J = 2.8 Hz, 1 H), 5.14 (m, NH), 5.88 (d, J = 1.3 Hz, 1 H), 5.90 (d, J = 1.3 Hz, 1 H), 6.20 (s, 1 H), 6.82 (s, 1 H), 7.1–7.3 (m, 5 H); MS $M^{\bullet+}$ calcd, 381; found, 381 (17).

Thermolysis of Acid 35. A solution of 3.8 mg (0.010 mmol) of acid **35** was heated in 2 mL of nitromethane for 4 h at 85–90 °C. The nitromethane was evaporated, and the residue was treated with excess diazomethane. An NMR spectrum of the total crude esters indicated a 5:1 ratio of **37a** to **38**. The yield of **37a** after plate chromatography was 51%.

Preparation of Podophyllotoxin Analogue 26 from 33. Crude acid **35**, obtained by hydrolysis of 1.65 g of **33** as described above, was heated for 5.5 h in 120 mL of nitromethane at 85–90 °C. The nitromethane was evaporated, and the residue was refluxed in aqueous LiOH (0.2 M, 200 mL) for 0.5 h. To the cooled reaction mixture were added 8 g of $KHPO_4$, 0.4 g of $NaNO_2$, and about 60 mL of 10% HCl to give a pH of approximately 4. The solution was stirred for 20 h and extracted with CH_2Cl_2. The crude product was purified by chromatography on silica gel and recrystallization from CH_2Cl_2–hexane to give 207 mg (15%) of **26** as white plates: mp 247–248 °C; IR (KBr) 3400 (s) 1760 (s) cm^{-1}; NMR δ 2.76 (m, 1 H), 2.86 (dd, J = 14.3, 4.8 Hz, 1 H), 4.08 (t, J = 9.4 Hz, 1 H), 4.57 (dd, J = 8.9, 7.1 Hz, 1 H), 4.63 (d, J = 4.8 Hz, 1 H), 4.76 (d, J = 9.2, 1 H), 5.94 (d, 2 H), 6.44 (s, 1 H), 7.1–7.3 (m, 6 H). Anal. Calcd for $C_{19}H_{16}O_3$: C, 70.36; H, 4.97. Found: C, 70.65; H, 5.36.

Preparation of Urethane 34. A solution of 0.405 g (1.70 mmol) of benzocyclobutyl acetate **32** dissolved in 10 mL of CH_2Cl_2 was added to 8 mL of methanol and 2 mL acetyl chloride at −5 °C. The reaction mixture was stirred for 5 h and then worked up as before for **7** to afford a carbon tetrachloride solution of the alcohol **29** [NMR δ 4.10 (s, 1 H), 4.96 (s, br, 2 H), 7.0–7.6 (m, 9 H); IR 3300–3500 cm^{-1}].

To the above solution of **29** were added 10 mL of methylene chloride, 0.237 g (1.68 mmol) of isocyanate **17**, and 85 mg of triphenyltin acetate. The solvent was evaporated at 0 °C on a rotary evaporator to produce a viscous oil, which was allowed to warm to room temperature. The crude product was purified on silica gel and gave 0.245 g (43%) of **34**: mp 93–94 °C; IR 1700–1730 (s), 3340 (m) cm^{-1}; NMR δ 3.73 (m, 3 H), 4.03 (m, 2 H), 4.64 (s, 1 H), 4.93 (m, NH), 5.67 (d, J = 1.4 Hz, 1 H), 5.97 (dt, J = 16.0, 2.0 Hz, 1 H), 6.93 (dt, J = 16.0, 4.9 Hz, 1 H), 7.2–7.6 (m, 9 H).

Preparation of Podophyllotoxin Analogue 27 from 34. A solution of 125 mg (0.371 mmol) of **34** was heated in DMF at 110 °C for 1 day. The DMF was evaporated to 2 mL, and 1.2 g (9.0 mmol) of LiI was added. The resulting solution was heated at 115 °C for 3 h while N_2 was passed over the surface of the solution. The reaction mixture was then cooled and added to 15 mL of 1% HCl. Extractive workup with ethyl acetate afforded a tan solid, which was refluxed in 75 mL of 0.2 M LiOH for 0.5 h. The solution was again cooled to 23 °C, and KH_2PO_4 (6 g), $NaNO_2$ (3 g), and 15 mL of 10% HCl were added. This solution was stirred for 20 h and then extracted with methylene chloride. The analogue **27** was obtained in 35% yield (36 mg) as white plates from methylene chloride–hexane after an initial silica gel chromatography: mp 226–227 °C; IR (KBr) 3420 (s), 1756 (s) cm^{-1}; NMR 2.06 (O-H), 2.85 (m, 1 H), 2.89 (dd, J = 14.2, 5 Hz, 1 H), 4.11 (t, J = 10.0 Hz, 1 H), 4.60 (dd, J = 9.3, 6.5 Hz, 1 H), 4.77 (d, J = 4.3 Hz, 1 H), 4.88 (d, J = 8.8 Hz, 1 H), 7.0–7.7 (m, 9 H). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.95; H, 5.85.

