Synthetic Studies on the Lythraceae Alkaloids. 11.[1] Model Studies for the Synthesis of Lythrancine V

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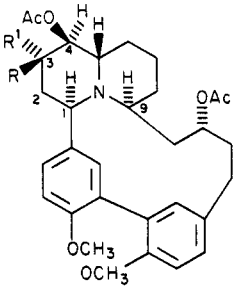
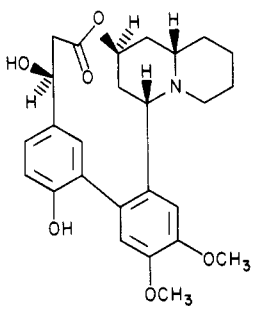
cis-1-(4-Methoxyphenyl)-3(e),4(e)-diacetoxyquinolizidine (**16**) was prepared via a stereoselective epoxidation of the corresponding olefin. The synthetic route was developed in a model study directed toward the synthesis of the type C Lythraceae alkaloids.

We have for some time, been interested in the synthesis of type C Lythraceae alkaloids.[2,3] These alkaloids contain a quinolizidine metacyclophane structure, **1**, as compared to the lactonic quinolizidine biphenyl structure of the type A alkaloids, **2**. An important difference between these is



1a, R = OAc; R¹ = H
b, R = H; R¹ = OAc



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the presence of vicinal dioxygen substitution in the quinolizidine ring of some type C alkaloids, for example, **1a** (lythrancine IV) or **1b** (lythrancine V). This substitution pattern interested us because we could find no other examples of vicinally dioxygenated quinolizidines. We report here the preparation of **16** as a model for the synthesis of these alkaloids.

The 1-aryl-3-quinolizidinone **3** was a key intermediate in the synthesis of **16**. The pelletierine condensation[5a] provided a convenient method for its preparation since the less stable *cis*-fused quinolizidinone **3** could be obtained as the major product. Thus, condensation of anisaldehyde with pelletierine in the presence of sodium hydroxide at 4 °C for 1.5 h afforded cis-fused [5b]quinolizidinone **3** in an isolated yield of 30%. Increasing amounts of the trans-fused isomer **4** were obtained at higher temperatures or longer reaction times. The two isomers could be conveniently separated by preparative high-performance liquid chromatography (HPLC).

Initial attempts at direct introduction of oxygen at C-4 were unsuccessful. Treatment of **3** with thallium trinitrate[6] produced a complex mixture from which none of the desired compounds could be isolated. Rearrangement (Ac_2O–AcCl–pyridine)[7] of the oxime of **3** was similarly unsuccessful.

In principle, the cis or trans diols should be available upon oxidation of an olefinic precursor such as **7** which is, in turn, available from **3** (Scheme I). A disadvantage to this route, however, is the potential for forming the isomeric olefin **9** in competition with **7**. The thermal elimination of the methyl carbonates of 2-decalinols is reported to provide a 1:1 mixture of the Δ^3 and Δ^2 olefins from both ring-junction isomers.[8] In contrast, in a study of the Bamford–Stevens elimination of the (methanylsulfonyl)-hydrazones of the 2-decalinones, it has been demonstrated that under aprotic conditions, the trans-fused isomer affords a 1:2 mixture of the Δ^3 and Δ^2 olefins.[9] A 1:1 mixture is, however, obtained from the elimination of the cis-fused isomer under all conditions and from the trans-fused isomer under protic conditions.[8] To our knowledge, a similar study of quinolizidines derivatized at position 3 has not been reported.

We first attempted the preparation of **7** by elimination of derivatives of 3-quinolizidinol. The reduction of **3** with $NaBH_4$ afforded two alcohols, **11a** and **12a**, in a 66:34 ratio. A much greater selectivity (91:9) was obtained with L-Selectride (Aldrich).[10] Surprisingly, of the several methods studied, only BH_3–THF and H_2–PtO_2 afforded a predominance of the presumably more stable alcohol **12a**. In both cases,, sustantial amounts of the trans-fused quinolizidinols were also formed. These presumably arise from epimerization of **3**.

Acetylation of the mixture of **11a** and **12a** afforded the corresponding acetates, which could be separated by preparative HPLC. The stereochemistry of the acetoxy groups in **11b** and **12b** was assigned by comparison of their NMR spectra.[10,11] The most striking difference was the splitting pattern displayed by the benzylic proton (H-1) resonance. In **11b** it appeared as a triplet (J = 5 Hz), while in **12b** the expected doublet of doublets (J_1 = 11 Hz, J_2 = 4 Hz) resulted. Rother and Schwarting have suggested that the most stable conformation of compounds such as **11b** is the one in which the acetoxy group is equatorial and, consequently, the aryl group is axial.[11] This appears to result from the conformational mobility associated with the cis ring fusion rather than nitrogen inversion, which would result in a trans ring fusion. In support, the infrared spectrum of **11b** does not display the Bohlmann bands

