# Total Synthesis of the Indole Alkaloids *dl*-Eburnamonine and *dl*-Vincamine

**J. L. Herrmann, R. J. Cregge, J. E. Richman, G. R. Kieczykowski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss, and R. H. Schlessinger***

*Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627.* *Received August 30, 1978*

**Abstract:** High yield total syntheses of racemic eburnamonine (**1**) and vincamine (**2**) are described. These syntheses utilize the tricyclic lactam **3** as a common intermediate. The latter compound is convergently prepared from tryptamine hydrochloride and 5-bromo-2-ethylvaleryl chloride. The lactam **3** is transformed via its dianion **4** into eburnamonine (**1**) by reaction with methyl bromoacetate followed by Bischler cyclization. Reduction of the resulting imine salt and subsequent lactamization afford **1** in 65% overall yield. Vincamine (**2**) is prepared by reaction of dianion **4** with methyl-2-methylthioacrylate. Bischler cyclization, imine reduction, and oxidative cyclization stereospecifically afford **2** in 40% overall yield.

## Introduction

Eburnamonine (**1**) and vincamine (**2**) are pentacyclic indole alkaloids isolated from the plants *Hunteria eburnea* (Apocyanaceae)[1] and *Vinca minor* (Apocyanaceae),[2] respectively. Eburnamonine is useful as a cerebrovascular agent,[3] while vincamine exhibits significant activity as an antihypertensive and sedative agent.[4] As a result, considerable activity with respect to the development of efficient total syntheses of these molecules has been forthcoming.[5,6]

In addition to the potential medicinal value of these alkaloids, our interest in their total synthesis stemmed from the possibility of constructing them from a common intermediate, lactam **3**—a substance which contains three of the requisite five rings present in these molecules but none of the required chiral centers. An intriguing synthetic possibility utilizing **3** involved selective carbon alkylation of the dianion **4**. In principle, the latter species could be obtained by deprotonation of both the hydrogen carried by the indole nitrogen and the methine hydrogen of the lactam. Addition of a two-carbon electrophile to the dianion would lead to eburnamonine, while addition of a three-carbon electrophile to **4** would provide an entrée to vincamine.[7] Hypothetically, the synthesis of these alkaloids reduced to two problems: finding a means of preparing **3** and development of methodology conducive to the chemoselective use of **4** as a nucleophile.

## Results

**i. Preparation of the Tricyclic Lactam 3.** At the outset of this work, the literature showed that Wenkert not only had prepared **3** but had successfully utilized this lactam for the stereospecific preparation of eburnamonine (**1**).[5] The reported preparation of **3**, although reproducible, did not give a high yield of the lactam, and attempts to improve this reaction sequence proved futile in our hands.[8] Thus, it was incumbent upon us to develop an alternative means of securing **3** in quantities sufficient for its elaboration into the target natural product.

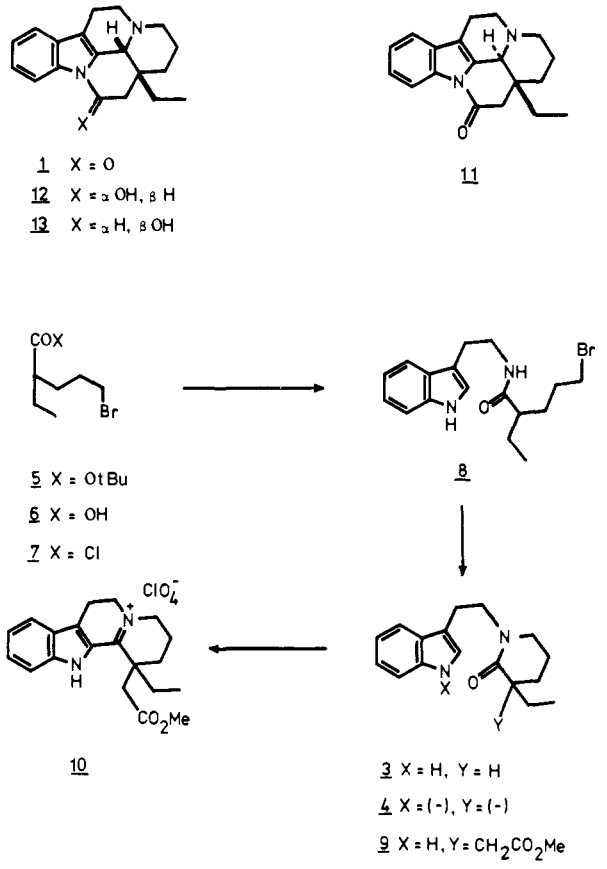
To this end, we carried out the preparation of **3** starting from *tert*-butyl butyrate. Reaction of *tert*-butyl butyrate with lithium diisopropylamide at −78 °C forms its corresponding ester enolate which on reaction with a 50% excess of 1,3-dibromopropane affords the bromo ester **5** in 85% yield.[9] Refluxing **5** in benzene solution containing a catalytic amount of *p*-toluenesulfonic acid and dimethylformamide gave the corresponding carboxylic acid **6**. Without further purification, we converted **6** into the acid chloride **7** using oxalyl chloride in benzene. After removal of the benzene solvent, **7** was immediately reacted with tryptamine hydrochloride and lithium hydride in THF solution. The amide **8** (mp 104–105 °C) was obtained from this reaction sequence in 90% overall yield from the ester **5**.

