A Formal Total Synthesis of (±)-Vernolepin and (±)-Vernomenin

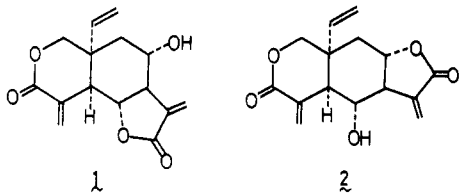
Takeshi Wakamatsu,* Hiromu Hara, and Yoshio Ban

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Received July 30, 1984

A formal total synthesis of (±)-vernolepin (1) and (±)-vernomenin (2) has been achieved starting from *cis*-4-cyclohexene-1,2-dicarboxylic acid monomethyl ester (5) via a novel intramolecular alkylation of 14 → 16. The penultimate target was directed toward the synthesis of Danishefsky's intermediate 4 which has previously been converted in six steps to 1 and 2 in racemic form.

Since the initial report in 1968 on the isolation and characterization of vernolepin (1) and vernomenin (2) from Ethiopian Compositae, *Veronia hymenolepis*,[1] these

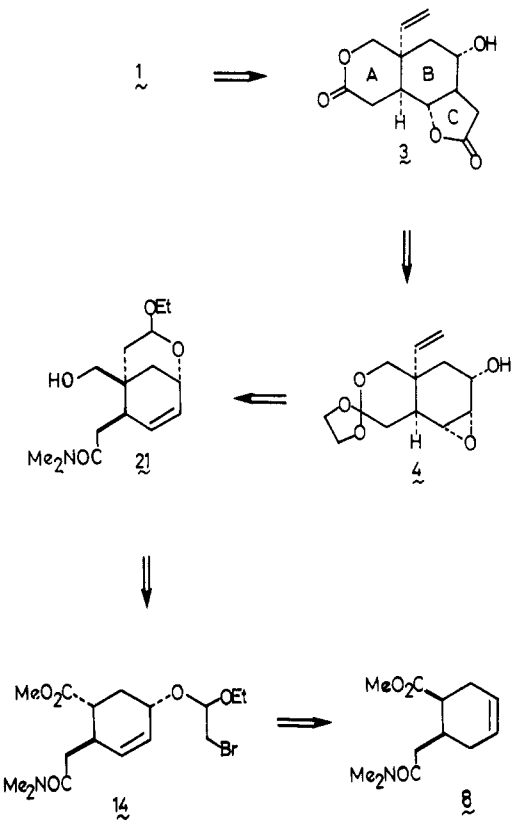


1 2

elemanolide sesquiterpene dilactones have been the subject of synthetic activity by numerous research groups,[2-14] culminating in the description of total synthesis.[2a,3a,4a,5b,6] Quite apart from the pronounced cytotoxic activity of vernolepin, and to a lesser extent vernomenin, interest in the synthesis of these sesquiterpenes arises from the impressive functional and stereochemical array that resides in the B ring of these natural products.

In the present paper we describe the details of our own results in this area, which involved an effective method for the formation of the oxabicyclo[3.3.1]nonene ring system by means of an intramolecular alkylation. From the retrosynthetic perspective (Scheme I) we envisioned that the formation of the cis-fused δ-valerolactone AB ring in the alcohol 21 followed by multistep chemical transformations would produce the target 4. The epoxide 4 was successfully converted by Danishefsky to vernolepin and vernomenin

Scheme I



via regiospecific epoxide ring opening with a two-carbon nucleophile followed by lactonization to the bisnorvernolepin 3. An intramolecular cyclization of the bromide 14 to the key intermediate 21 would be a very plausible way to introduce the necessary two-carbon unit at the angular position. The bromide 14 would be anticipated to be available starting from the cyclohexene derivative 8.

Results and Discussion

Reaction of the readily available *cis*-4-cyclohexene-1,2-dicarboxylic acid monomethyl ester (5)[15] with thionyl chloride in refluxing benzene afforded the corresponding acid chloride 6 (Scheme II). The crude chloride 6 was then treated with diazomethane in ether solution containing triethylamine[16] as base to give rise to the diazoketone 7 in 76% yield. The Wolff rearrangement of 7 with silver benzoate in the presence of dimethylamine in dioxane solution afforded the desired amide 8 in 91% yield. The next synthetic step required an effective epimerization of 8 at the methine hydrogen adjacent to the ester residue. Reaction of 8 with potassium hydride in tetrahydrofuran

(1) Kupchan, S. M.; Hemingway, R.; Werner, D.; Karim, A. *J. Am. Chem. Soc.* **1968**, *90*, 3596. Kupchan, S. M.; Hemingway, R.; Werner, D.; Karim, A.; McPhail, A.; Sim, G. A. *J. Org. Chem.* **1969**, *34*, 3903.

(2) (a) Grieco, P. A.; Nishizawa, M.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1976**, *98*, 1612. (b) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *Ibid.* **1977**, *99*, 5773. (c) Grieco, P. A.; Noguez, J. A.; Masaki, Y. *J. Org. Chem.* **1977**, *42*, 495.

(3) (a) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028. (b) Danishefsky, S.; Kitahara, T.; Mckee, R.; Schuda, P. F. *Ibid.* **1976**, *98*, 6715. (c) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *Ibid.* **1977**, *99*, 6066.

