compound prepared by hydrogenation of **53**.

A fraction containing 0.25 g of a mixture was followed by 0.82 g (2.0 mmol, 13%) of the 4β,5β isomer **50**: mp 210–220 °C (methanol–water); IR 1745, 1695 cm^{-1}; NMR δ 4.56 (t, 1 H, 17α-H), 2.04 (s, 3 H, 17β-OAc), 0.82 (s, 3 H, C18), 0.78 (s, 3 H, C19); NMR (C_6D_6) δ 4.60 (t, 1 H, 17α-H), 1.77 (s, 3 H, 17β-OAc), 0.75 (s, 3 H, C18), 0.58 (s, 3 H, C19); $[\alpha]^{25}_D$ −21.2 ± 3° (*c* 0.099, $CHCl_3$), $[\alpha]^{25}_{365}$ −218.2 ± 3°; ORD/CD $[\Phi]_{312}$ −392°, $[\Phi]_{294}$ 0°, $[\Phi]_{272}$ +4002°; a = −79; $[\theta]_{294}$ −6395°, a_{calcd} = −78.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.68; H, 9.74.

Acknowledgment. The author would like to thank the chromatography department, under the supervision of Mr. Robert Nicholson, for numerous separations, Dr. Jeremy Hribar for aid in the taking and interpreting of the mass spectra, and Lydia Swenton of the Physical Methodology Department for aid in obtaining and discussions of the NMR decoupling and europium shift experiments.

Registry No. **1**, 2352-19-4; **2**, 976-71-6; **3**, 1045-69-8; **4**, 38391-33-2; **5**, 38391-34-3; **6**, 71719-79-4; **7**, 38391-35-4; **8**, 38391-37-6; **9**, 38391-36-5; **11**, 71719-80-7; **12**, 65351-65-7; **13**, 65351-58-8; **14**, 71719-81-8; **15**, 65351-61-3; **16**, 71719-82-9; **17**, 71719-83-0; **18**, 71719-84-1; **19**, 71719-85-2; **20**, 71719-86-3; **21**, 71749-91-2; **22**, 65351-60-2; **23**, 65351-57-7; **24**, 71719-87-4; **25**, 71719-88-5; **26**, 71771-99-8; **27**, 71719-89-6; **28**, 71719-90-9; **29**, 71719-91-0; **30**, 65351-64-6; **31**, 633-34-1; **32**, 71719-92-1; **33**, 71772-00-4; **34**, 71719-93-2; **35**, 71719-94-3; **38**, 71719-95-4; **39**, 71719-96-5; **40**, 71719-97-6; **41**, 71749-86-5; **42**, 71719-98-7; **43**, 71719-99-8; **44**, 71720-00-8; **45**, 71720-01-9; **46**, 65351-59-9; **47**, 65351-63-5; **48**, 71720-02-0; **49**, 71720-03-1; **50**, 71720-04-2; **51**, 71772-01-5; **52**, 71772-02-6; **53**, 71720-05-3; **54**, 71720-06-4; **55**, 71720-07-5; **56**, 71720-08-6; **57**, 71720-09-7; **58**, 71720-10-0; 6-dehydrotestosterone, 2484-30-2; acetic anhydride, 108-24-7; butadiene, 106-99-0; 2,3-dimethylbutadiene, 513-81-5; 2-methylbutadiene, 78-79-5; 1-acetoxybutadiene, 1515-76-0; *trans,trans*-2,4-hexadiene, 5194-51-4; 1-vinylcyclohexene, 2622-21-1; 1,1′-bicyclohexenyl, 1128-65-0; 2,4-dimethyl-1,3-pentadiene, 1000-86-8; 1,3-cyclohexadiene, 592-57-4.

Experiments Directed toward the Total Synthesis of Terpenes. 23. Synthesis of 4a-Methyl-4,4a,7,8-tetrahydro-9*H*-benzocycloheptene-2(3*H*),5(6*H*)-dione (B-Homo Wieland–Miescher Ketone): A Versatile Intermediate for Terpene Synthesis[1]

Robert E. Ireland,* Paul A. Aristoff,[2] and Charles F. Hoyng

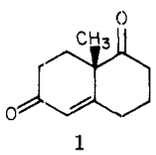
Contribution No. 5876 from the Chemical Laboratories, California Institute of Technology, Pasadena, California 91125

Received October 16, 1978

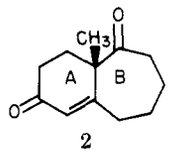
An efficient four-step synthesis of a B-homo Wieland–Miescher ketone (**2**) from 2-methoxybenzosuberone (**3**) in 36% overall yield is described. Entry into the hydrobenzosuberan series is also available through Diels–Alder reaction between the methoxy(silyloxy)butadiene **10** and 2-methylcycloheptenone (**11**). These syntheses make this useful intermediate readily available.

The Wieland–Miescher ketone **1** has served in numerous steroid and terpene syntheses[3a] and has been used as the substrate for several other synthetic transformations.[3b] The utility of this diketone stems from both its obvious structural relationship to the steroid–terpenoid series and also the versatility of the differentiable functional groups present. The value of this system has led to the development of efficient, large-scale synthetic procedures for its ready preparation.[4]

In connection with programs directed toward the total synthesis of several diverse natural products it became apparent that a similar, but potentially even more versatile, dicyclic starting material was the B-homo derivative **2**.[5]



1



2

Derivatives of this B-homo Wieland–Miescher ketone **2** possess the same basic structural characteristics as the diketone **1** but have the added feature that after an intramolecularly engineered contraction of the seven-membered B-ring, a standard six-membered ring results that has a functionally substituted one-carbon appendage at a predetermined site. Thus, further elaboration of ring systems and/or side chains on the basic decalin structure in a regiospecific manner becomes possible.

