

151. Access to Optically Active Ipsdienol from Verbenone

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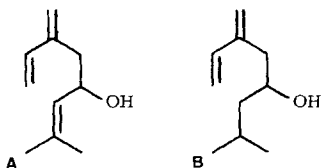
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Summary

Verbenone **1** or **2** is converted in three steps to ipsdienol **9** or **10** respectively. The diastereoisomeric 2(10)-pinen-4-ols **6** and **7** (or **5** and **8**), which have identical chirality at the carbon atoms bearing OH groups, afford ipsdienol **10** (or **9** respectively) with the same optical purity as the starting material.

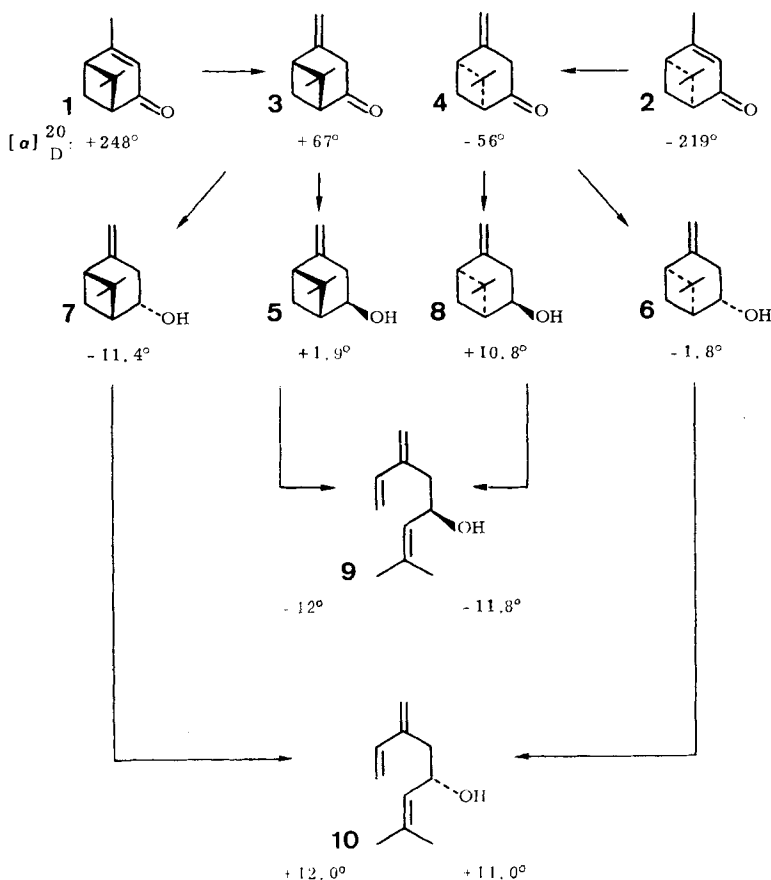
The monoterpenoid allyl alcohol ipsdienol (A) and its dihydro derivative ipsenol (B) are constituents of the pheromone system of several species of the bark beetle



genus *Ips* [1]. Several syntheses leading to racemic A and B [2–6] and a single multistep synthesis of the enantiomers have been reported; the latter affords the pheromones in modest yields and in a low degree of optical purity [7] [8].

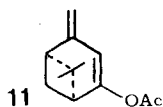
For further biological studies in this important area it was necessary to develop a simple synthesis of the pure enantiomers of these aggregation pheromones. In the case of (+)- and (–)-ipsdienol (**10** and **9**) we achieved this goal in a simple manner, by a chemical transformation of the optically active verbenones (**1** and **2**).

