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Synthesis of Methyl Substituted Bicyclo[3.2.0]hept-3-en-6-ones and 3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones.

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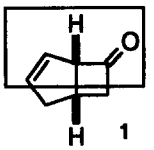
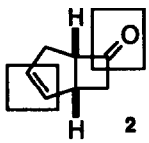
Abstract: Treatment of methyl mono- or bisubstituted 3-hydroxy-6-alkenoic acids in acetic anhydride and potassium acetate give the corresponding bicyclo[3.2.0]hept-3-en-6-ones in fair to good yields. This reaction appears to be of general applicability to prepare the methyl derivatives in all the positions of the five membered ring. The synthesis of 4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-one (filifolone) by an efficient bicyclization of 3-hydroxy-3-methyl-6-heptenoic acid followed by the geminal dimethylation of the intermediate 4-methylbicyclo[3.2.0]hept-3-en-6-one is reported. The latter reaction proved to be a general method when performed on bicyclo[3.2.0]hept-3-en-6-ones and on bicyclo[3.2.0]hept-2-en-6-one. 3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones, important starting materials in the synthesis of linear condensed triquinane sesquiterpenes, have been prepared in an efficient manner by the easy bicyclization of 3-hydroxy-6-heptenoic acids, followed by a Baeyer-Villiger oxidation of the bicyclo[3.2.0]hept-3-en-6-one intermediates.

Bicyclo[3.2.0]hept-3-en-6-one (**1**) and its derivatives have considerable potential in synthesis, since they could act as precursors of a wide variety of complex molecules. They are available by intramolecular [2+2] cyclization of an *in situ* generated unsaturated ketene with a peripheral olefinic residue.[1] The functional groups (C=C and C=O) in compound **1**, each located on a different cycle of a rigid molecule with two asymmetric centres, are both important. In addition to the classical reactivity of the two isolated groups, they could show a peculiar behaviour due to the combination of both the groups through a bridge headed carbon atom. On these bases the potential reactivity of compound **1** could result more rich and versatile with respect to that showed by the isomeric bicyclo[3.2.0]hept-2-en-6-one (**2**) and its derivatives, well known as important starting materials for the synthesis of prostaglandins[2] and of several other important natural products.[3]



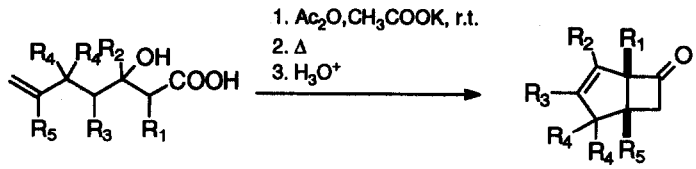
1



2

Recently, we have reported that bicyclo[3.2.0]hept-3-en-6-ones (**1**) can be prepared by treatment of 3-hydroxy-6-alchenoic acids (**3**) with potassium acetate in acetic anhydride, firstly at room temperature for two hours and then in reflux conditions for two-four hours (Scheme 1).[4] This procedure allowed the preparation in high yield (82 %) and in 100 g scale of 1,4-dimethylbicylco[3.2.0]hept-3-en-6-one (**1g**), key intermediate for the stereoselective synthesis of racemic grandisol and lineatin, two cyclobutane monoterpenes well konwn as components of pheromonic lures of important insects.[4] We have extended the reaction to other 3-

hydroxy-6-alchenoic acids to verify if this bicyclization reaction may be considered of general applicability and, to begin studies aimed to devise convenient utilizations of these compounds in the synthesis of complex molecules.

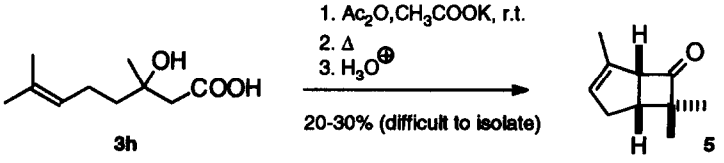


3 : R_1, R_2, R_3, R_4, R_5 = H	**1** : 62%
3a: R_1 = CH_3; R_2, R_3, R_4, R_5 = H	**1a**: 63%
3b: R_3 = CH_3; R_1, R_2, R_4, R_5 = H	**1b**: 63%
3c: R_5 = CH_3; R_1, R_2, R_3, R_4 = H	**1c**: 78%
3d: R_2 = CH_3; R_1, R_3, R_4, R_5 = H	**1d**: 79%
3e: R_3, R_5 = CH_3; R_1, R_2, R_4 = H	**1e**: 55%
3f: R_4 = CH_3; R_1, R_2, R_3, R_5 = H	**1f**: 48%
3g: R_2, R_5 = CH_3; R_1, R_3, R_4 = H	**1g**: 82%

Scheme 1: Bicylization of 3-hydroxy-6-heptenoic acids (**3-3g**) into bicyclo[3.2.0]hept-3-en-6-ones (**1-1g**).

Scheme 1 summarizes the results obtained working in standard conditions. 3-Hydroxy-alchenoic acids (**3-3g**) were obtained by Reformatsky reaction performed according to the procedure reported by Rathke and Lindert,[5] or by reaction of the dianion of ethyl or methyl acetoacetate with an allyl halide,[6] followed by the chemoselective reduction with sodium borohydride in methanol of the 3-ketoester intermediate. The saponification of 3-hydroxyesters was always accomplished by treatment with methanolic solution of potassium hydroxide for 12-24 h at room temperature.

As depicted in Scheme 1, bicyclo[3.2.0]hept-3-en-6-ones substituted in every position of the five membered ring can be prepared in fair to good yield in isolated product. Indeed, yields may be significantly higher since the volatility of these product makes the isolation difficult without losses.

