TETRAHYDROCANNABINOL REVISITED: SYNTHETIC APPROACHES UTILIZING MOLYBDENUM CATALYSTS

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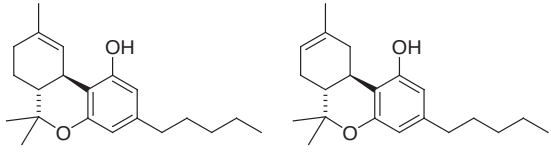
Dedicated to the memory of Dr Václav Černý.

Δ^9-Tetrahydrocannabinol **1** and its isomers were synthesized *via* domino-type methodology. The first approach, leading to (±)-**1**, relies on the Mo(IV)-catalyzed, one-pot cascade reaction of citral (**4**) with olivetol (**15**), affording (±)-Δ^9-tetrahydrocannabinol as a 69 : 31 mixture of the *trans*- (natural) and *cis*-isomers in 20% yield. The alternative approach, leading to natural (–)-**1**, commenced with epoxidation of (+)-limonene (*R*)-(+)-**16**; opening of the resulting *cis*-epoxide **17** with PhSeNa, followed by elimination, afforded tertiary alcohol **21**, whose acetate **22** was treated with olivetol **15** in the presence of Mo(II) catalyst **IV** to afford (–)-**1** in 52% yield.

Keywords: Terpenoids; Cannabinoids; Total synthesis; Asymmetric catalysis; Allylic substitution; Cascade reactions; Natural products.

Few natural products have enjoyed as much controversy as Δ^9-tetrahydrocannabinol **1** and its Δ^8-isomer **2** (Chart 1), the active constituents of marihuana[1]. While banned in most countries of the Western civilization, this ancient plant has been legalized in some, and its application in specific medicinal indications is being debated in others, thereby creating a gray area on the borderline between legality and criminal offense.

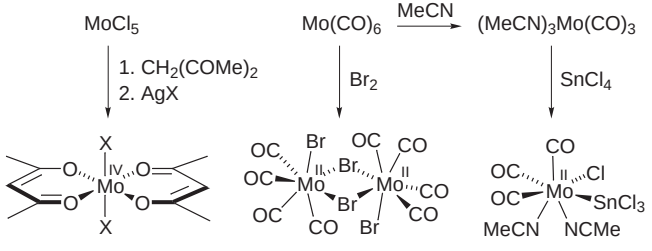


(–)-**1** (–)-**2**

CHART 1

In view of the recently revitalized debate on legalizing marihuana in the U.K. and other countries for terminally ill patients to ease their suffering, we felt that a new, preferably catalytic approach to **1**, **2**, and their analogues, would be justified. Furthermore, **1** and its isomers thus synthesized could also be employed as standards in forensic science and related disciplines concerned with drug-abuse detection. Herein, we present two straightforward syntheses, one producing a racemate in one step (and amenable to asymmetric catalysis) and the other utilizing the chiral pool.

We have recently developed a new set of Lewis-acidic Mo(II) catalysts, such as **IV** and **V** (Scheme 1), which proved to promote an intramolecular carbonyl-ene cyclization of citronellal (**3**), affording mainly the *cis*-product **5** (Scheme 2)[2]. By contrast, most of the known Lewis acids produce mainly the *trans*-isomer **7**. The molybdenum anomaly was attributed by us to the steric bulk of the catalyst, namely to the protruding CO group attached to Mo that renders the transition state leading to the *cis*-product lower in energy[2]. The same Mo(II) complex proved to catalyze allylic substitution of allylic acetates with silyl enol ethers[3] and electron-rich aromatics and heteroaromatics[4]. Whilst these substitution reactions were successful in the case of allylic esters, the corresponding alcohols proved inert. However, we have shown that allylic alcohols would react with Mo(IV) catalysts, such as **II** and **III** (ref.[5]), which can be readily generated from the acac complex **I** (which, in turn, is obtained from $MoCl_5$ and acac[6]) by an anion exchange with TfOAg (ref.[5]) or $AgSbF_6$ (**I** → **II** or **III**). Finally, we have also observed the electrophilic cyclization of olefinic phenols with both Mo(II) and Mo(IV) complexes in selected examples[4].



