Selective Synthesis of *trans*- and *cis*-*p*-Mentha-1,8-dien-5-ol from *trans*-Verbenol

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A selective synthesis of both *trans*- and *cis*-*p*-mentha-1,8-dien-5-ol from *trans*-verbenol is described. The sequence leading to *trans*-*p*-mentha-1,8-dien-5-ol consists of cleavage of the cyclobutane ring of pinene with *N*-bromosuccinimide in acetone to give the acetonide of 6-bromo-*trans*-*p*-menthene-5,8-diol, hydrodebromination with lithium aluminum hydride, and acidic treatment of the resultant acetonide of *trans*-*p*-menthene-5,8-diol. *cis*-*p*-Mentha-1,8-dien-5-ol is obtained by Swern oxidation of the *trans*-isomer and reduction of the resultant ketone with lithium tri-*sec*-butylborohydride. Acidic treatment of the acetonide of *cis*-*p*-menthene-5,8-diol (obtained from *cis*-verbenol) gives exclusively *p*-mentha-1(7),2-dien-8-ol.

In spite of their natural occurrence[1] and relatively simple structures, there is no mention in the literature of a selective synthesis of the monoterpene alcohols *trans*- and *cis*-*p*-mentha-1,8-dien-5-ol[2] (**1a** and **1b**, respectively). It has been reported that alcohol **1a** is formed during the thermolysis of *trans*-verbenol (**2a**)[3] but this reaction leads to a complex mixture containing only a small amount of **1a** besides other products of similar physical properties, the isolation of pure **1a** thus being very tedious. The same problems were encountered in the thermal rearrangement of *cis*-α-pin-2-en-7-ol leading inter alia to small quantities of presumed **1b**.[4] At least, the presence of the acetate of **1a** or **1b** in the numerous products of the acetoxy-thallation of 3-carene has been mentioned.[5]

In the course of a study related to a fragmentation of homoallylic cyclohexanols,[6] we needed both pure alcohols **1a** and **1b**. We considered the possibility of obtaining these alcohols by electrophilic isomerization of either *trans*- or *cis*-verbenol (**2a** and **2b**, respectively) which are easily accessible in enantiomerically enriched form from α-pinene.[7]

Such transformations of **1a** have been described for β-pinene, treatment of which with several electrophiles in a nucleophilic solvent leads to the formation of functionalized *p*-menthene derivatives.[8]

We first submitted *trans*-(−)-verbenol (**2a**) to the action of mercury(II) or thallium(III) salts [$HgCl_2$, $Hg(OAc)_2$, $Hg(OCOCF_3)_2$, $Tl(NO_3)_3$] in polar or unpolar solvents. In general, these reactions produced complex mixtures, led to polymerization, or resulted in substitution of the hydroxy group by the solvent.

Other electrophiles such as phenylselenium chloride in dichloromethane or *N*-bromosuccinimide in tetrachloromethane were also ineffective in the attempted transformation pinene → *p*-menthadiene. Fortunately, in the case of *N*-bromosuccinimide, the nature of the solvent has a dramatic effect: *trans*-verbenol (**2a**) is smoothly converted to the bromoacetonide **3a** by this reagent in acetone at room temperature. The unstable product **3a** can be purified by recrystallization from pentane and its structure deduced from its NMR spectra. The transformation **2a** → **3a** under these conditions shows, once more, that the formation towards a *p*-menthene derivative from the cation generated from an electrophilic addition to a pinene system requires high ionic strength and nucleophilic character of the reaction mixture.[9]

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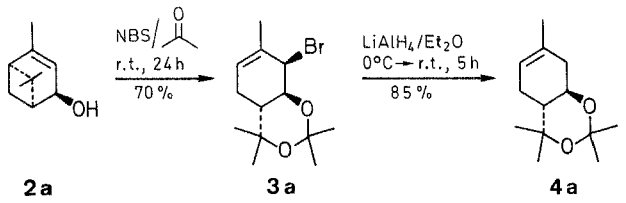
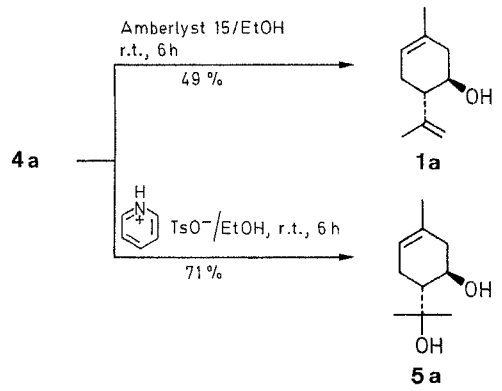
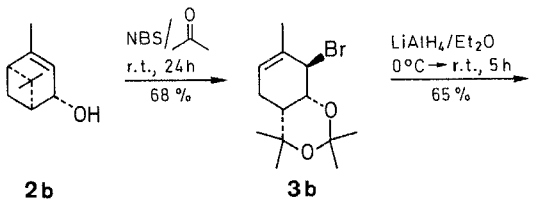
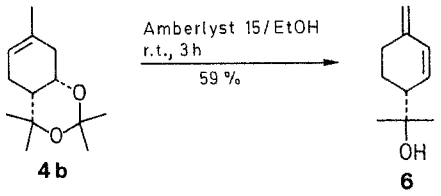