(4) (a) Kieczykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938. (b) Kieczykowski, G.; Roberts, M. R.; Schlessinger, R. H. *J. Org. Chem.* **1978**, *43*, 788. (c) Kieczykowski, G.; Quesada, M. L.; Schlessinger, R. J. *J. Am. Chem. Soc.* **1980**, *102*, 782.

(5) (a) Isobe, M.; Iio, H.; kawai, T.; Goto, T. *Tetrahedron Lett.* **1977**, 703. (b) Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, 100, 1938. (c) Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *Tetrahedron* **1979**, *35*, 941. (d) Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1979**, *101*, 6076.

(6) Zutterman, F.; Wilde, H. De; Mijingheer, R.; Clerq, P. De; Vandewalle, M. *Tetrahedron* **1979**, 2389.

(7) Marshall, J. A.; Seite, D. E. *J. Org. Chem.* **1975**, *40*, 534. Marshall, J. A.; Flynn, G. A. *Synth. Commun.* **1977**, *7*, 417. Marshall J. A.; Flynn, G. A. *J. Org. Chem.* **1979**, *44*, 1391.

(8) Wege, P. A.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144.

(9) Torii, S.; Okamoto, T.; Kadono, O. *Chem. Lett.* **1977**, 495.

(10) Boeckman, R. K., Jr.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1977**, 4485.

(11) Scheffold, R.; Rĕvĕsz, L.; Aebersold, J.; Schaltegger, A. *Chimica* **1976**, *30*, 57.

(12) Wakamatsu, T.; Hara, H.; Ban, Y. *Tetrahedron Lett.* **1979**, 1227.

(13) Fujimoto, Y.; Miura, H.; Shimizu, T.; Tatsuno, T. *Tetrahedron Lett.* **1980**, *21*, 3409.

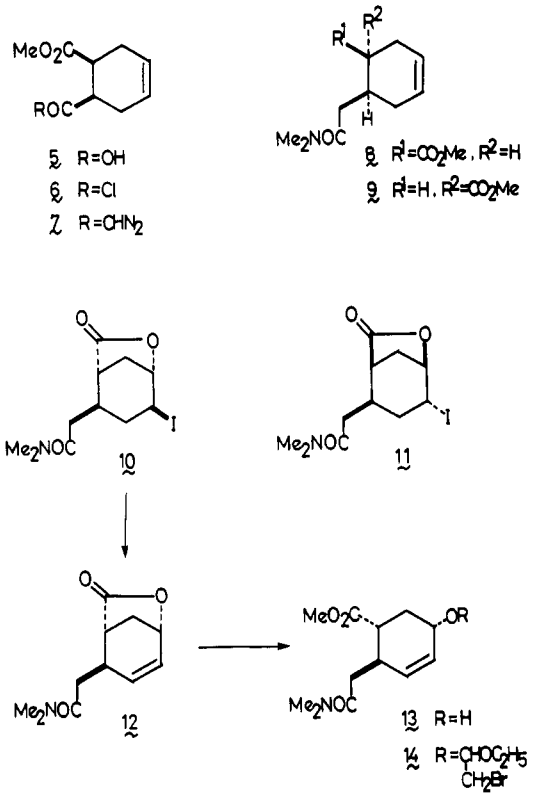
(14) Harding, K. E.; Clement, B. A.; Moreno, L.; Katalinic, J. P. *J. Org. Chem.* **1981**, *46*, 940.

(15) White, R. V.; Landis, P. S. *J. Org. Chem.* **1956**, *21*, 279.

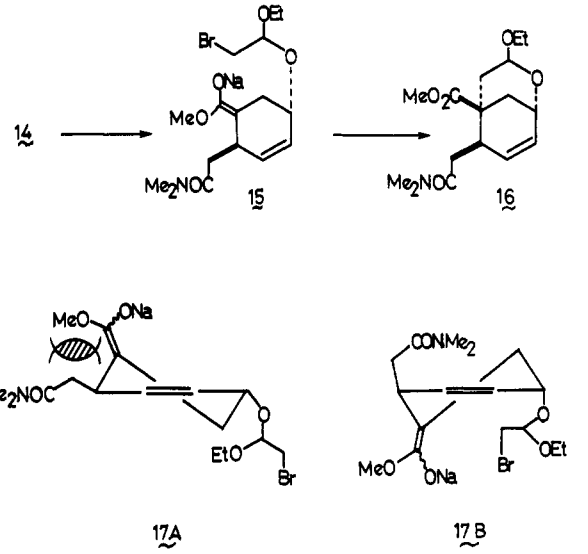
(16) Newman, M. S.; Beal, P., III. *J. Am. Chem. Soc.* **1949**, *71*, 1506.

