Pergamon

Tetrahedron Vol. 50, No. 10, pp. 3235-3250, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0031-N

Practical Preparation of Bicyclo[3.2.0]hept-3-en-6-ones and its Utilisation in Stereoselective Total Synthesis of Grandisol and Lineatin *via* a Versatile Intermediate.

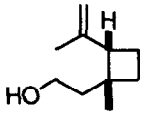
Giovanni Confalonieri,† Emanuela Marotta, Franco Rama,† Paolo Righi Goffredo Rosini,* Rossella Serra and Francesca Venturelli

Dipartimento di Chimica Organica "A. Mangini" dell'Università
Viale Risorgimento 4, I-40136, Bologna (Italy)
†ISAGRO S.r.L- Ricerca Fitofarmaci-ENICHEM
Via Fauser 4, I-28100, Novara (Italy)

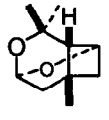
Abstract: New and efficient stereoselective total syntheses have been devised for racemic grandisol and lineatin, two important components of pheromonic blends. They are based on the utilisation of 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one as a pivotal intermediate. This compound, as well as other bicyclo[3.2.0]hept-3-en-6-ones, are now easily available by a practical bicyclization of the corresponding 3-hydroxy-6-alkenoic acids.

Since pheromones have been shown to have useful applications in modern and ecologically sound crop protection and forest defence, several industrial and academic laboratories involved in the synthesis and development of biologically active compounds are becoming more and more interested in this area.[1] Many examples of the successful utilisations of pheromonic blends in controlling insect pests are now known[2,3] and the development of economical syntheses of pure components of these blends certainly helps to achieve this goal.

Monoterpenes grandisol (**1**) and lineatin (**2**) are important pheromones with unusual cyclobutane structures that suggested a close biogenetic relationship.



1



2

(+)-Grandisol is well known as one of the components of the aggregation pheromone of the cotton boll weevil, *Anthonomus grandis* Boheman,[4] an important pest of cotton crops in the USA.[5] More recently (+)-lineatin has been isolated from the frass of the female ambrosia beetle *Trypodendron lineatum* Olivier,[6] and has been shown to elicit powerful secondary attraction in laboratory and field trials. *T. lineatum* is a deleterious pest to forests both in Europe and in North America, boring tunnels into the sapwood of a number of

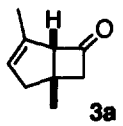
coniferous species. For practical purposes the preparation of racemic compounds is satisfactory since non adverse biological effects have been observed for the levorotating enantiomer of grandisol[7,8] and lineatin.[9]

Over the years, it has been found that both grandisol[10] and lineatin[11] are also pheromone components of other important species of insects. Thus, the economic interest in these compounds consistently increased.

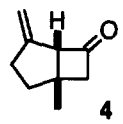
A number of syntheses of racemic and optically active grandisol[1,12-19] and lineatin[1,14,20] have been described in the literature. However, few procedures have the features that distinguish a process capable of being run on the desired scale in an economic manner.

In 1985, we reported[21] an efficient and practical synthesis of racemic grandisol. Later, we converted this procedure into an EPC one[22] having developed the preparation of both enantiomers of 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol, a key intermediate of in our route. Notwithstanding these accomplishments, two limitations could be ascribed to this synthetic scheme: (i) the procedure is based on one photochemical step which, although highly efficient and stereoselective, limits its applicability in large scale preparations; (ii) the synthesis is fully oriented toward the preparation of grandisol only. Therefore, we started to verify the possibility of developing a unified synthetic strategy that would provide access to both these important pheromone components through a procedure which, having no photochemical step, would not only be aesthetically satisfying but also commercially more acceptable.

From the outset the core structural feature of grandisol and lineatin was perceived to be the *cis*-substituted cyclobutane ring and 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one (**3a**) was viewed as an ideal pivotal intermediate to our targets showing the substitution pattern amenable for a practical and efficient conversion into compounds **1** and **2**.



3a



4

Compound **3a** could be prepared through an intramolecular [2+2] cycloaddition of an *in situ* generated α,β-unsaturated ketene with the peripheral double bond: Snider[23,24] reported that the slow addition of a toluene solution of 3,6-dimethyl-2,6-heptadienoic acid chloride to a refluxing solution of triethylamine in toluene gave the bicyclic ketone **4** in 43% yield, and only small and variable amounts of **3a**, the isomer with an endocyclic double bond, was observed. More recently, Baeckstrom et al.[20] have reported a procedure by which compounds **3a** and **4** were obtained in 62% yield and in 2:1 ratio by refluxing a complex mixture of isomeric heptadienoic acids in acetic anhydride and sodium acetate. The mixture of acids derived from the hydrolysis of ethyl 3,6-dimethyl-2,6-heptadienoates (E:Z = 4:1) with 10% KOH/MeOH under reflux conditions. Both these methodologies have been used in two formal syntheses of racemic lineatin.

So, with a view to large-scale synthesis, our first challenge was to devise a practical procedure to have a more satisfying yield of **3a** with a higher isomeric purity. We found that the treatment of 3,6-dimethyl-3-hydroxy-6-heptenoic acid **5a** with potassium acetate and acetic anhydride at room temperature for 2 h, followed by heating for 4 h under reflux gave compound **3a** in 82% isolated yield with only 2-5% of the isomer **4**. Table 1 summarises the results obtained by performing this bicyclization reaction with four different 3-hydroxy-6-heptenoic acids.[25]

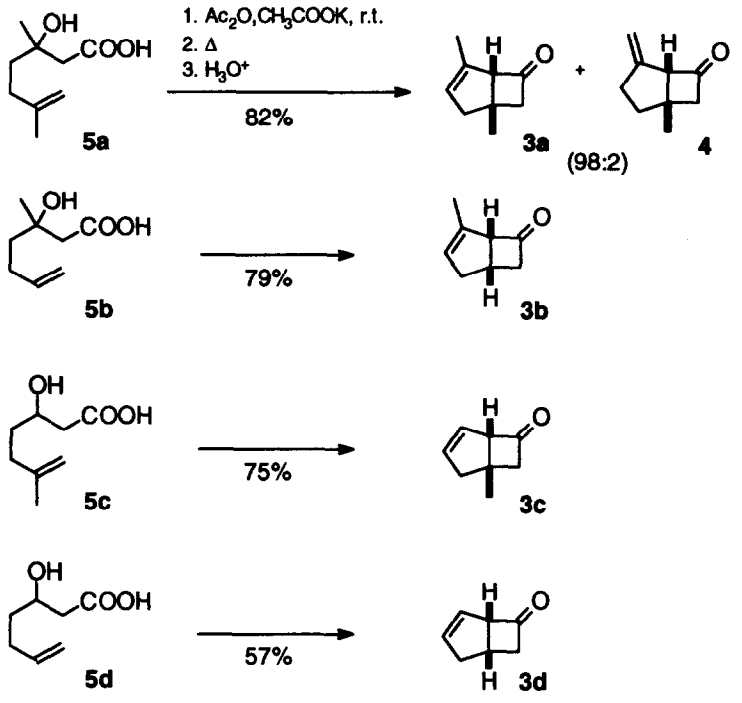
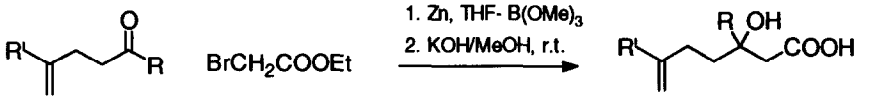


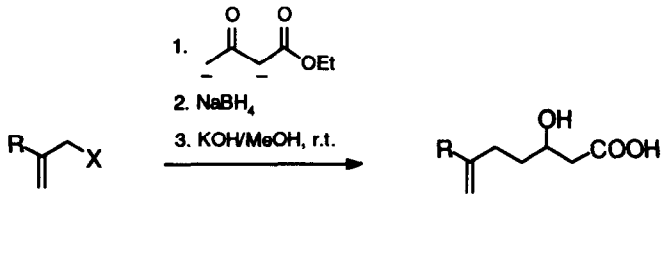
Table 1. Preparation of bicyclo[3.2.0]hept-3-en-6-ones by bicyclization of 3-hydroxy-6-alkenoic acids.

