Acta Chemica Scandinavica B 30 (1976) 664—668

New Syntheses of the Bark Beetle Pheromones 2-Methyl-6-methylene-7-octen-4-ol (Ipsenol) and 2-Methyl-6-methylene-2,7-octadien-4-ol (Ipsdienol)

STEINAR KARLSEN, PAUL FRØYEN and LARS SKATTEBØL *

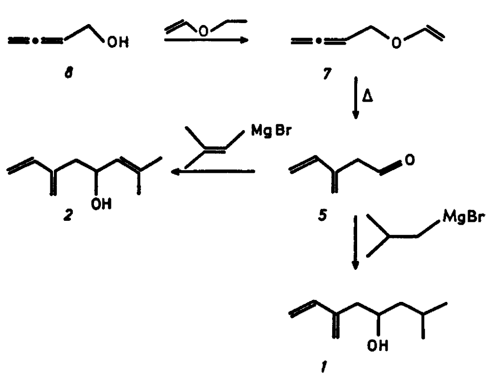
Department of Chemistry, University of Oslo, Oslo 3, Norway

3-Methylene-4-pentenal (*5*) was prepared by a thermal [3,3] sigmatropic rearrangement of 2,3-butadienyl vinyl ether (*7*). Treatment of *5* with isobutylmagnesium bromide provided 2-methyl-6-methylene-7-octen-4-ol (ipsenol, *1*) while with isobutenylmagnesium bromide 2-methyl-6-methylene-2,7-octadien-4-ol (ipsdienol, *2*) was obtained. Furthermore, use of (+)-(2*S*,3*S*)-*N*,*N*,*N'*,*N'*-tetramethyl-2,3-dimethoxybutan-1,4-diamine as chelating agent in the latter reactions produced optically active *1* and *2* albeit in low optical yields. The synthesis of 2-methyl-6-methylene-(3*E*)-7-octadien-2-ol (*3*) is also described. Acid-catalyzed rearrangement of *3* gave only a small amount of *2*.

Various species of bark beetles are important pests to coniferous forests throughout the world; among these are beetles of the genus *Ips*. Silverstein *et al.*[1,2] isolated and characterized the following four compounds from the boring frass of male *Ips paraconfusus*: *trans*-verbenol, ipsenol (*1*), ipsdienol (*2*), and 2-methyl-6-methylene-(3*E*)-7-octadien-2-ol (*3*). The first three compounds were found to be main components of the aggregation pheromone complex of a number of *Ips* species[3] including *Ips typographus*, a serious pest to North European spruce forests.[4] As part of a group effort aiming at the control of *Ips typographus* several grams of compounds *1* and *2* were needed for use in field testing. The published syntheses at the time[5] were not suitable for such a scale and the present paper describes work which led to the successful preparation of both alcohols on a multigram scale. A synthesis of compound *3* is also described. However, the origin as well as the biological significance of this compound remain uncertain.[2] After this work was completed alternative syntheses of compounds *1* and *2* were reported;[6–8] two of them represent considerable improvement over the original syntheses and with respect to convenience may well be comparable to those described here. They involve a Reformatsky-type reaction of 2-bromomethyl-1,3-butadiene (*4*) with isovaleraldehyde[6] and 3-methyl-2-butenal,[7] respectively.

The route reported here involved the combination of a six-carbon fragment, 3-methylene-4-pentenal (*5*), with the four-carbon fragments derived from isobutyl bromide and isobutenyl bromide, respectively, as depicted in Scheme 1.

The aldehyde *5* was unknown, but the corresponding alcohol *6* had previously been reported[9] as a product formed in good yield by



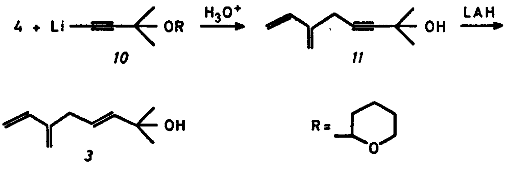
Scheme 1.

condensing isoprene with formaldehyde in the presence of stannic chloride. However, all attempts to reproduce this reaction were unsuccessful as only insignificant quantities of the alcohol were obtained.