0022-3263/85/1950-0108$01.50/0

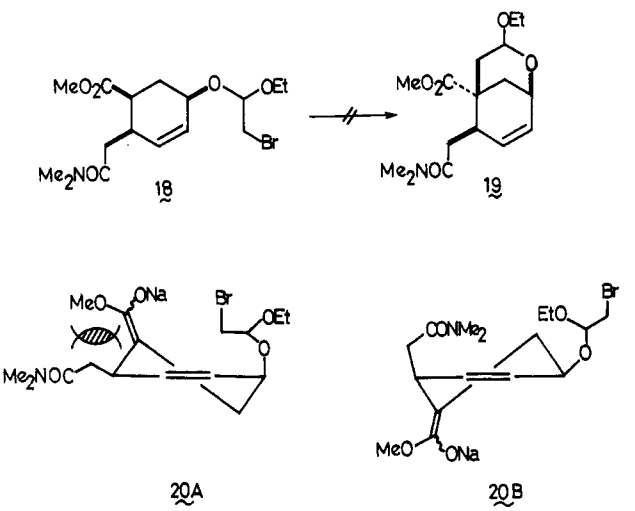
Scheme II



Scheme III



Scheme IV



resulted in preferential formation in a 4:1 ratio of the requisite ester **9** and the unchanged **8**. The resulting mixture of **8** and **9** obtained in this epimerization was saponified with aqueous lithium hydroxide and subsequent iodo lactonization with iodine–potassium iodide in aqueous sodium bicarbonate gave 53% of the iodo lactone **10** and 12% of the isomer **11**, respectively, after separation by chromatography on silica gel. The iodo lactone **10** was easily converted into the cyclohexene derivative **12** in 89% yield by treatment with diazabicycloundecene (DBU) in refluxing benzene. Treatment of the lactone **12** either with sodium methoxide in methanol or with boron trifluoride etherate in methanol afforded the hydroxy ester **13** in quantitative yield. As a two-carbon electrophile which could be convertible to a vinyl group at a later stage of the synthesis, β-bromovinyl ethyl ether[17] was chosen. The reaction of **13** with β-bromovinyl ethyl ether in the presence of catalytic amounts of camphorsulfonic acid (CSA) gave rise to the bromide **14** in 96% yield.

An examination of molecular models representing cyclization of the anion **15** obtained by deprotonation of **14** shows the anion to have two possible conformers **17A** and **17B** (Scheme III). It is considered from these models that a serious spacial repulsion[18] between either the methoxy group or alkoxide center and the methylene group in the planarity occurs in the conformer **17A**, while an interaction of this type does not occur in the conformer **17B** which would be capable of undergoing cyclization. In the event, the reaction of **14** proved to be entirely as expected. Thus, treatment of the bromide **14** with sodium bis(trimethylsilyl)amide in tetrahydrofuran at 60 °C for 5 min gave the bicyclic ester **16** in 85% yield. Though the ester **16** obtained in this way proved to be a diastereomeric mixture by ^{1}H NMR analysis, these isomers could not be separated by chromatography.

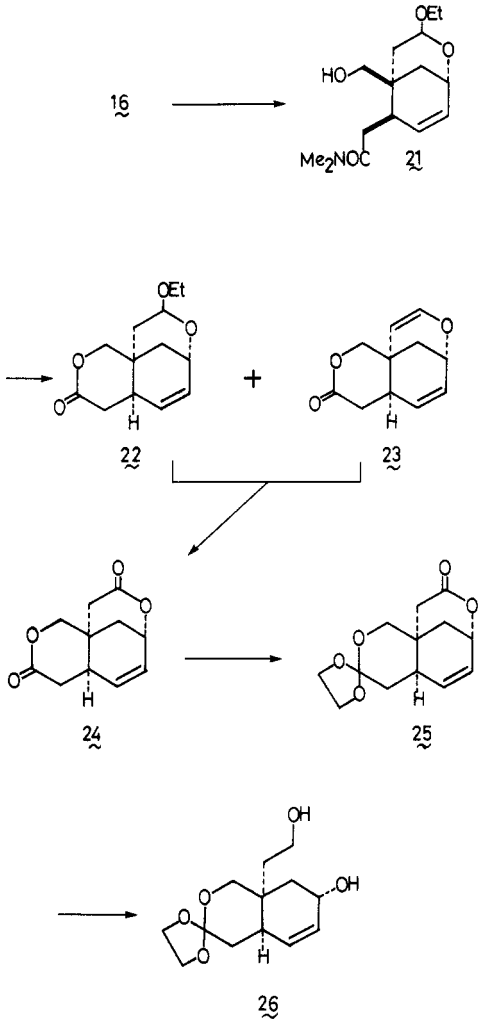
A similar sequence was further explored with respect to an intramolecular alkylation in the case of **18** → **19** (Scheme IV). The bromide **18** was readily prepared from the iodo lactone **11** in a similar manner as described in the series **10** → **14**. The crucial cyclization of the bromide **18** under the same basic conditions led to none of the corresponding bicyclic ester **19** and resulted wholly in decomposition of the starting material **18**. In the light of the foregoing effects predicted in **14**, these results suggest that the cyclization is not likely to occur from the form of the conformer **20A** due to the exclusive existence in the form of conformer **20B**. Obviously **20B** is unable to cyclize to **19** by the reason of a separation of reaction sites far from each other.