Thermolysis of 34. Preparation of 39a. A solution of 26.8 mg of **34** in 4 mL of DMF was heated to 110 °C for 1 day. The DMF was evaporated, and the product was separated by recrystallization and plate chromatography to give 15 mg (56%) of the trans-fused ester **39a** and 3 mg (11%) of the cis-fused analogue **40**. An NMR spectrum of the total crude reaction mixture indicated a 4:1 ratio of **39a**:**40**. Compound **39a** (mp 260 °C) had IR peaks at 1706 (s), 1728 (m), and 3420 (s) cm^{-1}; NMR peaks were at δ 2.70 (m, 1 H), 3.06 (t, J = 10.9 Hz, 1 H), 3.10 (dd, J = 10.9, 6.0 Hz, 1 H), 3.54 (s, 3 H), 3.75 (quintet, J = 5.2 Hz, 1 H), 4.65 (d, J = 5.8 Hz, 1 H), 5.11 (d, J = 3.9 Hz, NH), 5.18 (d, J = 10.2 Hz, 1 H), 6.9–7.8 (m, 9 H). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68. Found: C, 71.25; H, 5.65.

The cis analogue **40** had the following NMR data: δ 2.66 (m, 1 H), 3.15 (ddd, J = 2, 4, 12 Hz, 1 H), 3.29 (t, 12.2 Hz, 1 H), 3.48 (s, 3 H), 3.70 (dd, J = 12.7, 4.9 Hz, 1 H), 4.34 (d, J = 11.2 Hz, 1 H), 5.27 (m, NH), 5.40 (d, J = 2.5 Hz, 1 H), 6.7–7.4 (m, 9 H).

Rearrangement Approaches to Cyclic Skeletons. 6. Total Synthesis of (±)-Ptilocaulin on the Basis of Formal Bridgehead Substitution and Photochemical [1,3] Acyl Migration of a Bicyclo[3.2.2]non-6-en-2-one System[1]

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Received March 1, 1988

The total synthesis of (±)-ptilocaulin (1), the antimicrobial and cytotoxic guanidine-containing natural product, starting from 1-methoxybicyclo[3.2.2]non-6-en-2-one (3) is reported. The 3-*endo*-methyl derivative of **3**, **4**, was obtained selectively under kinetically controlled conditions. The bridgehead methoxy group of **4** was replaced by a butyl group, with inversion of absolute configuration, upon successive treatment with butyllithium and *p*-toluenesulfonic acid in benzene. The thus obtained 1-butyl-*exo*-8-methylbicyclo[3.2.2]non-6-en-2-one was transformed photochemically into the [5,6] fused-ring ketone, 4-butyl-*exo*-3-methylbicyclo[4.3.0]non-4-en-7-one (**7**). Transposition of the carbonyl group and the olefin of **7** to give a mixture of *exo*-3- and *endo*-3-butyl-4-*exo*-methylbicyclo[4.3.0]non-9-en-2-ones was achieved in a six-step sequence. From these conjugated ketones, (±)-ptilocaulin was derived by treatment with guanidine.

Ptilocaulin (1) is an antimicrobial and cytotoxic cyclic guanidine derivative isolated from the Caribbean sponge *Ptilocaulis* aff. *P. spiculifer* (Lamarck, 1814) by Rinehart and co-workers.[3] Because of these activities and the unusual structure, **1** is a significant synthetic target.[4-6] The absolute stereochemistry of natural (+)-ptilocaulin was

(1) Preliminary communications of this work: Uyehara, T.; Furuta, T.; Kabasawa, Y.; Yamada, J.; Kato, T. *J. Chem. Soc., Chem. Commun.* **1986**, 539. For part 5 in this series, see ref 2.

(2) Uyehara, T.; Yamada, J.; Furuta, T.; Kato, T.; Yamamoto, Y. *Tetrahedron* **1987**, *43*, 5605.

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(4) (a) Snider, B. B.; Faith, W. C. *Tetrahedron Lett.* **1983**, *24*, 861; (b) *J. Am. Chem. Soc.* **1984**, *106*, 1443.

(5) (a) Roush, W. R.; Walts, A. E. *J. Am. Chem. Soc.* **1984**, *106*, 721; (b) *Tetrahedron* **1985**, *41*, 3463.

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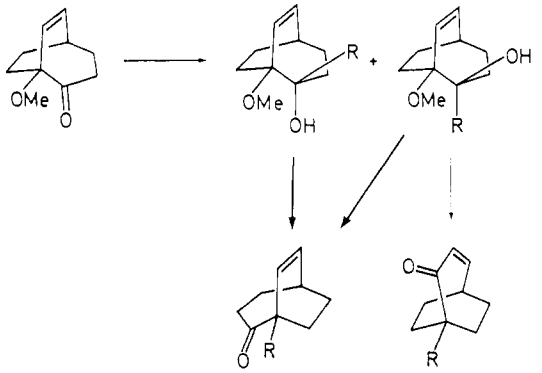
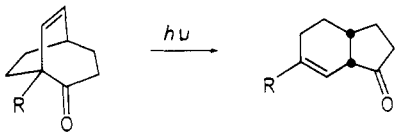
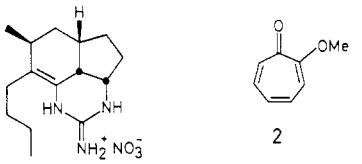
Scheme I. Method for Formal Bridgehead Substitution of 1-Methoxybicyclo[3.2.2]non-6-en-2-one



Scheme II. Photochemical Transformation of Bicyclo[3.2.2]non-6-en-2-one into the [5,6] Fused Ring Skeleton



established by total syntheses of the enatiomer.[4b,5] We report herein the details of a novel approach to (±)-1 starting from tropolone methyl ether **2**.



