

New Three-Step Syntheses of Racemic and Optically Active Ipsdienol from Myrcene

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2-Methyl-6-methylene-3,7-octatriene-2-ol (6), which is readily available from photooxidation of myrcene (5), was transformed into racemic and optically active ipsdienol (2). Treatment of the trienol 6 with perchloric acid in acetic acid yielded ipsdienyl acetate which on hydrolysis gave racemic ipsdienol (2) in 83% overall yield. Oxidation of the trienol 6 with pyridinium chlorochromate in the presence of pyridine hydrochloride furnished 2-methyl-6-methylene-2,7-octadien-4-one (8) in 43% yield. Reduction of this ketone with lithium aluminium hydride partially decomposed by one molar eq. each of ethanol and either (R)-(+)- or (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl gave (R)-(-)- or (S)-(+)-ipsdienol (2' or 2'') in 70% yield and 60-65% ee.

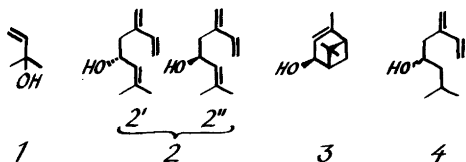
The bark beetles of the *Ips* genus are major pests in conifer forests. *Ips typographus* (L.) is responsible for mass attacks on Norway spruce *Picea abies* (L.) Karst. 2-Methyl-3-buten-2-ol (1),^{1,2} ipsdienol (2),²⁻⁴ (S)-cis-verbenol (3)¹⁻³ and ipsenol (4)³ are some of the known pheromone components of this insect. Compounds 2, 3 and 4 are also present in the pheromones of many other *Ips* spp. A lure of compounds 1, 2 and 3 is successfully used in Sweden and Norway for trapping *Ips typographus* on a large scale.⁵ The racemate of ipsdienol (2) is used in this lure. It is known, however, that in some *Ips* spp the activity of one enantiomer of a pheromone

component (e.g. ipsdienol) can be inhibited by the opposite one.^{6,7} It is not clear whether this is true for *Ips typographus*. In fact, except for the attractive power of the lure, the details of the behavioral responses elicited by the compounds 1-4 are not known. A thorough study of the biological effects of pheromone components is dependent on their availability. In cases of chirality, knowledge about their optical purities is of importance.

Although racemic ipsdienol (2) has been prepared via many⁸⁻¹⁵ routes and a few attempts have been made to synthesize the pure enantiomers^{*,16-18} 2' and 2'' (38-91% ee) starting from optically active natural products, there is still a need for simple and inexpensive procedures leading to these compounds.

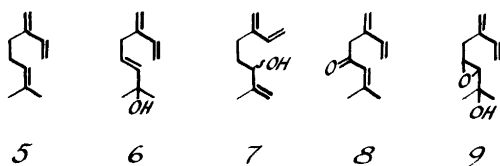
We now report simple methods for the syntheses of racemic ipsdienol (2) and mixtures considerably enriched in either optical isomer 2' or 2'' via the key intermediate (E)-2-methyl-6-methylene-3,7-octadien-2-ol (6).^{**} According to the synthetic plan, allylic rearrangements of the trienol 6 would furnish either ipsdienol (2) or, with simultaneous oxidation, the ketone 8. A suitable chiral reducing agent would transform the latter into predominantly one enantiomer of ipsdienol (2' or 2'').

The tertiary trienol 6 can be readily prepared from inexpensive myrcene (5) either by epoxidation, addition of PhSeH, oxidation and elimination²⁰ or more simply by sensitized photooxidation. The latter method was used here employing the one-pot procedure we recently published.²¹ In this reaction



* Ipsdienol isolated from *Ips paraconfusus* has been estimated to be of 75% ee.¹⁶

** Trienol 6 has been identified as a pheromone component of *Ips amitinus*⁴ and as a constituent of the frass of *Ips paraconfusus*.¹⁹



the two isomeric alcohols 6 and 7 are formed in equal amounts as the major products. The secondary allylic alcohol 7 has shown interesting biological properties in relation to *Ips typographus*. It gives a distinct response in electroantennographic (EAG) measurements²² and preliminary field tests show that it has attracting properties similar to that of ipsdienol itself.²³

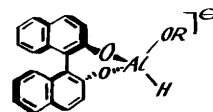
The tertiary trienol 6 has previously been transformed into racemic ipsdienol (2) via a five-step procedure involving chlorination and allylic rearrangement.¹⁰ An earlier attempt to perform a direct acid catalyzed allylic rearrangement of 6 was not successful¹¹ but Lewis acid treatment of the target molecule 2 to form the tertiary alcohol 6 has been reported.⁴

