Experimental Section

General Preparation of α-Hydroperoxy Acids. 1. α-Lithiation. A dry, 150-ml, two-necked, round-bottomed flask, provided with magnetic spinbar, rubber septum, and three-way stopcock, was attached to a nitrogen manifold and flushed with dry nitrogen for at least 5 min. While under a positive nitrogen pressure (ca. 50 mm, regulated with a mercury bubbler), the reaction vessel was charged by means of a syringe with 60 mmol of diisopropylamine (freshly distilled from calcium hydride) and 70 ml of anhydrous THF (freshly distilled from benzophenone ketyl radical). By means of a dry ice–methanol bath the reaction flask was cooled to −60 to −40° and while stirring vigorously, 63 mmol of *n*-butyllithium in *n*-hexane (standardized acidimetrically) was added with the help of a syringe. After complete addition (ca. 5 min), the cooling bath was removed and the reaction mixture allowed to reach room temperature (ca. 30°) while stirring. The reaction mixture was kept at room temperature for 10 min and cooled to −78° by means of a dry ice–methanol bath and a solution of 25 mmol of the carboxylic acid to be lithiated in 5 ml of anhydrous THF was added with the help of a syringe. Subsequently the reaction mixture was allowed to warm up to room temperature again and heated at 40° for 30 min while stirring. A pale yellow, clear solution of the dianion resulted, which exhibited a methyl iodide assay of better than 98% lithiation by NMR.

2. α-Oxygenation. A dry 250-ml, three-necked, round-bottomed flask, supplied with an efficient, hermetically sealed mechanical stirrer, a rubber septum, and a three-way stopcock, was attached to the nitrogen manifold and flushed with dry nitrogen. The flask was charged with 70 ml of anhydrous THF with the help of a syringe and cooled to −100 to −90° by means of a liquid nitrogen–THF bath, while keeping a positive nitrogen pressure (ca. 50 mm). The THF solution was saturated efficiently (ca. 10 min) with dry oxygen gas, allowed to enter through the rubber septum by means of a syringe needle. With the help of stainless steel capillary tubing (12G) as syphon, the dianion solution was transferred dropwise over a period of 1–2 hr (the dropping rate regulated with a blood serum proportionator which was attached to a nitrogen balloon) into the oxygen-saturated THF solution, keeping the oxygenation vessel at −100 to −90°, while passing a vigorous stream of dry oxygen gas through the reaction mixture during the entire process.

3. Hydrolysis. After complete addition of the dianion solution (ca. 1–2 hr), under efficient mechanical stirring and keeping the reaction mixture at −100 to −90°, by means of a syringe 120–125 mmol of a 15% aqueous hydrochloric acid solution was added. The resulting "sherbetlike" mixture was allowed to warm up to ca. −20° and transferred into a 500-ml separatory funnel, which contained 80 ml of NaCl-saturated ice water. The aqueous layer was efficiently extracted with ether (ca. 5 × 25 ml) and methylene chloride (ca. 3 × 25 ml), keeping the temperature during the extraction process between 0 and 5° by adding ice and NaCl. The combined organic extracts were dried over anhydrous $MgSO_4$ at 0°. The solvent was removed by rotary evaporation [−5 to 0° (3–4 mm)]. The oxygenation product was obtained as a colorless oil (ca. 95–100% crude yield), which crystallized on standing in the freezer. Iodometric analysis indicated a ca. 80% peroxide titer based on α-hydroperoxy acid. The crude product must be purified without delay at subzero temperature to minimize decomposition.