(1) (a) For part 10, see: Seitz, D. E.; Milius, R.; Quick, J. *Tetrahedron Lett.* **1982**, *23*, 1439. (b) For another in this series, see: Quick, J.; Ramachandra, R. *Tetrahedron* **1980**, *36*, 1301.
(2) Quick, J.; Mondello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705.
(3) We have previously termed these type II alkaloids.[2] We are now adopting the nomenclature and numbering utilized in a recent review.[4]
(4) Golebiewski, W. M.; Wrobel, J. T. In "The Alkaloids"; Academic Press: New York, 1981; Vol. XVIII, pp 263–322.
(5) (a) Quick, J.; Meltz, C. *J. Org. Chem.* **1970**, *44*, 573. (b) The terms "cis-fused" and "trans-fused" are used to denote stereochemistry of the ring junction. The use of cis and trans alone follows the conventional useage of these terms.
(6) McKillop, A.; Hunt, J. O. *J. Org. Chem.* **1972**, *37*, 3381.
(7) Reddy, G. S.; Bhatt, M. V. *Synthesis* **1981**, 223.
(8) Powell, J. W.; Whiting, M. C. *Tetrahedron* **1961**, *12*, 163.
(9) Powell, J. W.; Whiting, M. C. *Tetrahedron* **1961**, *12*, 168.
(10) Quick, J.; Meltz, C.; Ramachandra, R. *Org. Prep. Proced. Int.* *11*, 111.
(11) Rother, A.; Schwarting, A. E. *Lloydia* **1975**, *38*, 477.

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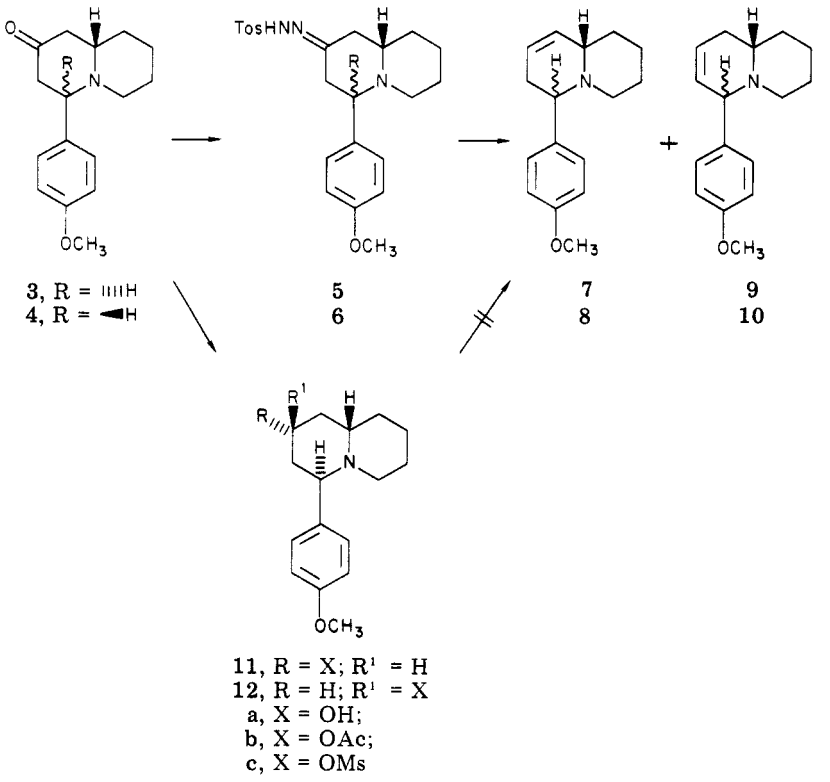
Scheme I



characteristic of trans ring fusion.

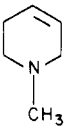
Attempts to prepare the olefins by thermal elimination of acetic acid from **11b** or **12b** or by treatment of mixtures (either 2:1 or 9:1) of the mesylates **11c** and **12c** with DBU gave complex mixtures of products with no indication of the presence of the desired material. The failure of this 1,2-elimination may result from a preferred heterolytic fragmentation.[12] The equatorial leaving groups in **11** and **12** are well suited to this.

To circumvent this problem, we turned to the Bamford–Stevens reaction of sulfonyl hydrazones.[9] The tosyl hydrazones of ketones **3** and **4** were prepared by treatment in ethanol with (*p*-tolylsulfonyl)hydrazide. A significant amount of trans-fused hydrazone **6** was obtained from the cis-fused ketone. This could result from the known isomerization of the cis-fused ketones or from a similar isomerization of the hydrazone. With benzene as solvent, isomerization was slow and **5** was obtained (84% after purification) with little, if any, **6**. In solution, **5** does isomerize slowly to **6**. Both **5** and **6** exist as mixtures of syn and anti isomers, which were detectable by thin-layer chromatography and HPLC but were not isolated.

