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*STEREOSELECTIVE TOTAL SYNTHESIS OF RACEMIC GRANDISOL via 3-OXIMINO-1,4,4-TRIMETHYLBICYCLO[3.2.0]HEPTANE. AN IMPROVED PRACTICAL PROCEDURE.***

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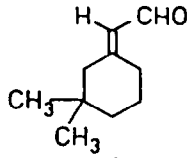
Abstract - (±)Grandisol was stereoselectively obtained via 1,4,4-trimethylbicyclo[3.2.0]heptane-3-one and its oxime by an improved procedure. 2,5,5-Trimethylhept-1,6-dien-4-ol, the open chain molecule, was synthesized by two routes. Its conversion into ( )grandisol was performed emploing the photobicyclization as key step.

The sex pheromone complex (grandlure) emitted by live male boll weevil (**Anthonomus grandis Boheman**) was identified[1,2] as a synergistic combination of four monoterpenes: three of them having a cyclohexane structure (1, 2 and 3) and one with a structure corresponding to (+)-cis-2-isopropenyl-1-methylcyclobutaneethanol (4), the trivial name of which is grandisol.



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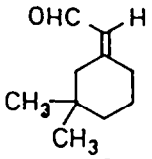

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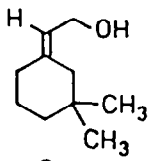

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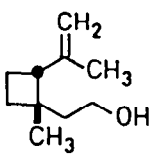

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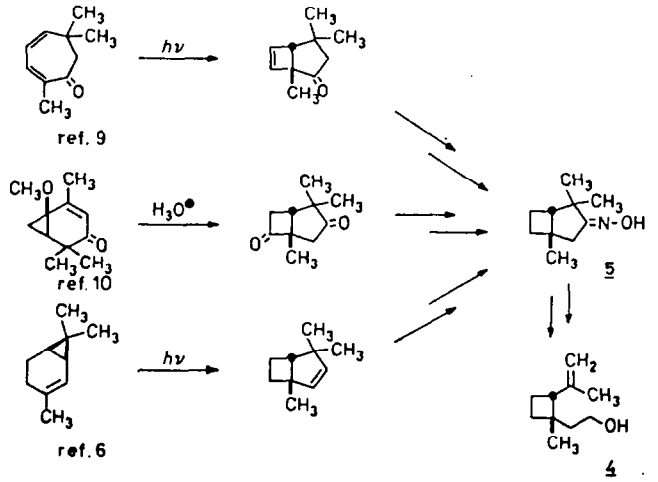
The synthesis of grandisol has been a challenge for many organic chemists and has resulted in several ingenious processes.[2-10]

In a previous paper[7] we outlined the objectives and our efforts to synthesize racemic grandisol. Our plans called for a synthesis amenable to large-scale preparation and based on inexpensive materials. A successful achievement of these goals was described in that paper.[7] Now we report on another convenient approach to 4.

** This work was presented by G.R. as a part of his lecture at the "Colloques sur la Chimie des Terpenes", Grasse, France (April, 1986). The chemical experimental part of this work was taken from the Tesi di Laurea of M.G. (March, 1986) at the University of Bologna, Faculty of Industrial Chemistry.

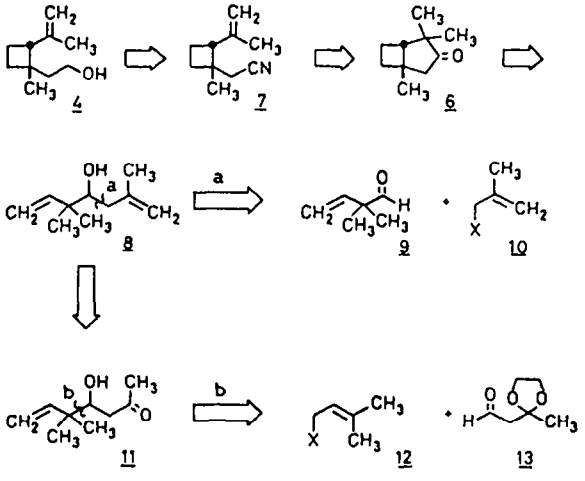
A survey of the literature revealed to us that three syntheses[6,9,10] of racemic grandisol use 3-oximino-1,4,4-trimethylbicyclo|3.2.0|heptane (5) as key intermediate.



Scheme 1.- 3-Oximino-1,4-4-trimethylbicyclo|3.2.0|heptane as key intermediate in syntheses of racemic grandisol.