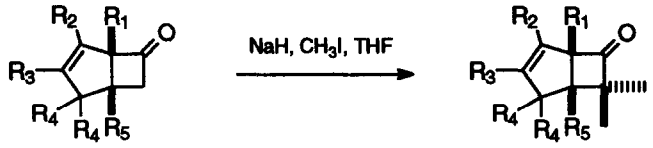


3h

However, it was observed that 3,7-dimethyl-3-hydroxy-6-octenoic acid (**3h**) gave a multitude of products: among them it was possible to identify, by gas-liquid chromatography (GLC), the 4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-one (**5**, filifolone[7]) only in 20-30% yield and its isolation and purification resulted very difficult.

Synthesis of geminal C7-dimethyl derivatives of bicyclo[3.2.0]hepten-6-ones.

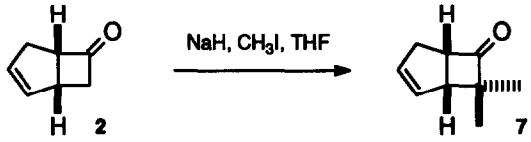
To overcome this limit, we have addressed the problem of the geminal dimetylation of C7 of bicylco[3.2.0]hept-3-en-6-ones. This conversion has been performed through the generation of thermodinamically more stable enolates with sodium hydride in tetrahydrofuran in the presence of an excess of methyl iodide. Neither self-condensation or ring openig was observed. Potassium hydride, described as more reactive and efficient,[8] gave worse results. Metal amides were avoided since the equivalent of amine which forms during the metalation would react with methyl iodide.



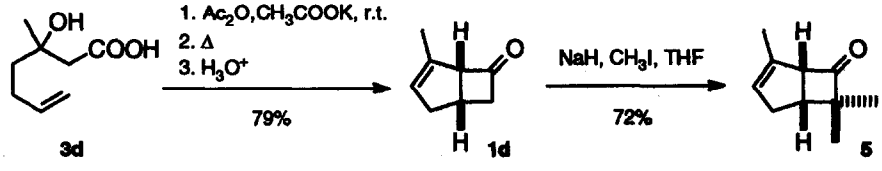
1 : R_1, R_2, R_3, R_4, R_5 = H — **6**: 58%
1a: R_1 = CH_3; R_2, R_3, R_4, R_5 = H — **6a**: 38%
1b: R_3 = CH_3; R_1, R_2, R_4, R_5 = H — **6b**: 41%
1c: R_5 = CH_3; R_1, R_2, R_3, R_4 = H — **6c**: 59%
1d: R_2 = CH_3; R_1, R_3, R_4, R_5 = H — **5**: 72%
1e: R_3, R_5 = CH_3; R_1, R_2, R_4 = H — **6e**: 75%
1f : R_4 = CH_3; R_1, R_2, R_3, R_5 = H — **6f**: 50%
1g: R_2, R_5 = CH_3; R_1, R_3, R_4 = H — **6g**: 62%

Scheme 2. Geminal C7 methylation of bicyclo[3.2.0]hept-3-en-6-ones **1-1g**.

The yields of isolated pure compounds obtained from several bicyclo[3.2.0]hept-3-en-6-ones (**1-1g**) and from the isomeric bicyclo[3.2.0]hept-2-en-6-one (**2**), a classical precursor in prostaglandine synthesis, demonstrate that the one-step introduction of two methyl groups on the C7 may be considered as a general reaction (Scheme 2).



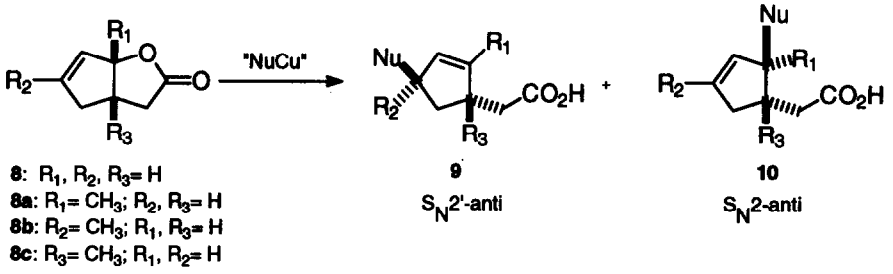
The efficient preparation of 4-methylbicyclo[3.2.0]hept-3-en-6-one (**1d**) followed by the geminal C7 dimethylation is a new and practical route to racemic filifolone (**5**).[9]



These results could be better appreciated considering the well documented lability of β,γ-unsaturated bicyclic cyclobutanones when treated with a base[10] and the possible utilizations of 7,7-disubstituted bicyclo[3.2.0]heptan-6-ones, bicyclo[3.2.0]hept-2-en-6-ones and bicyclo[3.2.0]hept-3-en-6-ones in synthesis.[6c,11,12]

Synthesis of methyl substituted 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones.

In 1986, Curran et al.[13] reported a very efficient reaction with high regiocontrol in the opening of 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones (**8**-**8c**) with organocopper reagents. They observed that the opening of vinyl lactones **8** by lithium dialkyl cuprates was controlled largely by the location of the substituents. In contrast, the reaction with "RCu"/$MgBr_2$ provided an operationally simple method to effect the S_N2'-anti opening of vinyl lactones **8**-**8c** with good to excellent regioselectivity (Scheme 3).



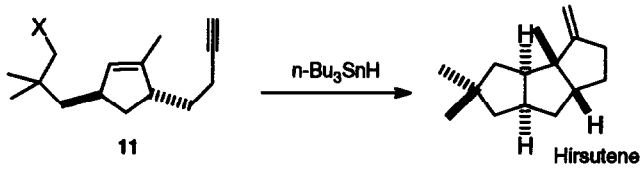
8: R_1, R_2, R_3= H
8a: R_1= CH_3; R_2, R_3= H
8b: R_2= CH_3; R_1, R_3= H
8c: R_3= CH_3; R_1, R_2= H

9
S_N2'-anti

10
S_N2-anti

Scheme 3. Regio- and stereochemical control in organocopper-promoted opening of 2*H*-cyclopenta[*b*]furan-2-ones.

