The Conversion of 3-Hydroxy-6-heptenoic Acids into Bicyclo[3.2.0]hept-3-en-6-ones

Emanuela Marotta, Massimo Medici, Paolo Righi, and Goffredo Rosini*

Dipartimento di Chimica Organica "A. Mangini" dell'Università, Viale Risorgimento, 4, I-40136 Bologna, Italy

Received June 27, 1994

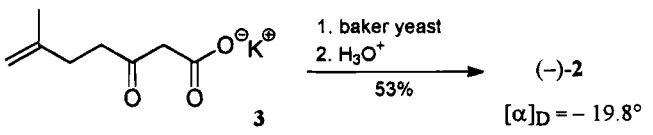
The stereospecific cycloaddition of ketenes to alkenes has been the subject of several studies and provides an attractive route to cyclobutanones. Snider, Ghosez, and others recognized that the intramolecular version of this reaction represents a general method for the synthesis of polycyclic cyclobutanones. All the studies concerning the intramolecular [2 + 2] additions of ketenes to double bonds leading to carbocycles were reviewed in 1988.[1] The most commonly used ketene precursors were α,β-unsaturated acid chlorides treated under high dilution conditions with triethylamine in refluxing benzene or toluene.

We have recently reported the easy conversion of 3-hydroxy-6-alkenoic acids into bicyclo[3.2.0]hept-3-en-6-ones by treatment with potassium acetate in acetic anhydride at room temperature (2 h) and then at reflux conditions for 2–4 h.[2] The efficient preparation of bicyclo[3.2.0]hept-3-en-6-ones should make them attractive starting materials or intermediates in synthesis of complex molecules.[2,3]

Although much work has been done to understand the mechanism of the cyclization of unsaturated acid chlorides, none has been reported for the cyclization of 3-hydroxyalkenoic acids.

The conversion of these hydroxy acids into bicyclo[3.2.0]hept-3-en-6-ones could occur through two alternative reaction paths depicted in Scheme 1. The presence of a chiral center in the starting 3-hydroxy-6-alkenoic acids induced us to verify if the intramolecular bicyclization step in acetic anhydride occurs either before or after the elimination of acetic acid to generate the corresponding α,β-unsaturated ketenes. If the first sequence is operative, the formation of the two additional chiral centers in bicyclo[3.2.0]hept-3-en-6-one could be affected by the chirality of the starting 3-hydroxy acid. If the elimination reaction occurs before the cyclization step, an achiral α,β-unsaturated ketene should form, with the loss of any possible asymmetric induction on the chirality of the forming chiral centers (Scheme 1).

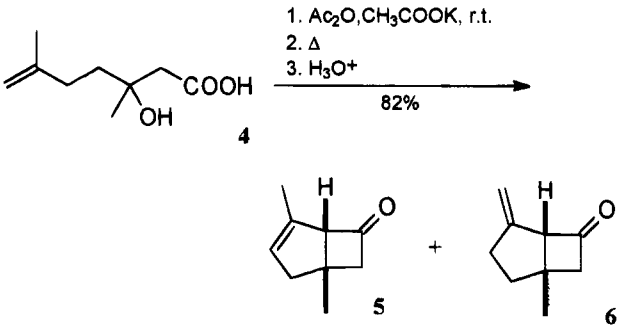
Thus, (3*R*)-3-hydroxy-6-methyl-6-heptenoic acid (**2**, ee = 95%) was prepared by bakers' yeast reduction of the potassium salt of 3-keto-6-heptenoic acid (**3**).[4]



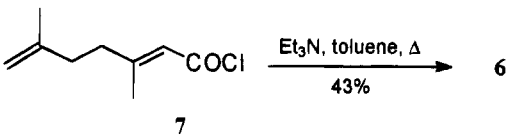
When treated with acetic anhydride and potassium acetate under standard conditions to effect the bicyclization, racemic 1-methylbicyclo[3.2.0]hept-3-en-6-one (**1**, ee = 0.00%) was obtained in 91% yield. This result strongly supports the reaction path 2 (Scheme 1) in which the elimination occurs as the first step.

To devise an hypothetical mechanism for this type of conversion, two additional main aspects are to be considered:

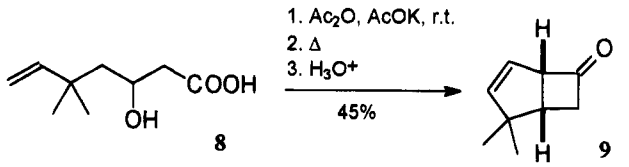
Thermodynamic products are selectively formed. The conversion of 3-hydroxy-3-methyl-6-heptenoic acids, such as **4**, gave the thermodynamically more stable bicyclo[3.2.0]hept-3-en-6-ones **5**, with low contamination by the exocyclic isomer **6**.[2] We found that **6** does not convert into **5**, when heated at reflux conditions in acetic anhydride, potassium acetate, and 2 equiv of acetic acid.



