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CYCLOPENTANOMONOTERPENE ENOL ACETATES FROM *NEPETA LEUCOPHYLLA*

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Key Word Index—*Nepeta leucophylla*; Labiatae; cyclopentanomonoterpenes; iridoids, iridodial enol acetates.

Astract—Three new iridodial derivatives, [1*R*-[1α, 2β(*E*),5β]]-2-[2-(acetyloxy)-1-methylethenyl]-5-methylcyclopentanecarboxaldehyde (iridodial β-monoenol acetate), [1-*R*-[1α,2β(*E*),5β]]-2-[2-(acetyloxy)-1-methylethenyl]-5-methylcyclopentyl] methyl acetate (dihydroiridodial diacetate), or their enantiomers, and [1(*E*)]-2-[2[(acetyloxy)methylene]-3-methylcyclopentyl]-1-propenyl acetate (iridodial dienol diacetate) of unknown configuration have been isolated from the essential oil of *Nepeta leucophylla* gathered in the Kumaun Region of India.

INTRODUCTION

Continuing our work on constituents of *Nepeta* species native to the Kumaun Region of India [1–3], we describe here the isolation and characterization of three previously undescribed cyclopentanomonoterpene enol acetates (**1–3**) from the essential oil of aerial parts of *N. leucophylla* Benth.

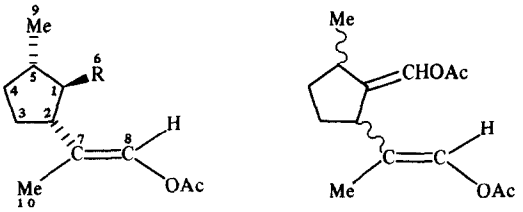
RESULTS AND DISCUSSION

Examination by GC-mass spectroscopy of the steam-volatile oil of *N. leucophylla* indicated the presence of more than 50 compounds, most with fragmentation patterns characteristic of monoterpenes or sesquiterpenes. The oil was decidedly different from the essential oil from aerial parts of *N. leucophylla* described by Gupta *et al.* in 1971 and 1973 [4, 5]. Several of the components that they identified, including nepetalactone (3%), citronellyl butyrate (11%) and a sesquiterpene alcohol they named nepetol, were present in no more than trace amounts. Several of the compounds in our oil with longer retention times than the sesquiterpenes had fragmentation patterns that suggested they were not oxygenated sesquiterpenes. Three of these, which made up 15.4% (**1**), 5.7% (**2**) and 0.8% (**3**) of the oil, as well as (−)-β-caryophyllene α-oxide [6], which made up another 12.0% of the oil, were obtained by column chromatography and separated by HPLC.

The HREI mass spectra of the compounds indicated the following molecular formulae: **1**, $C_{12}H_{18}O_3$; **2**, $C_{14}H_{22}O_4$; **3**, $C_{14}H_{20}O_4$. The three compounds had significant $[M-C_2H_2O]^+$ peaks, characteristic of enol acetates [7], and **3** had a significant $[M-C_4H_4O_2]^+$ peak as well, which suggested that it was a dienol diacetate. The mass spectra of **1** and **3** had intense peaks, 94–100%, BP, due to $[C_{10}H_{14}O]^+$ and $[C_9H_{11}O]^+$ and other similarities that suggested they had closely related structures. Common to the ^{1}H NMR spectra of the three compounds are upfield *d* at δ1.00–1.08, attributable to the methyl protons of a CHMe group, *br s* at δ1.60–1.64, attributable to vinyl methyl protons, *s* at δ2.09–2.14, assignable to methyl protons of an enol acetate, and *br s* at δ6.94–7.04, assignable to the α-proton of an enol acetate [8].