This reaction was essential in the construction of trans-3,5-disubstituted-cyclopentenes such as **11**, versatile precursors for a tandem radical cyclization to produce linear condensed triquinane sesquiterpenes such as hirsutene,[14,15] $\Delta^{9(12)}$-capnellene,[16] hypnophilin, and coriolin.[17] The Curran procedure is very elegant and efficient and therefore had served as the key step in several other syntheses.[18,19,20]

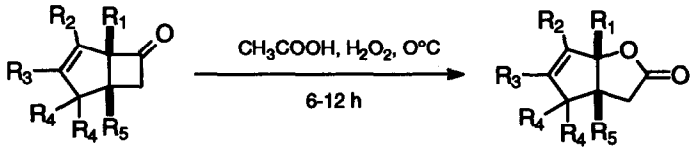


11

Hirsutene

It should be noted however that the preparation of the starting vinyl lactones is a long and time consuming sequence. Although the vinyl lactone **8** is readily available from norbornenone by Baeyer-Villiger oxidation followed by an acid catalysed rearrangement,[21] the preparation of vinyl lactones **8a**[16,17] and **8b**[18] stems on a synthetic sequence consisting into (i) Luche reduction ($NaBH_4$, $CeCl_3$) of 2- or 3-methylcyclopentenone, (ii) acetylation, (iii) Ireland ester enolate Claisen rearrangement *via* the *t*-butyldimethylsilyl ketene acetal, (iv) phenylselenolactonization, (v) oxidation, and finally (vi) elimination. On the other hand, the vinyl lactone **8c** has been prepared[18] by opening compound **8** with MeMgBr/CuBr·Me_2S, followed by a standard iodolactonization and a base promoted elimination with DBU.

The convenient preparation of bicyclo[3.2.0]hept-3-en-6-ones **1-1g** open a new route to 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones **8-8c**. It consists of the bicyclization reaction of 3-hydroxy-6-heptenoic acids into the corresponding bicyclo[3.2.0]hept-3-en-6-ones, followed by regioselective Baeyer-Villiger oxidation of them to generate the vinyl lactones.[22] The conversion of bicyclo[3.2.0]hept-3-en-6-ones **1-1g** into **8-8c** was carried out with 30% hydrogen peroxide in 90% acetic acid at 0°C for 6-12 h (Scheme 4).



1 : R_1, R_2, R_3, R_4, R_5 = H	**8**: 95%
1a: R_1 = CH_3; R_2, R_3, R_4, R_5 = H	**8a**: 82%
1b: R_3 = CH_3; R_1, R_2, R_4, R_5 = H	**8b**: 91%
1c: R_5 = CH_3; R_1, R_2, R_3, R_4 = H	**8c**: 95%
1d: R_2 = CH_3; R_1, R_3, R_4, R_5 = H	**8d**: 92%
1e: R_3, R_5 = CH_3; R_1, R_2, R_4 = H	**8e**: 91%
1f : R_4 = CH_3; R_1, R_2, R_3, R_5 = H	**8f**: 80%
1g: R_2, R_5 = CH_3; R_1, R_3, R_4 = H	**8g**: 95%

Scheme 4. Conversion of bicyclo[3.2.0]hept-3-en-6-ones **1-1g** into 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones **8-8g**.

The results obtained so far indicate this to be a general procedure, superior to the more traditional methods used to prepare 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (**8**) and its 3a-, 5- and 6a-methyl derivatives (**8a-c**) and to the last reported procedures to unsaturated bicyclic lactones.[23,24]

Further prospects for the utilization of bicyclo[3.2.0]hept-3-en-6-ones in organic synthesis are currently under investigation.

EXPERIMENTAL SECTION.

General. Melting points were obtained with a Buchi apparatus and are uncorrected. Yields are referred 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 4Å molecular sieves. All air-sensitive reactions were run under nitrogen.

Materials. The esters of 3-hydroxy-6-heptenoic acids **3d, 3f-3h** used as starting materials were prepared in good yields by a Reformatsky reaction performed according to the procedure of Rathke and Linder.[5] The esters of 3-hydroxyhept-6-enoic acids **3, 3a-3c, and 3e** were prepared by alkylation of the dianion of ethyl acetoacetate according to the procedure of Huckin and Weiler,[6] followed by chemioselective reduction of the carbonyl group with $NaBH_4$ in methanol. Acetic anhydride, potassium acetate, sodium

hydride, acetic acid, hydrogen peroxide, *n*-butyllithium, zinc dust, trimethylborate, ethyl acetoacetate, methyl propionylacetate, ethyl 2-methylacetoacetate, ethyl bromoacetate, 4-pentenal, 5-hexen-2-one, 5-methyl-5-hexen-2-one, allyl bromide, metallyl chloride, and methyl iodide, are commercial materials. 3,3-Dimethyl-4-pentenal has been prepared according to the procedure of Vogel and Buchi.[25]

Preparation of 3-hydroxyhept-6-enoic acids* 3-3h *by alkaline hydrolysis. General Procedure.

The ester (0.1 mol) was dissolved in a 10% methanolic solution of KOH (200 ml) and allowed to stand at room temperature. The hydrolysis was complete after two days. The methanol was evaporated at reduced pressure and the residue was dissolved with water (50 ml) and extracted with ether (3x 30 ml). Then, the basic aqueous solution of the salt was acidified with 1M HCl and extracted with ether (3x 50 ml). These latter ethereal extracts were washed with water and brine, dried (Na_2SO_4). The evaporation at reduced pressure furnished the compound (**3-3h**, 88-95% yield) that could be used without further purification.

3-Hydroxy-6-heptenoic Acid (3). As an oil. ^1H NMR: δ 7.3 (bs, 2H, disappears by D_2O exchange), 5.96-5.74 (m, 1H), 5.12-4.94 (m, 2H), 4.04 (m, 1H), 2.48 (AB system, 2H, J = 16 further coupled with C3H, J = 5 , and J = 9), 2.32-2.04 (m, 2H), 1.72-1.45 (m, 2H). ^{13}C NMR: δ 177.29, 138.19, 115.39, 68.14, 41.62, 36.08, 29.23.

