Preparation of Fused-Ring Cyclopropanol Derivatives by Reductive Cyclization of Bicyclic Enediones Related to the Wieland–Miescher Ketone

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Abstract: Reduction of eight alkyl-substituted derivatives of bicyclo[4.4.0]dec-1-ene-3,7-dione by solutions of lithium in ammonia has given, in every case, a cyclopropanol (derivatives of the 5-hydroxytricyclo[4.4.0.0^{1,5}]decan-9-one system) as the chief product. In some of these reductions trans-fused decalindiones were also produced, and conflicting reports concerning the course of the reaction with the Wieland–Miescher ketone are discussed. The half-wave reduction potentials of several members of the homoconjugated enedione series were over 0.1 V more positive than the potentials of analogues lacking the isolated carbonyl group, suggesting that the neighboring carbonyl function acts to facilitate addition of an electron to the enone moiety.

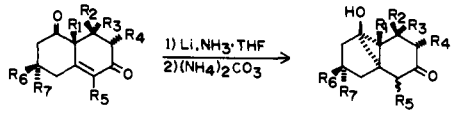
In 1968 we reported[1] a novel reductive cyclization of 6-allylbicyclo[4.4.0]dec-1-ene-3,7-dione (**2**) to 6-allyl-5-hydroxytricyclo[4.4.0.0^{1,5}]decan-9-one (**12**) on treatment with liquid ammonia solutions of alkali metals. Since the Wieland–Miescher ketone **1**[2] and its alkyl-substituted analogues (**2–8**) are important and versatile synthetic intermediates, we wanted to establish the scope of this reaction with such substrates, and to explore the nature of the potentially useful transformations that the resulting cyclopropanols might exhibit.[3]

In the first of this group of papers we present evidence supporting the general usefulness of our cyclopropanol synthesis, when applied to the compounds in Chart I. Our second paper outlines the extraordinary variety of reactions displayed by the parent system (**11**), and the third paper discusses the profound influence that alkyl substituents have on these reactions.

Results

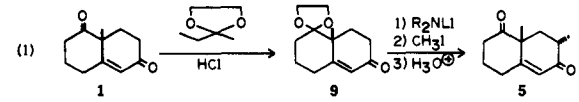
The reductions reported and discussed in this paper are outlined in Chart I.

Chart I



1[2]	$R_1 = CH_3$; R_2–$R_7 = H$	11
2[1]	$R_1 = CH_2CH{=}CH_2$; R_2–$R_7 = H$	12
3[4]	$R_1,R_2 = CH_3$; R_3–$R_7 = H$	13
4[4]	$R_1,R_3 = CH_3$; R_2,R_4–$R_7 = H$	14
5	$R_1,R_4 = CH_3$; R_2,R_3,R_5–$R_7 = H$	15
6[5]	$R_1,R_5 = CH_3$; R_2–$R_4,R_6,R_7 = H$	16
7[6]	$R_1,R_6,R_7 = CH_3$; R_2–$R_5 = H$	17
8	R_1,R_5–$R_7 = CH_3$; R_2–$R_4 = H$	18

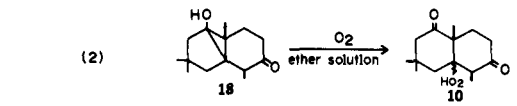
Substituted bicyclo[4.4.0]dec-1-ene-3,7-diones **1** through **8** (with the exception of **5**) were prepared either by the well-established Robinson annelation procedure described by Newman and Ramachandran,[2b] or the modified method devised by Coates and Shaw.[4a] The 4,6-dimethyl derivative **5** was made from the Wieland–Miescher ketone (**1**) by selective ketalization of the nonconjugated ketone function[8] followed by regioselective methylation of the kinetically favored dienolate anion[9] (eq 1).



Reductive cyclization of the enediones **1–8** was accomplished by dropwise addition of a solution of the substrate in tetrahydrofuran (THF) to a rapidly stirred solution of lithium (2 molar equiv) in freshly distilled ammonia containing additional THF. The characteristic blue color of the lithium/ammonia solution normally persisted throughout the addition and was dispelled after a brief reaction period by the addition of a few drops of 1,2-dibromoethane. The work-up procedures and further details are given in the Experimental Section.

In every case that we have investigated, the major reduction product was the corresponding cyclopropanol (**11–18**); however, purification of these sensitive compounds sometimes proved difficult and their isolated yields ranged from 50 to 90%. Compounds **11, 12,** and **16** were obtained as colorless, sharp-melting solids for which sound analytical and spectroscopic data support the assigned structures. Compounds **13, 15, 17,** and **18** remained oils, but the cyclopropanol structures assigned here are firmly supported by the spectroscopic characteristics and chemical reactions that these substances display. Cyclopropanol **14** was never completely separated from small amounts (ca. 10%) of the *trans*-decalindione (**19**), which was formed in about 20% overall yield in the course of the reduction. Likewise, cyclopropanols **17** and **18** contained from 10 to 30% of the unreduced enedione precursors (**7** and **8**), even though excess lithium was used and the characteristic blue color of the reducing solution persisted until workup.

