127. A Stereocontrolled Access to (±)-, (−)-, and (+)-Patchouli Alcohol

by **Ferdinand Näf, René Decorzant, Wolfgang Giersch** and **Günther Ohloff**

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

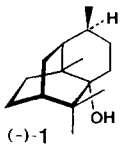
Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

(23.IV.81)

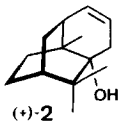
Summary

The racemate and both enantiomers of patchouli alcohol have been synthesized by stereocontrolled routes. The olfactive properties of the patchouli alcohols prepared are reported.

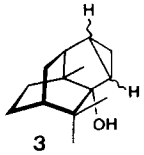
Introduction. – Pursuing our work on odour-structure relationships, in particular the effects exhibited by optical antipodes [1], we thought that patchouli alcohol ((−)-**1**) [2], the major constituent of patchouli oil [3] [4] would be a rewarding target for several reasons. Firstly, there is controversy about the odour of patchouli alcohol [5]: some authors persistently claim that pure patchouli alcohol of natural origin is totally odourless, and that the typical note of patchouli oil stems from norpatchoulenol (**2**) [4] [6] [7] and a closely related norsesquiterpene alcohol **3** [8].



(-)-1



(+)-2



3

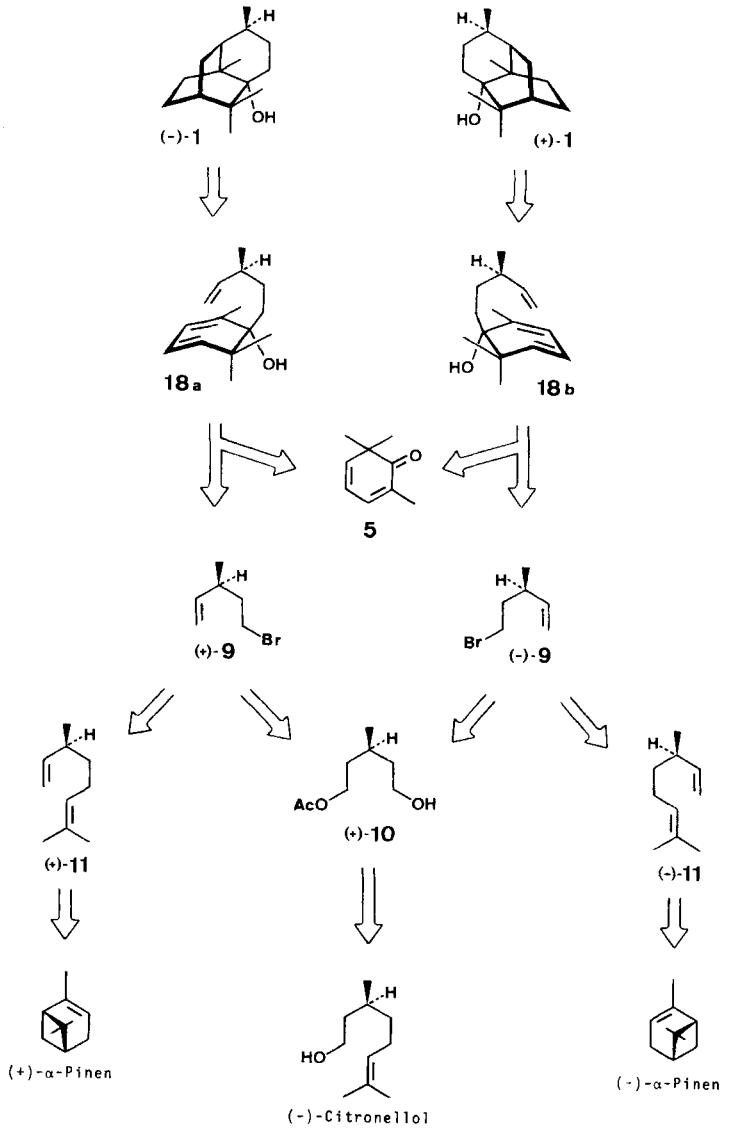
Secondly, we had a short, stereoselective synthesis of racemic patchouli alcohol ((±)-**1**) to hand [9] which seemed ideally suited for further elaboration of a synthesis of (−)- and (+)-patchouli alcohol by using optically active building blocks derived from commercially available, optically active monoterpenes (see the retrosynthetic *Scheme 1*).

This publication gives full experimental details of our preliminary communication on the total synthesis of racemic patchouli alcohol ((±)-**1**), and describes the successful preparation of both enantiomers of patchouli alcohol, (−)-**1** and (+)-**1** from (+)-**11** and (−)-**11** ((+)- and (−)-3,7-dimethyl-1,6-octadiene [10]) derived from (+)- and (−)-α-pinene [11][1]).

[1]) Up to now one synthesis of (−)-patchouli alcohol [12], and five syntheses of (±)-patchouli alcohol [9] [13–16] have been reported.

0018-019X/81/5/1387-11$01.00/0

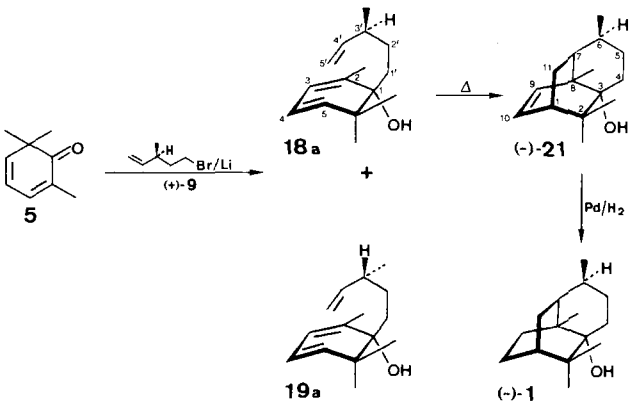
Scheme 1 (retrosynthetic)



The key step: an intramolecular *Diels-Alder* reaction. – The key step in all three cases, yielding the patchoulenols (±)-**21**, (−)-**21** and (+)-**21**, is an intramolecular *Diels-Alder* reaction[2]) of the trienols **18a/18b** (1:1), **18a** and **18b** *(Schema 2)*. Interestingly, their diastereoisomers **19a/19b** (1:1), **19a** and **19b** did not undergo this reaction, and therefore allowed direct use of the mixtures

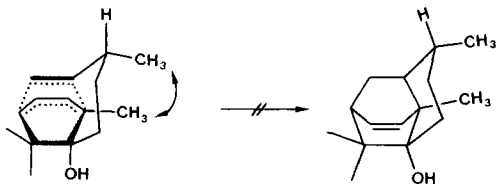
[2]) For recent reviews on intramolecular *Diels-Alder* reaction, see [17] [18].