The existing literature method for the conversion of **8** into the lactam **3** gave a mixture of products.[5] It was clear from spectral analysis that considerable intramolecular cyclization by oxygen displacement of the bromide had occurred. To circumvent this problem, a THF solution of the amide was deprotonated by slow addition of it to a heated suspension (60 °C) of potassium hydride (2.1 equiv)[10] in THF. Cyclization of **8** was rapid under these conditions and a crude yield of 97.5% was obtained for **3** (mp 118–123 °C, lit.[5] mp 124–125 °C). Further purification of the lactam was not necessary for the subsequent transformations described therein.

**ii. Preparation of Eburnamonine (1).** With the tricyclic lactam **3** "in hand", we were ready to commence the elaboration of this substance into our target natural products. As stated at the outset of this manuscript, it had been our intention to generate the dianion **4** from **3** in the hope that we could realize selective carbon alkylation of the lactam enolate. In order to confirm the feasibility of generating this dianion, we treated **3** with 2 equiv of lithium diisopropylamide at −78 °C. Somewhat to our surprise, a white solid believed to be **4** precipitated from solution. Deuteration of this heterogeneous mixture gave clean monodeuteration of the lactam residue of **3** according to mass spectral analysis. Encouraged by this result, we then carried out an alkylation of the dianion at −78 °C with methyl bromoacetate. To our gratification, a single product was obtained in 95% crude yield that exhibited spectroscopic properties consistent with those anticipated for the lactam ester **9**. Furthermore, the material isolated from this alkylation was of sufficient quality so that purification for subsequent use was not warranted.

It was at this juncture in our effort that we drew upon the elegantly crafted results of Wenkert to complete this synthesis.[5] Thus, Bischler cyclization of **9** with phosphorus oxychloride in acetonitrile followed by precipitation with lithium perchlorate gave the crystalline immonium perchlorate **10** in 90% yield (mp 102–110 °C). Consistent with Wenkert's findings, hydride reduction of the imine portion of **10** gave a 1:1 mixture of cis and trans tetracyclic bases. Also consistent with Wenkert's findings was the observation that catalytic reduction of **10** with palladium on carbon gave a different mixture of bases. Treatment of these tetracyclic materials with methoxide in methanol gave in 92% yield an 85:15 mixture of the pentacyclic alkaloids eburnamonine (**1**) and epieburnamonine (**11**), respectively. These materials were readily separated by chro-

0002-7863/79/1501-1540$01.00/0 © 1979 American Chemical Society

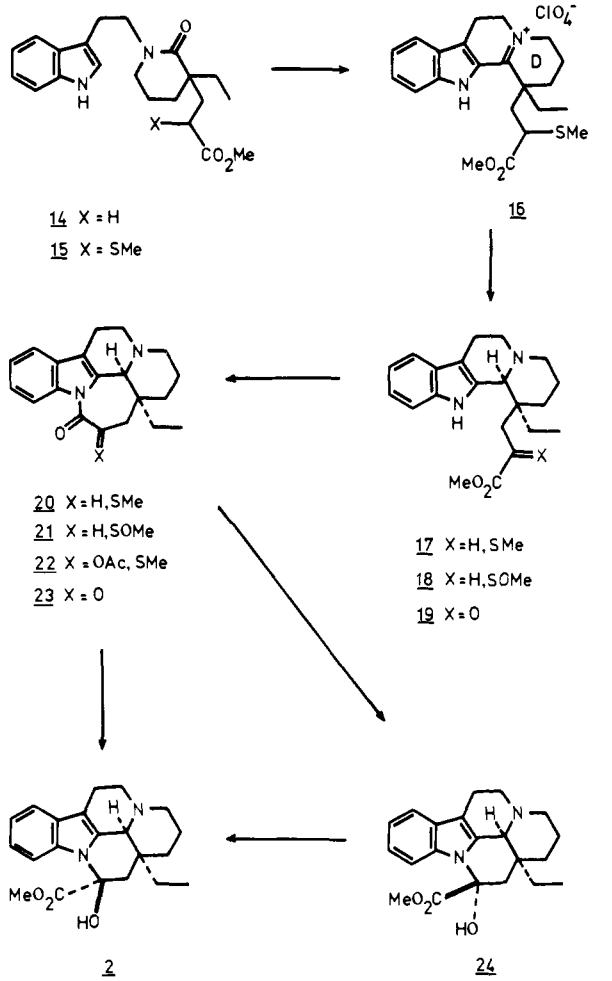



matography to give a 77% yield of racemic **1** (mp 200–202 °C, lit.[5] mp 201–202 °C). Additionally, lithium aluminum hydride reduction of **1** afforded eburnamine (**12**) and epieburnamine (**13**) in an 8:2 mixture, respectively. Chromatography of this mixture gave pure racemic **12** (mp 178–181 °C, lit.[2e] mp 179–181 °C). An overall yield of 65% was obtained for eburnamonine, while an overall yield of 50% was obtained for eburnamine.

iii. **Preparation of Vincamine (2).** Our opening gambit for the preparation of vincamine involved combination of the dianion **4** with a three-carbon nucleophile. Since the terminus of this electrophile ultimately was to be a methyl ester, the logical choice for the three-carbon unit was an electron-deficient olefin. Methyl acrylate immediately came to mind, and we attempted a reaction between it and the dianion. Although the desired adduct **14** was obtained, a material comprised of the elements of **4** and two acrylate residues also was obtained. Thus, the ester enolate resulting from conjugate addition was almost as reactive as **4**, suggesting that the reaction required termination with a less energetic ester enolate. Furthermore, it was desirable to use an electron-deficient olefin with "memory" on the $\alpha$ carbon since this atom in vincamine has a ketone oxidation state (e.g., a hydroxyl group and to the indole nitrogen). A simple solution to both problems was to employ an acrylate derivative bearing a latent carbonyl function on the $\alpha$ position—methyl 2-methylthioacrylate was chosen for this purpose.[11] This electrophile would yield a stable ester enolate upon reaction with the dianion **4**, and in addition it contains functionality conducive to the elaboration of its $\alpha$ carbon into the ketone oxidation state.