As attractive as this concept is for synthetic design, before the versatility of the homo diketone **2** can be realized, a convenient and efficient synthesis for the material must be available.

The diketone **2** has in fact been prepared in a two-step Robinson annelation of 2-methyl-1,3-cycloheptanedione with methyl vinyl ketone in 20–30% yield.[6] However, the synthesis of 2-methyl-1,3-cycloheptanedione involves a three-step ring expansion from the monoketal of dihydro-

(1) This investigation was supported by Grant No. CA18191, awarded by the National Cancer Institute, DHEW.

(2) Predoctoral Fellow of the National Science Foundation, 1973–1976.

(3) For instance, see: Stork, G. *Pure Appl. Chem.* **1964**, *9*, 131. (b) Venkataramaru, P. S.; Reusch, W. *Tetrahedron Lett.* **1968**, 5283. Grieco, P. A.; Ferrino, S; Oguri, T. *J. Org. Chem.* **1979**, *44*, 2593–94.

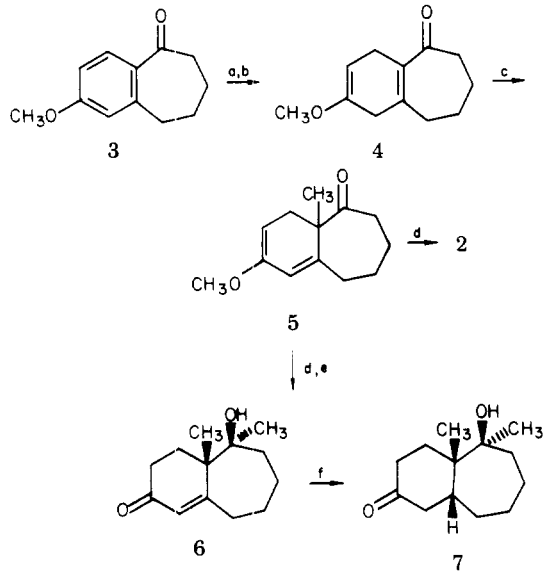
(4) Ramachandran, S.; Newman, M. S. *Org. Synth.* **1961**, *41*, 38.

(5) The term "Wieland–Miescher ketone" is used to refer to 4a-methyl-4,4a,7,8-tetrahydro-2(3*H*),5(6*H*)-naphthalenedione (Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215). While there are in principle several "homo-Wieland–Miescher ketones", the term as used here refers to the benzosuberone derivative **2** in which the B ring of the octalindione has been enlarged by the addition of a methylene group.

(6) Selvorajon, R; John, J. P.; Narayanan, K. V.; Swaminathan, S. *Tetrahedron* **1966**, 22, 949.

0022-3263/79/1944-4318$01.00/0 © 1979 American Chemical Society

Scheme I. 2-Methoxybenzosuberone Approach[a]



[a] a, Na, C_2H_5OH, NH_3-Et_2O; b, Al(O-*i*-Pr)$_3$, CH_3COCH_3, toluene; c, KNH_2, NH_3-Et_2O, CH_3I; d, H_3O^+, CH_3COCH_3; e, CH_3Li, Et_2O; f, Li, NH_3, Et_2O.

resorcinol (itself a relatively expensive compound) with an overall yield of only about 17%.[7] Hence, the overall yield of the B-homo Wieland–Miescher ketone **2** is only 4%—clearly unacceptable for the initial steps of any projected multistage synthesis. In view of these unfavorable reports, modification[8] of this route was rejected as a viable solution to this problem.

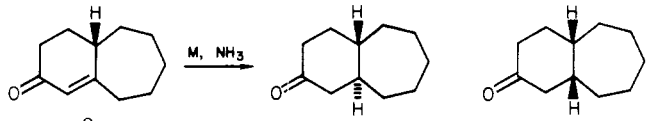
The first approach taken utilized commercially available[9] 2-methoxybenzosuberone (**3**) as the starting material in the Birch[10] scheme for the synthesis of the Wieland–Miescher ketone **2** itself (Scheme I). The sequence of operations used in the present conversion is essentially the same as that described by Birch[10] for the similar transformation of the lower homologue. In contrast to the results observed in the tetralone series, methylation of the ketone **4** leads *exclusively* to the desired angularly methylated ketone **5**, and no evidence was found for the formation of six-membered-ring methylated material. This reaction scheme provides an efficient means for the preparation of the B-homo Wieland–Miescher ketone **2**, which is now available on a large (50 g) scale in 36% overall yield from 2-methoxybenzosuberone (**3**).

While this procedure makes the B-homo Wieland–Miescher ketone **2** an easily accessible synthetic starting material, for maximum use in further transformations, two additional features are important—namely, the ability to achieve selectivity in carbonyl reactions and the ease and stereochemical control of the double-bond reduction.

