol) 1735, 1680 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.8; H, 5.9; N, 4.8. Found: C, 61.7; H, 5.9; N, 4.9.

3-Keto-6-methoxycarbonyl-2-piperidone (9a). Ozone (flow rate 0.1 mmol per min) was passed through a solution of the α-methylenelactam **6a** (1.1 g, 6.5 mmol) and methanol (50 ml) at −78° for 65 min. Dimethyl sulfide (5 ml) was added, and the solution was left under nitrogen at −78° for 22 hr. Evaporation of the methanol and excess dimethyl sulfide afforded the crude α-ketolactam **9a,** which was chromatographed on 100 g of silica gel using 10% methanol–ethyl acetate as the eluent, yield 0.19 g (17%) of the purified α-ketolactam **9a:** mass spectrum m/e 171 (M^+); NMR δ 2.2–2.8 (m, 4 H), 3.73 (s, 3 H), 4.2–4.5 (m, 1 H), 8.0–8.2 (s, 1 H).

Anal. Calcd for $C_7H_9NO_4$: C. 49.1; H, 5.3; N, 8.2. Found: C, 48.9; H, 5.3; N, 8.2.

6-Methoxycarbonyl-3-epoxymethylene-1-(*p*-methoxybenzyl)-2-piperidone (7b) and 8b. A solution of the α-methylenelactam **6b** (5.0 g, 17 mmol), *m*-chloroperbenzoic acid (6.0 g, 34 mmol), and methylene chloride (100 ml, distilled from P_2O_5) was stirred at room temperature for 40 hr. A precipitate of *m*-chlorobenzoic acid was obtained after 24 hr. The mixture was diluted with chloroform (100 ml), and this methylene chloride–chloroform solution was washed with a sodium bisulfite solution (5.2 g in 100 ml of water, 50 mmol) and then with a saturated sodium bicarbonate solution. After drying ($MgSO_4$), the chloroform was evaporated to yield 5.2 g of the crude epoxides present in a ratio of 8:1, **7b** to **8b,** by NMR. The epoxides were separated by column chromatography (silica gel, 400 g, Camag D-O) with ethyl acetate as the eluent.

Trans epoxide **7b:** yield 3.6 g (69%); TLC (ethyl acetate) R_f 0.7; NMR δ 1.5–2.5 (m, 4 H), 2.60 (d, 1 H, J = 7 Hz), 3.40 (d, 1 H, J = 7 Hz), 3.58–3.67 (m, 3 H), 3.69 (s, 3 H), 3.70–4.18 (m, 2 H), 5.07–5.43 (m, 1 H), 6.70 (d, 2 H, J = 9 Hz), 7.05 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.9; H, 6.3; N, 4.6. Found: C, 62.7; H, 6.5; N, 4.5.

Cis epoxide **8b:** yield 0.92 g (17.7%); TLC (ethyl acetate) R_f 0.6; NMR ($CDCl_3$) δ 1.46–2.4 (m, 4 H), 2.63 (d, 1 H, J = 7 Hz), 3.20 (d, 1 H, J = 7 Hz), 3.70 (s, 3 H), 3.74 (s, 3 H), 3.75–4.16 (m, 2 H), 5.09 (s, 0.5 H), 5.33 (s, 0.5 H), 6.72 (d, 2 H, J = 9 Hz), 7.06 (d, 2 H, J = 9 Hz); high-resolution mass spectrum, calcd for $C_{16}H_{19}NO_5$ (M^+), 305.1263; found, 305.1264.

3-Acetoxymethyl-6-methoxycarbonyl-3-hydroxy-1-(*p*-methoxybenzyl)-2-piperidone (17). A solution of epoxide **7b** (0.30 g, 1 mmol) and acetic acid (25 ml) was heated at reflux under nitrogen for 16 hr. The solution was cooled, and the acetic acid was removed under reduced pressure. The residue was dissolved in chloroform (25 ml) and washed with a solution of saturated sodium bicarbonate (20 ml). After drying ($MgSO_4$), the chloroform was evaporated to afford 0.37 g (100%) of the acetate **17,** crystallized from hexane–ethyl ether: mp 110–112°; mass spectrum m/e 365 (M^+); NMR δ 1.62–2.6 (m, 4 H), 1.97 (s, 3 H), 3.3–4.2 (m, 4 H), 3.61 (s, 3 H), 3.69 (s, 3 H), 5.0–5.4 (m, 1 H), 6.63 (d, 2 H, J = 9 Hz), 7.02 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{18}H_{23}O_7N$: C, 59.2; H, 6.4; N, 3.8. Found: C, 59.2; H, 6.3; N, 3.9.

