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Aust. J. Chem. **2005**, *58*, 785–791

The 3-Hydroxycineoles

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Data concerning the 3-hydroxycineoles **1** and **2** are provided to enable the ready identification of these metabolites and to determine their enantiomeric excess in mixtures. An unusual S_N2-type inversion at a tertiary center is observed during one synthetic approach.

Manuscript received: 20 June 2005.
Final version: 21 September 2005.

Introduction

The two 3-hydroxycineoles, the α-isomer **1** and the β-isomer **2**, have been frequently reported[1–14] as metabolites of the commonly occurring cineole **3**, arising by either animal or microbial ingestion or cell-culture biotransformation. Compounds **1** and **2** have often been obtained in low yield and reported only as gas chromatography peaks, sometimes of unspecified stereochemistry. Recently, the compounds have been tentatively identified in human urine.[15] Cineole **3** is achiral, but alcohols **1** and **2** are chiral. Optical rotations of isolated material, when recorded, vary considerably, and it is clear that enzymatic metabolism of cineole **3** need not be enantioselective. It seems likely in many systems that the prime aim of metabolic hydroxylation is simply to water-solubilize the somewhat toxic cineole in order to eliminate it. However, in some animals such as possums and koalas, where cineole may constitute a considerable portion of the diet and where cineole metabolites are then major components in the urine, the animal may also use these compounds as pheromones. The advantages in using an enantiomeric mixture, rather than the pure isomer, as a pheromone have already been discussed.[16]

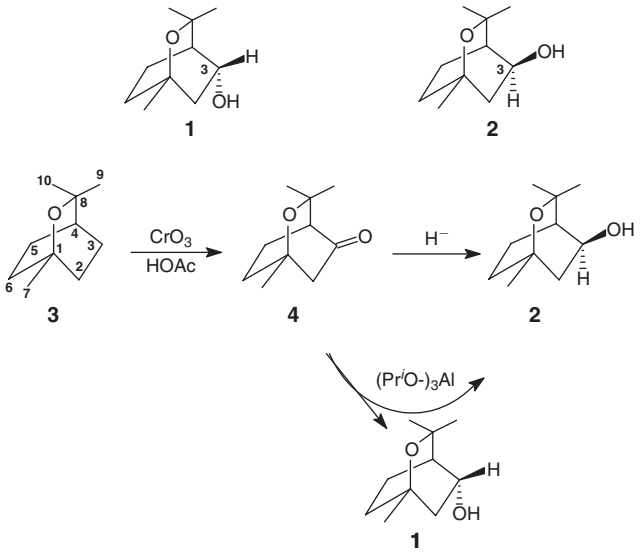
Since starting this synthetic project in 1990 we have supplied samples of synthetic alcohols **1** and **2** to several workers[11,12,14,15] to assist in their identifications. We now report our syntheses in this area. To enable enantiomeric excesses to be examined gas-chromatographically on a small scale, we include both the racemic and enatiomerically pure form, with detail of their chromatographic behavior on a chiral column.

Syntheses in this area have recently been reported by others,[17] but these workers have misnamed some of their compounds (e.g. 3-ketocineole) and misdrawn others, making their work very difficult to follow. Other syntheses in the field are noted.[18–23]

Discussion and Results

Racemic alcohols **1** and **2** are readily available as shown in Scheme 1. Chromic oxidation of cineole **3** affords racemic 3-ketocineole **4**. Hydride reduction of the carbonyl group from the less-hindered side yields the β-alcohol **2**, while reduction with aluminum isopropoxide under equilibrating conditions provides predominately the more stable α-alcohol **1**. Details of some of these steps are provided below.

The chiral alcohols **1** and **2** were synthesized by the route shown in Scheme 2. α-Terpineol **5** of known chirality, with *N*-bromosuccinimide in acetone, provides an equilibrating mixture of bromides **6** and **7** (∼4:1). Treatment of this mixture with potassium *tert*-butoxide affords the mixture of olefins **8**, **9**, and **10** (∼60:20:10). While these olefins can be separated by chromatography, in most runs the reaction sequence was



Scheme 1.

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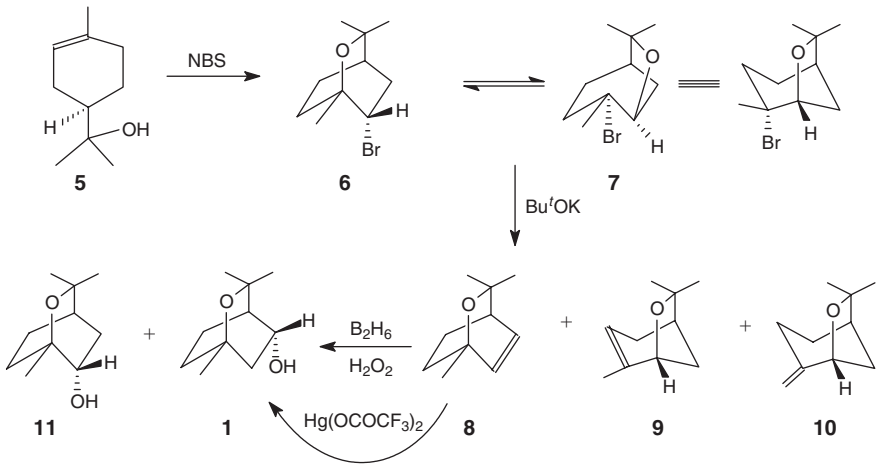
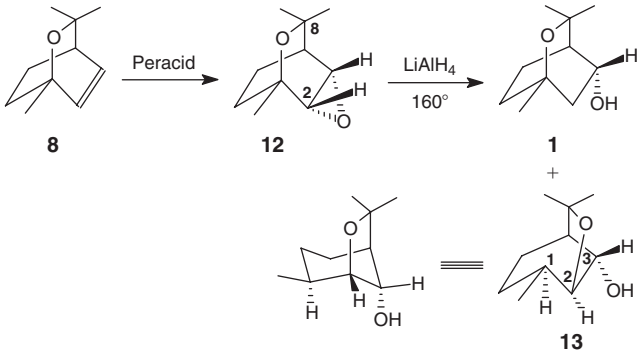


Scheme 2.



