Tetrahedron Vol 41, No. 20, pp 4633 to 4638, 1985
Printed in Great Britain.

0040-4020/85 $3.00+.00

STEREOSELECTIVE TOTAL SYNTHESIS OF RACEMIC GRANDISOL. AN IMPROVED CONVENIENT PROCEDURE

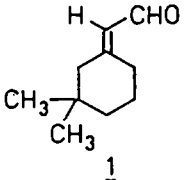
GOFFREDO ROSINI,* EMANUELA MAROTTA
Istituto di Chimica Organica, Università, V.le Risorgimento 4, I-40136 Bologna
and
MARINO PETRINI, ROBERTO BALLINI
Dipartimento di Scienze Chimiche, Università, Via S.Agostino 1, I-62032 Camerino

(*Received in UK* 27 *June* 1985)

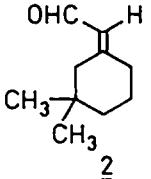
Abstract: (±) Grandisol has been stereoselectively synthesized in a 31% overall yield by a practical and convenient procedure employing the Salomon photobicyclization as the key-step.

The use of pesticides for insect control has been the focus for considerable criticism, especially owing to their harmful effects on wildlife and the human health hazards associated with pesticide residues found in our foods. However, chemical control will remain essential if production of food and natural fibre is to avoid falling to an unacceptable low level. In recent years, considerable attention has been focussed on finding alternative approaches to the use of conventional pesticides in the control of insect pests.[1] As a result, there has been a great interest in the understanding of the chemicals responsible for sensory communications among insects such as pheromones.[2-5] A large number of pheromones has been investigated, but of these, the ones that pertain to agricultural pests have received greater attention. In particular the boll weevil (**Anthonomus grandis Boheman**), one of the responsible for the major destruction of cotton crop.

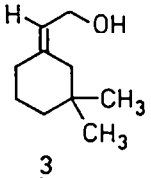
The sex pheromone complex (grandlure) emitted by live male boll weevils was identified[6,7] as a synergistic combination of (E)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (1), its (Z)-isomer (2), (Z)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (3), and (+)-cis-2-isopropenyl-1-methylcyclobutaneethanol (4), trivial name of which is grandisol.[8,9]



