are given in Table I. Gas chromatographic analysis showed no α-hydroxy ketones in the distilled products.

Kinetics Procedure for the Reaction of Trimethylsilyl Enol Ethers with Methanol–Triethylamine. A solution of given concentration of triethylamine in methanol was placed in a thermostated cuvette in a Cary 15 spectrophotometer. Approximately 16 μL of the given trimethylsilyl enol ether was injected via syringe into the temperature-equilibrated solution. Appearance of the carbonyl chromophore was measured as a function of time. The following wavelengths were used: **4**, 292 nm; **6**, 300 nm; **8**, 292 nm; **14**, 288 nm; **16**, 292 nm; and **18**, 290 nm. Rate constants were calculated in the usual manner using the method of least squares. Correlation coefficients were in all cases greater than 0.9997.

Acknowledgment. We would like to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Alfred P. Sloan Foundation for financial support.

Registry No.—**4**, 17082-61-0; **5**, 68900-48-1; **6**, 63715-72-0; **7**, 63715-73-1; **8**, 6838-66-0; **9**, 68900-49-2; **10**, 56514-07-9; **11**, 68900-50-5; **12**, 6838-67-1; **13**, 53638-19-0; **14**, 57722-40-4; **15**, 497-38-1; **16**, 66057-11-2; **17**, 53329-05-8; **18**, 66057-08-7; **19**, 30860-22-1.

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Hydroxylation of 6-Methyl-5-hepten-2-one Ethylene Ketal with Selenium Dioxide and with the Wittig Reaction

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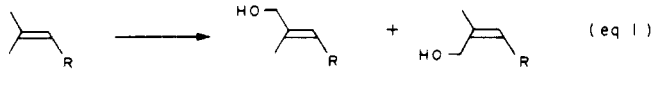
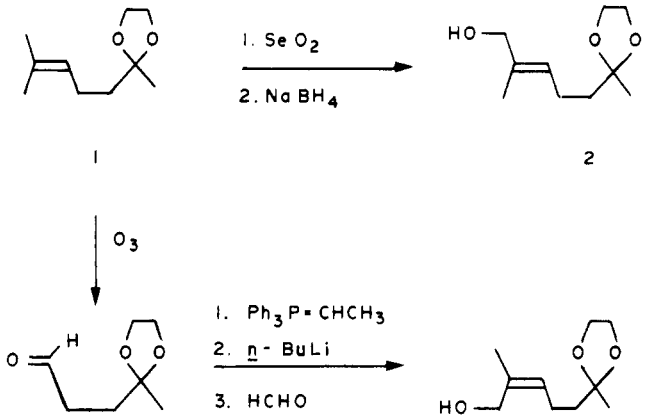
A number of investigators have shown that the isobutenyl functionality, present in diverse molecules such as pentazocine,[1] an analgesic of the benzomorphan series, and resmethrin,[2] a synthetic pyrethroid, is capable of undergoing metabolic monohydroxylation in animals according to eq 1. It was therefore of interest to synthesize the isomeric pairs of olefinic alcohols depicted in eq 1.



(eq 1)

The olefin that has been examined is 6-methyl-5-hepten-2-one ethylene ketal (**1**). On the basis of previous investigations, it was reasoned that **1** should be convertible to the target olefinic alcohols by two different approaches. The first approach was based on the use of selenium dioxide, a well-known reagent that regioselectively oxidizes an isobutenyl group at one of the methyl carbon atoms and that gives products (alcohols and aldehydes) with trans (*E*) stereochemistry predominantly.[3–6] The second approach involved a modification of the Wittig reaction,[7,8] termed the *scoopy* reaction by Schlosser et al.,[9–11] which is capable of yielding cis (*Z*) olefinic alcohols from aliphatic aldehydes.