Distillation of the salt obtained from **5** and *n*-butyllithium afforded the olefins **7** and **9** (91%, 1:1 ratio). No trans-fused dehydroquinolizidines were detected. Similar treatment of **6** afforded **8** and **10** (84%, 2:3). The formation and decomposition of the anion of **5** under protic conditions (ethylene glycol) gave mixtures of equal amounts of **7**, **8**, **9**, and **10** (70%). For large-scale reactions, it was convenient to use the crude **5**, prepared by the benzene method; any trans-fused dehydroquinolizidine (10%) that resulted was easily removed by preparative HPLC.

The double bond isomers are readily distinguished by their NMR and mass spectra. The mass spectra of Δ^2 olefins **9** and **10** display a fragment at m/z 160. This results from a retro-Diels-Alder fragmentation, which is not available to the Δ^3 compounds. In the NMR (270 MHz) spectra of the Δ^2 olefins **9** and **10**, the resonances due to the benzylic proton (H-1) appear as sharp singlets (δ 4.26 and 3.56, respectively), since the dihedral angle between H-1 and H-2 is 90° (J = 0 Hz). In the NMR spectra of the Δ^3 olefins **7** and **8**, the benzylic protons appear as a doublet (δ 3.89, J = 6.9 Hz) or as a doublet of doublets (δ 3.50, J_1 = 3.9 Hz and J_2 = 10.6 Hz), respectively. Although compound **8** apparently has the aryl group in the equatorial position, surprisingly, compound **7** has a pseudo-axial aryl as evidenced by the sharp doublet in the NMR spectrum.

Since the pure olefin **7** was available in only limited amounts, the commercially available *N*-methyl-1,2,5,6-tetrahydropyridine (**13**) was used as a model to investigate



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oxidation methods to provide the vicinal diol. On treatment of **13** with *m*-chloroperbenzoic acid (mCPBA), the *N*-oxide was obtained, while *N*-bromosuccinimide or osmium tetroxide provided a complex mixture of unidentified products. In contrast, the trifluoroacetic acid salt of **13** was inert to mCPBA but could be oxidized by trifluoroperacetic acid[13] to provide a unique substance with an NMR spectrum different from that of the *N*-oxide and in agreement with that expected for the desired epoxide.

Subsequent application of these epoxidation conditions to the olefin **7** gave **14** in 76% yield. The crude product was unstable. However, upon purification by flash chromatography, the apparent autocatalytic decomposition was

(12) (a) Grob, C. A.; Schiess, P. W. *Angew. Chem.* **1969**, *6*, 1. (b) Grob, C. A. *Ibid.* **1969**, *8*, 535.

(13) Emmons, W. D.; Pagano, A. S.; Freeman, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 3472.

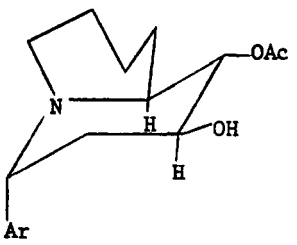
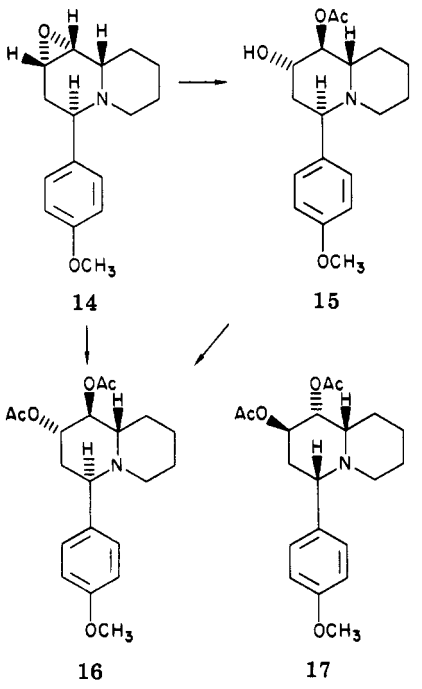


Figure 1.

terminated and the material could be readily stored. The high-field (270 MHz) NMR spectrum obtained for compound **14** is exceedingly complex, and even with decoupling experiments, the stereochemistry of the epoxide linkage could not be assigned unequivocally. However, the stereochemistry of the products of subsequent reactions of this epoxide provided substantial evidence for its structure.