Scheme 2



18a/18b/19a/19b (1:1:1:1), **18a/19a** (1:1), and **18b/19b** (1:1) as formed during the previous step.

The complete diastereoselectivity with respect to the desired tricyclic alcohols is accounted for by the presence of severe 1,3-diaxial methyl-methyl interactions in the transition state **19a**$^{\neq}$, disfavouring the formation of epi-patchouli alcohol (**22**).



Furthermore, no cycloadducts of type **23** (see *e.g.* [19]) could be isolated, which implies that our *Diels-Alder* reaction is also completely regioselective[3]). A third point to be emphasized bears on the reaction conditions used. Only in the presence of a little potassium *t*-butoxide, the cycloadduct could be obtained. Without this base, only the aromatic compound **26** was formed. The yield after chromatography

[3]) For a discussion of regioselectivity in intramolecular *Diels-Alder* reactions and for further examples related to our case, see [17].

of the patchoulenols was 48 to 50% based on the 'correct' precursors **18a**, **18b** and **18a/18b**[4]).

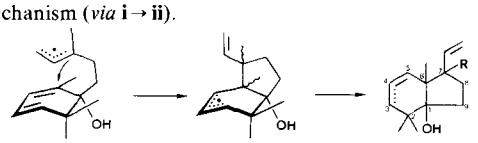
The odour profile of patchoulenol ((−)-**21**) can be described as patchouli-like camphoraceous whose earthy cellar note is there more pronounced than in (−)-patchouli alcohol ((−)-**1**). A slight galbanum scent is also recognized. The antipode (+)-**21** is much weaker, less earthy and also less patchouli-like; however, it possesses a weak but fine woody, warm amber tone.

The preparation of the trienols 18a/18b, 18a and 18b. – The racemic trienol **18a/18b** was readily accessible together with its useless diastereoisomers **19a/19b** as a (1:1)-mixture by a lithium-*Grignard* reaction between racemic 3-methyl-4-pentenyl bromide ((±)-**9**) and 2,6,6-trimethyl-2,4-cyclohexadien-1-one (**5**) [16] [21] (68% yield). The cleanest product resulted from an alkyllithium/ketone mixture with the ratio of about 1:1. A two-fold excess of alkyllithium led to a by-product (**20**)[5]) (~21% of the reaction mixture) in addition to the expected trienols **18a/18b/19a/19b** (58% of the reaction mixture).

Cyclohexadienone **5** was prepared in a new way, namely from the commercially available 2,6,6-trimethyl-2-cyclohexen-1-one (**4**)[6]) [22] by a sequence of *N*-bromosuccinimide bromination [23] and dehydrobromination (Li_2CO_3/dimethyl formamide, 56% overall yield). The racemic 3-methyl-4-pentenyl side chain was obtained from 2-butenyl bromide (**6**), magnesium powder and ethylene oxide *via* 3-methyl-4-penten-1-ol ((±)-**7**) [24] *(Scheme 3)*. Actually, this *Grignard* reaction led to a mixture of (±)-**7** and (*E*)-4-hexen-1-ol (**8**) (3:1 ratio, 90% yield) from which pure (±)-**7** was isolated by fractional distillation. Subsequent bromination (PBr_3/pyridine) furnished bromide (±)-**9** (80% yield).

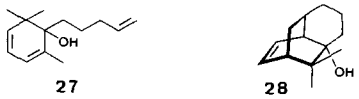
---

[4]) In several runs not using freshly purified trienols (perhaps containing peroxides), a hexahydroindene by-product was isolated (up to 30% of the reaction mixture) and assigned structure **24** on the basis of its spectral data (IR., ^{1}H- and ^{13}C-NMR., MS.). It is probably formed from **18** and **19** by a radical mechanism (*via* **i** → **ii**).



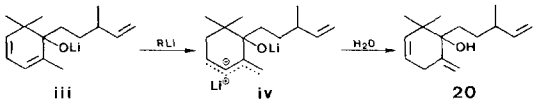
i **ii** **24** R = CH_3 **25** R = H

The same type of by-product (in this case **25**) was obtained when the nor-trienol **27** was heated to give the norpatchoulenol **28** [20].



27 **28**

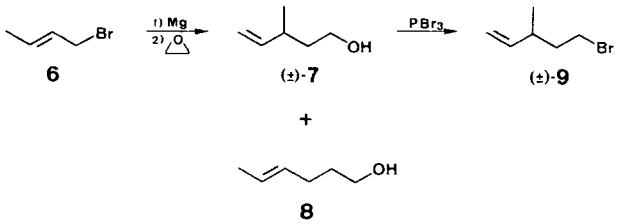
[5]) This by-product (**20**) is probably the result of metallation of intermediate **iii** by excess of alkyllithium followed by kinetic protonation of **iv** during work-up.



iii **iv** **20**

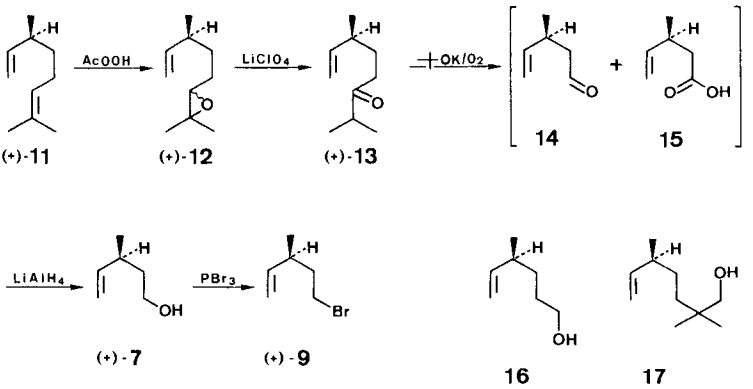
[6]) *BASF* AG, D-6700 Ludwigshafen.