1

2

Very recently, two different types of rearrangements of bicyclo[3.2.2]non-6-ene systems have been developed as strategic methodologies for natural product syntheses. One strategy is a formal bridgehead substitution of 1-methoxybicyclo[3.2.2]non-6-en-2-ones on the basis of the pinacol-type rearrangement shown in Scheme I.[2] In general, this pinacol-type rearrangement is highly stereoselective. An exo alcohol gives the bicyclo[3.2.2]non-6-en-2-one exclusively while the endo isomer yields the same β,γ-unsaturated ketone preferentially along with a small amount of the bicyclo[3.2.2]non-3-en-2-one. For the reactions of the endo alcohols, the ratio of the products depends the nature of the substituent, R. The proportion of the β,γ-unsaturated ketone is very high, if R is a cation-stabilizing substituent. This suggests that the rearrangement proceeds mainly via the C-2 carbocation intermediate.

The other strategy is the photochemical [1,3] acyl migration of a bridged bicyclic compound to the fused-ring system as shown in Scheme II.[7] This transformation proceeds in practical yield by direct irradiation in an aprotic solvent using a high-pressure mercury lamp through a Pyrex filter.

Results and Discussion

Our synthetic plan, shown in Scheme III, is based on a combination of the pinacol-type rearrangement of the tertiary alcohols **5** to give the bridgehead alkylated ketone **6** and the photochemical transformation of the resulting β,γ-unsaturated ketone **6** into the [5,6] fused-ring system **7**. According to this plan, the stereochemistry of the 8-methyl group of **6** corresponds with that of the 3-methyl group of **4**. Thus, the pinacol-type rearrangement approach means not only formal bridgehead substitution but also exchange of the bridges of the bicyclic system. Except for stereochemically controlled cycloadditions, there are few methods to obtain bridged compounds possessing an endo or exo side chain on the saturated bridge. This rearrangement strategy supplies an alternative choice. The α,β-unsaturated ketone **7** can be converted easily into the conjugated ketones **8a** and **8b**, Snider's synthetic intermediates for (±)-ptilocaulin.

Scheme III. Rearrangement Approach to (±)-Ptilocaulin

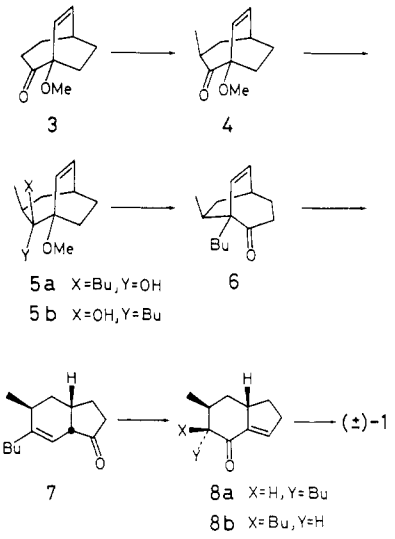


Table I. MM2 Steric Energies (SE, kcal/mol) of Bicyclo[3.2.2]non-6-enes

A conformer	SE	B conformer	SE
10A	19.22	**10B**	20.48
11A	17.17	**11B**	18.18
12A	17.92	**12B**	22.18
13A	22.05	**13B**	18.92

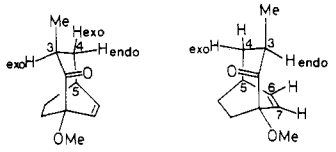
Our actual starting material is the bicyclic ketone **3** which was derived from 1-methoxybicyclo[3.2.2]nona-3,6-dien-2-one, which itself was prepared by Diels–Alder-type 1,4-addition of 2-methoxytropone (**2**) and ethylene followed by hydrosilylation and aqueous workup.[7b] The ketone **3** was prepared also from 1-methoxybicyclo[2.2.2]oct-5-en-2-one by ring enlargement using Tieffeneau–Demjanov-type conditions and by the related ring-expansion utilizing (trimethylsilyl)diazomethane.[7b]

Methylation of the ketone **3** was carried out under controlled conditions to avoid formation of a large amount of the dimethyl derivative. When the lithium enolate generated from **3** and 0.96 equiv of LDA was treated with methyl iodide at −30 °C, the *endo*-3-methyl derivative **4** was obtained in 63% yield along with a mixture of the exo isomer **9** and the dimethylated product (5.4:1, ca. 10%).

The exo orientation of the 3-methyl group of **9** is clearly supported by the ^{1}H NMR spectrum ($J_{endo\text{-}3,exo\text{-}4}$ = 11.0 Hz and $J_{exo\text{-}4,5}$ = 1.0 Hz) and the DNOE spectrum which shows an interaction between the 6-proton and *endo*-3-proton (δ 2.73). These data also indicate that the three-carbon bridge is bent toward the unsaturated two-carbon bridge (B conformer). On the other hand, the three-carbon bridge of the endo isomer **4** is suggested to be bent toward the saturated two-carbon bridge (A conformer; $J_{exo\text{-}3,endo\text{-}4}$ =

(6) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1986**, *27*, 1407.
(7) (a) Uyehara, T.; Kabasawa, Y.; Furuta, T.; Kato, T. *Tetrahedron Lett.* **1985**, *26*, 2343. (b) Uyehara, T.; Kabasawa, Y.; Kato, T.; Furuta, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 539.

11.2 Hz and $J_{endo\text{-}4,5}$ = 1.4 Hz). These conformational differences are anticipated on the basis of MM2 steric energies of the model compounds as listed in Table I.[8,9] In general, the A conformer of the bicyclic system is more stable than the corresponding B conformer. However, this is not the case for an *exo*-3-methyl derivative, such as **9**.