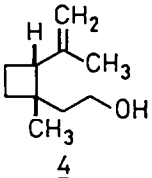
1



2



3



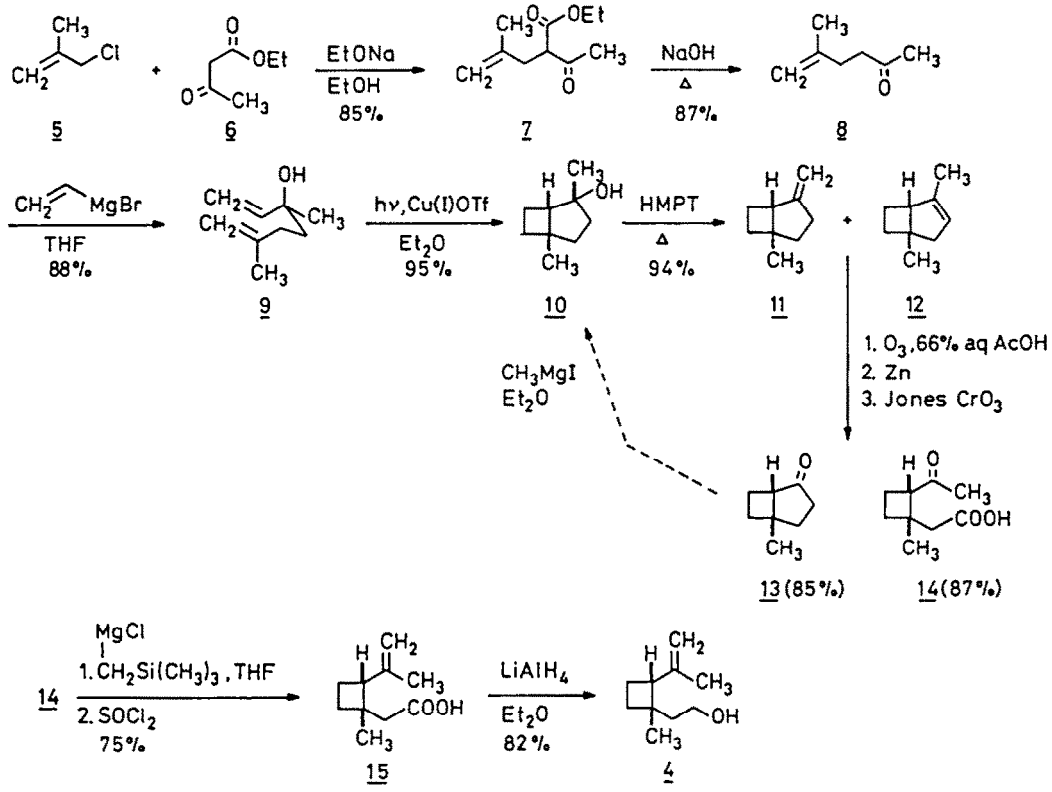
4

From a structural point of view, the most intriguing compound found in grandlure is grandisol. Because of its interesting structure and its potential commercial

importance, the synthesis of grandisol has been a challenge for many organic chemists and has resulted in several ingenious processes.[8,10-12] Although stereoselective photochemical and non-photochemical multi-step syntheses described in literature are elegant, we believe there is still a need for an approach that is stereoselective, and also practical. In undertaking the synthesis of (±) grandisol we attempted to designe a route which would not only be aesthetically satisfying but also commercially acceptable.

In a previous communication[10] one of us showed that cis-(±)2,5-dimethylbicyclo [3.2.0]heptan-2-ol (10) is clearly an ideal intermediate for the efficient and stereoselective preparation of cis-(±)2-acetyl-1-methylcyclobutaneacetic acid (14), a well known[8,10] precursor of 4.

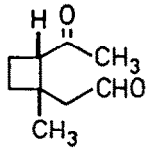
We now wish to present an highly efficient and practical synthesis of (±)grandisol in which all carbon atoms of target molecule are derived from readily available and cheap starting materials. Scheme 1 summarizes our strategy and the most relevant features of the execution of the plan are detailed below.



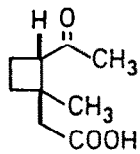
Scheme 1

Treatment of methallyl chloride (5) and ethyl acetoacetate (6) with sodium ethoxide in ethanol gave 7 that produced 2-methylhex-1-en-5-one (8) in 72% overall yield by hydrolisis and successive decarboxylation. Compound 8 has been converted in good yield (88%) to the dienic alcohol 9 with vinylmagnesium bromide. Photobicyclization of 3,6-dimethylhepta-1,6-dien-3-ol (9) was accomplished in presence of copper(I)trifluoromethansulfonate (CuOTf) as catalyst according to the procedure of

R.G. Salomon and coworkers.[13] cis-(±)-2,5-Dimethylbicyclo|3.2.0|heptan-endo-2- ol (**10**) was generated stereoselectively in a clean, high yield reaction in which 95% of conversion was observed after 12 hr of UV irradiation of 24 g of **9** with an Hanovia medium pressure 450 W mercury vapor lamp. By heating bicyclo|3.2.0|heptan-2-ol **10** in an excess of hexamethyl phosphoric triamide at 190-195°C, dehydration occurred and bicycloalkenes **11** and **12** distilled together with dimethylamine from the reaction mixture.[10] The crude olefinic material was obtained in nearly quantitative yield as a 7:3 mixture of endo- and exo-isomers as clearly indicated by ^{1}H N.M.R. spectrum. Cleavage of double bond was performed on the mixture of alkenes by ozonolysis[14] followed by reductive workup with zinc dust. The reaction mixture of bicycloketone **13** and ketoaldehyde **16**, in turn, was treated directly with Jones CrO_3 Oxidation proceed smoothly to give **13** and ketoacid **14** in respectively 85% and 87% yield. Once again a very simple workup allowed us to achieve the separation of acidic **14** from neutral **13**. The latter was recovered sufficiently pure to be converted to bicycloalcohol **10** by reaction with methyl magnesium iodide and could thus be recycled. Our procedure to perform oxidative cleavage was sufficiently mild to prevent the formation of the trans- isomer **17** from cis-keto-acid. This was evident in the ^{1}H N.M.R. of crude product, since the C-1 methyl protons of cis- isomer exhibit a peak at δ 1.40 while those of the trans- isomer[8] could exhibit a signal at δ 1.10. At this point our synthesis strategically intersects the procedure originally developed by Zurfluh and coworkers.[8] Methylenation of **14** was accomplished using trimethylsilylmethylmagnesium chloride and thionyl chloride[15] and gave **15** in 75% yield without epimerization occurred during the reaction. In agreement with earlier observations, the ^{1}H N.M.R. spectrum of crude **15** lacked signals attributable to the isomeric trans- derivative.[8] Finally lithium aluminium hydride reduction in diethyl ether provided racemic grandisol (**4**) which exhibited the physico-chemical properties identical with those reported.