The cyclopropanols described here are sensitive in varying degree to acid- and base-catalyzed rearrangement (see following papers), heat, and oxygen. For this reason, purification by GLC or conventional chromatography on silica gel or alumina is often not possible. Indeed, the care that must be taken in handling and identifying these compounds is well-illustrated by a misleading transformation suffered by **18.** We were pleased to find that an ether solution of **18** (>90% purity) slowly deposited crystals on standing in a refrigerator. Although the IR and ^{1}H NMR spectra of this substance were in accord with structure **18,** a mass spectrum clearly showed it to be the ring-opened hydroperoxide **10** (eq 2). Such reactions



of cyclopropanols with molecular oxygen are well-documented.[7]

Alkali metal in ammonia reductions of related bicyclic enone systems, lacking the neighboring carbonyl function that characterizes **1–8,** normally give *trans*-decalin derivatives.[10] Consequently, the isolation of **19** from the reduction of **4,** and the formation of **20**[5a] in 28% yield from **6** are not particularly

19 **20**

surprising. It is important, nevertheless, to identify such *trans*-decalins when they are present and to distinguish them from the corresponding cis isomers, because the latter are often produced in subsequent rearrangements of the cyclopropanols.

We must note, in this respect, a puzzling difference of opinion that exists concerning the reduction of the Wieland–Miescher ketone (**1**). Eight years prior to the appearance of our first report of this reductive cyclization,[1] Boyce and Whitehurst[11] observed that lithium/ammonia reduction of **1** gave a partially crystalline residue from which the bis-DNP derivative of the *trans*-decalindione **21** was obtained. Over a decade later, Bauduin and Pietrasanta[12] also recorded the isolation of **21**,[13] mp 58–59 °C, in 60% yield from the reduction of **1.** We have been concerned with these conflicting reports, and our investigations of this matter can be summarized by the following observations:

(1) The reduction of **1** has been effected in our laboratory more than 50 times by at least ten different experimentalists, and in every case cyclopropanol **11,** mp 98–100 °C, was obtained in 65–95% yield.

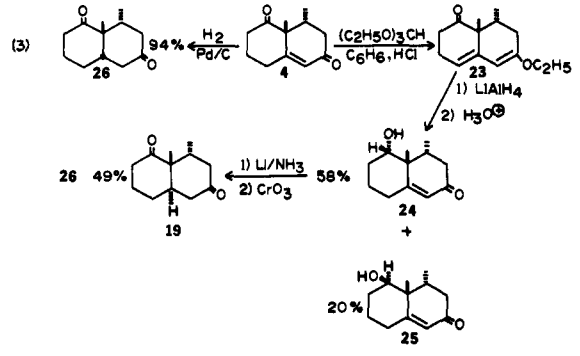
(2) Reductions of several hundred milligrams of **1** give high yields of **11;** however, larger scale reductions (e.g., 5 g) are not as efficient. Some **21** is also formed in the latter case. The experiments of the British[11] and French[12] groups were conducted with several grams of **1.**

(3) Ring-opening reactions of **11** under a variety of conditions (see the following paper) give only traces of the *trans*-decalin **21.** The cis isomer **22**,[5a] mp 65 °C, is often a major product from these reactions.

(4) Treatment of **11** with DNP reagent[14] gave, among other products, the bis-DNP derivatives of **21** and **22,** the latter predominating.

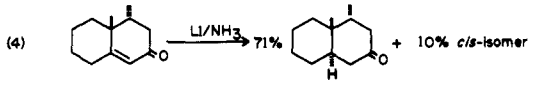
21 **22**

Our need to prepare authentic samples of the cis- and trans-fused dihydro derivatives of compounds **1** through **8** has been noted. In this respect, the synthesis of the isomeric dihydro derivatives of **4** (eq 3) not only illustrates one successful approach, but in practice revealed an interesting conformational influence on the stereochemistry of dissolving metal reductions.[10b]

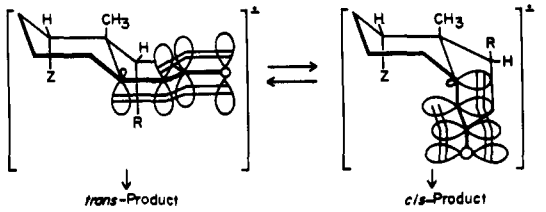


The dienol ether **23,** derived from compound **4,** gave a mixture of epimeric alcohols on reduction with lithium aluminum hydride. These epimers were separated, following hydrolysis of the dienol ether function, and the major epimer was assigned the axial hydroxyl configuration **24** on the strength of the relative chemical shifts of the methyl groups with respect to the equatorial isomer **25**[15] and the relative breadth of the carbinol proton multiplets observed at δ 4.14 (18-Hz wide) in **24** and δ 3.85 (12-Hz wide) in **25.** Reduction of **24** by lithium in ammonia, followed by oxidation with Collins' reagent, yielded a 5:3 mixture of the *trans*- and *cis*-decalindiones **19** and **26.** The cis isomer was also prepared in good yield by catalytic reduction of **4.** Separation of the products by preparative GLC gave crystalline samples of the two isomers, the IR, ^{1}H NMR, and mass spectra in each case being in accord with the assigned structures.

The substantial amount of cis isomer formed in the reduction of **24** exceeds that reported for the related deoxy compound (eq 4).[4a] Using the Stork and Darling model[10b] for these re-



actions, we can attribute this fact to a shift in the following conformational equilibrium.



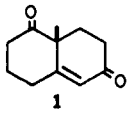
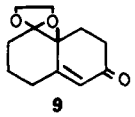
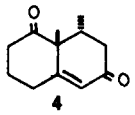
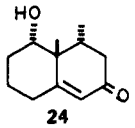
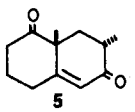
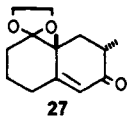
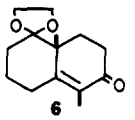
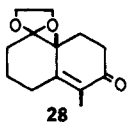
As R and Z become CH_3 and OH respectively, nonbonded interactions destabilize the trans conformer of the radical anion (or dianion) intermediate. The cis conformer therefore plays a larger role in the product-controlling protonation step. It is also possible that the cis conformer is stabilized by a lithium cation bridge when Z = O–Li.

