(calcd for $C_{21}H_{24}O_6N_2$ m/e 400.1631).

20-Deethyl-2β,16α-dihydro-17β-[(methylsulfonyl)oxy]-vincadifformine (4d). A solution of 200 mg (0.61 mmol) of hydroxy ester **4c**,[1] 60 μL (0.72 mmol) of methanesulfonyl chloride, and 0.5 mL of diisopropylethylamine in 6 mL of ethylene dichloride was stirred at 0 °C for 1 h and then poured into a saturated sodium bicarbonate solution. Extraction, drying, and evaporation gave a residue, whose crystallization from acetone–hexane afforded 197 mg (82%) of colorless, crystalline ester **4d**: mp 94–96 °C, UV λ_{max} 245 nm (log ε 4.27), 297 (3.91); IR 3400 (NH, w), 1738 (C=O, s), 1611 (C=C, m), 1340 (SO_2, s), 1180 (s) cm^{-1}; ^1H NMR δ 1.5–2.6 (m, 11, methylenes, methines), 3.06 (s, 3, SMe), 3.0–3.2 (m, 2, H-3, H-5), 3.75 (s, 3, OMe), 4.01 (d, 1, J = 10 Hz, H-2), 5.35 (d, 1, J = 2 Hz, H-17), 6.62, 7.09 (d, 1 each, J = 8 Hz, H-9, H-12), 6.73, 7.02 (t, 1 each, J = 8 Hz, H-10, H-11); ^{13}C NMR δ 21.7 (C-14), 26.2 (C-15), 35.8 (C-20), 38.4 (C-6), 39.0 (SMe), 50.2 (OMe), 52.2 (C-16), 52.9 (C-3), 53.6 (C-7), 54.0 (C-5), 63.0 (C-2), 65.1 (C-21), 80.1 (C-17), 110.0 (C-12), 118.8 (C-10), 121.7 (C-9), 128.0 (C-11), 133.4 (C-8), 148.3 (C-13), 172.0 (C=O); exact mass m/e (M^+ – 80) 310.1681 (calcd for $C_{19}H_{22}O_2N_2$ m/e 310.1691). Anal. Calcd for $C_{20}H_{26}O_5N_2S$: C, 59.07; H, 6.45; N, 6.89. Found: C, 58.85; H, 6.32; N, 6.74.

Olefinic Esters 5b and 8. A solution of 60 mg (0.15 mmol) of mesylate **4d** in 7.5 mL of dry acetonitrile was refluxed for 24 h and then poured into a saturated sodium bicarbonate solution. Workup as before and chromatographic elution with 2:1 hexane–ethyl acetate gave 20 mg (40%) of colorless, crystalline 20-deethyl-17-dehydro-2β-hydrovincadifformine (**5b**): mp 137–138 °C (hexane–acetone); UV $\lambda_{shoulder}$ 242 nm (log ε 4.34), λ_{max} 300 (3.97); IR 3410 (NH, w), 1708 (C=O, s), 1653 (C=C, m), 1612 (m) cm^{-1}; ^1H NMR δ 1.5–2.6 (m, 10, methylenes, methines), 3.05 (dd, 1, J = 11, 3 Hz, H-3 or H-5), 3.18 (dt, 1, J = 9, 4 Hz, H-3 or H-5), 3.76 (s, 3, OMe), 4.35 (d, 1, J = 1 Hz, H-2), 6.53, 7.01 (d, 1 each, J = 8 Hz, H-9, H-12), 6.68, 6.98 (t, 1 each, J = 8 Hz, H-10, H-11), 6.92 (d, 1, J = 1 Hz, H-17); ^{13}C NMR δ 22.4 (C-14), 28.7 (C-15), 32.8 (C-20), 39.9 (C-6), 51.6 (OMe), 52.5 (C-3 or C-5), 52.7 (C-5 or C-3), 53.5 (C-7), 62.9 (C-2), 68.3 (C-21), 108.7 (C-12), 118.2 (C-10), 122.7 (C-9), 128.0 (C-11), 131.0 (C-8 or C-16), 131.8 (C-16 or C-8), 144.7 (C-17), 150.6 (C-13), 167.2 (C=O); exact mass m/e 310.1655 (calcd for $C_{19}H_{22}O_2N_2$ m/e 310.1679). Anal. Calcd for $C_{19}H_{22}O_2N_2$: C, 73.05; H, 7.15; N, 9.03. Found: C, 72.98; H, 7.08; N, 8.67.

Elution with 1:1 hexane–ethyl acetate led to 12.5 mg (25%) of colorless, liquid 20-deethyl-17,20-didehydro-2β,16α-dihydrovincadifformine (**8**): UV $\lambda_{shoulder}$ 245 nm (log ε 4.30), λ_{max} 301 (3.95); ^1H NMR δ 1.6–3.3 (m, 12, methylenes, methines), 3.64 (d, 1, J = 9 Hz, H-2), 3.76 (s, 3, OMe), 5.55 (s, 1, H-17), 6.71, 7.15 (d, 1 each, J = 7 Hz, H-9, H-12), 6.77, 7.07 (t, 1 each, J = 7 Hz, H-10, H-11); exact mass m/e 310.1674 (calcd for $C_{19}H_{22}O_2N_2$ m/e 310.1679).

A suspension of 460 mg (1.13 mmol) of mesylate **4d** and 124 mg (3.1 mmol) of potassium hydride in 50 mL of dry tetrahydrofuran was stirred at 0 °C for 5 h and then at room temperature for 12 h. The mixture was poured into saturated sodium bicarbonate solution and worked up as above. Chromatographic elution with 2:1 hexane–ethyl acetate and crystallization from acetone–hexane led to 281 mg (81%) of colorless, crystalline olefinic ester **5b**.

20-Deethyl-17,20-didehydrovincadifformine (3b). A suspension of 150 mg (0.48 mmol) of ester **5b** and 230 mg (0.52 mmol) of lead tetraacetate in 15 mL of dry methylene chloride was stirred at 0 °C for 2 h and then at room temperature for 4 h. The mixture was poured into a saturated sodium bicarbonate solution and worked up as before. Chromatographic elution with 11:1 hexane–ethyl acetate led to the recovery of 50 mg of starting ester **5b**. The earlier eluates gave 60 mg (60% based on consumed **5b**) of colorless, crystalline diene ester **3b**:[2,3] mp 140–142 °C (hexane–acetone) (lit.[2] mp 139–140.5 °C); IR 3431 (NH, w), 3382 (m), 3342 (w), 1730 (C=O, s), 1678 (s), 1639 (C=C, s), 1605 (s) cm^{-1}; ^1H NMR δ 1.4–3.2 (m, 10, methylenes), 3.78 (s, 3, OMe), 3.83 (s, 1, H-21), 6.10 (s, 1, H-17), 6.87, 7.57 (d, 1 each, J = 8 Hz, H-9, H-12), 6.93, 7.17 (t, 1 each, J = 8 Hz, H-10, H-11); ^{13}C NMR δ 20.2 (C-14), 31.9 (C-15), 41.0 (C-6), 46.5 (C-5 or C-3), 47.6 (C-3 or C-5), 49.6 (C-7), 50.7 (OMe), 66.0 (C-21), 90.8 (C-16), 109.1 (C-12), 115.5 (C-17), 121.3 (C-10), 123.2 (C-9), 124.9 (C-20), 127.5 (C-11), 136.4 (C-8), 143.0 (C-13), 164.4 (C-2), 167.4 (C=O); exact mass m/e 308.1554 (calcd for $C_{19}H_{20}O_2N_2$ m/e 308.1523).

Acknowledgment. We are indebted to the Public Health Service for support for this work. M.J.P., expresses his gratitude to the Consejo Nacional de Investigaciones Cientificas y Technológicas (Argentina) for a 1986–1988 fellowship.

A New Synthesis of (±)-Sirenin and a Physiologically Active Analogue

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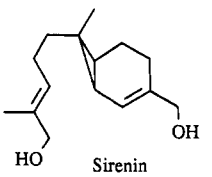
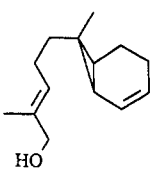
Received March 29, 1988

As part of a project to elucidate the chemical and biological processes involved in the chemotactic response of gametes of the aquatic fungus *Allomyces*,[1] it became necessary to prepare authentic samples of the female sexual pheromone sirenin (**1**)[2] for calibration of biological tests. Although several syntheses of sirenin have been reported,[3] it was decided to elaborate the synthesis of demethylsesquicarene developed earlier in these laboratories[4] into a new synthesis of racemic sirenin. Model studies conducted to develop the reactions necessary for the synthesis of sirenin resulted in the synthesis of the deoxy-nor analogue **2**. This compound has proven to be first sirenin analogue that exhibits chemotactic activity at physiological concentrations.



Sirenin
1



2

The method used[4] for synthesis of the bicyclo[4.1.0]-heptane skeleton involves the stereoselective addition of

(1) For a recent review, see: Pommerville, J. In *Sexual Interactions in Eukaryotic Microbes*; O'Day, D. H.; Horgen, P. A., Eds.; Academic: New York, 1981; pp 53–72.

(2) For discussions of the isolation and structure elucidation of sirenin, see: (a) Machlis, L. *Physiol. Plant.* **1958**, *11*, 181–192. (b) Machlis, L. *Physiol. Plant* **1958**, *11*, 845–854. (c) Machlis, L. *Nature (London)* **1958**, *181*, 1790–1791. (d) Machlis, L., Nutting, W. H.; Williams, M. W.; Rapoport, H. *Biochemistry* **1966**, *5*, 2147–2152. (e) Machlis, L.; Nutting, W. H.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 1674–1676. (f) Nutting, W. H.; Rapoport, H.; Machlis, L. *J. Am. Chem. Soc.* **1968**, *90*, 6434–6438.