4 9

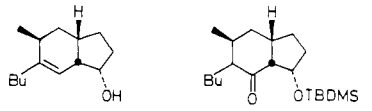
In this case, the more stable conformer has that group at the position remote from the syn-side bridge. This is a well-defined example of a substituent effect's capacity to induce a conformational change. The energy difference between **12A** and **13B** suggests the endo isomer **4** is thermodynamically more stable than **9**. In fact, a mixture of **4** and **9**, 2.7:1, was obtained by treatment of **4** with potassium *tert*-butoxide in THF. This validites the MM2 prediction and demonstrates that the *endo*-methyl product **4** is prepared from **3** under kinetically controlled conditions.

A B

10 W=X=Y=Z=H
11 W,X=O; Y=Z=H
12 W,X=O; Y=Me; Z=H
13 W,X=O; Y=H; Z=Me

Treatment of **4** with butyllithium at −80 °C gave **5a** and **5b** in 87% and 3% yields, respectively. These alcohols were converted to the bridgehead butyl ketone **6** in excellent yield by treating the mixture with an equivalent of *p*-toluenesulfonic acid (TsOH) in benzene at 80 °C for 1.5 h. The corresponding α,β-unsaturated ketone has not been detected so far. The ^{1}H NMR spectrum of **6** shows signals due to the 8-methyl group at the relatively higher field, δ 0.84 (d, J = 6.3 Hz). This suggests that the orientation of the 8-methyl is clearly syn to the unsaturated bridge. Photochemical transformation of **6** into **7** was carried out in 64% yield by irradition of a benzene solution of **6** by using a 100-W mercury lamp through a Pyrex filter.

Lithium aluminum hydride reduction of **7** gave the endo alcohol **14** in 64% yield along with 17% yield of the exo isomer. Exclusive formation of **14**, in 85% yield, was accomplished by employing lithium tri-*sec*-butylborohydride[10] as the reducing agent. After protection of the hydroxyl group with *tert*-butylchlorodimethylsilane,[11] hydroboration was carried out by using borane–methyl sulfide complex.[12] Alkaline hydrogen peroxide oxidation of the resulting boranes gave a mixture of the secondary alcohols in 81% yield. Collins oxidation[13] of the alcohols gave the ketone **15** in 97% yield. β-Elimination of the silanol from **15** was performed by treating **15** with potassium *tert*-butoxide in a mixture of *tert*-butyl alcohol and THF to give **8a** and **8b** (1:1) in 61% yield. Spectral characteristics of these conjugated ketones are identical with those reported previously.[4b]



14 15

(±)-Ptilocaline nitrate was derived from **8a** in 50% yield by the modified method of Snider and Faith[4] followed by the purification procudure of Roush and Walts.[5b] The spectral characteristics of (±)-**1**, including the ^{13}C NMR spectrum, were identical with those of (−)-ptilocaulin reported by Roush and Walts.[5b]

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were obtained at 90, 200, 270, and 400 MHz. ^{13}C NMR spectra were recorded at 22.5 and 67.5 MHz. THF and ether were distilled from benzophenone ketyl under argon immediately prior to use. Dichloromethane was distilled from P_2O_5 and stored over 4A molecular sieves. Benzene was distilled from P_2O_5 and stored over sodium wire. All reactions were monitored by analytical TLC using E. Merck precoated silica gel $60F_{254}$ plates. Column chromatography was carried out with E. Merck silica gel 60 (70–230-mesh ASTM). HPLC was performed on a Waters Associates Model R-401 liquid chromatograph using a 25 cm × 8 mm stainless steel column packed with Lichrosorb SI 100. Purities of compounds **5b**, **8a**, **8b**, and **9**, determined by HPLC (10:1 hexane–ethyl acetate), were greater than 98%.

1-Methoxy-*endo*-3-methylbicyclo[3.2.2]non-6-en-2-one (4). To a solution of LDA, generated from diisopropylamine (1.11 mL, 7.9 mmol) and 1.6 M butyllithium (in hexane, 4.75 mL, 7.6 mmol) in THF (10 mL), was added a solution of ketone **3** (1.32 g, 7.95 mmol) in THF (5 mL) at −78 °C, and the mixture was stirred for 1 h. To a solution of methyl iodide (5 mL, 10 equiv) in THF (5 mL) was added the resulting solution of the enolate of **3** at −30 °C. After being stirred for 14 h, the mixture was allowed to warm to room temperature and treated with saturated aqueous NH_4Cl solution, and the mixture was extracted with three portions of ether. The combined extracts were washed with 5% $Na_2S_2O_3$ solution and saturated brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography (80 g; 12:1 hexane–ethyl acetate) of the remaining oil (1.33 g) gave **4** (901 mg, 5.0 mmol, 63%), a mixture of other methylated products (130 mg), and recovered **3** (340 mg, 26%). **4**: colorless needles; mp 36.5–38 °C; IR (CCl_4) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.33 (H_6, ddd, J = 9.2, 7.8, and 0.8 Hz), 5.80 (H_7, dd, J = 9.2 and 0.8 Hz), 3.28 (MeO, s), 2.83 ($H_{exo\text{-}3}$, ddq, J = 11.2, 7.5, and 6.5 Hz), 2.62 (H_5, m), 2.47 (H_1, m), 2.12 ($H_{exo\text{-}4}$, ddd, J = 13.2, 7.5, and 6.2 Hz), 2.0–1.84 (3 H, m), 1.47 ($H_{endo\text{-}4}$, ddt, J = 13.2, 11.2, and 1.4 Hz), and 1.06 (Me, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 205.16 (s), 136.56 (d), 131.14 (d), 83.23 (s), 51.37 (q), 43.34 (t), 42.63 (d), 30.94 (d), 28.13 (t), 21.80 (t), and 15.93 (q); MS (25 eV), m/z (rel intensity) 180 (M^+, 8.9), 152 (1.3), and 110 (100). Found: C, 73.56; H, 9.07. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95.