Treatment of (+)- and (–)-verbenones (**1** and **2**) with sodium hydride in THF and subsequent quenching with boric acid [9] in separate operations led to the unknown deconjugated (+)- and (–)-2(10)-pinen-4-ones (**3** and **4**), whose reduction with LiAlH_4 gave selectively the corresponding *cis*-alcohols **5** and **6**. The latter (**6**) was also obtained by treatment with LiAlH_4 of the enol acetate **11** derived from (–)-verbenone (**2**). Exposure of ketones **3** and **4** to lithium in liquid ammonia containing *t*-butyl alcohol mainly caused isomerization to **1** and **2**, but also furnished the diastereoisomeric alcohols **5** and **7** (from **3**) and the diastereoisomeric alcohols **6** and **8** (from **4**). The *trans*-alcohols **7** and **8** were separated by preparative gaschromatography. Flash-pyrolysis (560°/1 sec) of (+)-(1*R*, 4*R*, 5*R*)-2(10)-pinen-4-ol (**5**) or (+)-(1*S*, 4*R*, 5*S*)-2(10)-pinen-4-ol (**8**) led to (–)-(R)-ipsdienol (**9**) ($[\alpha]_{\text{D}}^{20}$: –12°; $c = 10$, MeOH) in 40 to 60% yield, and similar pyrolysis of (–)-(1*R*, 4*S*, 5*R*)-alcohol **7**



or (-)-(1*S*,4*S*,5*S*)-alcohol **6** gave the naturally occurring (+)-(*S*)-ipsdienol (**10**) ($[\alpha]_D^{20}$: +11.1°; c =9.8, MeOH). The optical rotation of the natural pheromone **10** is reported to be $[\alpha]_D^{20}$: +10°; c =1, MeOH [1]. Our starting materials **1** and **2** had optical purities of 91% and 80%, respectively. Judging from previous experience with similar reaction sequences [11-13] we can assume that all of our steps take place without loss of optical activity; the final products **9** and **10** must therefore have the same optical purities as the verbenones **1** and **2**. Consequently, (+)-(*S*)-ipsdienol (**10**) ($[\alpha]_D^{20}$: +10°) which occurs in nature can be assumed to have an optical purity of about 75%; the corresponding value for synthetic material obtained by the published procedure [8] can be estimated to be *ca.* 38%.

Our method of preparation relies on the fact that the oxygen-bearing chiral center of alcohols **5** to **8** is solely responsible for the configuration of ipsdienols **9** and **10**; the two bridgehead chirality centers are destroyed during pyrolysis. This method



had already proved useful for the preparation of various other enantiomeric acyclic monoterpene alcohols [11–13] such as optically active fragrances whose sensory evaluation (and distinction) was achieved with the human [11–13] as well as an animal [14] olfactory system.

Experimental Part

(with the collaboration of *Béatrice Frei*)

General. Melting points are uncorrected. Preparative gas-chromatography (GC.) was performed on a *Wilkins Aerograph*, Model A 700 Autoprep, using glass columns of 3 m length (\varnothing 4 mm, 10% Carbowax 20 M on Chromosorb W 95) at temperatures of 140–210°. Specific rotations were measured on a *Schmidt & Hansch Polatron* 1 polarimeter (1 dm cell). – IR. spectra were recorded by means of *Perkin-Elmer* A 21 and 720 spectrometers (films or CCl_4 solutions; bands are given in cm^{-1}). – NMR. spectra were measured on *Varian* A-60 and *Bruker* HFX-90 instruments. Normally, 3–4% solutions in CCl_4 or CDCl_3 were used with $\text{Si}(\text{CH}_3)_4$ ($=0$ ppm) as the internal standard. Spectra are given in ppm (δ), coupling constants are given in Hz and the multiplicities are abbreviated as follows: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet; *br.* = broad. Assignments are indicated in brackets. Mass spectra (MS.) were determined on an *Atlas* CH4 instrument, electron energy: 70 V.

1. *Origin and chemical and optical purity of the substances used.* The (+)-*a*-pinene used was obtained from *Ega Chemie*, Steinheim/Albuch (West Germany) and had α_D^{20} : +40.8° from which an $[\alpha]_D^{20}$: +47.6° at a density d_4^{20} of 0.8569 ($[\alpha]_D^{25}$: +47.3°; $[\alpha]_D^{20}$: +55.2°, $c = 10$, MeOH; $[\alpha]_D^{20}$: +56.3°, $c = 10$, CHCl_3) was calculated. If the highest optical rotation of $[\alpha]_D^{25}$: +52.4° [15] measured for *a*-pinene is taken as 100%, the (+)-*a*-pinene used by us had an optical purity of 91%. The (–)-*a*-pinene used was obtained from *Fluka AG*, Buchs (Switzerland) and had $[\alpha]_D^{20}$: –41.9° ($[\alpha]_D^{20}$: –42.4°, $c = 10$, MeOH; $[\alpha]_D^{20}$: –48°, $c = 10$, CHCl_3) and an optical purity [15] of 80%. The enantiomeric verbenones **1** and **2** were prepared from the corresponding (+)-*a*- and (–)-*a*-pinenes, respectively, by *Criegee* oxidation [16] [17], subsequent saponification, isolation of the diastereoisomeric verbenols and oxidation with MnO_2 [18]. The optical rotation in methanol ($c = 10$) of the products purified by GC. were as follows:

	$\frac{[\alpha]_D^{20}}{\text{---}}$		$\frac{[\alpha]_D^{20}}{\text{---}}$
(–)- <i>cis</i> -verbenol	– 10.5°	(+)- <i>cis</i> -verbenol	+ 8.7°
(+)- <i>trans</i> -verbenol	+ 153°	(–)- <i>trans</i> -verbenol	– 121.3°
(+)-verbenone (1)	+ 248°	(–)-verbenone (2)	– 219° ¹⁾

If the values previously found for verbenone (**1**), $[\alpha]_D$: +273° [19], and *trans*-verbenol, $[\alpha]_D$: +168° [17] [19], are taken as 100%, the optical purities of the samples used in our investigations can be calculated as 90% and 91%, respectively, these values being well in agreement with the above-mentioned values calculated for *a*-pinene. Assuming that (–)-*ipsdienol* (**9**) ($[\alpha]_D^{20}$: –12°) prepared by us also has an optical purity of 90%, a 100% optically pure product should have the theoretical optical rotation of $[\alpha]_D^{20}$: –13.3°. Consequently, we can assume the natural product ($[\alpha]_D$: +10°) has an optical purity of 75%.

2. *Isomerization of verbenone.* a) (+)-(1*R*,5*R*)-2(10)-*Pinen-4-one* (**3**). 100 g of (+)-verbenone were added dropwise under argon, with vigorous stirring, to a suspension of 60 g of NaH in 1000 ml of THF. After stirring for 55 h, the reaction mixture was poured into an ice-cold solution of 360 g of boric acid in 6 l of water and extracted with ether. The combined ethereal extracts were washed basefree with brine, the solvent was evaporated on a *Büchi* rotary evaporator, and the residue was subjected to vacuum distillation; b. p. 52°/0.01 Torr; yield 88 g (88%); $[\alpha]_D^{20}$: +67.4° ($c = 10$, MeOH). As shown by gaschromatographic analysis the product was free from impurities. – IR. (film): 3080, 1723, 1650, 1461, 1388, 1298, 1270, 1242, 1198, 1098, 1028, 918, 880, 753. – NMR. (CCl_4): 0.768 (*s*, 3H); 1.37 (*s*, 3H); 1.74 (*m*, 1H); 2.5 to 3.3 (*m*, 5H); 4.82 (*m*, 2H). – MS. (*m/e*): 150 (11, M^+), 135 (4), 122 (5), 107 (16), 91 (12), 83 (100), 82 (23), 79 (20), 67 (12), 55 (34), 41 (13), 39 (16), 27 (13).

¹⁾ In CHCl_3 ($c = 10$) a value of $[\alpha]_D^{20}$: –217°, and in the absence of a solvent a value of $[\alpha]_D^{20}$: –218° were measured.

b) (–)-(1*S*,5*S*)-2(10)-Pinen-4-one (**4**). 25 g of (–)-verbenone were treated with 15 g of NaH in 250 ml of THF and the product then quenched in the manner described in section 2a. Yield: 21 g (84%); $[\alpha]_D^{20}$: -56° , $c=10$, MeOH. The spectra of **4** were identical with those of **3**.