Scheme 3.

taken a step or two further when the resultant alcohols can be more readily separated. Diborane treatment of compound **8** provides chiral alcohol **1** together with the 2-hydroxycineole **11** (~3:1; with traces of α-terpineol **5**[18]). Olefin **8** is resistant to mercuric acetate,[18] but treatment with mercuric trifluoroacetate gives the required alcohol **1** as major product. Alcohol **1** can then be oxidized to the ketone **4** and reduced with hydride to provide the other required chiral alcohol **2**. Alternatively, olefin **8** can be epoxidized with 100% attack from the less-hindered side of the double bond to afford epoxide **12** (Scheme 3). This epoxide is considerably hindered to hydride attack at either C2 or C3. However, lithium aluminum hydride at 160°C provides alcohol **1** together with the rearranged alcohol **13** (see below).

The behavior of compounds **1**, **2**, and **4** on a chiral gas chromatography column is listed in the Experimental section, and allows determination of the chirality and enantiomeric excess of any given GC sample. The acetates of both alcohols **1** and **2** were prepared for comparison purposes as these derivatives are also reported[10] to be naturally occurring. ^{13}C NMR data are provided in Table 1.

Interesting aspects of these reactions are now discussed.

*Oxidation of Cineole **3** to Ketone **4***

The remote oxidation of cineole **3** by using chromyl acetate was first discussed by Catalan[19,20] and subsequently used by others.[17,23] Since there appears to be good evidence that this oxidant acts via a radical mechanism,[24–27] where tertiary hydrogen atoms are abstracted very much faster than secondary than primary atoms, we suggest the mechanism depicted in Scheme 4, although the exact nature of the complex involved in the hydrogen atom transfer is not known. In support of this mechanism, we now find that 4-hydroxycineole **14**,[28] with no tertiary hydrogen atom, is completely stable under comparable oxidative conditions. The equilibrium in Scheme 4 involving the hydrogen migration is driven in the forward direction by removal of the right-hand product through further oxidation.

As reported by Catalan,[20] we also obtained over-oxidized material from the oxidation of cineole **3**, including up to 10% of the symmetrical 3,5-diketone **15**.

*Hydride Reduction of Epoxide **12***

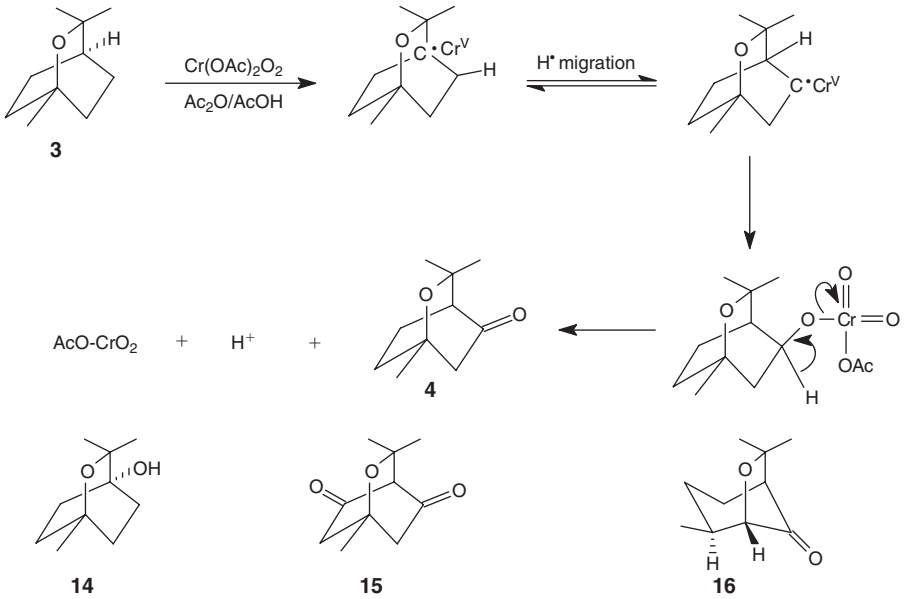
The highly hindered approach of hydride to the top (β) face of epoxide **12**, protected at C3 by the methyl group on C8 and at C2 by the electrons of the cineole ether oxygen, requires forcing conditions[18] with lithium aluminum hydride in a bomb at 160°C. The major product is then the required alcohol **1**. The minor product was not the expected 2-hydroxycineole **11**, formed by hydride attack at C3 at the back of the epoxide, but rather the novel rearranged alcohol **13**, a 3-hydroxypinol. Compound **13** provided consistent NMR spectra. H3 is a dd, with almost identical couplings to H2 and H4 consistent with the similar H2–C2–C3–H3 and H3–C3–C4–H4 torsion angles. Rather surprisingly, H2 is a sharp doublet, coupled only to H3 and not to H1, with which it makes a torsion angle approaching ~70°. The key element in the ^{1}H spectrum is the C1-Me, which appears as a doublet (*J* 6.7 Hz) requiring the presence of the C1 proton. The secondary alcohol **13** could be oxidized to the corresponding ketone **16**, which on hydride reduction regenerated alcohol **13**. The structure **13** was confirmed by X-ray crystallographic analysis (Fig. 1).

The mechanism required for the formation of the rearranged alcohol **13** is intriguing. A suggested pathway is provided in Scheme 5. This involves a rare[29,30] example

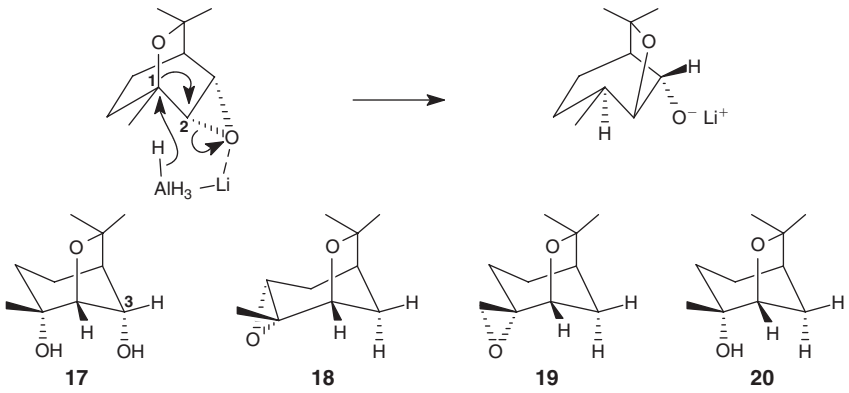
Table 1. ^{13}C chemical shifts
$CDCl_3$ solution, cineole carbon numbering throughout