β-Hydroxy acids **5a-b** were easily prepared by an improved procedure of the Reformatsky reaction[26] of ethyl bromoacetate and the commercially available 5-methyl-5-hexen-2-one and 5-hexen-2-one respectively, followed by quantitative hydrolysis with 10% KOH/MeOH at room temperature for two days. β-Hydroxy acids **5c-d** were obtained by reacting the dianion of ethyl acetoacetate with allyl bromide and metallyl chloride,[27] respectively, followed by sodium borohydride reduction of the β-keto ester intermediates and their alkaline hydrolysis performed at room temperature.



5a : R= R'= CH_3

5b : R= CH_3; R'= H



(2)

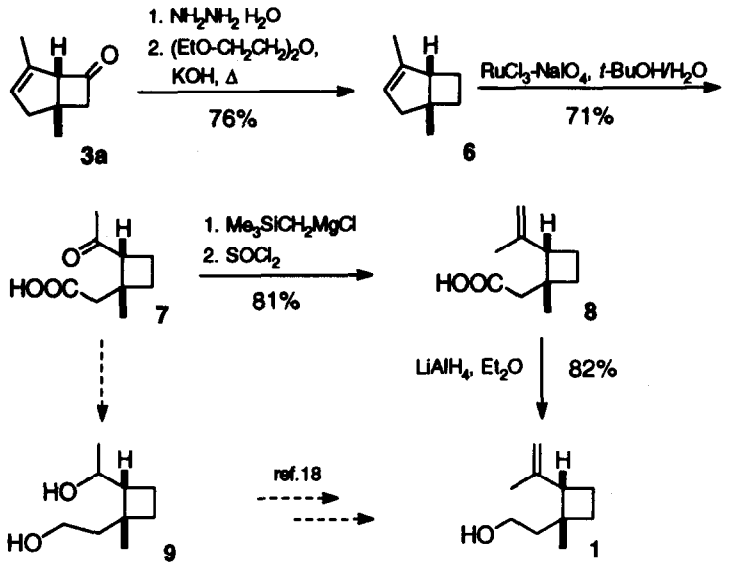
5c : R= CH_3
5d : R= H

Whatever the mechanistic details may be, a workable route to bicyclo[3.2.0]hept-3-en-6-ones was in hand; the individual steps were clean, efficient and simple to perform.

With compound **3a** available, we faced the selective modifications to be performed on each cycle of **3a** to convert this pivotal intermediate into grandisol (**1**) and lineatin (**2**).

Towards the synthesis of racemic grandisol (1).

The deoxygenation of **3a** by a Wolf-Kishner reduction was performed in bis(2-ethoxyethyl)ether and gave compound **6** which was easily separated and collected in 76 % yield by direct distillation from the reaction mixture.

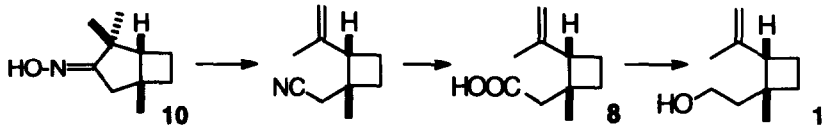


Scheme 1. Stereoselective conversion of compound **3a** into racemic grandisol (**1**).

Thus, the conversion of compound **3a** into 2,5-dimethylbicyclo[3.2.0]hept-2-ene (**6**) provides a direct link to the synthetic scheme we developed previously[21] and eliminates its main limitation: the photochemical step. Scheme 1 shows the conversion of the versatile intermediate **3a** into racemic grandisol (**1**). As a variation on

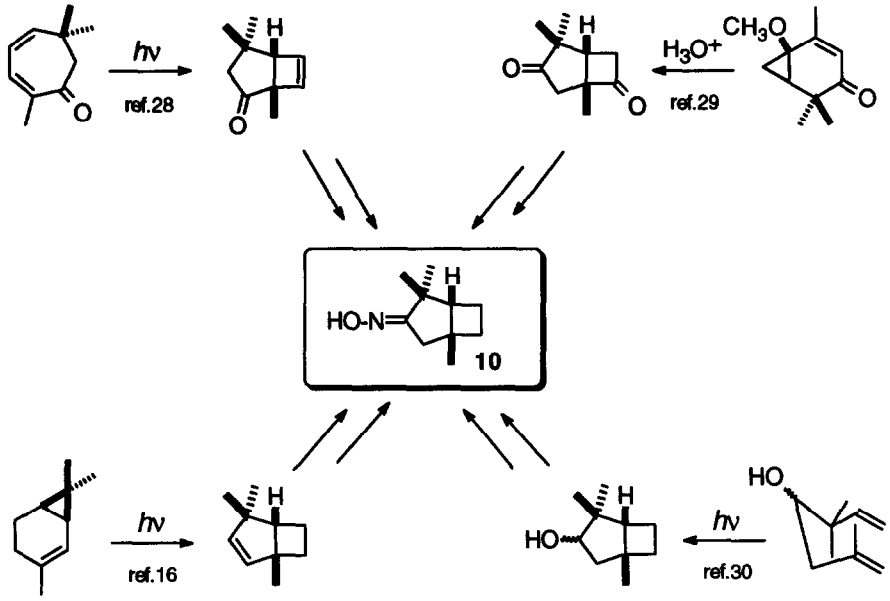
the original procedure,[21] the oxidative carbon-carbon double bond cleavage was accomplished by treating the alkene **6**, dissolved in a *t*-BuOH/H_2O (1:2), with $RuCl_3$ and sodium periodate as a co-oxidant. The keto acid **7** was obtained in a 71% yield without epimerization occuring *via* enolization. In addition, its reduction to the diol **9** should add to a very efficient part of the synthetic scheme devised by Narasaka et al.[18] to prepare grandisol.

In 1974, Ayer and Browne[28] devised a procedure by which eucarvone was converted into racemic grandisol *via* 3-oximino-1,4,4-trimethylbicyclo[3.2.0]heptane (**10**) that clearly is the key intermediate. In fact, this was efficiently converted into the target molecule by an easy Beckmann cleavage, followed by hydrolysis to the cyclobutane acetic acid **8** that finally underwent the reduction with $LiAlH_4$ to racemic grandisol (eq 3).