This one was efficiently converted into the target molecule:[9] in fact, an easy Beckmann cleavage of oxime, performed with phosporus pentachloride followed by hydrolysis, gave 2-isopropenyl-1-methylcyclobutane acetic acid that finally underwent reduction with lithium aluminum hydride to give racemic grandisol.

Unfortunately, all of the above routes suffer from certain relevant disadvantages in the preparation of 3-oximino-1,4,4-trimethylbicyclo|3.2.0|heptane (5). In Scheme 1 some peculiar aspects of these syntheses are summarized to stress the major drawbacks of them.[11]

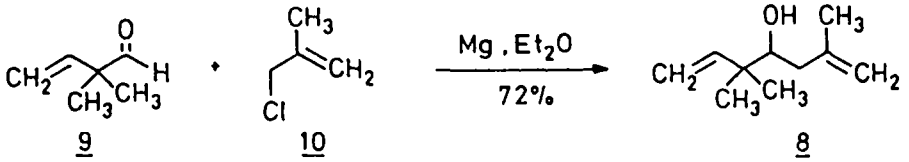


Scheme 2.- Retrosynthetic analysis of our synthetic plan to prepare 1,4,4-trimethylbicyclo|3.2.0|heptan-3-one.

The retrosynthetic analysis depicted in Scheme 2 illustrates the key steps of

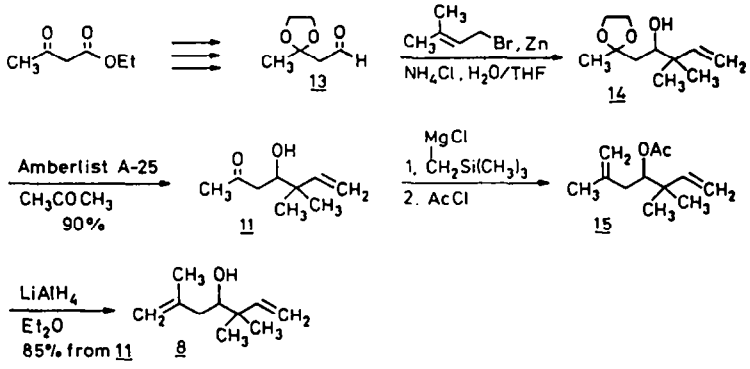
our synthetic plan. We based our strategy on the hypothesis that the preparation of the bicyclo|3.2.0|heptane system could be possible by a photobicyclization of a linear dienol, the 2,5,5-trimethylhept-1,6-dien-4-ol (**8**). The preparation of the latter could be accomplished by following two routes. The **a** route uses 2,2-dimethylbut-3-enal (**9**) and methallyl halide (**10**) as parent compounds. The **b** route is less direct and uses γ,γ-dimethylallyl halide (**12**) and the ketal of 3-oxobutanal (**13**) as parent compounds.

Several preparations of **9** are available,[12,17] but we chose the elegant and practical synthesis of M. Julià and M. Baillarge.[18] With the starting materials readily available, the preparation of compound **8**, via route **a**, was completed following the Barbier's procedure.[19]



9 **10** **8**

Scheme 3 show the execution of route **b** to prepare the same intermediate **8**. Our procedure uses compound **13** as starting material; this one is easily available from ethyl acetoacetate.[20,21] The allylation of compound **13** has been performed using a highly efficient procedure recently discovered by Luche et al.[22] The reaction was carried out adding zinc dust to a stirred suspension of aldehyde **13** and dimethylallyl bromide (**12**) in a mixture of saturated aqueous ammonium chloride and tetrahydrofuran (5:1).



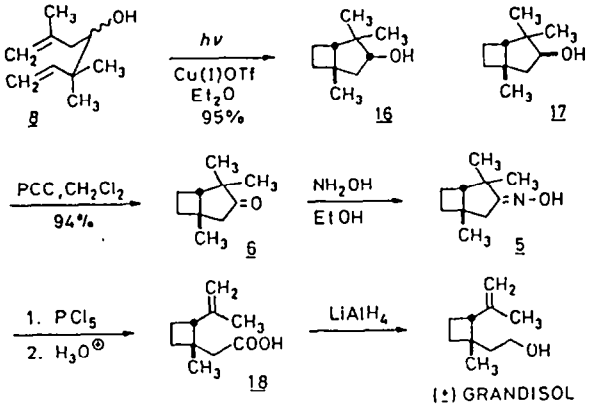
13 **14** **11** **15** **8**

Scheme 3.- Execution of route **b**.