Reaction of **4** with a 10% excess of methyl 2-methylthioacrylate at −78 °C gave rise to a 1:1 adduct, **15,** in essentially quantitative yield. This adduct consisted of a mixture of two epimeric materials which may be separated by liquid chromatography into compounds melting at 82–83 and 105–106 °C. The epimeric mixture (mp 90–95 °C) was used for all subsequent experiments, thus accounting for the melting point ranges reported for compounds **15–21** inclusively.

With all of the required carbon atoms now assembled, we were ready to address the first of two ring-closure reactions necessary to complete the synthesis. Cyclization of the lactam portion of **15** onto the indole ring was carried out in refluxing acetonitrile containing phosphorus oxychloride. The crude reaction mixture was treated with lithium perchlorate to give the immonium perchlorate **16** (mp 88–96 °C) in 93% yield. We had assumed from the outset of this work that hydride reduction of **16** would be considerably more stereospecific than that observed for reduction of the immonium salt **10.** This premise was based on the considerably greater steric bulk of the methyl 2-methylthiopropionate group of ring D relative to the geminal ethyl group. Thus, reduction of the immonium salt **16** with lithium tri-*tert*-butoxyaluminum hydride led exclusively to the desired cis stereochemistry for the tetracyclic base **17** (mp 102–104 °C). Sodium borohydride reduction of **16** gave a 4:1 mixture of **17** and its trans isomer, respectively.




Somewhat to our surprise, establishment of ring E of vincamine evolved into the most testing aspect of this synthesis, and our experimental solution, although gratifyingly efficient, was ad hoc in nature. We had originally conceived of using the sulfoxide analogue of **17,** compound **18,** within the context of a Pummerer rearrangement to secure the pyruvate **19** or its ring-closed analogue vincamine (**2**).[12] To this end, **17** was oxidized in 96% yield to the sulfoxide **18** (mp 110–115 °C) with *m*-chloroperbenzoic acid in methylene chloride. However, all attempts to obtain either **19** or **2** were not successful in acidic medium. The fate of **18** under these conditions yet remains a conundrum.

We then attempted to ring close the $\alpha$-methylthio ester **17** with base in the hope of securing compound **20**—a seven-membered-ring lactam system. It was our intention to oxidize this material into the corresponding sulfoxide **21,** and then to

carry out a Pummerer rearrangement to obtain the corresponding α-keto lactam **22.** Several attempts to form **20** from **17** by generation of the indole anion followed by cyclization were without success. Deuteration experiments indicated that both the indole anion and the α-methylthio ester enolate were generated under a variety of conditions, resulting in an electronically unfavorable circumstance for cyclization. Base-induced cyclization with the sulfoxide **18** was then attempted. Our rationale for trying this reaction was based on the following naive speculation. We felt that treatment of **18** with base under aprotic conditions surely would lead to formation of both the indole anion and the α-methylthiooxy ester enolate. Owing to the inherently greater electron-delocalizing ability of the α-sulfoxide residue relative to the α-sulfide residue, it was our hope that the ester moiety would retain sufficient reactivity as an electrophile to undergo intramolecular cyclization with the indole nitrogen. Such was found to be the case, for, when **18** was treated with 2 equiv of sodium hydride in THF solution, the lactam sulfoxide **21** (mp 75–77 °C) was obtained in 98% yield.

At this point, we intended to convert the lactam sulfoxide **21** into vincamine (**2**) by reaction of the sulfoxide with acetyl chloride to form the α-acetoxy sulfide **22.** Treatment of **22** with methoxide should yield the α-keto lactam **23** which, by attack of methoxide at the lactam carbonyl, would ring open into the methyl pyruvate derivative **19.** The latter was expected to undergo spontaneous ring closure into either vincamine (**2**) or epivincamine (**24**).

It seemed experimentally feasible to carry out this sequence of reactions in one pot; thus we treated **21** with 2.2 equiv of acetyl chloride followed by addition of 2.5 equiv of sodium methoxide in methanol. After stirring for 6 h, the reaction mixture was worked up in the usual manner to afford epivincamine (mp 203–204 °C). The latter substance was then further reacted with sodium methoxide (4 equiv) in methanol for 24 h to give pure *dl*-vincamine (mp 225–227 °C) in 80% yield. Alternatively, reaction of **21** with acetyl chloride (2.2 equiv) followed by treatment with sodium methoxide (7 equiv) for 24 h gave rise directly to vincamine in 85% yield.

The latter reaction concluded our synthetic construction of the natural product which proceeded in 40% overall yield. Comparison of synthetic vincamine with the naturally occurring racemic alkaloid showed these substances to be identical in all respects.[13] The utility of the dianion **4** as a nucleophilic component in the elaboration of indole alkaloids has been demonstrated by these syntheses, and it is our intention to employ it further in the elaboration of other natural products.