The main obstacle which prevents efficient conversion of 6 to 2 is hydrocarbon formation by loss of water. However, we found that when dissolved in acetic acid and treated with catalytic amounts of perchloric acid for 120 sec at room temperature the tertiary alcohol 6 smoothly gave ipsdienyl acetate (2, OH replaced by OAc) in 85% yield containing less than 5% of hydrocarbon. If a mixture of the two isomeric alcohols 6 and 7, resulting from photooxidation of myrcene, was treated in the same way, only the tertiary alcohol 6 was affected leaving the secondary alcohol 7 intact, which greatly simplified separation. Hydrolysis of ipsdienyl acetate with KOH in methanol gave a quantitative yield of ipsdienol (2).

Oxidative rearrangements of tertiary allylic alcohols leading to ketones have been performed with different chromium(VI) reagents.²⁴⁻²⁶ The best reported results have been achieved using pyridinium chlorochromate (PCC) in dichloromethane which works well for cyclic systems but less so for the acyclic counterparts.²⁶ Unfortunately when this method was applied to the trienol 6 the yield of the desired ketone 8 was only 10%. However, the yield was substantially improved by adding pyridine hydrochloride (PHCl) as a proton source. Oxidation with an equimolar amount of PCC in the presence of four molar equivalents of PHCl in refluxing dichloromethane gave a 33%

yield of the myrcenone 8 and a 34% yield of recovered starting material which again was subjected to oxidation. Thus the overall yield was increased to 43%. Not unexpectedly (*cf.* Ref. 27) an epoxide to which the structure 9 was assigned was also isolated, in a low yield. Using an excess of PCC in this reaction substantially reduced the amount of recovered starting material without improving the yield of the ketone.

The myrcenone 8 could also be prepared, in a similar yield, from ipsdienol (2) using the PCC, PHCl method. Various other chromium(VI) reagents and MnO₂ gave inferior results.



10': R = C₂H₅

11': R = CH₃

12': R =

10''-12'': mirror images of 10'-12'

The asymmetric reduction of the myrcenone 8 was accomplished using the recently described²⁸ chiral complexes 10' and 10''. These are reported to give good chemical and excellent optical yields of chiral alcohols from various unsaturated ketones.^{28,29} The reagent 10' reduced acetophenone as described to (+)-phenylmethylcarbinol (98% ee. Lit.²⁷ 96% ee). Similar reduction of the myrcenone 8 with the reagent 10' [from (R)-(+)-2,2-dihydroxy-1,1'-binaphthyl³⁰] at -80°C furnished (R)-(-)-ipsdienol in 70% chemical yield and 63% ee, as determined by NMR-measurements of the diastereomeric mixture obtained on esterification with (-)-α-methoxy-α-trifluoromethylphenylacetic acid [(-)-MTPA]. Similarly, (S)-(+)-ipsdienol was obtained using the reagent 10''. Modified reducing agents such as 11' and 12' gave lower optical yields of chiral ipsdienol.

Thus, the procedures reported here provide three-step syntheses of racemic and optically active ipsdienol from readily available myrcene.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian EM 360 (60 MHz) or a Bruker WP200 (200 MHz) spectrometer using deuteriochloroform containing

tetramethylsilane as solvent. Silica gel chromatography was performed with Merck Kieselgel 60, 230–400 mesh. GLC: capillary column, 25 m, coated with carbowax 20M, 70–180 °C. TLC: silica gel, 15% ethyl acetate in hexane, developed with vanillin–sulfuric acid.

2-Methyl-6-methylene-2,7-octadien-4-ol, racemic ipsdienol (2). Perchloric acid (90%, one drop) was added to glacial acetic acid (10 ml) and this solution was added (30 sec) to a stirred solution of (*E*)-2-methyl-6-methylene-3,7-octadien-2-ol (6, 1.28 g, 8.42 mmol) in glacial acetic acid (10 ml). No discoloration occurred. After additional 120 sec the reaction mixture was poured into brine (50 ml). Extraction with three portions of pentane followed by washing of the combined extracts once with NaHCO₃ solution, drying (MgSO₄) and solvent removal gave ipsdienyl acetate (1.42 g, 7.32 mmol, 87%) containing <5% hydrocarbon (GLC). The product was treated with KOH solution (10% in MeOH, 15 ml) at room temperature for 3 h, poured into brine (50 ml) and extracted with three portions of pentane. Drying (MgSO₄) and solvent removal gave essentially pure (GLC, TLC) 2 (1.06 g, 6.96 mmol, 95%) in 83% overall yield. Column chromatography on silica gel led to partial decomposition of the acetate. Hydrolysis of the collected acetate gave a quantitative yield of ipsdienol (2) but the overall yield was lowered to 60–75%.