Next synthetic attention was turned to the formation of the A ring in alcohol **21**. Selective reduction of **16** with lithium triethylborohydride in tetrahydrofuran at −40 °C gave alcohol **21** in quantitative yield (Scheme V). A mild lactonization of **21** was carried out by reaction with *tert*-butyldimethylchlorosilane[19] in tetrahydrofuran at room temperature for 16 h to provide a mixture of the tricyclic lactone **22** (35%) and the ticyclic diene **23** (20%), respectively. Oxidation of lactones **22** and **23** with Jones

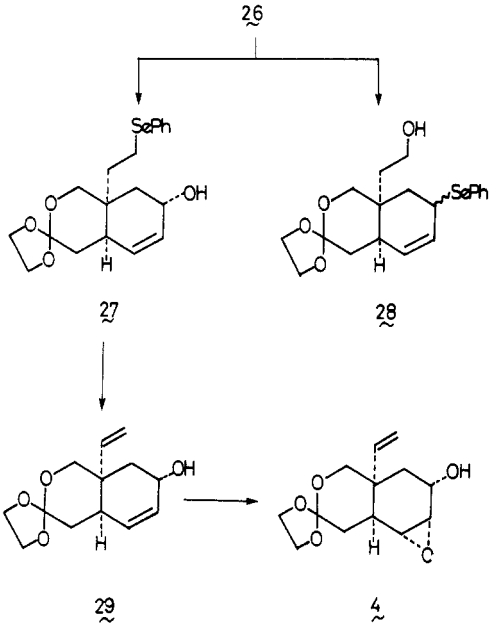
(17) Stork, G.; Tomasz, M. *J. Am. Chem. Soc.* **1964**, *86*, 471.
(18) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, 87, 5492. Malhotra, S. K.; Johnson, F. *Ibid.* **1965**, *87*, 5493.

(19) When **21** was treated with *tert*-butyldimethylchlorosilane in the presence of triethylamine and 4-(dimethylamino)pyridine in THF, the corresponding silyl ether was obtained in 89% yield together with small amounts of lactones **22** and **23**.

Scheme V



Scheme VI



reagent at 0 °C for 30 min offered the desired dilactone **24** in moderate yield. The A-ring lactone of **24** underwent a remarkably clean and regioselective ortho esterification by reaction with ethylene glycol in the presence of Dowex 50W and *p*-toluenesulfonic acid in refluxing benzene[3c] to afford the ortho ester **25**, which in turn was subjected to reduction with lithium aluminium hydride in tetrahydrofuran to give the diol **26** in 88% yield from **24**.

The diol **26** was then treated with *o*-nitrophenyl selenocyanate[20] in the presence of tri-*n*-butylphosphine in tetrahydrofuran to yield the requisite selenide **27** (22%) and the isomer **28** (11%) (Scheme VI). Finally, Henbest epoxidation[21] of **29** with *m*-chloroperbenzoic acid in dichloromethane solution afforded exclusively the α-epoxide **4** in 54% yield, whose spectral properties were identical in all respects with authentic sample of **4** kindly provided by Professor Danishefsky. Since Danishefsky[3a,c] had reported the successful conversion of **4** into vernolepin and vernomenin by a six-step sequence, the present synthesis of **4** means a formal total synthesis of **1** and **2**.

Experimental Section

Melting points were measured with a Yanaco MP-J2 hot stage microscope and with a Yamato MP-1 melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were obtained on a JASCO IRA-2 diffraction grating infrared spectrophotometer. Data are given in reciprocal centimeters with only the important diagnostic values reported. ^{1}H NMR spectra were recorded at 100 MHz on a JEOL JNM-FX 100 or at 200 MHz on a JEOL JNM-FX 200 spectrometer. Chemical shifts are reported in parts per million on the δ scale, relative to tetramethylsilane as an internal standard. Data are reported in the form of values of chemical shift (peak multiplicity, number of protons, coupling constant if appropriate). Mass spectra (MS) were recorded on a JEOL JMS-D 300 spectrometer. Elemental analyses were performed by the Center for Instrumental Analysis at our university. Thin-layer chromatography was carried out on Merck GF_{254} silica gel plates. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl in a recirculating still, with a deep blue color maintained in the distilling pot. Diethyl ether and benzene were dried over sodium metal.

Methyl *cis*-6-[(Diazomethyl)carbonyl]-3-cyclohexene-1-carboxylate (7). A solution of the half ester **5** (14.1 g, 78 mmol) and thionyl chloride (20 mL) in 100 mL of dry benzene was refluxed for 2 h. After removal of the solvent and excess thionyl chloride, the crude acid chloride **6** was dissolved in 50 mL of anhydrous ether. This solution was added dropwise over a period of 2 min at 0 °C to an etheral solution of diazomethane prepared from *N*-nitro-*N*-methyltosylamide (25 g, 115 mmol) in the presence of triethylamine (8 g, 80 mmol). After 2 h with stirring, the suspension was filtered off and the resulting yellow oil was purified by chromatography on silica gel. Elution with dichloromethane–hexane (3:2) gave 12.4 g (76%) of diazoketone **7** as a yellow oil: IR (neat) 2220, 1730, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30–2.56 (m, 4 H), 2.80–3.18 (m, 2 H), 3.67 (s, 3 H), 5.46 (s, 1 H), 5.69 (br s, 2 H).

Methyl *cis*-6-[2-(Dimethylamino)-2-oxoethyl]-3-cyclohexene-1-carboxylate (8). To a stirred solution of 12.4 g (60 mmol) of the diazoketone **7** in 100 mL of dioxane was added at 0 °C 60 mL of 15% dimethylamine in dioxane solution, and then 13.5 g (59 mmol) of silver benzoate was added over a period of 5 min to this solution. After being stirred for 10 min at 0 °C, the mixture was allowed to stir for an additional 10 min at room temperature. The solvent was evaporated in vacuo to give the black residue, which was filtered through a short pad of silica gel with dichloromethane. The resulting oily product (13.5 g) was chromatographed on silica gel with dichloromethane–acetone (8:1) to give 12.1 g (91%) of the amide **8** as a colorless oil: bp 72 °C (0.01 mmHg); IR (neat) 1725, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3 H), 2.99 (s, 3 H), 3.66 (s, 3 H), 5.65 (br s, 2 H); MS, *m/e* 225 (M^+).

