Favorable effect of Ce^{III} on the stereoselectivity of reduction of verbenone to *cis*-verbenol

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Reduction of verbenone with $NaBH_4$ in the presence of $Ce(NO_3)_3 \cdot 6H_2O$ (10—20 mol %) proceeds stereoselectively to give *cis*-verbenol in 89—94% yield.

Key words: verbenone, *cis*- and *trans*-verbenols, verbanols, reduction, sodium borohydride, cerium nitrate, stereoselectivity.

Chiral *cis*- and *trans*-verbenols[1] have been detected in the aggregation and sex pheromones of many species of *Ips* and *Dendroctonus* bark beetles. Study of the response of the insects to each possible stereoisomer shows that attraction of many species becomes much more efficient when a racemate is replaced by an enantiomer with absolute configuration of the natural pheromone or a synergistic mixture of enantiomers.

The practical use of such optically active low-molecular bioregulators will be economically efficient if they are produced by simple and preparatively convenient methods from accessible and cheap starting materials.

Chiral *cis*-verbenols are obtained by the Jones oxidation of *trans*-verbenols into verbenones followed by hydride reduction.[2—4]

Analysis of the literature data[3,5,6] on the reduction of verbenone (**1**) with aluminum hydrides shows insufficient stereoselectivity with respect to *cis*-verbenol (up to 18% of the *trans*-isomer is formed). With $NaBH_4$ as the reducing agent, the yield of the target alcohol does not exceed 47%.[2]

We propose a new convenient and selective method for the synthesis of *cis*-verbenol in a preparative yield that is much higher than all those reported previously. The method is based on reduction of ketone **1** with sodium borohydride in the presence of $Ce(NO_3)_3$ as a catalyst.

Lanthanide chlorides are known[7] to be effective modifiers of $NaBH_4$ for regioselective 1,2-reduction of α,β-enones. Presumably, Ln^{III} catalyzes mainly decomposition of BH_4^- by a hydroxyl-containing solvent (most often MeOH) to give alkoxyborohydrides, which are responsible for the observed regioselectivity. In addition, the process is more stereoselective since Ln^{III} ions favor an axial attack on the cyclohexane system. It is also known that reduction of α,β-unsaturated ketones with metal hydrides[8] can follow the mechanism of nucleophilic 1,2-addition to the C=O group or 1,4-addition to the conjugated C=C—C=O system. In the former case, allylic alcohols are formed; in the latter case, the resulting enol undergoes rapid tautomerization into a saturated ketone with subsequent reduction to a saturated alcohol.

We carried out a number of experiments aimed at reducing verbenone with $NaBH_4$ and an $NaBH_4$—$Ce(NO_3)_3$ (2—20 mol %) system in alcohols (EtOH and Pr^iOH) and their aqueous solutions at −12 to 20 °C with direct (slow addition of the compound to be reduced to a solution of a hydride) and reverse (slow addition of a solution of a hydride to the compound to be reduced) orders of mixing. The results obtained are given in Tables 1 and 2.

Indeed, the reduction of verbenone with $NaBH_4$ (see Table 1) affords a mixture of allylic alcohols, namely, *cis*- (**2**) and *trans*-verbenols (**3**), verbanols (**4**), and small amounts of verbanones (**5**) (Scheme 1). In addition, ethers were detected among the reaction products.*

Being too complex to be identified, the reaction mixture was subjected to oxidation. The starting ketone **1** formed from alcohols **2** and **3** upon the oxidation was isolated as a bisulfite derivative. The residue was chromatographed on SiO_2 to give a mixture of saturated ketones *cis*-**5** and *trans*-**5** in the 4 : 1 ratio (GLC). According to the IR and NMR spectroscopic data, the major component is *cis*-verbanone[9] (IR, ν/cm^{-1}: 1720 (C=O)). ^{1}H NMR, δ: 1.01 (s, 3 H, C(9)H$_3$); 1.17 (d, 3 H, C(10)H$_3$, J = 7.4 Hz); 1.34 (s, 3 H, C(8)H$_3$).

* Isolated as a mixture. The major component is ethyl (or isopropyl) *trans*-verbenyl ether, which was identified by comparison with a sample obtained by an independent synthesis; the minor components may be ethyl *cis*-verbenyl and ethyl verbanyl ethers.