In contrast to the Wieland–Miescher ketone **2** itself, selective borohydride[11a] or ketalization[11b] of the saturated seven-membered-ring ketone was not possible. The distortion of this ring over the lower homologue adds significant steric hindrance about the C5 carbonyl, and apparently this is sufficient to reduce the effective reactivity of this group to that of the α,β-unsaturated six-membered-ring ketone. The desired functional group selectivity could, however, be accomplished indirectly by virtue of the intermediacy of the keto dienol ether **5** in the synthetic scheme. Thus, methyllithium addition and then acid hydrolysis provide access to the hydroxy ketone **6** in which functional differentiation has been achieved.

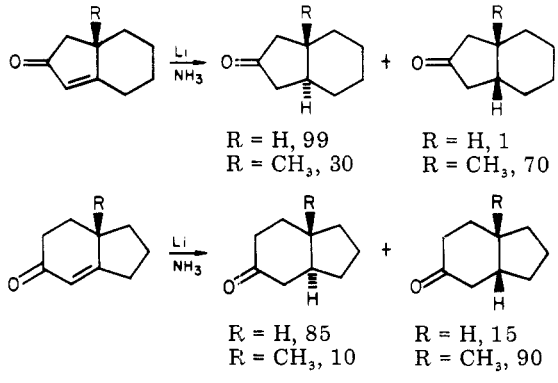
The double bond reduction results were similarly unusual. While catalytic hydrogenation of the diketone **2** itself was complicated by carbonyl reduction, lithium–ammonia reduction of the hydroxy ketone **6** proceeded smoothly to generate a saturated hydroxy ketone in high yield. Subsequent work[12] using this material in an aphidicolin synthesis led to the realization through X-ray analysis that this hydroxy ketone was the *cis-fused isomer* **7**. Several exploratory experiments[13] on other derivatives of this system in which the substitution at C5 was varied also led to cis-fused reduction products, and the trans-fused isomer of the saturated hydroxy ketone **7** was never obtained in preparatively useful amounts.

The only reported reductions of an enone of this type are for a study[14] of the stereochemistry of the reduction of the enone **8**. In this case, in which the angular methyl

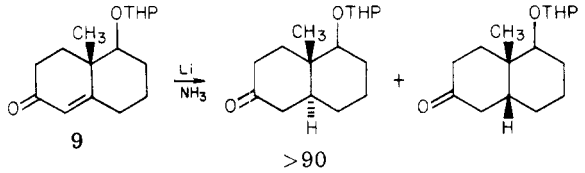


8

group is absent, the ratio of trans to cis product was (76–87)/(24–13) on reduction with lithium or sodium in ammonia. The dramatic effect of the angular methyl group on the stereochemical outcome of the reduction of two other enone systems is shown below.[15]



These latter results suggest that the virtually exclusive formation of the cis-fused hydroxy ketone **7** in the present situation was to be expected, were it not for the fact that the Wieland–Miescher ketone derivative **9**[16] (an octalone



9 >90

(7) Eistert, B.; Haupter, F.; Schank, K. *Justus Liebigs Ann. Chem.* **1963**, *665*, 55.

(8) Initially, a scheme based on a new synthesis of cycloheptane-1,3-dione was developed, but methylation of this relatively unstable diketone to form the required 2-methylcycloheptane-1,3-dione was very unsatisfactory (Aristoff, P. A. Ph.D. Thesis, California Institute of Technology, 1977). Later the same diketone synthesis was reported by: Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073.

(9) Material available from Aldrich Chemical Co.

(10) Birch, A. J.; Quartey, J. A. K.; Smith, H. *J. Chem. Soc.* **1952**, 1768.

(11) (a) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 2680. (b) Kitohara, Y.; Yoshikoshi, A.; Oida, S. *Tetrahedron Lett* **1964**, 1763.

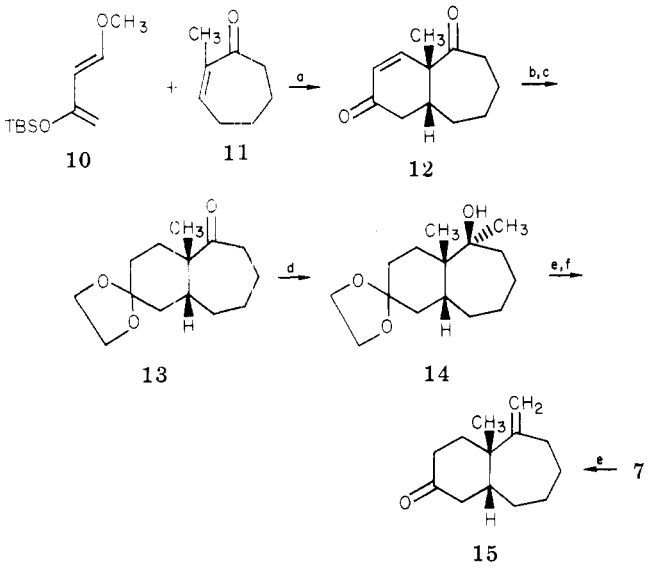
(12) Ireland, R. E.; Aristoff, P. A. *J. Org. Chem.*, following paper in this issue.

(13) Aristoff, P. A. Ph.D. Thesis, California Institute of Technology, 1977.

(14) Granger, R.; Chapat, J.-P.; Crassous, J.; Simon, F. *Bull. Soc. Chim. Fr.* **1968**, 4265.