The ^{1}H NMR spectrum of **1** also had *m* centred at about δ1.35 (1H), 1.65 (1H), 1.9 (2H) and 2.2 (2H), an apparent *quart.*, *J*app.=9.2 Hz, at δ2.81, and *d*, *J*=3.6 Hz, at δ9.49. The last signal, assignable to an aldehyde proton, was coupled with a proton at δ2.2. Irradiation at δ2.2 collapsed the upfield methyl *d* as well as the aldehyde proton *d* and simplified the signal at δ2.81 to an apparent *t*. Other decoupling experiments showed that the δ2.81 signal was coupled with two different protons at δ1.65 and 1.9 as well as the proton α to the formyl or methyl group. These data required that **1** is a cyclopentanecarboxaldehyde with –C(Me)=CHOAc and –Me substituents in which the former group was flanked by CH_2 and either –CHCHO or –CHMe. Of the four possible structures for **1**, the iridodial β-monoenolacetate structure seemed most likely because of the occurrence of structurally related cyclopentanomonoterpenes, such as the nepetalactones, in other *Nepeta* species [1].

In addition to the signals common to **1**, **2** and **3**, the ^{1}H NMR spectrum of **2** had upfield (δ<1.88) *m* due to methylene and methine protons (6H), a singlet at δ1.98, assignable to a methyl group next to a carbonyl, an apparent *quart.* *J*=9.2 Hz, at δ2.28, and *dd* at δ3.92, *J*=12.0 and 5.6 Hz, and 4.08, *J*=12.0 and 5.0 Hz, assignable to diastereotopic methylene protons of a $CHCH_2O$ group. These data suggest that **2** differs from **1** in having a CH_2OAc group in place of a formyl group. The corresponding dihydroiridodial diacetate structure for **2** is consistent with the shifts seen for the signals of the methine protons on substitution of $-CH_2OAc$ for –CHO, i.e. δ2.82 to 2.28 for –CHC(Me)=CHOAc, and δ2.2 to 1.9 for –CHMe.

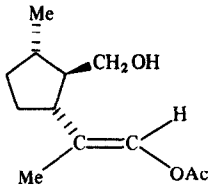


R

1 CHO

2 CH_2OAc

3



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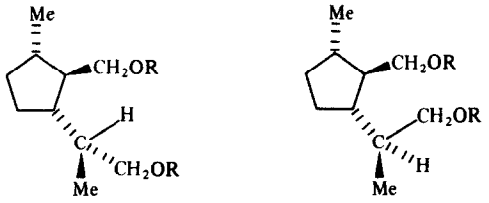
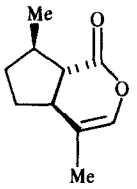


R

5a and **5b** H

6a and **6b** 3,5-$Cl_2C_6H_3CO$



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Compound **1** was converted to **2** by successive treatment with $NaBH_4$ and Ac_2O, thereby confirming that they had the same stereochemistry. The yield of the intermediate alcohol **4** was only about 20% because of accompanying reduction of the enol acetate function to give the diastereomeric iridodiols **5a** and **5b**. No attempt was made to maximize the yield of **4**. The mixed iridodiols were further characterized as their di-3,5-dichlorobenzoates **6a** and **6b**, which were purified by HPLC.

The ^1H NMR spectrum of **3**, besides the upfield methyl *d* and the signals due to C(Me)=CHOAc, consisted of *m* centred at about δ1.47 (1H), 1.74 (3H), 2.93 (1H) and 3.14 (1H), a methyl *s* at δ2.16 and a *br s* at δ6.85 (1H). The latter two signals were assignable to the second enol acetate group >C=CHOAc indicated by the mass spectrum. Irradiation at δ2.93 collapsed the upfield methyl *d* and simplified the *m* at δ1.47 and 1.74, while irradiation at δ3.14 affected only the δ1.74 region. This showed that the δ2.93 signal was due to the methine proton α to the methyl and the δ3.14 signal was due to the methine proton next to the C(Me)=CHOAc group. These data lead to the iridodial dienolacetate structure as they require that the =CHOAc group is flanked by CHMe and CHC(Me)=CHOAc.