Discussion

The fact that cyclopropanol products predominate in the reduction of compounds **1–8** requires that the isolated carbonyl function and the conjugated enone interact at some stage of the reaction. This interaction might follow the addition of an electron to the enone moiety, as it presumably does in the tosylate displacement reported by Stork et al.[16] In this event, the products are determined by a competition between protonation by solvent and internal electrophile attack at the nucleophilic β-carbon atom of the enone radical anion. If, on the other hand, such an interaction exists in the substrate prior to reduction, we might expect to observe its consequences spectroscopically or electrochemically. Our studies to this end, in which we were kindly assisted by Professor Peter Kissinger, are summarized in Table I.

Compounds **1, 4, 5,** and **6** were compared with derivatives (alcohols or ketals) in which the neighboring carbonyl function was masked. Although the $\pi \rightarrow \pi^*$ absorption of the enone chromophores proved to be relatively insensitive to this change, the half-wave reduction potentials[17] were over 0.1 V more positive when the carbonyl function was present. This suggests that the neighboring carbonyl group in compounds **1–8** facilitates the addition of an electron to the π-orbital system of the enone. The apparently conflicting nature of the spectroscopic observations is reconciled by considering the magnitude of the spectroscopic[18] and electrochemical[19] perturbations that occur when an equivalently substituted enone moiety becomes conjugated with an additional carbonyl function: C=CC=O, λ_{max} 240–250 nm, $E_{1/2}$ −2.0 to −2.1 V; O=CC=CC=O,

Table I. Ultraviolet Absorption and Half-Wave Potentials for Bicyclo[4.40]dec-6-ene-8-diones and Their Corresponding Derivatives

Compd	λ_{max}, nm	ϵ	Half-wave potential, V: Acetonitrile	Half-wave potential, V: DMF
 **1**	243.3	12 100	−1.96	−1.93
 **9**	242.0	13 130	−2.12	−2.03
 **4**	246.9	10 550	−1.95	−1.90
 **24**	242.2	13 680	−2.13	Undetermined
 **5**	243.3	11 400	−2.00	−1.95
 **27**	241.2	12 450	−2.15	−2.11
 **6**	251.7	11 900	−2.03	−1.95
 **28**	251.1	14 070	−2.17	−2.11

λ_{max} 250–265 nm, $E_{1/2}$ −0.5 to −0.8 V. Thus, the data in Table I are consistent with a homoconjugation effect in **1, 4, 5,** and **6,** which is about 10% that noted for full conjugation.

In conclusion, dissolving metal reductions of bicyclo[4.4.0]-dec-1-ene-3,7-diones such as **1–8** lead to moderately stable cyclopropanol derivatives in yields ranging from very good (80–95%) to fair (>50%) depending on the reaction scale. Since *trans*-decalindione products increase as the cyclopropanols decline in yield (large-scale reactions), it is possible that the three-membered ring formation step competes with β-protonation in the product-controlling stage. If this interpretation is correct, we might expect to find that reductions carried out in aprotic solvents should give increased yields of cyclopropanols. Although preliminary experiments with sodium naphthalide as an electron source in THF solution have resulted in conversion of **1** to **11,** the effective yield of **11** has been modest at best, and significant amounts of the saturated diketones **21** and **22** were also formed. We can only conclude that our understanding of this reaction and the factors that influence it is not yet complete.

Experimental Section

Melting points were determined in capillaries or on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer, using sodium chloride cells. Proton magnetic resonance (^{1}H NMR) spectra were obtained with either a Varian T-60 or a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. Ultraviolet spectra were determined in ethanol solution by means of a Cary 17 spectrometer. Mass spectra were obtained with Hitachi RMU-6 or LKB9000 mass spectrometers. Microanalyses were performed by Spang Microanalytical Labs, Ann Arbor, Mich.

Polarography was performed with a Princeton Applied Research Model 174 and recorded with a Hewlett-Packard 7045 XY recorder. Both dc polarography and current-sampled dc polarography were carried out. Spectrograde acetonitrile (Burdick and Jackson) was used as received; DMF was purified by vacuum distillation. The supporting electrolyte in all cases was tetraethylammonium perchlorate (recrystallized and dried). The height of the Hg column of the DME was 60.2 cm (uncor) and the drop time was 1.0 s. The concentration of the sample ketones ranged from 0.5 to 4.0 mM and all solutions were deoxygenated with nitrogen before measuring.

All reactions involving alkaline conditions have been carried out under dry N_2 or Ar, using solvents freshly purified by distillation from suitable drying agents.

Bicyclo[4.4.0]dec-1-ene-3,7-diones **1, 3, 4, 6,** and **7** were prepared by published methods (references are given in Chart I) and exhibited spectra consistent with the assigned structures.