(3) For previous syntheses of sirenin, see: (a) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318–4320. (b) Plattner, J. J.; Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 4933–4934. (c) Bhalerao, U. T.; Plattner, J. J.; Rapoport, H. *J. Am. Chem. Soc.* **1970**, *92*, 3429–3433. (d) Plattner, J. J.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 1758–1761. (e) Corey, E. J.; Achiwa, K. *Tetrahedron Lett.* **1970**, 2245–2246. (f) Katzenellenbogen, J. A. *Diss. Abstr. Int. B* **1970**, *31*, 1826. (g) Grieco, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 5660–5661. (h) Grieco, P. A. *Diss. Abstr. Int. B* **1971**, *32*, 1449. (i) Mori, K.; Matsui, M. *Tetrahedron Lett.* **1969**, 4435–4438. (j) Mori, K.; Matsui, M. *Tetrahedron* **1970**, *26*, 2801–2814. (k) Garbers, C. F.; Steenkamp, J. A.; Visagie, H. E. *Tetrahedron Lett.* **1975**, 3753–3756. (l) DuPreez, H. E.; Garbers, C. F.; Steenkamp, J. A. *S. Afr. J. Chem.* **1980**, *33*, 21–26. (m) Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 2362–2364. (n) Mandai, T.; Hara, K.; Kawada, M.; Nokami, J. *Tetrahedron Lett.* **1983**, *24*, 1517–1518. (o) Ono, T.; Tamaoka, T.; Yuasa, Y.; Matsuda, T.; Nokami, J.; Wakabaya-shi, S. *J. Am. Chem. Soc.* **1984**, *106*, 7890–7893. (p) Uyehara, T.; Yamada, J.; Ogata, K.; Kato, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 211–216.

(4) (a) Harding, K. E.; Trotter, J. W. *J. Org. Chem.* **1977**, *42*, 4157–4159. (b) Trotter, J. W. Ph.D. Dissertation, Texas A & M University, College Station, TX, December, 1975.

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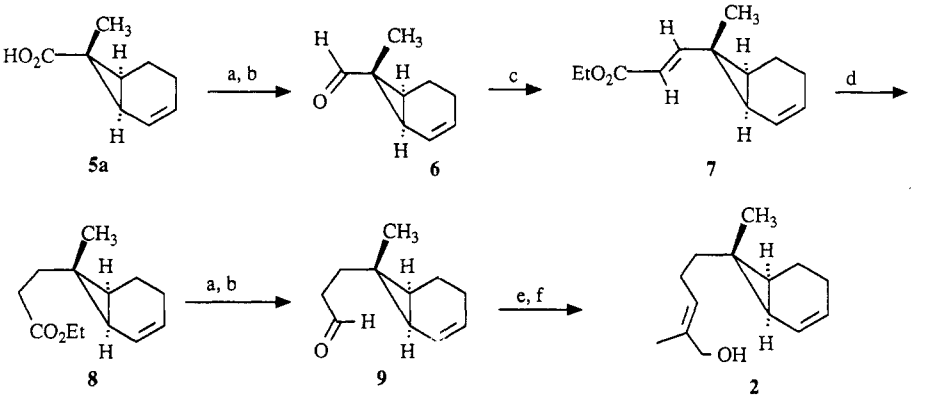
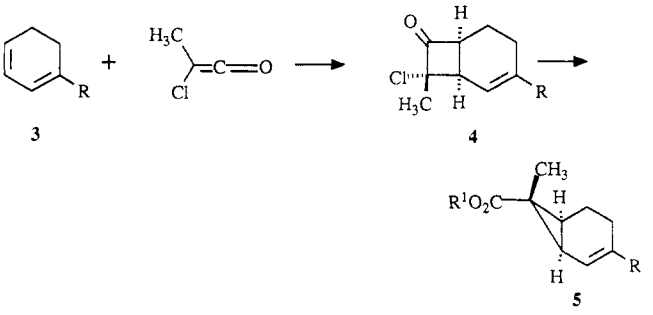
Scheme I[a]



[a] (a) $LiAlH_4$; (b) PCC; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (d) DIBAL-H, MeCu, HMPA; (e) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH; (f) $LiAlH_4$, $AlCl_3$.

methylchloroketene to a cyclohexadiene followed by a stereospecific ring contraction to a 7,7-disubstituted bicycloheptane (**3** → **4** → **5**). The problems presented by



this approach to the synthesis of sirenin center around the development of suitable methods for elaboration of the side chain at the neopentyl-like cyclopropylcarbinyl carbon. The elaboration of the sirenin side chain should avoid reactions that lead to cationic, anionic, or radical character at the cyclopropylcarbinyl carbon, owing to the rapid rearrangement of such intermediates to homoallylic systems. After several alternatives had been investigated, a procedure in which the five additional carbons are added in two stages was selected. The method was developed by using the previously described unsubstituted analogue **5a** (**5**, R = R^1 = H) derived from cyclohexadiene.[4,5] The reaction sequence for the side-chain elaboration is shown in Scheme I.

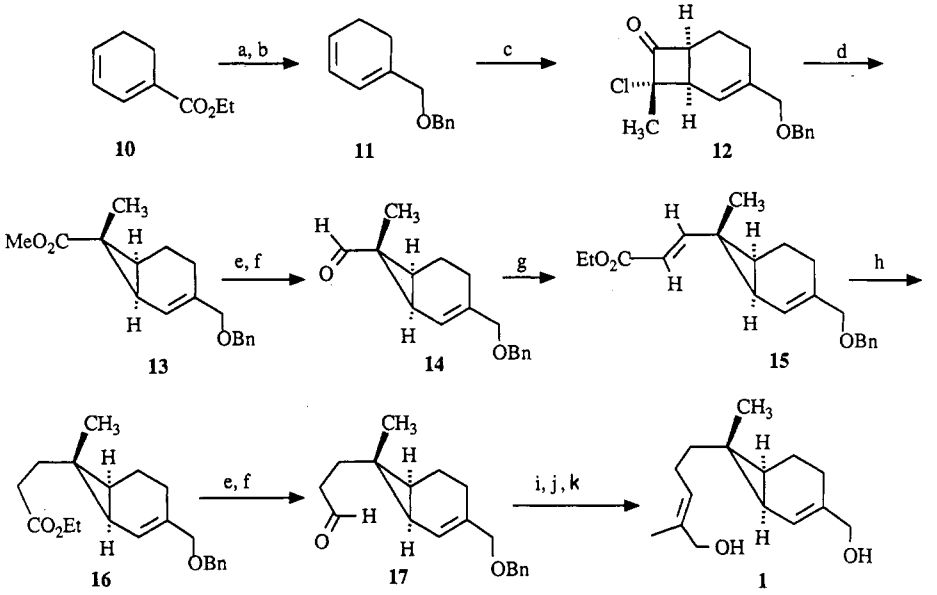
Acid **5a** was reduced with lithium aluminum hydride and oxidized with pyridinium chlorochromate to give aldehyde **6**. Treatment of aldehyde **6** with the sodium salt of triethyl phosphonoacetate according to the procedure of Marmor[6] gave the α,β-unsaturated ester **7** in 95% yield. Only the *E* isomer could be observed in the NMR spectra of the product. Selective reduction of the conjugated double bond was effected by the method of Tsuda[7] with diisobutylaluminum hydride in the presence of methylcopper and HMPA. The saturated ester **8** was isolated in 63% yield after Chromatotron purification to remove ~ 10% of unchanged **7**. Incomplete reaction was a greater problem if the methyllithium or cuprous iodide were not fresh. Reduction with lithium aluminum hydride and oxidation with pyridinium chlorochromate gave aldehyde **9** in 75% yield. Treatment of **9** with the sodium salt of triethyl 2-phosphonopropionate gave the unsaturated ester product as an 87:13 mixture of the *E* and *Z* isomers. Separation of the isomers by preparative thin-layer chromatography gave the *E* isomer in 72% yield. Reduction of the *E* isomer with aluminum hydride converted the ester into alcohol **2** in 95% yield.[8] Reduction of the *E* ester with lithium aluminum hydride gave alcohol contaminated with 8–10% of material that appeared, by NMR spectroscopy, to be the dihydroalcohol resulting from concomitant reduction of the conjugated double bond.

The application of this homologation procedure to a total synthesis of sirenin requires the use of an appropriately substituted cyclohexadiene **3**. Trotter had prepared the methoxymethyl derivative (**3**, R = CH_2OCH_3) and shown that the ketene cycloaddition and ring contraction reactions could be effected.[4b] However, the methyl ether protecting group was considered to be unsuitable for a total synthesis. A benzyl ether protecting group was selected for the synthesis after it was determined that addition of chloromethylketene to the MEM protected ether **3** (R = CH_2OMEM) gave the cyclobutanone product in less than 10% yield. The synthesis is shown in Scheme II.

The carbethoxy diene **10** was prepared by the procedure of Grob.[9,4b] Reduction with aluminum hydride gave the corresponding alcohol in 86% yield. This alcohol demonstrated a strong tendency to oxidize to benzyl alcohol during purification, so it was used without purification immediately after preparation. The benzyl ether **11** was prepared in 76% yield by treatment with sodium hydride and benzyl bromide. This compound slowly oxidized to dibenzyl ether upon exposure to air. Reaction of chloromethylketene (generated in situ from 2-chloropropionyl chloride and triethylamine)[4] with **11** gave a 3.6:1 mixture of the *endo*-methyl isomer **12** and the corresponding *exo*-methyl isomer. A large excess of chloromethylketene was required to insure complete reaction of the diene **11**. Adduct **12** was isolated in 63% yield by chromatography. The stereochemistry of **12** was assigned on the basis of the characteristic chemical shifts for the methyl groups in such adducts.[4,10] Reaction of ketone **12** with silver nitrate in refluxing methanol[4] produced ester **13** in 53% yield. The alternative ring contraction with lithium hydroxide[5] gave low yields of the expected carboxylic acid with major

(5) Creary, X. *J. Org. Chem.* **1976**, *41*, 3734–3739.
(6) Marmor, R. S. *J. Org. Chem.* **1972**, *37*, 2901–2904.
(7) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540.
(8) Jorgenson, M. J. *Tetrahedron Lett.* **1962**, 559–562.
(9) (a) Grob, C. A.; Ohta, M.; Renk, E.; Weiss, A. *Helv. Chim. Acta* **1958**, *41*, 1191–1197. (b) Hunig, S.; Kahanek, H. *Chem. Ber.* **1957**, *90*, 238–245.
(10) (a) Brady, W. T.; Roe, R., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1662–1664. (b) Brady, W. T. *Synthesis* **1971**, 415–422.