1-Methoxy-*exo*-3-methylbicyclo[3.2.2]non-6-en-2-one (9). (a) To a solution of LDA, generated from diisopropylamine (0.11 mL, 0.8 mmol) and 1.5 M butyllithium (in hexane, 0.47 mL, 0.71 mmol) in THF (3 mL), was added a solution of **4** (121 mg, 0.67 mmol) in THF (6 mL) at −78 °C. After being stirred for 1 h at 0 °C, the mixture was allowed to warm to room temperature, treated with saturated aqueous NH_4Cl solution, and then extracted with three potions of ether. The combined extracts were washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated. Silica gel chromatography of the remaining oil (134 mg) gave **9** (19.3 mg, 0.11 mmol, 16%) and recovered **4** (81.8 mg, 0.45 mmol, 68%).

(b) To a solution of potassium *tert*-butoxide (1 mg, 0.01 mmol) and 2-methyl-2-propanol (0.02 mL) in THF (1 mL), was added

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(9) We thank Professor Eiji Osawa for providing us with the MM2 program for personal computer.
(10) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(12) Braun, L. M.; Braun, R. A.; Crissman, H. R.; Opperman, M.; Adams, R. M. *J. Org. Chem.* **1971**, *36*, 2388.
(13) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

a solution of **3** (35.6 mg, 0.20 mmol) in THF (2 mL) at room temperature under argon. After being stirred for 4 days, the mixture was allowed to warm to room temperature, treated with saturated aqueous NH_4Cl solution, and then extracted with three potions of ether. The combined extracts were washed with water and saturated NaCl solution and dried over $MgSO_4$. Concentration of the solution gave a 2.7:1 mixture of **4** and **9** (34.3 mg, 96%).

9: colorless oil; IR 1715 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.34 (H_7, ddd, J = 9.5, 1.0, and 0.8 Hz), 6.30 (H_6, dd, J = 9.5 and 6.7 Hz), 3.32 (3 H, s), 2.76 (H_5, m), 2.73 ($H_{endo\text{-}3'}$ ddq, J = 11.0, 8.8, and 6.3 Hz), 2.18 ($H_{endo\text{-}4'}$ ddd, J = 13.4, 8.8, and 6.3 Hz), 1.86–1.76 (3 H, m), 1.49 (1 H, m), 1.18 ($H_{exo\text{-}4'}$ ddd, J = 13.4, 11.0, and 1.0 Hz), and 1.02 (3 H, d, J = 6.3 Hz); MS (25 eV), m/z (rel intensity) 180 (M^+, 67.5), 123 (29.1), 111 (26.7), and 110 (100); exact mass found m/z 180.1151, calcd for $C_{11}H_{16}O_2$ M, 180.1149.

***endo*-2-Butyl-1-methoxy-*endo*-3-methylbicyclo[3.2.2]non-6-en-*exo*-2-ol (5a) and Its C-2 Stereoisomer (5b).** To a solution of **4** (348 mg, 1.93 mmol) in THF (15 mL) was added 1.5 M butyllithium solution in hexane (1.95 mL, 2.93 mmol) at −100 °C under argon, and the mixture was stirred at −100 to −80 °C for 1 h. Saturated aqueous ammonium chloride solution was added and the aqueous layer was extracted with three portions of ether. The combined extracts were washed with water and saturated brine and dried over $MgSO_4$. After removal of the solvent, the remaining oil (480 mg) was chromatographed on silica gel (30 g; 17:1 hexane–ethyl acetate). **5a** (399 mg, 1.68 mmol, 87%) and **5b** (14.9 mg, 0.063 mmol, 3.2%) were obtained.

5a: colorless oil; IR 3580 (m), 3050 (w), 1470 (m), 1095 (s), 1075 (s), and 718 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.41 (1 H, dd, J = 9.5 and 7.5 Hz), 6.08 (1 H, d, J = 9.5 Hz), 3.32 (3 H, s), 2.41 (1 H, m), 2.11 (1 H, dqd, J = 12.0, 6.5, and 5.0 Hz), 2.0–1.15 (13 H, m), 0.92 (3 H, t, J = 7.0 Hz), and 0.87 (3 H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 136.36 (d), 133.36 (d), 82.25 ns), 78.07 (s), 50.33 (q), 36.10 (t), 5.12 (t), 34.86 (t), 30.42 (d), 27.81 (t), 25.72 (t), 23.89 (t), 22.13 (t), 16.58 (q), and 14.03 (q); MS (13.5 eV), m/z (rel intensity) 238 (M^+, 25.6), 220 (10.7), 181 (14.7), 125 (43.0), 124 (100), 123 (46.5), 122 (55.3), and 84 (33.3). Exact mass found m/z 238.1934, calcd for $C_{15}H_{26}O_2$ M, 238.1933. Anal. Found: C, 75.96; H, 10.97. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99.

5b: colorless oil; IR 3600 (br s), 3040 (w), 1465 (m), 1382 (m), 1090 (s), 1070 (sh), and 710 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.03 (1 H, dd, J = 9.5 and 7.6 Hz), 5.96 (1 H, d, J = 9.5 Hz), 3.29 (3 H, s), 2.48–2.36 (2 H, m), 1.86–1.08 (13 H, m), 0.92 (3 H, t, J = 6.8 Hz), and 0.90 (3 H, d, J = 6.8 Hz); MS (13.5 eV), m/z (rel intensity) 238 (M^+, 25.9), 220 (18.2), 206 (20.2), 164 (100), and 163 (25.2). Exact mass found m/z 238.1938, calcd for $C_{15}H_{26}O_2$ M, 238.1933.