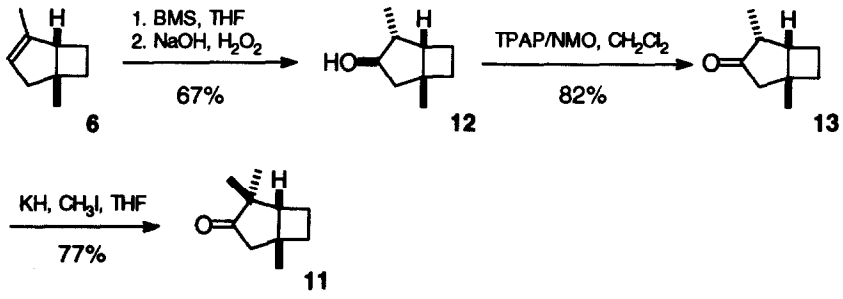
(3)

Since then, several efforts[29,30] were devoted to make compound **10**, or the parent ketone **11**, more conveniently available. Unfortunately, the Ayer and Browne route as well as the other procedures developed later to prepare **11**, suffer from certain disadvantages.



Scheme 2. Known procedures to prepare 3-oximino-1,4,4-trimethylbicyclo[3.2.0]heptane (**10**).

In the Scheme 2, some peculiar aspects of these syntheses are summarized to stress the major drawbacks of them: (i) the lack of stereoselectivity, (ii) the functional homogeneity on both rings, and/or (iii) a photocyclization or photorearrangement as the key step.



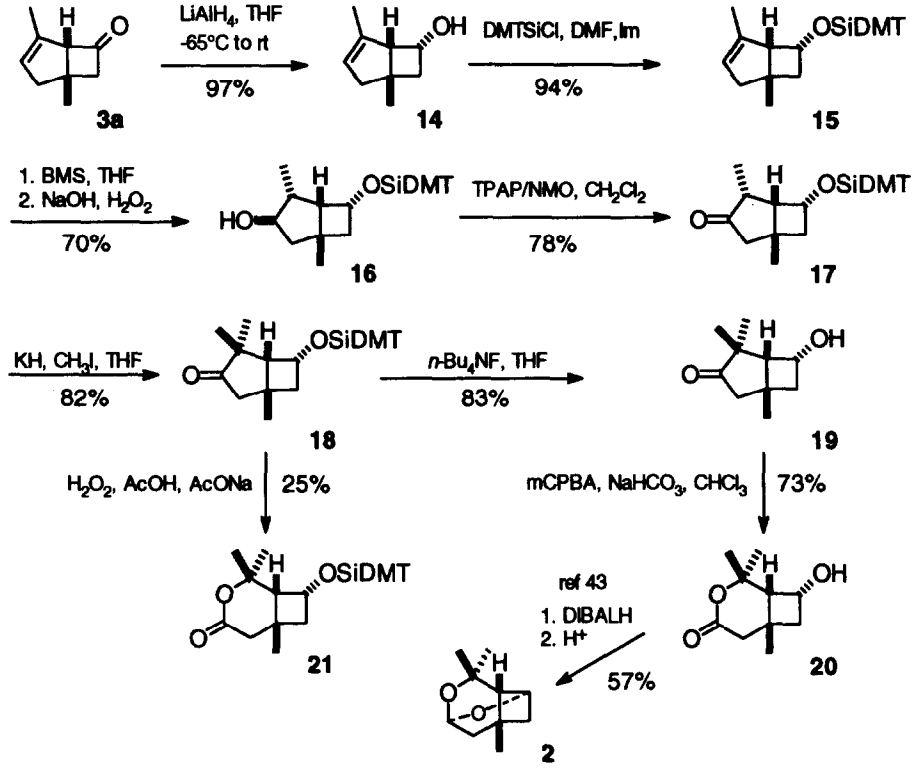
Scheme 3. The conversion of bicyclic alkene **6** into 1,4,4-trimethylbicyclo[3.2.0]heptan-3-one (**11**).

The Scheme 3 shows the conversion of bicyclic alkene **6** into the ketone **11** which we performed in regio- and stereoselective fashion. It starts with a straightforward hydroboration-oxidation step with borane-dimethylsulfide complex (BMS) in THF, followed by alkaline oxidation with hydrogen peroxide.[31] Then the oxidation of **12** with tetra-*n*-propylammonium perruthenate (TPAP)/ N-methylmorpholine N-oxide (NMO) in dichloromethane[32] gave the bicyclic ketone **13** in 82% yield. This compound underwent the regiospecific introduction of the required methyl group on C2 by adding methyl iodide to the thermodynamically more stable potassium enolate in THF, readily prepared by the addition of the ketone to a vigorously stirred suspension of potassium hydride in anhydrous tetrahydrofuran at 20°C.[33]

Towards the synthesis of racemic lineatin (2).

The route to racemic lineatin (**2**) is summarised in Scheme 4. Our approach asked for an efficient and highly stereoselective reduction of the carbonyl group of **3a** into the corresponding *endo*-alcohol **14**, where the hydroxy group is correctly positioned to permit a facile intramolecular acetalization. Notwithstanding the discouraging results of Baeckstrom et al.,[20] we successfully performed this reaction with a good control of the stereochemistry by treating compound **3a** with lithium aluminium hydride in tetrahydrofuran (THF) at low temperature (-65°C) and allowing this to raise to room temperature during the night. The work-up of the reaction mixture by quenching with aqueous saturated ammonium chloride gave **14** (>95% pure) in 95% yield. The *endo* hydroxy group was protected as dimethylthexylsilyl ether (**15**).

We now faced the manipulation of the five membered ring and, to avoid the loss of the stereochemical integrity by epimerization of the substituents on the cyclobutane ring, we chose to convert this into the intramolecular acetal structure of lineatin without cleaving the five-membered ring. Accordingly, compound **15** was converted into the bicyclic ketone **18** through hydroboration-oxidation, oxidation and regiospecific methylation: the straightforward steps of the same synthetic scheme used to prepare the bicyclic ketone **11**. The deprotection of compound **18** was performed very efficiently with tetra-*n*-butylammonium fluoride in tetrahydrofuran and gave the free hydroxy ketone **19** that underwent an easy lactonization by the Baeyer Villiger reaction[34] to give the hydroxy lactone **20**, the parent compound of racemic lineatin (**2**). On the other hand, the many attempts to effect the Baeyer Villiger reaction on the silyl derivative **18** met with failure, affording only unreacted starting material. Among the conditions employed were mCPBA/ $NaHCO_3$/ CH_2Cl_2,[35] mCPBA/ CF_3CO_2H/ CH_2Cl_2,[36] Na_2CO_3/ AcOH/ AcONa,[37] Oxone/ "wet-alumina"/ CH_2Cl_2,[38]



Scheme 4. Stereoselective conversion of compound **3a** into racemic lineatin (**2**).

MeOH/ H_2O/ NaOH,[39] MMPP/ MeOH/ H_2O,[40] $NaBO_3$/ CF_3CO_2H,[41] $(MeSiO)_2$/ TMSOTf/ CH_2Cl_2.[42] Only the reaction performed with hydrogen peroxide in acetic acid in the presence of sodium acetate[26] gave compound **21** in a 25% yield after 90 h at room temperature. The spectroscopic data and melting point of synthesised **20** were identical with those previously reported.[43] The final conversion of hydroxy lactone **19** into racemic lineatin (**2**) was achieved in 57% yield by the procedure already described by Mori *et al.*,[43] and consisting of a reduction of followed by acidification with hydrogen chloride. It should be pointed out that Mori *et al.* have also achieved the resolution of the hydroxy lactone **20** employing (1R,4R,5S)-(+)-4-hydroxy-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one[44] as resolving agent. Therefore, with this strategy both the enantiomers of lineatin (**2**) with good optical purity may be prepared.