Compound	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
1	70.9	42.9	65.3	40.4	13.9	31.0	27.1	73.2	28.3	28.9
1-Acetate	70.5	40.0	69.3	37.1	14.8	30.8	26.9	73.2	28.4	28.7
2	70.1	43.2	70.8	40.7	21.4	30.1	26.8	73.4	30.4	30.7
2-Acetate	72.7	40.1	69.9	37.3	20.9	30.0	26.6	73.0	30.0	30.3
3	69.1	31.7	23.0	33.1	23.0	31.7	27.4	73.0	28.8	28.8
4	73.5[A]	49.0	213.0	51.8	18.2	30.3	26.8	73.5[A]	30.5	26.2
6	73.0	52.3	37.0	34.6	21.7	26.0	26.0	74.1	28.1[A]	28.7[A]
7	68.7	83.0	36.7	41.0	24.3	36.7	32.9	83.5	29.9	22.5
8	71.0	135.3[A]	135.1[A]	39.4	20.3	31.2	24.6	74.2	28.9[B]	28.8[B]
9	138.5	76.6	30.3	41.8	34.5	120.1	21.3[A]	82.7	30.4	25.3[A]
10	150.5	80.6	38.7	42.5	27.2[A]	27.0[A]	105.2	82.1	30.4	23.0
11	72.7	71.0	34.7	34.3	22.2	25.0	24.1	73.5	28.6	29.0
12	74.1	52.3[A]	52.1[A]	36.4	17.4	30.2	25.2	72.7	28.5[B]	28.9[B]
13	18.9	80.9	71.1	45.1	19.4	26.0	23.9	80.2	30.9	28.2
15	75.9	49.4	202.5	74.4	202.5	49.4	25.2	73.9	29.1	29.1
17	77.6	77.3	73.3	44.7	17.1	32.6	32.6	80.6	30.7	28.7
18	59.2	79.1	27.6	41.1	30.7	57.6	18.8	81.8	30.0	25.8
19	61.4	80.9	25.5[A]	41.6	26.2[A]	36.5	52.0	82.7	30.2	22.8
20	72.3	82.6[A]	31.9	41.3	24.3	33.1	28.7	82.4[A]	33.1	23.4

[A,B] Values within a row may be reversed.



Scheme 4.



Scheme 5.

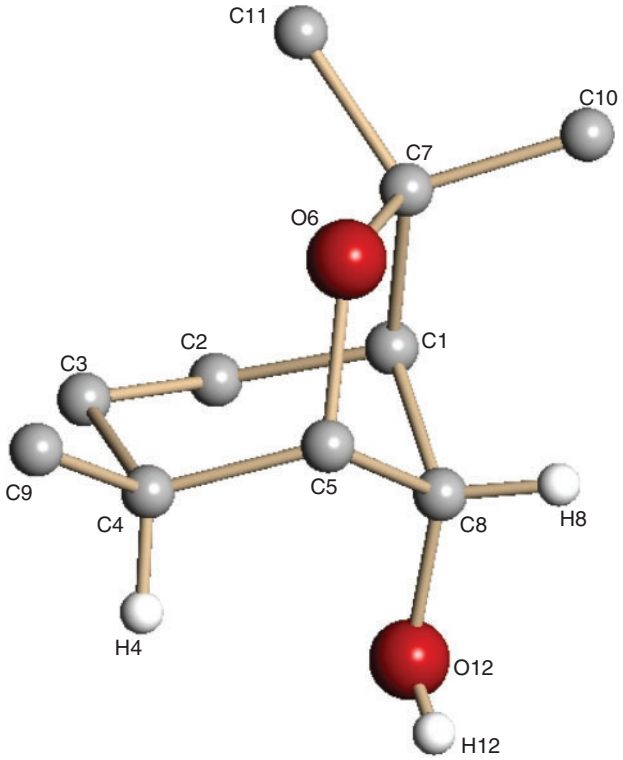


Fig. 1. The X-ray structure of alcohol **13** (crystallographer's numbering).

of S_N2 type attack at a tertiary center, involving inversion of stereochemistry at C1. In this instance there are several factors favouring this unusual and high-energy mechanism. (*a*) Alternative pathways are unfavorable due to the steric and electronic hindrance described above. (*b*) The conditions are extreme and excess hydride was employed. (*c*) Hydride is a very small nucleophile, and it is normally the size of the nucleophile which debars S_N2 attack at tertiary centers. (*d*) The cineole ether oxygen is known[31,32] to be an excellent participant in the displacement of α-C2 leaving groups. (*e*) The possibility of a six-membered transition state, with lithium attracted to the epoxide oxygen as shown in Scheme 5, which will deliver hydride to the appropriate site.

While the pathway in Scheme 5 is drawn as concerted, it is possible that there has been prior approach of the ether oxygen toward C2, assisted by the presence of lithium ion on the epoxide oxygen and by the high temperature involved. This trend toward a three-membered oxirane ring (O,C1,C2) will both increase the carbocation nature of C1 and open up the angle at the back of C1, allowing more facile approach of hydride.*

To provide a reference compound for the NMR examinations of compound **13**, epoxide **12** was treated with aqueous acid to afford the diol **17**. The mechanism for the formation of compound **17** is similar to that shown in Scheme 5, except that now the nucleophile is water, the epoxide is protonated for more-facile opening, and the transition state has much more carbocation character. Compound **17** provided H3 in the NMR spectrum as a dd, with couplings to H2 and H4 similar to those observed for compound **13**.

*Epoxy-Pinols **18** and **19***

The formation of 'pinol' **9** and 'isopinol' **10** from a bromocineole mixture has already been observed.[31] We have now also epoxidized these two olefins **9** and **10** to form epoxides **18** and **19**, respectively. In each case epoxidation occurred from the under (α) side. While epoxide **18** is well known,[33] epoxide **19** has not been previously reported. Both epoxides are then opened with hydride to give the same known[32,34] alcohol **20**.