***exo*-2-[2-(Dimethylamino)-2-oxoethyl]-*exo*-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (10) and *endo*-2-[2-(Dimethylamino)-2-oxoethyl]-*exo*-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (11).** To a solution of 5.69 g of the amide **8** in 60 mL of dry THF

(20) (a) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485. (b) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.
(21) Henbest, H. B.; Wilson, A. L. *J. Chem. Soc.* **1957**, 1958.

was added 1.0 g of potassium hydride and the whole mixture was stirred at room temperature for 16 h under argon atmosphere. The reaction mixture was cooled to 0 °C and 10 mL of methanol was added slowly. After neutralization with 10% hydrochloric acid followed by removal of the solvent, the residue was chromatographed on silica gel with hexane–dichloromethane–acetone (3:2:1) to give 5.41 g (95%) of a 1:4 mixture of **8** and **9**. The ratio of product was determined by gas–liquid-phase chromatographic analysis. This mixture was used for the next step without further separation. To a solution of the mixture (5.41 g) in 100 mL of methanol was added a solution of 1.5 N lithium hydroxide (24 mL), and then the solution was stirred at room temperature for 6 h. The solvent was removed in vacuo and 100 mL of water was added to the residue. After extraction with ether, the aqueous layer was neutralized by addition of Amberlite IRA 120 and then filtered off. The aqueous solution was evaporated under reduced pressure to give 5.48 g of the crude carbocyclic acid. A solution of the acid in 100 mL of saturated sodium bicarbonate was treated with iodine (8 g, 31 mmol) and potassium iodide (27 g, 162 mmol) dissolved in 60 mL of water at room temperature for 16 h. The aqueous solution was taken up in dichloromethane and the organic layer was washed with 10% sodium thiosulfate. Evaporation of the solvent, dried over anhydrous magnesium sulfate, gave 7.18 g of the product, which was chromatographed on silica gel. Elution with hexane–dichloromethane–acetone (3:2:1) gave 4.50 g (53%) of the iodo lactone **10** and 1.06 g (12%) of the isomer **11**, which were easily recrystallized from ethyl acetate–hexane. **10**: mp 128–129 °C; IR (Nujol) 1770, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (d, 1 H, J = 16 Hz), 2.33 (m, 1 H), 2.97 (s, 3 H), 3.07 (s, 3 H), 4.42 (m, 1 H), 4.88 (dd, 1 H, J = 5.9 and 3.9 Hz); MS, m/e 337 (M^+). Anal. Calcd for $C_{11}H_{16}INO_3$: C, 39.19; H, 4.78; N, 4.15; I, 37.64. Found: C, 39.20; H, 4.63; N, 4.33; I, 37.86. **11**: mp 119–122 °C; IR (Nujol) 1780, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (d, 1 H, J = 12.3 Hz), 2.96 (s, 3 H), 3.01 (s, 3 H), 4.49 (m, 1 H), 4.83 (m, 1 H); MS; m/e 337 (M^+). Anal. Calcd for $C_{11}H_{16}INO_3$: C, 39.19; H, 4.78; N, 4.15; I, 37.64. Found: C, 39.21; H, 4.64; N, 3.93; I, 37.85.

***exo*-2-[2-(Dimethylamino)-2-oxoethyl]-6-oxa-7-oxobicyclo[3.2.1]oct-3-ene (12).** To a solution of 398 mg (1.09 mmol) of the iodo lactone **10** in 10 mL of benzene was added at once 300 mg (1.97 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the reaction mixture was refluxed with stirring under argon atmosphere for 2 h. After filtration of the DBU salt formed, the filtrate was evaporated in vacuo to give the crude material, which was chromatographed on silica gel. Elution with hexane–dichloromethane–acetone (2:2:1) afforded 203 mg (89%) of the lactone **12**: mp 96–97 °C; IR (Nujol) 1765, 1635, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (d, 1 H, J = 11.2 Hz), 2.3–2.6 (m, 3 H), 2.86 (m, 1 H), 2.97 (s, 3 H), 3.02 (s, 3 H), 3.11 (m, 1 H), 4.76 (t, 1 H, J = 6 Hz), 5.84 (m, 1 H), 6.24 (m, 1 H); MS, m/e 209 (M^+). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.32; H, 7.14; N, 6.67.

Methyl *t*-2-[2-(Dimethylamino)-2-oxoethyl]-*c*-5-hydroxy-3-cyclohexene-*r*-1-carboxylate (13). Method A. To a solution of 2.28 g (10.9 mmol) of the lactone **12** in 30 mL of methanol cooled to 0 °C was added 800 mg (14.8 mmol) of sodium methoxide, and the whole mixture was stirred for 15 min. After addition of 10% hydrochloric acid, the solvent was removed in vacuo to afford the crude ester, which was purified by chromatography on silica gel. Elution with dichloromethane–acetone (2:1) gave 2.63 g (100%) of the pure hydroxy ester **13**.