6-Allylbicyclo[4.4.0]dec-1-ene-3,7-dione (2). A solution of 2-allylcyclohexane-1,3-dione[21] (16 g, 0.1 mol) and methyl vinyl ketone (9 g, 0.13 mol) in aqueous methanol containing a pellet of potassium hydroxide, was refluxed gently for 4 h. The residue remaining after the solvents were removed under reduced pressure was dissolved in ether and washed with water and brine. The crude Michael adduct obtained by evaporation of the dried ether solution was dissolved in 175 mL of dry benzene containing 2 mL of pyrrolidine. This solution was refluxed through a Dean–Stark trap until water ceased to form (ca. 2 h). The cooled reaction mixture was diluted with ether (50 mL), washed successively with 10% hydrochloric acid, water, and brine, and dried ($MgSO_4$). Evaporation of the organic solvents yielded an oily residue which crystallized on trituration with ether. The overall yield of compound **2,** mp 61.5–62.5 °C, proved to be 11.2 g (52%) after recrystallization from ethanol.

An analytical sample of **2** exhibited the following properties: IR (CCl_4) 1705, 1670, 1615, 980, 925 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.0–2.9 (m, 12 H), 5.2 (m, 3 H), 5.8 (m, 1 H).

Anal. ($C_{13}H_{16}O_2$) C, H.

***trans*-4,6-Dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione 3-Ethyleneketal (27).** A solution of 5.05 g (28.4 mmol) of Wieland–Miescher ketone (**1**)[2] in 200 mL of dry benzene and 2 mL of butan-2-one 2-ethyleneketal was acidified with dry hydrogen chloride to a pH< 1. An additional 3 mL of butanone 2-ethyleneketal was added after 3 days and, following a further 3-day reaction period, the mixture was washed with saturated sodium bicarbonate solution and water. The dried organic extracts were evaporated (reduced pressure) to give 6.2 g of crude product. Crystallization from 3 mL of ether gave 4.20 g of crystalline 6-methylbicyclo[4.4.0]dec-1-ene-3,7-dione 2-ethyleneketal (**9**), mp 69–70 °C (lit.[8] 66–67 °C). Chromatography of the mother liquors on 20 g of alumina (neutral, activity III) yielded an additional 0.92 g of product, total yield 86%.

To a solution of lithium diisopropylamide (LDA), prepared in THF (25 mL) by reacting 3.25 mL (24.8 mmol) of diisopropylamine with 10.4 mL of 2.4 M *n*-butyllithium, was added (dropwise at 0 °C) 5.0 g (22.5 mmol) of the previously prepared ketal in 15 mL of THF. The resulting enolate anion solution, upon warming to room temperature, was treated with 1.57 mL (25.0 mmol) of methyl iodide, and worked up after 90 min by dilution with benzene prior to washing with water and brine. The crude organic product, which showed two primary components by GLC analysis (20% SE30), was treated overnight with methanolic potassium hydroxide and extracted from the aqueous phase with benzene. Crystallization of the resulting oil from cold ether gave 3.97 g (75%) of the title compound: mp 109–110 °C; IR (CCl_4) 1673, 1622, 1369, 1112, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 6.0 Hz, 3 H), 1.40 (s, 3 H), 1.52–2.95 (m, 9 H), 4.00 (s, 4 H), 5.83 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 236 (4), 99 (100), 55 (10).

Anal. ($C_{14}H_{20}O_3$) C, H.

***trans*-4,6-Dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione (5).** Hydrolysis of a 6.2-g (26-mmol) sample of *trans*-4,6-dimethylbicyclo[4.4.0]-dec-1-ene-3,7-dione 3-ethyleneketal (prepared above) was accom-

plished in wet acetone (ca. 250 mL) containing 5 ml of concentrated hydrochloric acid. Following a 2-day reaction period, the solvent was removed by distillation and the residue was diluted with water and extracted with benzene. The organic extracts were washed sequentially with water, sodium bicarbonate solution, and brine. The residue remaining after removal of the solvent was crystallized from cold ether: first crop 1.90 g, secord crop 1.62 g, for a total yield of 3.52 g (70%) of **5**. An analytical sample displayed the following properties: mp 98–100 °C; IR (CCl_4) 1715, 1672, 1624, 1452, 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3 H), 1.52 (s, 3 H), 1.58–3.10 (m, 9 H), 6.84 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 192 (27), 177 (11), 174 (40), 164 (10), 150 (17), 137 (100), 121 (45), 108 (40), 93 (51), 55 (77).

Anal. ($C_{12}H_{16}O_2$) C, H.

2,6,9,9-Tetramethylbicyclo[4.4.0]dec-1-ene-3,7-dione (8). A freshly crystallized sample of 2,5,5-trimethylcyclohexane-1,3-dione (1.54 g, 0.01 mol), prepared by methylation of dimedone,[22] was converted to an enamine derivative by refluxing in a benzene solution containing 1.5 mL of pyrrolidine, until water no longer accumulated in a Dean–Stark trap. Michael addition of this enamine to ethyl vinyl ketone (1.5 ml, 0.015 mol) was accomplished by refluxing a benzene solution of the reactants to which a catalyst consisting of sodium acetate (625 mg), acetic acid (1.32 mL), and water (1.25 mL) had been added. After 1 h, GLC analysis (4% QF-1, 180 °C) showed that conversion to the Michael adduct was complete. Subsequent aldol cyclization was effected by the addition of *p*-toluenesulfonic acid (200 mg) to the reaction mixture, which was then refluxed through a Dean–Stark trap. A major portion of the benzene solvent was removed by evaporation, and an ether solution of the remaining dark liquid was washed with 10% hydrochloric acid and water. The dried ether extracts yielded 1.9 g of a yellow oil, which was crystallized from ethyl acetate to give 1.4 g (63%) of colorless crystals of **8**. An analytical sample displayed the following properties: mp 105–106 °C; IR (CCl_4) 1715, 1675, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (s, 3 H), 1.1 (s, 3 H), 1.35 (s, 3 H), 1.8 (s, 3 H), 2.0–3.0 (m, 8 H).