Scheme 3



The optically active trienols **18a/19a** and **18b/19b** were synthesized analogously from the optically active bromides (+)-**9** and (−)-**9**[7]) which, however, were not so easily accessible. Our early attempts to prepare both of them by degradation of (−)-citronellol *via* the relay compound (+)-**10** proved unsatisfactory because of low overall yields and partial racemization [27]. We finally found a new and efficient route *(Scheme 4)* to the key bromides (+)- and (−)-**9**, making use of the commercially available 3,7-dimethyl-1,6-octadienes (+)-**11** and (−)-**11** derived from (+)- and (−)-α-pinene [10]. Epoxidation ($AcOOH/AcONa/CH_2Cl_2$) of (+)-**11** gave the monoepoxide (+)-**12** [28] which was readily isomerized ($LiClO_4$/petroleum ether [29]) to the ketone (+)-**13** (63% yield). Autoxidative degradation [30–32] of ketone (+)-**13** led – as expected, with loss, of a C_4-unit – to a mixture of 3-methyl-4-pentenal (**14**) and 3-methyl-4-pentenoic acid (**15**) which was – without separation – directly reduced ($LiAlH_4$) to the desired alcohol (+)-**7** (39% yield based on (+)-**13**, $[\alpha]_D^{20} = +28.9°$ ($c = 1.05$, $CHCl_3$), enantiomeric purity[8]) ~70%). Apart from (+)-**7**, two minor, higher boiling by-products, **16** and **17**, were also formed. Bromination finally led to the optically active bromide (+)-**9** [26] (80% yield). Its antipode (−)-**9** [25] [26] was analogously prepared from (−)-**11**.

Scheme 4



[7]) In conjunction with the total synthesis of ionophor lasalocid A, (−)-**9** was first prepared by *Kishi et al.* [25] and recently by *Ireland et al.* [26], who also synthesized its antipode (+)-**9**.

[8]) Determined by NMR. spectroscopy using tris[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato]Eu(III (Eu(HFC)$_3$) as chiral shift agent [33].

The synthetic patchouli alcohols (±)-1, (−)-1 and (+)-1, and their olfactory properties. – The three synthetic patchouli alcohols (±)-**1**, (−)-**1** ($[\alpha]_D^{20} = -94.6°$ ($c = 1.21$, $CHCl_3$))[9]) and (+)-**1** ($[\alpha]_D^{20} = +82.0°$ ($c = 1.24$, $CHCl_3$)) were obtained from the corresponding patchoulenols (±)-**21**, (−)-**21** and (+)-**21** by catalytic hydrogenation (Pt/H_2, EtOH) as described by *Büchi et al.* [12c] for (−)-**1**.

The synthetic, nature-identical (−)-**1** exhibits a strong, typical patchouli scent with an earthy, slightly camphoraceous, powdery cellar note which is practically indistinguishable from natural patchouli alcohol. In contrast to the odour profile of (−)-**1**, the 'unnatural' (+)-**1** is much weaker, less characteristic, nearly indefinable and by no means reminiscent of patchouli. It might however have a β-santalol odour with a green undertone. The odour of the synthetic, racemic patchouli alcohol (±)-**1** is simply a blend of both enantiomers, the contribution of the nature-identical one, (−)-**1**, being greater.

Conclusion. – In the present investigation the importance of patchouli alcohol as a potent, characteristic fragrance of the woody type has been demonstrated by synthesis and odour evaluation of its (−)- and (+)-antipodes, as well as its racemate[10]). Thereupon, a further example has been found of the substantial differences in odour strength and quality between optical antipodes [1].

The authors wish to express their gratitude to Dr. *D. Kastner*, head of the product evaluation board, *Firmenich SA*, for providing the olfactory evaluation.

Experimental Part

General. – IR. spectra were recorded on a *Perkin-Elmer* 720 spectrometer; some characteristic absorption maxima are given in cm^{-1}. 360-MHz-^{1}H-NMR. spectra were recorded on a *Bruker* WH 360 instrument, 90.5-MHz-^{1}H-NMR. spectra and 22.6-MHz-^{13}C-NMR. spectra on a *Bruker* HX 90 instrument, and 60-MHz-^{1}H-NMR. spectra on a *Hitachi Perkin-Elmer* R-20B instrument, using $CDCl_3$ as solvent. Chemical shifts are expressed in ppm (δ scale) downfield from (TMS) as an internal standard; abbreviations: s = singlet, d = doublet, t = triplet, qa = quadruplet, m = multiplet, J = spin-spin coupling constant (Hz). The optical rotations were measured on a *Perkin-Elmer* 141 polarimeter. Gas chromatography (GLC.) was carried out on a *Carlo Erba Fractovap* GT, using 4 mm × 2.5 m glass columns with either 10% *Carbowax*, 10% SOMB of 4% SP 1000 *(Supelco)* on *Chromosorb* G NAW.

1. Synthesis of 2,6,6-trimethyl-2,4-cyclohexadien-1-one (**5**) (an alternative way). 2,6,6-Trimethyl-2-cyclohexen-1-one (**4**) (25 g, 0.181 mol) [22][6]), *N*-bromosuccinimide (43.1 g, 0.242 mol), azoisobutyronitrile (0.4 g) and anhydrous CCl_4 (200 ml) were heated at reflux for 2 h and cooled to 20°. The succinimide floating on the surface was removed by filtration over *Celite* and the filtrate was concentrated. The crude 4-bromo-2,6,6-trimethyl-2-cyclohexen-1-one (46.1 g) [23] was directly dehydrobrominated. It was mixed with Li_2CO_3 (47.06 g, 0.636 mol) and dimethylformamide (200 ml, *Merck*) and heated at reflux for 2.5 h. The black reaction mixture was cooled, poured onto a mixture of ice/water (~200 ml), and extracted with ether. The ethereal phase was washed (H_2O), dried ($MgSO_4$) and evaporated, yielding 27.1 g of crude **5**. This material was allowed to dimerize at 20° overnight. Repeated crystallization from petroleum ether (80–100°) gave 13.9 g (56%) of **5** as its dimer, m.p. 118°, its mixed m.p. with a sample from ref. [21] showed no depression.

---

[9]) Natural patchouli alcohol, isolated and purified by Dr. *B. Maurer, Firmenich SA*, showed $[\alpha]_D^{20} = -112.9°$ ($c = 0.95$, $CHCl_3$).

[10]) Reports claiming that patchouli alcohol is odourless are difficult to understand.