Treatment of the epoxide **14** with glacial acetic acid afforded *cis*-1(a)-(4-methoxyphenyl)-4(e)-acetoxyquinolizidin-3(e)-ol, **15**, in 85% yield. The assignment of protons



in **15** is derived from the 270-MHz NMR spectrum. This spectrum shows a triplet at δ 4.82 (J = 8.4 Hz), which is associated with a proton attached to a carbon that also bears an acetoxy group. It is evident that the presence of the acetoxy group at C-3 can be discounted since there are three protons vicinal to C-3 and the NMR signal would be expected to display greater complexity. The observed coupling correlates well with the values calculated[14] for the isomers in which the C-4 acetate is cis to the proton at the ring fusion and trans to the C-3 hydroxyl and which exists in the conformer in which the acetate and hydroxyl are diequatorial (Figure 1). The acetoxy attack apparently occurs primarily, if not exclusively, at C-4 of the α-epoxide **14** via a trans-diaxial ring opening. The trans-dioxy compound than undergoes a conformational change, as noted for the acetate **11b**, to the diequatorial conformer. The aryl ring is expected to be axial in this conformation; however, this could not be confirmed by the high-field NMR spectrum of **15** since the resonance of the benzylic proton was obscured by that of the C-3 proton (δ 3.96–4.03).

The diacetate **16** could be prepared from the epoxide directly by treatment with acetic anhydride–acetic acid (50% yield) or by treatment of **15** with acetic anhydride–pyridine. The material obtained by the two routes exhibited identical spectral and chromatographic properties. The benzylic proton resonance appeared as a triplet (J = 4.4 Hz) at δ 4.00 as expected for an equatorial proton. Thus, the aryl group is demonstrated to be axial in the predominant conformation of **16**. The same may be presumed for the precursor **15**.

In contrast to the ease of epoxidation of the cis-fused olefin **7**, the trans-fused olefin **8** required a prolonged treatment (6 days) with trifluoroperacetic acid. The reaction product could not be readily isolated and purified but was treated immediately with a mixture of acetic acid–acetic anhydride to provide a diacetate, **17**, in 20% purified yield. The NMR spectrum of **17** showed a broad singlet at δ 4.75. This is indicative of equatorial protons at C-3 and C-4. Consequently, we expect this product to be the diaxial diacetoxy conformer.

Thus, we are able to prepare quinolizidines substituted with trans-vicinal diols in the same relative stereochemistry as that exhibited by lythrancine V (**1b**). The yield from the 3-quinolizidinone is, however, low. In order to improve this, we are now considering methods for the preparation of 4-quinolizidinones that may be converted to the Δ^3 olefin with high selectivity and that might be more amenable to the introduction of the metacyclophane moiety.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary or Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer. High-field NMR spectra were recorded at the Massachusetts Institute of Technology. Spectra are expressed in parts per million from Me_4Si as internal standard. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. Microanalyses were performed by Atlantic Microlab, Inc. High-pressure liquid chromatographic separations were performed on a Waters Associates A 202 chromatogram (Porasil column or a Waters Associates Prep LC/System 500 (Prep Pak-500/silica column). Precoated TLC plates (silica gel 60F EM Reagent) were used for thin-layer chromatographic analyses and were visualized under ultraviolet light or exposure to I_2. A Varian Aerograph Model 1400 gas chromotograph (3% OV-17) was used for GC analyses. Mass spectra were measured at Cornell Univesity. Bulb-to-bulb distillations were performed with a Kugelrohr apparatus. Organic extracts were dried over anhydrous sodium sulfate.

***cis*-1-(4-Methoxyphenyl)quinolizidin-3-one (3) and *trans*-1-(4-Methoxyphenyl)quinolizidin-3-one (4).** A solution of 2-piperidylpropanone (pelletierine,[5] 7.06 mL, 50 mmol) and *p*-anisaldehyde (6.2 mL, 51 mmol) in 2:1 ethanol–water (40 mL) was chilled to 4 °C. To this was slowly added a chilled solution of sodium hydroxide (4.26 g, 107 mmol) in 2:1 ethanol–water (40 mL). After 1.5 h the solution was diluted with ice water (100 mL) and extracted with chloroform (3 × 50 mL). The combined organic fractions were washed with water and dried. The solvent was removed in vacuo to provide an orange oil (14 g). Preparative HPLC [CH_2Cl_2–CH_3CN–CH_3OH (19:0.67:0.4)] provided the cis-fused isomer **3** (30%) and a mixture of *p*-anisaldehyde and the trans-fused isomer **4**. This mixture was separated further by column chromatography (CH_2Cl_2–CH_3CN as eluent). Bulb-to-bulb distillation of **3** yielded a clear oil, which slowly crystallized: mp 79–80 °C; NMR ($CDCl_3$) δ 1.1–3.1 (br m, 13 H), 3.77 (s, 3 H, OMe), 4.20 (d of d, J_1 = 6 Hz, J_2 = 4 Hz, 1 H, H-4), 6.81, 7.02 (A_2B_2, J = 8 Hz, 4 H, aromatic); IR (KBr) 1710 (C=O) cm^{-1}. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

The trans-fused isomer **4**, purified by sublimation, yielded a white crystalline solid: mp 85–86 °C; NMR ($CDCl_3$) δ 1–3 (br m, 13 H), 3.29 (d of d, J_1 = 11 Hz, J_2 = 4 Hz, 1 H, H-4), 3.82 (s,

(14) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.