Homoallylic alcohol **14** was obtained in high yield and the crude hydroxyketone **11** was directly treated with an excess of trimethylsilylmethylmagnesium chloride. After working up, a mixture of the acetyl derivative **15** and compound **8** could be isolated in good yield and it was converted into pure 2,5,5-trimethylhept-1,6-dien-4-ol (**8**) by $LiAl_4H_4$ reduction.

The next task of our plan was the conversion of compound **8** into the bicyclo-

ketone **6**. Photobicyclization of 2,5,5-trimethylhept-1,6-dien-ol (**8**) was accomplished in presence of copper(I)trifluoromethansulfonate (CuOTf) as catalyst according to the procedure of Salomon and cow.[23] A mixture of bicycloalcohols **16** and **17** was obtained after 65 hr of UV irradiation of compound **8** (6.0 g) with a Hanovia medium pressure 450 W mercury vapor lamp. During this period it was possible to observe the complete disappearance of linear dienol **8**.



Scheme 4.- Photobicyclization and conversion into racemic grandisol.

The mixture of bicycloalcohols **16** and **17** was converted into the bicycloketone **6** by oxidation with pyridinium chlorochromate in dichloromethane. The sequence continues with a conversion of **6** into the corresponding oxime by the procedure of Wenkert and cow.[10] Finally, the treatment of oxime with phosphorus pentachloride followed by hydrolysis and successive reduction of compound with lithium alluminum hydride, according to the known procedure of Ayer and Brown,[9] let us obtain racemic grandisol.

In conclusion, our procedure is an improvement of previous synthetic schemes in which 3-oximino-1,4,4-trimethylbicyclo|3.2.0|heptane was obtained in a more convenient fashion, and requires a minimum amount of intermediate purification.

EXPERIMENTAL

Proton NMR spectra were recorded at 90 MHz on a Varian EM390 instrument and at 100 MHz on a Varian XL-100 operating in the CW mode. Proton noise decoupled ^{13}C spectra were recorded at 25.15 MHz with a Varian XL-100 by the FT technique. Resonance assignments were made with the aid of the off-resonance technique. ^{1}H NMR and ^{13}C shifts are given in parts per million from Me_4Si in $CDCl_3$ solvent. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer. Microanalyses were performed by using C,H,N Analyser model 185 from Hewlett-Packard Co. Vapor phase chromatographic analyses were performed on a Carlo Erba Fractovap 4160 HRCG instrument using capillary column of duran glass (0.3-0.32 mm x 25 mt), stationary phase OV1 (film thickness 0.4-0.45 nm). Irradiations were conduced under dry nitrogen in cylindrical Pyrex vessels with a quartz water-cooled double-walled immersion well. The reaction mixtures were stirred magnetically and irradiated internally with a Hanovia medium pressure 450 W mercury vapor lamp. Diethyl ether and tetrahydrofuran (THF) were obtained anhydrous by distillation over lithium alumninum hydride.

(±)3,3,6-Trimethylhepta-1,6-dien-4-ol (8). The reaction was performed in nitrogen atmosphere; to a 500 ml dry reaction vessel, provided with a mechanical stirrer and a reflux condenser, anhydrous diethyl ether (100 ml) and magnesium turnings (3.5 g, 0.15 g-atom) were added. The magnesium was attivated with few drops of 1,2-dibromoethane, and then methallyl chloride (8.7 g, 0.10 mol) and 2,2-dimethyl-3-butenal (9) (9.5 g, 0.10 mol) dissolved in dry diethyl ether (100 ml) were added to the reaction mixture. During this addition period the solvent reflux gently. After the addition was complete, the reaction mixture was allowed to stand at room temperature for additional 5 hr and then hydrolysed by pouring to ice/ammonium chloride. The ether layer was separated from the aqueous layer which was then further extracted with diethyl ether several times. The ether solution was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was distilled to give 10.6 g (72%) of 8 as an oil, b.p. 72-74°C/16 mmHg. IR (neat): ν = 1647 (C=C), 3479 (OH) cm^{-1}. ^1H NMR: δ 5.88 (dd,1H, J_1=19.5 Hz; J_2=10.0 Hz; 5.08 (m,1H); 4.86 (bs,1H); 4.80 (bs,1H); 3.43 (dd,1H, J_1=10.0 Hz; J_2=2.0 Hz); 2.23 (d,1H,J=13.5 Hz); 1.97 (m,1H); 1.76 (s,3H); 1.05 (s,6H) ppm. ^{13}C NMR: δ 145.17 (=CH-); 145.50 (=C); 113.20 (=CH_2); 112.70 (=CH_2); 74.87 (-CH); 41.00 (-C-); 40.50 (-CH_2); 22.84 (-CH_3); 22.70 (-CH_3); 22.12 (-CH_3) ppm. Anal Calcd for $C_{10}H_{18}O$: C,77.86; H,11.76. Found: C,77.95; H,11.85.