Scheme II[a]



[a] (a) $LiAlH_4$, $AlCl_3$; (b) NaH, $PhCH_2Br$; (c) $CH_3CHClCOCl$, Et_3N; (d) $AgNO_3$, MeOH, Δ; (e) $LiAlH_4$; (f) PCC, CH_2Cl_2; (g) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (h) DIBAL-H, MeCu, HMPA; (i) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH; (j) DIBAL-H; (k) Li, NH_3.

amounts of nonacidic byproducts. The ester **13** was converted to the aldehyde **14** and transformed to ester **15** in 59% overall yield. Conjugate reduction with diisobutylaluminum hydride and methylcopper gave ester **16** in 63% yield along with 28% of starting ester **15** after two treatments and chromatographic separation. Reduction of **16** with lithium aluminum hydride and oxidation with pyridinium chlorochromate produced the aldehyde **17** in 86% yield. Treatment of **17** with triethyl 2-phosphonopropionate gave an 88:12 mixture of the *E* and *Z* esters. The desired *E* isomer was isolated in 79% yield after Chromatotron purification of the mixture. Reduction of the ester with diisobutylaluminum hydride gave the allylic alcohol in 92% yield. Cleavage of the benzyl ether with lithium in ammonia gave racemic sirenin (**1**) in 92% yield (4.7% overall yield from **10**) after purification. All spectral data for this compound are in excellent agreement with literature data.[3a,b,g,i,j,o]

Both racemic sirenin (**1**) and the deoxy-nor analogue **2** were found to attract male gametes of *Allomyces* at concentrations as low as 10^{-11} M.[11] Alcohol **2** is the first structural or stereochemical analogue of natural *l*-sirenin to show chemotatic activity at physiological concentrations.[12] These synthetic studies thus provide a new route to the synthesis of sirenin and analogues that may prove useful for the preparation of radiolabeled analogues for further biological studies.

Experimental Section

General Procedures. All compounds prepared in this section are racemic; the designation "±" is omitted. Infrared spectra were recorded on a Sargent-Welch Model 3-200 or a Perkin-Elmer Model 297 spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution at 200 and 50 MHz, respectively. Assignments of ^{13}C NMR spectral peaks were made with the aid of attached proton test (APT) experiments, distortionless enhancement by polarization transfer (DEPT) experiments, and/or comparison to previously assigned spectra. GC analyses were performed on a Hewlett-Packard Model 5790A gas chromatograph equipped with a 12.5-m capillary column coated with cross-linked methyl silicone. In the workup procedures, "acid" refers to aqueous 2 N hydrochloric acid, "base" refers to aqueous 10% sodium hydroxide, "bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate, "brine" refers to a saturated aqueous solution of sodium chloride, and "concentration" indicates solvent removal by rotary evaporation (Büchi Rotavapor) at ca. 40 mmHg. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. Microdistillation refers to bulb-to-bulb (Kugelrohr) short-path distillation using a modified technique for the distillation of small samples.[14] The temperatures cited for these distillations are the maximum temperature of the oven during distillation. All boiling points and melting points are uncorrected.

Thin-layer chromatography (TLC) was performed with precoated plastic plates having a 0.2-mm layer of silica gel 60 F-254 (EM Reagents). Preparative TLC was carried out with precoated 20 × 20 cm glass plates having a 2-mm layer of silica gel GF (Analtech) that was activated overnight at 140 °C. Chromatotron purification refers to preparative centrifugal TLC[15] with a glass rotor coated with a 2-mm layer of silica gel 60 PF-254 (EM Reagents). Column chromatography was performed with Baker silica gel (40–140 mesh).

Ether was distilled from the sodium benzophenone ketyl under nitrogen immediately before use. Tetrahydrofuran (THF) was distilled from the potassium benzophenone ketyl under nitrogen immediately prior to use. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide under nitrogen immediately prior to use. Pentane was dried over 4-Å sieves. Triethylamine was distilled from calcium hydride before use. Hexamethylphosphoric triamide (HMPA) was distilled and stored over 4-Å sieves. All reactions were performed under a dry argon or nitrogen atmosphere.

Unless otherwise noted, the purity of all title compounds was shown to be ≥95% by ^1H and ^{13}C NMR spectroscopy and chromatographic analysis.

(11) (a) Pommerville, J. C.; Strickland, J. B.; Romo, D.; Harding, K. E. *Plant Physiol.* in press. (b) Strickland, J. B. Ph.D. Dissertation, Texas A & M University, College Station, TX, 1987. (c) For a description of the testing protocol, see: Pommerville, J. *Exp. Cell Res.* **1977**, *109*, 43–51.

(12) *d*-Sirenin, the epimer of sirenin differing in stereochemistry at C-7 of the bicyclo[4.1.0]heptane ring system, and all analogues lacking a hydroxyl group at the terminus of the side chain were shown to be inactive at low concentrations in early biological studies by Machlis and Rappoport.[13,3b-d] In other studies in these laboratories,[11] a variety of structural analogues that have structure-dependent attractive activity only at concentrations of 10^{-3}–10^{-6} M have been prepared.

(13) Machlis, L. *Plant Physiol.* **1973**, *52*, 527–530.

(14) Harding, K. E.; Kinnel, R. B. *Org. Prep. Proced.* **1970**, *2*, 313–315.

(15) Stahl, E.; Muller, J. *Chromatographia* **1982**, *15*, 493–497.

(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-ene-7-carboxylic Acid (5a).[5] A solution of lithium hydroxide monohydrate (5 g, 120 mmol) in 140 mL of water was added to (1α,6α,8α)-8-methyl-8-chlorobicyclo[4.2.0]oct-2-en-7-one (4, R = H; 6.65 g, 39.0 mmol) prepared as previously described.[4] The two-phase mixture was stirred at room temperature until the organic layer was consumed (ca. 4.5 h). The mixture was extracted with ether, and the aqueous layer was acidified to pH 2 with acid. The acidic solution was extracted with ether (3×), and the combined ether layers were dried ($MgSO_4$) and concentrated. The yield of crude acid **5a** was 85% (5.08 g): ^{1}H NMR (200 MHz) δ 1.14 (s, 3 H, CH_3), 1.85–2.10 (m, 6 H), 5.70–6.00 (m, 2 H, CH=CH), 10.7 (br s, 1 H, CO_2H). This acid was used without purification.

(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-ene-7-methanol. A solution of crude acid **5a** (5.08 g) in ether was added slowly to a suspension of LAH (7.6 g, 200 mmol) in 90 mL of ether at 0 °C. The mixture was stirred overnight at room temperature. The reaction was quenched at 0 °C by sequential addition of water (7.5 mL), base (7.5 mL), and water (20 mL).[16] The mixture was filtered, and the filtrate was washed (bicarbonate and brine), dried (Na_2SO_4), and concentrated. Evaporative distillation (0.4 mm/90 °C) provided 2.49 g (46% from ketone **4**) of alcohol, identical with material prepared previously:[4] IR (film) 3340 (br, OH), 3040, 2940–2860, 1645 (C=C), 1455, 1405, 1035 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.02 (s, 3 H, CH_3), 1.00–1.25 (m, 2 H, methines), 1.62–2.21 (m, 5 H, CH_2CH_2 and OH), 3.36 (dd, 2 H, CH_2OH), 5.75–5.90 (m, 2 H, CH=CH); ^{13}C NMR (50 MHz) δ 10.95 (CH_3), 16.45 (C-4 or C-5), 18.59 and 19.34 (C-1 and C-6), 22.23 (C-4 or C-5), 30.95 (C-7), 72.67 (CH_2OH), 124.63 and 126.70 (C-2 and C-3).

(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-ene-7-carboxaldehyde (6).[4] A mixture of the alcohol prepared above (0.43 g, 3.1 mmol), PCC (1.02 g, 4.7 mmol), and Celite (1 g/g of PCC)[17,18] in 30 mL of CH_2Cl_2 was stirred at room temperature for 5 h. The mixture was diluted with an equal volume of ether, and the solution was decanted. The black residue was washed with ether (3×), and the combined organic solutions were passed through a short column of Florisil. The filtrate was dried ($MgSO_4$) and concentrated to give the crude product. Evaporative distillation (0.4 mm/75 °C) gave 0.33 g (79%) of aldehyde **6**, identical with material prepared previously.[4] IR (film) 3040, 2940, 2740, 1705 (C=O), 1455, 945 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.17 (s, 3 H, CH_3), 1.70–2.23 (m, 6 H), 5.75–5.95 (m, 2 H, CH=CH), 8.82 (s, 1 H, CHO); ^{13}C NMR (50 MHz) δ 6.90 (CH_3), 15.36 and 21.80 (C-4 and C-5), 22.17 and 22.61 (C-1 and C-6), 40.03 (C-7), 121.36 and 128.92 (C-2 and C-3), 201.25 (CHO).