Ketal olefin **1** was oxidized with selenium dioxide in the presence of dioxane as the solvent. The ketal aldehyde, *trans*-2-methyl-6-oxo-2-hepten-1-al ethylene ketal, was isolated from the red colloidal mixture in 51% yield. A previous method[4] employed **1**, selenium dioxide, and ethanol, and the yield was 33%. In the present study, it was found that **1** was slow to react in ethanol but was completely oxidized after 5 h in refluxing dioxane. The NMR spectrum showed the aldehydic proton signal at 9.4 ppm, and in addition one of the methyl singlets for the isobutenyl group had disappeared. Reduction of the *trans*-ketal aldehyde with sodium borohydride in ethanol gave a brown mixture from which the desired *trans*-2-methyl-6-oxo-2-hepten-1-ol ethylene ketal (**2**) was obtained in 65% yield.



Ketal olefin **1** was also the starting material for the synthesis of the cis isomer of **2**. Ozonolysis of **1** in methylene chloride at −78 °C gave the unstable aldehyde **3** in good yield. Following some initial work with valeraldehyde,[12] ketal aldehyde **3** was then hydroxyisopropenylated by use of the cis selective modification of the Wittig reaction. The desired isomer, *cis*-2-methyl-6-oxo-2-hepten-1-ol ethylene ketal (**4**), was obtained in yields ranging from 35 to 45%.

Since the GLC and spectroscopic properties of both olefinic alcohols **2** and **4** were noticeably different, it was convenient to examine the stereoselectivity of the reactions for their formation. GLC examination of crude products from modified Wittig reactions revealed that the trans isomer was absent (**2** had a longer retention time than **4**). This remarkable cis selectivity to **4** contrasted with results from the selenium dioxide route to the trans isomer. Crude samples of **2** obtained by oxidizing **1** with selenium dioxide followed by reduction always showed ~6% of the cis isomer (94% trans selectivity). Some loss of stereoselectivity was attributed to equilibration at the aldehyde stage.[13]

Differences in NMR chemical shift values for protons at C-1 (methylene), C-2 (methyl), and C-3 (vinyl) were evident (Experimental Section) and were predictable from the pub-

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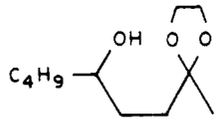
lished values[4,8] on isomers related to **2** and **4** but without the ethylene ketal group. The mass spectra were very similar except for relative abundances of the ions at *m/e* 171 ($M - CH_3$) and 153 ($M - CH_3 - H_2O$). Loss of water from the ion at *m/e* 171 was found to be more favorable in the cis isomer than in the trans isomer.

During the initial phase of this work, it was found that ethylidenetriphenylphosphorane was only partially generated at −78 °C. The unreacted *n*-butyllithium added to the carbonyl bond of **3** and resulted in the isolation of a secondary alcohol, assigned structure **5**, in some Wittig experiments. This side product was avoided by maintaining a temperature of 0–10 °C and allowing the deep red color of the ylide to develop. Another problem, recently discussed in connection with another study on the Wittig reaction,[14] was the formation of an ethylenic derivative (**6**). However, **6** was readily removed by vacuum distillation of the crude product.



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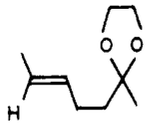

6

In summary, the procedures described are of relevance to the preparation of metabolites of compounds that possess the isobutenyl group.

Experimental Section

Boiling points are uncorrected. Infrared spectra were taken as liquid films on a Perkin-Elmer Model 137 Infracord spectrophotometer. The ^1H NMR spectra were obtained on a Varian EM-360A spectrometer. The chemical shifts are expressed as δ values (ppm) to Me_4Si as an internal standard. Gas–liquid chromatography was carried out on a Varian 2740-10 instrument, using a 1.8-m stainless steel column (3.2 mm o.d.) packed with 5% OV-101 on acid-washed DMCS-treated Chromosorb 750 (column A) or on a Hewlett-Packard Model 5838A reporting gas chromatograph equipped with a 1.2-m glass column (4 mm i.d.) packed with 5% OV-101 on acid-washed DMCS-treated Chromosorb 750 (column B). The nitrogen flow rate through column B was 60 mL/min. Mass spectra were recorded at 70 eV on a DuPont Model 21-491 mass spectrometer using the GLC inlet with column A. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Dr. C. Daessle, Montreal, Quebec.