The transformation **3a** → **1a** proved easier than expected. Crude **3a** is cleanly reduced by lithium aluminum hydride in ether to give regiospecifically the acetonide **4a** which can be converted into diol **5a** by treatment with pyridinium tosylate in ethanol. In our hands, all attempts to dehydrate this diol, or its mono silyl derivative, led to intractable mixtures. However, we found that **4a** can be directly converted into alcohol **1a** by using resinsulfonic acids such as Amberlyst 15 or Amberlite IR 120 in ethanol (use of the less acidic Amberlite IRC 84 leads to diol **5a**). Under these conditions, the yield of **1a** is 49%, product **1a** being contaminated by the isomeric *p*-mentha-1,5-dien-8-ol and *p*-mentha-1(7),2-diene-8-ol (**6**) from which it can be easily separated by flash chromatography. Compound **1a** was identified by its previously described ^{13}C-NMR spectrum.[10] Thus, the sequence reported here makes possible the preparation of (−)-**1a** from *trans*-(−)-verbenol (**2a**) in 29% overall yield.

In order to obtain the *cis*-isomer **1b**, we applied the same sequence to *cis*-(1*S*,4*S*,5*S*)-verbenol (**2b**). Without any problem, we obtained the acetonide **4b** by hydride reduction of the bromo derivative **3b**. However, the configuration at C-5 has a detrimental effect on the last step: treatment of **4b** with Amberlyst 15 in ethanol leads exclusively to *p*-mentha-1(7),2-dien-8-ol (**6**), already isolated from natural sources and as a by-product of the isomerization of 2-carene oxide.[11]





cis-Alcohol **1b** can be obtained from *trans*-alcohol **1a** by Swern oxidation[12] to ketone **7** and reduction of **7** with lithium tri-*sec*-butylborohydride, a reagent known to reduce 2-monosubstituted cyclohexanones to the corresponding *cis*-alcohols.[13]

Table 1. Bromoacetonides **3a** and **3b** and Acetonides **4a** and **4b** Prepared