1-Butyl-*exo*-8-methylbicyclo[3.2.2]non-6-en-2-one (6). (a) A solution of **5a** (1.1606 g, 4.87 mmol) and TsOH (930 mg, 4.9 mmol) in dry benzene (4.9 mL) was heated at 80 °C for 90 min. The solution was diluted with ether, washed with several portions of water, saturated aqueous $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and then concentrated in vacuo. Column chromatography (30 g of silica gel; 50:1 hexane–ethyl acetate) of the residue (980 mg) gave **6** in 89% yield (896.2 mg, 4.34 mmol).

(b) A similar treatment of a mixture of **5a** and **5b** (1.47 g, 6.17 mmol) to that described above gave only **6** (873.9 mg, 4.23 mmol) in 69% yield. No products which absorb UV light (254 nm) were detected by TLC.

6: colorless oil; bp 60 °C (0.06 Torr); IR 3050 (w), 1705 (s), 720 (m), and 715 (m) cm^{-1}; ^1H NMR δ 6.15 (1 H, dd, J = 9.0 and 7.5 Hz), 5.69 (1 H, d, J = 9.0 Hz),2.7–1.0 (14 H, m), 0.89 (3 H, t, J = 6.0 Hz), and 0.84 (3 H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 213.65 (s), 133.56 (d), 133.17 (d), 57.71 (s), 40.73 (t), 36.88 (t), 36.29 (d), 34.21 (t), 32.12 (t), 31.20 (d), 26.83 (t), 23.50 (t), 19.1 (q), and 13.97 (q); MS (25 eV), m/z (rel intensity) 206 (M^+, 48.8), 163 (44.1), 162 (47.2), 105 (45.5), and 93 (100). Anal. Found: C, 81.48; H, 10.87. Calcd for $C_{14}H_{24}O$: C, 81.50; H, 10.75.

4-Butyl-*exo*-3-methylbicyclo[4.3.0]non-4-en-7-one (7). A solution of **6** (340 mg, 1.94 mmol) in benzene (194 mL) was placed in an immersion well equipped with a Pyrex filter and degassed by sonication. The solution under nitrogen was irradiated by using a 100-W Rikou high pressure Hg lamp for 3 h. From the crude photolysate (450 mg), **7** (257 mg, 1.25 mmol, 64%) was isolated by column chromatography (25 g of SiO_2; 5:1 hexane–ethyl acetate). **7**: colorless oil; IR 1750 (s) cm^{-1}; ^1H NMR δ 5.32 (1 H, br s, $W_{1/2}$ = 6 Hz), 2.55 (2 H, br), and 2.3–0.8 (19 H, m); ^{13}C NMR ($CDCl_3$) δ 219.66 (s), 144.65 (s), 115.54 (d), 49.87 (d), 35.71 (t), 34.92 (t), 33.16 (t), 30.88 (d), 30.42 (d), 30.09 (t), 25.46 (t), 22.52 (t), 18.87 (q), and 13.97 (q); MS (25 eV), m/z (rel intensity) 206 (M^+, 44.6), 163 (30.6), 162 (43.3), 147 (13.2), 133 (18.0), 119 (26.5), 105 (56.0), 93 (83.8), and 28 (100). Anal. Found: C, 81.40; H, 10.86. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75.

4-Butyl-*exo*-3-methylbicyclo[4.3.0]non-4-en-*endo*-7-ol (14) and the *exo*-7 Isomer (14a). (a) To a suspension of lithium aluminium hydride (70 mg, 1.84 mmol) in THF (10 mL) under argon was added a solution of **7** (151.1 mg, 0.73 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 1 h and then successively treated with water (0.07 mL), 15% NaOH solution (0.07 mL), and water (0.21 mL). The granular solid was removed by filtration through Celite and the filtrate was concentrated. Chromatography on silica gel (10 g; 10:1 hexane–ethyl acetate) of the remaining oil (154.2 mg) gave **14** (98.2 mg, 0.47 mmol, 64%) and **14a** (26.5 mg, 0.13 mmol, 17%).

(b) To a solution of **7** (103.1 mg, 0.500 mmol) in THF (2.5 mL) under argon was added a 1 M solution of lithium tri-*sec*-butylborohydride in THF (1 mL) at −78 °C. The mixture was allowed to warm to room temperature and stirred for 12 h and then an excess of the hydride was decomposed by addition of methanol. To the solution were added 3 M sodium hydroxide solution (0.4 mL) and 30% hydrogen peroxide (0.4 mL), and the resulting mixture was stirred for 2 h at room temperature. After dilution with water, the mixture was extracted with three portions of ether. The combined extracts were washed with NH_4Cl solution, 5% $Na_2S_2O_3$ solution, and saturated brine, dried over $MgSO_4$, and concentrated. Chromatography on silica gel (10 g; 50:1 hexane–ethyl acetate) of the remaining oil (130 mg) gave **14** (88.2 mg, 0.423 mmol, 85%) as a colorless oil.