In conclusion, the preparation of bicyclo[3.2.0]hept-3-en-6-ones (**3a-d**) by an efficient and non-photochemical bicyclization of 3-hydroxy-6-alkenoic acids is the main outcome of our efforts. Fused ring systems that offer different functionalities on each ring are suitable for the stereocontrolled assembly of more complex structures and have ever been regarded as amazingly versatile intermediates and starting materials.

Bicyclo[3.2.0]hept-3-en-6-ones are not so easily accessible[45] as the isomeric hept-2-en-6-ones. These latters are well known as important and versatile educts in the stereoselective synthesis of many natural products.[46] The non-photochemical routes we have devised and depicted here for the synthesis of racemic

grandisol (**1**) and lineatin (**2**) are additional outcomes and are based on the easy availability of compound **3a** as a common starting material. They demonstrate the usefulness of bicyclo[3.2.0]hept-3-en-6-ones and show promise for further utilizations in the synthesis of complex molecules.

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 **5a** and **5b** used as starting materials were prepared in good yields by a Reformatsky reaction performed according to the procedure of Rathke and Linder.[26] The esters of 3-hydroxyhept-6-enoic acids **5c** and **5d** were prepared by alkylation of the dianion of ethyl acetoacetate according to the procedure of Huckin and Weiler,[27] followed by chemioselective reduction of the carbonyl group with $NaBH_4$ in methanol. Ethyl bromoacetate, 4-pentenal, 5-hexen-2-one, 5-methyl-5-hexen-2-one, allyl bromide and metallyl chloride are commercial materials.

Preparation of 3-hydroxyhept-6-enoic acids **5a-5d** *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 (**5a-d**, 88-95% yield) that could be used without further purification.

3,6-Dimethyl-3-hydroxy-6-heptenoic Acid (5a). ^1H 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 $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.18; H, 10.45.

3-Hydroxy-3-methyl-6-heptenoic Acid (5b). ^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).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.38; H, 10.12.

3-Hydroxy-6-methyl-6-heptenoic Acid (5c). ^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, CH_3).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.35; H, 9.87.

3-Hydroxy-6-heptenoic Acid (5d). ^{1}H 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).
Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 6.45; H, 9.57.

Bicyclization of 3-hydroxy-6-alkenoic acids **5a-5d**. *General Procedure.*[25]

3-Hydroxy ketone (**5a-d**, 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 distillation under reduced pressure gave bicyclic ketones **3a-d**.

1,4-Dimethyl-*cis*-bicyclo[3.2.0]hept-3-en-6-one (3a). Compound **3a** was obtained (5.57 g, 82 % yield) by bulb to bulb distillation (bp $_{60mmHg}$ 130°C) with only 4 % of the exocyclic isomer **4**. IR (liquid film): ν 2915, 2852, 1776, 1446 cm^{-1}. ^{1}H 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 (C=O), 135.93 (C), 127.42 (CH), 80.52 (CH), 59.28 (CH_2), 47.52 (CH_2), 35.73 (C), 24.37 (CH_3), 15.62 (CH_3).
Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.43; H, 8.75.

4-Methyl-*cis*-bicyclo[3.2.0]hept-3-en-6-one (3b). Compound **3b** (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, 1447 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).[47]
Anal. Calcd for $C_8H_{10}O$: C, 78.64; H, 8.26. Found: C, 78.71; H, 8.34.

1-Methyl-*cis*-bicyclo[3.2.0]hept-3-en-6-one (3c). Compound **3c** (4.60 g, 75 % yield) was obtained pure by flash chromatography eluting with 95:5 petroleum ether/ ether. IR (liquid film): ν 3059, 1780, 1602, 1443 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).[47]
Anal. Calcd for $C_8H_{10}O$: C, 78.64; H, 8.26. Found: C, 78.67; H, 8.31.

***cis*-Bicyclo[3.2.0]hept-3-en-6-one (3d).** Compound **3d** (3.07 g, 57 % 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.[48]
Anal. Calcd for C_7H_8O: C, 77.74; H, 7.46. Found: C, 77.78; H, 7.38.

2,5-Dimetyl-*cis*-bicyclo[3.2.0]hept-2-ene (6). The bicyclic ketone **5** (13.60 g, 0.1 mol) was added to 19.4 mL (0.4 mol) of 85% hydrazine hydrate and benzene (100 mL) in a 250 mL round bottomed flask equipped with a Dean-Stark trap and a condenser fitted with a $CaCl_2$ tube . The solution was heated to reflux for 22 h. Azeotropic distillation of benzene allowed the collection of 6 mL of water and to obtain a residue that was

extracted with ether (2x100 mL). These extracts were combined, washed with water (50 mL), with brine (2x 30 mL) and dried over $MgSO_4$. After filtration the ether was removed by rotary evaporation and the remaining oil (pink) was collected into a 100 mL round bottomed flask equipped with a condenser. The mixture was dissolved with bis(2-ethoxyethyl)ether (50 mL); KOH (pellets, 6.0 g) was added to the solution which was then heated to reflux for 3 h. Additional KOH (2.0 g) was added and the reaction mixture was refluxed for 10 h. After cooling, the condenser was replaced by a short path distillation head and 2,5-dimethyl[3.2.0]hept-2-ene (**6**) was distilled (first fraction, 95-100 °C) along with a small amount of water. A further distillation of this fraction gave 9.32 g (76% yield) of compound **6** contaminated by only 4% of 1-methyl-4-methylene-bicyclo[3.2.0]heptane. IR (liquid film): ν 3035, 2933, 2837, 1649, 1599, 1499 cm^{-1}.^{1}H NMR: δ 5.28 (bs, 1H), 2.50-2.40 (m, 1H), 2.06 (m, 3H), 2.30- 1.40 (m, 6H), 1.13 (s, 3H). Two signals at d 4.67 and at d 4.55 (2 m, 2H) and the singlet at d 1.25 (s, 3H) are diagnostic for the presence of the isomer 1-methyl-4-methylene-bicyclo[3.2.0]heptane as an impurity.^{13}C NMR: δ 143.57 (C), 124.70 (CH), 54.17(CH), 48.10 (CH_2), 44.94 (C), 33.68 (CH_2), 25.58 (CH_3), 23.35 (CH_2), 14.93 (CH_3) .

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.38; H, 11.63.

***cis*-2-Acetyl-1-methylcyclobutaneacetic Acid (7).** To a well-stirred mixture of 2,5-dimetylbicyclo[3.2.0]-hept-2-ene (**6**, 4.00 g, 32.8 mmol) in *t*-BuOH (35 mL) and water (70 mL) $NaIO_4$ (22.4 g, 104.7 mmol) was added at room temperature followed by $RuCl_3.3H_2O$ (134 mg, 0.04 mmol). This addition was followed by an increase in temperature of the reaction mixture (35°C) and the formation of a precipitate was observed. After being stirred for 0.5 h, the mixture was filtered and the filtrate was extracted with ethyl acetate. The extract was washed with saturated NaCl, dried over $MgSO_4$, and concentrate to give a brown oil which was purified by flash-chromatography on silica gel with 1:1 petrolether/ ethyl acetate as eluent to afford 3.98 g of compound **7** (71 % yield) as an oil which was identical in every respect with that reported previously: mp of p-toluenesulfonylhydrazone 192-193°C (lit.[21] 192-193°C); IR($CHCl_3$): ν 3515, 1710 cm^{-1}. ^{1}H NMR: δ 9.4 (very broad s, 1H, disappeared on treatment with D_2O), 3.10 (t, 1H, J = 7.0), 2.52 (AB system, 2H, J = 14.3), 2.30-1.72 (m, 4H), 2.12 (s, 3H), 1.42 (s, 3H). ^{13}C NMR: δ 210.15, 178.31, 55.26, 41.41, 39.94, 30.96, 30.63, 27.83, 17.65.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.45, H, 8.32.