(15) Dauben, W., private communication cited by: Caine, D. *Org. React.* **1976**, *23*, 104.

Scheme II. The Diels-Alder Approach[a]



[a] a, 200 °C, H_3O^+; b, 10% Pd-C, H_2, THF, c, $(CH_2OH)_2$, *p*-TsOH, C_6H_6; d, CH_3Li, Et_2O-C_6H_6; e, $SOCl_2$, Pyr, −15 °C; f, H_3O^+, THF.

rather than the above hydroindenones) leads virtually exclusively to the trans-fused reduction product. The present results, taken together with the previous work described above, seem to point to the conclusion that the stereochemical outcome of the octalone reduction is unique rather than general. A possible explanation for this observation may be that protonation of the intermediate allyl anion[17] from the α face of the molecule to give the trans-fused product forces the angular methyl group into close contact with the β-hydrogen at C7 in the seven-membered ring. This mode of attack is therefore less favorable than that from the β face to give cis-fused product on steric grounds.

Access to this same cis-fused system can also be accomplished through a Diels–Alder approach (Scheme II) which chemically confirms the designated cis fusion. The enedione **10** is constructed after the synthetic plan outlined by Danishefsky[18] for the corresponding octalinone system. Again it is not possible to differentiate the chemical reactivity of the two carbonyl groups in the unsaturated ketone **12**, but after saturation of the double bond, the less hindered six-membered-ring ketone may be selectively protected as its ketal. Carbonyl addition reactions are now possible at the seven-membered-ring ketone, and the addition of methyllithium to the ketone ketal **13** affords the hydroxy ketal **14**. The interrelation of the two series was accomplished through dehydration and hydrolysis of the hydroxy ketal **14** to the exocyclic enone **15**; this same enone **15** was also obtained by dehydration of the hydroxy ketone **7**. This correlation thereby confirms the assigned cis-fusion of these derivatives.

The ready availability of the B-homo Wieland–Miescher ketone **2** and these functionally differentiated derivatives allows their exploration in synthetic planning. One such application to a synthesis of aphidicolin is described elsewhere.[12]

(16) Jaeger, R. H. *Tetrahedron* **1958**, *2*, 326. Aristoff, P. A., unpublished results, these laboratories.

(17) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800.

(18) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

Experimental Section[19]

2-Methoxy-1,4,5,6,7,8-hexahydro-9*H*-benzocyclohepten-5-ol. To a solution of 100 g (0.526 mol) of commercial 2-methoxybenzosuberone (**3**) in 1150 mL of ethanol, 420 mL of dry ether, and 3 L of dry ammonia was added 90 g (4 mol) of sodium metal over 35 min so as to keep the solution a deep blue color. The ammonia was allowed to evaporate, and 1600 mL of water was added. The solution was extracted twice with 2-L portions of ether, and the ether layers were washed separately with 1 L of brine and then dried (K_2CO_3). Removal of the solvents at reduced pressure afforded a white solid which on short-path distillation in a base-washed apparatus at 80–110 °C (0.1 mm) gave 37 g (40%) of 2-methoxybenzosuberan (R_f 0.7 with 4:1 petroleum ether–ether). The pot residue consisted of 53 g (52%) of cycloheptenol (R_f 0.09 with 4:1 petroleum ether–ether) as a white solid, mp 86–88 °C. This material was usually used without further purification.

Recrystallization of a sample of this material from ether and petroleum ether afforded the analytically pure alcohol: mp 86–87.5 °C; IR ($CHCl_3$) 3590 (OH), 3430 (OH), 1680 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 3.52 (s, 3, OCH_3), 4.60 (m, 1, vinyl).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.18; H, 9.30.

2-Methoxy-1,4,7,8-tetrahydro-9*H*-benzocyclohepten-5(6*H*)-one (4). A solution of 47 g (0.24 mol) of cycloheptenol and 8.5 g (0.415 mol) of dry aluminum isopropoxide in 220 mL of dry acetone and 390 mL of dry toluene was heated at reflux for 9 h, cooled, and then added to a mixture of 45 mL of water and 100 mL of brine. The layers were separated, and the aqueous layer was extracted twice with 125-mL portions of ether. The combined ethereal layers were washed twice with 75-mL portions of brine and then dried (K_2CO_3). Removal of the solvents at reduced pressure left 55 g (<100%) of the ketone **4** as a colorless oil. Normally, this material was used directly without further purification.

An analytically pure sample, prepared by chromatography on silica gel with 4:1 petroleum ether–ether and then bulb-to-bulb distillation at 90–93 °C (0.05 mm), was a clear, colorless liquid (oily solid below 0 °C): IR ($CHCl_3$) 1695 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 2.92 (m, 4, bis allylic), 3.53 (s, 3, OCH_3), 4.7 (m, 1, vinyl).