Experimental

^1H and ^{13}C NMR spectra in $CDCl_3$ solution at ambient temperature were recorded upon a Jeol GX400 spectrometer. ^{13}C assignments were made using the DEPT pulse sequences. Gc analyses were performed upon a BP5 capillary column with helium carrier gas and flame ionization detection. Mass spectra were obtained upon a Hewlett Packard MSD 5970 spectrometer using a GC inlet (BP5 column). Column chromatography was performed over Kieselgel 60, 230–400 mesh.

*Ketone **4***

In an adaptation of the method of Catalan[19,20] which we found to often lead to spontaneous fires, chromium trioxide (96 g) was added portionwise over 30 min to a mixture of acetic acid (200 mL) and acetic anhydride (380 mL) kept at 0°C. This mixture was then added over 90 min to cineole **3** (10 g) in dichloromethane (300 mL) at 10°C. The mixture was allowed to warm to room temperature, and after 24 h the green solution was poured onto ice (∼300 g) and neutralized with sodium carbonate. The organic layer was decanted, washed with brine, dried ($MgSO_4$), and taken to dryness to give a mobile oil comprising cineole **3** (15%), 3-ketocineole **4** (56%), and 3,5-diketocineole **15** (13%). Chromatography (30% ether in hexane) provided the three separated compounds in the above order.

(1*RS*,4*RS*)-3-Ketocineole **4** was a colorless oil (Found: C 71.3, H 9.5. Calc. for $C_{10}H_{16}O_2$: C 71.4, H 9.6%). δ_H 2.31 (dd, H2β), 2.18 (d, H2α), 2.16 (ddt, H5β), 2.09 (dd, H4), 1.80 (dddd, H6β), 1.68 (dddd, H5α), 1.55 (ddd, H6α), 1.24, 1.16, 1.07 (s, 3× Me), with $J_{2\alpha,2\beta}$ −18.8, $J_{2\beta,6\beta}$ 3.0, $J_{4,5\alpha}$ 1.9, $J_{4,5\beta}$ 3.3, $J_{5\alpha,5\beta}$ −13.5, $J_{5\alpha,6\alpha}$ 11.5, $J_{5\alpha,6\beta}$ 6, $J_{5\beta,6\alpha}$ 3.3, $J_{5\beta,6\beta}$ 10.8, $J_{6\alpha,6\beta}$ −13.5 Hz, consistent with the literature[20] but showing considerably more dispersion. δ_C see Table 1. *m/z* consistent with the literature.[20] ν_{max}/cm^{-1} 1733.

3,5-Diketocineole **15** (Found: C 65.9, H 7.7. Calc. for $C_{10}H_{14}O_3$: C 65.9, H 7.7%). mp, δ_H, ν_{max}, and *m/z* consistent with the literature.[20] δ_C see Table 1.

4-Hydroxycineole **14**[28] when oxidized under the same chromic conditions provided only recovered starting material in ∼95% yield.

*Hydride Reduction of Ketone **4***

Sodium borohydride (0.4 g) was added to a stirred solution of racemic ketone **4** (0.5 g) in methanol (20 mL). After 2 h the mixture was diluted with ether (50 mL), washed with hydrochloric acid (5%, 20 mL) and water (20 mL), dried, and evaporated. Chromatography (30% ether in hexane) gave racemic 3β-hydroxycineole **2** (400 mg). Reduction of ketone **4** with lithium aluminum hydride afford the same product **2**.

(1*RS*,3*RS*,4*SR*)-3-Hydroxycineole **2** {(1*RS*,4*SR*,5*RS*)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-ol} was an oil (lit.[1,17] oil, lit.[20] mp 40°C) (Found: C 70.4, H 10.7. Calc. for $C_{10}H_{18}O_2$: C 70.5, H 10.7). δ_H 4.10 (ddd, H3α), 2.02 (dd, H2α), 1.99 (m, H5β), 1.65 (ddd, H2β), 1.52 (2H, m), 1.39 (3H, s, H9), 1.33 (2H, m), 1.20 (3H, s, H10), 1.07 (3H, s, H7), with $J_{2\alpha,2\beta}$ −13.8, $J_{2\alpha,3\alpha}$ 10.3, $J_{2\beta,3\alpha}$ 6.1, $J_{2\beta,6\beta}$ 3.2, $J_{3\alpha,4}$ 2.1 Hz, consistent with the literature[20] but showing considerably

* We thank a referee for discussion on this point.

more dispersion. δ_C see Table 1. *m/z* consistent with the literature.[20] ν_{max}/cm^{-1} 3422, 1458, 1363.

The acetate of alcohol **2**, racemic (1*RS*,3*RS*,4*SR*)-3-acetoxycineole, was a mobile oil (Found: C 63.7, H 10.6. $C_{12}H_{20}O_3$ requires C 63.8, H 10.7). δ_H 4.90 (ddd, H3α), 1.97 (3H, s, OAc), 1.28 and 1.16 (s, 2× 3H, H9 and H10), 1.03 (3H, s, H7). δ_C see Table 1, with additional acetate peaks at 170.2 and 21.1. *m/z* 212 (M^+, 0.3), 197 (7), 137 (7), 109 (13), 93 (15), 83 (11), 55 (8), 43 (100), 41 (15), 39 (8). ν_{max}/cm^{-1} (neat) 3440, 2925, 2850, 1738, 1646, 1463, 1455, 1365, 1242, 1089, 1036, 1023.

*Racemic Alcohol **1***

Aluminum isopropoxide was prepared from dry aluminum foil (2.75 g), anhydrous isopropyl alcohol (30 mL) and mercuric chloride (0.05 g) with carbon tetrachloride (three drops) at reflux. This mixture was then diluted to 500 mL with dry isopropyl alcohol. Racemic 3-ketocineole **4** and aluminum isopropoxide (200 mL of the above mixture) were distilled slowly until the acetone test on the distillate was weakly positive (2.5 h). Analysis (GC) showed compounds **1**, **2**, and **4** in the ratio 20:73:7. Heating was continued under total reflux for 150 h. The reaction mixture was evaporated under vacuum, diluted with water (20 mL), neutralized with hydrochloric acid (1%), and extracted with ether. The organic extracts were dried ($MgSO_4$), and evaporated to give a mixture (2 g, 55:45) of alcohols **1** and **2**. Repeated flash chromatography (30% ether in hexane, poor resolution) gave pure racemic alcohol **1** followed by racemic alcohol **2**.