***cis*-1-Methyl-2-(1-methylethenyl)-cyclobutaneacetic Acid (8).** The reaction was performed according to a procedure previously reported.[21] In a 250 mL three necked flask equipped with mechanical stirrer, condenser and a dropping funnel, trimethysilylmethylmagnesium chloride was prepared by a reported procedure starting from chloromethyltrimethylsilane (10.0 g, 0.08 mol) and magnesium turnings (2.0 g, 0.08 mol) in THF (100 mL). The ketoacid **7** (6.64 g, 0.04 mol) dissolved in anhydrous THF (20 mL) was added to this solution at such a rate that the mixture gently refluxed. After 3 h the mixture was cooled (ice-bath) and thionyl chloride (7.2 mL, 0.10 mol) added. The ice-bath was removed and stirring was continued at room temperature. After 1 h the reaction mixture was hydrolyzed by the dropwise addition of water and extracted with ether (3x 50 mL). Distillation on a rotating evaporator gave an oil which was dissolved in a mixture of n-pentane (50 mL) and ether (50 mL) and washed with saturated aqueous solution of Na_2CO_3 (20 mL). The separated aqueous phase was carefully acidified with a diluted HCl and the extracted with ether (3x 50 mL). The ether solution was washed with brine (2x 10 mL), dried (Na_2SO_4) and concentrated at reduced pressure. The crude product

was purified by flash-chromatography on silica gel eluting with 4:1 *n*-hexane/ ether. The evaporation of fractions afforded 5.45 g of compound **8** (81% yield). IR (liquid film): ν 3800, 2960, 1710, 890 cm^{-1}. ^1H NMR: δ 4.86 (bs, 1H), 4.65 (bs, 1H), 1.67 (bs, 3H).
Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.65.

***cis*-1-Methyl-2-(1-methylethenyl)-cyclobutaneethanol (1, Grandisol).** The conversion of compound **8** into grandisol (**1**) was performed according to a previously reported procedure.[21] In a 250 mL two necked flask equipped with a condenser and a dropping funnel, $LiAlH_4$ (1.0 g) was suspended in anhydrous ether (100 mL. A solution of **8** (7.72 g, 0.4 mol) in anhydrous ether (50 mL) was slowly added under nitrogen and with magnetic stirring. The mixture was stirred overnight at room temperature. Ethyl acetate (10 mL) was added to the stirred, ice-cooled suspension. After stirring for additional 3 h, water (2 mL) was added. The supernatant was decantated, dried (Na_2SO_4) and filtered. The solvent was removed by distillation at normal pressure and the crude residue was distilled at reduced pressure to give 5.10 g (82% yield) of racemic grandisol (**1**): bp_{15mmHg} (kugelrohr) 110-125 °C. The IR and ^1H NMR spectra were identical with those previously reported:[21] IR (liquid film): ν 3300, 2940, 1650, 885 cm^{-1}; ^1H NMR δ 4.85 (bs, 1H), 4.65 (bs, 1H), 3.58 (t, 2H, J = 7.0), 2.35 (bs, 1H, disappeared by treatment with D_2O, OH), 1.65 (bs, 3H), 1.15 (s, 3H).
Anal. Calcd for $C_{10}H_{18}O$: C, 77. 86; H, 11.76. Found: C, 77.93; H, 11.76.

1,4-Dimethyl-*cis*-bicyclo[3.2.0]hept-3-en-6,*endo*-ol (14). A solution of the bicyclic ketone **3a** (12.71 g, 93.4 mmol) in 80 mL of anhydrous THF was added dropwise to a stirred suspension of $LiAlH_4$ (5.34 g, 140.7 mmol) in 200 mL of anhydrous THF cooled at -68°C and under a nitrogen atmosphere. Stirring was continued for 24 h at -60°C. The temperature was allowed to rise to 0°C, ether (200 mL) was added and a saturated aqueous solution of NH_4Cl was slowly added (***caution !***) until a white solid precipitated. Cooling with an ice-bath is necessary during the addition. The clear solution was decanted into a separatory funnel, washed with a saturated solution of NaCl (2x 25 mL), dried over Na_2SO_4 and then evaporated at reduced pressure to give a residue (12.5 g, 97% yield) of almost pure **14**: IR (liquid film): ν 3347, 2947, 1447 cm^{-1}. ^1H NMR: δ 5.48 (m, 1H), 4.56-4.40 (m, 1H), 3.00-2.88 (m, 1H), 2.36-2.18 (m, 3H), 2.12 (bs, 1H, disappeared on treatment with D_2O, OH), 1.92-1.70 (m, 4H), 1.18 (s, 3H).
Anal Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.17; H, 10.24.

1,4-Dimethyl-6,*endo*-dimethylthexylsilyloxy-*cis*-bicyclo[3.2.0]hept-3-ene (15). To a solution of dimethylthexylsilyl chloride (9.01 g, 50.6 mmol) and imidazole (ImH) (4.30 g, 63.2 mmol) in DMF (7 mL) was added the alcohol **14** (3.56 g, 25.8 mmol) at ambient temperature. The warming was controlled by a water-bath. After being stirred at ambient temperature for 24 h, the mixture was diluted with n-hexane. The hexane phase was washed with water (2x25 mL) and then dried (Na_2SO_4). Concentration at reduced pressure followed by flash chromatography on silica gel column eluting with a mixture of 4:1 petroleum ether/ ether, gave the silyl ether **15** (6.77 g, 94% yield) as an oil: IR (liquid film): ν 2957, 1465, 1251, 1099, 832 cm^{-1}; ^1H NMR: δ 5.34 (m, 1H), 4.54-4.40 (m, 1H), 2.88-2.78 (m, 1H), 2.18-2.00 (m, 3H), 1.88-1.80 (m, 1H), 1.75 (s, 3H), 1.58 (hept, 1H, J = 6.95), 1.15 (s, 3H), 0.87 (d, 6H, J = 6.95), 0.80 (s, 6H), 0.05 (s, 6H). ^{13}C NMR: δ 141.66, 125.81, 68.08, 61.32, 48.35, 45.10, 37.31, 34.30, 25.15, 25.05, 20.51, 20.42, 18.64, 17.25, -2.54,-2.80.

Anal. Calcd for $C_{17}H_{32}OSi$: C, 72.79; H, 11.50. Found: C, 72.87; H, 11.55.

Hydroboration-oxidation of Bicyclic Alkenes **6** *and* **15**. *General Procedure:*

The hydroboration-oxidation of compound **6** or **15** was accomplished according to the procedure of C. F. Lane.[30] A dry 250 mL flask equipped with a mechanical stirrer, pressure-equilizing dropping funnel, and reflux condenser was flushed with dry nitrogen and mantained under a positive nitrogen pressure. The flask was then charged with the bicyclic alkene **6** or **15** (24.0 mmol) dissolved in dry THF (70 mL) and cooled at 0-5°C with an ice-water bath. Hydroboration was achieved by the dropwise addition of BMS (4.5 mL, 9 mmol) diluted with dry THF (20 mL). Following the addition of the hydride (15 min), the cooling bath was removed and the solution was stirred for 4 h at ambient temperature. Ethanol (45 mL) was then added followed by 3.0 mL of 3 M aqueous sodium hydroxide. After cooling to 0-5°C in an ice-water bath, hydrogen peroxide (3.0 mL of a 30% aqueous solution) was added dropwise at such a rate that the reaction mixture warmed at 25-35°C. Immediately following the addition of peroxide, the cooling bath was removed and the reaction mixture was heated at reflux for 1 h. The reaction mixture was then poured into 200 mL of ice and water and extracted with ether (2x 200 mL).