^{13}C NMR spectra of **1**–**3** are summarized in Table 1 using the numbering scheme shown for **1** and **2**. These data are consistent with the conclusions drawn from the mass spectra and ^1H NMR data. Analogy allows confident assignment of chemical shifts to unsaturated carbons [9], and reference to the ^{13}C NMR spectra of the four diastereomeric nepetalactones [1, 10] assisted in near unambiguous assignment of chemical shifts to the cyclopentane carbons and methyl carbons. Significantly, the high field methyl carbon signals show that the vinyl methyl is *cis* to the acetate in **1**–**3** [9].

Further comparison of the ^{13}C NMR spectrum of **1** with the spectra of the nepetalactones [1, 8] suggested that C-7, the fully substituted vinyl carbon, and C-9, the methyl carbon on the cyclopentane ring, of **1** are both *trans* to the aldehyde group. The vinyl carbons of the *trans*-fused nepetalactones that are equivalent to C-7 had chemical shifts of $\delta 120.4 \pm 0.1$, close to the observed chemical shift of δ121.5 for C-7, while the corresponding chemical shifts for the *cis*-fused nepetalactones were $\delta 115.2 \pm 0.2$. Similary, the chemical shifts of the cyclopentane methyl groups of the nepetalactones equivalent to C-9, where this methyl is *trans* to the carbonyl, were $\delta 20.4 \pm 0.1$, which is closer to the value of δ19.4 seen for C-9, than chemical shifts ($\delta 17.4 \pm 0.2$) observed for the cyclopentane methyls in the diastereomeric nepetalactones where the methyl and carbonyl groups are *cis*.

The relative stereochemistry thus suggested for **1** and **2** corresponds to that of (7*R*)-*trans*, *trans*-nepetalactone (**7**), which makes up about 80% of the essential oil of *N. elliptica*, also native to the Kumaun Region of India [1]. We reduced **7** with LAH to obtain the diastereomeric iridodiols **5a** and **5b** or their enantiomers. The diols were characterized by their GC retention times, identical with those from **1**, and, more convincingly, by conversion to their di-3,5-dichlorobenzoates **6a** and **6b**, whose complex ^1H NMR spectra were indistinguishable from those of the diesters obtained from **1**. Unfortunately, the optical rotations of the small amounts of samples obtained were too feeble to allow us to assign absolute configurations to **1** and **2**.

Regarding compound **3**, the only conclusion we can reach as to stereochemistry is the *cis*-relationship of the vinyl methyl and acetate groups of the sidechain. Treatment of **1** with isopropenyl acetate gave a complex mixture whose GC failed to indicate the presence of **3**. We wish to note that a minor component of the oil with a longer GC retention time than **3** gave a mass spectrum indistinguishable from that of **3**, and two minor components with slightly longer GC retention times than **1** gave mass spectra that are nearly identical with that of **1**.

We are unaware of any earlier report of iridoid enol acetates, although an iridoidial enol gentobioside and a dehydroiridodial enol gentobioside from *Actinidia polygama* were described [11]. As was suggested for these enol glycosides, we consider 10-hydroxygeraniol to be the likely acyclic biosynthetic precursor to the enol acetates **1**–**3**. Iridodial β-monoenol acetate **1** and its stereoisomers may be the first cyclopentanomonoterpenes formed in the biosynthetic pathway to the nepetalactones and other iridoids. Apparently, the genotype of *N. leucophylla* that we examined has lost its ability to hydrolyse **1**, and **2** and **3** are slowly formed

Table 1. ^{13}C NMR data ($CDCl_3$, 90.55 MHz) for enol acetates **1–3**

C	1*	2*†	3*§
1	63.1	48.9‡	133.9
2	45.6	46.9‡	46.7
3	29.8	29.0	29.4
4	33.6	33.4	33.1
5	36.3	37.2	35.0
6	203.5	65.4	131.6
7	121.5	122.6	121.7
8	130.6	130.4	130.3
9	19.4	19.7	19.1
10	11.0	10.1	10.3

*A quartet at $\delta 20.7 \pm 0.1$ and a singlet at $\delta 167.9 \pm 0.1$, assignable to acetate carbons, were also observed.

