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Diastereoselective Route to Enantiomerically Pure Homoallylic Pinene Alcohols from Myrtenyl Bromide and Aldehydes

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Abstract: With zinc dust in aq. NH_4Cl/THF, mytenyl bromide (**1**) reacts with aldehydes (**2**) to give simple new pinene alcohols (β-pinene-3-yl carbinols) (**3**), which are enantiomerically pure (100% de). The configuration of the new chiral centre at C-11 was determined by oxidation to the ketone **4** and stereoselective reduction to Cram alcohol **3**.

Mytenyl bromide (**1**) is an inexpensive terpenoid, which can easily be preparerd from optically pure myrtenol.[1] As an allylic bromide, **1** suffers easy debrominative self-dimerization to isomeric 1,5-hexadiene derivatives on contact with metals. For example, the Grignard reagent of **1** cannot be prepared by conventional techniques.[2] In the presence of a series of activated metals[3] **1** has now been found to combine with aldehydes to afford enantiopure β-pinene-3-yl carbinols **3**. Best results were observed using the triphase system zinc dust/saturated aq. NH_4Cl/THF.[4] Again, a side reaction was debrominative self-dimerization of **1** to isomeric 1,5-hexadienes.

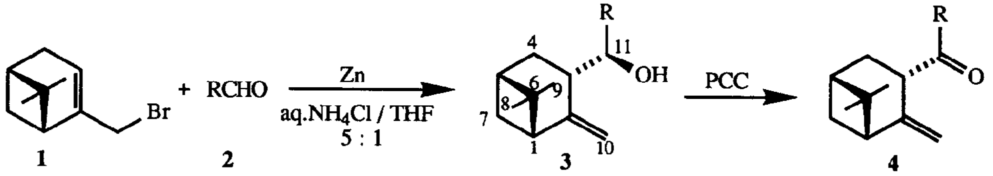

Table 1. Homoallylic Alcohols **3** Prepared

	2	**3** Yield [%][a]
a	CH_3CHO	32[b]
b	CH_3CH_2CHO	21[c]
c	$(CH_3)_2C{=}CHCHO$	25[d]
d	PhCHO	25[e]
e	$CH_3COCH_2CH_3$	0

[a] Only one diastereomer detected (GC, ^1H NMR, ^{13}C NMR). [b] $[\alpha]_D^{20}$ 27.64 (c = 0.955, MeOH). [c] $[\alpha]_D^{20}$ 45.33 (c = 0.77, MeOH). [d] $[\alpha]_D^{24}$ 19.03 (c = 1.455, MeOH). [e] $[\alpha]_D^{21}$ 34.47 (c = 0.795, MeOH).

Of the two possible diastereomeric alcohols, only one was formed. The alcohol was recognized as Cram alcohol **3** by oxidation to ketone **4** and preferential reduction to product alcohol **3** with various metal hydrides (Table 2). Electron transfer mediated reduction of **4a** gave mainly anti-Cram alcohol **5a**, as expected.[5] However, SET reduction of phenyl ketone **4d**[6] did *not* change the stereoselectivity and afforded Cram alcohol **3d** as major diastereomer (Table 2), similar to the reduction by metal hydrides.

In conclusion, pinene alcohols **3** have previously not been described (CAS-online). They are formed with high diastereoselectivity, albeit in modest chemical yield. The Barbier-Luche procedure is simple and the selective formation of **3** provides the first example for the stereochemistry of this reaction.[7]

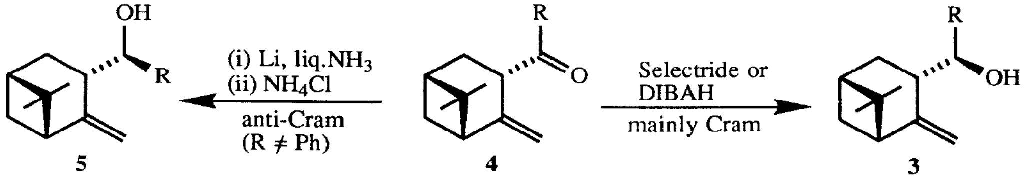

Table 2. Reduction of 4 to 3 and 5

	Homoallylic Alcohols **3** : **5**	
Reducing Agent	R = Me	R = Ph
L-Selectride	97 : 3	100 : 0
DIBAH	63 : 27	66 : 34
LiAlH$_4$	68 : 32	71 : 29
Li, liq. NH$_3$	22 : 78	83 : 17

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References and Notes

(1) (a) Ohloff, G.; Farnow, H.; Schade, G. *Chem.Ber.* **1956**, *89*, 1549; (b) Henc, B.; Pauling, H.; Wilke, G.; Krüger, C.; Schroth, G.; Hoffmann, E.G. *Liebigs Ann.Chem.* **1974**, 1820; (c) Rupe, H.; Héritier, A. *ibid.* **1927**, *459*, 171.