3-Acetoxymethyl-6-carboxy-3-hydroxy-1-(*p*-methoxybenzyl)-2-piperidone Lactone (18). The epoxide **8b** was treated as above with acetic acid to quantitatively yield the lactone acetate **18:** NMR δ 1.6–2.4 (m, 4 H), 2.13 (s, 3 H), 3.6–4.8 (m, 3 H). 3.77 (s, 3 H), 4.57 (s, 2 H). 6.77 (d, 2 H, J = 9 Hz), 7.12 (d, 2 H, J = 9 Hz); high-resolution mass spectrum, calcd for $C_{17}H_{19}O_6N$ (M^+), 333.1212; found, 333.1207.

Opening of Epoxide 7b with Ammonia. 6-Carboxy-3-hydroxy-1-(*p*-methoxybenzyl)-3-aminomethyl-2-piperidone (19) and 3-Amino-6-carboxy-1-(*p*-methoxybenzyl)-3-hydroxymethyl-2-piperidone Lactam (20). A mixture of epoxide **7b** (3 g, 10 mmol) and concentrated ammonium hydroxide (40 ml) was stirred at room temperature for 3 days. The resulting homogeneous solution was evaporated to dryness in vacuo, water was

added to the residue, and the aqueous solution (pH 6–7) was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated to afford 0.95 g (33%) of the diketopiperazine **20**, crystallized from ethanol: mp 171–173°; TLC (95% ethanol) R_f 0.55; mass spectrum *m/e* 290 (M^+), 291 ($M^+ + 1$); NMR δ 1.8–2.6 (m, 4 H), 3.34 (s, 2 H), 3.77 (s, 3 H), 3.7–4.0 (m, 1 H), 4.24 (d, 1 H, J = 13 Hz), 4.61 (s, 1 H), 4.90 (d, 1 H, J = 13 Hz), 6.43 (s, 1 H), 6.77 (d, 2 H, J = 7 Hz), 7.13 (d, 2 H, J = 7 Hz); ir (Nujol) 3380, 3300, 1670, 1650 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.0; H, 6.2; N, 9.6. Found: C, 61.9; H, 6.1; N, 9.6.

The aqueous layer was evaporated to dryness, and the residue (~2 g) was chromatographed on 150 g of silica gel using 3:1 1-propanol–water as the eluent to yield 1.6 g (54%) of the aminol **19**, crystallized from 95% ethanol: mp 206–208°; TLC (3:1 1-propanol–water, v/v, ninhydrin visualization) R_f 0.51; mass spectrum *m/e* 308 (M^+), 290 ($M^+ - H_2O$); NMR (D_2O) δ 1.6–2.2 (m, 4 H), 3.04 (d, 1 H, J = 13 Hz), 3.36 (d, 1 H, J = 13 Hz), 3.44–4.04 (m, 2 H), 3.64 (s, 3 H), 5.01 (s, 1 H), 5.25 (s, 1 H), 6.77 (d, 2 H, J = 9 Hz), 7.04 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.3; H, 6.5; N, 9.1.

Tabtoxinine-δ-lactam (1). A solution of the aminol **19** (200 mg, 0.65 mmol), anisole (400 mg, 3.7 mmol), and trifluoroacetic acid (5 ml) was heated at reflux for 44 hr under nitrogen. After cooling to room temperature, the excess trifluoroacetic acid was removed under reduced pressure, a solution (25 ml) of KH_2PO_4 (1 g) and K_2HPO_4 (1 g) was added to the residue, and the aqueous solution was extracted with chloroform. After again evaporating the aqueous layer to dryness, the resulting residue was digested in hot methanol. The hot methanolic mixture was filtered, and the filtrate evaporated to dryness. The residue thus obtained was chromatographed on silica gel (10 g) employing 3:1 1-propanol-water as the eluent to afford 0.080 g (66%) of (±)-tabtoxinine-δ-lactam (1). An analytical sample was obtained by dissolving the crude crystals in hot ethanol–water (1:1 v/v), allowing the solution to cool, and inducing crystal formation by the addition of acetone. Repetition of this procedure afforded the pure aminol 1: mp 234–236°; TLC (3:1 1-propanol–water, ninhydrin visualization) R_f (silica gel Camag) 0.15; mass spectrum *m/e* 170 ($M^+ - H_2O$, 8.98% RA, 0.37% TI), 159 ($M^+ - CH_2{=}NH$, 29.14% RA, 1.20% TI), 43 (100.00% RA, 4.12% TI); NMR (D_2O) δ 1.70–2.35 (m, 4 H), 3.07 (d, 1 H, J = 13 Hz), 3.38 (d, 1 H, J = 13 Hz), 3.81–4.12 (m, 1 H).

