BuOCOCl (8) was heated with 5 mol % 18-crown-6 at 100 °C for 44 h, it could be recovered in only 47% yield and again *i*-BuCl was obtained. Moreover, after 60 h at 100 °C with KF and no crown ether, only 7% of the original 8 was recovered. The fluoroformate 7 also was identified in ca. 8% yield, an indication that halogen exchange occurs though inefficiently, even in the absence of crown ether. In our reaction system, the fate of some other chloroformates is even more temperature dependent than that of 8. For example, *n*-BuOCOF was obtained in 84% yield when the chloroformate was reacted at room temperature but in only 1% yield at a reaction temperature of 125 °C; also the 89% yield of EtOCOF isolated at 0 °C decreased to 6% at 85 °C and the 95% yield of *i*-PrOCOF measured at 13 °C deteriorated to 8% at 95 °C. The carbamoyl chloride (6) reactions also were exceptionally temperature dependent, though these substrates are not subject to the decomposition pathways followed by the chloroformates. For example, the 95% yield of Me_2NCOF found in the room temperature reaction decreased to 54% at 110 °C and 5% at 145 °C; also the morpholinylcarbamoyl chloride exchange which was 97% efficient at room temperature gave a thick brown intractable tar and 0% carbamoyl fluoride at 130 °C. These latter decompositions are probably initiated by the precedented fragmentation:[16] $R_2NCOCl \rightleftarrows R_2N{=}C{=}O^+ + Cl^-$.

It should be noted, in conclusion, that the convenient fluoroformate synthesis described here has a preparative value beyond that discussed in the introduction. The ready availability of 3 now makes these species highly attractive intermediates in a known but previously impractical conversion of alcohols to alkyl fluorides.[7,17]

Experimental Section

Melting points were taken in a Thomas-Hoover apparatus equipped with a calibrated thermometer. Infrared spectra were obtained on a Perkin-Elmer 267 spectrophotometer and NMR spectra on a Varian A60-A spectrometer.

Potassium fluoride (Mallinckdrodt) was dried at 150 °C for 24 h, then finely pulverized and redried overnight at the same temperature in the reaction vessel. All chloroformates, acid chlorides, and carbamoyl chlorides were obtained commercially except cyclohexyl chloroformate[18] and the carbamoyl chlorides[19] of piperidine and morpholine which were made by standard acylations of the precursor alcohol or amines with phosgene. Before use, the liquid chloroformates and carbamoyl chlorides were distilled under N_2 and the acid chlorides were refluxed with PCl_5 and distilled under N_2. Glassware was dried at 150 °C, assembled hot in a stream of dry N_2, and set up to maintain a slight positive N_2 pressure during the main reaction sequences.

Isobutyl Fluoroformate. (Except for the variations indicated in Table I, liquid chloroformates, carbamoyl chlorides, and acid chlorides were allowed to react by the procedure given here.) Isobutyl chloroformate (26.3 g, 0.193 mol) was syringed into a three-neck flask containing dried KF (14.7 g, 0.253 mol) and 18-crown-6[10] (1.80 g, 0.0068 mol) and fitted with a Teflon stirring bar, a condenser topped by an N_2 gas inlet, a septum cap, and a ground glass stopper. The mixture then was stirred efficiently at room temperature until IR analysis of an aliquot indicated that no chloroformate remained (C=O stretch at 5.62 μm in CCl_4; fluoroformate C=O stretch at 5.46 μm). After a few more hours (total reaction time 45 h), the product fluoroformate was isolated directly from the reaction apparatus by simple distillation (stirred to minimize bumping, oil bath): yield 21.0 g (91%); bp 92–93 °C (atmospheric pressure) (lit.[9] bp 27 °C at 0.2 torr).

When the halide exchange was performed at 13 °C for 78 h with 1.3 equiv of KF and 7.5 mol % 18-crown-6, the fluoroformate yield was 87%. Only a 35% yield of fluoroformate was obtained at a reaction temperature of 100 °C (1.3 equiv of KF, 7.6 mol %, 18-crown-6, 24 h). A substantial forerun of isobutyl chloride was also obtained. When isobutyl chloroformate was heated with 18-crown-6 (5 mol %) at 100 °C for 44 h, only 47% of the chloroformate could be recovered. In contrast, isobutyl fluoroformate was recovered in 87% yield after similar treatment. After 10 g of isobutyl chloroformate was heated with KF (1.7 equiv) at 100 °C for 60 h, only 1.4 g of liquid remained. This analyzed as an ca. 1:1 mixture of chloroformate to fluoroformate. Isobutyl fluoroformate was recovered in 83% yield after analogous treatment.