Conversely, the dehydrohalogenation of the 3-methyl-3,6-heptadienoic acid chloride **7** furnished exclusively the kinetic product, 4-methylenebicyclo[3.2.0]heptan-6-one (**6**), in lower yields.[5]



5,5-Disubstituted alkenoic acids do cyclize in potassium acetate/acetic anhydride conditions. 3-Hydroxy-5,5-dimethyl-6-heptenoic acid (**8**) undergoes bicyclization to give 2,2-dimethylbicyclo[3.2.0]hept-3-en-6-one (**9**) in 45% yield.[3] No cyclobutanone was observed after



treating 5,5-dimethyl-2,6-heptadienoic acid chloride (**10**) with triethylamine in refluxing toluene.[6] The inability to effect the intramolecular cyclization was ascribed to the effect of the geminal methyls on the selective forma-

(1) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793–811 and references cited therein.
(2) Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P.; Rosini, G.; Serra, R.; Venturelli, F. *Tetrahedron* **1994**, *50*, 3235–3250.
(3) Marotta, E.; Pagani, I.; Righi, P.; Rosini, G. *Tetrahedron* **1994**, *50*, 7645–7656.
(4) Hirama, M.; Shimizu, H.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599–600.
(5) Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, *52*, 5413–5419. Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809–2810.
(6) Snider, B. B.; Allentoff, A. J.; Kulkarni, Y. S. *J. Org. Chem.* **1988**, *53*, 5320–5328.

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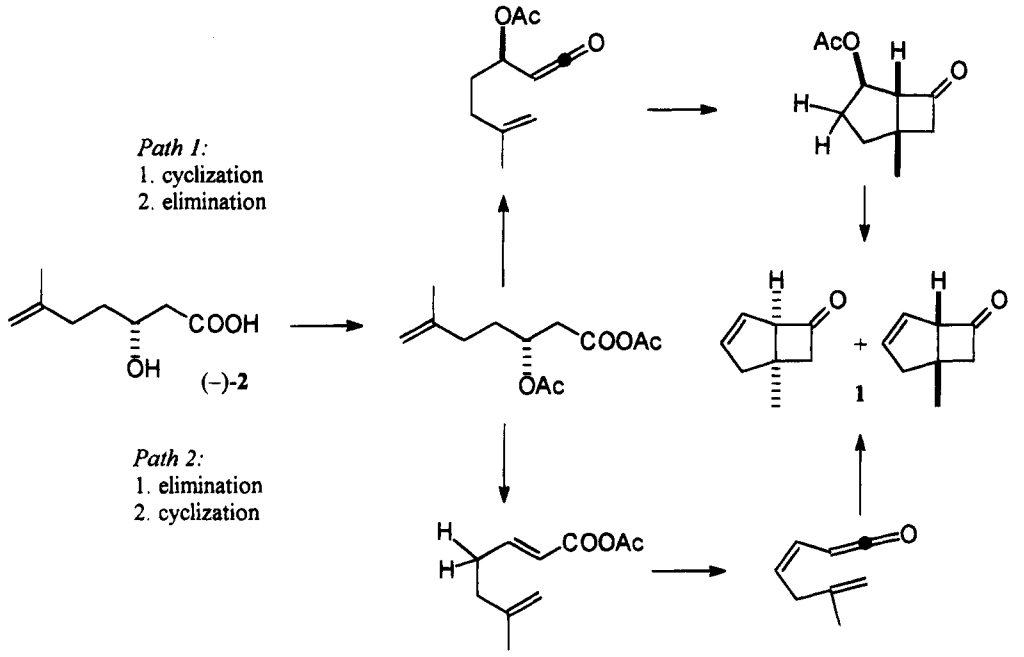
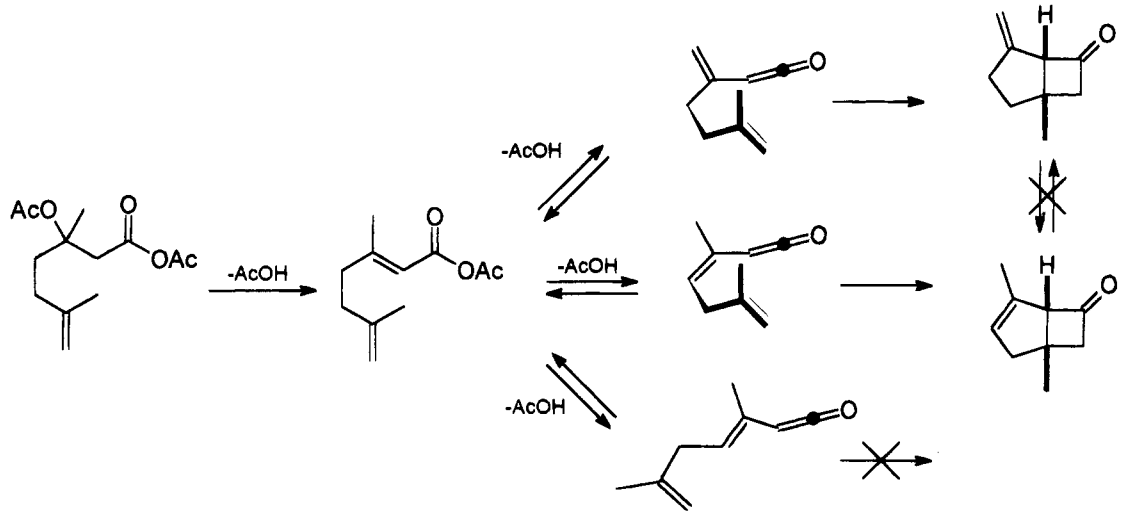
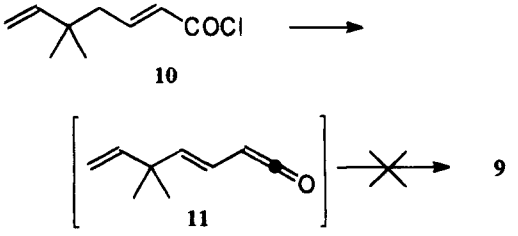
Scheme 1. Alternative Reaction Paths for the Conversion of 3-Hydroxy-6-heptenoic Acids into Bicyclo[3.2.0]hept-3-en-6-ones