SCHEME 1

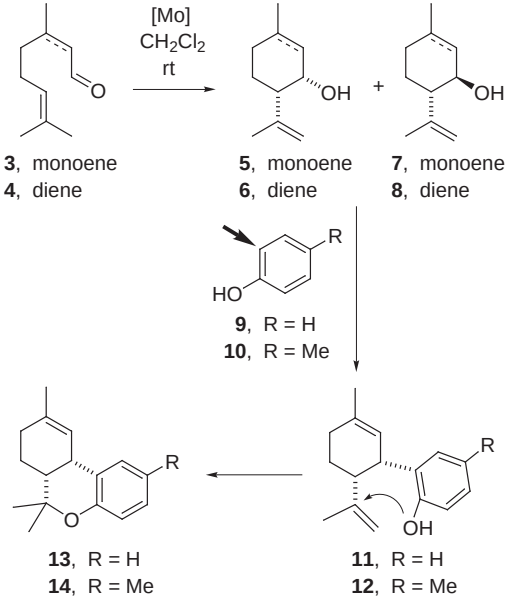
We reasoned that the three reactions, *i.e.*, ene-cyclization, allylic substitution, and electrophilic cyclization (*vide supra*), might be tamed to occur in a one-pot cascade, provided that suitably designed substrates are employed.

Thus, we have envisaged that cyclization of (*Z*)-citral (**4**) would generate cyclic dienol **6** (Scheme 2) that could react *in situ* with an electron-rich phenol, such as *p*-cresol (**10**), to furnish the *ortho*-substituted[4] product **12**, whose electrophilic cyclization would lead to the tricyclic skeleton **14**.

Model experiments with citral (**4**), commercially available as *ca* 1 : 1 (*E*/*Z*)-mixture[7], phenol (**9**), and the Mo(IV) catalyst **II** or **III** met with partial success. Thus, at room temperature and with hexafluoroantimonate **III** as catalyst, the expected tricyclic product **13** was formed in 24% yield[8] as a *ca* 7 : 1 mixture of *cis*- and *trans*-annulated isomers.[9]

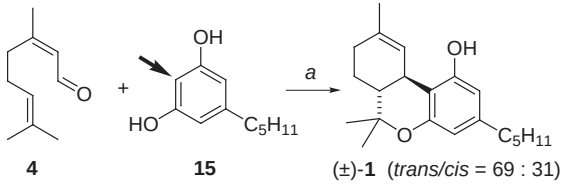
Since the relatively low yield in the case of phenol (**9**) can be partly attributed to the non-regioselective electrophilic aromatic substitution (furnishing the corresponding *para*-isomer along with **11**), we next carried out the same cyclization cascade with *p*-cresol (**10**), whose *para*-position is blocked. Indeed, an increased yield was observed (42%) and the tricyclic product **14** was isolated as a 3 : 1 *cis*-/*trans*-mixture (again with **III** as catalyst).

The ene-cyclization of **4** can be viewed as initially generating a mixture of epimers **6** and **8**, in which the former may prevail in analogy to the cyclization of **3**. However, the instability of the allylic alcohol precluded a detailed NMR analysis of the pure material.



SCHEME 2

Being encouraged by the successful model experiments, we then focused on the tetrahydrocannabinol itself. Indeed, the same sequence, this time carried out with olivetol (**15**) as the electron-rich phenol (CH_2Cl_2, room temperature, 4 h), and **III** as the catalyst [$(acac)_2MoCl_2$ (3 mole %), $AgSbF_6$ (6 mole %), CH_2Cl_2, room temperature, 4 h], produced[8] (±)-**1** (20%), isolated by flash chromatography as a 3 : 7 *cis*-/*trans*-mixture (Scheme 3). It is noteworthy that the stereochemistry of annulation has now been altered in favour of the natural *trans*-isomer. This effect can be attributed either to the influence of the additional phenolic hydroxyl in the allylic substitution step, or to the intervention of an alternative mechanism that would first involve the Lewis-acid catalyzed electrophilic attack by the carbonyl group of citral (**4**) at olivetol (**15**) followed by cyclization[9b,10] (Scheme 4). Since a gradual shift from *cis*- to *trans*-epimer correlates with the increasing electron density of the aromatic ring (phenol-cresol-olivetol), this alternative seems more likely.