We had previously shown [10] that 1,2,6-heptatriene rearranged thermally and quantitatively to 3-methylene-1,5-hexadiene. An analogous [3,3] sigmatropic rearrangement of 2,3-butadienyl vinyl ether (*7*) should lead to the aldehyde *5*. The allenic alcohol 2,3-butadienol (*8*) was a convenient starting material for the preparation of ether *7*. It was readily obtained from commercially available 2-butyne-1,4-diol by a simple two-step process.[11] Reaction of the allenic alcohol *8* with excess ethyl vinyl ether in the presence of stoichiometric amounts of mercury(II) acetate afforded the ether *7* in 60 % yield after 24 h. A by-product which was easily separated, proved to be 1-ethoxyethyl acetate probably formed by mercuric ion catalyzed addition of acetic acid to ethyl vinyl ether.[12] The use of catalytic amounts of mercury(II) acetate drastically reduced the yield of 7 and shorter reaction time had a similar effect. A better result was obtained employing mercury(II) trifluoroacetate [13] in the presence of 2,6-dimethylpyridine. Under these conditions the ether *7* was obtained in 69 % yield after one hour. The only by-product was a small amount (5 – 10 %) of acetaldehyde diethylacetal; ethanol is formed during the reaction. and its acid-catalyzed addition to ethyl vinyl ether must be responsible for the acetal formation.

The allenyl ether *7* was thermolysed by passing the compound under reduced pressure through a hot tube. The yields of aldehyde *5* varied depending on temperature and contact time. The latter was at first controlled by packing the tube with Pyrex wool. For complete conversion of the ether it was necessary to perform the reaction at tube temperature of 380 °C. However, at this temperature and in the presence of Pyrex wool the isomeric aldehyde 3-methyl-2,4-pentadienal (*9*) appeared as a by-product; it was invariably formed as a 5:1 mixture of (*E*)- and (*Z*)-isomers, respectively. The configuration of the isomers was established on the basis of the NMR spectrum. Due to the deshielding effect of the aldehyde group, the resonance for the methyl protons of the (*E*)-isomer appeared at δ 2.24, 0.19 ppm at lower field than that of the (*Z*)-isomer. At 395 °C compound *9* constituted the major part of the reaction product. It was possible to separate aldehyde *5* from the isomer *9* by fractional distillation, but not without significant loss of product. However, in the absence of Pyrex wool and with a tube temperature of 385 °C about 90 % conversion of *6* to aldehyde *5* occurred without formation of *9*. Apparently, the glass wool catalyzed the isomerization of *5*. Small amounts of isoprene were always detected in the thermolysis product showing that decarbonylation of *5* was a minor side reaction. The thermal conversion of *7* to *5*, an example of a [3,3] sigmatropic reaction, is the key reaction in the synthetic scheme. The reaction has recently also been studied by Cresson [14] who reports a quantitative conversion of *7* to aldehyde at 300 °C. The reaction conditions are not mentioned, and the aldehyde is only characterized by a UV spectrum. At least under our conditions at 300 °C a considerable amount of unreacted ether is present in the product.

Reaction of aldehyde *5* with isobutylmagnesium bromide in ether provided ipsenol in 62 % yield. A small amount of 3-methylene-4-penten-1-ol (*6*) was also formed; reduction of *5* would be expected with the above Grignard reagent, but the alcohol was easily separated from the main product. In a similar reaction between isobutenylmagnesium bromide and aldehyde *5* ipsdienol was obtained in 52 % yield. Replacing the Grignard reagents with the corresponding lithium derivatives in ether did not result in higher yields. The spectral properties of synthetic *1* and *2* were identical with those reported for the natural substances.[1,2] Furthermore, by reacting aldehyde *5* with the lithium compounds derived from each of the two bromides using equimolar amounts of (+)-(2*S*,3*S*)-*N*,*N*,*N'*,*N'*-tetramethyl-2,3-dimethoxybutan-1,4-diamine [15] as chelating agent, optically active ipsenol (*1*) and ipsdienol (*2*) were obtained. On the basis of the rotation values reported by Silverstein *et al.*[1,2] for the naturally occurring substances the optical yield for *1* was 6.3 % and for *2* 10.5 %. Optically active ipsenol has been recently prepared by Mori [16] from optically active starting material and the natural product has been shown,



Scheme 2.

to possess (S)-configuration. Work is in progress in our laboratory with the aim of establishing the absolute configuration of natural ipsdienol.