## Experimental Section[14]

**Preparation of *tert*-Butyl Butyrate.** To dry diethyl ether (250.0 mL) containing *tert*-butyl alcohol (103.0 mL, 81.4 g, 1.1 M) and *N,N*-dimethylaniline (152.0 mL, 145.2 g, 1.2 M) at 22 °C was added over 45 min butyryl chloride (124.0 mL, 127.9 g, 1.2 M). The reaction was heated to reflux with stirring for 20 h, cooled to 22 °C, diluted with water (100 mL), and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with 10% sulfuric acid, water, saturated sodium bicarbonate, and water until the aqueous wash was neutral. Filtration through anhydrous sodium sulfate followed by evaporation without external heating was continued until the total volume was 200 mL, at which point it was distilled at atmospheric pressure. After the residual ether was distilled, 103.0 g (65%) of *tert*-butyl butyrate was collected: bp 142–143 °C; IR ($CHCl_3$) 1725 $cm^{-1}$; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.40 (s, 9 H), 1.62 (m, 2 H), 2.20 (t, 2 H); mass spectrum *m/e* 144 (parent).

**Preparation of *tert*-Butyl α-Ethyl-δ-bromovalerate (5).** To a solution of diisopropylamine (6 mL, 8.8 g, 0.044 M) in dry tetrahydrofuran (40 mL) maintained at 4 °C was added a 2.2 M solution of *n*-butyllithium in hexane (20 mL, 0.044 M). After 15–20 min, the solution was cooled to −78 °C and *tert*-butyl butyrate (5.9 g, 0.041 M) was added (5 min). The mixture was stirred for 30 min at −78 °C, at which time 1,3-dibromopropane (12.1 g, 0.060 M) was added rapidly, followed by hexamethylphosphoramide (HMPA) (2.1 mL, 2.3 g, 0.013 M). After an additional 30 min at −78 °C, the reaction was transferred to an ice–water bath for 1 h. The reaction was acidified with 5% HCl and extracted with *n*-hexane. The organic solution was dried by filtration through anhydrous magnesium sulfate and then evaporated at reduced pressure. The resulting oil was distilled at 75–76 °C (0.8 mm) to give 10 g of **5**: 85% yield; IR ($CHCl_3$) 1725 $cm^{-1}$; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.41 (s, 9 H), 1.70 (m, 6 H), 2.18 (m, 1 H), 3.40 (t, 2 H).

**Preparation of α-Ethyl-δ-bromovaleric Acid (6).** To a solution of *p*-toluenesulfonic acid (1.4 g, 0.0075 M) in dry benzene (150 mL) was added **5** (5.8 g, 0.022 M) at 22 °C. The resulting mixture was heated to reflux for 1.5 h and then allowed to cool to 22 °C. The solution was washed with water (150 mL) and the aqueous layer was reextracted with benzene. The combined organic phases were then washed three times with an equal volume of water, dried through anhydrous magnesium sulfate, and evaporated to give 4.9 g of crude **6** (95% yield), used without further purification in the conversion to the acid chloride **7**; IR ($CHCl_3$) 1710 and 2600–3400 $cm^{-1}$; NMR ($CDCl_3$) δ 0.96 (t, 3 H), 1.78 (m, 6 H), 2.32 (m, 1 H), 3.42 (t, 2 H), 11.28 (s, 1 H).

**Preparation of α-Ethyl-δ-bromovaleryl Chloride (7).** The crude bromo acid (4.0 g, 0.019 M) was dissolved in dry benzene (80 mL) and cooled to 4 °C. Oxalyl chloride (2.8 mL, 4.19 g, 0.033 M) was added dropwise, followed by a catalytic amount of dimethylformamide. The reaction was heated to 40 °C and stirred for 1 h, whereupon the solvent was evaporated at reduced pressure to afford the crude acid chloride **7**, used without purification in the preparation of the bromo amide **8**, IR ($CHCl_3$) 1785 $cm^{-1}$.

**Preparation of Bromo Amide 8.** The crude acid chloride **7** was dissolved in THF (60 mL) and cooled to 0 °C. Tryptamine hydrochloride (3.7 g, 0.019 M) was added followed by the addition of lithium hydride (0.46 g, 0.057 M). The reaction was maintained at 4 °C for 1.5 h, until the evolution of gas had ceased, and then allowed to warm to 22 °C for 3 h, at which time the reaction appeared complete by TLC. The reaction was acidified to pH 4.0 by the addition of 10% HCl and extracted four times with an equal volume of methylene chloride. Filtration through anhydrous sodium sulfate and evaporation of the solvent at reduced pressure resulted in the formation of a white precipitate, which was collected by filtration (1.95 g, mp 105.5–106 °C). The filtrate was evaporated at reduced pressure to give a tan residue, which was dissolved in warm benzene. Petroleum ether was added and the product was allowed to crystallize, affording 4.02 g of **8**: 90% total yield; mp 104–105 °C; IR ($CHCl_3$) 1660, 3200–3400 (br), 3425 (sh), 3495 $cm^{-1}$; NMR ($CDCl_3$) δ 0.84 (t, 3 H), 1.62 (m, 7 H), 2.96 (t, 2 H), 3.28 (t, 2 H), 3.64 (q, 2 H), 5.68 (br s, 1 H), 6.82–7.40 (m, 4 H), 7.86 (m, 1 H), 8.56 (s, broad, 1 H).