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride and then redistilled immediately before use from sodium and benzophenone. Wittig reactions were performed under an atmosphere of dry nitrogen or argon. Vacuum distillations were done using a nitrogen inlet and a 130-mm Vigreux distillation column (Kontes Bantam-Ware no. 286700).

6-Methyl-5-hepten-2-one Ethylene Ketal (1). Following the reported procedure,[4] **1** was prepared in 85% yield from 6-methyl-5-hepten-2-one, ethylene glycol, and *p*-toluenesulfonic acid in refluxing benzene: bp 39–44 °C (0.5 mm) (lit.[4] bp 58 °C at 1.0 mm); retention time (column B, 120 °C) was 2.7 min; mass spectrum, *m/e* (relative intensity) 170 (M^+, 6), 155 (6), 111 (5), 108 (3), 88 (5), 87 (100), 82 (3), 69 (13), 59 (3), 55 (3), 43 (35), 41 (10).

***trans*-2-Methyl-6-oxo-2-hepten-1-al Ethylene Ketal.** The ketal **1** (42.2 g, 0.25 mol) and selenium dioxide (40 g, 0.36 mol) were heated with stirring in refluxing dioxane (400 mL) during 5 h. After being cooled, the black precipitate was removed by filtration and the red-brown filtrate was concentrated on a rotary evaporator. The crude product (GLC purity was ~70%) was distilled under vacuum. Those fractions distilling between 92 and 135 °C (0.5–2.0 mm) represented 23.2 g (50.8% yield) of the desired ketal aldehyde as a yellow viscous liquid: bp 98 °C (1 mm) (lit.[4] bp 102 °C at 1 mm); retention time (column B, 120 °C) was 8.5 min; mass spectrum, *m/e* (relative intensity) 184 (M^+, 0.1), 169 (14), 87 (100), 43 (32), 41 (6).

***trans*-2-Methyl-6-oxo-2-hepten-1-ol Ethylene Ketal (2).** To a 5 °C solution of the ketal aldehyde (23.2 g) in 95% ethanol was added dropwise with stirring a solution of sodium borohydride (16.5 g) in 95% ethanol (150 mL, pH adjusted to 8 with NaOH pellets). After the 30-min addition, the reaction mixture was stirred in the ice bath for 5 h and then at 21 °C overnight. Following workup, the crude yellow oil was distilled under vacuum to give 15.3 g (65%) of **2** as a nearly colorless oil. An analytically pure sample was obtained by column chromatography (SilicAR cc-7), eluting with hexane and hexane–ether mixtures: bp 87 °C (0.3 mm); retention time (column B, 120 °C) was 10.1 min; IR 3470 cm^{-1} (OH); NMR ($CDCl_3$) δ 5.47 (ragged t, C=CH), 4.00 (broadened s, CH_2OH, OCH_2CH_2O), 1.70 (s, $C=CCH_3$), 2.45–1.20 (m, 5, CH_2CH_2 and CH_2OH; the latter exchanged with D_2O), 1.36 (s, CH_3); mass spectrum, *m/e* (relative intensity) 171 ($M - 15$, 5), 153 (1), 111 (1), 109 (1), 105 (2), 103 (1.5), 95 (1), 88 (4), 87 (100), 84 (2), 81 (3), 59 (3), 55 (2), 45 (2), 43 (31), 41 (4). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.13; H, 9.78.

