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A Formal Synthesis of Sirenin

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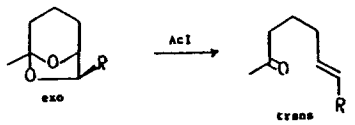
Cleavage of *exo*-7-substituted-6,8-dioxabicyclo[3.2.1]octanes with acetyl iodide results in the predominance of the *trans* alkene product. This bicyclic ketal fragmentation methodology is utilized to a formal synthesis of sirenin.

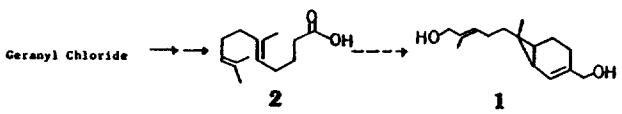
Introduction

Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane show unique feature in organic chemistry. Many insect pheromones, such as frontalin,[1] brevicomin,[2] and multistriatin,[3] have this kind of bicyclic ketal skeleton. Cleavage of these bicyclic ketals with acetyl iodide gives δ, ε-unsaturated ketones, that is also related to natural products such as the Douglas fir tussock moth pheromone[4] and solenopsin A.[5] It has been observed that the cleavage of exo-7-substituted bicyclic ketals results in formation of the *trans* alkene product.[6] (Scheme 1)



Scheme 1

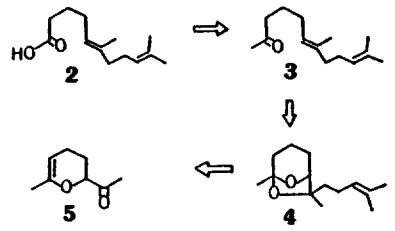
Sirenin(**1**) is a sperm attractant produced by the female gametes of the water mold *Allomyces*.[7] 6,10–Dimethyl-5,9-nonadienoic acid(**2**) has been known to be a useful intermediate in the synthesis of sirenin by Grieco(Scheme 2).[8] We would like to report a facile preparation of **2** as a formal synthesis of sirenin to demonstrate the utility of the bicyclic ketal fragmentation methodology.



Scheme 2

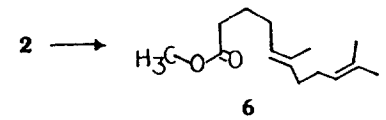
Results and Discussion

The intermediate **2** has a δ, ε-unsaturated ketone with a *trans* double bond, making this a prime target molecule for the application of the bicyclic ketal fragmentation protocol. The carboxylic acid moiety of **2** might be available from the methyl ketone of 7,11-dimethyldodeca-6,10-diene-2-one(**3**) by the reaction of haloform and also, **3** is the fragmentation product from 5,7-dimethyl-7-(4-methyl-3-pentene)-6,8-dioxabicyclo[3.2.1]octane(**4**). It is apparant that the compounds are intermediates by the retrosynthetic analysis shown in Scheme 3.



Scheme 3

To prepare the ketal **4**, 2-acetyl-6-methyl-3,4-dihydro-2H-pyran(**5**) was added to a solution of 4-methyl-3-pentenylmagnesium bromide in dry ether and the resulting alcohol was cyclized by adding 5% aqueous HCl solution. The *exo* and *endo* isomers of **4** were obtained in the ratio of 84:16 in 72% yield. The major *exo* isomer is the correct starting material for making the *trans* isomer of **3** by fragmentation. Cleavage with acetyl iodide gave the expected fragmentation product **3** in 20% yield. This was treated with a KI-I_2 reagent to give a positive yellow precipitate(CHI_3) which has a melting point of 119-121 °C. Due to low yield of the iodoform oxidation, we could not obtain a preparatively useful amount of **2**. Thus, the product was converted to the methyl ester **6** and characterized only by high resolution mass spectrometer. (Sheme 4)



6

Scheme 4

Experimental

Reported boiling point and melting point are uncorrected. All NMR spectra were recorded on a Bruker 250 MHz FT-NMR using TMS as an internal standard. Mass spectra were obtained by use of a VG MM16 mass spectrometer and accurate mass data were obtained by use of a VG 7070 high resolution mass spectrometer. IR spectra were taken on a Beckmann IR-5 spectrometer. GLC analysis were performed using a Varian Aerograph series 2700 gas chromatograph equipped with 11'×1/4", 10% OV-17 column. No effort was made to improve the yields.

2-Acetyl-6-methyl-3,4-dihydro-2H-pyran(**5**). A solution of 100m*l* (1.20 mole) of methyl vinyl ketone (3-butene-2-one), 0.5g of hydroquinone and 50m*l* of benzene was placed in a steel pressure bomb and heated at 175 °C for 3 hours. After cooling, the solvent was removed by a rotatory evaporator and the product was distilled(water aspirator). Collection from 74-77 °C gave 56.5g (0.40 mole) of a clear, colorless liquid (67% yield).