**Preparation of Lactam 3.** An oil dispersion of potassium hydride was washed five times with hexane and dried under nitrogen to a constant weight of 0.226 g (5.6 mM). THF (1 mL) was added and the resulting suspension heated to 60 °C, whereupon a solution of the bromo amide **8** (0.758 g, 2.16 mM) in 2.2 mL of tetrahydrofuran was added dropwise at 60 °C to the KH suspension over a 40-min period. After the suspension was stirred for an additional 20 min at 60 °C, a pale yellow precipitate was formed. The reaction mixture was cooled to 0 °C, acidified to pH 2.0 with 10% aqueous HCl, and extracted with methylene chloride; the organic solution was dried by filtration through anhydrous magnesium sulfate and then evaporated to dryness at reduced pressure. The residue was dissolved in methylene chloride, the solution was concentrated, and hexane was added until the solution became cloudy. Evaporation of the solvent afforded 0.566 g of **3**: mp 118–123 °C (lit.[8] mp 124–125 °C); 97.5% yield; IR ($CHCl_3$) 1620, 3200–3400 (br), 3495 $cm^{-1}$; NMR ($CDCl_3$) δ 0.82 (t, 3 H), 1.20–2.00 (m, 6 H), 2.20 (m, 1 H), 3.08 (m, 4 H), 3.60 (t, 2 H), 6.82–7.40 (m, 4 H), 7.86 (m, 1 H), 9.15 (s, br, 1 H); UV (EtOH) 220, 280 nm; mass spectrum *m/e* 270 (parent), 143 (100).

**Preparation of Lactam 9.** To a solution of diisopropylamine (0.224 mL, 1.6 mM) in dry THF (1.2 mL) maintained at 0–5 °C was added a 2.4 M solution of *n*-butyllithium in hexane (0.668 mL, 1.6 mM). After 15–20 min, the solution was cooled to −78 °C, at which time a solution of the tricyclic lactam **3** (0.216 g, 0.8 mM) in THF (0.8 mL) was added at a moderate rate. This solution was stirred at −78 °C until a white precipitate was formed, at which time methyl bromoacetate (0.306 g, 2.0 mM) was added. After stirring for an additional 30 min, the reaction mixture was quenched with a saturated ammonium chloride solution and extracted with methylene chloride.

The organic extract was dried by filtration through anhydrous magnesium sulfate and evaporated to dryness at reduced pressure to give 0.256 g of **9** determined by NMR to be 95% pure: IR ($CHCl_3$) 1625, 1730, 3200–3400 (br), 3495 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.84 (m, 3 H), 1.68 (m, 6 H), 2.52 (AB system, 2 H), 2.80–3.40 (m, 6 H), 3.52 (s, 3 H), 6.80–7.24 (m, 4 H), 7.50 (m, 1 H), 8.86 (s, 1 H); UV (EtOH) 220, 280 nm; mass spectrum *m/e* 342 (parent), 143 (100).

**Preparation of Immonium Perchlorate Salt 10.** To a solution of lactam ester **9** (0.065 g, 0.19 mM) in acetonitrile (4.2 mL) at 22 °C was added phosphorus oxychloride (520 $\mu$L, 0.872 g, 5.70 mM). The solution was heated to reflux (oil bath maintained at 100 °C) for 14 h, at which time it was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in water (0.4 mL) and heated to reflux for 35 min. This solution was filtered while still hot into a solution of lithium perchlorate (0.04 g, 0.38 mM) in water (0.2 mL). Upon cooling the aqueous solution, a crystalline material was formed. Filtration afforded 0.067 g (90%): mp 102–110 °C; IR ($CHCl_3$) 760, 110, 1250, 1620, 1730 $cm^{-1}$; UV (EtOH) 215, 355 nm.

**Catalytic Reduction of 10.** A suspension of the salt **10** (0.215 g, 0.51 mM), 10% palladium on charcoal (0.078 g, 28% by weight), and 70% perchloric acid (0.45 $\mu$L, 0.005 mM) in methanol (16 mL) was degassed three times. Hydrogen gas was added at a positive pressure of 2 cm until reduction was complete. The suspension was then filtered to remove the catalyst and the methanol was evaporated at reduced pressure. The residue was dissolved in chloroform and partitioned against a saturated ammonium acetate solution. The combined chloroform extracts were filtered through anhydrous magnesium sulfate and evaporated to dryness under reduced pressure, giving a mixture of methyl eburnamoninate and epieburnamoninate of undetermined composition.

**Preparation of Eburnamonine.** The mixture of esters obtained from the preceding experiment (0.030 g, 0.092 mM) was dissolved in a 0.1 M solution of sodium methoxide in methanol (2.5 mL) at 22 °C and stirred for 12 h. To this solution was added a saturated solution of ammonium acetate and the reaction was then extracted with chloroform. The chloroform extract was filtered through anhydrous magnesium sulfate and evaporated to dryness at reduced pressure. The residue (0.024 g) was chromatographed on a thick layer plate using chloroform as the eluting solvent to give 0.005 g (13.7%) of epieburnamonine (**11**), mp 133–136 °C (lit.[8] mp 135.5–137 °C), and 0.019 g (77.5%) of eburnamonine (**1**), mp 200–202 °C (lit.[8] mp 201–202 °C). Spectral data for eburnamonine are as follows: IR ($CHCl_3$) 1620, 1690 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.86 (t, 3 H), 1.06–3.10 (m, 12 H), 3.30 (t, 2 H), 3.96 (s, 1 H), 7.32 (m, 3 H), 8.44 (m, 1 H).

**Preparation of Eburnamine.** To a suspension of **1** (0.030 g, 0.102 mM) in THF (0.5 mL) maintained at 0–5 °C was added lithium aluminum hydride (0.008 g, 0.204 mM). After 20 min at 0–5 °C, the reaction was quenched by the addition of saturated sodium sulfate solution and extracted three times with ether. The combined ether extracts were filtered through anhydrous sodium sulfate and the solvent was removed at reduced pressure to give 0.029 g of a mixture of eburnamine (**12**) and isoeburnamine (**13**) in the ratio 58:42, as determined by high-pressure liquid chromatographic analysis. The mixture was dissolved in a 0.1 M solution of sodium methoxide in methanol (0.25 mL) and heated to 70 °C for 12 h. The reaction was quenched by the addition of saturated ammonium acetate solution and extracted with methylene chloride. The organic extract was filtered through anhydrous magnesium sulfate and the solvent was removed at reduced pressure. The ratio of eburnamine to isoeburnamine had increased to 79:21. A sample of eburnamine isolated by high-pressure liquid chromatography (LC) had a melting point of 178–181 °C (lit.[2e] mp 179–181 °C). Spectral data obtained for eburnamine were identical with those reported in the literature.