†A quartet at $\delta 20.8$ and a singlet at $\delta 171.2$, assignable to acetate carbons, were also observed.

‡Assignments may be reversed.

§A quartet at $\delta 20.7$ and a singlet at $\delta 167.8$, assignable to acetate carbons, were also observed.

from **1** in place of the corresponding iridodial. In addition to their biosynthetic role, the possible role of **1–3** and stereoisomeric enol acetates as insect repellants [*cf.* 12], and their occurrence in other *Nepeta* species, particularly the more than 30 that are native to the western Himalayas [13–15], remain to be determined.

EXPERIMENTAL

Plant material. Nepeta leucophylla Benth. in the flowering stage was collected from Nainital in September. Voucher specimens are deposited at the Forest Research Institute (accession no. 153826), Dehradun, and the Royal Botanical Garden (herbarium no. H8/2035/84), Kew, Surrey, where their identity was confirmed, respectively, by P. P. Muyal and B. M. Wadhwa.

Isolation of compounds **1–3**. The aerial parts of the freshly collected plant material (10 kg) were finely chopped and steam-distilled from a copper still fitted with spiral glass condensers. The essential oil was extracted from the NaCl-saturated distillate with *n*-hexane, and the organic soln was dried (Na_2SO_4) and concd by distillation. Removal of the last traces of solvent at red. pres. left 50 ml of essential oil.

The fresh crude oil was analysed using a 60 m × 0.25 mm fused silica capillary column, liquid phase DB-Wax, with N_2 as the carrier gas at 14 psi, FI. The column temp., initially 100°, was programmed at 4° min^{-1} for 25 min and held at 200° for 30 min. The enol acetates, subsequently identified as **1**, **2** and **3**, had R_ts 41.38, 50.29 and 60.69 min, respectively, and were estimated on the basis of their GC response to make up, respectively, 15.4%, 5.7% and 0.8% of the oil. GC-MS analysis of the oil was carried out at California State University, Sacramento, using a 30 m × 0.25 mm fused silica capillary column, liquid phase OV 101, with He as the carrier gas. The column temp., initially 80°, was programmed at 3° min^{-1} for 50 min; EI conditions, 70 eV.

CC of 30 g of the oil on 400 g of silica gel gave a hydrocarbon-containing fr., eluted with *n*-hexane, and a 5.2 g fr., eluted with 3:1 *n*-hexane–Et_2O, that contained **1–3**, (−)-β-caryophyllene α-oxide and at least 8 other oxygen-containing compounds as indicated by GC-MS. HPLC of the latter fr. on a 10 μ Porasil column using *n*-hexane–Et_2O (4:1) as the mobile phase gave **1**, **2**, **3** and (−)-β-caryophyllene α-oxide as colourless, viscous liquids.