Product	Molecular Formula	MS (70 eV)[e] *m/z* (%)	IR (NaCl)[d] ν(cm^{-1})	^{1}H-NMR (300 MHz) ($CDCl_3$/TMS)[e] δ, *J*(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ
3a	$C_{13}H_{21}BrO_2$[a] (289.2)	291–289 (2); 275–273 (80); 151 (100); 133 (80); 93 (100); 59 (55)	1260, 1200, 1130, 1070, 1010, 950, 870, 810, 660	1.18 (s, 3H); 1.26 (s, 3H); 1.39 (s, 3H); 1.44 (s, 3H); 1.79 (m, 3H); 1.88 (ddd, 1H, *J* = 17.5, 6, 4); 2.10 (ddd, 1H, *J* = 11.5, 11.5, 6); 2.15 (dd, 1H, *J* = 17.5, 11.5); 3.70 (dd, 1H, *J* = 4, 11.5); 5.43 (m, 1H, *J* = 4); 4.48 (d, 1H, *J* = 4)	21.3, 24.6, 25.3, 25.9, 31.0, 31.6, 56.7, 66.3, 72.7, 97.8, 124.3, 132.6
3b	$C_{13}H_{21}BrO_2$[b] (289.2)	275–273 (20); 171–173 (18); 151 (28); 93–92 (50); 59 (68)	1250, 1200, 1130, 1050, 1010, 970, 890, 840, 680	1.16 (s, 3H); 1.34 (d, 3H, *J* = 0.5); 1.45 (s, 3H); 1.49 (s, 3H); 1.84 (t, 3H, *J* = 4); 1.86 (d, 1H, *J* = 6); 2.08 (dd, 1H, *J* = 18.5, 6); 2.36 (ddd, 1H, *J* = 2, 6, 18.5); 2.35 (m, 1H); 4.39 (s, 1H); 4.58 (t, 1H, *J* = 2); 5.65 (dd, 1H, *J* = 4, 2)	21.6, 22.8, 24.7, 27.4, 28.5, 31.6, 32.7, 53.2, 68.8, 73.8, 99.5, 126.9, 130.4
4a	$C_{13}H_{22}O_2$[b] (210.3)	210 (2); 195 (38); 152 (34); 135 (92); 93 (35); 81 (46); 69 (40); 45 (100)	1380, 1260, 1250, 1200, 1120, 1060, 1100	1.22 (s, 3H); 1.24 (s, 3H); 1.40 (s, 3H); 1.50 (d, 3H, *J* = 0.5); 1.65 (m, 1H); 1.68 (d, 3H, *J* = 1); 2.00 (m, 2H); 2.07 (m, 2H); 4.29 (ddd, 1H, *J* = 9.5, 7.5, 3.5); 5.35 (d, 1H, *J* = 1)	21.9, 23.0, 23.1, 24.8, 30.3, 30.8, 32.1, 46.5, 66.2, 74.5, 98.6, 123.2, 136.8
4b	$C_{13}H_{22}O_2$[b] (210.3)	195 (23); 152 (15); 135 (94); 93 (39); 81 (31); 69 (26); 43 (100)	1380, 1250, 1230, 1200, 1170, 1130, 1060, 1030, 1010, 970, 960, 910, 890, 800	1.15 (s, 3H); 1.35 (s, 3H); 1.36 (s, 3H); 1.45 (s, 3H); 1.63 (m, 1H); 1.68 (s, 3H); 1.79 (m, 1H); 1.84 (m, 1H); 2.00 (m, 2H); 4.36 (m, 1H); 5.50 (d, 1H, *J* = 4)	18.6, 23.5, 29.1, 29.8, 30.9, 30.9, 31.9, 40.5, 61.7, 73.0, 98.3, 120.7, 141.0

[a] Too unstable to give a satisfactory microanalysis.
[b] Satisfactory microanalyses: C ± 0.32, H ± 0.12, O ± 0.19, Br ± 0.31.
[c] Obtained with a Delsi D1700-Nermag R10-109 spectrometer.
[d] Recorded on a Perkin Elmer 298 Infrared spectrophotometer.
[e] Recorded with a Bruker AM300 spectrometer [**3a** with a Bruker AM360; in this case, the coupling constants were measured in C_6D_6/C_6F_6 (1:1)].

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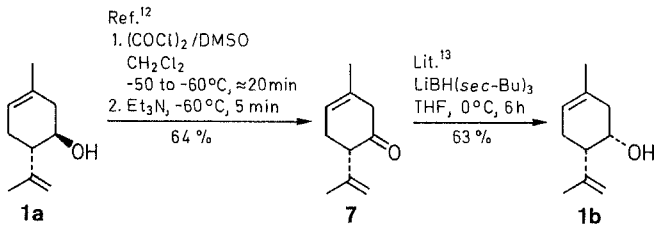
Table 2. Alcohols **1a**, **1b**, and **6** and Ketone **7** Prepared