Anal. Calcd for $C_7H_{12}O_3$: C, 65.60; H, 9.44. Found: C, 6.45; H, 9.57.

3-Hydroxy-2-methyl-6-heptenoic Acid (3a). As an oil. ^1H NMR: δ 6.76 (bs, 2H, disappears by D_2O exchange), 5.91-5.70 (m, 1H), 5.12-4.90 (m, 2H), 4.05-3.68 (m, 1H), 2.65-2.43 (m, 1H), 2.37-2.01 (m, 2H), 1.75-1.31 (m, 2H), 1.20 (d, 3H, J = 7.2).^{13}C NMR: δ 180.02, 138.45, 115.45, 73.22, 45.91, 33.75, 30.02, 14.33.

Anal. Calcd for $C_8H_{14}O_3$: C, 67.57; H, 9.92. Found: C, 67.38; H, 9.82

3-Hydroxy-4-methyl-6-heptenoic Acid (3b). As an oil. ^1H NMR: δ 4.88 (bs, 2H, disappears by D_2O exchange), 4.74 (m, 2H), 4.07-3.81 (m, 2H), 2.53 (m, 2H), 2.31-2.15 (m, 1H), 1.97-1.75 (m, 2H), 1.73 (s, 3H), 0.90 (d, 3H, J = 6.6).^{13}C NMR: δ 177.08, 137.15, 116.70, 71.89, 38.88, 38.19, 36.99, 13.91.

Anal. Calcd for $C_8H_{14}O_3$: C, 67.57; H, 9.92. Found: C, 67.45; H, 9.94.

3-Hydroxy-3-methyl-6-heptenoic Acid (3c). As an oil. ^1H NMR: δ 7.3 (bs, 2H, disappears by D_2O exchange), 5.92-5.70 (m, 1H), 5.09-4.92 (m, 2H), 2.55 (AB system, 2H, J = 16.0), 2.22-2.08 (m, 2H), 1.72-1.60 (m, 2H), 1.30 (s, 3H). ^{13}C NMR: δ 176.75, 138.69, 115.14, 71.94, 45.21, 41.30, 28.59, 26.80.

Anal. Calcd for $C_8H_{14}O_3$: C, 67.57; H, 9.92. Found: C, 67.35; H, 9.87

3-Hydroxy-6-methyl-6-heptenoic Acid (3d). Mp = 34-36°C. ^1H NMR: δ 7.3 (bs, 2H, disappears by D_2O exchange), 4.72 (m, 2H), 4.20 (m, 1H), 2.48 (AB system, 2H, J = 16 further coupled with C3H, J = 5 , and J = 9), 2.28-1.98 (m, 2H), 1.70-1.55 (m, 2H), 1.72 (s, 3H). ^{13}C NMR: δ 173.67, 145.61, 110.65, 71.76, 52.13, 41.76, 34.88, 34.06, 22.83.

Anal. Calcd for $C_8H_{14}O_3$: C, 67.57; H, 9.92. Found: C, 67.43; H, 10.03.

4,6-Dimethyl-3-hydroxy-6-hepetenoic Acid (3e). As an oil. ^1H NMR: δ 4.88 (bs, 2H, disappears by D_2O exchange), 4.74 (m,2H), 4.07-3.81 (m, 1H), 2.53 (m, 2H), 2.31-2.15 (m, 1H), 1.97-1.75 (m, 2H), 1.73 (s, 3H), 0.90 (d, 3H, J =6.6). ^{13}C NMR: δ 177.88, 144.30, 112.73, 72.11, 41.75, 38.85, 36.14, 22.25, 15.00.

Anal. Calcd for $C_9H_{16}O_3$: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.43.

5,5-Dimethyl-3-hydroxy-6-heptenoic Acid (3f). Mp = 49-51°C. ^1H NMR: δ 7.23 (bs, 2H, disappears by D_2O exchange), 5.87 (dd, 1H, J = 17.2, J = 10.5), 5.17-4.91 (m, 2H), 4.23-4.09 (m, 1H), 2.50 (d, 2H, J = 6.4), 1.63 (dd, 1H, J = 14.5, J = 8.4), 1.46 (dd, 1H, J = 14.5, J = 2.5). ^{13}C NMR: δ 177.34, 148.70, 11.51, 66.30, 49.23, 42.72, 37.31, 27.50, 27.20.

Anal. Calcd for $C_9H_{16}O_3$: C, 69.19; H, 10.32. Found: C, 69.25; H, 10.47.

3,6-Dimethyl-3-hydroxy-6-heptenoic Acid (3g). As an oil. ^{1}H NMR: δ 7.3 (bs, 2H, disappears by D_2O exchange), 4.72 (bs, 2H), 2.59 (AB system, 2H, J = 15.0), 2.20-2.03 (m, 2H), 1.80-1.65 (m, 2H), 1.74 (s, 3H), 1.32 (s, 3H).

Anal. Calcd for $C_9H_{16}O_3$: C, 69.19; H, 10.32. Found: C, 69.18; H, 10.45. ^{13}C NMR: δ 177.34,

6,7-Dimethyl-3-hydroxy-6-octenoic Acid (3h). As an oil. ^{1}H NMR: δ 7.49 (bs, 2H, disappears by D_2O exchange), 5.10 (m, 1H), 2.57 (AB, 1H, J =15.6), 2.51 (AB, 1H, J = 15.6), 2.16-1.95 (m, 2H), 1.68 (s,3H), 1.60 (s,3H), 1.73-1.51 (m, 2H), 1.29 (s, 3H). ^{13}C NMR: δ 176.92, 145.83, 110.56, 71.83, 44.92, 41.67, 38.10, 26.62, 22.32, 21.94.

Anal. Calcd for $C_{10}H_{18}O_3$: C, ; H, . Found: C, ; H, .