3 H, OMe), 6.88, 6.27 (A_2B_2, J = 8 Hz, 4 H, aromatic; IR (KBr) 2750 (Bohlmann band), 1710 (C=O) cm^{-1}. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

***cis*-1-(4-Methoxyphenyl)-3(a)-acetoxyquinolizidine (11b) and *cis*-1-(4-Methoxyphenyl)-3(e)-acetoxyquinolizidine (12b)** Sodium borohydride (1.5 g) was added to a chilled solution of **3** (3.91 g, 15.1 mmol) in methanol (100 mL), and the mixture was stirred first at 0 °C (1 h) and then at 23 °C (2 h). Ice water (200 mL) and chloroform (50 mL) were then added, and the organic layer was separated; the aqueous layer was extracted with chloroform (5 × 20 mL). The combined organic fractions were washed with water and dried, and the solvent was removed in vacuo. A yellow glass (**11a** and **12a**) (4.01 g) was obtained. Gas chromatography of the silylated alcohols (BSTFA) showed a mixture of 66% **11a** and 34% **12a**: NMR ($CDCl_3$) (**11a** and **12a**) δ 1.0–3.1 (br m, 14 H), 3.67 (s, 3 H, OMe), 3.8–4.3 (unresolved t, 2 H, H-4 and H-2), 6.79, 7.18 (A_2B_2 q, J = 9 Hz, 4 H, aromatic); IR ($CDCl_3$) 3650 (OH), 3200–3550 (H-bonded OH) cm^{-1}.

The mixture of **11a** and **12a** was acetylated by treatment with acetic anhydride (13 mL) and pyridine (11 mL) overnight. The solvent was removed under reduced pressure to leave a green-yellow oil, which was then stirred with saturated aqueous sodium bicarbonate (100 mL) and chloroform (50 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform (3 × 50 mL). The combined organic layers were washed with saturated sodium bicarbonate (100 mL) and then water (100 mL), dried (Na_2SO_4), and concentrated in vacuo, affording 4.29 g of a mixture of **11b** and **12b**. The acetates were separated by preparative HPLC (1.5% ethanol and 0.015% NH_4OH in $CHCl_3$). The chromatography yielded 0.54 g (12%) of pure equatorial acetate **12b** and 0.82 g (18%) of axial acetate **11b** while 2 g remained as the mixture. The acetate **11b** was further purified by a bulb-to-bulb distillation to afford a white crystalline material: mp 58–59 °C; NMR ($CDCl_3$) δ 2.03 (s, acetyl), 1.0–3.2 (br m, 16 H), 3.82 (s, 3 H, OMe), 4.03 (t, J = 5 Hz, 1 H, H-4), 4.85–5.5 (m, 1 H, H-2), 6.88, 7.29 (A_2B_2, J = 9 Hz, 4 H, aromatic); IR (film) 1730 cm^{-1} (C=O). Anal. ($C_{18}H_{25}NO_2$) C, H, N.

The acetate **12b** was recrystallized from hexane: mp 130–131 °C; NMR ($CDCl_3$) δ 1.93 (s, acetyl), 1.0–3.5 (m, 16 H), 3.80 (s, 3 H, OMe), 4.03 (d of d, J_1 = 11 Hz, J_2 = 4 Hz, 1 H, H-4), 4.7–6.3 (m, 1 H, H-2), 6.89, 7.28 (A_2B_2, J = 8 Hz, 4 H, aromatic); IR (KBr) 1730 (C=O) cm^{-1}. Anal. ($C_{18}H_{25}NO_3$) C, H, N.

Selectride Reduction of 3. L-Selectride (1 M in THF; 6 mL, 6 mmol) was injected into a solution of **3** (1.0 g, 3.9 mmol) in freshly distilled tetrahydrofuran (120 mL) at −78 °C under nitrogen. The mixture was stirred at this temperature for 1 h and then allowed to warm to 0 °C. The reaction was quenched with water (75 mL) and concentrated in vacuo, diluted with saturated aqueous sodium bicarbonate, and extracted with chloroform. The combined extracts were washed (saturated aqueous $NaHCO_3$), dried, and removed in vacuo to leave a brown oil (1.02 g); gas chromatographic (GC) analysis of the silylated (BSTFA) mixture indicated a 91:9 ratio of **11a** to **12a**. Recrystallization from hexane gave yellow crystals (0.69 g, 68%); mp 91–102 °C; **11a**:**12a** 94:6 by GC.