Generation of Ozone. Oxygen at a cylinder flow rate of 6.0 L/h was passed through two glass tubes, with each tube (60 cm × 4 mm i.d.) carrying a no. 20 gauge copper wire connected to separate high frequency generators (Electro-Technic, Model BD-10). The glass tubing was encased in a grounded copper pipe (46 × 1.27 cm i.d.). Oxygen entered the apparatus by way of a T-joint, which was located 5 cm below the cork-stoppered wire entrance. Ozone was delivered into the reaction medium by a glass pipet connected to the exit ends with Tygon tubing. A similar apparatus for microgram-scale ozonolyses has been described.[15]

4-Oxo-1-pentanal Ethylene Ketal (3). A soluton of ketal **1** (20 g) in methylene chloride (200 mL) was cooled to −78 °C (dry ice–acetone). Ozone was introduced into the stirred solution for 18 h, after which time the blue color of ozone persisted. The solution was swept with nitrogen gas during 30 min. Triphenylphosphine (28 g) was then added, and the mixture was gradually allowed to come to room temperature. The solvent was removed on the rotary evaporator. Hexane (100 mL) was added, and the precipitate was removed by filtration and washed well with hexane and ether. The combined filtrates were evaporated, and the crude product was immediately distilled under reduced pressure. There was obtained 13.04 g (77%) of the desired aldehyde[16] as a colorless oil: bp 42 °C (0.3 mm); retention time (column B, 120 °C) was 1.5 min; IR 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.78 (m, CHO), 3.93 (s, OCH_2CH_2O), 2.80–1.85 (m, CH_2CH_2), 1.33 (s, CH_3); mass spectrum, *m/e* (relative intensity) 129 ($M - 15$, 33), 87 (100), 85 (29), 84 (8), 73 (5), 71 (6), 57 (7), 55 (9), 43 (62). Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.18; H, 8.41.

***cis*-2-Methyl-6-oxo-2-hepten-1-ol Ethylene Ketal (4).** Ethylidenetriphenylphosphorane[17] was prepared from ethyltriphenylphosphonium bromide (33.42 g, 0.09 mol) dissolved in dry THF (150 mL) at 0 °C. *n*-Butyllithium (1.6 molar in hexane, 56.25 mL, 0.09 mol) was added by syringe during 20 min. The yellow reaction mixture was stirred for an additional 30 min at 0 °C and then allowed to approach 10 °C during 15 min. A deep red color developed. The mixture was cooled to −78 °C (dry ice–acetone), and the freshly distilled aldehyde **3** (12.97 g, 0.09 mol) was added by syringe during 5 min. After 10 min, the yellow solution of Wittig betaine was treated with 56.25 mL of *n*-butyllithium during 20 min. The resulting deep red β-oxido ylide was allowed to approach 0 °C during 30 min, and then paraformaldehyde (8.1 g, 0.27 mol, dried under vacuum with P_2O_5) was added in one portion. Stirring was continued at 0 °C for 1 h and then at 21 °C during 20 h. The reaction mixture, gradually becoming cream in color, was poured into ice water (250 mL) saturated with sodium chloride and stirred for 45 min. The organic layer was removed, and the aqueous phase was extracted with ether. The combined organic extracts were concentrated on the rotary evaporator, and the residue was stirred with hexane and ether. A precipitate was removed by filtration and washed with ether. The combined filtrate was dried ($MgSO_4$) and evaporated. The resulting crude oil was distilled under vacuum, and a volatile fraction (3.38 g, see below) was collected at 26–33 °C (0.2 mm). The second fraction represented the desired alcohol **4**, as a colorless oil (7.5 g, 45%). An analytically pure sample was obtained by column chromatography (SilicAR cc-7), eluting with hexane and hexane–ether mixtures: bp 83–87 °C (0.2 mm); retention time (column B, 120 °C) was 8.9 min; IR 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 5.30 (ragged t, C=CH), 4.13 (s, CH_2OH), 3.94 (s, OCH_2CH_2O), 1.80 (s, $C=CCH_3$), 2.40–1.40 (m, 5, CH_2CH_2 and CH_2OH; the latter exchanged with D_2O), 1.30 (s, CH_3); mass spectrum, *m/e* (relative intensity) 171 ($M - 15$, 2), 153 (2), 111 (1), 109 (2.5), 105 (1.5), 103 (2), 95 (1.5), 88 (4), 87 (100), 84 (3.5), 81 (5), 59 (4), 55 (3), 45 (3), 43 (39), 41 (5). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.22; H, 10.01.