(2) The Grignard reagent of **1** has been prepared using a special apparatus and low temperature: Oppolzer, W.; Kündig, E.P.; Bishop, P.M.; Perret, C. *Tetrahedron Lett.* **1982**, *23*, 3901; see also Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J.Org.Chem.* **1991**, *56*, 698.

(3) BiCl$_3$/Al, THF/H$_2$O (2.5 : 1) (18% yield of **3a**): Wada, M.; Ohki H.; Akiba, K. *J.Chem.Soc., Chem.Commun.* **1987**, 708. Al/PbBr$_2$, DMF (14% yield of **3a**): Tanaka, H.; Yamashita, S.; Hamatani, T.; Ikemoto, Y.; Torii, S. *Synth.Commun.* **1987**, *17*, 789. In/DMF (20% yield of **3a**): Araki, S.; Ito, H.; Butsugan, Y. *J.Org.Chem.* **1988**, *53*, 1833.

(4) Petrier, C.; Luche, J.J. *J.Org.Chem.* **1985**, *50*, 910.

(5) Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J.Am.Chem.Soc.* **1988**, *110*, 4475.

(6) A change of mechanism may be involved in the reduction of phenyl ketone **4d**. Cf. dianion vs. radical anion mechanism in the metal-ammonia reduction of acetophenone: Narisada, M.; Watanabe, F. *J.Org.Chem.* **1973**, *38*, 3887; El-Khawaga, A.M.; Hoffmann, H.M.R. *Methoden der organischen Chemie* (Houben-Weyl), in press.

(7) Experimental: (1R,5S)-Myrtenol (α_D -47.5, 97%, Janssen) was converted[1a] into (1R,5S)-myrtenyl bromide, α_D^{20} (neat) -34.4; $[\alpha]_D^{20}$ -29.2 (CHCl$_3$, c = 1.5 g/100 mL); $[\alpha]_D^{20}$ -25.1 (C$_6$H$_6$, c = 1.2 g/100mL). Lit.[8]; α_D^{20} (neat) - 29.25[1a]; $[\alpha]_D^{20}$ -25.1 (C$_6$H$_6$, c = 4.36)[1b]; $[\alpha]_D^{20}$ -35 (CHCl$_3$, c = 5)[1b]]. Allylic bromide **1** (6.5 g, 30 mmol) was mixed with freshly distilled acetaldehyde (1.1 g, 25.9 mmol), saturated aq. NH$_4$Cl (25 mL) and THF (5 mL) at room temperature. Powdered zinc (1.97 g, 30 mmol) was stirred into the mixture in small portions. After further stirring for 4.5 h, the mixture was worked up with water as usual. Kugelrohr distillation (65°C, 0.01 Torr) and chromatography (PE/Et$_2$O, 1 : 1) gave **3a** (1.45 g, 32%), colorless waxy mass, mp 33°C. ^{1}H NMR (CDCl$_3$) δ 0.74 (s, 3 H-9), 1.23 [d, obscured, CH$_3$(OH)], 1.26 (s, 3 H-8), 1.27 (d, obscured, *endo* H-7), 1.58 (m, H-4), 1.95 - 2.13 (m, H-4, H-5), 2.30 (m, H-3, *exo* H-7), 2.47 (dd, $J_{1/5} = J_{1/exo\text{-}7}$ = 5 Hz, H-1), 2.72 (s, OH), 3.58 (dq, J_d = 8 Hz, J_q = 6 Hz, H-11), 4.80 (bs, H-10), 4.85 (bs, H-10). ^{13}C NMR (CDCl$_3$) δ 20.61 (q, C-12), 21.54 (q, C-9), 25.83 (q, C-8), 26.75, 27.46 (t, C-4, C-7), 40.82 (d, C-5), 41.03 (s, C-6), 43.63 (d, C-1), 52.48 (d, C-3), 71.59 (d, C-11), 110.34 (t, C-10), 152.32 (s, C-2). MS (70 eV, r.t.) *m/z* 180 (M$^+$, 1), 93 (100).

^{1}H NMR spectra of Cram alcohol **3a**(1R,3S,5R,11R) and anti-Cram alcohol **5a** (1R,3S,5R,11S) differ characteristically in the position of the geminal methyl protons and of C(11)*H*. **3a**: 0.74 (H-9), 1.26 (H-8), 3.58 (dq, *J* = 8 Hz, 6 Hz, H-11). **5a:** 0.81, 1.33, 4.23 (dq, *J* = 12.5 Hz, 3 Hz). **3d**: 0.70 (H-9), 1.23 (H-8), 4.42 (d, *J* = 9 Hz, H-11). **5d**: 0.76, 1.30, 5.16 (bd, *J* = 3.5 Hz).

(8) Presumably, the myrtenol used in the literature[1a] had an optical purity of 85%. The absolute configuration of (-)-myrtenol is 1R,5S: Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*, Chapman and Hall, London 1974, p.85.