Product	C.A. RN, Lit.	Molecular Formula	MS (70 eV)[c] *m/z* (%)	IR (NaCl)[d] ν (cm^{-1})	^{1}H-NMR (300 MHz) ($CDCl_3$/TMS)[e] δ, *J* (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ
1a	[55820-19-4][10]	$C_{10}H_{16}O$ (152.2)	152 (6); 137 (38); 119 (21); 108 (33); 84 (95); 83 (51); 41 (100)	3400, 3080, 3020, 1640, 1440, 1380, 1040, 890, 800	1.65 (s, 3H); 1.73 (s, 3H); 1.97 (m, 1H); 2.14 (m, 2H); 2.22 (dd, 1H, *J* = 9, 7); 2.30 (dd, 1H, *J* = 16, 5); 3.76 (ddd, 1H, *J* = 16, 9, 6); 4.85 (s, 1H); 4.88 (s, 1H); 5.30 (m, 1H)	19.3, 23.1, 30.5, 39.0, 49.8, 68.2, 113.0, 119.9, 131.7, 146.3
6	[65293-09-6][11]	$C_{10}H_{16}O$ (152.2)	152 (14); 137 (17); 109 (32); 94 (100); 79 (71)	3400, 3090, 3010, 1640, 1600, 1380, 1120, 1070, 930, 880	1.18 (s, 3H); 1.23 (s, 3H); 1.35 (m, 2H); 1.90 (ddd, 1H, *J* = 4, 7.5, 9); 2.26 (m, 1H); 2.48 (dt, 1H, *J* = 15, 4); 4.78 (s, 2H); 5.91 (d, 1H, *J* = 10); 6.23 (dd, 1H, *J* = 3, 10)	24.8, 26.1, 27.9, 30.2, 47.3, 72.9, 104.2, 110.5, 130.8, 143.9
7	[1]	$C_{10}H_{14}O$ (150.2)	150 (57); 135 (17); 122 (18); 107 (32); 91 (26); 82 (100)	3080, 3040, 1720, 1680, 1650, 1450, 1270, 1250, 900, 780	1.71 (m, 3H); 1.76 (s, 3H); 2.49 (m, 2H); 2.81 (d, 2H, *J* = 9); 3.15 (t, 1H, *J* = 8); 4.81 (m, 1H); 4.95 (m, 1H); 5.59 (m, 1H)	21.3, 22.5, 30.2, 44.6, 55.1, 113.0, 120.4, 132.0, 142.5, 208.9
1b	[58461-28-2][4]	$C_{10}H_{16}O$ (152.2)	152 (2); 137 (17); 119 (21); 108 (21); 93 (35); 91 (35); 84 (46); 83 (38); 41 (100)	3400, 3080, 3020, 1640, 1440, 1070, 890, 870, 800, 760	1.66 (s, 3H); 1.80 (s, 3H); 1.95–2.27 (m, 5H); 4.10 (m, 1H); 4.83 (m, 1H); 4.93 (m, 1H); 5.43 (m, 1H)	22.7, 23.4, 24.1, 38.2, 44.3, 66.0, 110.9, 120.2, 130.1, 146.5

[c,d,e] See Table 1.



The isomeric alcohol **1b**, prepared from **1a** via **7** and purified by flash chromatography, is the pure *cis*-alcohol as shown by comparison of its ^{1}H-NMR spectrum with that previously described.[4]

Table 3. Optical Data for Compounds **1**, **2**, **6**, and **7**

Product	$[\alpha]^{20}$[a] (*c* = 1.0, $CHCl_3$)	ee[b] (%)
2a	−135°	76 (^{1}H, ^{13}C)
2b	− 10°	62 (^{1}H)
1a	− 41°	78 (^{13}C)
1b	− 5.3°	78 (^{13}C)
6	+ 40°	60 (^{13}C)
7	− 97°	

[a] Recorded on a Perkin-Elmer 241.
[b] Measured by ^{1}H-NMR (300 MHz) or ^{13}C-NMR spectroscopy according to Ref. 15.

Melting points are uncorrected. ^{1}H-NMR spectrum of **5a** was recorded on a Varian EM 360A spectrometer.

[1*S*-(1α,6β,10α)]-10-Bromo-3,3,5,5,9-pentamethyl-2,4-dioxabicyclo-[4.4.0]dec-8-ene (3a):
To a solution of NBS (3.6 g, 0.02 mol) in acetone (40 mL) is added a solution of *trans*-(−)-verbenol [**2a**; 3.0 g, 0.02 mol); obtained from (−)-α-pinene[14]] in acetone (40 mL). The mixture is allowed to stand at room temperature for 24 h, acetone is then evaporated, and the residual crude paste is dissolved in pentane (40 mL). Succinimide is filtered off and the solvent evaporated to give **3a**; yield: 4.1 g (70%); mp 80–81 °C (pentane).

[1*R*-(1β,6β,10α)]-10-Bromo-3,3,5,5,9-pentamethyl-2,4-dioxabicyclo-[4.4.0]dec-8-ene (3b):
The above procedure performed with *cis*-(1*S*,4*S*,5*S*)-verbenol [**2b**; obtained from (−)-verbenone[7]] affords **3b**; yield: 4.0 g (68%); mp 55–56 °C (pentane).

[1*R*-(*trans*)]-3,3,5,5,9-Pentamethyl-2,4-dioxabicyclo[4.4.0]dec-8-ene (4a):
A solution of crude **3a** (4.1 g, 0.014 mol) in Et_2O (30 mL) is added dropwise to a stirred suspension of $LiAlH_4$ (1.0 g, 0.026 mol) in Et_2O (30 mL) at 0 °C. Stirring is continued at room temperature for 5 h, the minimum of H_2O to hydrolyse the hydride is added, and the organic layer is dried ($MgSO_4$). Evaporation and flash chromatography (petroleum ether/Et_2O, 9:1) affords **4a**; yield: 2.5 g (85%).