Iridodial-β-monoenol acetate (**1**). HREIMS (probe) 70 eV, *m/z* (rel. int.): 210.1264 $[M]^+$ [$C_{12}H_{18}O_3$ requires 210.1256] (0.1), 168.1113 $[C_{10}H_{16}O_2]^+$ (14.7), 150.0999 $[C_{10}H_{14}O]^+$ (100.0), 135.0787 $[C_9H_{11}O]^+$ (94.1), 111.0771 $[C_7H_{11}O]^+$ (41.8), 108.0562 $[C_7H_8O]^+$ (75.9), 97.0587 $[C_6H_9O]^+$ (57.1), 81.0696 $[C_6H_9]^+$ (37.4), 71.0526 $[C_4H_7O]^+$ (66.3). IR ν_{max}^{film} cm^{-1} (% trans.): 835 (67), 930 (62), 1050 (59), 1090 (40), 1110 (39), 1140sh (52), 1225 (22), 1375 (40), 1450 (61), 1680sh (62), 1720 (30), 1755 (24), 2710 (70), 2825 (69), 2870 (50), 2930sh (49), 2960 (38) and 3100 (72). ^1H NMR (360 MHz, $CDCl_3$): $\delta 1.04$ (*d*, $J = 6.3$ Hz, H_3-9), 1.31–1.42 (*m*, 1H), 1.61–1.72 (*m*, 1H), 1.64 (*br s*, Me C=), 1.80–1.98 (*m*, 2H), 2.10 (*s*, MeCO), 2.12–2.30 (*m*, H-1, H-5), 2.81 (*ddd*, $J = 9.2$ Hz, H-2), 6.98 (*br s*, $W_{1/2} = 8.4$ Hz, =CH) and 9.49 (*d*, $J = 3.6$ Hz, CHO). ^{13}C NMR, Table 1. $[\alpha]_D^{25} + 13°$ (*c* 5.2, $CDCl_3$).

Dihydroiridodial β-enol diacetate (**2**). HREIMS (probe) 70 eV, *m/z* (rel. int.): 254.1531 $[M]^+$ [$C_{14}H_{22}O_4$ requires 254.1518] (3.1), 212.1449 $[C_{12}H_{20}O_3]^+$ (3.2), 152.1243 $[C_{10}H_{16}O]^+$ (100.0), 137.0981 $[C_9H_{13}O]^+$ (24.2), 123.1152 $[C_9H_{15}]^+$ (11.4), 123.0762 $[C_8H_{11}O]^+$ (13.3), 69.0700 $[C_5H_9]^+$ (14.9), 67.0565 $[C_5H_7]^+$ (15.0). ^1H NMR (360 MHz, $CDCl_3$): $\delta 1.00$ (*d*, $J = 6.3$ Hz, H_3-9), 1.22–1.32 (*m*, 1H), 1.48–1.88 (*m*, 5H), 1.60 (*s*, MeC=), 1.98 (*s*, $MeCO_2CH_2$), 2.09 (*s*, $MeCO_2C$=), 2.28 (*ddd*, $J = 9.2$ Hz, H-2), 3.92 (*dd*, $J = 12.0$, 5.6 Hz, CH_AH_BO), 4.08 (*dd*, $J = 12.0$, 5.0 Hz, CH_AH_BO) and 6.94 (*br s*, $W_{1/2} = 8.6$ Hz, =CH). ^{13}C NMR, Table 1. $[\alpha]_D^{25} - 18°$ (*c* 1.2, $CDCl_3$).

Iridodial dienol diacetate (**3**). HREIMS (probe) 70 eV, *m/z* (rel. int.): 252.1341 $[M]^+$ [$C_{14}H_{20}O_4$ requires 252.1361] (6.4), 210.1215 $[C_{12}H_{18}O_3]^+$ (5.9), 168.1134 $[C_{10}H_{16}O_2]^+$ (6.4), 150.1003 $[C_{10}H_{14}O]^+$ (94.7), 135.0785 $[C_9H_{11}O]^+$ (100.0), 111.0824 $[C_7H_{11}O]^+$ (28.0), 108.0580 $[C_7H_8O]^+$ (48.8), and 71.0515 $[C_4H_7O]^+$ (65.8). IR ν_{max}^{film} cm^{-1} (% trans.): 835 (70), 925 (68), 1050 (63), 1075 (51), 1100 (39), 1120 (47), 1225 (24), 1280 (64), 1375 (46), 1450 (64), 1680 (60), 1755 (26), 2875 (49), 2930sh (47), 2960 (42) and 3100 (56). UV: λ_{max} 212 nm. ^1H NMR (360 MHz, $CDCl_3$): $\delta 1.08$ (*d*, $J = 7.2$ Hz, H_3-9), 1.42–1.53 (*m*, 1H), 1.65–1.82 (*m*, 3H), 1.63 (*s*, MeC=), 2.14 (*s*, MeCO), 2.16 (*s*, MeCO), 2.93 (*m*, H-5), 3.14 (*m*, H-2), 6.85 (*br s*, =CHOAc) and 7.04 (*br s*, =CHOAc). ^{13}C NMR, Table 1. $[\alpha]_D^{25} + 184°$ (*c*0.6; $CDCl_3$).