Ethyl (*E*)-3-{(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-en-7-yl}-2-propenoate (7). The procedure of Marmor was followed.[6] A solution of triethyl phosphonoacetate (1.68 g, 7.5 mmol) in 6 mL of ether was added dropwise to a suspension of NaH (Aldrich, 60% dispersion in mineral oil, 0.3 g, 7.5 mmol) in 10 mL of ether at 0 °C. The mixture was heated at reflux for 15 min and then cooled to 0 °C. Aldehyde **6** (0.53 g, 3.83 mmol) was added as a solution in ether (6 mL) over a period of 30 min. The mixture was heated at reflux for 10 min and then allowed to cool to room temperature. The ether solution was decanted from the brown residue, and the residue was dissolved in water. The aqueous solution was extracted twice with ether. The combined ether layers were washed (bicarbonate, water, and brine), dried ($MgSO_4$), and concentrated. Purification by column chromatography (5% ethyl acetate/hexanes) afforded 0.75 g (95%) of ester **7**: IR (film) 3050, 3000, 2950, 1715 (C=O), 1640 (C=C), 1315, 1275, 1175, 1105, 1045, 1000, 960, 735 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.08 (s, 3 H, CCH_3) 1.28 (t, J = 7.1 Hz, 3 H, CH_3CH_2), 1.38–1.64 (m, 2 H, CHCH), 1.67–2.21 (m, 4 H), 4.18 (q, J = 7.1 Hz, 2 H, CH_3CH_2), 5.75 (d, J = 15.5 Hz, 1 H, CH=CHCO$_2$), 5.80 (br d, 2 H, ring CH=CH), 6.54 (d, J = 15.5 Hz, 1 H, CH=CHCO$_2$); ^{13}C NMR (50 MHz) δ 10.45 (CCH_3), 14.35 (CH_3CH_2), 16.11 and 21.92 (C-4 and C-5), 24.28 and 24.74 (C-1 and C-6), 31.05 (C-7), 59.92 (CH_3CH_2O), 115.24 (CHCO$_2$), 123.10 and 128.31 (C-2 and C-3), 158.29 (CCH=CH), 167.08 (CO_2).

Ethyl 3-{(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-en-7-yl}-propanoate (8). A modification of the procedure of Tsuda et al. was followed.[7] To freshly purified[19] CuI (0.10 g, 0.53 mmol) suspended in 40 mL of THF at −50 °C was added a solution of MeLi (Aldrich, 1.5 M in ether, 0.34 mL, 0.51 mmol) with a glass hypodermic syringe. To the resulting yellow suspension was added HMPA (8 mL) and a solution of DIBAL-H (Aldrich, 1.0 M in hexane, 4.7 mL, 4.7 mmol). The mixture was stirred for 30 min at −45 to −55 °C to produce a gray-brown solution. Ester **7** (0.74 g, 3.6 mmol) was introduced as a solution in THF (10 mL), and the mixture was stirred at −45 to −55 °C for 5 h. The reaction was quenched with 20 mL of 0.5 N HCl and diluted with ether. The aqueous layer was extracted twice with ether. The combined organic layers were washed (acid, bicarbonate, and brine), dried ($MgSO_4$), and concentrated. TLC analysis (10% ether/hexanes) indicated a mixture of product **8** (R_f 0.35) and starting material **7** (R_f 0.28). Careful Chromatotron purification furnished 0.09 g of starting material **7** and 0.46 g (63%; 70% based on recovered **7**) of the desired product **8**: IR (film) 3020, 2980, 2920, 1730 (C=O), 1645 (C=C), 1445, 1370, 1290, 1175, 1155, 1040 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.90 (s, 3 H, CCH_3), 0.93–1.09 (m, 2 H, CHCH), 1.26 (t, J = 7.1 Hz, 3 H, CH_3CH_2), 1.44–2.14 (m, 6 H), 2.39 (t, J = 8.0 Hz, 2 H, CH_2CO_2), 4.12 (q, J = 7.1 Hz, 2 H, CH_3CH_2), 5.62–5.72 (dt, J = 10.1 and 3.8 Hz, 1 H, CH=CH), 5.78–5.89 (m, 1 H, CH=CH); ^{13}C NMR (50 MHz) δ 12.23 (CCH_3) 14.22 (CH_3CH_2), 16.63 (C-4 or C-5), 21.08 and 21.68 (C-1 and C-6), 22.12 (C-4 or C-5), 28.06 (C-7), 32.17 (CH_2CO_2), 37.89 (CCH_2CH_2), 60.16 (CH_3CH_2), 125.10 and 126.19 (C-2 and C-3), 173.76 (CO_2); MS, m/e (percent) 208 (M^+, 24), 162 (11), 145 (24), 120 (83), 119 (26), 118 (38), 107, (70), 105 (75), 101 (20), 93 (23), 92 (21), 91 (80), 88 (97), 80 (23), 79 (100), 78 (39), 77 (42), 67 (19); accurate mass calcd for $C_{13}H_{20}O_2$ (M^+) 208.14632, found 208.14326.

3-{(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-en-7-yl}propan-1-ol. A solution of the ester **8** (0.40 g, 1.9 mmol) in ether was added to a suspension of LAH (0.20 g, 5.3 mmol) in 25 mL of ether at 0 °C. The mixture was stirred at room temperature for 4 h. The reaction was quenched by sequential addition of water (1 mL/g LAH), base (1 mL/g LAH), and water (3 mL/g LAH).[16] The floculent, white solid was removed by filtration, and the filtrate was washed (saturated NH_4Cl, bicarbonate, and brine), dried ($MgSO_4$), and concentrated to give 0.32 g (>99%) of alcohol as a colorless oil: IR (film) 3330 (br, OH), 3020, 2990, 2920, 1645 (C=C), 1445, 1375, 1055 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.90 (s, 3 H, CH_3), 0.85–1.03 (m, 2 H, CHCH), 1.14–1.44 (m, 2 H, $CH_2CH_2CH_2OH$), 1.61–2.14 (m, 6 H), 1.85 (br s, 1 H, OH), 3.62 (t, J = 6.6 Hz, 2 H, CH_2OH), 5.61–5.71 (m, 1 H, CH=CH), 5.80–5.90 (m, 1 H, CH=CH); ^{13}C NMR (50 MHz) δ 12.51 (CCH_3), 16.69 (C-4 or C-5), 21.16 and 21.89 (C-1 and C-6), 22.21 (C-4 or C-5), 28.30 (C-7), 30.12 ($CH_2CH_2CH_2$), 38.81 ($CCH_2CH_2CH_2$), 62.93 (CH_2OH), 125.36 and 125.89 (C-2 and C-3).

3-{(1α,6α,7α)-7-Methylbicyclo[4.1.0]hept-2-en-7-yl}propanal (9). Oxidation of the alcohol prepared as described above (0.32 g, 1.9 mmol) was effected in 4.5 h with PCC (0.62 g, 2.9 mmol) in 15 mL of CH_2Cl_2 following the general procedure described for oxidation to form **6**. Evaporative distillation (2 mm/130 °C) of the crude product afforded 0.24 g (75%) of aldehyde **9**: IR (film) 3020, 2990, 2910, 2850, 2710, 1720 (C=O), 1645 (C=C), 1445, 1380, 735, 715 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.90 (s, 3 H, CH_3), 0.90–1.07 (m, 2 H, CHCH), 1.43–2.13 (m, 6 H), 2.53 (td, J = 7.7 and 2.0 Hz, 2 H, CH_2CHO), 5.62–5.72 (dt, J = 10.1 and 3.7 Hz, 1 H, CH=CH), 5.78–5.89 (m, 1 H, CH=CH), 9.79 (t, J = 2.0 Hz, 1 H, CHO); ^{13}C NMR (50 MHz) δ 12.44 (C-8), 16.56 (C-4 or C-5), 21.29 and 21.92 (C-1 and C-6), 22.08 (C-4 or C-5), 27.85 (C-7), 34.99 (CH_2CHO), 41.84 (CCH_2CH_2), 124.91 and 126.33 (C-2 and C-3), 202.49 (CHO).

Ethyl (*E*)-2-Methyl-5-{(1α,6α,7α)-7-methylbicyclo[4.1.0]-hept-2-en-7-yl}-2-pentenoate. The procedure of Marmor was followed.[6] A solution of triethyl 2-phosphonopropionate (Aldrich, 0.52 g, 2.2 mmol) in 5 mL of ether was added dropwise to a suspension of NaH (Aldrich, 60% dispersion in mineral oil, 0.11 g, 2.7 mmol) in 10 mL of ether at 0 °C. The mixture was stirred at room temperature until H_2 evolution had ceased and then cooled to 0 °C. A solution of aldehyde **9** (0.24 g, 1.5 mmol) in 8 mL of ether was added dropwise, and the mixture was heated

(16) Micovic, V. M.; Mihailovic, M. L. J. *J. Org. Chem.* **1953**, *18*, 1190–1200.
(17) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650. (b) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245–258.
(18) (a) Andersen, N. H.; Uh, H.-S. *Synth. Commun.* **1973**, 115–123. (b) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744–2749.
(19) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9–12.