2. Preparation of the 3-methyl-4-pentenyl moieties. – *2.1. Synthesis of the racemic 3-methyl-4-pentenol* ((±)-**7**) [24]. A solution of 2-butenylmagnesium bromide was prepared from 2-butenyl bromide (**6**) (270 g, 2 mol), magnesium powder (144 g, 6 mol) and anhydrous ether (1 l) using a standard procedure [34]. A dry ice/acetone condenser was put on the reaction flask and gaseous ethylene oxide (88.1 g, 2 mol, *Fluka, purum*) was bubbled through the stirred reaction mixture. The temperature was kept below 30° by external cooling. After the addition, stirring was continued at 25° overnight. The reaction mixture was decomposed by subsequent addition of crushed ice and 1N aq. HCl-solution; the unreacted magnesium was removed by filtration, the layers were separated, and the organic phase was washed (H_2O), dried ($MgSO_4$), evaporated (231 g crude material) and distilled (48–53°/12 Torr) giving 176.57 g (88.5%) mixture of (±)-**7** and **8** (3:1). The desired alcohol (±)-**7** was isolated by fractional distillation using a *Fischer* MS 300 column (~40 plates).

Spectral data of (±)-**7**. – IR. (neat): 3320, 1638, 990, 910. – ^{1}H-NMR. (90 MHz): 1.03 (*d*, J=7, 3H, H_3C–C(3)); 1.57 (*d*×*t*, J_1=7, J_2=7, 2H, 2H–C(2)); 2.31 (*m*, 1H, H–C(3)); 3.64 (*t*, J=7, 2H, 2H–C(1)); 4.95 (*d*-like, J=10, 1H, H–C(5)); 4.98 ('*d*', J=18, 1H, the other H–C(5)); 5.74 (*d*×*d*×*d*, J_1=8, J_2=10, J_3=18, 1H, one of the two H–C(4)). – MS.: 100 (0, M^+), 82 (26), *67* (100), 55 (64), 41 (78), 27 (31).

Spectral data of (E)*-4-hexen-1-ol* (**8**): IR. (neat): 3320, 960. – ^{1}H-NMR. (60 MHz): 1.65 (*d*, J=5, 3H, H_3C–C(5)); 3.5 (*t*, J=6.5, 2H, 2H–C(1)); 5.4 (*m*, 2H, H–C(4) and H–C(5)). – MS.: 100 (2, M^+), 82 (50), *67* (100), 55 (50), 41 (78), 29 (28).

2.2. Synthesis of the racemic 3-methyl-4-pentenyl bromide ((±)-**9**). Alcohol (±)-**7** (44.3 g, 0.443 mol) was dissolved in anhydrous pyridine (10.3 g, 10.5 ml) and treated dropwise, while stirring, with phosphorous tribromide (48.0 g, 16.8 ml, 0.177 mol) at 0° (external dry ice/aceton cooling). The mixture was then allowed to react 3 h at 25°. The flask was equipped with a *Claisen* distilling head and heated in an oil bath. At 137–145°/750 Torr 65 g of crude bromide distilled over. The distillate was poured onto ice-water, and extracted with pentane. The pentane layer was washed (2N NaOH and H_2O), dried ($MgSO_4$) and evaporated with a *Büchi Rotovapor* (bath temp. ~25°). The bromide **9** obtained (58 g, 80%) was stored over molecular sieves *Linde* 4-A. – ^{1}H-NMR. (60 MHz): 1.0 (*d*, J=6.5, 3H, H_3C–C(3)); 2.31 (*m*, 1H, H–C(3)); 3.32 (*t*, J=7, 2H, 2H–C(1)); 4.96 ('*d*', J=17, 1H, H–C(5)); 4.96 ('*d*', J=9, 1H, H–C(5)); 5.65 (*d*×*d*×*d*, J_1=6.5, J_2=9, J_3=17, 1H, H–C(4)). – MS.: 162 (2, M^+), 107 (2), 83 (59), 69 (29), *55* (100), 41 (44), 27 (29).

2.3. Preparation of (+)-3-methyl-4-penten-1-ol ((+)-**7**). – *2.3.1. Synthesis of 3,7-dimethyl-6,7-epoxy-1-octene* ((+)-**12**) [28]. A stirred, cooled (dry ice/2-propanol) mixture of (+)-3,7-dimethyl-1,6-octadiene ((+)-**11**, $[\alpha]_D^{20}$ = +11.9° (c=1.26, $CHCl_3$)) (207 g, 1.5 mol), anhydrous sodium acetate (180 g) and anhydrous CH_2Cl_2 was treated dropwise at 0° to 5° with 40% peracetic acid-solution (300 g, 1.6 mol) and anhydrous sodium acetate (9 g). After the exothermic reaction had ceased, the mixture was stirred without cooling at 20° for 2 h. The insoluble sodium acetate was filtered off and the filtrate washed (H_2O, 5% Na_2CO_3-solution and H_2O), dried ($MgSO_4$) and evaporated. Distillation at 85–90°/12 Torr) using a *Widmer* column gave 161 g (69%) of epoxide (+)-**12**. For analytical data a small sample was further purified by GLC. (*Carbowax* 10%, 150°); $[\alpha]_D^{20}$ = +9.43° (c=1.47, $CHCl_3$). – ^{1}H-NMR. (90 MHz): 1.02 (*d*, J=7, 3H, H_3C–C(3)); 1.27 and 1.31 (2*s*, 6H, 2H_3C–C(7)); 2.15 (*m*, 1H, H–C(3)); 2.7 (*m*, 1H, H–C(6)); 4.91 ('*d*', J=9, 1H, H–C(1)); 4.94 ('*d*', J=17, 1H, H–C(1)); 5.69 (*d*×*d*×*d*, J_1=7, J_2=9, J_3=17, 1H, H–C(2)). – MS.: 154 (0, M^+), 139 (1), 111 (2), 95 (7), *81* (100), 68 (31), 59 (39), 55 (63), 41 (44), 27 (19).

