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Biomimetic Polyene Cyclizations.[1] The Synthesis and Cyclization of 2-(4-Pentenyl)-2-Cyclohexenol[2]

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The aim of this study was to ascertain whether the dienol **3** would undergo cyclization to yield products derived from the cation **4** in a manner similar to that of the lower homolog, **1** → **2**. The dienol **3** was synthesized by the sequence outlined in Scheme 1. Thus alkylation of the potassium salt of **5** with 1-bromo-4-pentene (**6**) gave the bisenol ether **7**. Hydrolysis of **7** followed by reduction of the resulting β-diketone afforded the desired dienol **3**. On treatment with anhydrous formic acid at 23°C, dienol **3** underwent cyclization to give as the major product the tricyclic alcohol **8**, evidently formed via further cyclization of the cation **4** (see Scheme 2). The structure **8** was confirmed by single-crystal X-ray diffraction analysis. The corresponding tricyclic chloride **9** could be obtained either directly from **8** upon treatment with thionyl chloride or by cyclization of **3** with stannic chloride in benzene. Pyrolysis of **9** with triphenyltin hydride gave the parent hydrocarbon **10**.

As part of an investigation of allylic cation-promoted biomimetic polyene cyclizations,[4] it was previously shown that the dienol **1**, on treatment with anhydrous formic acid at room temperature, underwent facile stereoselective ring closure to give the octalol **2** in 80% yield (*6*). The present study was undertaken to ascertain whether the homologous dienol **3** would undergo cyclization in a similar manner to yield products derived from the cation **4**.

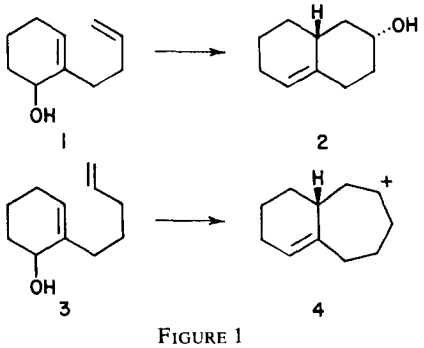

FIGURE 1

[1] For a recent paper in this series, see Ref. (*1*).

[2] This paper is contributed in the memory of S. Morris Kupchan with whom W.S.J. enjoyed a friendly and fruitful collaboration on a study of the configuration of the alkaloid cevine [see Refs. (*2–4*)].

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[4] For a recent review of biomimetic cyclizations, see Ref. (*5*).

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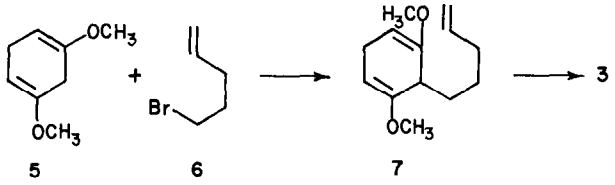
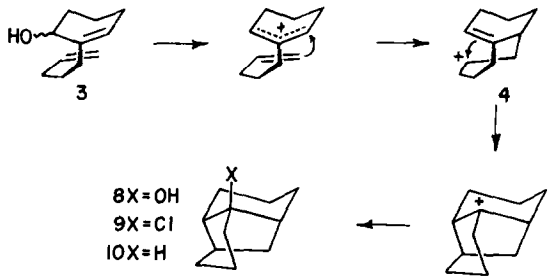
The synthesis of dienol **3** is outlined in Scheme 1. Alkylation of the potassium salt of dihydroresorcinol dimethyl ether (**5**) with 1-bromo-4-pentene (**6**) (*7*) in liquid ammonia gave the alkylated bisenol ether **7** in 44% yield. Hydrolysis of **7** with methanolic hydrochloric acid followed by lithium aluminum hydride reduction of the resulting β-diketone afforded the dienol **3**, which was obtained in 35% yield after purification by preparative vpc and evaporative distillation.