at reflux for 10 min. The mixture was allowed to cool to room temperature before 10 mL of water was added. The layers were separated, and the aqueous layer was extracted with ether. The combined ether layers were washed (bicarbonate, water (2×), and brine), dried ($MgSO_4$), and concentrated. TLC analysis (5% ether/hexanes) indicated two UV-active (254 nm) products with R_f 0.32 (*Z* isomer) and R_f 0.23 (*E* isomer). Chromatotron purification (3% ether/hexanes) was followed by preparative TLC purification (3% ether/hexanes, four developments) of the impure fractions to give 0.26 g (72%) of the desired *E* ester: IR (film) 3040, 3000, 2930, 2860, 1715 (C=O), 1650 (C=C), 1455, 1375, 1285–1270, 1185, 1145, 1105, 750 cm^{-1}; ^1H NMR (200 MHz) δ 0.91 (s, 3 H, CCH_3), 0.87–1.05 (m, 2 H, $CHCH$), 1.28 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.20–1.53 (m, 2 H, CH_2CH_2CH=C), 1.62–2.12 (m, 4 H), 1.83 (d, J = 1.4 Hz, 3 H, CH_3C=CH), 2.26 (br q, J = 7.6 Hz, 2 H, CH_2CH=C), 4.18 (q, J = 7.2 Hz, 2 H, CH_3CH_2) 5.61–5.72 (m, 1 H, CHCH=C*H*), 5.80–5.91 (m, 1 H, CHC*H*=CH), 6.77 (tq, J = 7.6 and 1.4 Hz, 1 H, CH_2CH=C); ^{13}C NMR (50 MHz) δ 12.25 and 12.46 (CCH_3 and CH_3CR), 14.31 (CH_3CH_2), 16.68 (C-4 or C-5), 21.31 and 22.04 (C-1 and C-6), 22.19 (C-4 or C-5), 26.37 (CH_2CH=), 28.42 (C-7), 41.56 (CCH_2CH_2), 60.30 (CH_3CH_2), 125.22 and 126.07 (C-2 and C-3), 127.31 ($O_2CC(CH_3)$=), 142.06 (CH_2CH=), 168.07 (CO_2); MS, *m/e* (percent) 248 (M^+, 1), 203 (8), 144 (53), 121 (35), 115 (72), 108 (70), 107 (76), 106 (38), 105 (100), 102 (83), 93 (80), 91 (84), 87 (85), 80 (49), 79 (96), 78 (33), 77 (73), 67 (39). The *Z* isomer was isolated in 11% yield (0.04 g): IR (film) 3020, 2980, 2920, 2850, 1710 (C=O), 1645 (C=C), 1455, 1370, 1240, 1185, 1140 cm^{-1}; ^1H NMR (200 MHz) δ 0.90 (s, 3 H, CCH_3), 0.88–1.04 (m, 2 H, $CHCH$), 1.18–1.51 (m, 2 H, CH_2CH_2CH=C), 1.31 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.67–2.10 (m, 4 H, ring $CHCH_2CH_2$), 1.89 (d, J = 1.4 Hz, 3 H, CH_3C=CH), 2.55 (br q, J = 7.6 Hz, 2 H, CH_2CH=C), 4.20 (q, J = 7.2 Hz, 2 H, CH_3CH_2), 5.60–5.70 (m, 1 H, CHCH=C*H*), 5.80–5.88 (m, 1 H, CHC*H*=CH), 5.92 (tq, J = 7.6 and 1.4 Hz, 1 H, CH_2CH=C); ^{13}C NMR (50 MHz) δ 12.47 (CCH_3), 14.33 (CH_3CH_2), 16.69 (C-4 or C-5), 20.71 (CH_3CR=), 21.24 and 21.98 (C-1 and C-6), 22.20 (C-4 or C-5), 27.23 (CH_2CH=), 28.53 (C-7), 42.48 (CCH_2CH_2), 59.96 (CH_3CH_2), 125.39 and 125.89 (C-2 and C-3), 126.75 ($O_2CC(CH_3)$=), 142.75 (CH_2CH=), 167.99 (CO_2).

(*E*)-2-Methyl-5-{(1α,6α,7α)-7-methylbicyclo[4.1.0]hept-2-en-7-yl}penten-2-ol (2). Aluminum chloride (Aldrich, 0.09 g, 0.7 mmol) was added to a suspension of LAH (0.06 g, 1.6 mmol) in 10 mL of ether at 0 °C.[8] The mixture was stirred for 30 min at 0 °C. A solution of *E* ester prepared as described above (98.3 mg, 0.396 mmol) in 10 mL of ether was added dropwise, and the mixture was stirred for 30 min at 0 °C. The mixture was then stirred for 7 h at room temperature. The reaction was quenched with water (0.6 mL) and base (0.4 mL), and the mixture was filtered. The filtrate was washed (saturated NH_4Cl, bicarbonate, and brine), dried ($MgSO_4$), and concentrated. The crude product (77.2 mg, 95%) was a colorless, viscous oil that was clean by TLC and NMR (^1H and ^{13}C). Purification by column chromatography (30% ether/hexanes) furnished 61.9 mg (76%) of alcohol **2** that was homogeneous when submitted to GC analysis. Microdistillation (0.03 mm/90 °C) provided a sample for biological assay: IR (film) 3320 (br, OH), 3020, 2980, 2920, 2850, 1645 (C=C), 1455, 1015 cm^{-1}; ^1H NMR (200 MHz) δ 0.91 (s, 3 H, CCH_3), 0.88–1.04 (m, 2 H, $CHCH$), 1.13–1.45 (m, 2 H, CH_2CH_2CH=C), 1.46 (br s, 1 H, O*H*), 1.68 (br s, 3 H, CH_3C=CH), 1.65–2.10 (m, 4 H, ring CH_2CH_2), 2.13 (br q, J = 7.6 Hz, 2 H, CH_2CH=C), 3.99 (s, 2 H, CH_2OH), 5.40 (tq, J = 7.6 and 1.4 Hz, 1 H, C*H*=C), 5.61–5.71 (m, 1 H, CHCH=C*H*), 5.81–5.91 (m, 1 H, CHC*H*=CH); ^{13}C NMR (50 MHz) δ 12.55 (CCH_3), 13.59 (CH_3CR=), 16.74 (C-4 or C-5), 21.24 and 21.99 (C-1 and C-6), 22.24 (C-4 or C-5), 25.19 (CH_2CH), 28.68 (C-7), 42.63 (CCH_2CH_2), 69.05 (CH_2OH), 125.56, 126.01, and 126.51 (C-2, C-3, and CH_2CH=), 134.39 (CH_3CR=).

1,3-Cyclohexadiene-1-methanol. Aluminum chloride (Aldrich, 12.2 g, 91.5 mmol) was added to a suspension of LAH (10.1 g, 266 mmol) in 150 mL of ether at 0 °C.[8] The slurry was stirred at 0 °C for 45 min. A solution of 1-(ethoxycarbonyl)-1,3-cyclohexadiene[4b,9] (**10**, 12.15 g, 79.8 mmol) in 40 mL of ether was added dropwise at 0 °C. The mixture was stirred at room temperature for 17 h. The reaction was quenched at 0 °C by successive addition of water (10 mL), base (20 mL), and water (20 mL).[16] The mixture was stirred (with difficulty) until the solid material appeared floculent and bubbling had ceased. The mixture was filtered, and the clear ether filtrate was washed (saturated NH_4Cl, bicarbonate, and brine), dried ($MgSO_4$), and concentrated to give 7.54 g (86%) of alcohol. This alcohol readily oxidized to benzyl alcohol and was used without purification: IR (film) 3320 (br, OH), 3040, 2930–2830, 1060, 1040, 990, 690 cm^{-1}; ^1H NMR (200 MHz) δ 1.7 (br s, 1 H, O*H*), 2.09–2.21 (m, 4 H), 4.11 (s, 2 H, CH_2OH), 5.72–5.83 (m, 1 H, olefinic), 5.86–5.98 (m, 2 H, olefinic); ^{13}C NMR (50 MHz) δ 22.67 and 23.38 (C-5 and C-6), 65.96 (C-7), 118.98 (C-2), 123.95 and 125.49 (C-3 and C-4), 137.97 (C-1).

1-[(Benzyloxy)methyl]-1,3-cyclohexadiene (11). A solution of the alcohol prepared above (7.5 g, 68 mmol) in THF (50 mL) was added to a stirred suspension of NaH (Aldrich, 60% dispersion in mineral oil, 3.25 g, 81 mmol) in 80 mL of THF. Six drops of absolute ethanol was added, and the mixture was heated at reflux for 2 h. Benzyl bromide (Eastman, redistilled, 9.6 mL, 81 mmol) was added at room temperature, and the mixture was stirred for 11 h. The reaction was quenched with 10 mL of water and concentrated. The residue was dissolved in ether, and the solution was washed (acid (2×), bicarbonate (2×), and brine), dried ($MgSO_4$), and concentrated. Vacuum distillation of the residue (0.6 mm/105–110 °C) gave 10.3 g (76%) of ether **11**. This ether contained small amounts of dibenzyl ether resulting from aromatization of the cyclohexadiene ring and used without further purification: IR (film) 3100–3040, 2930–2830, 1455, 1355, 1090, 1075, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 2.20 (s, 4 H, CH_2CH_2), 4.00 (s, 2 H, CH=CC*H*$_2$O), 4.50 (s, 2 H, PhC*H*$_2$O), 5.73–5.84 (m, 1 H, olefinic), 5.88–5.98 (m, 2 H, olefinic), 7.25–7.40 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 22.65 and 23.57 (C-5 and C-6), 71.64 and 73.47 (CH_2OCH_2), 121.38 (C-2), 124.05 and 126.00 (C-3 and C-4), 127.50, 127.70 and 128.33 (aryl CH), 135.29 (C-1), 138.46 (quaternary aryl).