Method B. To a solution of 49 mg (0.234 mmol) of **12** in 4 mL of methanol was added dropwise catalytic amounts of boron trifluoride etherate, and the mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was chromatographed on silica gel to give 52 mg (92%) of **13** as a colorless oil: IR (neat) 3400, 1740, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.94 (s, 3 H), 3.00 (s, 3 H), 3.70 (s, 3 H), 4.26 (m, 1 H), 5.75 (br s, 2 H); MS, m/e 241 (M^+).

Methyl *t*-2-[2-(Dimethylamino)-2-oxoethyl]-*c*-5-(1-ethoxy-2-bromoethoxy)-3-cyclohexene-*r*-1-carboxylate (14). A solution of 2.63 g (10.9 mmol) of the hydroxy ester **13** and 2.6 g (17 mmol) of β-bromovinyl ethyl ether in 50 mL of dichloromethane was treated with catalytic amounts of camphorsulfonic acid at room temperature for 48 h. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane–dichloromethane–acetone (2:2:1) to give 4.10 g (96%) of the bromide **14** as a colorless oil: IR (neat) 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 2.94 (s, 3 H), 3.01 (s, 3 H), 3.36 (d, 2 H, J = 6 Hz), 3.48–3.72 (m, 2 H), 3.70 (s, 3 H), 4.33 (m, 1 H, $w_{1/2}$ = 2.0 Hz), 4.80 (t, 1 H, J = 5 Hz), 5.74 (br s, 2 H); MS, m/e 379, 391 (M^+).

Methyl *exo*-2-[2-(Dimethylamino)-2-oxoethyl]-7-ethoxy-6-oxabicyclo[3.3.1]non-3-ene-1-carboxylate (16). To a refluxing solution of 3.00 g (7.67 mmol) of the bromide **14** in 50 mL of dry THF under an argon atmosphere was added dropwise a solution of 2.10 g (11.5 mmol) of sodium bis(trimethylsilyl)amide in 10 mL of dry THF. After the reaction mixture was refluxed for 5 min, the solvent was removed in vacuo to give the crude bicyclic ester. Purification by chromatography on silica gel using hexane–dichloromethane–acetone (2:2:1) afforded 2.02 g (85%) of the pure bicyclic ester **16**: mp 78–102 °C; IR (Nujol) 1735, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 and 1.19 (each t, 3 H, J = 6.8 Hz), 2.96 (s, 6 H), 3.03 (m, 1 H), 3.72 (s, 3 H), 3.67–3.78 (m, 2 H), 4.66 (quintet, 1 H, J = 2.9 Hz), 4.95 (dd, 1 H, J = 6.4 and 2.5 Hz), 5.75 (dd, 1 H, J = 9.7 and 5.8 Hz), 6.13 (dd, 1 H, J = 9.7 and 4.9 Hz); MS, m/e 311 (M^+). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.57; H, 8.07; N, 4.30.

***exo*-2-[2-(Dimethylamino)-1-oxoethyl]-7-ethoxy-1-(hydroxymethyl)-6-oxabicyclo[3.3.1]non-3-ene (21).** To a solution of 2.96 g (9.52 mmol) of the bicyclic ester **16** in 100 mL of dry THF cooled at −45 °C was added dropwise over a period of 10 min 28 mL of a 1 M solution of lithium triethylborohydride in dry THF. After being stirred for 4.5 h at −30 °C, the reaction was quenched by the addition of 6 mL of water. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel. Elution with dichloromethane–acetone (2:1) gave 2.69 g (100%) of alcohol **21**: mp 88–93 °C; IR (Nujol) 3410, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 and 1.25 (each t, 3 H, J = 7.0 Hz), 2.97, 3.00, 3.01, and 3.04 (each s, 6 H), 3.35–3.78 (m, 4 H), 4.19 (m, 1 H), 5.12 (m, 1 H), 5.58–5.80 (m, 2 H). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.49; H, 9.09; N, 4.93.

Preparation of the Tricyclic Lactones 22 and 23. A solution of 1.20 g (4.23 mmol) of the alcohol **21** in 20 mL of dry THF was treated with 1.28 g (8.5 mmol) of *tert*-butyldimethylchlorosilane at room temperature for 16 h. After removal of the solvent, the residue was chromatographed on silica gel using hexane–dichloromethane–acetone (5:2:1) to provide 355 mg (35%) of the lactone **22** and 159 mg (20%) of the lactone **23**, respectively. **22**: IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 and 1.24 (each t, 3 H, J = 6.8 Hz), 3.48 (m, 1 H), 3.72 (q, 1 H, J = 6.8 Hz), 3.89 (d, 1 H, J = 11.5 Hz), 4.07 (d, 1 H, J = 11.5 Hz), 4.47 (m, 1 H, $w_{1/2}$ = 12 Hz), 4.80 (m, 1 H, $w_{1/2}$ = 16 Hz), 5.92–6.06 (m, 2 H); MS, m/e 238 (M^+). **23**: IR (neat) 1720, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (dd, 1 H, J = 13.2 and 2.9 Hz), 1.93 (dt, 1 H, J = 13.2 and 2.4 Hz), 2.34 (dd, 1 H, J = 17.1 and 9.1 Hz), 2.50 (m, 1 H, $w_{1/2}$ = 24 Hz), 2.81 (dd, 1 H, J = 17.1 and 8.1 Hz), 4.08 (d, 1 H, J = 11.7 Hz), 4.25 (d, 1 H, J = 11.7 Hz), 4.42 (dd, 1 H, J = 5.9 and 2.5 Hz), 4.75 (quintet, 1 H, J = 2.7 Hz), 5.87 (dd, 1 H, J = 9.5 and 5.4 Hz), 5.98 (dd, 1 H, J = 9.5 and 4.4 Hz), 6.37 (d, 1 H, J = 5.9 Hz); MS, m/e 192 (M^+).