14: IR (CCl_4) 3580 (m), 2970 (s), 2940 (s), and 2880 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.33 (H_5, m, $W_{1/2}$ = 6.5 Hz, $J_{5,6}$ = 3.8 Hz), 4.13 (H_7, ddd, $J_{6,7}$ = 5.5, $J_{exo\text{-}8,7}$ = 4.2, and $J_{endo\text{-}8,7}$ = 2.0 Hz), 2.38 (H_6, m), 2.28 (H_1, m), 2.15 (H_3, m), 2.10–2.02 (2 H, m), 1.97 (1 H, dddd, J = 12.9, 9.0, 9.0, and 3.1 Hz), 1.83 ($H_{endo\text{-}8}$, m), 1.69 ($H_{exo\text{-}8}$, m), 1.61–1.22 (8 H, m), 1.02 (3 H, d, J = 7.1 Hz), and 0.91 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 149.81 (s), 116.85 (d), 75.33 (d), 45.03 (d), 37.14 (t), 35.51 (t), 33.49 (t), 31.92 (d), 31.92 (d), 30.42 (t), 29.90 (nt), 22.65 (t), 19.13 (q), and 14.03 (q); MS (25 eV), m/z (rel intensity) 208 (M^+, 24.0), 190 (52.8), 161 (21.8), 148 (57.8), 133 (100), 119 (21.6), and 105 (42.8). Anal. Found: C, 80.72; H, 11.60. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61.

14a: IR (CCl_4) 3580 (m), 2970 (s), 2940 (s), and 2880 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.36 (H_5, m, $W_{1/2}$ = 6.0 Hz), 3.91 ($H_{exdo\text{-}7}$, ddd, $J_{6,7}$ = 5.5, $J_{exo\text{-}8,7}$ = 5.5, and $J_{endo\text{-}8,7}$ = 5.5 Hz), 2.42 (H_1, m, $J_{1,6}$ = 8.5 Hz), 2.25 (H_6, m), 2.13 (H_3, m), 2.10–1.90 (4 h, m), 1.61–1.22 (8 H, m), 0.99 (3 H, d, J = 7.1 Hz), and 0.90 (3 H, t, J = 7.3 Hz); MS (13.5 eV), m/z (rel intensity) 208 (M^+, 100), 190 (56.7), 149 (15.4), 148 (41.2), 133 (53.4), 96 (11.1).

3-Butyl-*exo*-4-methyl-*endo*-9-(*tert*-butyldimethylsiloxy)bicyclo[4.3.0]nonan-2-one (15). The alcohol **14** (170.7 mg, 0.82 mmol) was treated with *tert*-butyldimethylchlorosilane (150 mg, 1.2 equiv) and imidazole (140 mg, 2.5 equiv) in DMF (2 mL) at room temperature for 14 h. The mixture was diluted with ether, washed with saturated NH_4Cl solution, water, and saturated brine, dried over $MgSO_4$, and concentrated. Chromatography of the remaining oil (281.3 mg) on silica gel (10 g, hexane) gave the silyl ether (263.6 mg, 0.82 mmol, 99%) as a colorless oil: IR 1260 (m) and 1080 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.33 (1 H, m), 4.17 (1 H, m), 2.4–1.9 (5 H, m), 1.8–1.3 (10 H, m), 1.07 (3 H, d, J = 7.0 Hz), 0.93 (3 H, m), 0.92 (9 H, s), and 0.09 (6 H, s).

To a solution of the silyl ether (152.7 mg, 0.47 mL) in THF (5 mL) was added borane–methyl sulfide complex (0.14 mL, 1.4 mmol) at 0 °C. After standing for 6 h at 0 °C, water was carefully added to the resulting solution. Most of the THF was removed under reduced pressure and the residue was dissolved in ethanol (5 mL). After successive addition of ethanol (4.5 mL), 3 M aqueous NaOH (0.5 mL), and 30% hydrogen peroxide (0.44 mL) at 0 °C, the reaction mixture was heated at 50 °C for 10 h. The mixture was extracted with two portions of ether. The ethereal extracts were combined, washed with saturated brine, and dried over $MgSO_4$. Evaporation of the solvent followed by chromatography (5 g of silica gel; 25:1 hexane–ethyl acetate) of the residue gave

a mixture of the secondary alcohols (130.0 mg, 0.38 mmol, 81%).

To a solution of Collins reagent (740 mg, 2.87 mmol) in CH_2Cl_2 (5 mL) was added a solution of the alcohols (99.4 mg, 0.29 mmol) in CH_2Cl_2 (2 mL). After 5 min being stirred at room temperature, the mixture was decanted and the black residue was washed with several portions of ether. The organic layer was combined, washed successively with 5% NaOH solution, 5% HCl, saturated $NaHCO_3$ solution, and saturated brine, dried over $MgSO_4$, and concentrated. Chromatography (3 g of silica gel; 5:1 hexane–ethyl acetate) of the residue gave **15** (95.7 mg, 0.28 mmol, 97%).

15: colorless oil; IR 1705 (s) and 1695 (s) cm^{-1}; ^1H NMR δ 4.57 (1 H, m), 2.7–2.45 (2 H, m), 2.2–1.2 (13 H, m), 1.07 (3 H, d, J = 6.5 Hz), 1.05–0.95 (3 H, br), 0.89 (9 H, s), 0.10 (3 H, s), and 0.07 (3 H, s).