Preparation of 2-Hydroperoxy-2-methylpropionic Acid. Following the general procedure, 25 mmol of 2-methylpropionic acid was converted in 97% crude yield to the corresponding α-hydroperoxy acid, exhibiting a 81% peroxide titer by iodometry. In view of its low thermal stability in the impure state (above 10° it decomposes with gas evolution) and high hygroscopic nature (dry crystals allowed to come in contact with atmospheric moisture diffuse within seconds), the crude product was recrystallized immediately several times from ether–pentane mixture at 5° in a glove bag under a dry nitrogen atmosphere. The crystalline product was obtained as white needles, better than 97% pure by iodometry, mp 44–46°, with gas evolution at 74°. The spectral data follow: 60-MHz NMR (CCl_4) δ (Me_4Si) 9.7 (2 H, singlet, $-CO_2H$ and $-O_2H$) and 1.5 ppm (6 H, singlet, $-CH_3$); ir (CCl_4) 3660 and 3480 (–OOH and $-CO_2H$), 3000–2800 (aliphatic CH), 1710 (carbonyl), and 1380 and 1360 cm^{-1} (*gem*-dimethyl).

Preparation of 3,3-Dimethyl-2-hydroperoxybutyric Acid. Following the general procedure, 25 mmol of 3,3-dimethylbutyric acid was converted in 93% crude yield to its corresponding α-hydroperoxy acid, exhibiting 78% peroxide titer by iodometry. The crude product was purified immediately by repeated recrystallization from ether–hexane mixture, preventing exposure to atmospheric moisture. Colorless needles were obtained, better than 99% pure by iodometry, mp 68–70° (lit.[3] 69–70°), with gas evolution at 74°. The spectral data follow: 60-MHz NMR (CCl_4) δ (Me_4Si) 10.3 (2 H, singlet, $-CO_2H$ and $-O_2H$), 4.3 (1 H, singlet, CH), and 1.0 ppm (9 H, singlet, *tert*-butyl); ir (CCl_4) 3500–3000 ($-CO_2H$ and $-O_2H$), 2960 (aliphatic CH), 1715 (carbonyl), and 1370 cm^{-1} (*tert*-butyl).

Acknowledgment. Financial support by the National Science Foundation is gratefully appreciated.

Registry No.—1 (R = R′ = Me), 57196-76-6; 1 (R = H; R′ = *t*-Bu), 36156-92-0; **5** (R = R′ = Me), 79-31-2; **5** (R = H; R′ = *t*-Bu), 1070-83-3.

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(3) W. Adam and J.-C. Liu, *J. Am. Chem. Soc.*, **94**, 2894 (1972).
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Studies Directed toward a Practical Synthesis of Brevicomin. IV. Formation and Hydrogenolysis of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane under Catalytic Hydrogenation Conditions

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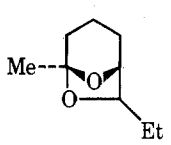
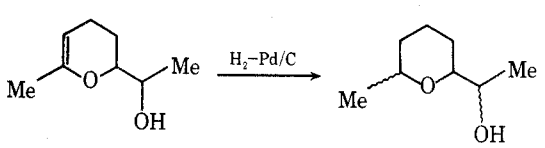
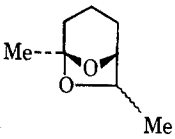
During the course of our investigations toward a practical synthesis of brevicomin (1), the aggregating sex pheromone of the pine bark beetle (*Dendroctonus brevicomis*),[1] we had the occasion to examine the hydrogenation of **2** → **3**. To our surprise we found a 13% yield of **4** as a secondary product of the reaction.[1c] In this paper we will present our findings on some of the unique chemistry associated with the reactions.



1



2 3



4

Attempts at utilizing this as a methodology for preparing, in high yield, bicyclic ketals of the type **4** met with uniform failure. Since we could not obtain increased yields of **4** we next decided to analyze whether or not **4** might simply be an intermediate in the reduction of **2** → **3**.