(±)6,6-Ethanediyldioxy-3,3-dimethylhept-1-en-4-ol (14). To an equimolar mixture of aldehyde 13 (6.5 g, 0.05 mol) and 1-bromo-3-methyl-2-butene (8.9 g, 0.06 mol) in THF (10 ml) and aqueous saturated NH_4Cl soln (50 ml), zinc dust (3.9 g, 0.06 mol) was added with ether (3 x 100 ml). The organic soln was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled to give 9.3 g of 14 (93%): b.p. 116-118°C/16.5 mmHg. IR (neat): ν =1637 (C=C), 3525 (OH)cm. ^1H NMR: δ 5.90 (dd,1H, J_1=19.5 Hz, J_2=10.0 Hz); 5.30-5.10 (m, 1H); 5.00-4.80 (m,1H); 4.00 (s,4H); 3.50 (dd,1H,J_1=10.0; J_2=2.0 Hz); 3.42 (bs,1H);2.00-1.50 (m,2H); 1.37 (s,3H); 1.07 (s,6H) ppm. Anal.Calcd for $C_{11}H_{20}O_3$: C, 65.97;H, 10.07. Found: C, 66.09; H, 9.93.

(±)3,3-Dimethylhept-1-en-4-ol-6-one (11). Amberlist A-15 (4.0 g) and water (6.0 ml) were added to a stirred solution of ketal 14 (20.0 g, 0.10 mol) in acetone (200 ml). The mixture was stirred for 24 hr at room temperature. Then it was filtered and the solution was evaporated at reduced pressure. The residue was taken with ether. The soln was washed with brine, dried (Na_2SO_4) and evaporated at reduced pressure to give 4.0 g of 3-hydroxy ketone 11 (90%). IR (neat): ν =1712 (C=O), 3482(OH)cm^{-1}. ^1H NMR:δ5.95 (dd,1H,J_1= 19.5 Hz; J_2= 10.0 Hz); 5.30-5.20 (m,1H); 5.10-4.90 (m,1H); 4.05-3.75 (m,1H); 2.70-2.45 (m,2H); 2.23 (s,3H); 1.07 (s,6H) ppm.

Conversion of compound 11 into (±) 3,3,6-Trimethylhepta-1,6-dien-4-ol (8). To a stirred solution of trimethylsilylmethylmagnesium chloride, made from chloromethyltrimethylsilane (16.2 g, 0.12 mol) and magnesium turnings (2.8 g, 0.12 mol) in dry diethyl ether (200 ml), was added a solution of -hydroxyketone 11 (9.1 g, 0.06 mol) in dry diethyl ether (80 ml). After 1 hr, acetyl chloride (12.4 ml, 0.21 mol) was added and the reaction mixture was allowed to stand under stirring for 20 hr at room temperature. Then it was cooled at 0°C and hydrolyzed by the dropwise addition of a saturated NH_4Cl soln. The coagulated solid was filtered off and washed with diethyl ether. The organic soln was washed with 10% aqueous Na_2CO_3 and brine, dried (Na_2SO_4) and evaporated to remove the solvent. Distillation of the residue gave 10.00 g of a mixture of 8 and the corresponding acetate 15 in a 3:2 ratio. This crude product (10.0 g) was dissolved in diethyl ether (80 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (2.2 g, 0.06 mol) in diethyl ether (180 ml). After 1 hr at room temperature, the reaction mixture was cooled with a ice-water bath and saturated aqueous soln of NH_4Cl was slowly added. The ethereal solution was separated, washed with brine, and dried (Na_2SO_4). Solvent was evaporated at reduced pressure. The residue was distilled to give 8 (7.7 g, 85%): b.p. 72-74°C/16 mmHg. The spectral data of this sample (IR, ^1H NMR) were identical with those registered on the compound obtained by route a.