16



17

Conclusions. We have described an improved highly efficient and stereoselective route to racemic grandisol in which every synthetic operation contributes concretely to the assembly of the target molecule. This eight steps procedure provides (±)grandisol in 31% overall yield based on starting methallyl chloride and ethyl acetoacetate, and requires a minimum amount of intermediate purification. Our route takes advantage of the Salomon's new method of cyclobutane synthesis by intramolecular photobicyclization[13], of an easy dehydration of **10** which occurs without any problem and an high yielding ozonolysis procedure.(±)-5-Methylbicyclo-|3.2.0|heptan-2-one (**13**), the only significant side product, can be used again by reaction with methylmagnesium iodide. Judging from readily available reagents employed and simple experimental operations, the present method seems promising for scale preparations of racemic grandisol.

EXPERIMENTAL

Proton NMR spectra were recorded at 90 MHz on a Varian EM 390 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 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 on a Carlo Erba Fractovap 4160 HRGC instrument using capillary column of fused silica (0.40-45 nm x 25 mt) with Carbovax 20 M. 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. Ozonolyses were performed by using an ELBE OZO/B ozone generator working at 11,000 volts with an oxygen flow of 20 l/h. Methallyl chloride, ethyl acetoacetate, vinyl bromide, cuprous trifluormethanesulfonate-benzene complex, methyl iodide, chloromethyltrimethylsilane, magnesium turnings and lithium aluminium hydride are commerciale materials. Diethyl ether and tetrahydrofuran (THF) were obtained anhydrous by distillation over lithium aluminium hydride under argon.

(±)3-Methyl-4-carboethoxyhexan-5-one (7). A 500 ml three necked flask equipped with mechanical stirrer, reflux condenser, dropping funnel and nitrogen flush was charged with 60 ml of abs ethanol and then metallic sodium (4.18 g, cut into pieces) was gradually added. After all the sodium was dissolved and temperature decreased until 15°C, ethyl acetoacetate (26.28 g, 0.20 mol) was added. The solution was stirred 1.5 h at room temperature and then -methallyl chloride (16.48 g, 0.18 mol) was added over a period of 1 h. The reaction was allowed to proceed overnight, and then completed by refluxing for additional 1 h. The NaCl formed was removed by filtration and washed with ethanol. The ethanol solution was distilled at normal pressure and the final product distilled at reduced pressure (bp 90-110 °C/15mmHg) to afford 28.5 g (85% yield) of ketoester 7. IR (neat) 1650 (C=C); 1720,1740 (C=O) cm^{-1}. ^{1}H NMR δ 4.83-4.67(m,2H,J=7.5 Hz); 4.19(q,2H,J=7.1 Hz); 3.8-3.43(m,1H); 2.57(d,2H,J=7.5 Hz); 2.24(s,3H); 1.74(s,3H); 1.26(t,3H,J=7.1 Hz). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.69.

2-Methylhex-1-en-5-one (8). Ketoester 7 (28.5 g, 0.15 mol) and 10% aqueous solution of NaOH (230 ml) were placed in a 500 ml two necked flask fitted with mechanical stirrer and reflux condenser. The mixture was refluxed 2 h. After cooling the mixture was extracted with ether. The resulting ethereal solution was dried over Na_2SO_4 and distilled to give 15.3 g (87% yield) of the product 8: bp 85-86°C/ 75 mmHg). IR (neat) 1650(C=C); 1720(C=O) cm^{-1}. ^{1}H NMR δ 4.80-4.58(m,2H); 2.71-2.49 (m,2H); 2.41(m,2H); 2.14(s,3H); 1.73(s,3H). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.11; H, 10.85.