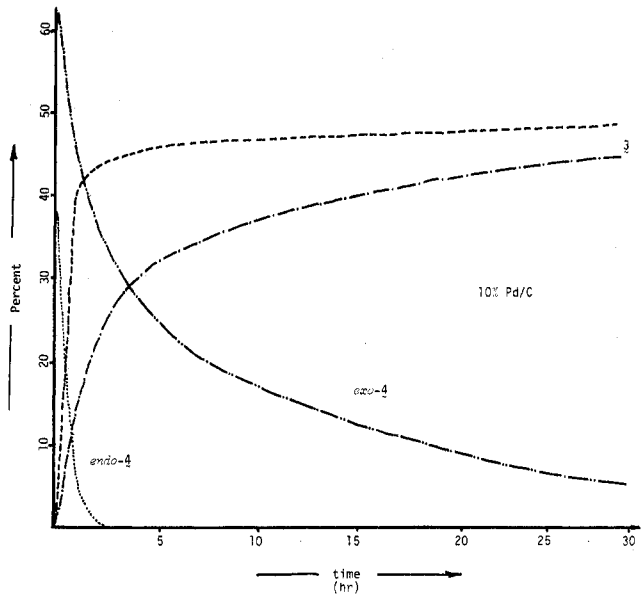
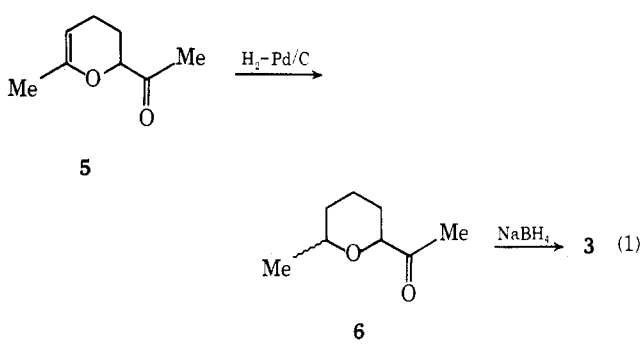


Figure 1. Hydrogenolysis of 5,7-dimethyl-6,8-dioxabicyclo-[3.2.1]octane.

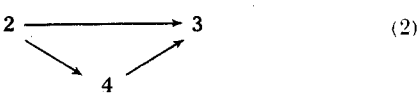
Beginning with a 60:40 mixture of *exo*- and *endo*-**4** it was observed that the endo isomer was rapidly hydrogenolyzed to the extent that in less than 3 hr this isomer could not be detected by GLC. The products of hydrogenolysis were the isomeric alcohols, **3**, which could be prepared by the unambiguous synthesis dilineated in eq 1. The exo isomer was



(1)

considerably less reactive, and even after 30 hr it could still be detected. Examination of molecular models suggested that the C-7 methyl group of the exo isomer might hinder approach of the ketal functionality to the catalyst surface. Figure 1 summarizes the hydrogenolysis results.

The catalytic hydrogenolysis of carbon–oxygen bonds in cyclic ethers and ketals is well documented.[2] The formation of ketals, however, under catalytic conditions is very rare indeed[3] and *this is the first bicyclic ketal to be prepared in such a fashion.* Formation of isomeric alcohols is thus suggested to arise from a multipath reaction (eq 2) in which some alcohol is formed via the more circuitous path involving ketal formation followed by hydrogenolysis.[4]



(2)

A relevant question, which now arises, is how did the bicyclic ketal form in the first place? In a recent study, Nishimura[3a] was able to classify two groups of metals as to their ability to form acetals. Osmium, ruthenium, and iridium belong to the group which catalyze acetal formation weakly while rhodium, palladium, and platinum belong to the group which catalyzes it efficiently. In total agreement with this we observed no ketalization of **2** using 5% ruthenium on carbon as catalyst. It is also known that hydrogen dissolved in or chemisorbed on palladium and platinum has been found to be positively charged.[5] This charge is weak, corresponding to $\frac{1}{15}$ of an electronic charge per atom, but in light of the propensity for enol ether **2** to cyclize[1c] it is not at all unreasonable to suggest that these metal catalysts are charged enough so as to act as an electrophile. Needless to say, when these experiments were repeated without catalyst, ketal formation was undetectable. In a similar way, when the reaction was run with **2** and catalyst, but without the hydrogen atmosphere, no cyclization to **4** could be detected. This suggests that cyclization does not occur by a palladation reaction and that the mixture of catalyst and hydrogen is required. The question of the electrophilicity of metal catalysts has been discussed before and it is maintained that there is enough hydronium ion character available to permit a pinacol type rearrangement of deoxydihydrowithaferin A to an *A*-nor-5-formyl derivative.[6] Likewise, we feel that enough hydronium-like character is present to allow the metal catalysts to act as an electrophile resulting in closure of **2** to 6,8-dioxabicyclic ketal **4.**