Synthetic experiments. Silica gel (220–400 μ) was used for CC and silica gel sheets were used for TLC work. PREPSEP silica gel cartridges (1″) were obtained from Fischer Scientific Co. Semiprep. HPLC was performed using a 25 cm × 9 mm column packed with Chromasil-10 μ. Capillary GC analysis was carried out using a 30 m × 0.25 mm fused silica column, liquid phase DB-5, and/or a 30 m × 0.26 mm fused silica column, liquid phase DB-Wax, with FI detector using He as the carrier gas.

Reduction of **1** *with* $NaBH_4$. (A) To a vigorously stirred soln of 360 mg of **1** in 10 ml abs. EtOH cooled in an ice-salt bath under N_2 was added in 10 min a soln of 26 mg $NaBH_4$ in 8 ml abs. EtOH. The reaction mixture was stirred for 10 min, the ice bath was removed, and stirring was continued for another 10 min. The reaction mixture was poured into 30 ml of satd NaCl soln and extracted with Et_2O (× 3 20 ml). The organic phases were combined, washed with satd NaCl solution (15 ml), dried ($MgSO_4$), and the solvent was removed by distillation, the last traces under vaccum. The residual oil (287 mg) was applied to a silica gel column (4.5 g) and eluted successively with 9:1 (5 ml), 7:3 (50 ml) and 3:2 (20 ml) *n*-hexane–Et_2O mixtures. The eluate