Anal. ($C_{14}H_{20}O_2$) C, H.

Lithium/Ammonia Reduction of Substituted Bicyclo[4.4.0]dec-1-ene-3,7-diones. The general method for the preparation of cyclopropanols from their corresponding enediones is illustrated by the reduction of the Wieland–Miescher ketone (**1**).

(a) (1*R,5α,6β)-5-Hydroxy-6-methyltricyclo[4.4.0.0^{1,5}]decan-9-one (11).** A solution of 1.34 g (193 mmol) of lithium in 500 mL of liquid ammonia (freshly distilled from sodium) and 25 mL of tetrahydrofuran was prepared in a three-necked flask equipped with an overhead stirrer and a dry-ice condenser. To this solution was added dropwise (80 min) 17.1 g (96 mmol) of Wieland–Miescher ketone (**1**)[2] in 125 mL of tetrahydrofuran. The resulting mixture was stirred for 20 min at −78 °C, following which it was decomposed by the addition of a large excess of anhydrous ammonium carbonate. The liquid ammonia was evaporated under a nitrogen stream, and the remaining slurry was taken up in a mixture of water and ether and extracted with ether, the organic extracts being washed with water and dried. Removal of the solvent at reduced pressure left an oil, which crystallized to give 16.0 g of a white solid. Recrystallization from ether gave 15.1 g (87%) of pure cyclopropanol **11**. Cyclopropanol **11** can be sublimed at 92 °C (0.05 Torr) without decomposition. An analytical sample exhibited the following properties: mp 98–100 °C; IR (CCl_4) 1710, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.60–2.48 (m, 12 H), 3.12 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 180 (100), 165 (47), 152 (15), 137 (73), 123 (57), 109 (43), 97 (46), 81 (49), 67 (37), 55 (90).

Anal. ($C_{11}H_{16}O_2$) C, H.

(b) (1*R,5α,6β)-5-Hydroxy-6-allyltricyclo[4.4.0.0^{1,5}]decan-9-one (12).** Reduction of **2** (20 g, 0.1 mol) by lithium/ammonia solutions according to the previous procedure yielded, after two crystallizations from ether–pentane, 10.5 g (50%) of **12**: mp 87–88 °C, IR (CCl_4) 3590, 1705, 1640, 985, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–2.4 (m, ca. 14 H), 4.15 (s, 1 H, disappears on D_2O addition), 4.8–5.9 (m, 3 H); mass spectrum (70 eV) molecular ion *m/e* 206.

Anal. ($C_{13}H_{18}O_2$) C, H.

(c) (1*R,5α,6β,7β)-5-Hydroxy-6,7-dimethyltricyclo[4.4.0.0^{1,5}]-decan-9-one (13).** Lithium/ammonia reduction of 258 mg (1.34 mmol) of *cis*-5,6-dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione (**3**) gave 262 mg of an oil which did not crystallize under various conditions even though the ^1H NMR spectrum suggested a single product predominated. This oil had the following properties: IR (film) 3450, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 1.01 (d, J = 6.5 Hz, 3 H), 1.12–2.80 (m, 11 H), 3.47 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity), 194 (23), 179 (25), 176 (32), 161 (27), 151 (31), 145 (40), 133 (46), 124 (49), 74 (75), 59 (100). The *m/e* 195 ion was 14.2% of the parent ion abundance (calcd to be 13.3% for $C_{12}H_{18}O_2$).

(d) (1*R,5α,6β,7α)-5-Hydroxy-6,7-dimethyltricyclo[4.4.0.0^{1,5}]-decan-9-one (14).** Lithium/ammonia reduction of 10.0 g (52.1 mmol) of *trans*-5,6-dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione (**4**), conducted as previously described, yielded 10.4 g of an oil. Crystallization at −78 °C yielded 6.4 g of crystalline material consisting of a 3:1 mixture of **14** and (1β,6α,10α)-1,10-dimethylbicyclo[4.4.0]decane-2,8-dione (**19**). Recrystallization did not alter this ratio; however, a careful Kugelrohr distillation substantially increased the purity of **14**: IR (CCl_4) 3475, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.15 (d, J = 6.5 Hz, 3 H), 1.40–2.75 (m, 11 H), 3.52 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (32), 179 (18), 176 (22), 161 (27), 151 (26), 135 (60), 123 (42), 109 (42), 95 (40), 69 (72), 55 (70), 41 (100). The *m/e* 195 ion was 14.2% of the parent ion abundance (calcd to be 13.3% for $C_{12}H_{18}O_2$).

An analytical sample of the minor product **19**, prepared by recrystallization from ether, had mp 82.5–83.5 °C and spectral properties identical with those recorded for the major product obtained from the dissolving metal reduction and subsequent oxidation of (5α,6β,7α)-7-hydroxy-5,6-dimethylbicyclo[4.4.0]dec-1-en-3-one (**24**).

(e) (1*R,5α,6β,8α)-5-Hydroxy-6,8-dimethyltricyclo[4.4.0.0^{1,5}]-decan-9-one (15).** Lithium/ammonia reduction of 1.50 g (7.82 mmol) of *trans*-4,6-dimethylbicyclo[4.4.0]dec-1-en-3,7-dione (**5**) yielded 1.53 g of an oil which did not crystallize. The ^1H NMR spectrum of this material suggested that it consisted of a single major component; however, GLC analysis indicated the presence of a small amount (<3%) of **5**. The assignment of structure **15** to the major product was supported by: IR (film) 3350, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, J = 6.5 Hz, 3 H), 1.10 (s, 3 H), 1.15–2.90 (m, 11 H), 3.96 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (84), 179 (59), 174 (31), 166 (25), 151 (96), 137 (70), 124 (80), 123 (80), 109 (65), 95 (100), 81 (65), 69 (75), 55 (85). The *m/e* 195 ion was 12.8% of the parent ion abundance (calcd to be 13.3% for $C_{12}H_{18}O_2$).