(±)1,4,4-Trimethylbicyclo[3.2.0]heptan-3-one (6). Hydroxyheptadiene 8 (7.3 g, 0.047 mol) in diethyl ether (300 ml) with coprous trifluormethanesulphonate-benzene complex (0.4 g, 0.008 mol) was irradiated with an internal 450-W Hanovia mercury lamp. Complete conversion of 8 into two epimers 16 and 17 (3:1) was observed after 65 hr by capillary chromatography of the reaction mixture. The ethereal solution was quenched with a mixture of ice (100 g) and 15% NH_4OH (100 ml). The aqueous phase was extracted with ether (3 x 50 ml) and the combined extracts were washed again with brine (3 x 30 ml) and then dried with Na_2SO_4. Solvent was removed by evaporation at normal pressure and then at reduced pressure by rotary evaporation. The residue was distilled to give a mixture of 16 and 17 (6.6 g, 90%): b.p. 125-140°C/2.5 mmHg. The stirred mixture of 16 and 17 (5.02 g, 0.032 mol) was dissolved in dichloromethane (200 ml) and added with pyridinium chlorochromate (PCC) (10.5 g, 0.049 mol) and Celite (9.7 g). The stirring was continued at room temperature during 4 hr and reaction progress was monitored by vapor phase chromatography. The residue was diluted with ether (300 ml) and decanted. The residue was washed several times with ether. The ethereal soln was filtered through Fluorisil. Removing of the solvent under reduced pressure afforded 6 (4.58 g, 94%): IR (neat): ν=1740 (C=O) cm^{-1}. ^1H NMR: δ 2.49 (d,1H,J=19.0 Hz); 2.30 (d,1H,J=19.Hz); 2.00-1.40 (m,3H); 1.30-1.00 (m,2H); 1.31,0.97,0.95(s, 3H each) ppm. Anal. Calcd for $C_{10}H_{16}O$: C,78.89; H,10.51. Found: C,79.05; H,10.68.

(±)3-Oximino-1,4,4-trimethylbicyclo|3.2.0|heptane (5). Oximation of bicyclo|3.2.0|heptanone **6** (3.04 g, 0.02 mol) was performed with hydroxylamine hydrochloride (2.78 g, 0.04 mol) and potassium carbonate (5.52g, 0.04 mol) in refluxing ethanol (40 ml). After 3 hr the solution was cooled and evaporated at reduced pressure. Then the residue was taken with chloroform (50 ml) and washed with brine, dried (Na_2SO_4) and evaporated. Crystallization of the residue from aqueous ethanol gave **5** (2.67 g, 80%): m.p. 119°C (lit. 118-119°C). Anal. Calcd for $C_{10}H_{17}NO$: C,71.81; H, 10.25; N,8.38. Found: C,72.05; H,10.32; N,8.15.

(±)Grandisol (4). The conversion of **5** into **4** was performed according to the procedure previously reported. Oxime **5** (3.0 g, 0.018 mol) was treated with phosphorus pentachloride (3.74 g, 0.018 mol) and 2,6-lutidine (3.0 ml) in dry ether (200 ml) to give crude seconitrile that was hydrolyzed with potassium hydroxide (2.5%) in a mixture of ethylene glycol-triethylene glycol dimethyl ether (1:1) in a sealed tube at 200°C for 38 hr. Work-up of the mixture gave **18** (1.87 g, 70%) that was taken with dry ether (100 ml). Cyclohexylamine (1.7 ml, 0.015 mol) was added to this ethereal soln and the suspension was allowed to stand at room temperature for 1 hr; then it was cooled and a soln of $LiAlH_4$ in dry ether (1M, 20 ml) was added dropwise. The reaction mixture was stirred for 5 hr, at room temperature and then water was added to destroy the hydride excess. The ethereal soln was washed with 5% HCl, brine and dried (Na_2SO_4). Ether was removed at normal pressure and the residue was distilled and gave 1.35 g of racemic grandisol (**4**): b.p. (bath temperature) 100-125°C/ 15 mmHg. The IR, ^1H NMR and GC retention time were identical with those of an authentic sample prepared in a indipendent way.[7]

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11. The most relevant limits of the Ayer and Browne[9] procedure are the following: a long period of irradiation (7 days), a low yield of bicyclo product (52%) and the necessity to carry out the migration of the carbonyl into the adjacent position. In the Wenkert and al. procedure,[10] functional homogeneity of bicyclo |3.2.0|heptanedione is the major hindrance of their elegant procedure. Further, partial thioketalization, chromatographic separation, purification, regeneration of bicyclo |3.2.0|heptanedione and its reutilization are all redundant operations of a difficult work-up to perform the selective deoxygenation of the carbonyl in C6. Finally, in the synthesis of Sonawane et al.[6] the high diluition needed to effect the photoinduced vinylcyclopropane rearrangement of Δ^2-carene to 1,4,4-trimethylbicyclo|3.2.0|-hept-2-ene, and the low stereoselectivity in the epoxydation, made this quite a time consuming and unpractical route. In fact, a mixture of 3- and 2-ketobicyclo isomers was obtained from the mixture of endo- and exo-epoxide by consecutive reduction and oxidation.
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