**Preparation of Lactam 15.** Compound **3** (1.62 g, 6.0 mM) dissolved in THF (7 mL) was added at −78 °C to lithium diisopropylamide (13.2 mM) in THF (14 mL). The resulting mixture was stirred for 1 h, whereupon methyl 2-methylthioacrylate (0.95 g, 7.2 mM) dissolved in THF (7 mL) was added over 10 min. After stirring for 1 h at −78 °C, the reaction mixture was quenched at this temperature with 10% HCl, extracted with methylene chloride, dried by filtration through magnesium sulfate, and evaporated to a brown oil. The oil was taken into a 1:1 mixture of ether and ethyl acetate extracted with 5% HCl and 5% sodium hydroxide, dried by filtration through magnesium sulfate, and evaporated to give **15** (2.36 g, 98%) as a cream-colored solid. Recrystallization from benzene–petroleum ether gave material melting at 105–106 °C. This material could be separated by LC ($CHCl_3$, 1.5 mL/min) into two epimeric materials of mp 109–110 and 83–84 °C. The spectral data recorded were on a mixture of these epimers (mp 100–102 °C): IR ($CHCl_3$) 3480 (m), 1730 (s), 1675 (s) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.83 (t, 3 H), 1.60 (m, 7 H), 2.10 (s, 2 H, SMe), 2.15 (s, 1 H, SMe), 2.42 (m, 1 H), 3.05 (m, 4 H), 3.60 (m, 3 H), 3.75 (s, 3 H), 7.20 (m, 4 H), 7.60 (d, 1 H), 8.50 (br s, 1 H); mass spectrum (parent) *m/e* calcd 402.1977, obsd 402.1966. Anal. Calcd for $C_{22}H_{30}N_2O_3S$: C, 65.64; H, 7.51; N, 6.96. Found: C, 65.69; H, 7.48; N, 6.95.

**Preparation of Immonium Perchlorate Salt 16.** A solution of **15** (1.08 g, 2.5 mM), phosphoryl chloride (8 mL), and acetonitrile (30 mL) was refluxed at 100 °C for 14 h. The mixture was then stirred to dryness, whereupon a saturated solution of lithium perchlorate (0.530 g) was added. Upon cooling to 4 °C, a yellow solid was deposited which on removal of water and drying gave **16** (1.08 g, 93%): mp 86–96 °C; IR ($CHCl_3$) 3300 (w), 1735 (m), 1700 (m), 1525 (m), 1440 (m), 1335 (s), 1100 (s) $cm^{-1}$. Mass spectrum and $^1H$ NMR data could not be obtained for this material.

**Preparation of Tetracyclic Base 17.** To a solution of the perchlorate **16** (0.328 g, 0.68 mM) dissolved in THF (1.5 mL) at 4 °C was added a solution of lithium tri-*tert*-butoxyaluminum hydride (0.535 g, 2.16 mM) dissolved in THF (2.5 mL). The reaction was then stirred at 22 °C for 3 h and then quenched by addition of a mixture of saturated sodium sulfate and methylene chloride. The organic extract was dried by filtration through magnesium sulfate and then evaporated to dryness. Chromatography on alumina (activity grade II, 2 g) using 1:1 ether–chloroform as the eluant gave **17**: mp 101–103 °C; 0.259 g, 98.5%. Two recrystallizations from ether–petroleum ether gave material of mp 103–104.5 °C. Physical data are reported for this material: mp 101–103 °C; IR ($CHCl_3$) 3500 (m), 2940 (s), 1725 (s), 1460 (m), 1155 (s) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.08 (d of t, 3 H), 1.66 (m, 6 H), 1.95 (s, 3 H), 2.80 (m, 9 H), 3.58 (s, 3 H), 3.60 (m, 1 H), 7.20 (m, 4 H), 7.71 (br s, 1 H); mass spectrum *m/e* 386. Anal. Calcd for $C_{22}H_{30}N_2O_2S$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.41; H, 7.80; N, 7.24.

**Preparation of Tetracyclic Sulfoxide 18.** A mixture of **17** (0.22 g, 0.575 mM), 85% pure *m*-chloroperbenzoic acid (0.232 g, 1.150 mM), anhydrous sodium carbonate (0.037 g, 0.35 mM), and methylene chloride (3.5 mL) was stirred at 22 °C until the reaction was determined to be over by thin layer chromatography. The reaction mixture was then evaporated to dryness and the resulting mass chromatographed on neutral alumina (grade II, 1.0 g) using chloroform as the eluant. Evaporation of the eluant gave **18** as white crystals: mp 110–115 °C; 0.220 g, 95%; IR ($CHCl_3$) 3500 (m), 2940 (m), 1725 (s), 1045 (m) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.06 (t, 3 H), 1.67 (m, 6 H), 2.20 (s, 3 H), 2.63 (m, 4 H), 3.60 (m, 5 H), 3.90 (s, 3 H), 4.20 (m, 1 H), 7.20 (m, 4 H), 8.40 (br s, 1 H); mass spectrum *m/e* 402.