Experimental Section

Hydrogenation of 2-(1-Hydroxyethyl)-6-methyl-2,4-dihydropyran (2). See ref 1c.

Hydrogenolysis of *exo*- and *endo*-5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (4). Typically 1 g of ketal and 0.5 g of catalyst were added to 20 ml of anhydrous ethanol and shaken at ambient temperatures in a Parr low-pressure hydrogenation device at 30–35 psi hydrogen. The reaction was interrupted at various times and aliquots were directly withdrawn and analyzed by GLC on a 20% Carbowax column operating at 100°C, 40 psi He. Areas were calculated by triangulation methods. Since we were analyzing isomeric mixtures,[7] no attempt was made to calibrate the GLC instrument and peak areas were directly related to percent composition. The preparation of the alcohols by an unambiguous synthesis is presented below.

Preparation of 2-Acetyl-6-methyltetrahydropyran (6). One gram of **5**[1c] and 0.25 g of 10% Pd on carbon were placed in 20 ml of anhydrous ethanol and hydrogenated with 40 psi hydrogen gas for 24 hr at ambient temperature. GLC analysis (10% Ucon-50 on Chromosorb W) indicated that no starting material remained. The product was distilled, bp 97° (20 mm). The NMR spectrum exhibited the following characteristics: δ 1.2, 3 H, doublet, J = 6 Hz; 2.05–1.40, 6 H, multiplet; 2.19, 3 H, singlet; 3.25–3.93, 2 H, multiplet. The infrared spectrum (NaCl disk) exhibited a carbonyl (1715 cm^{-1}) and the loss of enol ether. MS: calcd and found, 142.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.23; H, 9.41.

Preparation of 3. Reduction of **6** with sodium borohydride was carried out in routine fashion, giving an isomeric mixture of **3.** The NMR spectrum exhibited (for the mixture) δ 1.10, 3 H, overlapping doublets, J = 6 Hz; 1.20–2.0, 6 H, methylene envelope; 3.0, 1 H, singlet; 3.05–3.85, 3 H, multiplet. The mass spectrum gave a molecular weight of 144.

Anal. Calcd for $C_8H_{16}O_2$: C, 66.66; H, 11.11. Found: C, 66.50; H, 10.98.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. Financial assistance of the USDA, Forest Service, is also acknowledged.

Registry No.—**1**, 20290-99-7; **3**, 56057-17-1; *exo*-**4**, 56057-15-9; *endo*-**4**, 56057-16-0; **5**, 28450-02-4; **6**, 57015-77-7.

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(3) (a) S. Nishimura and I. Itaya, *Chem. Commun.*, 422 (1967); (b) S. Nishimura, M. Katagiri, T. Watanabe, and M. Uramoto, *Bull. Chem. Soc. Jpn.*, **44**, 166 (1971); (c) L. A. Hamilton, U.S. Patent 3,454,596.

(4) We have no proof for the competitive reduction of **2** and hydrogenolysis of **4**. However, the quantitative conversion of **5** to **6** demonstrates that the enol ether functionality is quite receptive to catalytic reduction; and thus it seems that some of the alkene bond of **2** might suffer similar reduction.

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(7) The stereochemistry of the products formed from this reaction is not yet known.