***cis*-1-(4-Methoxyphenyl)quinolizidin-3-one (*p*-Tolylsulfonyl)hydrazone (5).** A mixture of the cis-fused ketone **3** (3.37 g, 0.13 mmol) and (*p*-tolylsulfonyl)hydrazide (2.44 g, 0.13 mmol) in benzene (100 mL) was brought to reflux for 2 h under nitrogen. The solvent was removed under reduced pressure, and the residue obtained (5.6 g) was separated by flash chromatography with 10% ethanol (1% ammonium hydroxide) in chloroform as eluent. The two trans-fused hydrazones **6** (55 mg, 1%) and the desired cis-fused products **5** (5.2 g, 94%) were obtained along with a small amount of unreacted starting material. Compound **5** slowly isomerized to form the trans-fused hydrazone **6**. The cis hydrazone **5** was obtained as a yellow foam: NMR ($CDCl_3$) δ 0.95–3 (m, 16 H), 2.43 (S, Ar CH_3), 3.80 (s, 3 H, OCH_3), 3.90 (t, 1 H, 1-H), 4.5–5.5 (br, 1 H, NH), 6.6–8 (m, 8 H, aromatic).

***trans*-1-(4-Methoxyphenyl)quinolizidin-3-one (*p*-Tolylsulfonyl)hydrazone (6).** A mixture of the trans-fused ketone **4** (0.253 g, 0.97 mmol) and (*p*-tolylsulfonyl)hydrazide (0.181 g, 0.97 mmol) was brought to reflux in ethanol under nitrogen. The product **6** was obtained as a yellow foam upon removal of the solvent in vacuo; mp 95–98 °C; NMR ($CDCl_3$) δ 1.00–3.33 (m, 18 H), 2.43 (br, Ar CH_3), 3.78 (s, 3 H, OCH_3), 6.6–8.0 (br, 8 H).

***cis*-3,4-Didehydro- and *cis*-2,3-Didehydro-1-(4-methoxyphenyl)quinolizidines (7 and 9).** Freshly prepared hydrazone **5** (5.6 g, 13 mmol) in anhydrous ether (225 mL) was cooled to 0 °C under nitrogen. To this was added 2.3 M butyllithium (6.3 mL, 14 mmol) in hexane. The heterogeneous mixture was stirred at 0 °C for 2 h and the ether distilled off under vacuum at 23 °C. The remaining yellow residue was decomposed during bulb-to-bulb distillation (170–240 °C (0.035 mmHg)) to yield a pale yellow oil (2.2 g, 69% yield from **3**). Separation by preparative HPLC [silica gel; 25% ethanol (containing 1% NH_4OH) in chloroform] afforded **7** (48%) and **9** (42%) along with **8** and **10** (10%). The use of *purified* **5** in this procedure gave **7** and **9** (91%) with no detectable **8** and **10**.

The olefin **7** was further purified (bulb-to-bulb distillation) to afford a yellow solid: mp 61–62 °C; NMR (270 MHz, $CDCl_3$) δ 1.1–2.9 (br m, 11 H), 3.76 (s, 3 H, OCH_3), 3.87 (d, 1 H, 1-H), 5.56 (d, 1 H, 4-H), 5.87 (m, 1 H, 3-H), 6.87, 7.20 (A_2B_2 q, 4 H, aromatic, J = 8.5 Hz); MS, m/z (relative intensity) 243 (100), 242 (74), 228 (20), 136 (23), 134 (46), 121 (30). Anal. ($C_{16}H_{21}NO$) C, H, N.

The olefin **9** was also purified by distillation (bulb-to-bulb) to afford a yellow oil: NMR (270 MHz, $CDCl_3$) δ 0.85–2.76 (br m, 11 H), 3.78 (s, 3 H, OCH_3), 4.26 (s, 1 H, H-1), 5.69–5.88 (br, 2 H, vinylic), 6.84, 7.16 (A_2B_2, J = 8.5 Hz, aromatic); MS, m/z (relative intensity) 243 (19), 160 (100), 159 (35), 145 (15), 136 (18), 129 (23). Anal. ($C_{16}H_{21}NO$) C, H, N.

***trans*-3,4-Didehydro- and *trans*-2,3-Didehydro-1-(4-methoxyphenyl)quinolizidines (8 and 10).** A cooled (0 °C) solution of 2.3 M *n*-butyllithium in hexane (0.3 mL, 0.69 mmol) was added to hydrazone **6** (293 mg, 0.68 mmol) in ether at 0 °C under nitrogen. After distillation, a mixture of the olefins **8** and **10** was obtained. Separation by HPLC [silica gel; 4% acetonitrile (containing 1% NH_4OH) in chloroform] afforded **8** (33%) and **10** (51%).