(f) (1*R,5α,6β,10ξ)-5-Hydroxy-6,10-dimethyltricyclo-[4.4.0.0^{1,5}]-decan-9-one (16).** Lithium/ammonia reduction of 20.13 g (104.5 mmol) of 2,6-dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione (**6**),[5] conducted as previously described, yielded 19.73 g of an oil. Crystallization from ether gave 13.20 g (65%) of a colorless solid. An analytical sample prepared by several recrystallizations from ether–hexane exhibited the following properties: mp 115–118 °C; IR ($CHCl_3$) 3572, 2980–2850, 1695, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.22 (d, J = 6.5 Hz, 3 H), 1.40–2.80 (m, 11 H), 3.42 (s, 1 H, disappears on D_2O addition); ^1H NMR (C_6D_6) resolves the methyl doublet to a pair of doublets at δ 1.11 and 1.34 (J = 7.0 Hz in each case) having a 30:70 intensity ratio. This epimeric mixture did not give an entirely satisfactory microanalysis; however, the parent ion at *m/e* 194 in the mass spectrum (70 eV) displayed P + 1 and P + 2 ions at *m/e* (rel abundance) 195 (13.2) and 196 (ca. 1.0) which agree well with the calculated abundances for $C_{12}H_{18}O_2$ (13.3 and 1.2, respectively).

In addition to cyclopropanol **16**, the mother liquor contained ca. 28% of the *trans*-decalindione **20**,[5a] which could be readily separated from **16** by preparative GLC (4% QF-1, 180 °C). A purified sample had mp 73–75 °C (lit. 76–77 °C); IR (CCl_4) 1710, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.62 (d, J = 7 Hz, 3 H), 0.94 (s, 3 H, $\Delta W_{h/2}$ = 0.61 Hz (sweep width 50 Hz)), 1.05–2.40 (m, 12 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (53), 127 (100), 5).

(g) (1*R,5α,6β)-5-Hydroxy-3,3,6-trimethyltricyclo[4.4.0.0^{1,5}]-decan-9-one (17).** Reduction of enedione **7** (206 mg, 1 mmol) by a solution of lithium (2 mmol) in ammonia–THF gave 200 mg of a colorless oil, after the usual workup. The mass spectrum (70 eV) of this material showed it to be largely (ca. 80%) a dihydro derivative of **7** (*m/e* 208), with no significant tetrahydro component. Strong hydroxyl absorption at 3400 cm^{-1} in the infrared and at δ 3.95 in the ^1H NMR together with a strong carbonyl band at 1700 cm^{-1} indicated cyclopropanol **17** to be the major product. Weak absorption at 1665 (sh) and 1615 cm^{-1} in the infrared and at δ 5.75 in the ^1H NMR suggested that unreacted **7** was the chief contaminant, a conclusion supported by a small *m/e* 206 ion in the mass spectrum. The methyl region of the ^1H NMR spectrum showed sharp signals at δ 0.9, 1.05, and 1.15 accompanied by weaker bands, as expected from the previous

conclusion.

(h) (1*R,5α,6β,10ξ)-5-Hydroxy-3,3,6,10-tetramethyltricyclo[4.4.0.0^{1,5}]decan-9-one (19).** Reduction of enedione **8** (220 mg, 1 mmol) by a solution of lithium (2 mmol) in ammonia–THF gave 200 mg of a colorless oil, after the usual workup. The mass spectrum (70 eV) of this material showed it to be largely (ca. 70%) a dihydro derivative of **8** (*m/e* 222) with no significant tetrahydro component. The major product was identified as the corresponding cyclopropanol (**18**) on the evidence of strong hydroxyl ano carbonyl absorptions at 3400 and 1700 cm^{-1} in the infrared and a single proton hydroxyl resonance at δ 3.8 in the ^{1}H NMR (disappears on treatment with D_2O). Weak IR absorptions at 1660 (sh) and 1605 cm^{-1} suggested that unreacted **8** was the chief contaminant, a conclusion supported by a modest *m/e* 220 ion in the mass spectrum. The methyl region of the ^{1}H NMR spectrum (δ 0.8–1.3) shows a complex array of overlapping sharp signals, which is 11–12 times as intense as the hydroxyl signal.

A sample of the crude reduction product described above (i.e., crude **18**) slowly crystallized from an ether–pentane solution, yielding 110 mg (50%) of colorless crystals: mp 95–97 °C; IR (CCl_4) 3100–3500, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.15 (d, J = 6.0 Hz, 3 H), 1.25 (s, 3 H), 1.8–2.8 (m, 9 H), 4.1 (br s, 1 H, exchanges with D_2O). The mass spectrum (70 eV) of this compound exhibited a parent ion at *m/e* 154, suggesting the hydroperoxide formula **10.** The isotope ions at *m/e* 155 and 156 have abundances relative to the parent ion that agree well with the formula $C_{14}H_{22}O_4$: calcd for 155, 15.6%; found, 16.2%; calcd for 156, 1.94%; found, ca. 2%.