Bicyclization of 3-hydroxy-6-alkenoic acids* 3-3h. *General Procedure.

3-Hydroxy acid (**3-3h**, 50 mmol), acetic anhydride (40 ml) and potassium acetate (10.0 g) were charged into a 100 ml flask equipped with a reflux condenser fitted with a $CaCl_2$ tube. The reaction mixture was left under magnetic stirring at ambient temperature for 2 h. The temperature was then rised and the reaction mixture was mantained at reflux (4 h). After cooling at room temperature, the reaction mixture was 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 kept under magnetic stirring for 12 h at ambient temperature. The organic layer was separated in a separatory funnel, washed with 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, by flash column chromatography or by distillation at reduced pressure, gave bicyclic ketone **1-1h.**

Bicyclo[3.2.0]hept-3-en-6-one (1). Compound **1** (3.35 g, 62 % yield) was obtained pure by flash cromatography eluting with 95:5 petroleum ether/ ether. IR (liquid film): ν 3059, 1780, 1602, 1443 cm^{-1}. ^{1}H NMR: δ 5.96-5.88 (m, 1H), 5.66-5.56 (m, 1H), 4.32-4.20 (m, 1H), 3.32-3.14 (m, 1H), 2.82-2.72 (m, 3H), 2.56-2.37 (m, 1H). ^{13}C NMR: δ 208.29, 133.90, 125.86, 74.09, 53.52, 40.60, 25.96.

Anal. Calcd for C_7H_8O: C, 77.74; H, 7.46. Found: C, 77.78; H, 7.38.

5-Methylbicyclo[3.2.0]hept-3-en-6-one (1a). Compound **1a** (3.84 g, 63 % yield) was obtained pure by flash chromatography eluting with 95:5 petroleum ether/ ether. IR (liquid film): ν 2963, 2922, 1773 cm^{-1}. ^{1}H NMR: δ 5.85 (m, 1H), 5.45 (m, 1H), 3.19 (dd, 1H, J = 17.7, J = 8.9), 2.91 (ddd, 1H, J = 17.7, J = 7.5, J = 2.6, J = 2.0), 2.75 (dd, 1H, J = 17.7, J = 5.8), 2.48 (m, 2H), 1.30 (s, 3H). ^{13}C NMR: δ 210.87, 132.31, 131.31, 79.89, 51.16, 40.58, 33.39, 16.95.

Anal. Calcd for $C_8H_{10}O$: C, 78.64; H, 8.26. Found: C, 78.51; H, 8.33

3-Methylbicyclo[3.2.0]hept-3-en-6-one (1b). Compound **1b** (3.80 g, 63 % yield) was obtained pure by flash chromatography eluting with 9:1 petroleum ether/ ether. IR (liquid film): ν 2914, 1777 cm^{-1}. ^{1}H NMR: δ 5.10 (m, 1H), 4.11 (m,1H), 3.20-2.96 (m, 1H), 2.81-2.53 (m, 2+1H), 1.69 (s, 3H). ^{13}C NMR: δ 208.24, 144.26, 119.72, 73.97, 53.36, 44.66, 26.78, 16.44.

Anal. Calcd for $C_8H_{10}O$: C, 78.64; H, 8.26. Found: C, 78.54; H, 8.31.

1-Methylbicyclo[3.2.0]hept-3-en-6-one (1c). Compound **1c** (4.76 g, 78 % yield) was obtained pure by flash chromatography eluting with 95:5 petroleum ether/ ether. IR (liquid film): ν 3059, 1780 cm^{-1}. ^{1}H 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 and J = 4.5, 2H), 2.62 (m, 2H), 1.42 (s, 3H). ^{13}C NMR: δ 209.4, 134.32, 126.35, 78.25, 59.34, 47.89, 35.17, 24.44.

Anal. Calcd for $C_8H_{10}O$: C, 78.64; H, 8.26. Found: C, 78.67; H, 8.31.

4-Methylbicyclo[3.2.0]hept-3-en-6-one (1d). Compound **1d** (4.82 g, 79 % yield) was obtained pure by flash chromatography eluting with 9:1 petroleum ether/ ether. IR (liquid film): ν 2915, 2852, 1779 cm^{-1}. ^{1}H NMR: δ 5.47 (m, 1H), 4.04 (m, 1H), 3.35-3.15 (m, 1H), 2.83 (m, 2H), 2.77 (m, 1H), 2.46- 2.30 (m, 1H), 1.75 (s, 3H). ^{13}C NMR: δ 207.04, 135.53, 126.89, 76.81, 53.82, 40.63, 27.25, 15.46.

Anal. Calcd for $C_8H_{10}O$: C, 78.64; H, 8.26. Found: C, 78.71; H, 8.34.

1,3-Dimethylbicyclo[3.2.0]hept-3-en-6-one (1e). Compound **1e** (3.74 g, 55 % yield) was obtained pure by flash chromatography eluting with 9:1 petroleum ether/ ether. IR (liquid film): ν 2919, 1718 cm^{-1}. ^1H NMR: δ 5.18 (m, 1H), 3.70 (m, 1H), 3.06 (dd, 1H, J = 17.5, J = 2.8), 2.83 (dd, 1H, J = 17.4, J = 4.5), 2.49 (m, 2H), 1.76 (s, 3H), 1.37 (s, 3H). ^{13}C NMR: δ 209.33, 144.65, 120.19, 78.01, 59.00, 51.66, 35.57, 24.36, 16.83.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.43; H, 8.75.