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.7; H, 6.4; N, 14.9. Found: C, 44.8; H, 6.2; N, 14.6.

The R_f's of the synthetic and natural material were identical in three different systems: (1) silica gel G, 2:1 1-propanol–water, R_f 0.24 (lit.[10] R_f 0.24); (2) Whatman No. 1, 2:1 1-propanol–water, R_f 0.23 (lit.[10] R_f 0.23); (3) Whatman No. 1, 4:1 phenol–water, R_f 0.49 (lit.[10] R_f 0.48).

Registry No.—**1**, 56599-17-8; **6a**, 56599-18-9; **6b**, 56599-19-0; **7b**, 56599-20-3; **8b**, 56599-21-4; **9a**, 56599-22-5; **9b**, 56599-23-6; **13**, 2207-52-5; **14**, 100-26-5; **15a**, 56599-24-7; **15b**, 56650-75-0; **16a**, 56599-25-8; **16a** HCl, 56599-26-9; **16b**, 56599-27-0; **17**, 56650-76-1; **18**, 56599-29-1; **19**, 56599-29-2; **20**, 56599-30-5; trichloroacetyl chloride, 76-02-8; anisyl alcohol, 105-13-5; 2,4-dimethoxybenzyl alcohol, 7314-44-5; ozone, 10028-15-6; *m*-chloroperbenzoic acid, 937-14-4.

References and Notes

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(8) Solvent evaporations were carried out in vacuo using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian T-60 spectrometer; peak positions are given as δ values in $CDCl_3$ (unless otherwise noted) downfield from tetramethylsilane as internal standard, expect that sodium trimethylsilylpropanesulfonate was used as internal standard in aqueous solutions. Mass spectra were obtained on an AEI MS-12 and high-resolution mass spectra were obtained on a CEC 21-110B spectrometer. Gas chromatography was performed on a Varian 90-P chromatograph. Thin layer chromatography (TLC) was performed on plates utilizing Camag D-5 silica gel unless otherwise specified. E. Merck silica gel 60 was employed for column chromatography. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.
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(10) Referred to as compound "282" in ref 2 and later shown to be identical with tabtoxinine-δ-lactam (1): ref 1.

General Methods of Alkaloid Synthesis. XI. Total Synthesis of the Sceletium Alkaloid A-4 and an Improved Synthesis of (±)-Mesembrine

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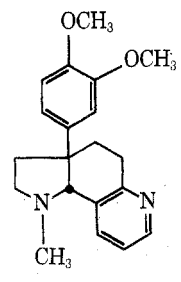
An efficient total synthesis of the pharmacologically interesting alkaloid Sceletium A-4 (1) is presented together with an improved synthesis of mesembrine (3). Key steps in these syntheses utilize the acid-promoted rearrangement of cyclopropylimine 9 to 2-pyrroline 10 and acid-catalyzed annelation of this intermediate with methyl vinyl ketone or methyl 5-oxohept-6-enoate.

Interest in the so-called Mesembrine alkaloids[3] has been renewed with the discovery[4–7] of several new bases found in various *Sceletium* species. Extracts of these plants are used by the natives of Southwest Africa in the preparation of a pharmacologically interesting drug known as "Channa" or "Koegoed". Since nearly all of the alkaloids from these plants which have been isolated thus far are not available in sufficient quantity for biological evaluation, we have been actively pursuing a program of total synthesis.[8,9] Of particular interest in the present study are the pyridine alkaloids Sceletium A-4 (1) and its seco analog tortuosamine (2).[6,7] These two substances represent completely new structural types and differ from the more common Mesembrine alkaloids such as mesembrine itself (3) by the interesting addition of a fused pyridine ring.



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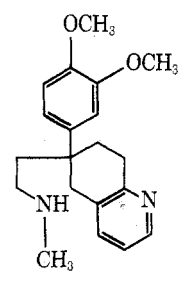

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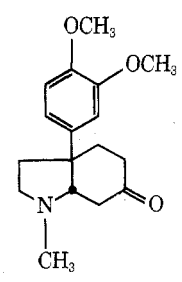

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