Oxidation of Lactones 22 and 23. Preparation of the Tricyclic Dilactone 24. To a solution of 240 mg (1.01 mmol) of **22** and 153 mg (0.8 mmol) of **23** in 2 mL of acetone cooled to 0 °C was added dropwise 2 mL (5.34 mmo) of Jones reagent, and the whole mixture was stirred for 30 min. After addition of isopropyl alcohol (0.5 mL) was complete, the reaction mixture was diluted with 25 mL of brine, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave the crude material, which was chromatographed on silica gel. Elution with hexane–dichloromethane–acetone (1:2:1) afforded 144 mg (38%) of crystalline dilactone **24**: mp 153–156 °C; IR (Nujol) 1725 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (dd, 1 H, J = 14.1 and 2.9 Hz), 2.11 (dt, 1 H, J = 14.1 and 2.5 Hz), 2.36 (dd, 1 H, J = 17.1 and 8.2 Hz), 2.49 (d, 1 H, J = 1.5 Hz), 2.64 (tdd, 1 H, J = 8.2, 4.2, and 1.5 Hz), 2.86 (dd, 1 H, J = 17.1 and 8.2 Hz), 4.04 (d, 1 H, J = 11.7 Hz), 4.18 (d, 1 H, J = 11.7 Hz), 4.95 (ddd, 1 H, J = 5.9, 2.9 Hz), 5.91 (dd, 1 H, J = 9.7 and 4.3 Hz), 6.18 (ddt, 1 H, J = 9.7, 5.9, and 1.2 Hz); MS, m/e 208 (M^+). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.33; H, 5.76.

***cis*-3,3-(Ethylenedioxy)-7α-hydroxy-9α-(2-hydroxyethyl)-2-oxaoctal-5-ene (26).** To a solution of 171 mg (0.822 mmol) of the dilactone **24** in 1.9 mL of ethylene glycol was added 130 mL of dry benzene. The mixture was vigorously stirred with 1.93 g of anhydrous magnesium sulfate, 112 mg of Dowex 50W×8 (H^+ form), and 19 mg of *p*-toluenesulfonic acid. Reflux under a Dean–Stark separator, with vigorous stirring, was continued for 1.5 h. After filtration of the solid, the filtrate was washed with 20 mL of 4:3:3 saturated sodium bicarbonate/saturated sodium chloride/water. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 199 mg of ethylene ortho ester **25**: mp 198–202 °C; IR (Nujol) 1725, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.43 (d, 1 H, J = 11.7 Hz), 3.57 (d, 1 H, J = 11.7 Hz), 3.89–4.08 (m, 4 H), 4.85 (quntet, 1 H, J = 2.7 Hz), 5.90 (dd, 1 H, J = 9.8 and 4.4 Hz), 6.03 (dd, 1 H, J = 9.8 and 5.4 Hz); MS, m/e 252 (M^+).

To a solution of 199 mg of **25** in 3 mL of dry THF cooled to 0 °C was added 96 mg (2.5 mmol) of lithium aluminum hydride, and the whole mixture was allowed to stir at room temperature for 50 mim. After addition of sodium sulfate·$10H_2O$ was complete, the reaction mixture was filtered off and the filtrate was evaporated in vacuo to give the crude diol **26**, which was purified by chromatography on silica gel. Elution with dichloromethane–methanol (20:1) gave 185 mg (88%) of diol **26**: mp 86–87 °C; IR (Nujol) 3220, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97–4.14 (m, 4 H), 4.31 (m, 1 H), 5.73 (d, 1 H, J = 10.3 Hz), 5.80 (d, 1 H, J = 10.3 Hz); MS m/e 256 (M^+). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.89. Found: C, 60.64; H, 7.64.

***cis*-3,3-(Ethylenedioxy)-7α-hydroxy-9α-[2-[(*o*-nitrophenyl)seleno]ethyl]-2-oxaoctal-5-ene (27).** To a solution of 57 mg (0.223 mmol) of diol **26** in 2 mL of dry THF was added 50 mg (0.22 mmol) of *o*-nitrophenyl selenocyanate and 65 μL (0.26 mmol) of tri-*n*-butylphosphine under an argon atmosphere. The whole mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure to give the crude selenides. Purification of product by chromatography on alumina using benzene–ethyl acetate (1:1) afforded 22 mg (22%) of the selenide **27** and 11 mg (11%) of the selenide **28**, respectively. **27**: IR (neat) 3450, 1590, 1510 cm^{-1}; MS, m/e 443, 441, 439, 438, 437, 435 (M^+); UV (EtOH) 255 nm. **28**: IR (neat) 3450, 1590, 1566, 1510 cm^{-1}; MS, m/e 443, 441, 439, 438, 437, 435 (M^+); UV (EtOH) 255 nm.