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Table 1. Reduction of verbenone with $NaBH_4$

Entry	Order of reagent mixing	Molar ratio ketone : $NaBH_4$	Solvent	Reaction time /h	*T*/°C	Conversion (%)	Content (%) (GLC)	
							2/3	**4 + 5** [a]
1	Direct	1 : 0.5	EtOH	24	20	100	33/14	45
2	Direct	1 : 1	EtOH	24 [b]	−10—20	98	34/16	33
3	Direct	1 : 0.4	EtOH	5	50—55	80	7/18	37
4	Reverse	1 : 0.25	Pr^iOH	24 [c]	3—20	91	19/30	37

[a] Ethers as by-products.
[b] At −10 °C for 10 h, then at ~20 °C.
[c] At 3 °C for 5 h.

Lowering of the temperature to −10 °C virtually does not change the reaction selectivity; an increase in the temperature to 50—55 °C increased the content of 1,4-reduction products **4** and **5** and more stable *trans*-isomer **3**. The reverse order of mixing with the addition of a minimum (stoichiometric) amount of $NaBH_4$ is least preferred since *trans*-verbenol is dominant under deficiency of the hydride. Thus, the reduction of verbenone with $NaBH_4$ alone is a lengthy and nonselective process yielding, at best, 33—34% of *cis*-verbenol.

Subsequently, we carried out the reaction according to an original procedure: a solution of $Ce(NO_3)_3 \cdot 6H_2O$ in the starting ketone was added to an alcoholic solution of the hydride (Table 2).

Table 2. Reduction of verbenone with $NaBH_4$—$Ce(NO_3)_3$ (10 mol %) (ketone : hydride molar ratio was 1 : 1)

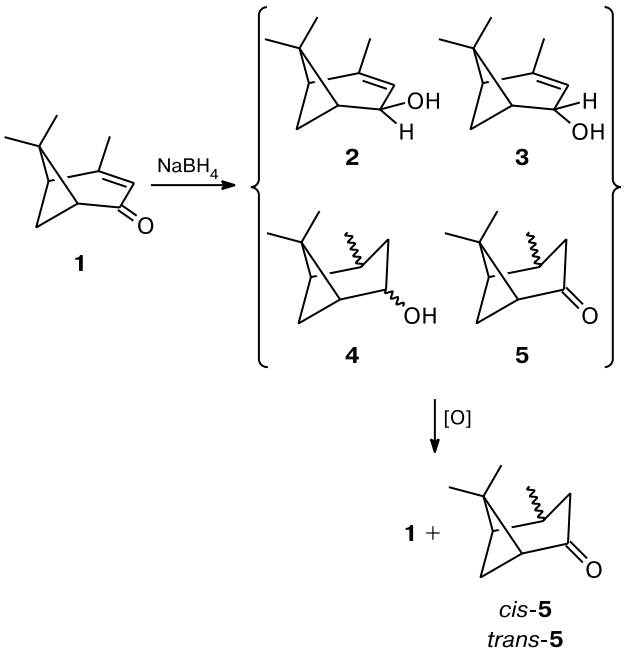
Entry	Order of reagent mixing	Solvent	Reaction time/h	*T*/°C	Content (%) (GLC)	
					2/3	**4 + 5**
1	Direct	40% EtOH	6 [a]	−1—20	89/4	5
2	Direct	EtOH	3	0	90/4	6
3	Direct	EtOH	2	−10	91/2	5
4	Direct	Pr^iOH—H_2O (5 : 1)	1.5	−10	94/2	3
5	Direct [b]	Pr^iOH—H_2O (5 : 1)	1.5	−10	93/4	2
6	Direct [c]	Pr^iOH—H_2O (5 : 1)	24 [d]	−8—20	41/10	38
7	Direct [e]	EtOH	24 [f]	−6—20	61/4	30
8	Reverse	Pr^iOH—H_2O (5 : 1)	24 [g]	−10—20	18/47	7 [h]

[a] Mixing of the reagents at −1 °C over 1 h, then at ~20 °C.
[b] $Ce(NO_3)_3$ (20 mol %).
[c] $Ce(NO_3)_3$ (2 mol %).
[d] At −8 °C for 10 h.
[e] The reductive system was prepared by mixing solutions of $NaBH_4$ and $Ce(NO_3)_3$.
[f] At −6 °C for 4 h.
[g] At −10 °C for 4 h.
[h] The by-product is isopropyl *trans*-verbenyl ether (28%).