(1α,6α,8α)-3-[(Benzyloxy)methyl]-8-methyl-8-chlorobicyclo[4.2.0]oct-2-en-7-one (12). To a stirred solution of diene **11** (8.22 g, 41.0 mmol) and triethylamine (57 mL, 410 mmol) in 250 mL of pentane was introduced a solution of 2-chloropropionyl chloride (Aldrich, 53 g, 410 mmol) in 100 mL of pentane over a period of 4 h. The mixture was stirred for 16 h, and 30 mL of 2 N HCl was added. The pentane layer was washed with acid (2×), bicarbonate, and brine. The aqueous layers were carefully combined and extracted with ether. All organic solutions were combined, dried ($MgSO_4$), and concentrated to give an orange oil. Preparative HPLC separation (15% ether/hexanes) furnished a fraction containing 30 g of unidentified ketene byproducts followed by a fraction containing 7.50 g (63%) of the desired *endo*-methyl isomer **12**: IR (film) 3090–3040, 2930, 2860, 1785 (C=O), 1455, 1375, 1095, 1070, 915, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 1.48 (s, 3 H, CH_3), 1.52–1.67 (m, 1 H), 1.82–2.17 (m, 3 H), 3.15–3.26 (m, 1 H, CHCH=CH), 3.92 (s, 2 H, CH=CC*H*$_2$O), 4.05–4.17 (m, 1 H, O=CC*H*), 4.47 (s, 2 H, PhC*H*$_2$O), 5.89 (br d, 1 H, CHC*H*=C), 7.23–7.42 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 19.07 (C-4 or C-5), 19.44 (CH_3), 22.40 (C-4 or C-5), 40.53 (C-1), 54.39 (C-6), 72.16 and 73.82 (CH_2OCH_2), 77.20 (C-8), 120.23 (C-2), 127.62, 127.69, and 128.41 (aryl CH), 138.05 (quaternary aryl), 140.05 (C-3), 206.02 (C-7). A third fraction contained 2.77 g (23%) of the *exo*-methyl isomer: IR (film) 3080–3030, 2930, 2850, 1790 (C=O), 1640 (C=C), 1455, 1090–1070, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 1.50–1.72 (m, 1 H), 1.83 (s, 3 H, CH_3), 1.88–2.25 (m, 3 H), 2.99–3.08 (m, 1 H, CHCH=C), 3.69–3.79 (m, 1 H, O=CC*H*), 3.97 (s, 2 H, CH=CC*H*$_2$O), 4.48 (s, 2 H, PhC*H*$_2$O), 5.86 (br d, 1 H, CHC*H*=C), 7.25–7.40 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 19.38 and 22.04 (C-4 and C-5), 26.21 (CH_3), 38.18 (C-1), 52.07 (C-6), 71.44 and 73.88 (CH_2OCH_2), 76.45 (C-8), 121.56 (C-2), 127.50, 127.71, and 128.29 (aryl CH), 138.28 (C-3 and quaternary aryl), 206.51 (C-7).

Methyl (1α,6α,7α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]hept-2-ene-7-carboxylate (13). The procedure of Harding and Trotter was followed.[4] A mixture of ketone **12** (1.66 g, 5.71 mmol) and silver nitrate (1.48 g, 8.7 mmol) in 30 mL of methanol (EM Science, special anhydrous) was heated at reflux (oil bath temperature 71–72 °C) for 47 h. Brine was added, the mixture was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in ether, and the resulting solution was washed (bicarbonate (2×), and brine), dried ($MgSO_4$), and concentrated. Preparative HPLC purification (20% ether/hexanes) of the crude product afforded 0.87 g (53%) of ester **13**: IR (film) 3090–3030, 2920, 2850, 1720 (C=O), 1455, 1435, 1310,

1240, 1200, 1145, 1125, 1095, 1075, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 1.14 (s, 3 H, CCH_3), 1.62–2.21 (m, 6 H), 3.65 (s, 3 H, CO_2CH_3), 3.91 (s, 2 H, $CH{=}CCH_2O$), 4.44 (s, 2 H, $PhCH_2O$), 5.78 (br d, 1 H, $CH{=}C$), 7.21–7.38 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 9.40 (CH_3C), 16.24 and 23.04 (C-4 and C-5), 23.30 and 24.71 (C-1 and C-6), 30.82 (C-7), 51.91 (CH_3O), 71.69 and 74.12 (CH_2OCH_2), 120.14 (C-2), 127.56, 127.67, and 128.36 (aryl CH), 137.52 (C-3), 138.34 (quaternary aryl), 175.65 (CO_2); MS, *m/e* (percent) 286 (M^+, 1), 178 (25), 163 (5), 146 (4), 135 (8), 119 (10), 118 (8), 107 (5), 105 (12), 92 (11), 91 (100), 79 (14), 77 (11), 65 (10); accurate mass calcd for $C_{18}H_{22}O_3$ (M^+) 286.15689, found 286.15699.

(1α,6α,7α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]-hept-2-ene-7-methanol. Reduction of ester **13** (3.26 g, 11.4 mmol) was effected in 4 h with LAH (1.7 g, 45 mmol) in 200 mL of ether via the procedure described for the reduction of ester **8**. The reaction provided 2.79 g (95%) of alcohol: IR (film) 3400 (br, OH), 3090–3000, 2930, 2860, 1455, 1090–1060, 1030, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.99 (s, 3 H, CH_3), 1.00–1.08 (m, 1 H, $CHCH_2CH_2$), 1.13–1.21 (dd, J = 8.5 and 4.3 Hz, 1 H, $CHCH{=}C$), 2.55 (br s, 1 H, OH), 3.32 (dd, J = 15.2 and 11.0 Hz, 2 H, CH_2OH), 3.91 (s, 2 H, $CH{=}CCH_2O$), 4.42 (s, 2 H, $PhCH_2O$), 5.84 (br d, j = 4.3 Hz, 1 H, $CH{=}C$), 7.20–7.35 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 11.16 (CH_3C), 17.09 (C-4 or C-5), 19.01 and 19.20 (C-1 and C-6), 23.60 (C-4 or C-5), 31.16 (C-7), 71.37 (CH_2O), 72.51 (CH_2OH), 74.61 (CH_2O), 122.73 (C-2), 127.49, 127.71, and 128.33 (aryl CH), 135.06 (C-3), 138.48 (quaternary aryl).

(1α,6α,7α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]-hept-2-ene-7-carboxaldehyde (14). Oxidation of the alcohol prepared above (2.79 g, 10.8 mmol) was effected in 5 h with PCC (3.49 g, 16.2 mmol) in 100 mL of CH_2Cl_2 via the procedure described for the oxidation to give **6**. No byproducts were observable in the crude product (2.54 g, 92%) by NMR (^1H and ^{13}C) spectroscopy. Column chromatography (25% ether/hexanes) furnished 1.80 g (65%) of aldehyde **14** as a clear colorless oil: IR (film) 3090–3030, 2930, 2850, 2725, 1705 (C=O), 1455, 1090, 945, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 1.14 (s, 3 H, CH_3), 1.71–2.24 (m, 6 H), 3.94 (s, 2 H, $CH{=}CCH_2O$), 4.47 (s, 2 H, $PhCH_2O$), 5.81 (d, J = 4 Hz, 1 H, $CH{=}C$), 7.22–7.40 (m, 5 H, aromatic), 8.82 (s, 1 H, CHO); ^{13}C NMR (50 MHz) δ 7.19 (CH_3C), 16.02 (C-4 or C-5), 22.05 (C-1 or C-6) 23.19 (C-4 or C-5), 23.36 (C-1 or C-6), 40.14 (C-7), 71.83 and 73.95 (CH_2OCH_2), 118.74 (C-2), 127.60, 127.65, and 128.37 (aryl CH), 137.70 (C-3), 138.24 (quaternary aryl), 201.44 (CHO); MS, *m/e* (percent) 256 (M^+, 1), 165 (4), 148 (24), 119 (6), 105 (4), 92 (10), 91 (100), 79 (10), 77 (9), 67 (6), 65 (12); accurate mass calcd for $C_{17}H_{20}O_2$ (M^+) 256.14633, found 256.14644.

Ethyl (*E*)-3-{(1α,6α,7α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]hept-2-en-7-yl}-2-propenoate (15). The procedure of Marmor was followed.[6] A solution of triethyl phosphonoacetate (2.9 g, 13 mmol) in 20 mL of ether was added to a suspension of NaH (Aldrich, 60% dispersion in mineral oil, 0.51 g, 13 mmol) in 50 mL of ether at 0 °C. The mixture was heated at reflux for 10 min and then cooled to 0 °C. An ether solution (25 mL) of aldehyde **14** (1.65 g, 6.44 mmol) was added dropwise, and the resulting solution was heated at reflux for 10 min. The reaction mixture was allowed to cool to room temperature before 20 mL of water was added cautiously. The ether layer was separated and washed (bicarbonate, water, and brine). All aqueous layers were combined and extracted with ether. The combined ether layers were dried ($MgSO_4$) and concentrated. Column chromatography (20% ether/hexanes) of the crude product mixture provided 2.01 g (96%) of pure ester **15**: IR (film) 3090–3030, 2980–2850, 1715 (C=O), 1635 (C=C), 1455, 1365, 1310, 1265, 1170, 1040, 985, 950, 735, 700 cm^{-1}; ^1H NMR (200 MHz) δ 1.05 (s, 3 H, CCH_3), 1.26 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.35–1.50 (m, 1 H, $CHCH_2CH_2$), 1.56–1.65 (dd, J = 8.6 and 4.3 Hz, 1 H, $CHCH{=}C$), 1.66–2.20 (m, 4 H, CH_2CH_2), 3.91 (s, 2 H, $CH{=}CCH_2O$), 4.16 (q, J = 7.2 Hz, 2 H, CH_3CH_2), 4.44 (s, 2 H, $PhCH_2O$), 5.74 (d, J = 15.6 Hz, 1 H, $CH{=}CHCO_2$), 5.81 (br d, 1 H, $CH{=}C$), 6.54 (d, J = 15.6 Hz, 1 H, $CH{=}CHCO_2$), 7.20–7.35 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 10.68 (CH_3C), 14.33 (CH_3CH_2), 16.74 and 23.35 (C-4 and C-5), 24.08 and 25.49 (C-1 and C-6), 31.18 (C-7), 59.93 (CH_3CH_2), 71.65 and 74.19 (CH_2OCH_2) 115.38 ($=CHCO_2$), 120.57 (C-2), 127.51, 127.60, and 128.31 (aryl CH), 136.96 (C-3), 138.37 (quaternary aryl), 158.13 ($CCH=$), 167.07 (CO_2); MS, *m/e* (percent) 326 (M^+, 1), 218 (45), 189 (25), 161 (28), 145 (33), 143 (15), 133 (30), 131 (39), 105 (18), 92 (29), 91 (100), 79 (21), 77 (22), 65 (22); accurate mass calcd for $C_{21}H_{26}O_3$ (M^+) 326.18819, found 326.18894.