(19) All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded with a Varian T-60, a Varian A-60, or a Varian EM390 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ_{Me_4Si} 0.0) as an internal standard. Gas–liquid phase chromatographic (VPC) analyses were determined on a Hewlett-Packard 5750 gas chromatograph using helium carrier gas at a flow rate of 60 mL/min. All analytical VPC was conducted on a 5 ft × 0.125 in column packed with 4% SE-30 on 60–80 mesh Chromosorb WAS DMCS. Preparative layer chromatography (PTLC) was carried out on precoated PLC plates with a 20 × 20 × 2 mm layer of silica gel 60F-254 on glass plates manufactured by E. Merck. Alumina used for chromatography refers to the grade I, neutral variety manufactured by M. Woelm made up to grade II or III as indicated by addition of 3 or 6% water prior to use. Silica gel columns used the 0.05–0.2 mm silica gel manufactured "for column chromatography" by E. Merck. Preparative medium-pressure column chromatography was performed by using $^1/_2$ × 20 in. or 2 × 20 in. glass columns with fittings supplied by Chromatronix, Inc., and an instrument minipump supplied by Milton Roy Co. The columns were packed with silica gel H "for tlc acc. to Stahl" (10–40) manufactured by E. Merck. Ether and petroleum ether were degassed under water aspirator vacuum prior to use. "Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran were distilled from lithium aluminum hydride, *tert*-butyl alcohol, pyridine, and benzene were distilled from calcium hydride, dichloromethane and iodomethane were distilled from phosphorus pentoxide, and methanol was distilled from magnesium turnings. "Ether" refers to anhydrous diethyl ether which was supplied by Mallinckrodt. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 35–60 °C, which was supplied by J. T. Baker Co., and was not further purified. All water used in the reactions and workups was distilled water. Brine refers to a saturated aqueous solution of sodium chloride. All reaction flasks and syringes were dried for at least 12 h in an oven (at 140 °C) and cooled in a desiccator over anhydrous calcium sulfate prior to use. All reactions (except the photooxygenations and hydrogenations) were run under an atmosphere of argon, and at the beginning of all reactions, the solutions were degassed. Mass spectral analyses were performed by Ms. Beth Irwin, UCLA, Los Angeles, Calif. Microanalyses were performed by Spang Microanalytical Laboratory.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.34.

2-Methoxy-4α-methyl-4,4α,7,8-tetrahydro-9*H*-benzocyclohepten-5(6*H*)-one (5). To 2.5 L of dry ammonia containing 0.25 g of ferric nitrate hydrate was added 12 g (0.306 mol) of potassium metal. After 30 min a solution of 51 g (0.265 mol) of the ketone **4** in 750 mL of dry ether was added dropwise over a 30-min period. After an additional 5 min, 50 mL (114 g, 0.80 mol) of dry methyl iodide was added over a 2-min period. After another 15 min the ammonia was allowed to evaporate, and 500 mL of water was added. The layers were separated and the aqueous layer was extracted twice with 500-mL portions of ether. The combined organic layers were washed twice with 300-mL portions of brine and then dried (K_2CO_3). After removal of the solvents at reduced pressure there remained 54 g (100%) of the methylated ketone **5**, which was generally used in the next step without further purification.

An analytically pure sample was prepared by chromatography on silica gel with 9:1 petroleum ether–ether (R_f 0.4) as a white solid (mp 50–52 °C) which was distilled at 90–95 °C (0.05 mm): IR ($CHCl_3$) 1690 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.18 (s, 3, C-4a CH_3), 3.57 (s, 3, OCH_3), 4.2 (m, 1, vinyl), 5.6 (m, 1, vinyl).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 8.79.

4a-Methyl-4,4a,7,8-tetrahydro-9*H*-benzocycloheptene-2(3*H*),5(6*H*)-dione (Homo Wieland–Miescher Ketone) (2). A solution of 5.4 g (26 mmol) of ketone **5** and 2.4 mL of 4% hydrochloric acid in 100 mL of acetone was heated at reflux for 2 h, cooled, and added to a mixture of 400 mL of water and 400 mL of ether. The layers were separated, and the aqueous layer was extracted twice more with 400-mL portions of ether. The combined organic layers were washed twice with 200-mL portions of brine and then dried ($MgSO_4$). After removal of the solvents at reduced pressure and crystallization of the residue from ether, there was obtained 2.3 g (46%) of the dione **2** as a white solid. Chromatography of the mother liquors on silica gel with 2:1 petroleum ether–ether furnished an additional 1.2 g (R_f 0.25) of the same material and resulted in a total yield of 3.5 g (70%) of dione **2**: mp 70–72 °C (lit.[6] mp 71.5–72 °C); IR ($CHCl_3$) 1704 (C=O), 1665 (unsaturated C=O), 1618 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.38 (s, 3, C-4a CH_3), 5.99 (s, 1, vinyl).

2-Methoxy-4aβ,5α-dimethyl-4,4a,5,6,7,8-hexahydro-9*H*-benzocyclohepten-5β-ol. To 360 mL (0.66 mol) of 1.8 M ethereal methyllithium in 500 mL of dry ether at 0–5 °C was added dropwise 53 g (0.26 mol) of ketone **5** in 500 mL of dry ether over a 2-h period. After an additional 2 h at room temperature, the reaction was carefully quenched with 50 mL of water. Another 800 mL of water was added, the layers were separated, and the aqueous layer was extracted twice with 800-mL portions of ether. The combined organic layers were washed twice with 400-mL portions of brine and then dried (K_2CO_3). After removal of the solvents at reduced pressure there remained 58 g (100%) of the corresponding alcohol which was generally used without further purification in subsequent steps. An analytically pure sample of the alcohol was obtained by chromatography (R_f 0.39) of a portion of this material on silica gel with 2:1 petroleum ether–ether and then bulb-to-bulb distillation of the material so obtained at 95–100 °C (0.05 mm): IR ($CHCl_3$) 3600 (OH), 1663, 1659 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.16 (s, 3, C-4a CH_3), 1.29 (s, 3, C-5 CH_3), 4.51 (s, 3, OCH_3), 4.5 (m, 1, vinyl), 5.7 (m, 1, vinyl).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.59; H, 10.09.