3. Reduction of the 2(10)-pinen-4-ones. a) (+)-(1*R*,4*R*,5*R*)-2(10)-Pinen-4-ol (**5**). 60 g of **3** were added dropwise under argon to a stirred solution of 4.2 g of LiAlH_4 in 600 ml of ether. After refluxing for 1 h the mixture was cooled and poured into ice-cold dilute hydrochloric acid. The mixture was washed neutral with brine, the solvent was evaporated on a Büchi rotary evaporator, and the residue was distilled i. V., b. p. 110° (bath temperature)/0.01 Torr; yield: 43 g (71%); m. p. $62\text{--}62.5^\circ$ /petroleum ether; $[\alpha]_D^{20}$: $+1.9^\circ$ ($c=10$, MeOH). – IR. (film): 3380, 3080, 1645, 1475, 1300, 1245, 1057, 1015, 937, 870, 850. – NMR. (CCl_4): 0.97 (s, 3H); 1.28 (s, 3H); 2.0 to 3.3 (m, 6H); 2.9 (OH); 4.30 (m, 1H); 4.67 (m, 2H). – MS. (*m/e*): 152 (4, M^+), 137 (6), 134 (14), 119 (18), 109 (22), 91 (27), 85 (100), 81 (25), 79 (25), 69 (19), 67 (23), 55 (19), 41 (43), 29 (15), 27 (15).

b) (–)-(1*S*,4*S*,5*S*)-2(10)-Pinen-4-ol (**6**). 20 g of **4** were treated with 1.4 g of LiAlH_4 in 200 ml of ether in the manner described in section 3a. B. p. 110° (bath temperature)/0.01 Torr; yield: 19 g (94%); m. p. $62\text{--}62.5^\circ$ (petroleum ether); $[\alpha]_D^{20}$: -1.8° ($c=10$, MeOH). The spectra of **6** were identical with those of **5**.

4. Reduction of (–)-(1*S*,5*S*)-2(10)-pinen-4-one (**4**) to give (1*S*,4*R*,5*S*)-(+)-2(10)-pinenol (**8**). To a solution of 3 g of **4** in 100 ml of liquid ammonia (distilled from sodium), 20 ml of abs. THF, and 20 ml of *t*-butyl alcohol, 2 g of lithium were added in small portions with vigorous stirring at -60° . The NH_3 was allowed to evaporate overnight, the residue was extracted with ether, and the extract was treated in the usual manner. B. p. 150° (bath temperature)/0.1 Torr; yield: 2.3 g. (+)-*trans*-Alcohol **8** formed in a proportion of 11% was separated by prep. GC. from (–)-*cis*-alcohol **6** (17%) and (–)-verbenone (**2**) (60%). The pure alcohol **8** had the following constants and spectra: $[\alpha]_D^{20}$: $+10.8^\circ$ ($c=10$, MeOH). – IR. (CCl_4): 3360, 3080, 1650, 1045, 890. – NMR. (CCl_4): 0.70 (s, 3H); 1.28 (s, 3H); 1.5 to 3.0 (m, 7H); 4.12 (t, $J=7.6$, 1H); 4.6 (br. s, 2H). – MS. (*m/e*): 152 (1.5, M^+), 137 (1.5), 134 (2), 119 (5), 109 (11), 91 (10), 85 (100), 67 (13), 57 (7), 55 (7), 41 (28).

5. Meerwein-Ponndorf-Verley reduction of the 2(10)-pinen-4-ones. a) (–)-(1*R*,4*S*,5*R*)-2(10)-Pinenol (**8**). 9 g of **4** and 25 g of aluminium isopropoxide were refluxed for 3 h with mechanical stirring in 300 ml of 2-propanol. The solvent was then slowly distilled off on a Vigreux, the residue poured into ice-water, the mixture was extracted with ether, and the ethereal extract treated in the usual manner; b. p. 150° (bath temperature)/0.1 Torr; yield: 8 g. 14% of (+)-*trans*-alcohol **8** had been formed as shown by GC. analysis. Alcohol **8** could be separated by prep. GC. from the simultaneously formed (–)-*cis*-alcohol **6** (10%), (+)-*cis*-verbenol (13%) and (–)-*trans*-verbenol (62%). The spectra of the sample of **8** so obtained were identical with those of the sample of **8** obtained in section 4.

b) (–)-(1*R*,4*S*,5*R*)-2(10)-Pinenol (**7**). By treating 9 g of **3** in the manner described above (section 5a), 8 g of a mixture of alcohols corresponding to that obtained from **4**, but having the opposite sign of optical rotation, was obtained from which **7** could be isolated in pure form. $[\alpha]_D^{20}$: -11.4° ($c=10$, MeOH).