In another synthetic approach to the alcohol *2* the isomeric compound *3* was prepared by the sequence of reactions outlined in Scheme 2.

The rather difficultly accessible 3-bromomethyl-2,5-dihydrothiophene-1,1-dioxide was distilled under reduced pressure through a hot tube to give the bromide *4* in high yield.[17] Reaction of the bromide with the lithium derivative of 1,1-dimethyl-2-propynyl tetrahydropyranyl ether (*10*) in THF gave after hydrolysis the alcohol *11* in 39 % yield. Attempts to hydrogenate partially the triple bond using Lindlars catalyst, Pd/C or Pd/CaCO$_3$, were unsuccessful as more extensive reduction took place. The alcohol 2-methyl-6-hepten-3-yn-2-ol (*12*) was then prepared [18] as a model substance for further reduction studies. It was found that lithium aluminium hydride (LAH) in refluxing THF reduced *12* quite smoothly to 2-methyl-(3*E*)-6-heptadien-2-ol (*13*). When these conditions were applied to the alcohol *11* a 50 % yield of (*E*)-*3* was isolated. Its spectral properties were identical with those of the substance isolated from natural sources by Silverstein *et al.*[2] However, acid-catalyzed rearrangement of *3* gave a variety of products besides a minor amount of ipsdienol. Recently this rearrangement was achieved by Mori [8] *via* the acetate, but the reaction did not go to completion. Other synthetic routes to compound *3* have recently been reported.[20]

EXPERIMENTAL

NMR spectra were recorded on Varian A60A and HA100-15D spectrometers. Mass spectral data were obtained using an A.E.I. MS 902 mass spectrometer. A Perkin-Elmer model 457 spectrophotometer was used for IR spectra, and UV spectra were recorded on a Cary 14 spectrophotometer. Gas chromatographic analyses were performed with Varian Aerograph Models 90P and 711. Elemental analyses were carried out by Ilse Beetz Microanalytical Laboratory, 8640 Kronach, West Germany. All reactions were carried out under pure nitrogen.

2,3-Butadien-1-ol (8). The procedure was essentially that of Bailey and Pfeifer.[11] A solution of 200 g (1.91 mol) of 4-chloro-2-butyne-1-ol [21] in 300 ml of dry ether was slowly added to a stirred suspension of 100 g (2.63 mol) of lithium aluminium hydride in 2.5 l of dry ether. The reaction mixture was then heated under reflux overnight. Excess hydride was decomposed with water, and 20 % hydrochloric acid was added to bring the pH to about 2. The organic layer was separated and the water layer was extracted continuously for 48 h. The ether extracts were dried over anh. K$_2$CO$_3$ and the ether removed through a Vigreux column. Fractionation of the residue gave 82 g (62 %) of *8*, b.p. 60 °C/40 mmHg, n_D^{20} 1.4753 (lit.[10] 68 – 69°/45 mmHg, n_D^{20} 1.4754). NMR (CDCl$_3$): δ 2.62 (1 H, s), 4.1 (2 H, m), 4.8 (2 H, m), 5.28 (1 H, q). The IR spectrum was in accordance with that reported.[21] The compound is sensitive to oxygen, but can be stored for some time under N$_2$, preferably in the cold.

2,3-Butadienyl vinyl ether (7). In a typical run 1.8 g (4.2 mmol) of mercury(II) trifluoroacetate was added to 1 l of ethyl vinyl ether under vigorous stirring. 1.1 g (0.01 mol) of 2,6 dimethylpyridine was added and then 30 g (0.5 mol) of *8*. The reaction was monitored by GLC and was complete after 0.5 – 1 h at room temperature. Some K$_2$CO$_3$ was then added, and the volatile material was distilled through a Vigreux column. The residue was fractionated to yield 32 g (69 %) of *7*, b.p. 52 °C (120 mmHg), n_D^{23} 1.4645; ^{1}H NMR (CCl$_4$): δ 4.0 (2 H, m), 4.2 (2 H, m), 4.8 (2 H, m), 5.20 (1, H, q), 6.38 (1 H, dd). IR, ν_{max} (film): 1920 (s), 1640 (s) cm^{-1}.