5β-Hydroxy-4aβ,5α-dimethyl-4,4a,5,6,7,8-hexahydro-9*H*-benzocyclohepten-2(3*H*)-one (6). A solution of 56 g (0.252 mol) of the crude alcohol above and 63 g (0.50 mol) of oxalic acid dihydrate in 180 mL of water and 2.5 L of methanol was stirred for 2 h at room temperature and then made basic with 53 g (0.50 mol) of sodium carbonate. Most of the methanol was removed at reduced pressure and 500 mL of water and 1 L of ether were added. The layers were separated, and the aqueous layer was extracted twice with 500-mL portions of ether. The combined organic layers were washed twice with 250-mL portions of brine and then dried (K_2CO_3). Removal of the solvents at reduced pressure afforded 47 g (90%) of ketone **6** (R_f 0.36 with 100% ether), mp 135–138 °C. This material was generally used in subsequent steps without further purification.

One recrystallization of a portion of this yellow-white solid from ether and petroleum ether furnished an analytically pure sample of the ketone **6** as white crystals: mp 139–140.2 °C; IR ($CHCl_3$) 3600 (OH), 1650 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.23 (s, 3, C-4a CH_3), 1.42 (s, 3, C-5 CH_3), 5.79 (s, 1, $w_{1/2}$ = 2 Hz, vinyl).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.02; H, 9.67.

5β-Hydroxy-4aβ,5α-dimethyl-3,4,4a,5,6,7,8,9aβ-octahydro-9*H*-benzocyclohepten-2(1*H*)-one (7). To a solution of 7.6 g (1.1 mol) of lithium wire in 500 mL of dry ether and 4.5 L of dry ammonia was added dropwise 44.3 g (0.213 mol) of the ketone **6** in 500 mL of dry ether over a 1-h period. After an additional 20 min, anhydrous sodium benzoate was added until the blue color was discharged. Then 60 g (1.1 mol) of ammonium chloride was added, and the ammonia was allowed to evaporate. The residue was treated with 1 L of water and 2 L of ether, the layers were separated, and the aqueous layer was extracted with 1 L of ether. The combined ethereal layers were washed twice with 400 mL of saturated aqueous sodium bicarbonate and then twice with 400 mL of brine. The organic layers were dried (K_2CO_3) and the solvents were then removed at reduced pressure. Short-path distillation at 140–144 °C (0.05 mm) afforded 38 g (85%) of the saturated hydroxy ketone **7** (a single component to the extent of 98% by VPC at 200 °C).

Chromatography on silica gel with 100% ether followed by crystallization from ether–petroleum ether gave an analytically pure sample of this ketone **7** (R_f 0.35) as a white solid: mp 74–75.5 °C; IR ($CHCl_3$) 3600 (OH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.24 (s, 3, CH_3), 1.26 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.22; H, 10.51.

4aβ-Methyl-5-methylene-3,4,4a,5,6,7,8,9aβ-octahydro-9*H*-benzocyclohepten-2(1*H*)-one (15). To a solution of 78 mg (0.37 mmol) of alcohol **7** in 5.0 mL of dry pyridine at −15 °C was added 0.08 mL (130 mg, 1.1 mmol) of thionyl chloride. After 15 min at −15 to −10 °C, the solution was poured onto 25 mL of ice, and then 25 mL of water was added. The solution was extracted twice with 50-mL portions of ether. The combined ethereal layers were washed with 50 mL of saturated aqueous sodium bicarbonate, 50 mL of water, and 50 mL of brine and then dried ($MgSO_4$). Removal of the solvents at reduced pressure (using a cyclohexane azeotrope to remove the pyridine) gave 47 mg (66%) of the exocyclic olefin ketone **15**, which consisted of a single component by VPC (at 200 °C) and TLC (R_f 0.29 with 7:3 petroleum ether–ether). This material was prepared analytically pure by chromatography on silica gel with 7:3 petroleum ether–ether and then bulb-to-bulb distillation at 80–85 °C (0.05 mm) as a clear, colorless liquid: IR ($CHCl_3$) 1702 (C=O), 1623 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.30 (s, 3, C-4a CH_3), 4.84 (s, 2, vinyl).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.18; H, 10.62.

1-Methoxy-3-[(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene (10). A solution of lithium diisopropylamide was prepared by the addition of 94 mL (220 mmol) of a 2.34 M solution of *n*-butyllithium in hexane to a cold (0 °C) solution of 29.4 g (297 mmol) of diisopropylamine in 60 mL of dry hexane with rapid stirring. After removal of the solvent and excess amine by evaporation at 0 °C (0.1 mm), the white, amorphous solid residue was dissolved in 150 mL of dry tetrahydrofuran. The solution was chilled to −78 °C and rapidly stirred. A solution of 20.0 g (200 mmol) of 4-(methyloxy)-3-buten-2-one in 50 mL of dry tetrahydrofuran was added via syringe over a period of 10 min. The dark mixture was stirred for 30 min and then diluted with 20 mL of dry hexamethylphosphoric triamide. A solution of 32.8 g (218 mmol) of *tert*-butyldimethylsilyl chloride in 100 mL of dry tetrahydrofuran was added dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Excess lithium diisopropylamide was decomposed by the careful addition of 20 mL of water, and then the mixture was poured into 300 mL of *n*-pentane. The organic layer was separated, washed with water (3 × 150 mL) and saturated aqueous brine solution (1 × 100 mL), and then dried (K_2CO_3). After filtration of this mixture through a short pad of Celite, concentration of the filtrates under reduced pressure gave a dark liquid. Distillation of this oil afforded 17.5 g (41%) of the desired diene **10** as a colorless