Cholesteryl Fluoroformate. (This procedure was followed when the chloride precursor was a solid.) The chloroformate of cholesterol (Aldrich) (6.79 g, 0.0151 mol) was dissolved in the minimum amount of CH_2Cl_2 (5 mL). KF (3.5 g, 0.059 mol) and 18-crown-6 (0.60 g, 0.0023 mol) were added and the mixture was stirred at room temperature until reaction completion (53 h). After adding more CH_2Cl_2, the mixture was filtered and the filtrate was evaporated at reduced pressure. The yellow solid product residue was recrystallized from dry acetonitrile: yield 5.82 g (89%); mp 112–113 °C.

Anal. Calcd for $C_{28}H_{45}O_2F$: C, 77.7; H, 10.5. Found: C, 77.7; H, 10.4.

Acknowledgment. We are grateful to the National Institutes of Health for the grant which supported this research.

Registry No.—Ethyl chloroformate, 541-41-3; isopropyl chloroformate, 108-23-6; isobutyl chloroformate, 543-27-1; butyl chloroformate, 592-34-7; cyclohexyl chloroformate, 13248-54-9; cholesteryl chloroformate, 7144-08-3; phenyl chloroformate, 1885-14-9; dimethylcarbamic chloride, 79-44-7; 1-piperidinecarbonyl chloride, 13939-69-0; 4-morpholinecarbonyl chloride, 15159-40-7; butanoyl chloride, 141-75-3; benzoyl chloride, 98-88-4.

References and Notes

(1) (a) R. A. Olofson, J. Cuomo, and B. A. Bauman, *J. Org. Chem.*, **43**, 2073 (1978); (b) R. A. Olofson, B. A. Bauman, and D. J. Wancowicz, *ibid.*, **43**, 752 (1978).
(2) (a) R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, *Tetrahedron Lett.*, 1563 (1977); (b) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *ibid.*, 1567 (1977); (c) R. A. Olofson and R. C. Schnur, *ibid.*, 1571 (1977); (d) R. A. Olofson and J. P. Pepe, *ibid.*, 1575 (1977). Other uses will be described in future publications: see footnote 17 in ref 1b.
(3) R. A. Olofson and J. Cuomo, submitted for publication.
(4) See, for example: (a) H. J. Emeleus and J. F. Wood, *J. Chem. Soc.*, 2183 (1948); (b) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **21**, 1319 (1956).
(5) Made by heating $COCl_2$ with SbF_3, SbF_5, SiF_4, AsF_3, CuF_2, NaF, HF, etc., at elevated temperature and pressure [(a) K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **29**, 3007 (1964); **30**, 1639 (1965); (b) F. S. Fawcett, C. W. Tullock, and D. D. Coffman, *J. Am. Chem. Soc.*, **84**, 4275 (1962), also ref 4a], treatment of CO with BrF_3 [ref 4b], or reaction of Cl_3CF with oleum [(c) G. Siegmund, *Angew. Chem., Int. Ed. Engl.*, **12**, 919 (1973); L. Wackeski and I. Ugi, *Synthesis*, 598 (1975)].
(6) G. A. Olah and A. Pavlath, *Acta Chim. Acad. Sci. Hung.*, **3**, 191 (1953).
(7) S. Nakaniski, T. C. Myers, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 3099 (1955).
(8) Simple acyl fluorides also have been made in special apparatus using anhydrous hydrogen fluoride or KHF_2 as the halogen transfer agent; see, for example: G. A. Olah, S. J. Kuhn, and S. Beke, *Chem. Ber.*, **89**, 862 (1956); G. A. Olah and S. J. Kuhn, *Org. Synth.*, **45**, 3 (1965).
(9) (a) For example, diazotization of $ROCONH_2$ in poly(hydrogen fluoride pyridine): G. A. Olah and J. Welch, *Synthesis*, 654 (1974); (b) also see R. J. Harder and W. C. Smith, *J. Am. Chem. Soc.*, **83**, 3422 (1961).
(10) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974); also available from Aldrich.
(11) Though this is presumably an equilibrium reaction, the thermodynamics so overwhelmingly favor **3** and **4** that the concentrations of **5** and **6** are below detectable limits.
(12) M. E. Childs and W. P. Weber, *J. Org. Chem.*, **41**, 3486 (1976); W. P. Weber and G. W. Gokel, "Phase Transfer Catalysis in Organic Synthesis", Springer-Verlag, New York, 1977, p 102.
(13) C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974).
(14) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 237 (1961).
(15) E. S. Lewis and W. C. Herndon, *J. Am. Chem. Soc.*, **83**, 1955, 1959, 1961 (1960); W. E. Depuy and H. R. Hudson, *J. Chem. Soc., Perkin Trans. 2*, 1715 (1972), and references therein.
(16) G. D. Buckley, H. A. Piggott, and A. J. E. Welch, *J. Chem. Soc.*, 864 (1945).
(17) The thermal conversion of phenyl fluoroformate to fluorobenzene also has been achieved: K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 3170 (1965).
(18) J. H. Saunders, R. J. Slocombe, and E. E. Hardy, *J. Am. Chem. Soc.*, **73**, 3796 (1951).
(19) W. R. Boon, *J. Chem. Soc.*, 307 (1947).