GLC showed that a small amount of a second product was formed. This was separated by preparative GLC and identified as acetaldehyde diethylacetal by comparison with an authentic sample.

Method B. The reaction between *8* and ethyl vinyl ether was carried out using mercury(II) acetate in an analogous manner to that described in the literature.[22] Distillation gave *7* in 60 % yield. A second fraction, b.p. 58 – 65 °C (115 mmHg), which amounted to about half the weight of the ether *7*, was shown by GLC to consist of mainly one compound. This was separated by preparative GLC and identified as 1-ethoxyethyl acetate;[12] ^{1}H NMR (CDCl$_3$): δ 1.20 (3 H, t), 1.39 (2 H, d), 2.08 (3 H, broad s), 3.63 (2 H, m), 5.94 (1 H, q); the assignments are based on decoupling experiments.

3-Methylene-4-pentenal (5). Pyrolysis of 2,3-butadienyl vinyl ether (7) was carried out in a 2 cm wide and 60 cm long tube of pyrex glass kept at 385 – 390 °C in an electric oven. The ether was distilled into the tube at 0.2 mmHg, and the product was collected in a flask held at – 78 °C.

As a rule only 20 – 30 g of 2,3-butadienyl vinyl ether was pyrolyzed each time, which required about 4 – 5 h. The product consisted of the aldehyde *5* contaminated with starting material and isoprene. Distillation provided pure *5* (80 %), b.p. 57 – 59 °C (60 mmHg), n_D^{24} 1.4743; IR (liq): 2710, 1710 (CHO), 1650, 1580, 980, 900 cm^{-1} (olefinic); ^{1}H NMR (CCl_4): δ 3.18 (2 H, d), 4.95 – 5.32 (4 H, m), 6.45 (1 H, dd), 9.55 (1 H, m).

The *2,4-dinitrophenylhydrazone* was prepared from *5* in the usual way, m.p. 123 °C (from methanol). Anal. $C_{12}H_{12}N_4O_4$: C, H, N.

With the tube at 395 °C and packed with 15 g of Pyrex wool *7* was converted to a product consisting of 10 % *5*, 75 % of a 5:1 mixture of (*E*)- and (*Z*)-3-methyl-2,4-pentadienal (*9*), and 15 % of unidentified products; ^{1}H NMR ($CDCl_3$) of (*E*)-isomer: δ 2.24 (3 H, s), 5.48 (1 H, d), 5.76 (1 H, d), 5.94 (1 H, d), 6.51 (1 H, d), 10.13 (1 H, d). The (*Z*)-isomer exhibited an identical spectrum except that the methyl resonance at 2.24 was shifted to 2.05.

2-Methyl-6-methylene-7-octen-4-ol (ipsenol), 1). A solution of 24 g (0.25 mol) of 3-methylene-4-pentenal (*5*) in 100 ml of dry ether was slowly added to a stirred solution of the Grignard reagent prepared from 38 g (0.28 mol) of 1-bromo-2-methyl-propane, 6.8 g (0.28 g.at.) Mg, in 200 ml dry ether. During the addition the reaction mixture was held at – 20 °C. The cooling bath was removed and the mixture was stirred at room temperature overnight. The mixture was then cooled (ice) and saturated aqueous NH_4Cl was added. The aqueous layer was extracted with ether and the combined extracts were dried over $MgSO_4$. The solvent was removed on a rotatory evaporator and distillation of the residue through a short Vigreux column afforded 24.2 g (62 %) of *1*, b.p. 52 °C/1.3 mmHg, n_D^{24} 1.4692 (lit.[6] 109 – 110 °C/10 mmHg). ^{1}H NMR (CCl_4): δ 0.81 (3 H, d), 0.92 (3 H, d), 1.25 (2 H, m), ~1.70 (1 H, m), 2.02 (1 H, s), 2.22 (2 H, t), 3.7 (1 H, m), 4.9 – 5.4 (4 H), 6.37 (1 H, dd).