Ethyl 3-{(1α,6α,8α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]hept-2-en-7-yl}propanoate (16). A modification of the procedure of Tsuda et al. was followed.[7] To freshly purified[19] CuI (57 mg, 0.3 mmol) suspended in 10 mL of THF at −55 °C was added a solution of MeLi (Aldrich, 1.4 M in ether, 180 μL, 0.25 mmol) with a glass hypodermic syringe. To the resulting yellow suspension was added HMPA (1.8 mL) and DIBAL–H (Aldrich, 1.0 M in hexane, 1.8 mL, 1.8 mmol). This mixture was stirred for 30 min at −50 °C to produce a gray-brown solution. Ester **15** (0.43 g, 1.3 mmol) was introduced as a solution in 5 mL of THF, and the reaction mixture was stirred for 4 h at −45 to −55 °C. The reaction was quenched with 10 mL of 1 N HCl and diluted with ether. The organic layer was separated and washed (1 N HCl, bicarbonate, and brine). The combined aqueous solutions were extracted with ether, and the combined ether layers were dried ($MgSO_4$) and concentrated to give a mixture (TLC, 30% ether/hexanes) of product **16** (R_f 0.43) and starting materials **15** (R_f 0.37). The crude product mixture was subjected to identical reaction conditions with those described above. The reaction mixture was stirred for 5 h, and the product was isolated as before. Careful Chromatotron purification (20% ether/hexanes) afforded 0.12 g of starting material **15** and 0.27 g (63%, 87% based on recovered **15**) of the desired product **16**: IR (film) 3090–3030, 2980–2920, 1735 (C=O), 1455, 1370, 1165, 1095, 1070, 735, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.88 (s, 3 H, CCH_3), 0.90–1.00 (m, 1 H, $CHCH_2CH_2$), 1.04–1.13 (dd, J = 8.6 and 4.4 Hz, 1 H, $CHCH{=}C$), 1.24 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.43–2.16 (m, 6 H), 2.38 (t, J = 8.2 Hz, 2 H, $CH_2CH_2CO_2$), 3.90 (s, 2 H, $CH{=}CCH_2O$), 4.11 (q, J = 7.2 Hz, 2 H, CH_3CH_2), 4.42 (s, 2 H, $PhCH_2O$), 5.83 (br d, J = 4.4 Hz, 1 H, $CH{=}C$), 7.20–7.37 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 12.50 (CH_3C), 14.23 (CH_3CH_2), 17.32 (C-4 or C-5), 21.45 and 21.77 (C-1 and C-6), 23.56 (C-4 or C-5), 28.32 (C-7), 32.13 (CH_2CO_2), 37.81 (CCH_2CH_2), 60.20 (CH_3CH_2), 71.35 and 74.71 (CH_2OCH_2), 123.20 (C-2), 127.43, 127.65 and 128.29 (aryl CH), 134.66 (C-3), 138.59 (quaternary aryl), 173.83 (CO_2).

3-{(1α,6α,7α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]hept-2-en-7-yl}propanol. Reduction of ester **16** (332.5 mg, 1.01 mmol) was effected in 3 h with LAH (0.15 g, 4.0 mmol) in 18 mL of ether via the procedure described for the reduction of ester **8**. The reaction provided 282.3 mg (97%) of alcohol: IR (film) 3380 (br, OH), 3090–3030, 2920, 2850, 1455, 1060, 735, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.88 (s, 3 H, CH_3), 0.85–0.96 (m, 1 H, $CHCH_2CH_2$), 1.00–1.08 (dd, J = 8.6 and 4.5 Hz, 1 H, $CHCH{=}C$), 1.11–1.42 (m, 2 H, $CH_2CH_2CH_2OH$), 1.54–1.67 (m, 2 H, CH_2CH_2OH), 1.67–2.16 (m, 4 H, $CHCH_2CH_2$), 2.92 (br s, 1 H, OH), 3.52 (t, J = 6.6 Hz, 2 H, CH_2OH), 3.90 (s, 2 H, $CH{=}CCH_2O$), 4.41 (s, 2 H, $PhCH_2O$), 5.85 (br d, J = 4.3 Hz, 1 H, $CH{=}C$), 7.19–7.34 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 12.78 (CH_3C), 17.35 (C-4 or C-5), 21.62 and 21.82 (C-1 and C-6), 23.60 (C-4 or C-5), 28.61 (C-7), 29.98 (CH_2CH_2OH), 38.76 (CCH_2), 62.54 (CH_2OH), 71.19 and 74.74 (CH_2OCH_2), 123.80 (C-2), 127.43, 127.67 and 128.26 (aryl CH), 134.06 (C-3), 138.41 (quaternary aryl).

3-{(1α,6α,7α)-3-[(Benzyloxy)methyl]-7-methylbicyclo[4.1.0]hept-2-en-7-yl}propanal (17). Oxidation of the alcohol described above (282.3 mg, 0.99 mmol) was effected in 5 h with PCC (0.32 g, 1.5 mmol) in 18 mL of CH_2Cl_2 via the procedure described for oxidation to give **6**. Normal workup gave 248.3 mg (89%) of aldehyde **17**: IR (film) 3090–3030, 2920, 2850, 2720, 1725 (C=O), 1455, 1090, 1070, 735, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.86 (s, 3 H, CH_3), 0.90–0.98 (m, 1 H, $CHCH_2CH_2$), 1.02–1.11 (dd, J = 8.6 and 4.1 Hz, 1 H, $CHCH{=}C$), 1.40–2.20 (m, 6 H), 2.48 (td, J = 7.7 and 1.6 Hz, 2 H, CH_2CHO), 3.89 (s, 2 H, $CH{=}CCH_2O$), 5.83 (d, J = 4.1 Hz, 1 H, $CH{=}C$), 7.18–7.38 (m, 5 H, aromatic), 9.72 (t, J = 1.6 Hz, 1 H, CHO); ^{13}C NMR (50 MHz) δ 12.66 (CH_3C), 17.22 (C-4 or C-5), 21.62 and 21.92 (C-1 and C-6), 23.49 (C-4 or C-5), 28.06 (C-7), 34.81 (CH_2CHO), 41.71 (C-9), 71.33 and 74.61 (CH_2OCH_2), 122.90 (C-2), 127.38, 127.58, and 128.24 (aryl CH), 134.73 (C-3), 138.53 (quaternary aryl), 202.40 (CHO).

Ethyl (*E*)-2-Methyl-5-{(1α,6α,7α)-3-[(benzyloxy)-methyl]-7-methylbicyclo[4.1.0]hept-2-en-7-yl}-2-pentenoate. The procedure of Marmor was followed.[6] A solution of triethyl 2-phosphonopropionate (Aldrich, 0.41 g, 1.7 mmol) in ether (5 mL) was added to a suspension of NaH (Aldrich, 60% dispersion

in mineral oil, 70 mg, 1.7 mmol) in ether (7 mL) at 0 °C. The mixture was heated at reflux for 10 min and then cooled to 0 °C. Aldehyde **17** (247.4 mg, 0.870 mmol) in ether (10 mL) was added dropwise, and the resulting mixture was heated at reflux for 10 min. Water (8 mL) was added at room temperature, and the ether layer was separated and washed (bicarbonate, water, and brine). The combined aqueous layers were extracted with ether, and the combined ether layers were dried ($MgSO_4$) and concentrated to give a crude mixture of the expected *E* and *Z* isomers. Chromatotron purification (15% ether/hexanes) of the crude product afforded an initial set of fractions that contained 253.0 mg (79%) of the desired *E* ester: IR (film) 3090–3030, 2980–2850, 1710 (C=O), 1650 (C=C), 1450, 1365, 1280–1265, 1100–1075, 740, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.91 (s, 3 H, CCH_3), 0.86–0.97 (m, 1 H, ring CH CH_2CH_2), 1.01–1.10 (dd, J = 8.6 and 4.3 Hz, 1 H, $CHCH$=C), 1.27 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.21–1.52 (m, 2 H, CH_2CH_2CH=C), 1.67–2.17 (m, 4 H, ring $CHCH_2CH_2$), 1.84 (d, J = 1.3 Hz, 3 H, CH_3C=CH), 2.26 (br q, J = 7.6 Hz, 2 H, CH_2CH=C), 3.90 (s, 2 H, CH=CCH_2O), 4.16 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.42 (s, 2 H, PhCH_2O), 5.85 (br d, J = 4.3 Hz, 1 H, $CHCH$=C), 6.78 (tq, J = 7.6 and 1.3 Hz, 1 H, CH_2CH=C), 7.18–7.36 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 12.24 (CH_3C(R)=), 12.69 (CH_3C), 14.30 (CH_3CH_2), 17.33 (C-4 or C-5), 21.76 and 21.96 (C-1 and C-6), 23.61 (C-4 or C-5), 26.29 (CH_2C-H=), 28.62 (C-7), 41.46 (CCH_2CH_2), 60.26 (CH_3CH_2), 71.32 and 74.72 (CH_2OCH_2), 123.30 (C-2), 127.40 (CH_3C(R)= and *p*-aryl CH), 127.61 and 128.27 (aryl CH), 134.50 (C-3), 138.60 (quaternary aryl), 142.04 (CH_2CH=), 168.04 (CO_2); MS, *m/e* (percent) (no M^+), 260 (2), 186 (6), 159 (8), 158 (10), 146 (6), 141 (10), 133 (8), 128 (6), 119 (20), 115 (9), 105 (10), 99 (7), 95 (7), 92 (10), 91 (100), 79 (10), 77 (8). A second set of fractions contained a mixture of the *E* and *Z* isomers (7 mg, 2%). A third set of fractions contained 33.8 mg (11%) of the *Z* isomer: IR (film) 3090–3030, 2980–2850, 1710 (C=O), 1455, 1375, 1240, 1190, 1145, 1100–1070, 735, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.90 (s, 3 H, CCH_3), 0.90-0.99 (m, 1 H, ring $CHCH_2CH_2$), 1.03–1.12 (dd, J = 8.6 and 4.3 Hz, 1 H, $CHCH$=C), 1.15–1.50 (m, 2 H, CH_2CH_2CH=C), 1.31 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.65–2.20 (m, 4 H, ring $CHCH_2CH_2$), 1.89 (d, J = 1.3 Hz, 3 H, CH_3C=CH), 2.56 (br q, J = 7.6 Hz, 2 H, CH_2CH=C), 3.91 (s, 2 H, CH=CCH_2O), 4.20 (q, J = 7.2 Hz, 2 H, CH_3CH_2), 4.43 (s, 2 H, PhCH_2O), 5.85 (m, 1 H, $CHCH$=C), 5.92 (tq, J = 7.6 and 1.3 Hz, 1 H, CH_2CH=C), 7.22–7.38 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 12.76 (CH_3C), 14.33 (CH_3CH_2), 17.37 (C-4 or C-5), 20.72 (CH_3C(R)=), 21.76 and 21.94 (C-1 and C-6), 23.65 (C-4 or C-5), 27.21 (CH_2CH=), 28.86 (C-7), 42.43 (CCH_2CH_2), 60.04 (CH_3CH_2), 71.29 and 74.84 (CH_2OCH_2), 123.70 (C-2), 126.92 (CH_3C(R)=), 127.45, 127.71, and 128.32 (aryl CH), 134.30 (C-3), 138.63 (quaternary aryl), 142.86 (CH_2CH=), 168.16 (CO_2).