2.3.2. Synthesis of 2,6-dimethyl-7-octen-3-one ((+)-**13**) [28]. A mixture of epoxide (+)-**12** (154 g, 1 mol), $LiClO_4$ (10 g) and petroleum ether, b.p. 50–70° (1 l) was heated with stirring at reflux for 5 h. The reaction mixture was diluted with H_2O to dissolve the solids, the layers were separated and the organic phase was washed (aq. $NaHCO_3$- and sat. HCl-solution), dried ($MgSO_4$) and evaporated. The crude ketone was taken up in ether (100 ml) and vigorously stirred with a 30% aq. $NaHSO_3$-solution (50 ml) at 20° for 3 h in order to remove aldehydic by-products. The organic phase was separated, washed (H_2O), dried ($MgSO_4$) and evaporated. The residue (173 g) was distilled through a *Widmer* column at 72°/12 Torr to give 96.87 g (63%) of pure ketone (+)-**13**, apart from 47 g polymers. An analytical sample was specially purified by GLC. (*Carbowax* 10%, 120°; $[\alpha]_D^{20}$ = +10.1° (c=1.1, $CHCl_3$)). – ^{1}H-NMR. (90 MHz): 0.98 (*d*, J=7, 3H, H_3C–C(6)); 1.07 (*d*, J=7, 6H, 2H_3C–C(2)); 2.1 (*m*, 1H, H–C(6)); 2.42 (*t*, J=7, 2H, 2H–C(4)); 2.62 (*qa*, J=7, 1H, H–C(2));

4.91 (*'d'*, $J=17$, 1H, H–C(8)); 4.91 (*'d'*, $J=9$, 1H, H–C(8)); 5.62 ($d\times d\times d$, $J_1=7$, $J_2=9$, $J_3=17$, 1H, H–C(7)). – MS.: 154 (8, M^+), 139 (1), 125 (1), 111 (16), 93 (4), 83 (21), 71 (59), 69 (34), *55* (100), 43 (56), 27 (18).

2.3.3. Synthesis of (+)-3-methyl-4-penten-1-ol ((+)-**7**). A solution of ketone (+)-**13** (7.7 g, 50 mmol) in anhydrous glyme (75 ml) was treated with potassium *t*-butoxide (16.8 g, 150 mmol) and oxygenated with efficient magnetic stirring at ~20° (cooling with ice-water necessary). After uptake of ~3.2 l of oxygen (after 90 min), the reaction mixture was diluted with water, acidified to pH ~2 (20% aq. HCl-solution), and extracted with ether (3 times). The extract was washed (H_2O), dried ($MgSO_4$) and evaporated to give a mixture (~11 g) with aldehyde **14** and acid **15** (detected by ^{1}H-NMR. spectroscopy) as main constituents. The mixture was diluted with anhydrous ether (20 ml) and immediately reduced by dropwise addition to a stirred suspension of $LiAlH_4$ (3.8 g, 0.1 mol) in anhydrous ether (20 ml) at 10–15°. The reaction mixture was heated at reflux with stirring for 8 h. The cold mixture (0–10°) was decomposed by addition of H_2O (10 ml) followed by aq. 10% HCl-solution. The organic layer was separated, washed ($NaHCO_3$, H_2O), dried ($MgSO_4$), and evaporated to yield 4.7 g of product mixture. GLC. analysis (10% *Carbowax*, 150°) showed the following main products (% of mixture/retention time in seconds [s]): (+)-**7** (87%/75 s), **16** (2%/110 s) and **17** (11%/192 s). *Vigreux* distillation gave 1.43 g of pure (+)-**7** (b.p. 48–51°/10 Torr), and 1.4 g of a mixture (b.p. 51–70°/0.01 Torr), containing ~40% of (+)-**7**. Yield of (+)-**7**: ~39% based on (+)-**13**; $[\alpha]_D^{20}=+28.9°$ ($c=1.05$, $CHCl_3$), the enantiomeric purity (determined by ^{1}H-NMR.[8]), $Eu(HFC)_3$/substrate 3:1) being 70%. For spectral data of (+)-**7** see section 2.1.

Spectral data of 4-methyl-5-hexen-1-ol (**16**): ^{1}H-NMR. (90 MHz): 0.98 (*d*, $J=7$, 3 H, H_3C–C(4)); 2.11 (*m*, 1H, H–C(4)); 3.62 (*t*, $J=6$, 2 H, 2 H–C(1)); 4.91 (*'d'*, $J=10$, 1H, H–C(6)); 4.93 (*'d'*, $J=17$, 1H, H–C(6)); 5.67 ($d\times d\times d$, $J_1=7$, $J_2=10$, $J_3=17$, 1H, H–C(5)). – MS.: 114 (0, M^+), 96 (4), 81 (69), 70 (58), 68 (54), *55* (100), 41 (63).

Spectral data of 2,2,5-trimethyl-6-hepten-1-ol (**17**): IR. (neat): 3350, 1635, 900. – ^{1}H-NMR. (360 MHz): 0.86 (*s*, 6 H, 2 H_3C–C(2)); 1.0 (*d*, $J=7$, 3 H, H_3C–C(5)); ~1.2 (*m*, 4 H, 2 H–C(3) and 2 H–C(4)); 2.04 (*m*, 1H, H–C(5)); 3.31 (*d*, $J=5$, 2 H, 2 H–C(1)); 4.92 (*'d'*, $J=10$, 1H, H–C(7)); 4.96 (*'d'*, $J=18$, 1H, H–C(7)); 5.69 ($d\times d\times d$, $J_1=8$, $J_2=10$, $J_3=18$, 1H, H–C(6)); addition of D_2O transforms *d* at 3.31 into *s*. – MS.: 156 (0, M^+), 138 (1), 125 (5), 109 (7), 97 (6), 83 (32), *69* (100), 55 (71), 41 (53), 29 (18).

2.4. Synthesis of (+)-3-methyl-4-pentenyl bromide ((+)-**9**) [26]. It was prepared from (+)-**7** as described for the racemate (section 2.2.). An analytical sample was further purified by GLC.; $[\alpha]_D^{20}=+38.8°$ ($c=1.27$, $CHCl_3$). For spectral data see also section 2.2.

2.5. Synthesis of (–)-3-methyl-4-pentenyl bromide ((–)-**9**) [25] [26] *from* (–)-**11** via (–)-**12**, (–)-**13** *and* (–)-**7**. Experimental details and spectral data for the optically active compounds (–)-**12**, (–)-**13** and (–)-**7** are identical with those of the (+)-series. The specific rotations ($[\alpha]_D^{20}$ in $CHCl_3$) were as follows: (–)-**11**: –11.6° ($c=0.6$); (–)-**12**: –10.09° ($c=1.5$); (–)-**13**: –9.9° ($c=1.31$); (–)-**7**: –25.8° ($c=1.2$); (–)-**9**: –31.2° ($c=1.22$). Enantiomeric purity (see 2.3.3.) of (–)-**7**: ~68%.