2,2-Dimethylbicyclo[3.2.0]hept-3-en-6-one (1f). Compound **1f** (3.26 g, 48 % yield) was obtained pure by flash chromatography eluting with 95:5 petroleum ether/ ether. IR (liquid film): ν 2919,1718 cm^{-1}. ^1H NMR: δ 5.66 (dd, 1H, J = 5.4, J = 2.2), 5.47 (dd, 1H, J = 5.4, J = 2.6), 4.20 (m, 1H), 3.13 (ddd,1H, J = 17.9, J = 6.3, J = 3.1), 2.88 (ddd, 1H, J = 17.9, J = 8.4, J= 4.4), 2.54 (ddd, 1H, J = 8.6, J = 6.2, J = 6.1), 1.18 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: δ 206.64, 144.75, 123.55, 73.22, 47.37, 41.50, 37.56, 30.64, 21.16.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.33; H, 8.84.

1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one (1g). Compound **1g** was obtained (5.58 g, 82 % yield) by bulb to bulb distillation (bp $_{60mmHg}$ 130°C) with only 4 % of the exocyclic isomer, 1-methyl-4-metilidenebicyclo[3.2.0]heptan-6-one. IR (liquid film): ν 2915, 2852, 1776 cm^{-1}. ^1H NMR: δ 5.45 (m, 1H), 3.58 (m, 1H), 3.04 and 2.86 (AB system, J = 18.0, further coupled with C3H, J = 2.8 and J = 4.5, 2H), 2.60-2.52 (m, 2H), 1.76-1.68 (m, 3H), 1.38 (s, 3H).^{13}C NMR: δ 208, 135.93, 127.42, 80.52, 59.28, 47.52, 35.73, 24.37, 15.62.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.28; H, 8.95.

4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one (1h, *filifolone*). The reaction performed in the same conditions gave, after work-up a mixture in which, compound **1h** was detected by GLC as component (20-30 % yield) togheter with a multitude of side products. Every attempt to isolate from the reaction mixture and, to purify compound **1h** was unsuccessfull.

C7 Geminal Dimethylation of Bicyclo[3.2.0]hept-3-en-6-ones* 1-1g *and Bicyclo[3.2.0]hept-2-en-6-one* (2). *General Procedure:

The high volatility of methyl iodide suggested the use of a dry ice condenser on the reaction flask. A solution of bicyclo[3.2.0]hepten-6-one (40 mmol) in THF (20 ml) was slowly added at room temperature to a suspension of NaH (2.4 g, 0.1 mol) in THF (80 ml) containing MeI (0.15 mol), and the mixture was stirred overnight. During the first hour the evolution of hydrogen was observed and the increase in temperature to 40°C was controlled with a water bath. The colour of the reaction mixture turned to brown and after one hour a white product began to precipitate. The reactions were monitored by GC and TLC using silica gel plates and the mixture petrolether/ diethyl ether 9:1 as eluent. After ten hrs the reaction was stopped by adding diethyl ether (100 ml) and water (20 ml). The organic layer was washed with water (3 x 20 ml) and dried (Na_2SO_4). The solvent was distilled at ambient pressure to avoid loss of product. The residue was purified by bulb to bulb distillation (kugelrohr), or by flash column chromatography using the mixture petrolether/ diethyl ether 9:1 as eluent.

7,7-Dimethylbicyclo[3.2.0]hept-3-en-6-one (6). The reaction gave compound **6** (3.15 g, 58 % yield) as an oil: bp(kugelrohr) = 110°C (15 mmHg). IR (film): ν = 1766, 1449, 1103, 1054, 810 cm^{-1}. MS (70 eV): *m/z* (%) = 136 ($M^{+\cdot}$,9), 108 (42), 93 (72), 91 (29), 86 (52), 84 (73), 79 (12), 77 (28), 70 (100), 66 (43), 65 (12), 47 (16), 42 (36), 41 (22), 39 (29). ^1H NMR: δ 5.92 (m, 1H), 5.64 (m, 1H), 4.28 (m, 1H), 2.75- 2.53 (m, 3H), 1.20 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: δ 214.28 (C6), 134.80 (C4), 126.63 (C3), 69.88 (C5), 60.97 (C7), 39.53 (C1), 33.92 (C2), 24.59, 19.20 (each for CH_3).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.33; H, 8.84.

5,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one (6a). The reaction gave compound **6a** (2.28 g, 38 % yield) as an oil: bp(kugelrohr) = 140°C (15 mmHg). IR (film): ν = 2956, 2923,1771 cm^{-1}. ^1H NMR: δ 5.83 (m, 1H), 5.47 (m,1H), 2.70 (dddd, 1H, J = 17.9, J = 7.6, J = 2.4, J = 2.0), 2.28 (m, 2H), 1.33 (s, 3H), 1.26 (s, 3H), 1.21 (s,3H). ^{13}C NMR: δ 218.22, 133.76, 132.48, 76.17, 58.53, 46.77, 34.09, 25.19, 19.34, 18.15.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.03; H, 9.43.

3,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one (6b). The reaction gave compound **6b** (2.46 g, 41 % yield) as an oil: bp(kugelrohr) = 115°C (15 mmHg). IR (film): ν = 2968, 1775 cm^{-1}. ^1H NMR: δ 5.20 (m, 1H), 4.20 (m,1H), 2.76-231 (m, 3H), 1.75 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: δ 214.98, 145.10, 120.43, 69.74, 60.36, 40.39, 38.09, 24.48, 18.68, 16.15.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.07; H, 9.47.

1,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one (6c). The reaction gave compound **6b** (3.54 g, 59 %, yield) as an oil: bp(kugelrohr) = 115°C (15 mmHg). IR (film): ν = 2966, 1775 cm^{-1}. ^1H NMR: δ 5.85 (m, 1H), 5.65 (m, 1H), 3.80 (m, 1H), 3.78 (m, 1H), 2.30 (m, 1H), 1.34 (s, 3H), 1.19 (s, 3H), 1.12 (s, 3H). ^{13}C NMR: δ 215.99, 135.15, 127.13, 76.48, 61.85, 42.99, 42.30, 21.96, 21.75, 19.92.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.85; H, 9.35.