As can be seen from Table 2, the reduction rate is considerably increased in the presence of Ce^{III} ions; it was noted that the reaction proceeds the faster the lower is the temperature. The major reaction products were allylic alcohols, while saturated compounds are formed in minor amounts (2—6%).

But the main effect of Ce^{III} ions consists in sharp enhancement of the reduction stereoselectivity; the content of *cis*-verbenol in the reaction products was increased from 33—34% (with $NaBH_4$ alone) to 89—95%. The formation of $Ce(BH_4)_3$ is hardly probable since the content of $Ce(NO_3)_3$ was mostly 10 mol % with respect to $NaBH_4$ and the reactions were carried out at reduced temperature. The reactions of $NaBH_4$ with rare-earth metal salts[10]

Scheme 1



are known to proceed rather slowly (10—30 h), often at elevated temperatures and with a large excess of the salts. In addition, alcohols are virtually not used as solvents in the synthesis of metal borohydrides. Most probably, Ce^{III} ions catalyze the formation of alkoxyborohydrides,[11] which are known to be more potent and, because of a larger effective volume, more stereospecific reducing agents than $NaBH_4$. A twofold increase in the concentration of Ce^{III} had almost no effect on both the reaction stereoselectivity and rate. Low temperature favors the kinetic regime of the reaction; the more reactive alkoxyborohydrides formed *in situ* reduce verbenone much more rapidly.

The use of only 2 mol % $Ce(NO_3)_3$ is insufficient for rapid and selective reduction of verbenone. The conversion over 6 h was ~50% (TLC data). For the reaction to be completed, the mixture was left for ~16 h; however, the content of saturated compounds upon the corresponding workup was about 38%, *i.e.*, it is $NaBH_4$ that mostly acts as a reducing agent.

So-called mixed hydrides, which are composed of a complex hydride and a catalyst (a salt, usually metal chloride), are also known as reducing agents.[12] Reactions with such hydrides can be carried out in several ways. Making a recourse to the most common one, we added verbenone to a solution containing $NaBH_4$ and $Ce(NO_3)_3$ (direct order of mixing). Mixing of alcoholic solutions of $NaBH_4$ and $Ce(NO_3)_3$ led to a rise in temperature (by 15 °C), evolution of hydrogen, and the formation of a precipitate; such a reducing system proved to be poorly active and nonstereoselective.

When the starting reagents were mixed in the reverse order, the major reaction products were *trans*-verbenol and isopropyl *trans*-verbenyl ether isolated by chromatography on SiO_2 and identified by spectroscopy. The formation of this ether was also observed in the reduction of verbenone to *cis*-verbenol with aluminum isopropoxide.[13]

In all experiments, we used verbenone synthesized by catalytic oxidation of (+)-α-pinene with $[\alpha]_D$ +20 (*ee* ~40%). Such a "poor" (from the viewpoint of optical purity) starting compound afforded the corresponding (+)-verbenone with $[\alpha]_D$ +119 (*ee* ~43%), the reduction of which yielded both (+)- and (−)-*cis*-verbenols. Crystallization of alcohol **2** from hexane yields needle-like crystals (~25—30%), $[\alpha]_D$ −13.0±0.3 (*c* 0.92, EtOH) and +10.1 (*c* 0.98, $CHCl_3$), m.p. 70—71 °C; purity 97—98%, verbanols 2—3% (GLC). The above constants are close to the data for 1*R*,2*R*,5*R*-*cis*-verbenol ($[\alpha]_D$ −12.8 (MeOH), +9.3 ($CHCl_3$), m.p. 70—71 °C).[4] The remaining part of alcohol **2** was isolated as a crystalline mixture with high percentage of the (+)-form. The overall yield of *cis*-verbenol after crystallization was 72—76%.

Earlier,[4] the enantiomers of *cis*-verbenol have been isolated by means of a rather labor-consuming operation, namely, synthesis of 3β-acetoxyetienic esters, their recrystallization, and hydride reduction for the recovery of the target alcohols. In our case, *trans*-verbenol was formed in only 2—4% yield, and crystallization gave compound **2** virtually free from the *trans*-isomer.