[1*S*-(*cis*)]-3,3,5,5,9-Pentamethyl-2,4-dioxabicyclo[4.4.0]dec-8-ene (4b):
The procedure performed with **3b** (4.0 g, 0.014 mol) affords **4b**; yield: 1.9 g (65%).

[5*R*-(*trans*)]-*p*-Mentha-1,8-dien-5-ol (1a):
A mixture of Amberlyst 15 (50 mg), acetonide **4a** (1.25 g, 0.006 mol), and EtOH (6.5 mL) is stirred for 6 h at room temperature. Filtration through silica gel (10 g) and evaporation of the solvent afford a mixture of alcohols (0.9 g) from which alcohol **1a** is isolated by flash chromatography (petroleum ether/Et_2O, 3:2); yield: 440 mg (49%).

(4*R*)-*p*-Mentha-1(7),2-dien-8-ol (6):
cis-Acetonide **4b** (550 mg, 2.6 mmol) is stirred with Amberlyst 15 (30 mg) in EtOH (2 mL) for 3 h. Filtration through silica gel (10 g), evaporation of solvent, and purification by flash chromatography (petroleum ether/Et_2O, 3:2) gives alcohol **6**; yield: 320 mg (59%); oil.

(4*S*)-*p*-Mentha-1,8-dien-5-one (7):
trans-*p*-Mentha-1,8-dien-5-ol (**1a**; 400 mg, 2.6 mmol) is dissolved in CH_2Cl_2 (3 mL) and treated[12] successively with DMSO (0.51 mL, 7.0 mmol) activated by oxalyl chloride (0.30 mL, 3.4 mmol) in CH_2Cl_2 (9 mL) at −60 °C for 20 min, and Et_3N (2.1 mL, 15 mmol) at −60 °C for 5 min, then at 25 °C for 1 h. Hydrolysis with H_2O (20 mL), extraction with CH_2Cl_2 (30 mL) affords extracts, which are washed with saturated NaCl solution (30 mL) and dried ($MgSO_4$). Evaporation and flash chromatography (petroleum ether/Et_2O, 1:1) gives **7**; yield: 256 mg (64%); oil.

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[5*S*-(*cis*)]-*p*-Mentha-1,8-dien-5-ol (1b):
p-Mentha-1,8-dien-5-one (**7**; 200 mg, 1.3 mmol) is dissolved in THF (10 mL) and reduced[13] by 1 M lithium tri-*sec*-butylborohydride in THF (1.7 mL, 1.7 mmol) at 0 °C for 6 h. H_2O (0.25 mL) and Et_2O (10 mL) are added, and organic layer washed with sat. NH_4Cl solution (1 mL), then H_2O (2 × 1 mL), and dried ($MgSO_4$). Removing of the solvent, dilution in AcOH (2 mL), neutralization with 5 N KOH solution (7 mL), addition of Et_2O (10 mL), stirring overnight with 1.5 N KOH solution (3 mL) and 30% H_2O_2 (1.5 mL), and extraction with Et_2O (2 × 10 mL) affords extracts, which are dried ($MgSO_4$). After concentration of the extract *in vacuo*, flash chromatography (petroleum ether/Et_2O, 3:1) gives **1b**; yield: 125 mg (63%); oil.

[5*R*-(*trans*)]-1-*p*-Menthene-5,8-diol (5a):
Acetonide **4a** (600 mg, 2.9 mmol) is stirred with pyridinium tosylate (55 mg, 0.22 mmol) in EtOH (10 mL) at room temperature for 6 h. Filtration through silica gel (10 g), evaporation, and flash chromatography (Et_2O/CH_2Cl_2, 3:1) of the filtrate gives diol **5a**; yield: 350 mg (71%); mp 67–68 °C (pentane) (Lit.[16] mp 70–72 °C).

IR (NaCl): ν = 3400, 3070, 1380, 1200, 1120, 1040, 1010 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.1 (s,m, 3H); 1.2 (s, 3H); 1.6 (s, 3H); 1.8–2.1 (m, 5H); 4.2 (m, 1H); 5.2 (m, 1H).

The authors thank Rhône-Poulenc Recherches for their interest and for financial support, and Dr. F. Gobert for the NMR spectra.

Received: 22 April 1988; revised: 25 July 1988

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