3. The trienol mixtures 18a/18b/19a/19b, 18a/19a and 18b/19b. – *3.1. Synthesis of the racemic trienols* **18a/18b/19a/19b** (1-(3-methyl-4-penten-1-yl)-2,6,6-trimethyl-2,5-cyclohexadien-1-ol). Preparation of the organolithium reagents: one mol-equiv. of bromide in anhydrous ether (one-molar solution) was allowed to react with three mol-equiv. of granulated lithium (containing 1.5% of Na, *Metallgesellschaft*, Frankfurt/M.) at –8° under argon. After the exothermic reaction was over, the mixture was stirred at 0° for 1 h, filtered through anhydrous glass wool and finally analysed for its alkyllithium content by simple acidimetric titration.

3.1.1. Alkyllithium/ketone (1:1). A solution of 7.5 mmol alkyllithium reagent in anhydrous ether (15 ml), prepared from racemic bromide ±9, was treated dropwise at 0° with a cold solution (~ –60°) of monomeric ketone **5** (1.02 g, 7.5 mmol) which had been prepared by heating its dimer (bath temp. 220°) under atmospheric pressure and collecting the monomer in a flask cooled by dry-ice/2-propanol. The stirred mixture was allowed to warm to 25° within 30 min, poured into ice-water, and extracted with ether. The ethereal extract was dried (K_2CO_3), evaporated (1.59 g) and bulb-distilled at 85–105°/0.03 Torr to give 1.3 g mixture of **18a/18b/19a/19b** (87% pure by GLC., *Supelco* 4% SP-1000, 140–220°; 68% yield, based on ketone). – IR. (neat): 3620, 1637, 990, 910. – ^{1}H-NMR.

(90 MHz): 0.98 (*d*, $J=7$, 3 H, $H_3C-C(3')$); 1.02 and 1.04 (2 *s*, 6 H, $2\,H_3C-C(6)$); 1.84 (*s*, 3 H, $H_3C-C(2)$); 4.89 (*'d'*, $J=10$, 1 H, H–C(5')); 4.91 (*'d'*, $J=16$, 1 H, H–C(5')); 5.3–5.9 (4 H, H–C(3), H–C(4), H–C(5), H–C(4')). – MS.: 220 (19, M^+), 202 (9), 187 (1), 177 (1), 159 (1), 147 (19), *137* (100), 119 (44), 109 (27), 91 (18), 77 (12), 69 (9), 55 (25), 43 (22), 41 (22).

3.1.2. Alkyllithium/ketone (2:1). Under the same reaction conditions 71.5 mmol of alkyllithium in anhydrous ether (110 ml) with 35 mmol of ketone (4.76 g) yielded 9.9 g of crude product, containing (determined by GLC., *Supelco* 4% SP-1000, 140–220°) the desired mixture of **18a/18b/19a/19b** (58%) together with the double bond isomer **20** (2,2-Dimethyl-2-methylene-1-(3'-methyl-4'-pentenyl)-3-cyclohexen-1-ol) (21%). Column chromatography of the crude product (9.5 g) on basic aluminum oxide, activity III (280 g, *Woelm*) allowed the isolation of pure **20** (eluted with hexane) and pure mixture of **18a/18b/19a/19b** (eluted with hexane/ether 9:1).

Spectral data of **20**: IR. (neat): 3610, 1710, 1635, 990, 910. – ^{1}H-NMR. (90 MHz): 0.95 (*s*, 3 H, $H_3C-C(2)$); 1.0 (*d*, $J=7$, 3 H, $H_3C-C(3')$); 1.03 (*s*, 3 H, $H_3C-C(2)$); 2.8 (*m*, 2 H, 2 H–C(5)); 4.93 (*m*, 2 H, $H_2C=C(6)$); 5.36 (*m*, 2 H, H–C(3) and H–C(4)). – MS.: 220 (2, M^+), 205 (2), 187 (3), 177 (6), 164 (7), 151 (7), 137 (31), 121 (17), 109 (54), 95 (56), 82 (23), *69* (100), 55 (58), 43 (83), 41 (74), 29 (20).

3.2. Preparation of the optically active trienols **18a/19a** *and* **18b/19b**. The distilled crude product **18a/19a** (4.73 g), obtained from (+)-**9** as described for the racemic case (section 3.1.1.), was further purified by chromatography on basic alumina, activity III (150 g) with hexane, and hexane/ether 95:5 as solvents. Purity ~98%; $[\alpha]_D^{20} = +1.5°$ ($c=1.18$, $CHCl_3$). The spectral data are identical with those of the racemic material (see section 3.1.1.).

The trienol mixture **18b/19b** (98% pure) was analogously prepared from (–)-**9** and purified; $[\alpha]_D^{20} = -5.7°$ ($c=1$, $CHCl_3$).

4. The intramolecular *Diels-Alder* reaction. – *4.1. Synthesis of the racemic patchoulenol* (±)-**21** (2,2,6,8-tetramethyltricyclo[5.3.1.0^{3,8}]undec-9-en-3-ol). Trienol **18a/18b/19a/19b** (1.23 g, 4.2 mmol, 76% pure) in anhydrous *p*-xylene (8 ml) was degassed by bubbling dry argon through the solution, and after addition of sublimed potassium *t*-butoxide (~30 mg), heated in a sealed pyrex tube at 280° for 24 h. The cold reaction mixture was diluted with ether, washed (H_2O), dried (K_2CO_3), evaporated, and bulb-distilled. Up to 90–100°/12 Torr the xylene was removed and the product distilled at 90–130°/0.03 Torr (0.63 g volatiles, residue ~0.6 g). GLC. analysis of the volatiles showed 36% patchoulenol ((±)-**21**) content (24% yield based on **18a/18b/19a/19b** or 48% based on **18a/18b**). Pure patchoulenol (±)-**21** was isolated by preparative GLC. (30% *SOMB*, 250°). – IR. (neat): 3610, 3490, 1040, 980, 700. – ^{1}H-NMR. (90 MHz): 0.82 (*d*, $J=6.5$, 3 H, $H_3C-C(6)$); 0.91 (*s*, 3 H, $H_3C-C(8)$); 1.18 (*s*, 6 H, $2\,H_3C-C(2)$); 5.81 (*d*, $J=8$, 1 H, H–C(9)); 6.36 (*d*×*d*, $J_1=6$, $J_2=8$, 1 H, H–C(10)). – MS.: 220 (7, M^+), 205 (9), 202 (8), 187 (6), 177 (5), 159 (18), 145 (5), 132 (42), 119 (23), 107 (13), *93* (100), 86 (52), 71 (29), 55 (18), 43 (43), 41 (32).