SCHEME 1

When the substrate **3** was treated with anhydrous formic acid at room temperature, it had completely disappeared after 11 min as evidenced by vpc. Treatment of the crude cyclization product with lithium aluminum hydride, to convert any formates into the corresponding alcohols, gave material consisting of one predominant component corresponding to 66% of the total vpc peak area. This material was isolated in 30% yield, by preparative vpc followed by vacuum sublimation, as colorless crystals, mp 91.0–91.5°C. Elemental analysis corresponded to the formula $C_{11}H_{18}O$ and the ir spectrum exhibited absorptions at 2.78 and 2.90 μm, characteristic of an alcohol. The nmr spectrum in carbon tetrachloride exhibited absorptions in the region δ 1.0–2.2 ppm with a sharp signal at 1.6 ppm; the spectrum in pyridine displayed unresolved absorptions at δ 1.0–2.2 ppm with no sharp signal. There was no absorption in the ir, nmr, or uv, indicative of an olefinic bond. Moreover, the new alcohol was resistant to hydrogenation over 5% palladium-on-carbon in ethanol or over platinum in acetic acid. These observations, taken together with the fact that the new alcohol gave no color with tetranitromethane, provided fairly convincing, albeit negative, evidence that the alcohol was tricyclic. Jones reagent (*8*) failed to oxidize the alcohol, indicating, along with the nmr data (see above), that it was tertiary, and therefore could be formulated as the tricyclic substance **8**, rationalized to result from further cyclization of cation **4** as shown in Scheme 2. The presumed structure **8** has been confirmed by single-crystal X-ray diffraction analysis (*9*).



SCHEME 2

The corresponding tricyclic chloride **9** was obtained directly from alcohol **8** upon treatment with thionyl chloride in refluxing carbon tetrachloride. Alternatively, cyclization of the dienol **3** with stannic chloride in benzene at 23°C afforded chloride **9**

as the major product, which was isolated in 16% yield after preparative vpc followed by evaporative distillation. Pyrolysis of **9** with triphenyltin hydride gave the parent hydrocarbon **10**, namely, tricyclo[5.4.0.0^{3,8}]undecane, as a colorless liquid.

EXPERIMENTAL

The prefix "DL" has been omitted from the names of all racemic compounds described in this section. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. Nuclear magnetic resonance spectra were determined under the supervision of Dr. L. J. Durham on Varian Associates A60 and T60 spectrometers. Unless otherwise stated, deuterochloroform was used as the solvent with chemical shifts reported as δ values in parts per million relative to tetramethylsilane = 0. Low-resolution mass spectra were determined under the direction of Dr. A. M. Duffield on an A.E.I. MS-9 spectrometer. Infrared (ir) spectra were recorded on Perkin Elmer Models 137 and 421 spectrometers and ultraviolet (uv) spectra were recorded on a Cary Model 14 spectrometer using 1-cm quartz cells. Refractive indexes were determined with a Spencer refractometer. Vapor-phase chromatographic (vpc) analyses were performed on Wilkens Aerograph Hy-Fi Models A-600B and A-600C chromatographs using a 7½ ft × ⅛ in. column packed with 15% Carbowax 20M on 60/80 Chromosorb W, and on a Hewlett–Packard HP-402 chromatograph using a 6 ft × 6 mm glass column packed with 22% Carbowax 20M on 60/80 Chromosorb W and a 4 ft × 6 mm glass column packed with 3.8% SE-30 on 80/100 Diatoport S. Preparative vpc separations were achieved using a Varian Aerograph Series 200 chromatograph equipped with a 20 ft × 0.75 in. column packed with 20% Carbowax 20M on 45/60 Chromosorb W. Silica gel G (E. Merck) was used for thin-layer chromatography (tlc). Spots were detected by spraying with a 2% solution of cerric sulfate in 2 *N* sulfuric acid. Silica gel GF (E. Merck) was used for preparative tlc. Anhydrous formic acid was prepared by distillation from boric anhydride at reduced pressure according to a published procedure (*10*) and stored at 5°C. "Evaporative distillation" refers to bulb-to-bulb short-path distillation in which the bulb was heated in a hot-air oven. The cited temperatures for these distillations pertain to the oven temperature and are thus not true boiling points.

2,4-Dimethoxycyclohexa-1,4-diene (**5**). A modification of a published procedure (*11*) was employed. A solution of 80.9 g (0.586 *M*) of resorcinol dimethyl ether in 250 ml of ether and 150 ml of ethanol was slowly added to 1 liter of ammonia (distilled through a soda-lime column); then 34.4 g (1.50 g-atom) of sodium was added in small pieces. The mixture was stirred at room temperature for 1 hr; then the ammonia was allowed to evaporate and 300 ml of ice-water was added. Extraction with ether[5] afforded 78.6 g of

[5] In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate or magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure (water aspirator) using a rotary evaporator. The term "wash" indicates washing the combined organic layers with saturated aqueous sodium bicarbonate solution ("base wash"), with dilute aqueous hydrochloric acid ("acid wash"), or with the specified solution prior to the above-mentioned washing with water.

crude diene **5** as a yellow liquid. The crude diene was distilled through a Vigreux column to give 72.7 g (89% yield) of **5** as a clear, colorless liquid, bp 109–111°C/35 mm (lit. bp 95°C/18 mm) (*12*).