6. Preparation of verbenyl acetate (**11**) and its reduction with LiAlH_4 . a) (+)-(1*S*,5*S*)-2(10)-3-Pinadien-4-yl acetate (**11**). 2 g of **2** were heated with 150 ml of isopropenyl acetate and a few crystals of *p*-toluenesulfonic acid and the acetone formed was removed by distillation through a Vigreux column. After distillation for 60 h the residue was taken up in ether, the ethereal extract was washed neutral and purified by distillation i. V.; b. p. 150° (bath temperature)/0.1 Torr; yield: 2.4 g (93%); $[\alpha]_D^{20}$: $+32.3^\circ$ ($c=9.5$, MeOH). – IR. (CCl_4): 1720, 1695, 1230, 885. – NMR. (CCl_4): 0.935 (s, 3H); 1.4 (s, 3H); 2.1 (s, 3H); 4.68 (br. s, 2H); 5.7 (s, 1H). – MS. (*m/e*): 192 (1, M^+), 150 (90), 135 (100), 108 (90), 107 (74), 91 (20), 79 (15), 55 (21), 43 (63).

b) (–)-(1*S*,4*S*,5*S*)-2(10)-Pinen-4-ol (**6**). 3.3 g of **11**, 0.5 g of LiAlH_4 and 50 ml of ether were refluxed for 1 h under argon. The reaction mixture was then poured into ice-cold dilute hydrochloric acid. The mixture was washed neutral with brine and then treated in the usual manner; b. p. 100° (bath temperature)/0.1 Torr; yield: 2.2 g (86%). As shown by GC. the product consisted of the pure alcohol **6** the spectral data of which were identical with those of the sample obtained in section 3b²).

²) With NaBH_4 enol acetate **11** gives 2(10)-pinen-4-yl acetate. Private communication, Mme Yvonne Bessière.

7. *Pyrolysis of 2(10)-Pinen-4-ols 5 to 8.* a) (–)-(R)-*Ipsdienol* (9). A solution of 300 mg of (+)-*trans*-alcohol 5 in 1.8 ml of pyridine was introduced into the pyrolysis oven described previously [20]. The quartz tube of the oven was 25 cm long and partially filled with sintered quartz rings. The quartz tube was heated to 550° and its interior pressure reduced to 0.01 Torr. The pyrolysate was collected in a trap cooled to –80°. After removal of the pyridine by distillation i.HV. at 20° the residue was chromatographed on silica gel, using hexane/ether 95:5 as the eluant, and then subjected to a further purification by prep. GC. (3 m Carbowax 15%/140°). In this way 120 mg (40%) of (–)-(R)-*ipsdienol* (9) were obtained which showed the following physical and spectra constants: $[\alpha]_D^{20}$: –9° (*c* = 9.8, MeOH). – IR. (film): 3350, 3100, 1685, 1600, 1455, 1385, 1030, 1000, 920. – NMR. (CCl₄): 1.63 (*d*, *J* = 1, 3 H); 1.7 (*d*, *J* = 1, 3 H); 2.0 (OH); 2.32 (*d*, *J* = 6, 2 H); 4.37 (*d*, *t*, *J*₁ = 6, *J*₂ = 8, 1 H); 4.9 to 5.4 (*m*, 5 H); 6.35 (*d* × *d*, *J*₁ = 11, *J*₂ = 17, 1 H). – MS. (*m/e*): 152 (1, *M*⁺), 134 (2), 119 (4), 85 (100), 67 (13), 55 (8), 41 (32). The spectra were identical with those described in sections 1, 2, 3 and 6.

The pyrolysis of 10 g of (+)-*cis*-alcohol 5 in the same manner yielded 4.8 g (48%) of (–)-(R)-*ipsdienol* (9) with $[\alpha]_D^{20}$: –12° (*c* = 10, MeOH).

b) (–)-(R)-*Ipsdienol* (9). 10 g of (–)-*cis*-alcohol 6 were pyrolysed as described in section 7a. Pure 9 was obtained in 42% yield; $[\alpha]_D^{20}$: +11.8° (*c* = 10, MeOH). The spectra were identical with those of 10.

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