In the course of several experiments it was observed that the use of not freshly purified (distilled or chromatographed) trienol **18a/18b/19a/19b** (probably containing traces of peroxides) led – under otherwise identical conditions – to appreciable amounts (up to 30% of the distilled product) of a hexahydroindene by-product (**24**) (2,2,6,7-tetramethyl-7-vinylbicyclo[4.3.0]non-4(or 3)-en-1-ol). – IR. (CCl_4): 3620, 1635. – ^{1}H-NMR. (360 MHz): 0.98 (*s*, 3 H, $H_3C-C(6)$); 1.0 (*s*, 3 H, $H_3C-C(7)$); 1.04 (*s*, 3 H, $H_3C-C(2)$); 1.2 (*s*, 3 H, $H_3C-C(2)$); 4.88 (*d*×*d*, $J_1=2$, $J_2=17$, 1 H, $=CH_2$); 4.97 (*d*×*d*, $J_1=2$, $J_2=10$, 1 H, $=CH_2$); 5.33 (*d*×*d*, $J_1=3$, $J_2=10$, 1 H, =CH–); 5.47 (*d*×*d*×*d*, $J_1=2$, $J_2=6$, $J_3=10$, =CH–); 5.82 (*d*×*d*, $J_1=10$, $J_2=17$, $-CH=CH_2$). – ^{13}C-NMR. (22.63 MHz): 15.9 (*qa*), 22.0 (*qa*), 23.3 (*qa*), 25.2 (*qa*), 34.9 (*t*), 35.3 (*t*), 37.9 (*s*), 38.4 (*t*), 50.7 (*s*), 52.4 (*s*), 85.3 (*s*), 111.8 (*t*), 123.1 (*d*), 135.1 (*d*), 145.9 (*d*). – MS.: 220 (18, M^+), 202 (10), 187 (14), 173 (2), 164 (17), 149 (9), 138 (69), *123* (100), 119 (79), 109 (72), 95 (52), 81 (39), 67 (29), 55 (33), 43 (99). Under the same *Diels-Alder* conditions, but in the absence of potassium *t*-butoxide, trienol **18a/18b/19a/19b** led exclusively to the substituted benzene **26** 2,3,6-trimethyl-1-(3-methyl-4-penten-1-yl)benzene. – ^{1}H-NMR. (90 MHz): 1.1 (*d*, $J=7$, 3 H, $H_3C-C(3')$); 2.2 (*s*, 3 H, H_3C-Ph); 2.27 (*s*, 3 H, H_3C-Ph); 2.29 (*s*, 3 H, H_3C-Ph); 5.0 (*d*, $J=10$, 1 H, H–C(5')); 5.04 (*d*, $J=17$, 1 H, H–C(5')); 5.82 (*d*×*d*×*d*, $J_1=7$, $J_2=10$, $J_3=17$, 1 H, H–C(4')); 6.91 (*s*, 2 H, H–C(4) and H–C(5)). – MS.: 202 (27, M^+), 187 (1), 179 (4), 164 (6), 147 (18), 134 (46), *133* (100), 119 (32), 105 (13), 91 (19), 77 (10), 69 (7), 55 (15), 43 (25).

4.2. Synthesis of (+)-patchoulenol ((+)-**21**). Trienol **18b/19b** (0.94 g, 4.2 mmol, 98% pure), anhydrous xylene (50 ml) and potassium *t*-butoxide (~40 mg) were degassed and heated in a sealed pyrex tube at 270–300° for 24 h. After evaporation and bulb-distillation at 80–130°/0.005 Torr 1 g of an oil was obtained, which was then chromatographed on basic alumina, activity III (50 g) with hexane/ether 97:3 to 95:5 to 90:10. 235 mg (25% yield based on **18b/19b**, 50% yield based on **18b**) of pure (+)-**21** was isolated, $[\alpha]_D^{20} = +55.2°$ ($c = 1$, $CHCl_3$), its special data being identical with those of the racemic compound (section 4.1).

4.3. (−)-Patchoulenol ((−)-**21**). Experimental details are identical with those of the preparation of (+)-patchoulenol ((+)-**21**). $[\alpha]_D^{20} = +58.7°$ ($c = 0.96$, $CHCl_3$). For spectral data see section 4.1.

5. Hydrogenation of the patchoulenols [12c]. – *5.1. Synthesis of racemic patchouli alcohol* (±)-**1** (2,2,6,8-tetramethyltricyclo[5.3.1.$0^{3,8}$]undecan-3-ol). Patchoulenol ((±)-**21**) (52 mg, 0.24 mmol) in pure ethanol (5 ml) was hydrogenated using PtO_2 (25 mg). After hydrogen take-up has ceased, the solution was filtered over *Celite* and bulb-distilled at 90–105°/0.01 Torr, giving ~50 mg of racemic patchouli alcohol (±)-**1**. – IR. ($CHCl_3$): 3600. – ^{1}H-NMR. (90 MHz): 0.79 (*d*, $J = 7$, 3 H, H_3C–C(6)); 0.84 (*s*, 3 H, H_3C–C(8)); 1.08 (*s*, 6 H, 2 H_3C–C(2)). – MS.: 222 (76, M^+), 207 (30), 189 (15), 179 (18), 161 (42), 147 (13), 138 (70), 125 (56), 109 (52), 98 (83), 83 (94), 69 (65), 55 (76), 43 (96), *41* (100), 29 (31).

5.2. Synthesis of the nature-identical (−)-patchouli alcohol ((−)-**1**). 220 mg (1 mmol) of (−)-patchoulenol ((−)-**21**) ($[\alpha]_D^{20} = -58.7°$ ($c = 0.96$, $CHCl_3$)) was hydrogenated in pure ethanol (5 ml) using PtO_2 (50 mg). After take-up of ~30 ml H_2, the reaction mixture was filtered, evaporated and bulb-distilled at 110–120°/0.01 Torr, giving 178 mg of pure (GLC., 10% *Carbowax*, 200°) (−)-**1**, $[\alpha]_D^{20} = -94.6°$ ($c = 1.2$, $CHCl_3$)[9]), its spectral data being identical with those of the racemic compound (section 5.1).