3-(4-Pentenyl)-2,4-dimethoxycyclohexa-1,4-diene (**7**). A crystal of ferric nitrate nonahydrate followed by 1.55 g (0.04 g-atom) of potassium in small pieces was added to 250 ml of liquid ammonia (distilled from potassium); then 5.58 g (0.04 *M*) of diene **5** (bp 109–111°C/35 mm) was slowly added with stirring to produce a dark red mixture. Addition of 5.92 g (0.04 *M*) of 1-bromo-4-pentene (**6**) (*7*) (bp 123–126°C; $[n_D^{25}$ 1.4610) was begun. After about two-thirds of the bromide had been introduced, the mixture turned green, indicating that the endpoint had been reached. An additional 0.73 g (0.019 g-atom) of potassium and 2.80 g (0.02 *M*) of diene **5** were added, resulting in a dark red color. The remaining bromide was added and the mixture again turned green. The ammonia was allowed to evaporate; then 100 ml of water followed by 100 ml of ether were added. Extraction with ether[5] afforded 10.1 g of green liquid. Evaporative distillation of the crude product at 90–145°C/17 mm gave 9.4 g of colorless liquid. A 6.7-g portion of this material was purified by preparative vpc (200°C) to give 2.6 g (44% yield) of the alkylated diene **7**: ir λ_{max}^{film} 5.91 (–CH=COMe), 6.01 (C=C), and 10.97 μm (–CH=CH_2); nmr 1.0–1.7 (m, 4H, C-1 and C-2 sidechain CH_2's), 2.0 (q, 2H, C-3 sidechain CH_2), 2.75 (m, 3H, C-3 CH and C-6 CH_2), 3.5 (s, 6H, $-OCH_3$), 4.4 (m, 2H, C-1 and C-5 vinyl protons), 4.7–5.1 (m, 2H, CH=C$\underline{H}_2$), and 5.6–6.0 (m, 1H, C$\underline{H}$=CH_2). The mass spectrum exhibited an M^+ peak at *m/e* 208.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.53.

2-(4-Pentenyl)-cyclohex-2-en-1-ol (**3**). A mixture of 1.94 g (9.3 m*M*) of the triene **7** (purified by preparative vpc), 60 ml of methanol, and 4 ml of 50% aqueous hydrochloric acid was stirred under nitrogen at room temperature for 23 hr. The mixture was concentrated at reduced pressure, diluted with water, and extracted with chloroform[5] to afford a mixture of colorless crystalline solid and yellow oil. This mixture was dissolved in 100 ml of ether, 5.0 g (0.132 *M*) of lithium aluminum hydride was added, and the resulting mixture was heated at reflux for 7 hr. The excess hydride was decomposed by cautious addition of saturated aqueous sodium sulfate and the mixture was then dried over anhydrous magnesium sulfate. The crude product, obtained after removal of the solvent at reduced pressure, was purified by preparative vpc (194°C) followed by evaporative distillation at 130–140°C/18 mm to give 0.535 g (35% yield) of the allylic alcohol **3** as a colorless liquid. A sample of comparable material from another run was submitted to combustion analysis: ir γ_{max}^{film} 3.0 (OH), 6.1 (C=C), 10.05 and 10.95 μm (CH=CH_2).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.33; H, 11.18.

The *3,5-dinitrobenzoate* was obtained as pale yellow flat rods, mp 42.5–44.5°C, after chromatography on Florisil (benzene) followed by repeated recrystallization from petroleum ether: ir $\lambda_{max}^{CHCl_3}$ 5.82 (C=O), 6.5, 7.45 (NO_2), 8.6 and 9.3 μm (C–O); uv $\lambda_{max}^{95\%EtOH}$ 240 nm (ε 15,500).

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.98; H, 5.55: N, 8.11.