Racemic (1*RS*,3*SR*,4*SR*)-3-hydroxycineole **1** {(1*RS*,4*SR*,5*SR*)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-ol} had mp 55°C (hexane). (lit.[1] 55–55.5°C, lit.[20] oil) (Found: C 70.5, H 10.7. Calc. for $C_{10}H_{18}O_2$: C 70.5, H 10.7%). δ_H 4.43 (dddd, H3β), 2.09 (ddd, H2β), 2.02 (dddd, H5α), 1.75 (ddddd, H5β), 1.60 (dddd, H6β), 1.51 (ddd, H4), 1.47 (ddd, H6α), 1.28 (dd, H2α), 1.7 (s, OH), 1.27 and 1.19 (2× 3H, s, H9 and H10), 1.04 (3H, s, H7), with $J_{2\alpha,2\beta}$ −14.3, $J_{2\alpha,3\beta}$ 2.8, $J_{2\beta,3\beta}$ 9.5, $J_{2\beta,6\beta}$ 3.3, $J_{3\beta,4}$ 3.6, $J_{3\beta,5\beta}$ 1.6, $J_{4,5\alpha}$ 2.3, $J_{4,5\beta}$ 3.5, $J_{5\alpha,5\beta}$ −13.6, $J_{5\alpha,6\alpha}$ 11.8, $J_{5\alpha,6\beta}$ 6.1, $J_{5\beta,6\alpha}$ 3.5, $J_{5\beta,6\beta}$ 11.3, $J_{6\alpha,6\beta}$ −13.3 Hz, consistent with the literature[20] but showing considerably more dispersion. δ_C see Table 1. *m/z* consistent with the literature.[20] ν_{max}/cm^{-1} 3417, 1462, 1376, 1363.

The acetate of alcohol **1**, racemic (1*RS*,3*SR*,4*SR*)-3-acetoxycineole, was an oil (Found: C 63.6, H 10.7. $C_{12}H_{20}O_3$ requires C 63.8, H 10.7%). δ_H 5.27 (ddd, H3β), 2.02 (3H, s, OAc), 1.24 and 1.23 (2× 3H, s, H9 and H10), 1.03 (3H, s, H7). δ_C see Table 1, with additional acetate peaks at 170.7 and 21.3. *m/z* 212 (M^+, 1), 197 (3), 137 (14), 109 (19), 93 (18), 83 (10), 55 (8), 43 (100), 41 (14), 39 (7).

Reaction of α-Terpineol with N-*Bromosuccinimide*

N-Bromosuccinimide (50.85 g) was added to a stirred solution of *R*-(+)-α-terpineol **5** (40 g) in dry acetone (350 mL) and stirring continued for 0.5 h. The mixture was evaporated to dryness, and the residue taken into hexane (100 mL). Succinimide was filtered off, and the organic solution was washed with brine (30 mL), dried over $MgSO_4$, and evaporated to give 55.8 g (93%) of a 83:17 mixture (by ^{13}C NMR) of 2α-bromocineole **6** {(1*S*,4*R*,6*S*)-6-bromo-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane} and 1α-bromopinol **7** {(1*R*,2*R*,5*R*)-2-bromo-2,6,6-trimethyl-7-oxabicyclo[3,2,1]octane}.

2α-Bromocineole **6** had δ_C consistent with the literature,[31] with peaks at 74.1 (C8), 73.0 (C1), and 52.3 (C2) valuable for integration and characterization purposes.

1α-Bromopinol **7** had δ_C consistent with the literature,[32] with peaks at 83.5 (C8), 83.0 (C2), and 68.7 (C1) valuable for integration and characterization purposes.

This mixture **6** + **7** was used in the next step without purification.

*Dehydrobromination of the Mixture **6** + **7***

Bromide mixture **6** + **7** (48 g) in dimethyl sulfoxide (20 mL) was added dropwise to potassium *tert*-butoxide (66 g) in dry dimethyl sulfoxide (200 mL) and stirred for 1 h. Water (100 mL) was added, and the black solution was extracted with hexane (2 × 100 mL). The organic extracts were washed with water, brine, dried over $MgSO_4$, and evaporated to give 25 g (79%) of a mixture comprising dehydrocineole **8**, pinol **9**, and isopinol **10** (67:19:7 by GC). Repeated flash chromatography (3% diethyl ether in hexane, poor resolution using 100:1 ratio of silica to sample) gave dehydrocineole **8**, followed by pinol **9** and isopinol **10**.

(1*S*,4*R*)-Dehydrocineole **8** {(1*S*,4*R*)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]oct-5-ene} was a colorless minty-smelling oil (Found: C 78.8, H 10.5. $C_{10}H_{16}O$ requires C 78.9, H 10.5%). δ_H 6.40 (dd, H3), 6.04 (dd, H2), 2.23 (dddd, H4), 1.97 (dddd, H5β), 1.68 (ddd, H6β), 1.28 (s, Me7), 1.22 (s, Me10), 1.20 (ddd, H6α),1.15 (dddd, H5α), 0.93 (s, Me9); with $J_{2,3}$ 8, $J_{2,4}$ 1.0, $J_{3,4}$ 6.5, $J_{4,5\alpha}$ 4.5, $J_{4,5\beta}$ 2.5, $J_{5\alpha,5\beta}$ −10, $J_{5\alpha,6\alpha}$ 7, $J_{5\alpha,6\beta}$ 3.5, $J_{5\beta,6\alpha}$ 4, $J_{5\beta,6\beta}$ 9.5, $J_{6\alpha,6\beta}$ −11.5 Hz; consistent with the literature but now with better resolution. δ_C see Table 1. *m/z* 152 (M^+, 4), 137 (M-CH_3, 1), 124 (13), 109 (100), 94 (121), 79 (45), 77 (14), 43 (48), 41 (15), 39 (22). ν_{max}/cm^{-1} 3045, 2967, 2928, 2853, 1456, 1375, 1367, 1360, 1308. This compound is naturally occurring.[35,36]

Pinol **9** {(1*S*,4*R*)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]oct-2-ene} was a colorless minty-smelling oil. δ_H consistent with the lit.[37] δ_C see Table 1. *m/z* 152 (M^+, 12), 137 (M-CH_3, 25), 95 (10), 94 (35), 93 (56), 91 (18), 81 (10), 79 (100), 77 (25), 69 (9), 67 (10), 53 (12), 51 (11), 45 (17), 43 (87), 41 (32), 39 (35).