(*E*)-2-Methyl-5-{(1α,6α,7α)-3-[(benzyloxy)methyl]-7-methylbicyclo[4.1.0]hept-2-en-7-yl}-2-penten-1-ol. A solution of DIBAL-H (Aldrich, 1.0 M in hexane, 1.9 mL, 1.9 mmol) was added to a solution of the ester prepared above (236.4 mg, 0.641 mmol) in ether at 0 °C. The mixture was stirred for 1 h at 0 °C. The reaction was quenched by dropwise addition of acid. The organic layer was washed (acid, bicarbonate, and brine), dried ($MgSO_4$), and concentrated to give a clear, colorless oil. Chromatotron purification furnished 192.2 mg (92%) of alcohol: IR (film) 3380 (br, OH), 3090–3030, 2990–2850, 1455, 1070, 735, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.90 (s, 3 H, CCH_3), 0.85–0.95 (m, 1 H, ring $CHCH_2CH_2$), 1.02–1.09 (dd, J = 8.6 and 4.3 Hz, 1 H, $CHCH$=C), 1.13–1.44 (m, 2 H, CH_2CH_2CH=C), 1.65 (s, 3 H, CH_3C=CH), 1.60–2.05 (m, 4 H, ring $CHCH_2CH_2$), 2.12 (m, 2 H, CH_2CH=C), 2.35 (br s, 1 H, O*H*), 3.90 (s, 2 H, CH=CCH_2O) and 3.92 (s, 2 H, CH=CCH_2O), 4.42 (s, 2 H, PhCH_2O), 5.37 (br t, J = 7.0 Hz, 1 H, CH_2CH=C), 5.86 (br d, J = 4.3 Hz, 1 H, $CHCH$=C), 7.18–7.35 (m, 5 H, aromatic); ^{13}C NMR (50 MHz) δ 12.81 (CH_3C), 13.54 (CH_3C(R)=), 17.39 (C-4 or C-5), 21.72 and 21.89 (C-1 and C-6), 23.62 (C-4 or C-5), 25.11 (CH_2CH=), 28.94 (C-7), 42.59 (CCH_2CH_2), 68.62 (CH_2OH), 71.18 and 74.74 (CH_2-OCH_2), 123.80 (C-2), 125.96 (CH_2CH=), 127.43, 127.68, and 128.27 (aryl CH), 134.09 and 134.44 (C-3 and CH_3C(R)=), 138.46 (quaternary aryl).

(±)-Sirenin, (*E*)-2-Methyl-5-{(1α,6α,7α)-3-(hydroxymethyl)-7-methylbicyclo[4.1.0]hept-2-en-7-yl}-2-penten-1-ol (1). To 10 mL of liquid NH_3 (distilled from a solution of lithium metal in liquid NH_3) was added 5 mg of lithium metal ($^1/_4$-in. wire). The initial blue color slowly disappeared to produce a cloudy white solution.[20] The monobenzyl ether described above (36.8 mg, 0.113 mmol) was introduced as a solution in THF (2 mL). Small pieces of lithium (2-3 mg) were added until the blue color persisted for at least 15 min (total lithium: 17 mg, 2.4 mmol). Solid NH_4Cl was added, the solution was diluted with ether, and the mixture was stirred without a condenser until the NH_3 had evaporated. The ether solution was washed (saturated NH_4Cl and brine), dried ($MgSO_4$), and concentrated. Purification by column chromatography (60% ether/hexanes) gave 24.4 mg (92%) of sirenin (**1**) as a viscous, colorless oil. Microdistillation (0.07 mm/140–145 °C) provided samples for biological analysis. All spectral values were in excellent agreement with those previously reported:[3a,b,g,i,j,o] IR (film) 3340 (br, OH), 2990, 2920, 2860, 1665, 1450, 1385, 1065, 1020–990 (br), 910, 735 cm^{-1}; ^1H NMR (200 MHz) δ 0.87 (s, 3 H, CCH_3), 0.88–0.96 (m, 1 H, ring $CHCH_2CH_2$), 1.00–1.08 (dd, J = 8.5 and 4.3 Hz, 1 H, ring $CHCH$=C), 1.13–1.44 (m, 2 H, CH_2CH_2CH=C), 1.67 (s, 3 H, CH_3C=CH), 1.68–2.05 (m, 6 H, ring CH_2CH_2 and hydroxyls), 2.12 (br q, J = 7.6 Hz, 2 H, CH_2CH=C), 3.98 (s, 2 H, CH_2OH) and 4.00 (s, 2 H, CH_2OH), 5.40 (tq, J = 7.3 and 1.2 Hz, 1 H, CH_2CH=C), 5.84 (br d, J = 4.3 Hz, 1 H, $CHCH$=C); ^{13}C NMR (50 MHz) δ 12.68 (CH_3C) 13.59 (CH_3C(R)=), 17.49 (C-4 or C-5), 21.63 and 21.68 (C-1 and C-6), 23.40 (C-4 or C-5), 25.13 (CH_2CH=), 28.84 (C-7), 42.56 (CCH_2-CH_2), 67.40 and 68.84 (two CH_2OH), 121.31 (C-2), 126.24 (CH_2CH=), 134.42 and 137.12 (two C=CH); MS, *m/e* (percent) (no M^+), 218 (4), 200 (5), 187 (8), 148 (47), 135 (47), 133 (34), 131 (47), 119 (44), 117 (23), 109 (26), 107 (48), 105 (67), 93 (44), 91 (100), 81 (42), 79 (85), 77 (47), 67 (61); accurate mass calcd for $C_{15}H_{22}O$ ($M^+ - H_2O$) 218.16706, found 218.16764; accurate mass calcd for $C_{15}H_{20}$ ($M^+ - 2H_2O$) 200.15650, found 200.15685.

Acknowledgment. We thank the Robert A. Welch Foundation (Grant A-442) for support of this research. Initial studies were funded by a NIH Biomedical Sciences Support Grant through Texas A & M University.

(20) Although the ammonia had been redistilled and all normal measures for keeping the reaction free of water had been taken, it is obvious that quenching of lithium by water was taking place in this reaction.

On the Structure of Isobongkrekic Acid, a Novel Δ^2-*E* Isomer of the Antibiotic Bongkrekic Acid

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Received February 16, 1988

Bongkrekic acid (BA, Ia) is a toxic antibiotic produced by the microorganism *Pseudomonas cocovenenans* and was found responsible for the fatal food poisoning that used to frequently occur in Indonesia after consumption of an infected coconut product "bongkrek".[1] The high toxicity of bongkrekic acid has been attributed to its affinity for the ATP/ADP translocator protein residing in the mitochondrial inner membrane, thus preventing oxidative phosphorylation.[2]

(1) (a) Isolation: Lijmbach, G. W. M.; Cox, H. C.; Berends, W. *Tetrahedron* **1970**, *26*, 5993. (b) Structure elucidation: Lijmbach, G. W. M.; Cox, H. C.; Berends, W. *Ibid.* **1971**, *27*, 1839. Bruijn, J. de., Frost, D. J.; Nugteren, D. H.; Gaudemer, A.; Lijmbach, G. W. M.; Cox, H. C.; Berends, W. *Ibid.* **1973**, *29*, 1541. (c) Synthesis: Corey, E. J.; Tramontano, A. *J. Am. Chem. Soc.* **1984**, *106*, 462.

(2) van Veen, A. G.; Mertens, W. K. *Recl. Trav. Chim. Pays-Bas* **1934**, *53*, 257.

0022-3263/88/1953-4883$01.50/0