Further purification of **8** (bulb-to-bulb distillation) afforded a solid: mp 39–41 °C; NMR (270 MHz, $CDCl_3$) δ 0.9–2.7 (br m, 11 H), 3.25 (d of d, 1 H, 1-H, J_1 = 10.5 Hz, J_2 = 3.9 Hz), 3.78 (s, 3 H, OCH_3), 5.49 (d, 1 H, 4-H, J = 9.9 Hz), 5.71–5.73 (m, 1 H, 3-H), 6.85, 7.24 (A_2B_2 q, 4 H, aromatic, J = 8.2 Hz); MS, m/z (relative intensity) 243 (100), 242 (74), 136 (22), 134 (38), 121 (32). Anal. ($C_{16}H_{21}NO$) C, H, N.

Similar purification of **10** afforded an oil: NMR (270 MHz, $CDCl_3$) δ 1.2–2.8 (br m, 11 H), 3.56 (s, 1 H, 1-H), 3.73 (s, 3 H, OCH_3), 5.40 (d, 1 H, 2-H, J = 9.7 Hz), 5.65 (m, 1 H, 3-H), 6.81–7.24 (A_2B_2 q, 4 H, aromatic, J = 8.5 Hz), MS, m/z (relative intensity) 243 (32), 242 (27), 160 (100), 159 (30), 136 (21). Anal. ($C_{16}H_{21}NO$) C, H, N.

***cis*-3,4-Epoxy-1-(4-methoxyphenyl)quinolizidine (14).** Trifluoroacetic anhydride (0.9 mL, 6.4 mmol) was added dropwise to a solution of hydrogen peroxide (50% aqueous, 0.1 g) in dichloromethane (20 mL) at 0 °C. The solution was stirred at 0 °C for 3 h, and to this was added *cis*-1-(4-methoxyphenyl)-quinolizidin-3-ene (**7**, 0.243 g, 1.0 mmol) in trifluoroacetic acid (1 mL). The reaction was stirred at 23 °C for 3 h, and then stored for 8 h at 0 °C. Saturated aqueous sodium bisulfate was added, and the organic layer was separated, washed with aqueous sodium bicarbonate and water, dried, and concentrated in vacuo to provide an oil, which was immediately purified by flash chromatography to provide the epoxide **14** as an oil (0.197 g, 76%): NMR (270 MHz, $CDCl_3$) δ 1.12–1.77 (m, 6 H), 2.05 (d of d, 1 H, J_1 = 11.8 Hz, J_2 = 2.9 Hz), 2.16 (m, 1 H), 2.55 (m, 2 H), 2.72 (d, 1 H, J = 11.7 Hz), 3.12 (m, 1 H), 3.52 (t, 1 H, J = 4.46 Hz), 3.67 (d of d, 1 H, J_1 = 6.8 Hz, J_2 = 2.5 Hz), 3.81 (s, 3 H, OCH_3), 6.87 and 7.14 (A_2B_2 q, 4 H, Ar H, J = 8.75 Hz).

***cis*-1-(4-Methoxyphenyl)-4(e)-acetoxy-3(e)-hydroxyquinolizidine (15).** The epoxide **14** (230 mg, 0.89 mmol) was stirred with acetic acid (2 mL) at 23 °C for 3 days. The reaction mixture was then concentrated in vacuo and dichloromethane (25 mL) was added. The organic layer was washed consecutively with aqueous sodium bicarbonate and water and dried. Evaporation in vacuo provided 0.20 g (71%) of an oily product of which 73 mg was purified by HPLC to provide **15** (66 mg) as an oil: IR (neat) 1730 (C=O), 3400 (OH) cm^{-1}; NMR (270 MHz, $CDCl_3$), δ 1.25–2.95 (m, 11 H), 2.12 (s, 3 H, $COCH_3$), 3.80 (s, 3 H, OCH_3), 3.96–4.03 (m, 2 H, 1-H, 3-H), 4.84 (t, 1 H, 4-H, J = 8.4 Hz), 6.86 and 7.30 (A_2B_2 q, 4 H, Ar H, J = 9 Hz); MS, m/z (relative intensity) 319 (6), 260 (11), 259 (33), 242 (33), 134 (100); accurate

mass determination, calcd for $C_{18}H_{25}NO_4$ 319.1783, found 319.1780.

***cis*-1-(4-Methoxyphenyl)-3(e),4(e)-diacetoxyquinolizidine (16). Method A.** Monoacetate **15** (13 mg, 0.04 mmol) was dissolved in pyridine (0.5 mL) and acetic anhydride (0.5 mL) was added. The reaction mixture was stirred at room temperature for 10 h and concentrated in vacuo. Dichloromethane (25 mL) was added and the mixture washed with saturated aqueous sodium bicarbonate and water. The organic extract was dried and concentrated in vacuo to provide **16** as an oil (13 mg, 88%).