Isopinol **10** {(1*S*,4*R*)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]oct-2(8)-ene} was a colorless 'fruity'-smelling oil. δ_H 4.57 and 4.49 (2× br s, C=CH_2), 4.41 (d, H2 with $J_{2,3\alpha}$ 6.4, $J_{2,3\beta}$ ~0 Hz), 1.36 and 1.18 (2× s, Me). δ_C see Table 1. *m/z* 152 (M^+, not observed), 138 (5), 137 (M-CH_3, 51), 109 (12), 95 (9), 94 (31), 93 (54), 91 (16), 79 (84), 77 (20), 67 (12), 55 (16), 53 (13), 43 (100), 41 (33), 39 (32). ν_{max}/cm^{-1} 3070, 2966, 2929, 2864, 1457, 1379, 1364, 1309.

*Oxymercuration of Dehydrocineole **8***

Mercuric trifluroacetate (2.1 g, 4.9 mmol) was added to a rapidly stirred solution of dehydrocineole **8** (250 mg, 1.6 mmol) in tetrahydrofuran (20 mL) in water (10 mL). The mixture was stirred for 24 h although the reaction was essentially complete after 4 h (disappearance of starting material by GC). Sodium hydroxide (10%, 5 mL) was added followed by sodium borohydride (0.2 g, in 5 mL 10% NaOH). The solution was diluted with tetrahydrofuran (50 mL) and salted out with solid sodium chloride. The organic layer was decanted, washed with water and brine, dried ($MgSO_4$), and evaporated to give a gum (230 mg). Chromatography (30% ether in hexane) gave initially 2α-hydroxycineole **11** followed by 3α-hydroxycineole **1** {(1*S*,3*R*,4*R*)-3-hydroxycineole, (1*S*,4*R*,5*R*)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-ol}, 150 mg, mp 68–69°C (lit.[3,5,18] 55–56°, 68–69°C), $[\alpha]_D$ −18.5° (*c*, 2.5 in EtOH) (lit.[3,5,18] −6, −19, +5.4° (for the enantiomer?)), with spectra identical to those of the racemic compound **1**.

The enantiomers of alcohol **1** did not separate cleanly on a β-cyclodextrin GC column, and the alcohols were converted into their trifluroacetates with trifluroacetic anhydride. The (1*S*,3*R*,4*R*)-enantiomer **1** was then the second enantiomer eluted when compared with the two peaks available from the trifluroacetate of racemic **1** (baseline resolution).

*Hydroboration—Oxidation of Dehydrocineole **8***

Dehydrocineole **8** (1 g) in anhydrous tetrahydrofuran (30 mL) was treated with an excess of borane–methyl sulfide complex at 15°C and stirred at room temperature for 1 h. Excess hydride was decomposed with water and the organoborane was oxidized with hydrogen peroxide (30%, 4 mL) and sodium hydroxide (6 mol, 4 mL), with stirring (1 h) at 60°C. The mixture was salted out with solid sodium chloride, extracted with ether (100 mL), and the ether extracts were washed with brine. Removal of solvent gave a viscous oil (1.1 g) comprising three components, α-terpineol **5**, 3α-hydroxycineole **1**, and 2α-hydroxycineole **11** in the ratio 10:65:25 (GC). Chromatography (30% diethyl ether in hexane, poor resolution), gave initially α-terpineol **5**, followed by impure 2α-hydroxycineole **11**, and finally impure 3α-hydroxycineole **1**. Fractions containing 3α-hydroxycineole **1** were recrystallized (hexane–ether) to give pure compound with mp 68–69°C.

*Chiral Ketone **4***

Alcohol **1** (850 mg), 3 Å sieves (2 g), and pyridium chlorochromate (3.2 g) were stirred in dichloromethane (20 mL) for 2 h. Diethyl ether

(50 mL) was added and the mixture stirred for 10 min. The solution was filtered through celite, and evaporated. Flash chromatography (20% diethyl ether in hexane) gave (1*S*,4*S*)-3-ketocineole **4** {(1*S*,4*S*)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]-octane-5-one}, 650 mg (78%) as a colorless oil. Spectral data (NMR, IR, and *m/z*) were identical to that of the racemate.

This (1*S*,4*S*)-enantiomer **4** was the second enantiomer eluted when compared with the two peaks available when racemic **4** was passed through a β-cyclodextrin GC column (baseline resolution).

*Chiral Alcohol **2***

Lithium aluminum hydride (50 mg) was added to a stirred solution of (1*S*,4*S*)-3-ketocineole **4** (250 mg) in anhydrous ether. After 1 h, excess hydride was decomposed by the cautious addition of MeOH (10 mL), water (10 mL), followed by KOH (1 mol, 10 mL). The mixture was filtered and the residue washed with ether. The filtrate was dried, evaporated (190 mg), and placed directly onto the top of a chromatography column filled with silica. Flash chromatography (30% ether in hexane) gave 3β-hydroxycineole **2** {(1*S*,3*S*,4*R*)-3-hydroxycineole, (1*S*,4*R*,5*S*)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-ol} as transparent crystals, mp 91°C (lit.[17,18] 90–92°), $[\alpha]_D$ +50.0° (*c*, 2.5 in EtOH) (lit.[3,17,18] 2.8°, 49.8°, 50.5°, −45.3° for the enantiomer) (Found: C 70.5, H 10.9. Calc. for $C_{10}H_{18}O_2$: C 70.5, H 10.7%). The spectral data (NMR, IR, and *m/z*) were identical to that of the racemate.

Reduction of ketone **4** (250 mg) with sodium borohydride afforded the same alcohol **2** (200 mg crude yield).