α-Trimethylsiloxy Ketones from Bis(trimethylsiloxy) Enol Ethers

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The Schräpler–Rühlman modification[2] has become the standard method for carrying out acyloin condensations. In

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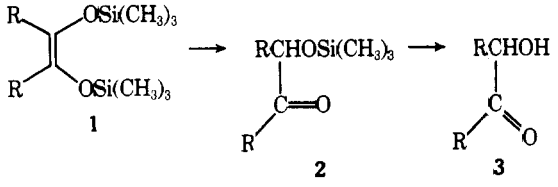
this modification, chlorotrimethylsilane quite effectively traps the intermediate enediolate as the bis(trimethylsilyl) enol ether (1). These derivatives can be converted to α-hydroxy ketones (3) by aqueous acid[1,2] or by treatment with methanol.[3] Although it is quite apparent that the trimethylsiloxy ketone (2) must be an intermediate in the overall transformation, we



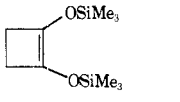
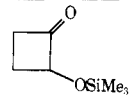
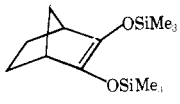
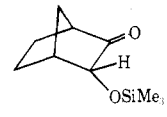
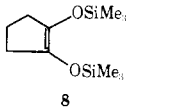
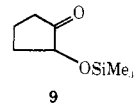
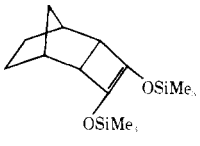
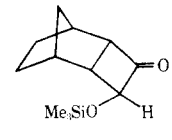
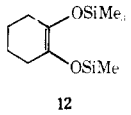
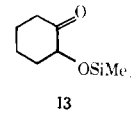
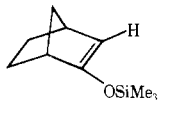
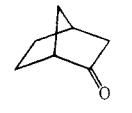
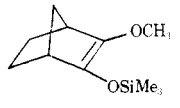
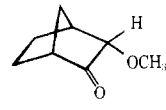
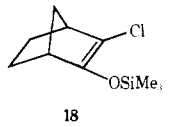
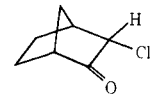
1 2 3

are aware of no reports in which such intermediates have been isolated under hydrolytic conditions.[4] In connection with another study, we wanted to prepare these protected acyloins (2) from the bis(trimethylsilyl) enol ethers (1), which were readily available. We also wanted to establish the reasons for the disparity in reaction rates and formation of side products when methanolysis procedures slightly different from those recommended by Bloomfield[3b] were employed. Reported here are the results of these studies.