The low-boiling fraction from the above distillation on analysis by GLC showed a complex mixture. Olefin **6** (stereochemistry not known) was found as a major component (retention time, column B, 120 °C, was 1.7 min) as indicated by GLC and mass spectrometry. Ions were seen at *m/e* 156 (M^+, 1), 141 ($M - 15$, 7), 87 (100), 69 (4), 55 (9), 43 (40), and 41 (5).

In Wittig reactions where ethyltriphenylphosphonium bromide was allowed to react with *n*-butyllithium at −78 °C, none of the desired product **4** was formed.The main products indicated by GLC and mass spectrometry were **6** (10–20%) and a ketal alcohol (70–80%). The latter component had a retention time of 12 min (column B, 120 °C) and was assigned structure **5** on the basis of fragment ions occurring at *m/e* 187 (M − 15, 5), 169 (4), 145 (10), 101 (6), 99 (5), 97 (4), 88 (6), 87 (100), 83 (13), 82 (4), 73 (7), 71 (6), 59 (6), 55 (11), 45 (4), 43 (36), and 41 (6). In reactions at 0 °C (as described), formation of **5** was avoided completely, whereas **6** was present in the crude reaction mixture to the extent of 6–8%.

Acknowledgments. The author would like to thank Mr. Art Hewitt for technical assistance, Mr. Jim Elder for running the mass spectra, and Dr. D. W. A. Roberts for use of a gas chromatograph. The author would also like to thank Dr. A. Benderly and Dr. R. T. Coutts, University of Alberta, for helpful discussions.

Registry No.—**1**, 3695-38-3; **2**, 21488-96-0; **3**, 24108-29-0; **4**, 68965-53-7; **5**, 68965-54-8; **6**, 6539-85-1; 6-methyl-5-hepten-2-one, 110-93-0; *trans*-2-methyl-6-oxo-2-hepten-1-al ethylene ketal, 31925-20-9.

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(10) M. Schlosser and D. Coffinet, *Synthesis*, 380 (1971).
(11) M. Schlosser and D. Coffinet, *Synthesis*, 575 (1972).
(12) Valeraldehye,[4] hexanal,[10] and heptanal[8] had previously been cis hydroxyisopropenylated by this procedure. In the present work, *cis*-2-methyl-2-hepten-1-ol was obtained (45% distilled yield) from valeraldehyde (under conditions described for the preparation of **4**), and the NMR spectrum was identical with the reported spectrum.[4]
(13) By removing aliquots from the reaction of **1** with 0.5–1.5 mol equiv of selenium dioxide and determining cis–trans isomer distributions by GLC peak area ratios, less than 2% of **4** and greater than 98% of **2** were found. Trans selectivity could thus be improved by stopping the oxidation at the alcohol stage. However, this would be cumbersome because in dioxane the aldehyde represented a major product before **1** was consumed.
(14) W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 790 (1978).
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(16) Yields of **3** from ozonolyses varied from 25 to 77%. Flushing the cold solution with nitrogen gas before adding triphenylphosphine was essential. Decomposition occurred on storing distilled samples of **3** for more than a week.
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Synthesis of 4,5,6,7-Tetrahydro-1(3*H*)-isobenzofuranones by Reaction of *N,N*-Dimethyl-2-lithio-1-cyclohexenecarboxamide with Aldehydes and Ketones