**Preparation of Pentacyclic Lactam Sulfoxide 21.** Compound **18** (0.1 g, 0.284 mM) in THF (2 mL) was added to a suspension of pentane washed sodium hydride (0.025 g, 0.59 mM) in THF at 4 °C. The reaction was stirred at 0 °C for 1 h, quenched with saturated ammonium chloride, and extracted with methylene chloride. Evaporation of the organic extracts followed by chromatography of the residue on neutral alumina (grade II, 1.0 g) gave, on elution with chloroform and evaporation of the eluant, **21** as a white solid: 0.092 g, 98%; mp 75–77 °C; IR ($CHCl_3$) 2940 (m), 1675 (s), 1450 (s), 1375 (m), 1030 (m) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.96 (t, 3 H), 1.45 (m, 6 H), 1.95–3.80 (m, 9 H), 2.60 (s, 1 H, SOMe), 2.80 (s, 2 H, SOMe), 4.00 (br s, 1 H), 7.30 (m, 3 H), 8.30 (m, 1 H); mass spectrum *m/e* 370.

**Preparation of Vincamine (2).** To a solution of **21** at 4 °C (0.024 g, 0.0648 mM) in methylene chloride (148 $\mu$L, degassed by bubbling $N_2$ through the solvent) was added acetyl chloride (9.87 $\mu$L, 0.163 mM, degassed by three freeze–thaw cycles). The mixture was stirred at 4 °C for 7 min, warmed to 22 °C for 15 min, and then treated with sodium methoxide prepared from sodium metal (0.010 g, 0.435 mM) and methanol (800 $\mu$L). The resulting mixture was then stirred at 22 °C for 24 h, worked up by addition of saturated ammonium chloride, extracted with methylene chloride, and dried by filtration through magnesium sulfate. Evaporation of the extracts gave crystalline racemic vincamine (**2**): 0.0195 g, 85%; mp 225–227 °C; IR ($CHCl_3$) 3500 (br, OH), 2935 (m), 2840 (sh), 1730 (s, C=O) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.95 (t, 3 H), 1.40 (m, 6 H), 2.07 (q, 2 H), 2.60 (m, 3 H), 2.98 (m, 2 H), 3.28 (m, 2 H), 3.85 (s, 3 H), 3.90 (br s, 1 H), 7.22 (m, 3 H), 7.52 (m, 1 H); mass spectrum (rel intensity) *m/e* 354 (100), 295 (50), 267 (60), 252 (70), 237 (15), 224 (25). Authentic naturally occurring racemic vincamine obtained from Professor M. P. Cava (Department of Chemistry, University of Pennsylvania) with a melting

point of 225–227 °C exhibited spectral and chromatographic behavior identical with that of the synthetic material described above.

**Acknowledgment.** We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Hoffmann-La Roche Foundation, and the Shermann-Clark Fund for support of this work.

## References and Notes

(1) For isolation and structure proof of eburnamonine, see (a) M. F. Bartlett, W. I. Taylor, and Raymond-Hamet, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **249**, 1259 (1959); (b) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960); (c) J. Mokrý, I. Kompiš, and P. Šefčovič, *Tetrahedron Lett.*, 433 (1962).

(2) (a) E. Schlittler and R. Furlenmeier, *Helv. Chim. Acta*, **36**, 2017 (1953); (b) J. Trojánek, O. Štrouf, J. Holubek, and Z. Čekan, *Tetrahedron Lett.*, 702 (1961); (c) J. Mokrý, M. Shamma, and H. E. Soyster, *ibid.*, 999 (1963); (d) M. F. Bartlett, R. Sklav, A. F. Smith, and W. I. Taylor, *J. Org. Chem.*, **28**, 2197 (1963); (e) J. Trovjánek, Z. Koblicová, and K. Bláha, *Chem. Ind. (London)*, 1261 (1965).

(3) (a) M. F. Bartlett, W. I. Taylor, and Raymond-Hamet, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **240**, 1470 (1955); (b) E. A. Trutneva and V. V. Berezhinskaya, *Farmakol. Toksikol.*, **29**, 171 (1966).

(4) (a) L. Szporny and K. Szász, *Arch. Exp. Pathol. Pharmakol.*, **236**, 296 (1959); (b) Z. Szabo and Z. Nagy, *Arzneim.-Forsch.*, **10**, 811 (1960); (c) L. Szporny and P. Gorog, *Arch. Int. Pharmacodyn. Ther.*, **138**, 451 (1962); (c) M. Foldi, F. Obal, and G. Szeghy, *Med. Welt*, **37**, 2122 (1965); (d) F. Solti, *Ther. Hung.*, **13**, 101 (1965).

(5) For total syntheses of eburnamonine and related alkaloids, see E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965); also see ref 1b. Very recently, a new and elegant approach to these substances has been reported by E. Wenkert, T. Hudlický, and H. D. Hollis Showalter, *ibid.*, **100**, 4893 (1978).

(6) For total syntheses of vincamine, see (a) J. F. D. Barton and J. Harley-Mason, *Chem. Commun.*, 298 (1965); (b) K. H. Gibson and J. E. Saxton, *ibid.*, 799, 1490 (1969); (c) K. H. Gibson and J. E. Saxton, *J. Chem. Soc., Perkin Trans. 1*, 2776 (1972); (d) C. Thal, T. Sevenet, H. P. Husson, and P. Potier, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **275**, 1295 (1972); (e) Atta-ur-Rahman, *J. Chem. Soc., Perkin Trans. 1*, 731 (1972); (f) C. Szántay, L. Szabo, and G. Kalaus, *Tetrahedron Lett.*, 191 (1973); (g) C. Thal, T. Imbert, H. P. Husson, and P. Potier, *Bull. Soc. Chim. Fr.*, 2010, 2013 (1973); (h) G. Hugel, J. Levy, and J. LeMen, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **274**, 1350 (1972); (i) D. L. Coffen, D. A. Katonak, and F. Wong, *J. Am. Chem. Soc.*, **96**, 3966 (1974); (j) P. Pfäffli, W. Oppolzer, R. Wenger, and H. Hauth, *Helv. Chim. Acta*, **58**, 1131 (1975); (k) C. Szántay, L. Szabo, and G. Kalaus, *Tetrahedron*, **33**, 1803 (1977); (l) W. Oppolzer, H. Hauth, P. Pfäffli, and R. Wenger, *Helv. Chim. Acta*, **60**, 1801 (1977). For the original synthesis of vincamine, see M. E. Kuehne, *J. Am. Chem. Soc.*, **86**, 2946 (1964).