1,4,*endo*-Dimethyl-*cis*-bicyclo[3.2.0]heptan-3,*exo*-ol (12). The ethereal solution was washed with water (3x 30 mL), with saturared aqueous NaCl, dried over anhydrous potassium carbonate, filtered and, concentrated at reduced pressure to give 2.76 g of a light yellow oil. The crude product was purified by flash column chromatography eluting with 3:2 petroleum ether/ ether to obtain 2.25 g of compound **12** (67% yield). IR (liquid film): ν 3334, 2943, 2860, 1644, 1372, 1077, 1052 cm^{-1}. ^1H NMR: δ 4.18-4.02 (m, 1H), 2.32-2.20 (m, 1H), 2.00-1.58 (m, 7H, the signal becomes for 6H after treatment with D_2O), 1.4-1.10 (m, 1H), 1.22 (s, 3H), 1.00 (d, 3H, J = 6.8). ^{13}C NMR: δ 78.65 (CH-OH), 49.35 (CH_2), 46.80 (CH), 46.66 (CH), 41.09 (C), 32.03 (CH_2), 28.15 (CH_3), 15.21 (CH_2), 11.74 (CH_3).
Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.21; H, 11.54.

1,4,*endo*-Dimethyl-6,*endo*-dimethylthexylsilyloxy-*cis*-bicyclo[3.2.0]heptan-3,*exo*-ol (16). The work-up of the reaction mixture gave a crude product. Flash column chromatography on silica gel eluting with 4:1 petroleum ether/ ether gave 5.01 g (70% yield) of pure **16**: IR (liquid film): ν 3339, 2956, 1252, 1076, 831 cm^{-1}. ^1H NMR: δ 4.50-4.22 (m, 2), 2.42-2.30 (m, 1H), 2.18-1.48 (3 m, 6H), 1.38-1.20 (m, 1H), 1.17 (d, 3H, J = 7.2), 1.08 (s, 3H), 0.80 (d, 6H, J = 6.4), 0.74 (s, 6H), 0.00 (s, 6H). ^{13}C NMR: δ 78.94 (CH-OH), 65.85 (CH-Si), 52.68 (CH), 49.83 (CH_2), 46.11 (CH), 44.98 (CH_2), 35.68 (CH), 34.20 (CH_3), 27.28 (CH_3), 25.04 (C), 20.47 (CH_3), 20.35 (CH_3), 18.74 (CH_3), 18.68 (CH_3), 12.60 (CH), -2.56 (CH_3), -2.93 (CH_3).
Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 68.43; H, 11.41.

Oxidation of Bicyclic Alcohols **12** *and* **16**. *General Procedure:*

The oxidation of bicyclic alcohols **12** and **16** was performed according to the methodology of W. P. Griffith and S. V. Ley.[31] Solid tetra-n-propylammonium tetra-oxoruthenate(VII) (TPAP, 0.375 g, 1.07 mmol) was added in one portion to a stirred mixture of the alcohol **12** or **16** (21.3 mmol), N-methylmorpholine N-oxide (4.50 g, 38.4 mmol), and powdered 4Å molecular sieves (10 g) in dichloromethane (120 mL) at ambient temperature under nitrogen. On completion, the reaction mixture was filtered through a pad of silica eluting with dichloromethane. The filtrate was evaporated at reduced pressure and the residue was dissolved with ether to separate the catalyst which was collected by filtration.

1,4,*endo*-Dimethyl-*cis*-bicyclo[3.2.0]heptan-3-one (13). The ethereal filtrate was evaporated and the residue purified by flash chromatography eluting with 3:2 petroleum ether/ ether to obtain **13** (2.42 g, 82 % yield) as an oil. IR (liquid film): ν 2938, 2863, 1740 cm^{-1}. ^1H NMR: δ 2.72-2.47 (m, 2H), 2.33 (AB system, 2H, J = 13), 2.08-1.40 (m, 4H), 1.30 (s, 3H), 0.98 (d, 3H, J = 7.0). ^{13}C NMR: δ 220.78 (C=O), 51.16 (CH_2), 47.47 (CH), 46.50 (CH), 39.09 (C), 33.38 (CH_2), 27.86 (CH_3), 17.89 (CH_2), 8.84 (CH_3).
Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.25; H, 10.15.

1,4,*endo*-Dimethyl-6,*endo*-dimethylthexylsilyloxy-*cis*-bicyclo[3.2.0]heptan-3-one (17). The ethereal solution was concentrated at reduced pressure and the residue purified by column flash chromatography eluting with 1:1 petroleum ether/ ether. Compound **17** (4.91 g, 78 % yield) was obtained as an oil: IR (neat): ν 2957, 1745, 1253, 1040, 834 cm^{-1}. ^1H NMR: δ ($CHCl_3$) 4.42 (dt, 1H, J_d = 1.8, J_t = 6.2), 2.70-2.12 (m, 5H), 1-76-1.65 (m, 1H), 1.53 (hept, 1H, J_{hept} = 6.8), 1.18 (s, 3H), 1.10 (d, 3H, J = 7.2), 0.78 (d, 6H, J = 7.2), 0.74 (s, 6H), 0.00 (s, 6H). ^{13}C NMR: δ ($CHCl_3$) 219.35 (C=O), 67.58 (CH-OSi), 51.84 (CH2), 51.43 (CH), 46.30 (CH), 44.77(CH_2), 36.77 (C), 33.90 (CH_3), 27.42 (CH_3), 24.93 (C), 20.04 (CH_3), 18.62 (CH_3), 9.62 (CH), -2.61 (CH_3), -3.13 (CH_3).
Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.93; H, 11.02.

Methylation of Bicyclic Ketones **13** *and* **17.** *General Procedure.*

The introduction of the geminal methyl was accomplished by the procedure developped by C. A. Brown.[32] The metalation of **13** and **17** occurred readily by addition of the bicyclic ketones (18.45 mmol) dissolved in anhydrous THF (50 mL) to a vigorously stirred suspension of KH (3.60 g of 20% oil dispersion, 18.0 mmol) in anhydrous THF (50 mL) at 20°C. Hydrogen evolution commences immediately and is vigorous; the reaction mixture turned bright orange and then brown. When the evolution of hydrogen is complete (10 min) the reaction mixture was cooled at -45°C and methyl iodide (2.28 mL, 36.9 mmol) dissolved in anhydrous THF (15 mL) was slowly added under stirring. The reaction temperature was mantained at -45°C for 25 min and then allowed to rise 30°C. After 1 h, ether (200 mL) was added. The mixture was quenched into water (20 mL). The organic fraction was separated and washed twice with brine (20 mL), dried on Na_2SO_4, filtered and evaporated at reduced pressure.