Tricyclo[5.4.0.0^{3,8}]undecan-7-ol (**8**). A mixture of 488 mg (2.9 m*M*) of the distilled dienol **3** and 25 ml of anhydrous formic acid was stirred at room temperature for 11 min. The mixture was diluted with 100 ml of ice-water and extracted with pentane using a base wash[5] to give 658 mg of colorless liquid. This material was dissolved in 100 ml of

ether and heated at reflux for 0.5 hr with 492 mg (13.0 m*M*) of lithium aluminum hydride. The excess hydride was decomposed by careful addition of saturated aqueous sodium sulfate, then the resulting mixture was dried over anhydrous magnesium sulfate and filtered. Removal of the solvent at the rotary evaporator followed by evaporative distillation at 25–170°C/18 mm yielded 389 mg of semisolid material. Further purification by preparative vpc (190°C) followed by sublimation at 65°C/15 mm afforded 145 mg (30% yield) or tricyclic alcohol **8** as colorless needles, mp 91.0–91.5°C, which appeared to be pure by vpc (7.5 ft-Carbowax, 150°C): ir $\lambda_{max}^{CCl_4}$ 2.78 (OH), 2.9 (OH), and 9.35 μm (C–O). The nmr (CCl_4) spectrum exhibited unresolved absorptions between 1.0 and 2.2 ppm, with a sharp peak appearing at 1.6 ppm. The mass spectrum exhibited peaks at *m/e* 166 (M^+, 33%), *m/e* 123 (41%), *m/e* 97 (44%), and *m/e* 84 (100%).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92: Found: C, 79.22; H, 10.72.

7-Chlorotricyclo[5.4.0.0^{3,8}]*undecane* (**9**). (*A*) *From the tricyclic alcohol* **3**. An adaptation of a published procedure (*13*) was employed, whereby a mixture of 103 mg (0.62 m*M*) of tricyclic alcohol **8**, mp 91.0–91.5°C, 5 ml of thionyl chloride, and 5 ml of carbon tetrachloride was heated at reflux for 3 hr. The solvent was removed at reduced pressure and the residue was purified by preparative tlc (R_f 0.52–0.82, benzene) followed by evaporative distillation at 40°C/0.05 mm to afford 77 mg (67% yield) of tricyclic chloride **9** as colorless crystals, mp 69–71°C, which appeared to be pure by vpc (6ft-Carbowax, 150°C): nmr, 1.2–2.4 ppm (complex multiplet).

Anal. Calcd for $C_{11}H_{17}Cl$: C, 71.51; H, 9.28; Cl, 19.21. Found: C, 71.43; H, 9.16; Cl, 19.31.

(*B*) *Via cyclization of dienol* **3** *with stannic chloride*. A mixture of 108 mg (0.65 m*M*) of the distilled dienol **3**, 0.4 ml of stannic chloride, and 50 ml of dry benzene was stirred under nitrogen for 11 min at 23°C. The mixture was shaken with 50 ml of 10% aqueous sodium hydroxide and extracted with ether[5] to afford 87 mg of oil. Preparative tlc of the crude product (R_f 0.41–0.76, pentane) afforded 65 mg of liquid. This material was further purified by preparative vpc (185°C) followed by evaporative distillation at 70–120°C/18 mm to give 19 mg (16% yield) of colorless crystals, mp 68.0–70.5°C. The ir and nmr spectra, mass spectral fragmentation pattern, and vpc behavior of this material were identical with the corresponding properties of the chloride prepared from tricyclic alcohol **8**.

Tricyclo[*5.4.0.0*^{3,8}]*undecane* (**10**). An adaptation of a published procedure (*14*) was employed, whereby a mixture of 30 mg of chloride **9** (97% pure by vpc), 200 mg of triphenyltin hydride, and several crystals of azobisisobutyronitrile was heated in a sealed glass tube at 100°C for 24 hr. The pyrolysate was evaporatively distilled at 25–150°C to afford 10 mg of tricyclic hydrocarbon **10** as a clear, colorless liquid which appeared to be pure by vpc (SE-30, 59°C): ir λ_{max}^{film} 3.4, 5.7, and 6.8 μm; nmr, 1.4–1.6 ppm (unresolved multiplet). The mass spectrum exhibited a molecular ion peak at *m/e* 150.

Anal. Calcd for $C_{11}H_{18}$: C, 87.91; H, 12.09. Found: C, 87.60; H, 11.88.

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