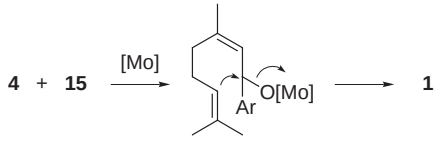


4 **15** (±)-**1** (*trans*/*cis* = 69 : 31)

a, $(acac)_2Mo(OTf)_2$, CH_2Cl_2, rt, 4 h

SCHEME 3

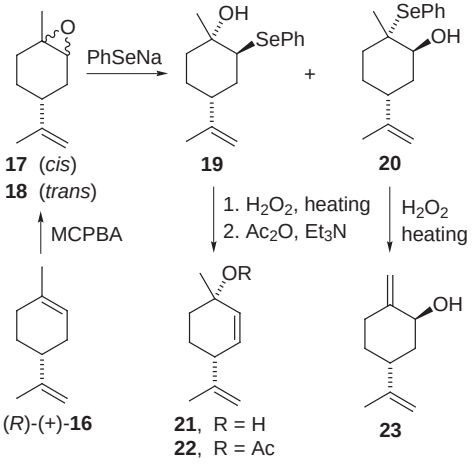
The one-pot procedure highlighted in Scheme 3 should be amenable to asymmetric catalysis, where a chiral catalyst would control the absolute stereochemistry of the initial ene-cyclization[11]. However, our experiments with various chiral ligands, including our recently developed chiral bipyridines[12], were unsuccessful to date. Therefore, in order to synthesize natural (–)-**1**, we turned to the chiral pool and employed a modified strat-



SCHEME 4

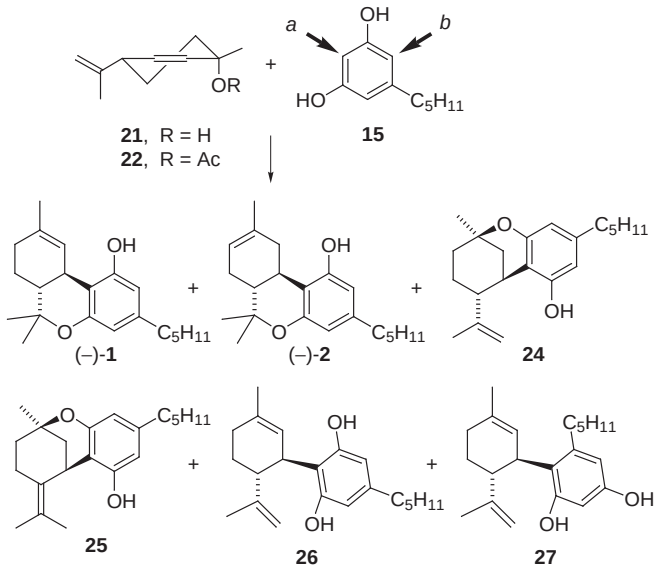
egy. The crude *cis*-/*trans*-mixture (*ca* 1 : 1) of epoxides **17** and **18**, obtained by epoxidation of (*R*)-(+)-limonene (*R*)-(+)-**16** (88% ee) with MCPBA

(Scheme 5)[13], was treated with PhSeNa (PhSeSePh, $NaBH_4$, EtOH, reflux, 2 h) to afford a mixture of isomeric phenylselenenyl derivatives **19** and **20** (refs[13,14]) which, without purification, was subjected to oxidation (30% aqueous H_2O_2, THF, room temperature, 5 h). While the seleneoxide arising from **20** spontaneously eliminated at room temperature to produce **23**, that derived from **19** proved stable, which allowed a simple separation of the liquid olefin **23** from the solid seleneoxide by extracting the former with petroleum ether. Heating of the seleneoxide thus obtained from **19** in pure state at reflux in $CHCl_3$ for 30 min afforded pure[13–15] **21** (30% overall from limonene)[16]. The latter allylic alcohol **21** was then acetylated (Ac_2O, DMAP, Et_3N, Et_2O, room temperature, 4 h) to produce tertiary acetate **22** (85%).