was collected in 3-ml fractions, and a sample of each was developed on a TLC plate and visualized using UV and anisaldehyde spray. Dihydroiridodial enol acetate **4** had a smaller R_f than **1** and was visualized with UV as well as anisaldehyde; the diastereomeric iridodiols **5a** and **5b** had even smaller R_f values and visualized only with anisaldehyde. Frs containing **4** were combined and concd, and semiprep. HPLC of the concentrate (3:2 *n*-hexane–Et_2O) gave 77 mg of **4** that was 93% pure as indicated by GC-MS and ^{13}C NMR. HREIMS (probe) 70 eV, *m/z* 212.1407 $[M]^+$ [$C_{12}H_{20}O_3$ requires 212.1413]. LREIMS (GC-MS) 70 eV, *m/z* (rel. int.): 212 $[M]^+$ (1), 194 $[M-H_2O]^+$ (7), 170, $[M-C_2H_2O]^+$ (1), 152 $[C_{10}H_{16}O]^+$ (100), 137 $[C_9H_{13}O]^+$ (40), 134 $[C_{10}H_{14}]^+$ (31), 123 $[C_8H_{11}O]^+$ (42), 95 $[C_6H_7O]^+$ (48), 43 $[C_2H_3O]^+$ (55). ^1H NMR (300 MHz, $CDCl_3$): δ1.02 (*d*, *J* = 6.5 Hz, H_3-9), 1.25–1.36 (*m*, 1H), 1.38–1.52 (*m*, 1H), 1.56–1.80 (2 *m*, 4H), 1.65 (*d*, *J* = 1.4 Hz, MeC=), 2.13 (*s*, MeCO), 2.33 (*ddd*, *J* = 9.2 Hz, H-2), 3.60 (*d*, *J* = 5.0 Hz, CH_2O) and 6.95 (*q*, *J* = 1.4 Hz, =CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ10.2 (MeC=), 19.9 (C-9), 20.8 (MeCO), 29.1 (C-3), 33.5 (C-4), 36.3 (C-5), 47.0 (C-2), 52.3 (C-1), 64.0 (CH_2O), 124.2 (>C=), 130.2 (HC=) and 168.4 (O_2CH=). $[\alpha]_D^{25}$ +71° (*c* 5.8; $CDCl_3$). (B) To a vigorously stirred soln of 57 mg $NaBH_4$ in 20 ml abs. EtOH cooled with an ice-salt bath was added in small portions a soln of 312 mg of **1** in 4 ml of *n*-hexane–Et_2O (50:50). The reaction mixture was stirred for 20 min, the cooling bath was removed, and stirring was continued for 20 min. The reaction mixture was added to 50 ml satd NaCl soln, and the mixture that resulted was extracted with Et_2O (×4 25 ml). The residual oil (221 mg), which capillary GC analysis (DB-Wax) indicated was an 18:82 mixture of **4** and the diastereomeric iridodiols **5a** and **5b**, was applied to a silica gel column (6.0 g) and eluted successively with 40 ml *n*-hexane–Et_2O (7:3) and 20 ml Et_2O. The eluate was collected in 2-ml fractions, and each fraction was analysed as described in the preceding experiment. Frs rich in the iridodiols were combined, and the solvent was removed to yield 117 mg of residual oil. Capillary GC analysis indicated that the oil was 97% of a 71:29 mixture of **5a** and **5b**. LREIMS (GC-MS) 70 eV, *m/z* (rel. int.): 154 $[M-H_2O]^+$ (0.5), 139 $[C_9H_{15}O]^+$ (2.8), 123 $[C_9H_{15}]^+$ (100.0), 121 $[C_9H_{13}]^+$ (14.7), 109 $[C_8H_{13}]^+$ (18.5), 95 $[C_7H_{11}]^+$ (73.6), 81 $[C_6H_9]^+$ (100), 67 $[C_5H_7]^+$ (36.2), 55 $[C_4H_7]^+$ (27.0), 41 $[C_3H_5]^+$ (16.6). ^1H NMR (360 MHz, $CDCl_3$): δ0.84 (*d*, *J* = 6.8 Hz, **5a**), 0.95 (*d*, *J* = 6.5 Hz, **5b**), 1.00 (*d*, *J* = 6.5 Hz, **5a** and **5b**), 1.15–2.06 (*ms*), 3.48 (*m*), 3.71 (*m*). $[\alpha]_D^{25}$, +74° (*c* 1.3; $CDCl_3$).

Compound **2** *from* **4**. A mixture prepared by the successive addition of 28 mg of **4**, 50 mg NaOAc and 100 μl Ac_2O to 5 ml THF was stirred under N_2 for 2 days. The mixture was concd under a stream of N_2, and the aq. mixture was extracted with Et_2O (×4 5 ml). Chromatography of the concentrate gave 21 mg of product indistinguishable from naturally occurring **2**.

Di-3,5-dichlorobenzoates **6a** *and* **6b** *of diastereomeric iridodiols from* **1**. To a stirred solution of 50 mg of the diastereomeric iridodiols **5a** and **5b** from **1**, 182 μl pyridine and 4 ml THF under N_2 and cooled with an ice-salt bath was added 243 mg 3,5-dichlorobenzoyl chloride. The cold mixture was stirred for 10 min, the cooling bath was removed, and stirring was continued for 3 days. Ice water (5 ml) was added, and the mixture was extracted with Et_2O (×3 10 ml). The organic solns were combined, washed successively with ice cold 1M NaOH (1 ml), saturated NaCl (2 ml), 1M HCl (1 ml) and saturated NaCl (×2 3 ml), and dried ($MgSO_4$). The semi-solid residue (273 mg) obtained by removal of the solvent was triturated with 1 ml *n*-hexane–Et_2O (50:50). The diastereomeric di-3,5-dichlorobenzoates of **5a** and **5b** (**6a** and **6b**) were obtained as homogeneous 6.2 and 3.0 mg samples from the mixture by successive chromatography on a PREPSEP column (20 ml *n*-hexane–Et_2O, 80:20) and a silica gel column (5g, 20 ml *n*-hexane–Et_2O, 90:10; 20 ml *n*-hexane–Et_2O, 80:20) followed by HPLC (*n*-hexane–Et_2O, 95:5).