A compound present in the forerun was isolated by prep. GLC and shown to be 3-methylene-4-penten-1-ol (*6*); ^{1}H NMR ($CDCl_3$): δ 2.53 (2 H, t), 3.78 (2 H, t), 5.0 – 5.4 (4 H, m), 6.40 (1 H, dd).

2-Methyl-6-methylene-2,7-octadien-4-ol (ipsdienol, 2). To a cold (– 30 °C) stirred solution of a Grignard reagent prepared from 40 g (0.3 mol) of 1-bromo-2-methyl-1-propene and 8 g (0.33 g.at.) Mg in 150 ml of THF and 700 ml of dry ether was added a solution of 24 g (0.25 mol) of the aldehyde *5* in 100 ml of dry ether. The cooling bath was then removed and the mixture stirred at room temperature overnight. The reaction mixture was decomposed with aqueous NH_4Cl and worked up as described under compound *1* above. Distillation gave 19.9 g (52 %) of *2*, b.p. 53 °C/0.05 mmHg (lit.[7] 54 – 59°/0.15 mmHg); ^{1}H NMR (CCl_4): δ 1.63 (3 H, d), 1.70 (3 H, d), 1.89 (1 H, s), 2.31 (2 H, d), 4.37 (1 H, m), 4.9 – 5.4 (4 H), 6.32 (1 H, dd).

2-Methyl-6-hepten-3-yn-2-ol (12). To a stirred solution of 50.3 g (0.3 mol) of 1,1-dimethyl-2-propynyl tetrahydropyranyl ether (*10*)[23] in 250 ml dry THF 135 ml of methyllithium (2.28 M in ether; 0.31 mol) was added at room temperature. After 2 h 36.3 g (0.3 mol) of allyl bromide was added with stirring. The reaction mixture was heated with reflux overnight and decomposed with water. The organic layer was separated and the solvents evaporated under reduced pressure. The residue was decomposed with aqueous methanol containing some *p*-toluenesulfonic acid and worked up in the usual way. Distillation gave 21.2 g (57 %) of *12*, b.p. 63 – 65 °C (9 mmHg), n_D^{20} 1.4620 (lit.[18] 68 – 69.5 °C (13 mmHg), n_D^{20} 1.4592); ^{1}H NMR ($CDCl_3$): δ 1.50 (3 H, s), 2.26 (1 H, s), 2.95 (2 H, m), 4.9 – 5.5) (4 H), 5.67 (1 H, dd).

*2-Methyl-3*E*,6-heptadien-2-ol (13).* The alcohol *12* (1.12 g; 9 mmol) in 25 ml dry THF was added dropwise to a cooled (ice) suspension of 0.33 g (7.8 mmol) lithium aluminium hydride in 35 ml dry THF. The reaction was followed by GLC, and all of the starting material had been consumed after 22 h. The product consisted essentially of *13* which was isolated by preparative GLC.

The IR spectrum was in accordance with published data.[19] ^{1}H NMR ($CDCl_3$): δ 1.30 (6 H, s), 1.67 (1 H, s), 2.8 (2 H, m), 5.0 (2 H, broad d, *J ca.* 14 Hz), 5.5 – 6.1 (3 H, m).

2-Methyl-6-methylen-7-octen-3-yn-2-ol (11). To a stirred solution of 35.3 g (0.2 mol) of the pyranyl ether *10*[23] in 150 ml of dry THF was added at room temperature 100 ml ethereal methyllithium (2.1 M; 0.21 mol). After 2 h 20.2 g (0.14 mol) of the bromide *4* in 50 ml THF was added dropwise. The reaction mixture was heated under reflux for 3 h and decomposed with water.

The organic layer was separated, and solvents evaporated under reduced pressure. The residue was treated with aqueous methanol containing some *p*-toluenesulfonic acid and worked up in the usual way. Distillation gave 7.7 g (36 %) of *11*, b.p. 61 – 63 °C (1.4 mmHg); ^{1}H NMR ($CDCl_3$): δ 2.53 (2 H, t), 3.78 (2 H, t), 5.0 – 5.4 (4 H, m), 6.40 (1 H, dd).