(±)2,5-Dimethylhepta-1,6-dien-3-ol (9). In a 250 ml three necked flask equipped with a mechanical stirrer, dry-ice acetone condenser and dropping funnel, magnesium turnings (4.13 g) was covered with 20 ml of dry tetrahydrofuran and stirred under nitrogen. The reaction was started by adding a small amount (0.5 ml) of vinyl bromide and then the rest (19.68 g, 0.18 mol) dissolved in dry tetrahydrofuran (60 ml) was added at such a rate as to mantain a gentle refluxing. The reaction was completed by refluxing for 0.5 h. After cooling the dry-ice acetone condenser was replaced by a water condenser and the ketone 8 (15 g, 1.34 mol) dissolved in dry tetrahydrofuran (40 ml) was added with cooling. The reaction mixture was heated under reflux for two h, stirred at room temperature for additional 45 h and finally hydrolized with saturated aqueous solution of NH_4Cl. The mixture was extracted with ether, washed with brine and dried over Na_2SO_4. The solvent was removed by distillation at normal pressure and the final product distilled at reduced pressure to afford 16.5 g (88% yield) of alchool 9: bp 70-72°C/12mmHg. IR (neat) 1650 (C=C); 3400 (OH) cm^{-1}. ^{1}H NMR δ 4.82-4.64(m,2H); 2.24-1.92(m,2H); 1.88(s,1H, disappeared by treatment with D_2O); 1.72(s,3H); 1.70-1.52(m,2H); 1.29(s,3H). ^{13}C NMR δ 146.1(s); 145.0(d); 111.8(t); 109.8(t); 73.2(s); 40.2(t); 32.2(t); 27.6(q); 22.6(q). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 78.15; H, 11.61.

cis-(±)2,5-Dimethylbicyclo[3.2.0]heptan-2-ol (10). Hydroxyheptadiene 9 (20 g, 0.14 mol) in diethyl ether (200 ml) with cuprous trifluormethanesulfonate-benzene complex (0.4 g, 0.8 mmol) was irradiated with an internal 450-W Hanovia mercury

lamp. 95% Conversion of **9** into only one epimer (**10**) was observed after 12 h by capillary gaschromatography of the reaction mixture. The ethereal solution was quenched with a mixture of ice (100 g) and water (100 ml). The aqueous phase was extracted with ether (3x50 ml) and the combined ethereal extracts were washed with brine (3x30 ml) and dried with Na_2SO_4. Solvent was removed by evaporation at normal pressure and then at reduced pressure by rotary evaporation. A solid white product was obtained (19.2 g, 95% yield): mp 56-57°C from n-hexane, lit.[10] 56-57°C. IR (KBr) 3220 (OH) cm^{-1}. ^1H NMR δ 2.1-1.0(m,9H); 1.85(s,3H); 1.35(s,1H), disappeared on treatment with D_2O); 1.2(s,3H). ^{13}C NMR δ79.4(q); 52.8(d); 43.4(s); 39.3(t); 38.2(t); 31.0(t); 28.3(q); 27.9(q); 14.6(t). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.15; H, 11.47.

cis-(±)5-Methyl-2-methylidenebicyclo|3.2.0|heptane (11) and cis-( )2,5-Dimethylbicyclo|3.2.0|hept-2-ene (12). Hexamethylphosphoric triamide (60 ml) and alcohol **10** (14 g, 0.1 mol) was heated in a flask equipped with a Claisen head; the colorless solution turned yellow and foamed just below 190°C (oil bath). After 0.5 h at this temperature the mixture was further heated and products **11** and **12** together with dimethylamine distilled at 130-137°C. The distillate was washed several times with saturated aqueous sodium chloride solution to remove dimethylamine; yield: 11.3 g (94%) of an almost pure mixture of isomers **11** and **12** (3:7 by ^1H NMR).
11 : ^1H NMRδ4.8 and 4.7(2m,2H,C=CH_2); 1.20(s,3H,C-CH_3)
12 : ^1H NMRδ5.28(m,1H,CH_3-C=C<u>H</u>-); 1.71(bs,3H,C<u>H</u>$_3$-C=CH-); 1.25(s,3H,C-CH_3).
Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.48; H, 11.61.