The enantiomers of alcohol **2** did not separate cleanly on a β-cyclodextrin GC column, and the alcohols were converted into their trifluroacetates with trifluroacetic anhydride. The (1*S*,3*S*,4*R*)-enantiomer **2** was then the second enantiomer eluted when compared with the two peaks available from the trifluroacetate of racemic **2** (poor resolution). If enantiomeric identification of alcohol **2** is required by using a β-cyclodextrin column, it might be better to first oxidize alcohol **2** to ketone **4** when the separation of enantiomers is baseline (see above).

*Epoxide **12***

(1*S*,4*R*)-Dehydrocineole **8** (10 g) and *m*-chloroperbenzoic acid (25 g, 50%) were stirred in dichloromethane (250 mL) for 24 h. The solution was washed with NaOH (5%), water, and brine, and dried ($MgSO_4$) to give oily α-epoxide **12** (10.1 g, 90%). Flash chromatography (30% ether in hexane) gave pure (1*S*,2*S*,3*S*,4*R*)-2-epoxycineole **12** {(1*S*,4*R*,5*S*,6*S*)-5,6-epoxy-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane} as a colorless oil (Found: C 71.3, H 9.5. $C_{10}H_{16}O_2$ requires C 71.4, H 9.6%). δ_H 3.33 (t, H3), 3.08 (d, H2), 1.86 (dt, H4), 1.63–1.42 (3H, m), 1.33–1.23 (1H, m), 1.17, 1.16 and 1.13 (3× s, Me); with $J_{2,3}$ 4.8, $J_{3,4}$ 4.7, $J_{4,5} = J_{4,5'}$ 3.0 Hz, consistent with the 60 MHz lit.[18] δ_C see Table 1. *m/z* 168 (M^+, 2), 153 (M-CH_3, 2), 150 (M-H_2O, 6), 138 (10), 110 (17), 109 (13), 95 (41), 83 (11), 82 (22), 81 (19), 79 (11), 69 (10), 67 (12), 55 (13), 53 (12), 43 (100), 41 (31), 39 (28). ν_{max}/cm^{-1} 2971, 2928, 1458, 1376, 1364, 1244, 1226, 1179, 1164, 1156, 982, 934.

*Reduction of Epoxide **12***

Epoxycineole **12** (10 g) and lithium aluminum hydride (5.0 g) in dry tetrahydrofuran (100 mL) were sealed in an autoclave tube and heated (3 h, occasional shaking) to 165°C. After cooling overnight, excess hydride was decomposed with careful addition of methanol (20 mL) followed by water (20 mL) and potassium hydroxide (1 mol, 20 mL). The mixture was filtered, the organic phase separated, washed with brine, dried ($MgSO_4$), and evaporated to give 8.0 g (80%) of a mixture of two alcohols (20:1). Flash chromatography (chloroform followed by 30% diethyl ether in hexane) gave initially the minor product *3-hydroxypinol* **13** followed by (1*S*,3*S*,4*R*)-3α-hydroxycineole **1**. No reduction was observed with lithium aluminum hydride in refluxing tetrahydrofuran or 1,4-dioxan, or with lithium triethylborohydride in refluxing tetrahydrofuran or toluene.

(1S,2S,5R,8S)-2,6,6-Trimethyl-7-oxabicyclo[3.2.1]octan-8-ol **13** ('3-hydroxypinol') was obtained as colorless needles, mp 102°C (from hexane) (Found: C 70.5, H 10.7. $C_{10}H_{18}O_2$ requires C 70.5, H 10.7%). δ_H (cineole numbering) 4.60 (dd appearing as a t, H3), 3.75 (sharp d, H2), 1.90 (1H, m), 1.84 (1H, m), 1.75 (dt, H4), 1.49 (2H, m), 1.47 and 1.22 (2× s, Me9, and Me10), 1.27 (1H, m), 0.82 (d, *J* 6.9 Hz, Me7); with $J_{1,2}$ ~0, $J_{2,3}$ 6.1, $J_{3,4}$ 5.8, $J_{4,5\alpha}$ ~ $J_{4,5\beta}$ 2.9 Hz. δ_C see Table 1. *m/z* 170 (M^+, 0.6), 155 (73), 137 (11), 112 (19), 109 (12), 97 (21), 95 (16), 94 (12), 93 (45), 85 (41), 84 (12), 83 (13), 82 (12), 81 (29), 79 (19), 71 (13), 70 (13), 69 (25), 67 (18), 59 (16), 57 (23), 55 (28), 53 (12), 45 (11), 43 (100), 41 (61), 39 (26).

Small scale oxidation of this compound **13** (chromium trioxide in acetone) gave a more volatile product (GC) with complete removal of starting material. Reduction of this product (sodium borohydride) regenerated compound **13** (GC and GC/MS).

It is possible that this compound **13** is the same compound as that uncharacterized material previously reported[18] in ~5% yield from the hydride reduction of epoxide **12**.

*Diol **17***

Epoxide **12** (100 mg) in acetone (5 mL), water (1 mL), and sulfuric acid (15% aq, 2 mL) was stirred for 24 h. Ether extraction of this solution gave *(1R,2R,5R,8S)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]octan-2,8-diol* **17** *{1α,3α-dihydroxypinol}* as a gum (100 mg) which failed to crystallize even after chromatography (Found: C 64.4, H 9.7. $C_{10}H_{18}O_3$ requires C 64.5, H 9.8%). δ_H (cineole numbering) 4.78 (t, H3), 3.61 (d, H2), 2.12 (dddd, H5α), 1.90 and 1.57 (2× m, H4, H5β, H6α, and H6β), 1.33 and 1.24 (2× s, Me9 and Me10), 1.18 (s, Me7); with $J_{2,3}$ 5.9, $J_{3,4}$ ~5.9, $J_{4,5\alpha}$ 2.9, $J_{5\alpha,6\alpha}$ 11.0, $J_{5\alpha,6\beta}$ 5.2 Hz. δ_C see Table 1. *m/z* 186 (M^+, not observed), 111 (11), 110 (100), 97 (19), 95 (46), 69 (16), 55 (13), 43 (78), 41 (36), 39 (19). ν_{max}/cm^{-1} 3352, 2932, 1454, 1371, 1289, 1225, 1030, 964.