*2-Methyl-6-methylene-(3*E*)-7-octadien-2-ol (3).* A solution of 3.0 g (0.02 mol) of *11* in 50 ml dry THF was added dropwise to a stirred and ice-cooled suspension of 0.68 g (0.08 mol) lithium aluminium hydride in 90 ml dry THF. The reduction was complete after heating under reflux for 39 h as shown by GLC. When cold, 12 ml methanol and 40 ml saturated aqueous NH_4Cl was added successively.

The product was isolated with ether, and worked up in the usual way. Distillation gave 1.6 g (50 %) of *3*, b.p. 55 – 57 °C (1.4 mmHg); ^1H NMR ($CDCl_3$): δ 1.30 (6 H, s), 1.63 (1 H, s), 2.92 (2 H, m), 4.9 – 5.75 (6 H), 6.40 (1 H, dd).

Acknowledgement. We want to thank The Agricultural Research Council of Norway for financial assistance.

REFERENCES

1. Silverstein, R. M., Rodin, J. O. and Wood, D. L. *Science 154* (1966) 509.
2. Silverstein, R. M., Rodin, J. O., Wood, D. L. and Browne, L. E. *Tetrahedron 22* (1966) 1929.
3. Vite, J. P., Bakke, A. and Renwick, J. A. A. *Can. Entomol. 104* (1972) 1967.
4. Postner, M. In Schwenke, W., Ed., *Die Forstschädlinge Europas II.* Paul Parey, Hamburg and Berlin 1974.
5. Reece, C. A., Rodin, J. O., Brownlee, R. G., Duncan, W. G. and Silverstein, R. M. *Tetrahedron 24* (1968) 4249; Vig, O. P., Anand, R. C., Kad, G. L. and Sehgal, J. M. *J. Indian Chem. Soc. 47* (1970) 999.
6. Katzenellenbogen, J. A. and Lenox, R. S. *J. Org. Chem. 38* (1973) 326.
7. Riley, R. G., Silverstein, R. M., Katzenellenbogen, J. A. and Lenox, R. S. *J. Org. Chem. 39* (1974) 1957.
8. Mori, K. *Agric. Biol. Chem. 38* (1974) 2045; Wilson, S. R. and Phillips, L. R. *Tetrahedron Lett.* (1975) 3047.
9. Klimova, E. and Arbuzov, Yu. *Dokl. Akad. Nauk SSSR, 190* (1970) 102.
10. Skattebøl, L. *J. Org. Chem. 31* (1966) 2789; see also Frey, H. M. and Lister, D. H. *J. Chem. Soc. A* (1967) 26.
11. Bailey, W. J. and Pfeifer, C. R. *J. Org. Chem. 20* (1955) 1337.
12. Scheeren, J. W. and Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas 90* (1971) 974; Sosnovsky G. *J. Org. Chem. 28* (1963) 2934.
13. Huché, M. and Cresson, P. *Bull. Soc. Chim. Fr.* (1974) 2040.
14. Cresson, P. *C. R. Acad. Sci. Ser. C 279* (1974) 859.
15. Seebach, D., Dörr, H., Bastani, B. and Ehrig, V. *Angew. Chem. 81* (1969) 1002.
16. Mori, K. *Tetrahedron Lett.* (1975) 2187.
17. Thomas, A. F. *J. Am. Chem. Soc. 91* (1969) 3281.
18. Kurz, P. *Justus Liebigs Ann. Chem. 658* (1962) 6.
19. Colonge, J. and Varagnat, A. *Bull. Soc. Chim. Fr.* (1964) 561.
20. Sharpless, K. B. and Lauer, R. F. *J. Am. Chem. Soc. 95* (1973) 2697.
21. Bailey, E. J. and Fujiwara, E. *J. Am. Chem. Soc. 77* (1955) 165.
22. Church, R. F., Ireland, R. E. and Marshall, J. A. *J. Org. Chem. 31* (1966) 2526.
23. Robertson, D. N. *J. Org. Chem. 25* (1960) 931.

Received December 18, 1975.