Scheme 2. Equilibrium System in the Conversion of 3-Hydroxy-6-heptenoic Acids into Bicyclo[3.2.0]hept-3-en-6-ones

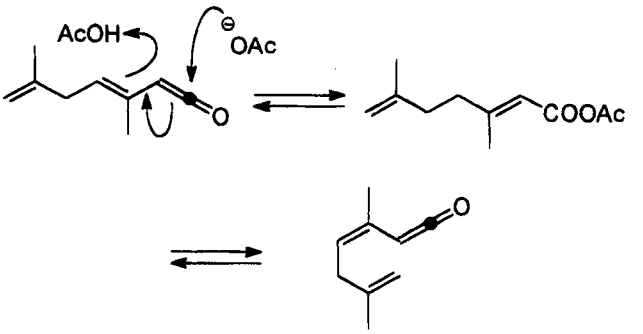


tion of the (*E*)-α,β-unsaturated ketene **11** in the deprotonation of this 5,5-disubstituted alkadienoic acid chloride.



All these observations are taken into account in Scheme 2, which depicts the reaction path for the conversion of 3-hydroxy-6-alkenoic acids into bicyclo-[3.2.0]hept-3-en-6-ones when treated with acetic anhydride and potassium acetate.

The main feature of this proposed mechanism is the reversible ketene generation made possible by the presence of the acetate anion in the reaction media. In this way the otherwise unused (*E*)-α,β-unsaturated ketene can be recycled for cyclization through a dynamic equilibrium with the (*Z*)-isomer.



This equilibrium can also explain the selective formation of the thermodynamically more stable ketene, which in turn gives the more stable product.

The results we have collected until now indicate this method to be of general application for a practical and convenient preparation of bicyclo[3.2.0]hept-3-en-6-ones, and the mechanism depicted here provides a rationalization for the differences, complementary in some cases, observed with respect to the procedure developed by Snider and co-workers.[1]

Experimental Section

General. Melting points were obtained with a Büchi apparatus and are uncorrected. Yields refer to isolated products. Proton and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ solvent. If not already stated, chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in hertz. Signal multiplicities were established by DEPT experiments. Flash chromatographic separations were performed using Merck silica gel 60 (70–230 mesh ASTM). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. Diethyl ether (ether) and tetrahydrofuran (THF) were freshly distilled from sodium metal using benzophenone ketyl as indicator. Chloroform and dichloromethane were distilled from P_2O_5 and stored over 4 Å molecular sieves. All air-sensitive reactions were run under nitrogen.