*Epoxypinol **18***

Pinol **9** (0.5 g) and *m*-chloroperbenzoic acid (1.25 g, 50%) were stirred (3 h) in dichloromethane (20 mL). The solution was washed with sodium hydroxide (5%), water and brine, and dried ($MgSO_4$) to give epoxide (0.5 g, 91%). Flash chromatography (30% ether in hexane) gave pure 1,6α-epoxypinol **18** {(1*R*,2*R*,3*R*,5*R*)-2,3-epoxy-2,6,6-trimethyl-7-oxabicyclo[3.2.1]octane} as a colorless oil (lit.[34] oil) (Found: C 71.2, H 9.5. $C_{10}H_{16}O_2$ requires C 71.4, H 9.6%). δ_H 4.11 (d, H2), 2.83 (d, H6) 1.96–1.75 (5H, m), 1.31 (s, Me7), 1.22 and 1.13 (2× s, Me9 and Me10); with $J_{2,3\alpha}$ 5 Hz, $J_{2,3\beta\alpha}$ ~0, $J_{5\alpha,6\beta}$ 4.8 Hz, consistent with the lit.[34,37] but with better dispersion. δ_C see Table 1. *m/z* 168 (M, not observed), 153 (5), 109 (10), 97 (20), 95 (12), 82 (19), 71 (14), 69 (34), 67 (16), 55 (13), 43 (100), 41 (37), 39 (25). ν_{max}/cm^{-1} 2969, 2878, 1450, 1435, 1380, 1365, 1305, 1259, 1223, 1213, 1184, 1124, 1103, 1062, 967, 909.

*Epoxypinol **19***

Isopinol **10** (0.5 g) and *m*-chloroperbenzoic acid (1.25 g, 50%) were stirred in dichloromethane. Normal workup gave 0.5 g (91%) of oily product. Flash chromatography (30% ether in hexane) gave pure *1,7α-epoxypinol* **19** *{(1R,2S,5R)-2,9-epoxy-2,6,6-trimethyl-7-oxabicyclo[3.2.1]octane}* as a colorless oil (Found: C 71.3, H 9.6. $C_{10}H_{16}O_2$ requires C 71.4, H 9.6%). δ_H 3.59 (d, H2), 2.54 (ABq, H7 and H7′, with $\Delta_{7,7'}$ 0.08 ppm), 2.45 (dddd, H5β), 2.36 (m, H6β), 1.95 (dt, H4), 1.89 (m, H3β), 1.55 (2H, m, H5α and H6α), 1.38 and 1.18 (2× s, Me), 1.28 (dd, H3α); with $J_{2,3\alpha}$ 6.7, $J_{3\alpha,3\beta}$ −14.0, $J_{3\beta,4}$ ~ $J_{4,5\alpha}$ 2.9, $J_{4,5\beta}$ 3.2, $J_{5\alpha,5\beta}$ −13.8, $J_{5\beta,6\alpha}$ 10.0, $J_{5\beta,6\beta}$ 4.7, $J_{6\beta,7H'}$ 1.5 Hz, and $J_{7,7'}$ 4.7 Hz. δ_C see Table 1. *m/z* 168 (M, not observed), 153 (33), 110 (19), 109 (16), 95 (29), 93 (15), 83 (11), 81 (19), 80 (10), 79 (49), 77 (17), 69 (26), 67 (26), 55 (40), 53 (16), 43 (1000), 41 (60), 40 (14), 39 (37). ν_{max}/cm^{-1} 2936, 2867, 1460, 1382, 1366, 1295, 1208, 1137, 1107, 1076, 1019, 914, 890, 850.

*Reduction of Epoxides **18** and **19***

Lithium aluminum hydride (50 mg) was added to a stirred solution of epoxide **18** (0.5 g) in anhydrous ether (50 mL). After 3 h excess hydride was destroyed by careful addition of methanol (10 mL), followed by water (10 mL) and KOH (1 mol, 10 mL). The solution

was filtered and taken to dryness. Flash chromatography (20% ether in hexane) gave 2α-hydroxypinol **20** {(1*R*,2*R*,4*R*)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]octan-2-ol} as transparent needles, mp 76°C (lit.[34] 75–76°). δ_H consistent with the lit.[34] δ_C see Table 1.

The same product **20** was formed by similar reduction of epoxide **19**.

*Crystallographic Data for Alcohol **13***

$C_{10}H_{18}O_2$: *M* 170.24, mp 102°C, colorless needles, crystal dimensions 0.82 mm × 0.30 mm × 0.30 mm, monoclinic, space group $P2_1$, *a* 6.811(7), *b* 10.159(8), *c* 7.763(8) Å, *β* 98.753(14)°, *V* 530.9(9) Å^3, *Z* 2, *F*(000) 188, D_c 1.065 g cm^{-3}, linear absorption coefficient 0.072 mm^{-1}, *θ*-range for data collection 2.65 to 25.00°, index ranges $-7 \le h \le 8$, $-4 \le k \le 10$, $-9 \le l \le 9$, data/restraints/parameters 941/1/113, goodness of fit on F^2 1.03, final *R* indices $[I > 2\sigma(I)]$ R_1 0.0670, wR_2 0.1841, *R* indices (all data) R_1 0.0746, wR_2 0.1695, largest difference peak and hole 0.439 and −0.366 e Å^{-3}.

Intensity data were collected at 158(2) K on an Siemens P4 diffractometer, equipped with a Siemens SMART 1K charge-coupled device (CCD) area detector using the program *SMART* ver 5.045 (Bruker AXS 1998) and a graphite monochromated $Mo_{K\alpha}$ radiation (λ 0.71073 Å). Of the 2151 reflections obtained, 1261 were unique (R_{int} 0.1802). Processing used Siemens *XSCANS* data collection, Siemens *SHELXTL* data reduction, Siemens *XSCANS* cell refinement, *SHELXS-97* direct method structure solution, and *SHELXL-97* structure refinement by full-matrix least-squares on F^2 hydrogen atoms were fixed in geometrically calculated positions and treated as riding. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. The atomic nomenclature is defined in Fig. 1. Crystallographic data are deposited with the Cambridge Crystallographic Data Base (CCDC Deposition number 267911).

Acknowledgment

We thank Tommy Karoli for early investigations into these systems.

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