Studies Directed toward a Practical Synthesis of Brevicomin. V. Isomer Enrichment of Bicyclic Ketals in the 6,8-Dioxabicyclo[3.2.1]octane Series by Complexation with Titanium Tetrachloride

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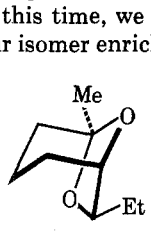
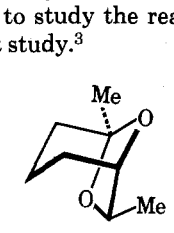
Received June 24, 1975

As part of a continuing effort directed toward a practical synthesis of brevicomin (**1**),[1] the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*, we initiated a study of methods for effecting isomer enrichment. Since it is well documented that powerful synergistic effects are noted for compound mixtures in testing, an effective method to remove unwanted isomers became quite important.[2] In our synthetic methodologies to date, we have always prepared a mixture isomeric about C-7.

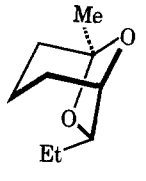
Since **1** has proven to be relatively difficult to obtain in quantity at this time, we chose to study the readily available **2** for our isomer enrichment study.[3]



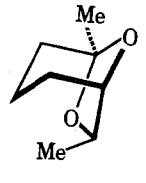
exo-**1**



exo-**2**



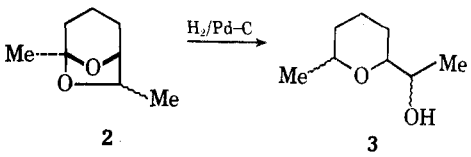
endo-**1**



endo-**2**

Substituted 1,3-dioxolane and dioxane derivatives have been generally observed to suffer cleavage and rearrangement to an appropriate ester in the presence of titanium tetrachloride.[4] Though this is a well-known Lewis acid capable of complexing ligands having heteroatom functionality,[5] *no ketal complexation has been reported.* We have observed, however, that titanium tetrachloride readily forms a complex with **2**, and this complex can be hydrolyzed with water to recover 93% of the initial bicyclic ketal.

We had previously noted[6] that hydrogenolysis of *endo*-**2** proceeded much faster than *exo*-**2** (**2** → **3**). This was rationalized as a steric effect of the exo methyl group on the catalyst surface. Taking advantage of this observation we envisioned preparing a $TiCl_4$ "surface" on which one isomer might selectively interact. This was accomplished by preparing a dilute $TiCl_4$–CCl_4 frozen matrix at liquid nitrogen temperature. Typically, 0.005 mol of $TiCl_4$ in 20 ml of carbon tetrachloride was frozen in liquid nitrogen. To the surface formed was added 0.01 mol of ketal, and the solution was allowed to warm, unperturbed, to room temperature. The complex was filtered through a fritted glass filter and the filtrate was reduced in volume. GLC analysis indicated, that as expected, the endo isomer was selectively complexed. Hydrolysis of the filtered complex with water, followed by extraction with methylene chloride, yielded an enriched endo-isomer mixture. If the experiment is carried out without solvent, selectivity is decreased. This enrichment procedure can be repeated as many times as necessary to reach a desired isomeric purity. Starting with **2** having an exo–endo ratio of 15.9:9.4, three cycles increased the ratio to 16:2.7. This constitutes an enrichment of 71.5% by an experimentally simple procedure.



2 **3**

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1**, 20290-99-7.

References and Notes

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Radical Decomposition of α-Hydroperoxy Ketones. A Facile Scission of Benzoyl Radical[1]

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Received June 17, 1975

The β-scission of *tert*-alkoxy radicals has been established,[2] and previous reports include the information on the scission of halomethyl,[2a,h] alkoxymethyl,[2h,i] and alkoxycarbonyl radicals,[2h,i] and of acyl radical.[3,4] In the course of our study on the basic decomposition of α-hydroperoxy ketones,[5] **1**, the facile fission of benzoyl radical was observed.