5.3. (−)-Patchouli alcohol ((+)-**1**). Prepared from (+)-patchoulenol ((+)-**21**) (137 mg, 0.62 mmol; $[\alpha]_D^{20} = +55.2$ ($c = 1$, $CHCl_3$)) as described for its antipode (section 5.2); $[\alpha]_D^{20} = +82.9°$ ($c = 1.24$, $CHCl_3$), for spectral data see section 5.1.

REFERENCES

[1] *G. Ohloff, Ch. Vial, H.R. Wolf, K. Job, E. Jégou, J. Polonsky & E. Lederer*, Helv. Chim. Acta *63*, 1932 (1980); *G. Ohloff*, in 'Olfaction and Taste' IV, p. 156 (D. Schneider, Ed.), Wissenschaftliche Verlagsgesellsch. Stuttgart 1972; *ibid., idem* VII, p. 3 (H. van der Starre, Ed.), IRL Press Ltd., London & Washington DC. 1980; *W. Skorianetz, H. Giger & G. Ohloff*, Helv. Chim. Acta *54*, 1797 (1971).

[2] *M. Dobler, J.D. Dunitz, B. Gubler, H.P. Weber, G. Büchi & O.J. Padilla*, Proc. Chem. Soc. *1963*, 383.

[3] *E. Gildemeister & F. Hoffmann*, in «Die ätherischen Öle», 4. Aufl., Bd. 7, p. 449, Akademie-Verlag, Berlin 1961.

[4] *P. Teisseire, P. Maupetit & B. Corbier*, Recherches (Paris) *1974* (19), 8; *P. Teisseire*, Riv. Ital. Essenze, Profumi, Piante Off., Aromi, Saponi, Cosmet., Aerosol *55*, 572 (1973); Chem. Abstr. *80*, 124571h (1974).

[5] *D. Kastner*, Riechst., Arom., Kosmet. *27*, 79 (1977).

[6] *P. Teisseire, P. Maupetit, B. Corbier & P. Rouillier*, Recherches (Paris) *1974* (19), 36.

[7] *W.E. Oberhänsli & P. Schönholzer*, Recherches (Paris) *1974* (19), 62.

[8] *B.D. Mookherjee, K.K. Light & I.D. Hill*, 178th ACS National Meeting, Washington D.C., Sept. 10–14, 1979.

[9] *F. Näf & G. Ohloff*, Helv. Chim. Acta *57*, 1868 (1974).

[10] *R. Rienäcker & G. Ohloff*, Angew. Chem. *73*, 240 (1961).

[11] *D.V. Banthorpe & D. Wittaker*, Chem. Rev. *66*, 643 (1966).

[12] a) *G. Büchi, W.D. MacLeod, jr. & O.J. Padilla*, J. Am. Chem. Soc. *86*, 4438 (1964); b) *G. Büchi & W.D. MacLeod, jr.*, J. Am. Chem. Soc. *84*, 3205 (1962); c) *G. Büchi, R.E. Erickson & N. Wakabayashi*, J. Am. Chem. Soc. *83*, 927 (1961).

[13] *S. Danishefsky & D. Dumas*, Chem. Commun. *1968*, 1287.
[14] *R.N. Mirrington & K.J. Schmalzl*, J. Org. Chem. *37*, 2871 (1972).
[15] *K. Yamada, Y. Kyotani, S. Manabe & M. Suzuki*, Tetrahedron *35*, 293 (1979).
[16] *M. Bertrand, P. Teisseire & G. Pelerin*, Tetrahedron Lett. *21*, 2055 (1980).
[17] *G. Brieger & J.N. Bennett*, Chem. Rev. *80*, 63 (1980).
[18] *W. Oppolzer*, Angew. Chem. *89*, 10 (1977); *idem* Int. Ed. Engl. *16*, 10 (1977).
[19] *G. Fràter*, Helv. *57*, 172 (1974).
[20] *F. Näf & R. Decorzant*, unpublished results, 1974.
[21] *D.Y. Curtin & A.R. Stein*, Org. Synth. *46*, 115 (1966).
[22] *M. Baumann, W. Hoffmann & A. Nürrenbach*, Liebigs Ann. Chem. *1979*, 1945.
[23] *Z. Horii, T. Yagami & M. Hanaoka*, Chem. Commun. *1966*, 634.
[24] *O.P. Vig, K.L. Matta & I. Raj*, J. Indian Chem. Soc. *41*, 752 (1964); Chem. Abstr. *62*, 9177g (1965); *L.K. Montgomery, J.W. Matt & J.R. Webster*, J. Am. Chem. Soc. *89*, 923 (1967).
[25] *T. Nakata, G. Schmid, B. Vranesić, M. Okigawa, T. Smith-Palmer & Y. Kishi*, J. Am. Chem. Soc. *100*, 2933 (1978).
[26] *R.E. Ireland, G.J. McGarvey, R.C. Anderson, R. Badoud, B. Fitzsimmons & S. Thaisrivongs*, J. Am. Chem. Soc. *102*, 6178 (1980).
[27] *F. Näf & G. Ohloff* (Firmenich S.A.), Ger. Offen. 2,537,417 (4.3.1976); Chem. Abstr. *85*, 46894c (1976).
[28] *K.H. Schulte-Elte & G. Ohloff*, Tetrahedron Lett. *1964*, 1143.
[29] *B. Rickborn & R.M. Gerkin*, J. Am. Chem. Soc. *93*, 1693 (1971).
[30] *Th.J. Wallace, H. Pobiner & A. Schriesheim*, J. Org. Chem. *30*, 3768 (1965).
[31] *E. Elkik*, Bull. Soc. Chim. Fr. *1959*, 933.
[32] *W.v.E. Doering & R.M. Haines*, J. Am. Chem. Soc. *76*, 482 (1954).
[33] *C. Kutal*, in 'Natural Magnetic Resonance Shift Reagents', p. 87 (ed. by R.E. Sievers), Academic Press, New York 1973.
[34] *W.G. Young, A.N. Prater & S. Winstein*, J. Am. Chem. Soc. *55*, 4908 (1933).