SCHEME 5

The catalytic reaction of both alcohol **21** and its acetate **22** with olivetol (**15**) was investigated with several molybdenum catalysts (Scheme 6 and Table I). Thus, the reaction of alcohol **21**, catalyzed by the Mo(IV) triflate complex **II** in CH_2Cl_2 at room temperature, gave a mixture of two tricyclic products, namely Δ^8-tetrahydrocannabinol (–)-**2** and its isomer[17] **25**, in which the former prevailed (Table I, entry 1). While the formation (–)-**2** results from the isomerization of the initially generated Δ^9-THC (–)-**1** to its thermodynamically more stable isomer, **25** arises from a "wrong" cyclization of the same intermediate in the final step. Lowering the reaction temperature to –20 °C led to a longer reaction time and formation of bicyclic products **26** and **27** (entry 2). Apparently, the final cyclization was disabled in this instance by the low temperature. Acetate **22** gave similar re-



SCHEME 6

TABLE I

Molybdenum-catalyzed reaction of allylic substrates **20** and **21**[a] with olivetol **15** in CH_2Cl_2 at room temperature

Entry	Allyl comp.	Catalyst	Temp. °C	Time	Yield, %						Total yield %
					1	**2**	**24**	**25**	**26**	**27**	
1	**21**	**II**	20	15 min		56		14			70
2	**21**	**II**	–20	3 h					20	52	72
3	**22**	**II**	20	15 min		52			[b]	[b]	52
4	**22**	**II**	–10	30 min		13			22	30	65
5	**22**	**III**	20	15 min		74			[b]	[b]	74
6	**22**	**IV**	20	4 h	51		23				72
7	**22**	**V**	20	4 h	39		12		14		65

[a] The enantiopurity of the starting alcohol **21** and acetate **22** and of the product should reflect that of (+)-limonene **16** (88% ee; *vide supra*). [b] The compound has not been isolated.

sults with the same catalyst (entries 3 and 4). The Mo(IV) hexafluoroantimonate catalyst **III** gave a much cleaner reaction, with (–)-**2** being the only isolable product in 74% yield (entry 5).

While the Mo(IV) catalysts induced the double bond isomerization to produce the Δ^8-isomer (–)-**2** (Table I, entries 1–5), switching to Mo(II) proved to eliminate this problem and, although their application lead to the deceleration of the cascade, the desired Δ^9-isomer (–)-**1** became the main product. Thus, with bromide **IV**, natural Δ^9-THC (–)-**1** was obtained in 51% yield (entry 6) along with the product of "wrong" cyclization **24** (23%). With the bimetallic catalyst **V**, the final cyclization was incomplete, affording Δ^9-THC (–)-**1** (39%) and its bicyclic precursor **26** (14%), again along with a small amount of the "wrong" tricyclic product **24** (entry 7). In view of the slightly lower overall yield of the latter reaction, it appears that the dibromide complex **IV** can be regarded as the most suitable catalyst, with practically no isomerization of Δ^9- to Δ^8-THC.

In none of these transformation we could detect more than trace amounts of the *cis*-annulated diastereoisomer (–)-**1** or (–)-**2** (that would be analogous to **13**/**14**). This effect can be understood in view of the single diastereoisomer of **21**/**22** being employed as an intermediate in this route, as opposed to the diastereoisomeric mixture of alcohols **6** and **8**, generated *in situ* in the one-pot approach.