Ozonolys of the mixture of 11 and 12. Dry ozone was bubled into a cooled mixture of <u>endo</u>- and exo-bicycloalkenes **11** and **12** (10 g, 82 mmol) in 66% aqueous acetic acid (30 ml). After about 4 hrs at 0°C, the reaction mixture became homogeneous and the ozone started to escape free from the reaction vessel. Excess of ozone was removed by bubbling nitrogen. The solution was diluted with water (70 ml) and zinc dust was added, a small pinch at a time, until a total of 5 g was introduced; the temperature rose to 60°C within few minutes and stirring was continued for an additional hour under nitrogen until the temperature fall to about room temperature. The aqueous solution was extracted with ether (3x50 ml). The ether layer was washed with water (2x20 ml) and then with 10% sodium bicarbonate aqueous solution (3x20 ml) and finally with brine (2x20 ml). The ethereal solution was dried (Na_2SO_4) and concentrated at reduced pressure to give 11.5 g of a product which was dissolved in acetone (100 ml). Jones CrO_3 (8N, 15 ml) was added dropwise to the stirred and cooled solution at 0°C-5°C. The stirring was continued for 4 hrs at the same temperature. The exceding CrO_3 was destroyed by addition of iso-propanol. The acetone solution was separated by decantation. The residue was washed with acetone (5x20 ml). The combined acetone solution was concentrated at reduced pressure, added with water (50 ml) and extracted with ether (3x50 ml). The combined extracts were washed with 10% aqueous sodium carbonate solution (2x20 ml). The ether layer was dried (Na_2SO_4) and evaporated to give **13** (2.59 g, 85%). The aqueous alkaline phase was acidified with dilute hydrochloric acid, extracted with diethyl ether (3x50 ml), and the ethereal solution was dried with Na_2SO_4. Evaporation of the solvent at reduced pressure leaved pure **14** (8.48 g, 87%).
(±)-5-Methylbicyclo|3.2.0|heptan-2-one (13): bp 90-95°C/40 mmHg; lit bp 88-90/36 Torr. IR (neat): 1730 (C=O) cm^{-1}. ^1H NMR δ 3.00-1.45(m,9H); 1.35(s,3H). Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.57; H, 9.81.
cis-(±)-2-Acetyl-1-methylcyclobutaneacetic acid (14): mp of p-toluensulfonylhydrazone 192-193°C. IR ($CHCl_3$): 3515 (COOH); 1710 (C=O) cm^{-1}. ^1H NMR δ 9.10(s,1H,-COOH disappeared on treatment with D_2O); 3.10(t,1H,J=7.0 Hz); 2.47(s,2H); 2.09(s,3H); 2.65-1.6(m,4H); 1.40(s,3H). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.63; H, 8.16.

cis-(±)2-Acetyl-1-methylcyclobutaneacetaldehyde (16). A sample (2 g) of reaction mixture obtained from the reductive ozonolys was purified by column chromatography (SiO_2, 150 g) eluing with cyclohexane-ethylacetate 7:3 to obtain bicycloketone **13** (0.57 g, 95%) and ketoaldehyde **16** (1.62 g, 92%) as an oil: IR (neat): 1720 and 1700 cm^{-1}. ^1H NMR δ 9.7(t,1H,1.8 Hz); 3.09(t,1H,J=7.2 Hz); 2.55(d,2H,J=1.8 Hz); 2.08(s,3H); 2.5-1.5(m,4H); 1.4(s,3H). Anal. Calcd for $C_9H_{14}O_2$; C, 70.10; H, 9.15. Found: C, 70.25; H, 9.08.

cis-(±)2-Isopropenyl-1-methylcyclobutaneacetic Acid (15). In a 250 ml three necked

flask equipped with mechanical stirrer, condenser and a dropping funnel, trimethylmagnesium chloride was prepared by reported procedures starting from chloromethyltrimethylsilane (10.0 g, 0.08 mol) and magnesium turnings (2.0 g, 0.08 mol) in tetrahydrofuran (100 ml). To this solution ketoacid **14** (6.64 g, 0.04 mol) dissolved in anhydrous tetrahydrofuran (20 ml) was added at such a rate that the mixture gently refluxed. After 3 h the mixture was cooled in an 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 diethyl ether (3x50 ml). Distillation on a rotating evaporator gave an oil which was dissolved in a mixture of n-pentane (50 ml) and diethyl ether (50 ml) and washed with saturated aqueous solution of sodium carbonate (20 ml). The separated aqueous phase was carefully acidified with a diluted HCl and then extracted with diethyl ether (3x50 ml). The ether solution was washed with brine (2x10 ml), dried (Na_2SO_4) and concentrated at reduced pressure. The crude product was chromatographed over SiO_2 eluing with n-hexane/diethyl ether (4:1). Evaporation of fractions afforded **15** (5.04 g, 75% yield) IR(neat) 3800(OH); 2960(C=C); 1710(C=O); 890(C=CH_2)cm^{-1}. ^1H NMR δ 10.65(s,1H, disappeared on treatment with D_2O); 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,9.71.