We have found that when triethylamine is used in conjunction with methanol, in certain cases the conversion of 1 to 2 is much faster than that of 2 to 3. This fact allows the actual isolation of 2 directly from 1. Table I gives isolated yields of α-trimethylsiloxy ketones prepared from bis(trimethylsilyl) enol ethers and methanol containing triethylamine. Little of the α-hydroxy ketone is formed in the reaction of four- and five-membered ring bis(trimethylsilyl) enol ethers under the given reaction conditions. Isolation of the product involves simply solvent evaporation and distillation. Any traces of hydroxy ketone can be readily removed by a short chromatography column. Although limited to small ring bis(trimethylsilyl) enol ethers, this is the method of choice for formation of these α-trimethylsiloxy ketones.

Methanolysis of 12 is not an efficient method of forming 13 because of the relatively slow initial reaction. However, 12 can be converted to the α-trimethylsiloxy ketone 13 by the con-

Table I. Reactions of Trimethylsilyl Enol Ethers

compd	conditions	product	% yield	$10^2 k$,[a] s^{-1}	k_{rel}
 4	0.01 M Et_3N	 5	75	2.30	14
 6	0.16 M Et_3N 0.14 M Et_3N 0.10 M Et_3N 0.05 M Et_3N 0.01 M Et_3N CH_3Li/DME	 7	97 67	2.50 2.15 1.57 0.81 0.22	1.4
 8	0.05 M Et_3N CH_3Li/DME	 9	83 45	0.60	1.0
 10	0.05 M Et_3N	 11	94		
 12	0.05 M Et_3N	*b*		*c*	
	CH_3Li/DME	 13	46		
 14	0.01 M Et_3N	 15	*d*	4.28	26
 16	0.01 M Et_3N	 17	*d*	1.21	7.4
 18	0.01 M Et_3N	 19	*d*	8.74	54

[a] 25.0 °C; monitored spectrophotometically, (see Experimental Section); rates were significantly slower under preparative conditions, which contained ~10% substrate. [b] Comparable amounts of 2-hydroxycyclohexanone and 2-(trimethylsiloxy)cyclohexanone were found. [c] Very slow reaction; mostly unreacted 12 remained after 2 days. [d] Absolute yield was not determined.

ventional but more tedious treatment with 1 equiv of methyllithium.[5] Other pertinent examples are given in Table I. Rates are much faster in dimethoxyethane (DME) than in ether. However, isolated yields are only in the moderate range. This general procedure provides an alternative to the triethylamine-catalyzed methanolysis for the formation of α-trimethylsiloxy ketones from bis(trimethylsilyl) enol ethers.

Attention was next turned to mechanistic aspects of the triethylamine-catalyzed methanolyses. For bis(trimethylsilyl) enol ether **6**, a plot of the rate constants given in Table I vs. triethylamine concentration is linear ($r = 0.999$) over the range studied. A question arises as to the actual catalyst in this transformation. Methoxide ion derived from a prior equilibrium of triethylamine and methanol (eq 1) was considered and

$$Et_3N + CH_3OH \overset{K}{\rightleftharpoons} Et_3N^+H + {}^-OCH_3 \qquad (1)$$

ruled out. If the equilibrium was far to the right, then the reaction rates should be linear in triethylamine concentration as observed, but methoxide ion derived from sodium methoxide should give comparable rates at comparable concentrations. This is clearly not the case. With sodium methoxide concentrations as low as 0.01 M, rates of methanolysis of **6** were much too rapid to measure using standard techniques. On the other hand, if the equilibrium constant is small, then methoxide concentration will vary approximately as $[Et_3N]^{1/2}$, as can be shown by simple acid–base equilibrium. Therefore, if methoxide were the actual catalyst, observed rate constants should be approximately linear as a function of $[Et_3N]^{1/2}$. Therefore, methoxide ion does not appear to be the catalytic species.

The data are consistent with either triethylamine or a methanol–triethylamine complex such as **20** (if such hydrogen bonding is complete in a methanol solution of triethylamine) as the active catalyst.