In summary, we have synthesized racemic Δ^9-tetrahydrocannabinol **1** from the two commercially available precursors **4** and **15** in a cascade, one-pot reaction, catalyzed by the Lewis-acidic Mo(IV) complex **III** (Scheme 3). An alternative route, starting with scalemic limonene (*R*)-(+)-**16** and employing the Mo(II) complex **IV** as the optimal catalyst, afforded (–)-**1** (Schemes 5 and 6). This methodology has the advantage of giving cleaner products, compared to the conventional Lewis acids[1,10,11].

EXPERIMENTAL

General Methods

Optical rotations were measured on a Perkin–Elmer 341 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^{1}H at 250 and 400 MHz and ^{13}C at 62.9 and 100.6 MHz with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard; 2D-techniques were used to establish the structures and to assign the signals. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. The GC MS analysis was performed with RSL-150 column (25 m × 0.25 mm). All reactions were performed under an atmosphere of dry, oxygen-free nitrogen. Solvents and solutions were transferred by a syringe-septum technique. All re-

agents were purchased at highest commercial quality and used without further purification, unless otherwise stated. Yields are given for isolated product showing one spot on a TLC plate. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. Most of the products are known compounds. Complexes **I**, **IV**, and **V** were prepared following literature procedures.

General Procedure *A*: Reaction of Citral (**4**) with Phenols **9**, **10**, and **15** Catalyzed by Mo(IV) Complex **III**

$(acac)_2MoCl_2$ complex[5,6] (10 mg, 0.029 mmol, *ca* 3 mole %) was added to a stirred solution of citral **4** (2.0 mmol) and an aromatic compound (1.0 mmol) in CH_2Cl_2 (5 ml) at room temperature, followed by addition of solid silver hexafluoroantimonate or triflate (*ca* 0.060 mmol). The mixture was stirred under nitrogen for 4 h, then diluted with ether (20 ml), and the ethereal solution was washed successively with 5% aqueous $NaHCO_3$ and water and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give a crude product, which was purified by flash chromatography on a neutral silica gel column with a 9 : 1 mixture of hexane–ethyl acetate.

General Procedure *B*: Reaction of Olivetol (**15**) with Allylic Substrates **21** and **22** Catalyzed by Mo(IV) Complex **III**

$(acac)_2MoCl_2$ complex[5,6] (5 mg, 0.014 mmol, *ca* 3 mole %) was added to a stirred solution of the allylic substrate **21** or **22** (*ca* 0.5 mmol) and olivetol **15** (0.6 mmol) in CH_2Cl_2 (5 ml) at room temperature, followed by addition of solid silver hexafluoroantimonate or triflate (*ca* 0.060 mmol). The mixture was stirred under nitrogen at the temperature specified. After the reaction was complete (control by TLC, silica gel, hexane–ethyl acetate 9 : 1), work-up procedure was performed as described in the previous experiment. For yields and other reaction conditions see Table I.

General Procedure *C*: Reaction of Olivetol (**15**) with Allylic Acetate **22** Catalyzed by Mo(II) Complexes **IV** and **V**

Complex **IV** or **V** (refs[3,4]) (*ca* 3–5 mole %) was added to a stirred solution of the allylic acetate **22** (*ca* 0.5 mmol) and olivetol **15** (0.6 mmol) in CH_2Cl_2 (5 ml) at room temperature. The mixture was stirred under nitrogen at the temperature specified (Table I). Work-up procedure was performed as described in General Procedure *A*. For yields and other reaction conditions see Table I.

(±)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol [other name (±)-Δ^9-tetrahydrocannabinol] (±)-(**1**)[9b]. Obtained from **4** and **15** as a 69 : 31 mixture of *trans*-/*cis*-isomers as a viscous pale yellow oil (20%). EI MS, *m/z* (%): 314 (86, $M^{\bullet+}$), 299 (88), 271 (53), 258 (35), 231 (100), 193 (19), 119 (10), 91 (10). *Cis*-isomer: ^{1}H NMR (taken in a mixture with (±)-Δ^9-*trans*-THC): 0.90 (t, 3 H, *J* = 6.6, MeC_4H_8); 1.27 and 1.39 (2 × s, 2 × 3 H, 6-Me_2); 1.69 (br s, 3 H, 9-Me); 3.55 (br s, 1 H, 10a-H); 5.00 (br s, 1 H, OH); 6.13 and 6.24 (2 × s, 2 × 1 H, 2,4-H); 6.27 (br s, 1 H, 10-H).