liquid: bp 92–98 °C (0.7 mm); IR (CCl_4) 1650, 1580, 1460, 1320, 1210, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) 0.20 (s, 6 H, $(CH_3)_2Si$), 0.98 (s, 9 H, $(CH_3)_3CSi$), 3.54 (s, 3 H, CH_3O), 4.03 (br s, 2 H, $H_2C{=}C$), 5.30 (d, J = 12.5, 1 H, C-2 vinyl), 6.83 (d, J = 12.5 1 H, C-1 vinyl).

4aβ-Methyl-4a,7,8,9aβ-tetrahydro-9*H*-benzocycloheptene-2(1*H*),5(6*H*)-dione (12). A dry, base-washed glass tube was charged with a solution of 17.1 g (80.0 mmol) of 1-(methyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene (**10**) and 6.2 g (50.0 mmol) of 2-methyl-2-cycloheptenone (**11**)[20] in 4.0 mL of dry xylene. The mixture was degassed, and the glass tube was sealed under vacuum. The reaction tube was heated to 200 °C and maintained at that temperature for a period of 23 h. After cooling to room temperature, the contents of the sealed tube were transferred to a distillation flask, and the volatile materials were separated by atmospheric distillation at an oil bath of temperature ≤260 °C. The dark residue was taken up in 35 mL of tetrahydrofuran and treated with 5.0 mL of 6.0 N hydrochloric acid. After this mixture was stirred at room temperature for 8 h, the dark solution was diluted with 80 mL of ether, washed with 10% aqueous potassium hydroxide solution (4 × 100 mL) and water (2 × 50 mL), and dried ($MgSO_4$). Concentration of the filtrate under reduced pressure left a dark liquid which on chromatography on silica gel (ethyl acetate–hexane gradient elution) afforded 6.5 g (68%) of keto enone **12** as a pale yellow liquid: IR (CCl_4) 1705, 1680, 1450, 1170 cm^{-1}; ^1H NMR (CCl_4) 1.38 (s, 3 H, C-4aβ methyl), 5.80 (d, J = 10.5, 1 H, C-3 vinyl) 7.15 (dd, J_1 = 10.5, J_2 = 2, 1 H, C-4 vinyl).

An analytical sample was obtained by evaporative distillation of a portion of this material at 160 °C (0.2 mm).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.90; H, 8.31.

4aβ-Methyl-3,4,4a,7,8,9aβ-hexahydro-9*H*-benzocycloheptene-2(1*H*),5(6*H*)-dione (13). A solution of 2.22 g (11.6 mmol) of keto enone **11** in 50 mL of dry tetrahydrofuran was added to a suspension of 171 mg of 10% palladium-on-charcoal in 10 mL of dry tetrahydrofuran. The resultant mixture was stirred under an atmosphere of hydrogen until the uptake of hydrogen had ceased. The reaction mixture was then filtered through a short pad of Celite with 50 mL of anhydrous ether. Concentration of the combined filtrates under reduced pressure gave 2.22 g (99%) of the diketone **13** as a yellow liquid: IR (CCl_4) 1720, 1705 cm^{-1}; ^1H NMR (CCl_4) 1.32 (s, 3 H, C-4aβ methyl). This material was shown by thin-layer chromatographic analysis to consist of a single compound and was used without further purification in the synthesis of the corresponding ketal ketone.

Chromatography of a small sample on silica gel (1:4 ethyl acetate–hexane) provided a colorless liquid which crystallized on standing. Recrystallization from ethyl ether yielded colorless prisms, mp 52.5–54.5 °C. An analytical sample was prepared by evaporative distillation at 130 °C (0.6 mm).

2,2(1*H*)-(Ethylenedioxy)-4aβ-methyl-3,4,4a,7,8,9aβ-hexahydro-9*H*-benzocyclohepten-(6*H*)-one. A solution of 536 mg (2.76 mmol) of diketone **13**, 770 mg (12.4 mmol) of ethylene glycol, and a trace of *p*-toluenesulfonic acid in 15 mL of dry benzene was heated to reflux. This reaction mixture was maintained at reflux until thin-layer chromatographic analysis indicated the absence of diketone **13**. The solution was cooled to room temperature, diluted with an equal volume of ether, and washed with saturated aqueous sodium bicarbonate solution (2 × 40 mL) and saturated aqueous brine solution (1 × 40 mL). The organic layer was dried (K_2CO_3) and then concentrated under reduced pressure. Chromatography of the residual colorless liquid on silica gel (2:25 ethyl acetate–hexane) provided 481 mg (73%) of the six-membered ring ketal ketone: IR (CCl_4) 1700, 1440, 1125, 1100, 1065 cm^{-1}; ^1H NMR (CCl_4) 1.11 (s, 3 H, C-4aβ methyl), 3.78 (s, 4 H, OCH_2CH_2O). On standing under an argon atmosphere, the sample crystallized as colorless needles, mp 55–58 °C.