Treatment of a mixture of the alcohols 6 and 7 in an identical manner provides ipsdienyl acetate and unchanged secondary alcohol 7. Due to the large difference in *R_f* values, these compounds were easily separated by column chromatography in contrast to the two alcohols 6 and 7.²¹

2-Methyl-6-methylene-2,7-octadien-4-one (8). (*E*)-2-Methyl-6-methylene-3,7-octadien-2-ol (6, 3.04 g, 20 mmol) in methylene chloride (160 ml) was refluxed under nitrogen. A solution of pyridinium chlorochromate (4.50 g, 20.9 mmol) and pyridine hydrochloride (4.50 g, 39 mmol) in methylene chloride (150 ml) was added *via* a syringe pump during 3 h. After refluxing for an additional hour the mixture was diluted with pentane washed with dilute hydrochloric acid, water, sat. sodium bicarbonate solution, brine and finally dried (MgSO₄). The solvent was evaporated leaving a mixture (2.1 g) which was subjected to silica gel chromatography. Elution with pentane containing increasing amounts of ethyl acetate (0–15%) gave first the desired ketone (1.00 g) followed by the slightly impure starting alcohol 6 (1.03 g). This was oxidized with PCC (1.75 g) and PPhCl (2.0 g) as described above. An additional amount (0.30 g) of the ketone 8 was obtained giving a total of 1.30 g (43%) in addition to starting alcohol 6 (0.31 g, 10%) and a product A (0.17 g, 6%, *vide infra*). The NMR-spectrum of the myrcenone 8 obtained was identical

to that described.⁸ Oxidation of ipsdienol with Cr(VI) reagents gave the best results with PCC and PPhCl which furnished the ketone 8 in 30–40% yield. A minor side product in these oxidations was a product B (*vide infra*).

3,4-Epoxy-2-methyl-6-methylene-7-octen-2-ol (9, product A, described above) NMR (60 MHz): δ 1.20, 1.27 [6H, 2s, >(CH₃)₂], 2.15 (1H, bs, OH), 2.35–2.55 (2H, bd, –CH₂–, *J* 6 Hz), 2.70 [1H, d, –CH(O)–, *J* 3 Hz], 3.15 [1H, dt, –CH(O)–, *J* 3 and 6 Hz], 4.95–5.30 (4H, m, =CH₂ and =CH₂), 6.33 (1H, dd, –CH=, *J* 11 and 18 Hz).

2,3-Epoxy-2-methyl-6-methylene-7-octen-4-ol (product B, mentioned above) NMR (60 MHz): δ 1.23, 1.30 [6H, 2s, >C(CH₃)₂], 2.3–2.8 [2H, m, –CH₂–], 2.72 [1H, d, –CH(O)–, *J* 8 Hz], 3.4–3.8 [1H, m, –CH(OH)–], 5.0–5.25 (4H, m, =CH₂ and =CH₂), 6.33 (1H, dd, –CH=, *J* 11 and 18 Hz).

Preparation of the chiral aluminiumhydride reagents 10'–12'. Lithium aluminium hydride (LAH, 25 g) was refluxed in dry THF (100 ml) for 2 h. The solution was cooled and filtered in a nitrogen atmosphere through a pad of celite (dried at 200 °C overnight). The resulting clear solution (0.250 ml) was titrated under nitrogen with a standard solution (0.01 M) of dried distilled pentanol in dry THF containing a small amount of 2-(2,4-dihydroxyphenyl)naphthoquinone. The orange-red quinone³¹ is reduced by LAH to the colorless anion of the hydroquinone. When all the hydride is consumed the bright blue anion³¹ of the quinone is formed on further addition of the titration solution.