(–)-(6aR,10aR)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol [other name (–)-trans-Δ^9-tetrahydrocannabinol] (–)-(**1**)[9b]. ^{1}H NMR (taken in a mixture with **24**): 0.87 (t, 3 H, *J* = 6.6, MeC_4H_8); 1.08 and 1.40 (2 × s, 2 × 3 H, 6-Me_2); 1.67 (br s, 3 H, 9-Me); 3.20

(br d, 1 H, *J* = 10.7, 10a-H); 5.18 (br s, 1 H, OH); 6.12 and 6.26 (2 × d, 2 × 1 H, *J* = 1.3, 2,4-H); 6.32 (br s, 1 H, 10-H).

(–)-(6aR,10aR)-6,6,9-Trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6H-benzo[c]chromen-1-ol [other name (–)-trans-Δ^8-tetrahydrocannabinol] (–)-(**2**)[9b]. Viscous pale yellow oil, $[\alpha]_D^{21}$ –225.0 (*c* 1.35, EtOH) (ref.[17] gives $[\alpha]_D$ –246 (*c* 0.11, EtOH) for enantiopure **2**). ^{1}H NMR: 0.88 (t, 3 H, *J* = 6.6, MeC_4H_8); 1.08 and 1.40 (2 × s, 2 × 3 H, 6-Me_2); 1.29 (m, 4 H); 1.55 (m, 2 H); 1.67 (br s, 3 H, 9-Me); 1.80 (m, 3 H); 2.12 (m, 1 H); 2.43 (m, 2 H); 2.69 (m, 1 H); 3.20 (dd, 1 H, *J* = 16.3 and 4.1, 10a-H); 4.90 (br s, 1 H, OH); 5.42 (d, 1 H, *J* = 4.4, 7-H); 6.09 and 6.27 (2 × d, 2 × 1 H, *J* = 1.3, 2,4-H). ^{13}C NMR: 14.4 (Me), 18.9 (Me), 22.9 (CH_2), 23.9 (Me), 27.9 (Me), 28.3 (CH_2), 31.0 (CH_2), 31.9 (CH_2), 32.0 (6a-CH), 35.8 (CH_2), 36.4 (CH_2), 45.3 (10a-CH), 77.1 (6-C), 108.1 and 110.4 (2,4-CH), 111.0 (C), 119.7 (8-CH), 135.2 (C), 143.1 (C), 155.1 (C), 155.2 (C).

(±)-cis-6,6,9-Trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (±)-(**13**). Obtained from **4** and **9** as a viscous pale yellow oil (24%). ^{1}H NMR: 1.29 and 1.43 (2 × s, 2 × 3 H, 6-Me_2); 1.59–2.08 (m, 5 H); 1.70 (br s, 3 H, 9-Me); 3.55 (br s, 1 H, 10a-H); 5.94 (d, 1 H, *J* = 4.1, 10-H); 6.74 (d, 1 H, *J* = 7.8, 4-H); 6.85 (t, 1 H, *J* = 7.5, 2-H); 7.05 (t, 1 H, *J* = 7.5, 2-H); 7.25 (d, 1 H, *J* = 7.5, 1-H). EI MS, *m/z* (%): 228 (100, $M^{\bullet+}$), 213 (60), 186 (11), 185 (67), 171 (13), 160 (21), 159 (12), 157 (12), 146 (10), 145 (73), 135 (16), 131 (12), 128 (11), 115 (15), 107 (16), 91 (17), 77 (12). EI HRMS, *m/z*: 228.15142 (calculated for $C_{16}H_{20}O$: 228.15142; $M^{\bullet+}$).