An analytical sample was obtained by evaporative distillation at 150 °C (2.5 mm).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.43; H, 9.26.

(20) Compare: Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.

2,2(1*H*)-(Ethylenedioxy)-4aβ,5α-dimethyl-3,4,4a,5,6,7,8,9aβ-octahydro-9*H*-benzocyclohepten-5β-ol (14). A solution of 4.47 g (18.7 mmol) of the above six-membered ring ketal ketone in 20 mL of dry benzene was added via syringe to a cold (0 °C) mixture of 60.0 mL (96.0 mmol) of a 1.6 M solution of methyllithium in ether and 60 mL of dry benzene. This mixture was stirred at 0 °C under an argon atmosphere for 1 h and then for an additional 4 h at room temperature. The excess methyllithium was decomposed by the careful addition of water. The organic layer was separated and washed with water (1 × 60 mL) and then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a pale yellow liquid. The above procedure was repeated twice with 60.0 mL (96.0 mmol) of the methyllithium solution each time. Chromatography of the resulting crude product on 200 g of silica gel (ethyl acetate–hexane gradient elution) afforded 3.75 g (79%) of ketal alcohol **14** as a colorless liquid: IR (CCl_4) 3500, 1100 cm^{-1}; ^1H NMR (CCl_4) 0.94 (s, 3 H, C-5α methyl), 1.14 (s, 3 H, C-4aβ methyl), 3.82 (s, 4 H, OCH_2CH_2O).

An analytical sample was prepared by evaporative distillation at 180 °C (0.6 mm).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.81; H, 10.29.

4aβ-Methyl-5-methylene-3,4,4aα,5,6,7,8,9aβ-octahydro-9*H*-benzocyclohepten-2(1*H*)-one (15). A solution of 843 mg (3.32 mmol) of ketal alcohol **14** in 15 mL of dry pyridine was cooled to −15 °C, and 0.60 mL (8.30 mmol) of thionyl chloride was added via syringe. The mixture was stirred for 60 min under an argon atmosphere and then poured onto 10 g of ice. This solution was diluted with 25 mL of water and then extracted with ether (2 × 20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (2 × 30 mL) and water (1 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The removal of residual traces of pyridine was aided by coevaporation with toluene. Chromatography of the residue on 20 g of silica gel (1:19 ethyl acetate–hexane) provided 415 mg (53%) of a colorless liquid as the only product: IR (film) 1620, 1100 cm^{-1}; ^1H NMR (CCl_4) 1.08 (s, 3 H, C-4aβ methyl), 3.79 (s, 4 H, OCH_2CH_2O), 4.72 (s, 2 H, $H_2C{=}C$). This material was assigned the structure of the corresponding ketal exocyclic olefin.

An analytical sample was obtained by evaporative distillation at 65 °C (0.1 mm).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.13; H, 10.26.

A solution of 82.3 mg (0.35 mmol) of the above purified ketal exocyclic olefin in 3 mL of tetrahydrofuran and 0.5 mL of 3 N hydrochloric acid was stirred at room temperature for a period of 5 h. This mixture was then diluted with 30 mL of ether and washed with 5% aqueous sodium bicarbonate solution (2 × 30 mL) and water (1 × 30 mL). After the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure, there remained 61.2 mg (92%) of keto exocyclic olefin **15** as a colorless liquid: IR ($CHCl_3$) 1705, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 1.20 (s, 3 H, C-4aβ methyl), 4.80 (s, 2 H, $H_2C{=}C$).

Chromatography of this material on 8 g of silica gel (3:97 ethyl acetate–hexane) provided 53.6 mg of the keto olefin **15** as a colorless liquid. Comparison of the spectral data (IR, NMR, TLC) of this material with those of the same substance prepared by the 2-methoxybenzosuberone (**3**) route revealed their identity.

In general preparative runs the ketal exocyclic olefin above was isolated but not extensively purified by chromatography. In this instance the overall yield of the ketone exocyclic olefin **15** from the hydroxy ketal **14** was 81%.

Registry No. **2**, 5971-47-1; **3**, 6500-65-8; **4**, 71734-97-9; **5**, 71734-98-0; **6**, 71734-99-1; **7**, 71735-00-7; **10**, 71735-01-8; **11**, 65371-57-5; **12**, 71735-02-9; **13**, 71735-03-0; **14**, 71766-71-7; **15**, 71735-04-1; **15** ethylene ketal, 71735-05-2; 2-methoxy-1,4,5,6,7,8-hexahydro-9*H*-benzocyclohepten-5-ol, 71735-06-3; 2-methoxy-4aβ,5α-dimethyl-4,4a,5,6,7,8-hexahydro-9*H*-benzocyclohepten-5β-ol, 71735-07-4; 4-(methyloxy)-3-buten-2-one, 4652-27-1; *tert*-butyldimethylsilyl chloride, 18162-48-6; 2,2(1*H*)-(ethylenedioxy)-4aβ-methyl-3,4,4a,7,8,9aβ-hexahydro-9*H*-benzocyclohepten-5(6*H*)-one, 71735-08-5; ethylene glycol, 107-21-1.