4,7,7-Trimethylbicyclo[3.2.0]hept-3-en-6-one (5, *filifolone*). The reaction gave compound **5** (4.32 g, 72 % yield) as an oil: bp (kugelrohr) = 150°C (12mmHg). All the spectroscopic data are in agreement with the those previously reported. MS (70 eV): *m/z* (%) = 150 ($M^{+\cdot}$,9), 122 (23), 107 (48), 105 (7), 91 (22), 81 (9), 80 (100), 79 (44), 77 (12), 70 (28), 53, (6), 51 (6), 42 (12), 41 (14), 39 (16). IR (film): ν = 1769, 1449, 1064 cm^{-1}. ^1H NMR: δ 5.44 (m, 1H), 4.20 (m, 1H), 2.70-2.40 (m, 3H), 1.75 (m, 3H), 1.20 (s, 3H), 1.12 (s, 3H). ^{13}C NMR: δ 213.60 (C6), 136.37 (C4), 127.74 (C3), 72.43 (C5), 61.14 (C7), 40.88 (C1), 34.01 (C2), 24.89, 19.52, and15.75 (each for CH_3).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.87; H, 9.55.

1,3,7,7-Tetramethylbicyclo[3.2.0]hept-3-en-6-one (6e). The reaction gave compound **6e** (5.28 g, 75 % yield) as an oil, purified by flash chromatography. IR (film): ν = 2967, 1769 cm^{-1}. ^1H NMR: δ 5.27 (m, 1H), 3.70 (m, 1H), 2.75-2.57 (m, 1H), 2.32-2.15 (m, 1H), 1.77 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H), 1.09 (s, 3H). ^{13}C NMR: δ 216.22, 145.24, 121.08, 76.47, 47.11, 43.03, 21.74, 21.36, 19.84, 16.31.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.73; H, 9.23.

2,2,7,7-Tetramethylbicyclo[3.2.0]hept-3-en-6-one (6f). The reaction gave compound **6f** (3.52 g, 50 % yield) as an oil: IR (film): ν = 2967, 1769 cm^{-1}. ^1H NMR: δ 5.70 (dd, 1H, J = 5.5, J = 2.5), 5.45 (dd, 1H, J = 5.3, J = 2.5), 4.11 (ddd, 1H, J = 6.1, J = 5.1, J = 2.5), 2.21 (d, 1H, J = 6.1), 1.23 (s, 3H), 1.20 (s,3H), 1.10 (s, 3H), 0.96 (s, 3H). ^{13}C NMR: δ 215.26, 145.35, 124.05, 68.59, 60.51, 52.07, 46.67, 33.10, 25.85, 24.34, 21.92.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.84; H, 9.21.

1,4,7,7-Tetramethylbicyclo[3.2.0]hept-3-en-6-one (6g). The reaction gave compound **6** (4.37 g, 62 % yield) as an oil: bp (kugelrohr) = 150°C (12 mmHg). MS (70 eV): *m/z* (%) = 164 ($M^{+\cdot}$,4), 149 (6), 123 (5), 121 (6), 105 (8), 95 (66), 94 (100), 79 (36), 67 (11), 55 (13). IR (film): ν = 1766, 1449, 1103, 1054, 810 cm^{-1}. ^1H NMR: δ 5.40 (m, 1H), 3.56 (m, 1H), 2.72 (d with additional fine structure, J = 16.8 Hz, 1H), 2.23 (d with additional fine structure, J =16.8 Hz , 1H), 1.73 (m, 3H), 1.22, 1.18 and 1.12 (three s, each for 3H). ^{13}C NMR: δ = 214.67 (C6), 136.80 (C4), 127.89 (C3), 78.93 (C5), 61.94 (C7), 43.30 (C1), 42.99 (C2), 22.17, 21.99, 20.15, and 15.99 (each for CH_3).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.81; H, 9.20.

7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one (7). The reaction gave of compound **7** (3.53 g, 65 % yield) as an oil: bp = 163°C. MS (70 eV): *m/z* (%) = 136 ($M^{+\cdot}$,5), 121 (6), 108 (46), 93 (55), 91 (18), 81 (6), 79 (11), 78 (6), 77 (23), 71 (7), 70 (100), 67 (7), 66 (47), 65 (20), 63 (5), 53 (6), 51 (7), 43 (7), 42 (45), 41 (27), 40 (14), 39 (42), 32 (7). IR (film): ν = 1775, 1461, 1444, 1048, 790 cm^{-1}. ^1H NMR: δ 5.76 (m, 1H),

5.66 (m, 1H), 3.86 (ddd, J = 7.4, and 1.8 Hz, 1H), 3.12 (m, 1H), 2.54 (d with additional fine structure, J =17.1 Hz, 1H), 2.30 (d with additional fine structure, J = 17.1 Hz, 1H), 1.22 and 0.90 (two s, each for 3H). ^{13}C NMR: δ = 218.51 (C6), 134.03 (C3), 130.89 (C2), 64.58 (C7), 58.04 (C5), 50.78(C1), 34.13 (C4), 24.68, and 17.45 (each for CH_3).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.45; H, 8.78.

Oxidation of Bicyclo[3.2.0]hept-3-en-6-ones* 1-1g. *General Procedure:

To a solution of bicyclo[3.2.0]hept-3-en-6-one **1-1g** (10 mmol) in 90% aqueous acetic acid (40 ml) cooled at 0°C was added 30% hydrogen peroxide (24 mmol) dissolved in 90% aqueous acetic acid (20 ml). The reaction was stirred at 0°C for 12-24 h. The product was extracted with ether and washed with 10% aqueous sodium sulfite and saturated sodium bicarbonate. The ether layer was dried ($MgSO_4$) and the solvent was removed at reduced pressure. Compounds **8-8g** were obtained pure by flash chromatography eluting with petroleum ether : diethyl ether = 1:1.