Method B. A mixture of *cis*-3,4-epoxy-1-(4-methoxyphenyl)quinolizidine (**14**) (225 mg, 0.869 mmol), acetic acid (2.5 mL), and acetic anhydride (2.5 mL) was stirred, at 23 °C, for 3 days. The solution was concentrated in vacuo, dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (50 mL) were added, and the mixture was stirred for 2 h at 23 °C. The organic layer was separated and washed consecutively with saturated aqueous sodium bicarbonate and water, dried, and concentrated to provide **16** as an oil (240 mg, 77%). The product was further purified by flash chromatography to provide **16** (154 mg, 49%): IR (Neat) 1735 (C=O); NMR (270 MHz, $CDCl_3$) δ 1.25–2.90 (multiplets, 11 H), 2.040 and 2.048 (two s, 6 H, $COCH_3$), 3.81 (s, 3 H, OCH_3), 4.00 (t, 1 H, 1-H, J = 5.1 Hz), 5.09–5.19 (m, 2 H, 3-H, 4-H), 6.88 and 7.38 (A_2B_2 q, 4 H, Ar H, J = 8.8 Hz); MS, (relative intensity) m/z 361 (5), 302 (20), 301 (13), 243 (11), 242 (70), 159 (96); accurate mass determination, calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1894.

***trans*-1-(4-Methoxyphenyl)-3(a),4(a)-diacetoxyquinolizidine (17).** Trifluoroacetic anhydride (0.9 mL, 6.4 mmol) was added dropwise to a solution of hydrogen peroxide (50% aqueous, 0.1 g) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred for 3 h at 23 °C, and a solution of *trans*-1-(4-methoxyphenyl)-3,4-didehydroquinolizidine (**8**, 0.48 g, 2.00 mmol) in trifluoroacetic acid (1 mL) was added at ambient temperature. The mixture was stirred for 6 days at ambient temperature. Saturated aqueous sodium bisulfite was added, and the separated organic layer was washed consecutively with aqueous sodium bicarbonate and water and then dried. The residue obtained after concentration in vacuo was dissolved in acetic acid (2.5 mL) and acetic anhydride (2.5 mL) and stirred at 23 °C for 3 days. After concentration in vacuo, the residue was dissolved in dichloromethane (25 mL) and washed consecutively with saturated aqueous sodium bicarbonate and water. The organic extract was dried, filtered, and concentrated in vacuo to provide a thick oil (0.41 g, 57%), which on flash chromatography gave a product (**17**, 122 mg, 17%): IR (neat) 2700–2900 (Bohlmann bands), 1730 (C=O) cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 1.0–2.9 (m, 11 H), 2.05 and 2.10 (two s, 6 H, $COCH_3$), 3.10 (d of d, 1 H, 1-H, J_1 = 4 Hz, J_2 = 11 Hz), 3.72 (s, 3 H, OCH_3), 4.75 (m, 2 H, 3-H, 4-H), 6.75 and 7.15 (A_2B_2 q, 4 H, Ar H, J = 8 Hz); MS, m/z (relative intensity) 361 (5), 302 (20), 301 (12), 243 (10), 242 (55), 159 (80); accurate mass determination, calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1861.

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Registry No. **1b**, 40179-98-4; **3**, 86933-78-0; **4**, 86933-77-9; **5** (isomer 1), 87781-81-5; **5** (isomer 2), 87781-91-7; **6** (isomer 1), 87781-82-6; **6** (isomer 2), 87781-92-8; **7**, 87781-83-7; **8**, 87781-85-9; **9**, 87781-84-8; **10**, 87781-86-0; **11a**, 87781-79-1; **11b**, 86880-50-4; **12a**, 87781-80-4; **12b**, 86880-49-1; **14**, 87781-87-1; **15**, 87781-88-2; **16**, 87781-89-3; **17**, 87781-90-6; 2-piperidylpropanone, 4396-01-4; *p*-anisaldehyde, 123-11-5; (*p*-toluenesulfonyl)hydrazide, 1576-35-8.

Molecular Structures of the Briantheins, New Insecticidal Diterpenes from *Briareum polyanthes*[1]

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Extracts of the soft coral *Briareum polyanthes*, recently found for the first time in Bermudian waters, have yielded three related diterpenes, briantheins X, Y, and Z. Detailed analysis of the spectral data and chemical correlation of briantheins X and Z established the gross structures of these highly oxidized, chlorinated diterpenes; X-ray diffraction studies confirmed the placement of the butyrate ester in briantheins Y and defined the absolute configuration for the trio. The chemotaxonomic significance and the insecticidal activity of the briantheins is discussed.

The soft coral *Briareum asbestinum* is widely distributed and fairly abundant in Caribbean waters and has been the subject of chemical investigation by several groups. These studies have revealed a rich diterpene chemistry and have resulted in the identification of briarein A (**1**)[2] and the asbestinins.[3] Briarein A possesses a novel carbon skeleton which has since been observed only in compounds from sea pens (distantly related coelenterates): stylatulide (**2**)[4] from *Stylatula sp.*, ptilosarcone (**3**)[5] from *Ptilosarcus gurneyi*, and **4**–**6** from *Scytalium tentaculatum*[6] (Chart I).

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