Compound **6a**. LREIMS 70 eV, *m/z* (rel. int.): 520 $[C_{24}H_{24}{}^{35}Cl_2{}^{37}Cl_2O_4]^+$ (14), 518 $[C_{24}H_{24}{}^{35}Cl_3{}^{37}ClO_4]^+$ (34), 516 $[C_{24}H_{24}{}^{35}Cl_4O_4]^+$ (24), 326 $[C_{17}H_{20}{}^{35}Cl_2O_2]^+$ (100), 285 $[C_{14}H_{15}{}^{35}Cl_2O_2]$ (92). ^1H NMR (360 MHz, $CDCl_3$): δ1.01 (*d*, *J* = 6.2 Hz, 3H), 1.21–1.34 (*m*, 1H), 1.57–2.00 (*ms*, 5H), 2.18 (*app p*, *J* = 6.9 Hz, 1H), 4.18 (*dd*, *J* = 10.9, 6.9 Hz, 1H), 4.27 (*dd*, *J* = 10.9, 6.5 Hz), 4.32 (*dd*, *J* = 10.9, 5.7 Hz) and 4.36 (*dd*, *J* = 10.9, 5.6 Hz) (3H), 7.51 (2*t*, $\delta\nu$ = 2.1 Hz, *J* = 1.8 Hz) and 7.83 (2*d*, $\delta\nu$ = 1.5 Hz, *J* = 1.8 Hz).

Compound **6b**. ^1H NMR ($CDCl_3$, 300 MHz): δ1.07 (*d*, *J* = 6.6 Hz) and 1.10 (*d*, *J* = 6.9 Hz) (6H), 1.28–1.38 (*m*, 1H), 1.54–1.66 (*m*, 1H), 1.70–1.94 (*ms*, 4H), 2.00–2.12 (*m*, 1H), 4.16 (*dd*, *J* = 10.9, 7.4 Hz, 1H), 4.27 (*dd*, *J* = 10.9, 6.1 Hz, 1H, 4.37 (*dd*, *J* = 10.9, 5.1 Hz, 2H), 7.52 (2*t*, $\Delta\nu$ = 0.4 Hz, *J* = 1.8 Hz, 2H), 7.85 (2*d*, $\delta\nu$ = 1.0 Hz, *J* = 1.8 Hz, 4H).

Reduction of (7R)-trans,trans-*nepetalactone with* $LiAlH_4$. To a rapidly stirred soln of 258 mg of (7*R*)-*trans,trans*-nepetalactone in 10 ml dry Et_2O under N_2 and cooled with an ice bath was added 10 ml 1.5 M $LiAlH_4$ in Et_2O in 10 min. The ice bath was removed, stirring was continued overnight, and the reaction mixture was added to 40 g of ice. The mixture that resulted was brought to pH 4–5 by the dropwise addition of 6 M HCl and extracted with Et_2O (×3 40 ml). The ether solns were combined, washed with satd NaCl (×2 10 ml) and dried ($MgSO_4$). Removal of the solvent gave 203 mg of oil from which was obtained 56 mg of a 42:58 mixture of compounds with the identical GC retention times as the iridodiols **5a** and **5b** from $NaBH_4$ reduction of **1**.

Di-3,5-dichlorobenzoates of iridodiols from $LiAlH_4$ *Reduction of* (7R)-trans,trans-*nepetalactone*. These were prepared from 56 mg of the above iridodiols by treatment with 200 μl pyridine and 150 mg 3,5-dichlorobenzoyl chloride in 6 ml dry Et_2O. Workup and separation, essentially as described above for **6a** and **6b**, gave 3.2 and 4.5 mg samples of products whose ^1H NMR spectra were indistinguishable from those of **6a** and **6b**.

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