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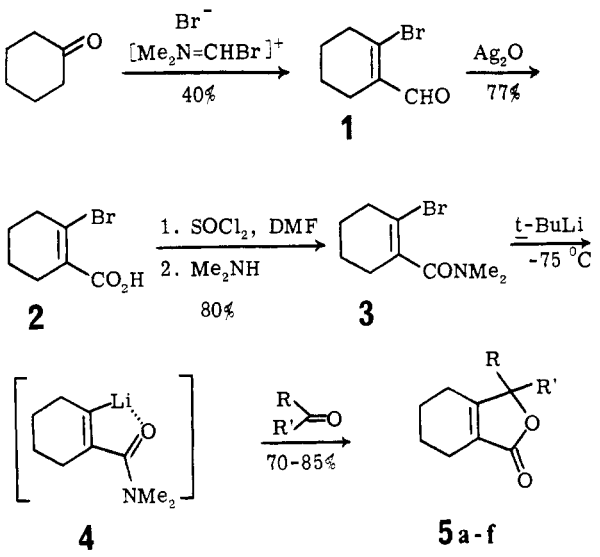
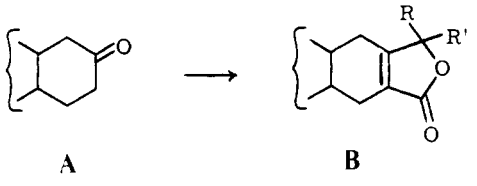
Received September 19, 1978

The frequent occurrence of α,β-unsaturated γ-lactones in many types of natural products has stimulated considerable interest in the synthesis of $\Delta^{\alpha,\beta}$-butenolides.[1] Although a great variety of synthetic routes to these compounds may be found in the literature, there appear to be few reports of syntheses of bicyclic $\Delta^{\alpha,\beta}$-butenolides with a carbocycle fused across the α and β positions, such as 4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranones (**5**).[1-3] The necessity of preparing fused bicyclic butenolides from cyclohexanone and related compounds (A → B) has prompted us to develop a new synthetic route to

Scheme I





these compounds. The key reaction in the synthesis (Scheme I) involves the generation of the lithio derivative of *N,N*-dimethyl-2-bromo-1-cyclohexenecarboxamide (**3**) by bromine-lithium exchange with *tert*-butyllithium in tetrahydrofuran (THF)–pentane at −75 °C and subsequent reaction of the vinyllithium reagent (**4**) with aldehydes and ketones.

2-Bromo-1-cyclohexenecarboxaldehyde (**1**), prepared by condensation of cyclohexanone with the bromo Vilsmeier reagent as described by Arnold and Holy,[4] was oxidized with silver oxide to the crystalline bromo acid (**2**) in 77% yield. The dimethylamide was obtained by reaction of the corresponding acid chloride with dimethylamine in pentane at −78 °C.

Parham and co-workers have demonstrated that *o*-bromobenzoic acid and its esters undergo bromine–lithium exchange to produce ortho-lithiated benzoates upon reaction with *n*-butyllithium in THF–hexane at −100 °C.[5] For example, metalation of *o*-bromobenzoic acid followed by addition of valerophenone provided 3-*n*-butyl-3-phenylphthalide in 67% yield.[5a] Recently, this procedure has been utilized to effect the lithiation of 2-bromo-3-methyl-2-butenoic acid.[6] Tertiary benzamides have been metalated regiospecifically in the ortho position by deprotonation with *sec*-butyllithium–tetramethylethylenediamine in THF and the resulting lithium reagent trapped by reaction with benzophenone to give 3,3-diphenylphthalide.[7] These findings provided precedent and guidance in a search for suitable procedures for the preparation of butenolides **5** from bromo acid **2** and bromo amide **3**.

Reaction of bromo acid **2** with 2 equiv of *n*-butyllithium or bromo amide **3** with 1 equiv of *n*-butyllithium in a mixture of THF–hexane at −80 to −85 °C for 15–30 min and subsequent addition of 2.1 equiv of benzaldehyde gave rise to phenyl-substituted lactone **5a** in 45–50% yield after hydrolysis with 25% aqueous acetic acid and column chromatography to separate unidentified polar byproducts. In order to improve the yield of lactone, we carried out a series of experiments in which the conditions and reactants were varied and the yield