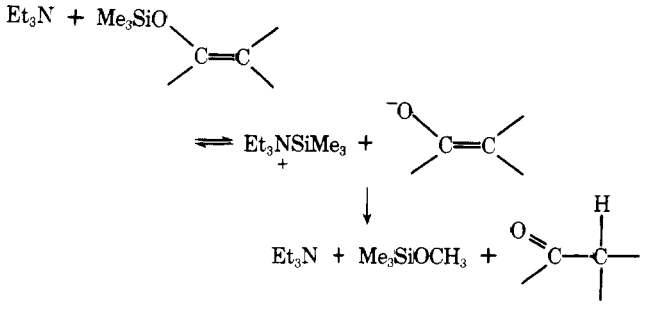
$$Et_3N\text{- - -}H\text{–}O\text{–}CH_3$$

20

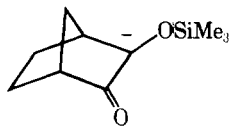
We do not feel that the first possibility can be eliminated despite the fact that trimethylsilyl enol ethers are, in general, inert to triethylamine in aprotic solvents.[6] A scheme such as that shown in Scheme I cannot be ruled out with the available data in the polar protic methanol solvent. Neither can rate-limiting reaction of **20** with the silyl enol ether be excluded.

The effect of ring size on the triethylamine-catalyzed methanolysis rate is also apparent from the data in Table I. The rate trend as a function of ring size is 4 > 5 > 6. This trend parallels that seen in the base-catalyzed deuterium exchange in cyclic ketones[7] and rates of base-catalyzed bromination of cyclic ketones.[8] These findings indicate the involvement of enolate anions in the triethylamine-catalyzed methanolysis reaction of silyl enol ethers with increased rates in the more strained systems reflecting increased stability of the more strained enolate.[7] The reactivity of the norbornyl system **6** is between that of the four- and five-membered ring systems. The six-membered ring system, **12**, undergoes relatively slow methanolysis such that subsequent methanolysis of **13** is competitive.

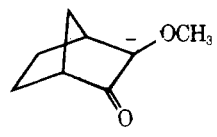
Scheme I



A comparison of the methanolysis rate of bis(trimethylsilyl) enol ether **6** with other substituted norbornyl silyl enol ethers is also informative. Table I shows that the effect of substituents on methanolysis rate is Cl > H > OCH_3 > $OSiMe_3$. These trends can be interpreted in terms of intermediate enolate anions in which the effect of the trimethylsiloxy group in **21** is destabilizing relative to hydrogen and even *more* destabilizing than the methoxy substituent in **22**.

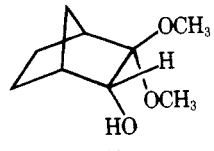


21



22

The methanolysis of **6** was also investigated in the acidic range. Trifluoroacetic acid concentrations as low as 10^{-4} M catalyze rapid methanolysis of **6** at room temperature. However, subsequent methanolysis of **7** is also rapid and this method cannot be used to efficiently produce **7**. As the concentration of trifluoroacetic acid is increased (10^{-2} M), ketalization of the α-hydroxy ketone begins to occur at a significant rate, giving **23**. Traces of **23** can also be seen after 1



23

h when triflic acid (CF_3SO_3H) concentrations as low as 10^{-4} M are used in the methanolysis of **6**. It is therefore necessary to use carefully distilled bis(trimethylsilyl) enol ethers as recommended by Bloomfield (to remove any acid-producing materials such as chlorotrimethylsilane) when carrying out "neutral" methanolyses to produce α-hydroxy ketones. This ensures reproducible rates and avoids ketalization and subsequent rearrangement of the hydroxy ketals.[9]

Experimental Section

Preparation of Bis(trimethylsiloxy) Enol Ethers. The preparations of compounds **4**,[3c] **6**,[10] **8**,[2] **10**,[11] **12**,[2] **14**,[12] **16**,[13] and **18**[13] have previously been described.

Methanolysis of Bis(trimethylsiloxy) Enol Ethers with Triethylamine. General Procedure. A 40-mL amount of 0.05 M triethylamine in methanol was added to 4.0 g of the bis(trimethylsiloxy) enol ether with stirring at room temperature. The reaction was monitored by gas chromatography, and after ~5 half-lives the methanol solvent was removed by a rotatory evaporator. The product trimethylsiloxy ketones **5**, **7**, **9**, and **11** were isolated by distillation at reduced pressure. Isolated yields of distilled products are given in Table I. Gas chromatographic analysis of the distillate from reaction of **4** shows about 1% α-hydroxycyclobutanone. Reaction of **6** gave about 2% *endo*-3-hydroxynorcamphor. Reaction of **8** gave about 8% of 2-hydroxycyclopentanone. Rapid chromatography through a short neutral alumina column using 5% ether–Skelly F completely removed the 2-hydroxycyclopentanone.