(7) (a) For a preliminary report of this methodology leading to eburnamonine, see J. L. Herrmann, G. R. Keiczykowski, S. E. Normandin, and R. H. Schlessinger, *Tetrahedron Lett.*, 801 (1976). (b) For a preliminary description of the synthesis of vincamine prepared in this manner, see J. L. Herrmann, R. J. Cregge, J. E. Richman, C. L. Semmelhack, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **96**, 3702 (1974).

(8) Wenkert and Wickberg prepared **3** starting from diethyl ethylmalonate; see ref 5.

(9) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. F. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).

(10) Originally, 10 equiv of potassium hydride were used for this reaction; see ref 7b.

(11) A convenient and high yield preparation of this compound is described by K. D. Gundermann and H. Schulze, *Chem. Ber.*, **94**, 3254 (1961). For the application of this acrylate derivative in conjugate addition reactions, see R. J. Cregge, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2063 (1973).

(12) The inspiration for this intended sequence stemmed from similar work reported by Saxton.[6b]

(13) We thank Professor M. P. Cava, Department of Chemistry, University of Pennsylvania, for a generous sample of naturally occurring racemic vincamine.

(14) Melting points were taken on a Fisher-Johns melting point block and are reported uncorrected. Analyses were performed by Spang Microanalytical Laobratories, Ann Arbor, Mich. Reactions were run in either insulated cryostats (for temperatures of <0 °C) or thermostated silicone oil baths with a temperature accuracy of 1°. Solvents were evaporated to dryness using a rotary evaporator at steam-bath temperatures and reduced pressures. Anhydrous solvents were distilled immediately before use. Tetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane were distilled from lithium aluminum hydride, *tert*-butyl alcohol was distilled from calcium hydride, and methanol was distilled from magnesium turnings. Other solvents were at least reagent grade and used as received. Reagents were distilled at least once prior to use. Amines were distilled from calcium hydrogen under a nitrogen atmosphere. Hydrogenations were carried out in a slanted manifold all glass apparatus at 1 atm at 0 °C. The system was evacuated by a water aspirator and then filled with hydrogen while stirring (this was repeated four times). Thin layer chromatography was performed on microscope slides coated by dipping in a slurry of either silica gel G or silica gel HF-254 (Brinkman) suspended in chloroform. High pressure liquid phase chromatography was performed on a Water's Associates ALC-202 instrument equipped with both ultraviolet and differential refractometer detectors. Vapor phase chromatography was performed on a Hewlett-Packard 5700A instrument with TC detector and HP-5702A temperature programmer. Column chromatography was carried out using Brinkmann alumina. Infrared spectra were recorded on either a Perkin-Elmer 700 or a Perkin-Elmer 467 spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a JEOLCO C-60 HL or a JEOLCO MH-100 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal reference, and are expressed as $\delta$ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Ultraviolet spectra were recorded on a Perkin-Elmer Digital 602 spectrophotometer.

# A Total Synthesis of Racemic Avenaciolide

**John L. Herrmann, Mitchel H. Berger, and R. H. Schlessinger***

*Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627.* *Received August 30, 1978*

**Abstract:** A stereospecific total synthesis of racemic avenaciolide (**1**) has been realized in 64% overall yield starting from 5-*n*-octyl-2(5*H*)-furanone (**3**). The salient features of this synthesis include stereospecific substitution of both the $\beta$ and $\alpha$ positions of **3** via a conjugate addition–halogenation sequence, and transformation of an $\alpha$-methyl-$\alpha$-thiomethylbutyrolactone into an $\alpha$-methylene butyrolactone. The anion derived from ethyl propiolate has been utilized for the efficient synthesis of several 5-substituted 2(5*H*)-furanones.

## Introduction

Avenaciolide (**1**) is an antifungal agent first isolated by Turner from *Aspergillus avenaceaus*[1] and later by others from *Aspergillus fischeri*.[2] The structure of **1**, deduced by Turner from both degradation and nuclear magnetic resonance studies,[3] is an unusual $\alpha$-methylene bis(butyrolactone) system containing three chiral centers. The structurally novel nature of avenaciolide has prompted a measure of synthetic activity resulting in the description of three total syntheses.[4] Johnson was the first to synthesize **1**, beginning with tricarballylic acid,[4a] whereas Fraser-Reid prepared optically active **1** starting from D-glucose.[4c] These interesting and elegant syntheses, while starting from widely divergent substances, proceed to avenaciolide through a common intermediate, bislactone **2**.

Our own synthetic strategy involved a multiple-bond-forming process which combined one nucleophile with two electrophiles under aprotic conditions.[4b] This methodology, applied to an unsaturated carbonyl system, would yield a new carbonyl substance substituted in both the $\beta$ and $\alpha$ positions.

0002-7863/79/1501-1544$01.00/0 © 1979 American Chemical Society