(3*R*)-3-Hydroxy-6-methyl-6-heptenoic Acid [(−)-2]. To a three-necked 500-mL flask charged with a solution of methyl 6-methyl-3-oxo-6-heptenoate (6.00 g; 38.0 mmol) in ethanol (100 mL) was added with stirring an aqueous solution of KOH (1 M, 75 mL, 75 mmol). The reaction mixture was kept at 25 °C for 8 h. The disappearance of the starting ester was monitored by TLC (petroleum ether:diethyl ether = 7:3). Ethanol was evaporated *in vacuo* and the residue taken up with water to a volume of 400 mL. A three-necked 2-L reaction vessel equipped with a mechanical stirrer and a thermometer was charged with water (550 mL), D-glucose (220 g), bakers' yeast (200 g; Eridania), K_2HPO_4 (470 mg), and $MgSO_4$ (240 mg). This suspension was stirred at 25 °C for 30 min. The aqueous solution obtained from the hydrolysis of the β-keto ester was added to the vigorously fermenting mixture. Stirring was continued for another 48 h at 25 °C, and the reaction was monitored by TLC (petroleum ether:diethyl ether:acetic acid = 60:40:1). Celite (290 g) was added, and the mixture was stirred for another 30 min and then filtered through a Celite pad. The filtrate was extracted once with $CHCl_3$ (100 mL) and the organic phase discarded. The solution was acidified to pH 2 with concd HCl, and the aqueous phase was extracted with $CHCl_3$ (4 × 100 mL). The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure, furnishing 3.01 g of a yellowish solid. The solid was purified by silica gel flash chromatography (petroleum ether: diethyl ether:acetic acid = 60:40:1), obtaining 2.90 g of a white solid (53% yield, mp 74–76 °C).

The enantiomeric excess of (3*R*)-3-hydroxy-6-methyl-6-heptenoic acid [(−)-**2**] was estimated to be >95% by GLC analysis performed after esterification with diazomethane and acetylation. The enantiomer separation was achieved on a Megadex 5 column (silica fused, 25 m × 0.25 mm) containing dimethyl-*n*-pentyl-β-cyclodextrin in OV 1701 from Mega S.n.C.: carrier gas: helium, 80 kPa; temperature: iso 110 °C; retention time: 27.33 min; $[\alpha]^{24}_D$ −19.8° (*c* 1.09; $CHCl_3$); ^1H NMR δ 7.32 (bs, 2H), 4.72 (m, 2H), 4.07 (m, 1H), 2.59 (dd, 1H, J_{AB} = 16.0, *J* = 4.0), 2.51 (dd, 1H, J_{AB} = 16.0, 8.2), 2.14 (m, 2H), 1.74 (s, 3H), 1.68 (m, 2H) ppm; ^{13}C NMR δ 177.0, 145.5, 110.7, 68.2, 41.3, 34.8, 33.8, 22.2 ppm. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.81; H, 9.01.

(±)-1-Methyl-*cis*-bicyclo[3.2.0]hept-3-en-6-one (1). A 50 mL flask equipped with a reflux condenser fitted with a $CaCl_2$ tube was charged with (3*R*)-3-hydroxy-6-methyl-6-heptenoic acid [(−)-**2**, 2.00 g, 12.7 mmol), potassium acetate (4.98 g, 50.8 mmol, 4 equiv), and acetic anhydride (25 mL). The reaction mixture was magnetically stirred at ambient temperature for 2 h. The temperature was then raised to reflux and the reaction course monitored by GLC. After 45 min the reaction was complete, and the mixture was cooled to room temperature and added to light petroleum ether (100 mL) in a 250 mL flask equipped with a condenser. Water (50 mL) was added, and the mixture was magnetically stirred for 12 h at ambient temperature. The organic layer was separated, washed with an aqueous solution of $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed by distillation at ambient pressure to avoid loss of product. A crude product was collected, which was purified by silica gel flash chromatography (petroleum ether:diethyl ether = 95:5) affording 1.41 g (yield 91%) of a pale yellow oil.

The GLC analysis of compound **1** revealed a 1:1 mixture of two enantiomers: The enantiomer separation was obtained on a Megadex 5 column (silica fused, 25 m × 0.25 mm) containing dimethyl-*n*-pentyl-β-cyclodextrin in OV 1701 from Mega S.n.C.: carrier gas: helium, 80 kPa; temperature: 80–120 °C (1.5 °C/min); retention time: 6.71 and 7.07 min; $[\alpha]^{24}_D$ 0.00° (*c* 1.22; $CHCl_3$); IR (liquid film) ν 3059, 1780, 1602, 1443 cm^{-1}; ^1H NMR δ multiplets centered at 5.85 (1H), 5.58 (1H), 3.80 (1H); 2.52 and 2.44 (AB system, *J* = 18.0, further coupled with C3H, *J* = 2.7, 4.5, 2H), 2.62 (m, 2H), 1.42 (s, 3H); ^{13}C NMR δ 209.4, 134.3, 126.3, 78.2, 59.3, 47.9, 35.2, 24.4 ppm. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.59; H, 8.25.

Acknowledgment. This research was supported in part by research grants from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy; the Consiglio Nazionale delle Ricerche (CNR), Italy, and the Progetto Finalizzato Chimica Fine II of CNR, Italy.