Previous[14] controversial data on the physicochemical characteristics of *cis*-verbenol are associated with admixtures of the *trans*-isomer in the isolated samples. Insofar as *trans*-enantiomers have $[\alpha]_D$ +141 or −135 (*i.e.*, an order of magnitude higher),[15] even small proportion of *trans*-isomer **3** contributes greatly to the optical rotation value. In addition, samples obtained by reduction with $NaBH_4$ could contain saturated compounds **4** and **5**. For instance, single crystallization of a reaction mixture containing >30% saturated alcohols (Table 2, entries *6*, *7*) gave a product with $[\alpha]_D^{18}$ −6.6 (*c* 0.50, EtOH) and m.p. 60—64 °C comprising *cis*-verbenol (81%) and verbanols (19%).

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400.13 and 100.62 MHz) and Bruker DRX-500 (500.13 MHz) spectrometers in $CDCl_3$. IR spectra were recorded on a Specord M-80 spectrophotometer (thin films and KBr pellets). GLC analysis was carried out with a Hewlett Packard 4890-A instrument (capillary column 30 m×0.3 mm, RTX-1 as a stationary phase, argon as a carrier gas). Optical rotation was measured on a Krugovoi SM-3 polarimeter. TLC was performed on Silufol plates in Et_2O—hexane (2 : 1) or hexane—AcOEt (10 : 1), visualization with a solution of vanillin (vanillin (3 g) + 95% EtOH (100 mL) + conc. H_2SO_4 (0.5 mL)). Silica gel L (Czechoslovakia) was used for column chromatography.

(+)-α-Pinene used for preparation of enone **1** was isolated by fractional distillation of turpentine (b.p. 46—48 °C (13 Torr), d^{20} 0.8569, n_D^{20} 1.4668, purity 95% (camphene 3%, β-pinene 2%), $[\alpha]_D^{20}$ +20 (pure liquid)*, *ee* ~40%). *trans*-Verbenol **3** was identified by comparing with an authentic sample (TLC and GLC). In all experiments, (+)-verbenone (98% purity, GLC) was used, b.p. 100—101 °C (13 Torr), d^{20} 0.9777, n_D^{20} 1.4965, $[\alpha]_D^{20}$ +119 (pure liquid), *ee* ~43%. IR, ν/cm^{-1}: 3050 (=C—H), 1690 (C=O), 1625 (C=C). ^1H NMR, δ: 0.86 (s, 3 H, C(9)H_3); 1.35 (s, 3 H, C(8)H_3); 1.87 (d, 3 H, C(10)H_3, J = 1.5 Hz); 1.92 (d, 1 H, H_α(7), J = 9.1 Hz); 2.28 (1 H, H(1)); 2.48 (1 H, H(5)); 2.66 (1 H, H_β(7)); 5.56 (1 H, H(3)).

Reduction of verbenone (1). A solution of $Ce(NO_3)_3 \cdot 6H_2O$ (1.43 g, 0.0033 mol) in verbenone (5 g, 0.033 mol) was added dropwise with vigorous stirring at −10 to −12 °C to a solution of $NaBH_4$ (1.26 g, 0.033 mol) in 60 mL of a propan-2-ol—water mixture (5 : 1, v/v) . After the reaction was completed (TLC), the excess of hydride was decomposed by careful addition of aqueous 5—10% HCl; the reaction mixture was diluted with water and the products were extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$, and concentrated. The resulting crystalline mass (4.9 g, 98%) contained

* For (+)-α-pinene (purissimum grade, >99.5% (GLC), Fluka), [α] +51±2 (pure liquid).