cis-(±)2-Isopropenyl-1-methylcyclobutaneethanol (16) (Grandisol). In a 250 ml two necked flask equipped with a condenser and a dropping funnel lithium aluminium hydride (1.0 g) was suspended in anhydrous diethyl ether (100 ml). A solution of **15** (3.36 g, 0.2 mol) in anhydrous diethyl ether (50 ml) was slowly added under nitrogen and with magnetical stirring. The mixture was stirred overnight at room temperature. Ethyl acetate (10 ml) was added to the stirred and ice-cooled mixture. After stirring for additional 3h, water (2 ml) was added. The mixture was 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 (±)grandisol (2.53 g, 82% yield): bp_1 (bath temp.) 100-125°C/15mmHg. IR(neat) 3300(OH); 2940, 1650 and 885 (C=CH_2) cm^{-1}. ^1H NMR δ 4.85(bs,1H); 4.65(bs,1H); 3.58(t,2H,J=7.0 Hz); 2.35(bs,1H,disappeared by treatment with D_2O); 1.65(bs,3H); 1.15(s,3H). Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H,11.76. Found: C, 77.91; H, 11.76.

Acknowledgements. We thank Dr. D. Casarini for helpful discussions concerning ^{13}C NMR spectra. E.M. thanks AGIP PETROLI S.p.A. for a Research Studentship.

This work has been supported by C.N.R. (Consiglio Nazionale delle Ricerche) Progetto Finalizzato Chimica Fine e Secondaria (Sottoprogetto C, Tematica Cb2).

REFERENCES

1. R.M. Silverstein, Science, **213**, 1326 (1981) and references cited.
2. M. Jacobson, "Insect Sex Attractants", Interscience, New York, N.Y., 1965.
3. J.A. Katzenellenbogen, Science, **194**, 139 (1976).
4. C.A. Henrick, Tetrahedron, **33**, 1845 (1977).
5. R. Rossi, Synthesis, 413 (1978).
6. J.H. Tumlinson, D.D. Hardy, R.C. Gueldner, A.C. Thompson, P.A. Hedin, J.P. Minyard, Science, **166**, 1010 (1969).
7. J.H. Tumlinson, R.C. Gueldner, D.D. Hardee, A.C. Thompson, P.A. Hedin, J.P. Minyard, J.Org.Chem., **36**, 2616 (1971).
8. R.L. Zurfluh, L.L. Durham, V.L. Spain, J.P. Siddall, J.Am.Chem.Soc., **92**, 425 (1970).
9. More recently grandisol and its corresponding aldehyde, grandisal, have been isolated from males of both **Pissodes strobi** and **Pissodes approximatus** bark weevils and implicated as components of their aggregation pheromones: D.C. Booth, T.H. Phillips, A. Claesson, R.M. Silverstein, G.N. Lanier, J.R. West, J.Chem.Ecol., **9**, 1 (1983).
10. G. Rosini, A. Salomoni, F. Squarcia, Synthesis, 942 (1979) and references cited.
11. J.B. Jones, M.A.W. Finch, I.J. Jakovac, Can.J.Chem., **60**, 2007 (1982).
12. E. Negishi, L.D. Boordman, J.M. Tour, H. Sawada, C.L. Rand, J.Am.Chem.Soc., **105**, 6346 (1983).
13. R.G. Salomon, D.J. Coughlin, S. Ghosh, M.G. Zagorski, J.Am.Chem.Soc., **104**, 998 (1982).
14. H.E. Eschinazi, J.Org.Chem., **26**, 3072 (1961).
15. T.H. Chan, E. Chang, J.Org.Chem., **39**, 3264 (1974).