^{1}H NMR($CDCl_3$): δ (ppm) 4.46(1H, m), 4.13(1H,m), 2.13(3H, s), 1.88 and 1.76(7H, m with two prominant peaks).

Exo/endo-5,7-Dimethyl-7-(4-methyl-3-pentene)-6,8-dioxabicyclo[3.2.1]octane(**4**). 5-Bromo-2-methyl-2-pentene(2.0g, 0.012 mole) was slowly added to 0.30g (0.012 mole) of magnesium in 30m*l* of dry ether at room temperature under nitrogen. The reaction mixture was stirred at 0 °C for 2 hours until a dark gray solution formed, at which point 1.4g (0.010 mole) of MVK dimer **5** in 10m*l* of dry ether was slowly added via syringe and stirred 10 hours at rom temperature. 20m*l* of 5% aqueous HCl was added and the reaction mixture was extracted with ether. The extracts were washed with brine, dried over anhydrous magnesium sulfate and reduced in vacuo to give 1.6g(0.0070 mole) of liquid (72% yield). GLC analysis of the product showed that the exo:endo isomeric ratio was 84;16.

^{1}H NMR($CDCl_3$) of exo-**4**: δ(ppm) 5.09(1H, br t,J = 7Hz), 3.92(1H, br d,J = 3.4Hz), 2.15-1.45(10H, m), 1.66(3H, s), 1.59(3H, s), 1.40(3H, s), 1.33(3H, s).

^{13}C NMR($CDCl_3$) of exo-**4**: δ (ppm) 131.3(s), 124.4(d), 107.1(s), 82.9(s), 79.9(d), 41.3(t), 34.2(t), 25.7(t), 25.6(q), 24.2(t) 23.1(q), 17.9(q), 17.5(t), 17.3(q).

MS of exo-**4**: 224(M^+), 164, 142, 121, 113, 98, 93, 82, 69, 55, 43(base).

HRMS of exo-**4**: Calcd for $C_{14}H_{24}O_2$: 224.1776. Observed: 224.1764.

IR of exo-**4**(neat): 2907, 1379, 1241, 1198, 1176, 1105, 1041 $Cm.^{-1}$

^{1}H NMR($CDCl_3$) or endo-**4**: δ(ppm) 5.11(1H, br t), 3.88(1H, br d), 2.15-1.45(10H, m) 1.67(3H, s), 1.60(3H, s), 1.41(3H, s), 1.26(3H, s).

MS of endo-**4**: 224(M^+), 182, 164, 141, 135, 121, 107, 98, 93, 81, 67, 55, 43(base).

HRMS of endo-**4**: Calcd fo $C_{14}H_{24}O_2$: 224.1776. Observed: 224.1766.

Trans-7,11-Dimethyldodeca-6,10-diene-2-one(**3**). A solution of 0.17g (0.00076 mole) of the bicyclic ketal **4** in 10m*l* of acetonitrile was subjected to the general cleavage procedure by using acetyl iodide[6] to give 0.032g(0.00015 mole) of reaction product. GLC analysis, by using capillary column (SE-30), confirmed the product **3**, but it was difficult to separate the pure **3**(20% yield).

MS: 208(M^+), 193, 175, 150, 135, 123, 119, 107, 95, 79, 67, 43(base).

HRMS: Calcd for $C_{14}H_{24}O$: 208.1827. Observed: 208.1822.

6,10-Dimethyl-5,9-nonadienoic acid(**2**) and Methyl 6,10-dimethyl-5,9-nonadienoate(**6**). The crude mixture (0.11g) of **3** was dissolved in 2m*l* of water and 1m*l* of dioxane to produce a homogeneous solution. Addition of 1m*l* of 10% NaOH and the KI-I_2 reagent dropwise was followed by shaking until a definite dark color of iodine persisted. The mixture was heated in water bath(60 °C) for 2 minutes. Excess iodine was removed by the addition of few drops of NaOH solution then dilute with water and allowed to stand 15 minutes. The yellow precipitate(CHI_3) was filtered and shown to have melting point at 119-121 °C. The filtrate was acidified and extracted with ether. Evaporation of the solvent gave a crude acid which was not purified, but was refluxed in 10m*l* of methanol with 10 drops of sulfuric acid for 1 hour. The methanol was evaporated and 20m*l* of water was added and extracted with ether. After drying over $MgSO_4$, evaporation of solvent gave 15mg of crude product.

MS of **6**: 224(M^+), 209(base), 168, 135, 123, 95, 69, 55, 41.

HRMS of **6**: Calcd for $C_{14}H_{24}O_2$: 224.1776. Observed: 224.1805.

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