1,4,4-Trimethyl-*cis*-bicyclo[3.2.0]heptan-3-one (11). The crude product was purified by flash chromatography on silica gel eluting with 95:5 petroleum ether/ ether to obtain 2.18 g of **11** (77 % yield) as an oil. All spectroscopic data are in perfect agreement with those previously reported.[16,27-29] IR (liquid film): ν 2966, 2866, 1736 cm^{-1}. ^1H NMR: δ 2.52 (d, 1H, J_{gem} = 19, C2H), 2.32 (d, 1H, J_{gem} = 19), 2.29 (t, 1H, J = 6.0), 2.08-1.28 (m, 4H), 1.35 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H). ^{13}C NMR: δ 223.13 (C=O), 53.74 (CH), 51.00 (C), 49.85 (CH_2), 38.29 (C), 32.98 (CH_2), 29.22 (CH_3), 26.30 (CH_3), 19.09 (CH_2), 18.05 (CH_3).
Anal. Calcd for $C_{10}H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.14; H, 11.48.

1,4,4-Trimethyl-6,*endo*-dimethylthexylsilyloxy-*cis*-bicyclo[3.2.0]heptan-3-one (18). The crude product was purified by flash chromatography on silica gel eluting with 4:1 petroleum ether/ ether to obtain 4.68 g of **18** (82% yield). IR (neat): ν 2961, 1737, 1252, 1098, 833 cm^{-1}. ^1H NMR: δ ($CHCl_3$) 4.35 (dt, 1H, J_d = 1.9, J_t = 6.4), 2.45 (AB, 2H, J = 18.7), 2.28 (d, 1H, J = 6.3), 1.77-1.63 (m, 1H), 1.54 (hept, 1H, J = 7.0), 1.27 (s, 3H), 1.12 (s, 3H), 0.92 (s, 3H), 0.80 (d, 3H, J = 6.9), 0.79 (d, 3H, J = 6.9), 0.76 (s, 3H), 0.74 (s, 3H), 0.00 (s, 6H). ^{13}C NMR: δ ($CHCl_3$) 221.88 (C=O), 67.27 (CH-OSi), 58.93 (CH_2), 50.39 (CH), 49.52 (C), 44.63

(CH_2), 36.25 (C), 33.94 (CH_3), 28.93 (CH_3), 27.38 (CH_3), 25.00 (C), 20.14 (CH_3), 20.07 (CH_3), 18.80 (CH), 18.64 (CH_3), -2.54 (CH_3), -3.12 (CH_3).
Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.75; H, 11.13.

1,4,4-Trimethyl-*cis*-bicyclo[3.2.0]heptan-6,*endo*-ol-3-one (19). Tetrabutylammonium fluoride (18.7 mL of 1M solution in THF) was added to a stirred solution of compound **18** (2.64 g, 8.52 mmol) in THF (25 mL). After 5 h at ambient temperature the reaction was quenched into a saturated aqueous solution of NH_4Cl and was extracted twice with ether. The organic phase was washed with brine, filtered, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 7:3 petroleum ether/ ether to obtain the free acohol **19** (1.20 g, 83% yield) as an oil. IR (liquid film): ν 3456, 2926, 1731 cm^{-1}. ^1H NMR: δ 4.35 (dt, 1H, J_d = 1.9, J_t = 6.4), 2.45 (AB, 2H, J = 18.7), 2.28 (d, 1H, J = 6.3), 2.12 (dd, 1H, J = 6.4), 2.00 (bs, 1H, OH), 1.77-1.63 (m, 1H), 1.30 (s, 3H), 1.15 (s, 3H), 0.93 (s, 3H).
Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.34; H, 9.51.

2,2,6-Trimethyl-3-oxa-*cis*-bicyclo[4.2.0]octan-8,*endo*-ol-4-one (20). To a solution of **19** (1.60 g, 9.52 mmol) in dry $CHCl_3$ (80 mL) was added anhydrous $NaHCO_3$ (1.92 g, 22.84 mmol). m-CPBA (4.12 g of commercial 50% m-CPBA, 23.80 mmol) was dissolved in $CHCl_3$ (60 mL) and the chloroformic phase was slowly dropped. The reaction mixture was stirred in the dark at ambient temperature for 7 h. After addition of 10 % Na_2SO_3 (10 mL) the reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated $NaHCO_3$ solution. Purification of the crude product by flash column chromatography eluting with ether gave **20** (1.28 g, 73% yield) as a white solid: mp 42-44°C. IR (KBr): ν 3428, 2957, 1699 cm^{-1}. ^1H NMR: δ 4.60 (dt, 1H, Jd = 4.6, Jt = 7.6), 3.50 (bs, 1H, OH), 2.53 (AB, 2H, J = 18.7), 2.43-2.25 (m, 2H), 1.87-1.72 (m, 1H), 1.62 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H). ^{13}C NMR: δ 176.80 (C=O),173.83, 83.20, 65.26, 51.36, 43.97, 42.40, 33.33, 30.09, 27.07.
Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.11; H, 8.69.

8,*endo*-Dimethylthexylsilyloxy-2,2,6-trimethyl-3-oxa-*cis*-bicyclo[4.2.0]octan-4-one (21). To a solution of **18** (0.23 g, 0.7 mmol) in CH_3COOH (2 mL) were added sodium acetate (0.41 g, 5 mmol) and 30% H_2O_2 (0.015 mL, 5 mmol). After standing four days at room temperature in the dark, to the reaction mixture was added a solution of $NaHSO_3$ (2.52 g in 7 mL of water). The mixture was then extracted with $CHCl_3$ and the organic layer was washed with saturated $NaHCO_3$. Purification of the crude product by flash chromatography (petroleum ether : ether = 7 : 3) afforded **21** (60 mg, 25% yield) as a clear oil. IR (film): ν 2958, 1742, 1253, 1047, 834 cm^{-1}. ^1H NMR: 4.58 (dt, 1H, Jd=5.1, Jt=7.7), 2.50 (AB system, 2H, J_{AB}=17.1), 2.15-2.32 (m, 2H), 1.58 (s, 3H),1.54-1.92 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H), 0.86 (d, 6H), 0.80 (d, 6H), 0.07 (2s, 6H).
Anal. Calcd. for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.29; H, 10.47.

Acknowledgments. 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. We gratefully acknowledge Istituto Guido Donegani- Novara-ENICHEM Group- for the provision of a Research Fellowship (to R.S.).

References and notes

1 For an excellent and autoritative review, see: Mori, K. *"The Synthesis of Insect Pheromones, 1979-1989"* in The Total Synthesis of Natural Products, J. ApSimon Ed. Vol IX, John Wiley & Sons, New York, 1992.

2 Campion, D. G. *"Survey of Pheromone Uses in Pest Control"* in Techniques in Pheromone Research, H. E. Hummel and T. A. Miller Ed.s, Cap. 14, Springer-Verlag, New York, 1984.

3 Ritter, F. J. *Agricolture, Ecosystems and Environment*, **1988**, *27*, 460. Silverstein, R. M. *Pure Appl. Chem.* **1982**, *54*, 2479-2488.

4 Tumlinson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thomson, A. C.; Hedin, P. A.; Minyard, J. P: *Science* **1969**, *166*, 1010-1012.