3-Ethoxy-*trans*-5,6-dimethylbicyclo[4.4.0]dec-1(10),2-dien-7-one (23). To a solution of 1.00 g (5.20 mmol) of *trans*-5,6-dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione (**4**) in 40 mL of benzene was added 0.2 mL of ethanol and 2 mL of redistilled ethyl orthoformate. Dry hydrogen chloride was then introduced until a pH <1 was obtained. The reaction mixture was stirred for 2 h at room temperature, and then washed sequentially with saturated sodium bicarbonate, water, and saturated sodium chloride solution. Evaporation of the solvent gave 1.170 g of crude product, which solidified to a yellow solid on cooling. Crystallization from an ether–hexane solution gave 0.792 g of white crystals. Chromatography of the mother liquors on 20 g of Woelm neutral alumina (activity III) (elution with 10–30% ethyl acetate in hexane) gave an additional 0.128 g of the dienol ether **25** for a combined yield of 0.920 g (79%). Recrystallization from ether–pentane gave an analytical sample: mp 95–96 °C; IR (CCl_4) 1710, 1650, 1625, 1380, 1355, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 7.0 Hz, 3 H), 1.17 (s, 3 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.42–2.95 (m, 7 H), 3.79 (q, J = 7.0 Hz, 2 H), 5.24 (s, 1 H), 5.66 (dd, 1 H, J = 3.0 Hz, J' = 3.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 220 (100), 205 (9), 192 (41), 177 (58), 163 (44), 149 (30), 135 (58), 121 (17), 91 (30), 77 (20).

Anal. ($C_{14}H_{20}O_2$) C, H.

Reduction and Hydrolysis of 3-Ethoxy-*trans*-5,6-dimethylbicyclo[4.4.0]dec-1(10),2-dien-7-one (23). A solution of 500 mg (2.27 mmol) of dienol ether **23** in 10 mL of dry THF was added to a suspension of 200 mg of lithium aluminum hydride in 50 mL of dry THF, and this mixture was refluxed under a nitrogen atmosphere overnight. The reaction mixture was then cautiously decomposed with water and the solvent was removed at reduced pressure. The residue was dissolved in 100 mL of acetone containing 3 mL of water, acidified to pH <1 with hydrochloric acio, and stirred at room temperature for 0.5 h. After most of the acetone was evaporated at reduced pressure, ether was added and the organic phase was washed with water and saturated sodium bicarbonate solution and then dried over magnesium sulfate. Evaporation at reduced pressure gave a semicrystalline solid, which on crystallization from ether yielded 250 mg (58%) of (5α,6β,7α)-7-hydroxy-5,6-dimethylbicyclo[4.4.0]dec-1-en-3-one (**24**): mp 122–123 °C; IR (CCl_4) 3600, 3380, 1572, 1620, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 7.0 Hz, 3 H), 1.21 (s, 3 H), 1.45–3.20 (m, 9 H), 4.14 (m, 1 H), 6.06 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (48), 176 (16), 161 (100), 138 (41), 123 (61).

Anal. ($C_{12}H_{18}O_2$) C, H.

GLC analysis (4% QF-1, 190 °C) indicated that, in addition to **24,** the mother liquor contained ~50% of the (5α,6β, 7β)-7-hydroxy-5,6-dimethylbicyclo[4.4.0]dec-1-en-3-one (**25**), which was isolated (preparative GLC) as a crystalline solid: mp 117–119 °C; IR (CCl_4) 3600, 3390, 1668, 1612, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 7.0 Hz, 3 H), 1.29 (s, 3 H), 1.41–3.01 (m, 9 H), 3.85 (m, 1 H), 5.83 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (33), 176 (23), 161 (100), 138 (36), 123 (51), 91 (51), 41 (64).

Anal. ($C_{12}H_{18}O_2$) C, H.

Lithium/Ammonia Reduction and Oxidation of (5α,6β,7α)-7-Hydroxy-5,6-dimethylbicyclo[4.4.0]dec-1-en-3-one (24). Lithium metal was added in small pieces to a solution of 130 mg (0.67 mmol) of **24** in 75 mL of ammonia (liquid) and 25 mL of dry THF at −33 °C until a blue color persisted. The reaction mixture was stirred for 15 min, quenched with ammonium chloride, evaporated to a slushy residue, and then extracted with ether. The dried ether extracts yielded an oil which was dissolved in 2 mL of methylene chloride and treated with freshly prepared Collins reagent.[20] After a 15-min reaction period, the solution was decanted from a tarry residue, which was then washed with several portions of ether. The combined organic extracts were then washed with aqueous base (5% NaOH), dilute acid (5% HCl), and water, and on evaporation yielded 105 mg of an oil composed of two compounds in a 62:38 ratio. These were isolated by preparative GLC (4% QF-1, 170 °C).

The major component was the *trans*-decalin **19:** mp 82.5–83.5 °C; IR (CCl_4) 1710, 1440, 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.36 (s, 3 H), 1.40–3.00 (m, 12 H); mass spectrum (70 eV) *m/e* (rel abundance) 194 (54), 179 (13), 161 (33), 123 (53), 111 (49), 95 (39), 69 (100), 44 (61).

Anal. ($C_{12}H_{18}O_2$) C, H.

The minor component was the *cis*-decalin **26,** recovered as an oil, and shown by GLC and IR analysis to be identical with the single product obtained from catalytic hydrogenation of *trans*-5,6-dimethylbicyclo[4.4.0]dec-1-ene-3,7-dione (**4**).