94% of *cis*-verbenol (GLC). Crystallization from hexane gave *cis*-verbenol (1.15 g), 97.5% purity (GLC), $[\alpha]_D^{29}$ −12.9 (*c* 0.92, EtOH) and +10.1 (*c* 0.98, $CHCl_3$), m.p. 70—71 °C. IR, ν/cm^{-1}: 3440 (O—H), 3040 (=C—H), 1660 (C=C), 1044, 1012, 1005 (C—O). ^{1}H NMR, δ: 1.06 (s, 3 H, C(9)H_3); 1.28 (d, 1 H, H_α(7), J = 9 Hz); 1.33 (s, 3 H, C(8)H_3); 1.65 (1 H, CHO<u>H</u>); 1.71 (s, 3 H, C(10)H_3); 1.96 (1 H, H(1)); 2.27 (1 H, H(5)); 2.42 (1 H, H_β(7)); 4.45 (1 H, C<u>H</u>OH); 5.35 (1 H, H(3)). ^{13}C NMR, δ: 22.6 (C(9), C(10)); 26.8 (C(8)); 35.4 (C(7)); 38.9 (C(6)); 47.6 (C(5)); 48.1 (C(1)); 74.4 (C(4)); 119.2 (C(3)); 147.3 (C(2)). An additional 2.4 g of *cis*-verbenol was isolated from the mother liquor; the optical purity of this sample was $[\alpha]_D^{20}$ −6.8 (*c* 1.9, EtOH) and +16.7 (*c* 1.9, $CHCl_3$), m.p. 66—68 °C.

Isopropyl *trans*-verbenyl ether. A mixture (1.55 g) obtained in entry *8* (see Table 2) was chromatographed on SiO_2 in hexane to give a colorless liquid (0.32 g, 21%) with a pleasant odor (96% purity (GLC), n_D^{20} 1.4606). IR, ν/cm^{-1}: 3040 (=C—H), 2980, 2936, 2876, 1662 (C=C), 1474, 1450, 1380, 1370 (CMe_2), 1344, 1328, 1260, 1218, 1178, 1148, 1128 ($CHMe_2$), 1050 (C—O—C), 1012, 948, 900, 862, 808, 776. ^{13}C NMR, δ: 147.7 (C(2)); 117.7 (C(3)); 75.1 (C(4)); 69.0 (C(11)); 47.7 (C(1)); 45.4 (C(6)); 44.5 (C(5)); 28.7 (C(7)); 26.6 (C(8)); 23.2 (C(9)); 22.6 (C(12), C(13)); 20.4 (C(10)). ^{1}H NMR, δ: 0.87 (s, 3 H, C(9)H_3); 1.14 (d, 3 H, C(13)H_3, J = 6.1 Hz); 1.16 (d, 3 H, C(12)H_3, J = 6.1 Hz); 1.32 (s, 3 H, C(8)H_3); 1.45 (d, 1 H, H_α(7), J = 8.3 Hz); 1.70 (s, 3 H, C(10)H_3); 1.98 (td, 1 H, H(1), J = 5.2 Hz, J = 1.1 Hz); 2.17—2.24 (2 H, H(5), H_β(7)); 3.68 (septet, 1 H, H(11), J = 6.1 Hz); 3.97 (d, 1 H, H(4), J = 1.45 Hz); 5.31 (m, 1 H, H(3), J = 1.45 Hz).

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References

1. A. M. Moiseenkov, K. V. Lebedeva, and B. A. Cheskis, *Usp. Khim.*, 1984, **53**, 1709 [*Russ. Chem. Rev.*, 1984, **53** (Engl. Transl.)].
2. C. A. Reece, J. O. Rodin, R. G. Brownlee, W. G. Duncan, and R. M. Silverstein, *Tetrahedron*, 1968, **24**, 4249.
3. M. A. Cooper, J. R. Salmon, and D. Whittaker, *J. Chem. Soc., B*, 1967, **12**, 1259.
4. K. Mori, N. Mizumachi, and M. Matsui, *Agric. Biol. Chem.*, 1976, **40**, 1611.
5. CSSR Pat. 239411, 1985.
6. A. F. Regan, *Tetrahedron*, 1969, **25**, 3801.
7. A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
8. W. R. Jackson and A. Zurqiyan, *J. Chem. Soc.*, 1965, 5280.
9. C. Nishino and H. Takayanagi, *Agric. Biol. Chem.*, 1979, **43**, 1967.
10. N. M. Mal´tseva and V. S. Khain, *Borogidrid natriya* [*Sodium Borohydride*], Nauka, Moscow, 1985, 207 pp. (in Russian).
11. A. Hajos, *Complex Hydrides and Related Reducing Agents in Organic Synthesis*, Elsevier, New York, 1969.
12. H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567.
13. US Pat. 2 972 632; *Chem. Abstr.*, 1961, **55**, 12445e.
14. D. V. Banthorpe and D. Whittaker, *Chem. Rev.*, 1966, **6**, 643.
15. K. Mori, *Agric. Biol. Chem.*, 1976, **40**, 415.

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