The LAH solution (4 mmol) was added to dry THF (10 ml) and stirred at 0 °C under N₂. Ethanol, methanol or 2,6-di-*t*-butylphenol (4.2 mmol) in THF (5 ml) was added followed by (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl³⁰ {1.20 g, 4.2 mmol, [α]_D²⁰ + 37.0° (MeOH)} in THF (10 ml). The milky solutions of the reagents 10'–12' were stirred for 1 h at room temperature prior to use. We found that the reagent 10' gave (*R*)-(+)-phenylmethyl carbinol in 98% ee (Lit.²⁸ 96% ee) from acetophenone.

(*R*)-(–)-*Ipsdienol (2')*. The chiral reducing agent 10' was cooled to –100 °C and stirred under N₂. 2-Methyl-6-methylene-2,7-octadien-4-one (8, 152 mg, 1 mmol) in dry THF (5 ml) was added. The reaction was followed by TLC. After 72 h the reaction was quenched by addition of moist ether. After warming, the solution was exhaustively extracted with sodium hydroxide solution (2M, to remove the dihydroxybinaphthyl). The ether phase was washed with hydrochloric acid (2 M), sat. sodium bicarbonate solution and brine. After drying (MgSO₄) the solvent was evaporated to give an oil, which was subjected to silica gel chromatography. This gave unconverted ketone 8 (20 mg, 13%) followed by ipsdienol (105 mg, 70%), [α]_D²⁰ –7.0° ± 1.5° (c 3, MeOH) (Lit.¹⁶ –13.2° – –13.6°

estimated for pure (*R*)-(–)-ipsdienol). Reduction of the ketone with the reagent 10" prepared from (*S*)-(–)-2,2'-dihydroxy-1,1'-binaphthyl,³⁰ $[\alpha]_D^{20} - 35.8^\circ$ (MeOH) furnished (*S*)-(+)-ipsdienol in similar chemical and optical yields. The optical yields were determined more accurately by an NMR-method *vide infra*.

Ester of (R)-(–)-ipsdienol with (–)- α -methoxy- α -trifluoromethyl- α -phenylacetic acid (MTPA) (*R*)-(–)-ipsdienol {10 mg, $[\alpha]_D^{20} - 7.0^\circ$ (MeOH)} in chloroform (0.1 ml) was stirred at room temperature. The chloride (30 mg) from (–)-MTPA was added, followed by pyridine (0.1 ml). The mixture was heated for 90 min at 70 °C, cooled and poured into water. After stirring for 15 min the mixture was extracted with ether. The ether solution was washed with hydrochloric acid (1 M), sat. sodium bicarbonate solution and water. After drying the solvent was evaporated and the residue purified by chromatography (pentane as eluent) to give the MTPA ester (23 mg, 95%). NMR (200 MHz): δ 1.73 (6 H, m, $(CH_3)_2C=$), 2.53 (2 H, 12 line m, $C-CH_2-C$), 3.55 (3H, m, OCH_3), 4.85–5.35 (4H, m, 4 vinylic H), 5.71 (1H, m, $=CH-CH-(OMTPA)-CH_2-$), 6.35 (1H, 6 line m, $-C(=CH_2)-CH=CH_2$), 7.30–7.65 (5H, m, C_6H_5). Irradiation at δ 5.71 gave a six line signal at δ 2.52. This signal represents the sum of two pairs of doublets ($=C^4H(OMTPA)-C^5H_AH_B-C^6(=CH_2)-$) arising from the diastereotopic protons on carbon 5 of the ipsdienyl moiety. The H_A and H_B protons of the (*R*)-(–)-ipsdienyl moiety give rise to the two doublets at δ 2.45 (*J* 13.8 Hz) and δ 2.60 (*J* 13.8 Hz). The H_A and H_B protons of the (*S*)-ipsdienyl moiety give rise to the two doublets at δ 2.38 (*J* 13.8 Hz) and δ 2.62 (*J* 13.8 Hz). The ratio of the integral of the signals from the (*R*)-form to that of the (*S*)-form was 4.33/1. The six line signal at δ 6.35 can similarly be analyzed to be composed of the sum of one doublet of doublets (*J* 8.3 and 13.1 Hz) centered at δ 6.33 (integral 1) and another at δ 6.37 (*J* 8.3 and 13.1 Hz, integral 4.65). The ee of the ipsdienyl moiety is thus 62–65%.

Acknowledgements. This paper is submitted in honour of Professor Holger Erdtman on the occasion of his 80th birthday in appreciation of his contributions to organic chemistry.

We thank *Stiftelsen Nils och Dorthi Troëdssons Forskningsfond* and the Swedish Natural Science Research Council for financial support.

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Received March 22, 1982.