(1β,6β,10α)-1,10-Dimethylbicyclo[4.4.0]decane-2,8-dione (26). A solution of 100 mg (0.52 mmol) of *trans*-5,6-dimethylbicyclo[4.4.0]-dec-1-ene-3,7-dione (**4**) in 1 mL of ethanol was added to a prehydrogenated suspension of 10 mg of 10% palladium on charcoal in 5 mL of ethanol, and the resulting mixture was shaken in a Parr hydrogenator (50 psi, room temperature). Hydrogen uptake ceased after 25 min; the suspension was then filtered and the catalyst washed with hot ethanol. Chromatography of the crude organic product on silica gel gave 95 mg (94%) of (1β,6β,10α)-1,10-dimethylbicyclo[4.4.0]-decane-2,8-dione (**26**) as an oil: IR (CCl_4) 1720, 1705, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6.0 Hz, 3 H), 1.43 (s, 3 H), 1.52–3.20 (m, 12 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (35), 179 (3), 161 (10), 123 (20), 110 (91), 95 (28), 81 (29), 69 (75), 55 (47), 41 (100).

Anal. ($C_{12}H_{18}O_2$) C, H.

Reaction of Cyclopropanol 1 with 2,4-Dinitrophenylhydrazine. A 200-mg sample of **1** in ethanol solution was treated with an excess of 2,4-DNP reagent, prepared according to ref 14. After an overnight reaction period, the resulting yellow solid was filtered and chromatographed ($CHCl_3$ + 5% CH_3OH) on silica gel. The two major products proved to be the bis-2,4-DNP derivatives of the *cis*- and *trans*-decalindiones **3** and **4** (roughly 60:40 proportions). The identity of these derivatives was confirmed by direct comparison with authentic compounds prepared from pure **3** and **4**: bis-2,4-DNP of **3,** mp 229–230 °C (lit.[11] 230 °C); bis-2,4-DNP of **4,** mp 235 °C (lit.[11] 231 °C); mmp 170–200 °C.

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Transformations of Cyclopropanol Intermediates. 3. Ring-Opening Reactions of 6-Methyl-5-hydroxytricyclo[4.4.0.0^{1,5}]decan-9-one

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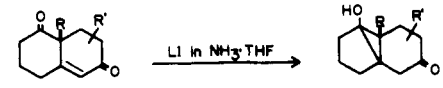
Abstract: The tricyclic title compound (**1**) was transformed under a variety of acid- or base-catalyzed conditions to bicyclic isomers having spiro[5.4]decane (**2**), decalin (**3** and **4**), or perhydroindene (**5**) skeletons. Each of these isomeric classes could be favored by an appropriate choice of reaction conditions. Methanolic hydrochloric acid converted **1** to a mixture of isomeric cyclopropanol methyl ethers (**6** and **7**), which slowly reacted further to give ring-opened products. Acetate derivatives of the same isomeric cyclopropanols (**25** and **26**) were obtained when the conjugate base of **1** was quenched with acetic anhydride. Reactions of **1** with methanolic acid and base were compared with equivalent reactions of the corresponding diol, **19**, prepared by reduction of **1**. The dramatic influence of the carbonyl function in **1** on the cyclopropanol ring-opening reactions is clearly evident in the results. The ring-cleavage reactions of **19** were also compared with similar reactions of *endo*-7-hydroxybicyclo[4.1.0]-heptane (**22**) reported by Wharton and Bair.

Alkyl-substituted 5-hydroxytricyclo[4.4.0.0^{1,5}]decane derivatives are readily prepared by the reductive cyclization shown in eq 1.[1] Since these cyclopropanols are potentially

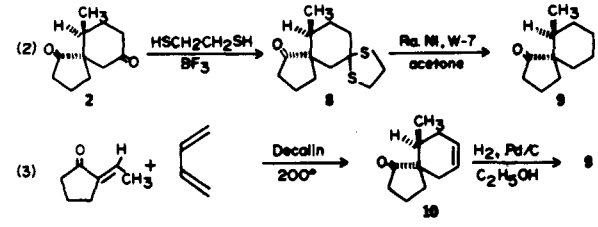


useful intermediates, we have studied their ring-opening reactions under a variety of acid- and base-catalyzed conditions. In this paper we discuss the behavior of cyclopropanol **1** derived from the Wieland–Miescher ketone (eq 1, R = CH_3, R′ = H), and shall endeavor to point out the ways in which its chemistry parallels or deviates from that of simpler analogues.

Results

The products obtained from the treatment of **1** with several different ring-opening reagents are listed in Table I. These reactions were monitored by a combination of TLC (silica gel) and GLC (QF-1), and pure samples of each major component were isolated by preparative GLC and/or crystallization. Identification of these compounds was achieved by a combination of mass spectrometric, infrared, and ^{1}H NMR measurements. The reactions were usually permitted to proceed to completion (TLC) before collecting the products, because unreacted **1** decomposes to several of the same compounds in the hot injection chamber of the gas chromatograph.

Authentic samples of *cis*- and *trans*-decalindiones **3** and **4** were prepared by established methods,[2] and their configurations were confirmed by the characteristic peak shapes of the angular methyl ^{1}H NMR signals.[3] The spirodiketone **2** was identified by its characteristic spectra (Experimental Section), and its conversion to spiroketone **9** (eq 2), which was independently synthesized by catalytic reduction of the Diels–Alder adduct from *trans*-2-ethylidenecyclopentanone[4] and 1,3-butadiene (eq 3).



Our elucidation of the structure of *trans*-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (**5**) was accomplished in two independent stages. In the first, we effected a conversion of **5** to the saturated ketone **13** (eq 4), which was then compared