***endo*-3- and *exo*-3-Butyl-*exo*-4-methylbicyclo[4.3.0]non-1(9)-en-2-ones (8a and 8b, Respectively).** To a solution of potassium *tert*-butoxide (37.0 mg, 0.33 mmol) in THF (8 mL) was added a solution of **15** (100.0 mg, 0.295 mmol) and *tert*-butyl alcohol (0.05 mL) in THF (2 mL) under argon at room temperature. After being stirred for 30 min, the mixture was treated with saturated NH_4Cl solution and extracted with three portions of ether. The ethereal extracts were combined, washed with saturated brine, and dried over $MgSO_4$. Evaporation of the solvent, followed by chromatography of the residue on silica gel (5 g; 60:1 hexene–ethyl acetate), gave a mixture of **8a** and **8b** (56.7 mg, 0.27 mmol, 92%). Analytical samples of these isomers were obtained by careful fractionation of the eluate.

8a: colorless oil; IR (CCl_4) 2920 (s), 2860 (s), 1680 (s), and 1615 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.57 (1 H, ddd, J = 2.3, 2.3, and 2.3 Hz), 3.08 (1 H, br, $W_{1/2}$ = 5 Hz), 2.5–2.0 (6 H, m), 1.85–1.15 (8 H, m), 1.06 (3 H, d, J = 7.2 Hz), and 0.89 (3 H, m); MS (25 eV), m/z (rel intensity) 206 (M^+, 2.1), 191 (1.5), 151 (13.4), and 150 (100).

8b: colorless oil; IR (CCl_4) 2930 (s), 2860 (s), 1685 (s) and 1620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (1 H, ddd, J = 2.3, 2.3, and 2.3 Hz), 3.11 (1 H, br, $W_{1/2}$ = 5 Hz), 2.5–2.15 (5 H, m), 2.12–1.8 (3 H, m), 1.8–1.0 (6 H, m), 0.92 (3 H, m), and 0.91 (3 H, d, J = 7.0 Hz); MS (25 eV), m/z (rel intensity) 206 (M^+, 2.0), 191 (4.0), 150 (59.1), and 135 (100); exact mass found m/z 206.1654, calcd for $C_{14}H_{22}O$ M 206.1670.

(±)-Ptilocaulin (1). (a) A solution of guanidine was prepared from the carbonate (22.0 mg, 0.12 mmol) by sonication for 5 min with sodium methoxide (13.0 mg, 0.24 mmol) in methanol under argon. The reaction mixture was carefully filtered and the filtrate was concentrated in vacuo. The reaction flask containing the residue was fitted with a Soxhlet extractor in which were placed 4A molecular sieves and charged with nitrogen and a solution of **8a** (27.6 mg, 0.13 mmol) in benzene (25 mL). The mixture was heated under reflux for 25 h under a nitrogen atmosphere and then allowed to cool to room temperature. The solution was neutralized with 1% HNO_3 (2 mL) and the aqueous layer was extracted with three portions of $CHCl_3$. The extracts were combined, washed with saturated $NaNO_3$ solution,[4b] dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel (5 g; $CHCl_3$–MeOH, 85:15) gave (±)-ptilocaulin nitrate (18.8 mg, 0.060 mmol, 50%).

(b) When a mixture of **8a** and **8b** (44.6 mg, 0.216 mmol) was treated by a similar procedure to that described above (±)-**1** was derived in 27% yield (18.1 mg, 0.058 mmol).

(±)-**1**: mp 151–152 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.96 (1 H, br s, $W_{1/2}$ = 5 Hz), 8.30 (1 H, br s, $W_{1/2}$ = 8 Hz), 7.39 (2 H, br s, $W_{1/2}$ = 10 Hz), 3.77 (1 H, m), 2.55–2.3 (4 H, m), 2.2–1.95 (2 H, m), 1.95–1.1 (9 H, m), 1.05 (3 H, d, J = 6.8 Hz), and 0.90 (3 H, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 151.77, 126.99, 121.01, 53.22, 36.52, 33.98, 33.09, 32.22, 29.65, 27.79, 26.95, 24.65, 22.44, 19.53, 14.00; exact mass found m/z 247.2020, calcd for $C_{15}H_{25}N_3$ M 247.2047.

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Robustadials. 2. Total Synthesis of the Bicyclo[3.2.0]heptane Structure Proposed for Robustadials A and B

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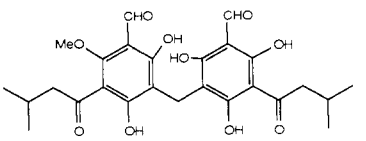
Total synthesis of the bicyclo[3.2.0]heptane structure **2a** proposed for robustadial A was achieved. The molecular architecture of the synthetic product was unambiguously established by X-ray crystallographic analysis of an intermediate in the synthesis. However, spectral comparison clearly shows that **2a** is not the correct structure for the natural product robustadial A. Intramolecular copper(I)-catalyzed $2\pi + 2\pi$ photocycloaddition was exploited as the key step for generating the bicyclo[3.2.0]heptane portion of **2a** from the 1,6-heptadiene **16**, which was assembled from 1,3,5-trimethoxybenzene in six steps. Photocyclization of **16** proceeded smoothly, affording **17** in 75–80% yield.

A global resurgence of malaria,[1] the appearance of strains of which are resistant[2] to quinine, its analogues, and many of the relatively small number of known antimalarial drugs, provides an urgent need for the identification and total synthesis of new antimalarial natural products. Several active compounds are contained in an antimalarial ethanol extract of *Eucalyptus robusta* leaves, a plant used in Chinese herbal medicine.[3] Robustaol A (**1**) was the first



1

component isolated from this extract which showed in vivo antimalarial activity against *Plasmodium berghei* in mice. The structure of **1** was established by total synthesis.[3] A

(1) The disease affects about 250 million to 300 million people worldwide each year, causing debilitating illness.
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