5 Hedin, P. A.; *CHEMTECH* **1976**, 444-451.

6 MacConnell, J. G.; Borden, J. H.; Silverstein, R. M.; Stokkink, E. *J. Chem. Ecol.* **1977**, *3*, 549-561.

7 Dickens, J. C.; Mori, K. *J. Chem. Ecol.* **1989**, *15*, 517-528.

8 Mori, K.; Tamada, S.; Hedin, P. A. *Naturwissenschaften* **1978**, 65, 653-4.

9 (a) Borden, J. H.; Handley, J. R.; Johnston, B. D.; Mac Conell, J. G.; Silverstein, R. M.; Slessor, K. N.; Swigar, A. A.; Wong, D. T. W. *J. Chem. Ecol.* **1979**, *5*, 681-689. (b) Borden, J. H.; Oehlschlager, A. C.; Slessor, K. N.; Chong, L.; Pierce, H. D. *Can. Entomol.* **1980**, *112*, 107-109. (c) King, C. J.; Oehlschlager, A. C.; Borden, J. H. *Angew. Entomol.* **1983**, *95*, 531-533.

10 Grandisol is also released by females of the ambrosia beetle *Trypodendron signatum* L. (Francke, W. - *Convergency and Diversity in Multicomponent Insect Pheromones.* In "Advances in Invertebrate Reproduction- 4" M. Porchet, J.-C. Audries, and A. Dhainant Editors- Elsevier Science Publishers, **1986**, 327-336.), by males of bark beetles *Pityophthorus pityographus* (Francke, W.; Pan, M.-L.; Konig, W. A.; Mori, K.; Puapoomchareon, P.; Heuer, H.; Vitè, J. P.; *Naturwissenschaften* **1987**, *74*, 343-345), of *Pityogenes quadridens* and of *P. calcaratus* (Francke, W.; Bartels, J.; Krohn, S.; Schulz, S.; Baader, E.; Tengo, J.; Schneider, D. *Pure Appl. Chem.* **1989**, *61*, 539-542), of *Pissodes memorensis* (Phillips, T. W.; West, J. R.; Foltz, J. L.; Silverstein, R. M.; Lanier, G. N. *J. Chem. Ecol.* **1984**, *10*, 1417-1423.) and other *Pissodes* weevils (Booth, D. C.; Phillips, T. W.; Claeson, A.; Silverstein, R. M.; Lanier, G. N.; Wesr, J. R. *J. Chem. Ecol.* **1983**, *9*, 1-12.).

11 Lineatin is also produced by *T. signatum*, together with grandisol (Francke, W. *-Convergency and Diversity in Multicomponent Insect Pheromones.* In "Advances in Invertebrate Reproduction- 4" M. Porchet, J.-C. Audries, and A. Dhainant Editors- Elsevier Science Publishers, **1986**, 327-336.) and it was shown that sticky traps containing (+)-lineatin attracted the predator *Thanasimus formicaris*. The results indicated that *T. lineatum* is an important prey for *T. formicarius* (Tommeras, B. A. *Experientia* **1988**, *44*, 536-537; Tommeras, B. A.; Mustaparta, H. *Naturwissenschaften* **1985**, *72*, 604-606.)

12 Mori, K.; Fukumatsu K. *Liebigs Ann. Chem.* **1992**, 489-493.

13 Langer, K.; Mattay, J.; Heidbreder, A.; Moller, M. *Liebigs Ann. Chem.* **1992**, 257-260.

14 Hoffmann, N.; Scharf, D. *Liebigs Ann. Chem.* **1991**, 1273-1277.

15 Mori, K.; Nagano, E. *Liebigs Ann. Chem.* **1991**, 341-344.

16 Sonawane, H. R.; Naik, V. G.; Bellur, N. S.; Shah, V. G.; Purohit, P. C.; Kumar, M. U., Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron* **1991**, *38*, 8259-8276.

17 Grandguillot, J.-C.; Rouessac, F. *Tetrahedron* **1991**, *47*, 5133-5148.

18 Narasaka, K.; Kusama, H.; Hayashi, Y. Bull. *Chem. Soc. Jpn.* **1991**, *64*, 1471-1478.

19 Kim, D.; Lee, Y. K.; Jang, Y. M.; Kim, I. O. Kim; Park, S. W *J. Chem. Soc. Perkin Trans. 1* **1990**, 3221-3224.

20 Baeckstrom, P.; Li, L.; Polcv, I.; Unelius, C. R.; Wimalisiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358-3362.

21 Rosini, G.; Marotta, E.; Petrini, M.; Ballini, R. *Tetrahedron* **1985**, *41*, 4633-4638.

22 Rosini, G.; Marotta, E.; Raimondi, A.; Righi, P. *Tetrahedron: Asymmetry* **1991**, *2*, 123-138.

23 Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, 5413-5419.

24 For an excellent review on the intramolecular cycloadditions reactions of ketenes and ketenimminium salts with alkenes, see: Snider, B. B. *Chem. Rev.* **1988**, *88*, 793-811.

25 Rosini, G.; Serra, R.; Rama, F.; Confalonieri, G.-ENICHEM S.p.A.-Istituto Guido Donegani S.p.A-European Patent Application n.92201957.5 (1 July 1992).

26 Rathke, M. W.; Lindert, A. *J. Org. Chem.* **1970**, *35*, 3966-3967.

27 Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082-1087.

28 Ayer, W. A.; Browne, L. M. *Can. J. Chem.* **1974**, *52*, 1352-1360.

29 Wenkert, E.; Berges, D. A.; Golob, N. F. *J. Am. Chem. Soc.* **1978**, *100*, 1263-1278.

30 Rosini, G.; Geier, M.; Marotta, E.; Petrini, M.; Ballini, R. *Tetrahedron* **1986**, *42*, 6027-6032.

31 Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437-1438.

32 Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627. Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13-20.

33 Brown, C. A. *J. Org. Chem.* **1974**, *39*, 1324-1325.

34 Matsuo, K.; Kinuta, T.; Tanaka, K. *Chem. Pharm. Bull.* **1981**, *29*, 3047-3050.

35 Grudzinski, Z.; Roberts, S. M.; Howard, C.; Newton, R. F. *J. Chem. Soc. Perkin I* **1978**, 1182-1186.

36 Canan Koch, S. S.; Chamberlin A. R. *Synth. Commun.* **1989**, *19*, 829-833.

37 Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423-425.

38 Hirano, M.; Oese, M.; Morimoto, T. *Chem. Letters* **1991**, 331-332.

39 Grieco, P.A.; Vedananda, T. R. *J. Org. Chem.* **1983**, *48*, 3497-3502.

40 Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney,H.; Thompson, N. *Synthesis* **1987**, 1015-1017.

41 McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987**, *43*, 1753-1758.

42 Suzuki, M.; Takada, R.; Noyori, R.; *J. Org. Chem.* **1982**, *47*, 902-904.

43 Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron* **1983**, *39*, 1735-1743..

44 Ortiz de Montellano, P. R.; Dinizo, S. E. *J. Org. Chem.* **1978**, *43*, 4323-4328.

45 Fleming, I. *Chem. & Ind. (London)* **1975**, 449. Fleming, I.; Au-Yeung, B.-W. *Tetrahedron (suppl)* **1980**, 13-24.

46 For excellent and autoritative reviews, see: Bellus, D.; Ernst, B. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 797-827. Ali, S. M.; Lee, T. V.; Roberts, S. M. *Synthesis* **1977**, 155-166.

47 Schiess, P.; Fünfschilling, P. *Helv. Chim. Acta* **1976**, *59*, 1745-1755.

48 Snider, B. B.; Allentoff, A. J.; Kulkarni, Y. S. *J. Org. Chem.* **1988**, *53*, 5320-5328.

(*Received in UK* 22 *October* 1993; *revised* 31 *December* 1993; *accepted* 7 *January* 1994)