***cis*-9α-Ethenyl-3,3-(ethylenedioxy)-7α-hydroxy-2-oxaoctal-5-ene (29).** A solution of 16 mg (0.036 mmol) of the selenide **27** in 0.5 mL of THF was treated with a 30% hydrogen peroxide (50 μL) solution at room temperature for 18 h. After removal of the solvent, the residue was purified by chromatography on alumina. Elution with dichloromethane–methanol (50:1) gave 8 mg (93%) of the vinyl alcohol **29**: mp 129–133 °C; IR (melt) 3470, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (dd, 1 H, J = 14.2 and 5.6 Hz), 2.35 (dd, 1 H, J = 14.2 and 5.6 Hz), 2.64 (m, 1 H, $w_{1/2}$ = 20 Hz), 3.54 (d, 1 H, J = 11.7 Hz), 3.62 (d, 1 H, J = 11.7 Hz), 3.97, 4.18 (m, 4 H), 4.20 (m, 1 H, $w_{1/2}$ = 24 Hz), 5.19 (dd, 1 H, J = 17.6 and 1.0 Hz), 5.21 (dd, 1 H, J = 10.8 and 1.0 Hz), 5.82 (br, 2 H), 5.87 (dd, 1 H, J = 17.6 and 10.8 Hz); MS, m/e 238 (M^+).

***cis*-9α-Ethenyl-3,3-(ethylenedioxy)-7α-hydroxy-2-oxa-5α,6α-oxirenodecalin (4).** To a solution of 7 mg (0.029 mmol) of the vinyl alcohol **29** in 0.5 mL of dichloromethane was added 8 mg (0.05 mmol) of *m*-chloroperbenzoic acid, and the resulting mixture was stirred at room temperature for 1.5 h. After addition of sodium sulfite followed by filtration, the organic layer was washed with saturated sodium bicarbonate solution and then brine. The solvent, dried over anhydrous sodium sulfate, was evaporated in vacuo to give the crude product, which was chromatographed on alumina. Elution with dichloromethane–methanol (50:1) gave 4.0 mg, 54%) of epoxide **4**: mp 131–132 °C; IR ($CHCl_3$) 3550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27–1.92 (5 H), 2.18–2.30 (m, 2 H), 3.37–3.43 (m, 2 H), 3.49 (d, 1 H, J = 12.2 Hz), 3.67 (d, 1 H, J = 12.2 Hz), 4.00–4.16 (m, 4 H), 5.14 (dd, 1 H, J = 10.7 and 1.0 Hz), 5.20 (dd, 1 H, J = 17.6 and 1.0 Hz), 5.88 (dd, 1 H, J = 17.6 and 10.7 Hz); MS, m/e 253 ($M^+ - 1$). the ^1H NMR, IR, and mass spectra were identical with those of authentic sample **4** kindly provided by Professor S. Danishefsky.

Acknowledgment. We express our thanks to Professor Danishefsky for his generous gift of authentic sample **4**. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Registry No. (±)-**1**, 59598-29-7; (±)-**2**, 59598-30-0; (±)-**4**, 59955-20-3; (±)-**5**, 93603-11-3; (±)-**6**, 93531-06-7; (±)-**7**, 74207-04-8; (±)-**8**, 74320-39-1; (±)-**9**, 93531-07-8; (±)-**10**, 93531-08-9; (±)-**11**, 93603-12-4; (±)-**12**, 93531-09-0; (±)-**13**, 93531-10-3; **14**, 93531-11-4; **16**, 93531-12-5; **21**, 93531-13-6; **22**, 93531-14-7; (±)-**23**, 93531-15-8; (±)-**24**, 93531-16-9; (±)-**25**, 93531-17-0; (±)-**26**, 93531-18-1; (±)-**27**, 93531-19-2; **28**, 93531-20-5; (±)-**29**, 93531-21-6; β-bromovinyl ethyl ether, 18519-95-4; *o*-nitrophenyl selenocyanate, 51694-22-5.

Notes

Synthesis and Crystal Structure of an Oxidizable Polycyclic Metacyclophane Derived from Hexacyclen and Hexafluorobenzene

Margaret C. Etter*[1a]

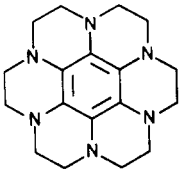
3M Company, St. Paul, Minnesota 55144

Jack E. Richman[1b]

Chemistry Department, University of Idaho, Moscow, Idaho 83843

Received April 23, 1984

Benzoquinone reacts with 1,4,7,10,13,16-hexaazacyclooctadecane (hexacyclen) to produce as yet uncharacterized species which are intensely colored and are undoubtedly the result of redox reactions.[2] In an attempt to identify the species responsible for these properties, we sought to prepare I, a compound referred to as the "wheel"



I

by Breslow[3] and of general interest because of its potential

* Address correspondence to 119 Smith Hall, Chemistry Department, University of Minnesota, 207 Pleasant Street S.E., Minneapolis, MN 55455.

(1) (a) University of Minnesota. (b) 3M Company, St. Paul, MN 55144.

(2) Presented in preliminary form by J. E. Richman and M. R. Asiravatham at the Second Symposium on Macrocyclic Compounds, Provo, Utah, August 14–16, 1978.

0022-3263/85/1950-0112$01.50/0