3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (8): obtained as a clear oil (1.17 g, 95 % yield). IR (film) ν 1769 cm^{-1}. ^1H NMR: δ 6.05 (m,1H), 5.79 (m, 1H), 5.45 (m, 1H), 3.09 (m, 1H), 2.77 (dd, 1H, J = 18.0, J = 10.6), 2.71 (m, 1H), 2.25 (m, 1H), 2.23 (dd, 1H, J = 18.0, J = 5.5). ^{13}C NMR: δ 177.3 (C), 137.3 (CH), 129.4 (CH), 89.73 (CH), 39.66 (CH_2), 36.05 (CH_2), 35.24 (CH).

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 7.46. Found: C, 67.68; H, 7.42.

3,3a,4,6a-Tetrahydro-6a-methyl-2*H*-cyclopenta[*b*]furan-2-one (8a): obtained as an oil (1.13 g, 82 % yield). IR (film) ν 1767 cm^{-1}; ^1H NMR: δ 5.85 (m, 1H), 5.69 (m, 1H), 2.55-2.91 (m, 3H), 2.22 (m, 2H), 1.49 (s, 3H). ^{13}C NMR: δ 176.7(C), 134.4(CH), 134.1(CH), 98.28(C), 42.15(CH), 39.46(CH_2), 37.40(CH_2), 24.89(CH_3).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.58; H, 7.38.

3,3a,4,6a-Tetrahydro-5-methyl-2*H*-cyclopenta[*b*]furan-2-one (8b): obtained as an oil (1.25 g, 91 % yield). IR (film) ν 1765 cm^{-1}. ^1H NMR δ 5.41 (m, 2H), 2.95-3.18 (m, 1H), 2.76 (dd, 1H, J=10.7, J = 18.5), 2.59 (dd with further fine couplings, 1H, J=16.7, J = 7.9), 2.15 (dd, 1H, J=18.5, J = 5.2), 2.10 (d with further fine couplings, 1H, J=17), 1.63 (s, 3H); ^{13}C NMR: δ 178.0 (C), 148.6 (C), 123.7 (CH), 90.68 (CH), 43.87 (CH_2), 36.48 (CH_2), 36.11 (CH), 16.47 (CH_3).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.47; H, 7.25.

3,3a,4,6a-Tetrahydro-3a-methyl-2*H*-cyclopenta[*b*]furan-2-one (8c): obtained as an oil (1.31 g, 95 % yield). IR (film) ν 1765 cm^{-1}. ^1H NMR: δ 6.05 (m, 1H), 5.85 (m, 1H), 5.05 (m, 1H), 2.30-2.65 (m, 4H), 1.35 (s, 3H); ^{13}C NMR: δ 177.2 (C), 137.3 (CH), 129.1 (CH), 95.51 (CH), 46.49 (CH_2), 44.34 (C), 43.27 (CH_2), 25.17 (CH_3).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.63; H, 7.28.

3,3a,4,6a-Tetrahydro-6-methyl-2*H*-cyclopenta[*b*]furan-2-one (8d): obtained as an oil (1.28 g, 92% yield). IR (film) ν 1765 cm^{-1}. ^1H NMR: δ 5.60 (s, 1H), 5.30 (d, 1H, J = 7.0), 3.15 (m, 1H), 2.90-2.60 (m, 2H), 2.35-2.10 (m, 2H), 1.80 (s, 3H). ^{13}C NMR: δ 177.8 (C), 138.4 (C), 129.8 (CH), 92.25 (CH), 39.1 (CH_2), 35.9 (CH), 14.32 (CH_3).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.58; H, 7.38.

3,3a,4,6a-Tetrahydro-3a,5-dimethyl-2*H*-cyclopenta[*b*]furan-2-one (8e): obtained as an oil (1.38 g, 91% yield). IR (film) ν 1770 cm^{-1}. ^1H NMR: δ 5.45 (m, 1H), 4.97 (m, 1H), 2.53 (d, 1H, J = 18.0), 2.43 (d, 1H, J = 18), 2.37 (m, 2H), 1.78 (s, 3H), 1.33 (s, 3H). ^{13}C NMR: δ 176.47 (C), 148.17 (C), 123.53 (CH), 96.25 (CH), 50.86 (CH_2), 44.80 (C), 43.73 (CH_2), 25.71 (CH_3), 16.78 (CH_3).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.95; H, 7.93.

3,3a,4,6a-Tetrahydro-4,4-dimethyl-2*H*-cyclopenta[*b*]furan-2-one (8f): obtained as an oil (1.21 g, 80 % yield). IR (film) ν 1782 cm^{-1}. ^1H NMR: δ 5.91 (dd, 1H, J = 5.5, J = 0.7), 5.73 (dd, 1H, J = 5.6, J = 1.9),

5.52 (ddd, 1H, J = 6.8, J = 1.9, J = 0.7), 2.75 (ddd, 1H, J = 9.1, J = 6.8, J = 6.8), 2.58 (dd, 1H, J = 17.8, J = 9.2), 2.50 (dd, J = 17.6, J = 6.9), 1.13 (s, 3H), 1.07 (s, 3H). ^{13}C NMR: δ 177.99 (C), 148,47 (CH), 125.98 (CH), 89.72 (CH), 47.48 (CH), 46.67 (C), 30.88 (CH_2), 30.18 (CH_3), 24.61 (CH_3).

Anal. Calcd for $C_9H_{12}O_2$:C, 71.02; H, 7.95. Found: C, 70.97; H, 8.05.

3,3a,4,6a-Tetrahydro-3a,6-dimethyl-2*H*-cyclopenta[*b*]furan-2-one (8f): obtained as an oil (1.44 g, 95 % yield). IR (film) ν 1782 cm^{-1}. ^{1}H NMR: δ 5.65 (m, 1H), 4.80 (s, 1H), 2.50 (m, 2H), 2.40 (m, 2H), 1.80 (s, 3H), 1.35 (s, 3H). ^{13}C NMR: δ 177.0 (C), 138.20 (C), 129.50 (CH_2), 97.65 (CH), 45.86 (CH_2), 43.76 (CH_2), 25.94 (CH_3), 14.33 (CH_3).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.12; H, 8.03.

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