Reaction of Bis(trimethylsiloxy) Enol Ethers with Methyllithium. General Procedure. Approximately 3 g of the bis(trimethylsiloxy) enol ether was dissolved in 6 mL of dry dimethoxyethane, and the mixture was cooled in an ice bath. Methyllithium (1.0 equiv of a 1.6 M solution in ether) was added dropwise over a 5-min period. After being stirred for 30 min at room temperature, the mixture was diluted with 15 mL of pentane and cooled to −40 °C. Water was then added. The organic phase was separated, washed with water and saturated sodium chloride solution, and dried over magnesium sulfate. After filtration, the solvent was removed by a rotatory evaporator. The products were isolated by distillation at reduced pressure. Yields

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.

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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.

References and Notes

(1) Alfred P. Sloan Fellow, 1977–1979.
(2) U. Schräpler and K. Rühlman, *Chem. Ber.*, **96**, 2708 (1963); **97**, 1383 (1964).
(3) (a) J. J. Bloomfield, *Tetrahedron Lett.*, 587 (1968); (b) J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976); (c) *Org. Synth.*, **57**, 1 (1977).
(4) α-Trimethylsiloxy ketones can be prepared by epoxidation of trimethylsilyl enol ethers. See (a) G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Lett.*, 4319 (1974); (b) A. G. Brook and D. M. Macrae, *J. Organomet. Chem.*, **77**, C19 (1974); (c) A. Hassner, R. H. Reuss, and H. W. Pinnick *J. Org. Chem.*, **40**, 3427 (1975).
(5) For representative examples of this procedure applied to simple trimethylsilyl enol ethers, see (a) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462, 4464 (1968); (b) P. A. Tardella, *Tetrahedron Lett.*, 1117 (1969); (c) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974); (d) G. Stork and J. Singh, *ibid.*, **96**, 6181 (1974). For a related cleavage of bis-(trimethylsilyl) enol ethers with 2 equiv of methyllithium, see T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.*, 3879 (1974).
(6) One of the common procedures for formation of trimethylsilyl enol ethers employs triethylamine, chlorotrimethylsilane, and the carbonyl compound; see H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(7) H. Shechter, M. Collis, R. Dessy, Y. Okuzumi, and A. Chem. *J. Am. Chem. Soc.*, **84**, 2905 (1962).
(8) A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3164 (1962).
(9) X. Creary and A. J. Rollin, *J. Org. Chem.*, **42**, 4231 (1977).
(10) X. Creary, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1973.
(11) X. Creary, *J. Org. Chem.*, **40**, 3326 (1975).
(12) X. Creary and A. J. Rollin, *J. Org. Chem.*, **42**, 4226 (1977).
(13) C. Kowalski, X. Creary, A. J. Rollin, and M. C. Burke, *J. Org. Chem.*, **43**, 2601 (1978).

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

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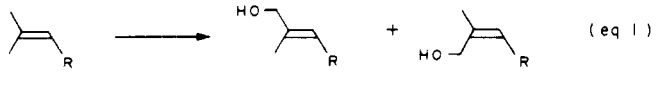
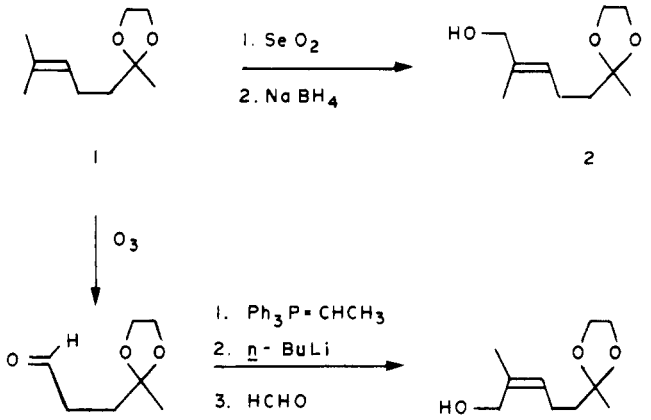
A number of investigators have shown that the isobutenyl functionality, present in diverse molecules such as pentazocine,[1] an analgesic of the benzomorphan series, and resmethrin,[2] a synthetic pyrethroid, is capable of undergoing metabolic monohydroxylation in animals according to eq 1. It was therefore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