(±)–2,6,6,9-Tetramethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (±)-(**14**). Obtained from **4** and **10** as a 3 : 1 mixture of *cis*-/*trans*-isomers as a viscous pale yellow oil (42%). EI MS, *m/z* (%): 242 (100, $M^{\bullet+}$), 227 (46), 231 (12), 202 (11),199 (62), 197 (10), 185 (14), 174 (20), 171 (11), 165 (10), 159 (99), 145 (18), 135 (21), 128 (15), 121 (23), 115 (15), 107 (12), 105 (12), 91 (20), 84 (45), 77 (16). EI HRMS, *m/z*: 242.16712 (calculated for $C_{17}H_{22}O$: 242.16707; $M^{\bullet+}$). *Cis*-isomer: ^{1}H NMR (taken in a mixture with the *trans*-isomer): 1.26 and 1.41 (2 × s, 2 × 3 H, 6-Me_2); 1.50–2.12 (m, 5 H); 1.71 (br s, 3 H, 9-Me); 2.26 (s, 3 H, 2-Me); 3.52 (br s, 1 H, 10a-H); 5.93 (d, 1 H, *J* = 4.4, 10-H); 6.65 (d, 1 H, *J* = 8.2, 4-H); 6.86 (br d, 1 H, *J* = 8.2, 3-H); 7.06 (br s, 1 H, 1-H). ^{13}C NMR (taken in a mixture with the *trans*-isomer): 20.3 (CH_2), 21.2 (Me), 24.0 (Me), 25.9 (Me), 27.0 (Me), 30.9 (CH_2), 31.3 (6a-CH), 39.9 (10a-CH), 76.0 (6-C), 117.5 (CH), 122.6 (CH), 124.9 (C), 128.1 (CH), 129.2 (CH), 129.6 (C), 135.5 (C), 150.2 (C). *Trans*-isomer: ^{1}H NMR (taken in a mixture with the *cis*-isomer): 2.29 (s, 3 H, 2-Me); 3.19 (br d, *J* = 10.5, 10a-H).

(–)-(2R,5R,6R)-5-Isopropenyl-2-methyl-9-pentyl-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocan-7-ol [other name (–)-Δ^8-iso-THC] (–)-(**24**)[9b]. ^{1}H NMR (taken in a mixture with (–)-Δ^9-THC, **1**): 3.48 (br s, 1 H, 6-H); 4.92 and 4.97 (2 × s, 2 × 1 H, 5-CH_2=); 5.02 (br s, 1 H, OH); 6.11 and 6.28 (2 × s, 2 × 1 H, 8-H and 10-H).

(–)-(2R,6R)-5-Isopropylidene-2-methyl-9-pentyl-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocan-7-ol [other name (–)-Δ^6-iso-THC] (–)-(**25**)[9b]. Viscous pale yellow oil, $[\alpha]_D^{27}$ –160.0 (*c* 1.15, $CHCl_3$). ^{1}H NMR 0.88 (t, 3 H, *J* = 6.6, MeC_4H_8); 1.29 (m, 4 H, Me**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$); 1.35 (s, 3 H, 2-Me); 1.59 (m, 4 H); 1.66 and 1.92 (2 × s, 2 × 3 H, 5-Me_2); 1.82 (m, 2 H); 2.04 (m, 1 H); 2.44 (m, 3 H); 4.16 (br s, 1 H, 6-H); 4.50 (br s, 1 H, OH); 6.12 and 6.29 (2 × d, 2 × 1 H, *J* = 1.5, 8-H and 10-H). ^{13}C NMR: 14.4 (Me), 20.4 (Me), 21.0 (Me), 23.0 (CH_2), 23.4 (CH_2), 29.2 (Me), 30.4 (6-CH), 31.2 (CH_2), 32.0 (CH_2), 36.1 (CH_2), 37.4 (CH_2), 40.8 (CH_2), 74.7 (2-C), 106.8 and 108.5 (8,10-CH), 110.5 (C), 122.0 (C), 132.2 (C), 143.1 (C), 153.0 (C), 157.3 (C).

(–)-2-(p-Mentha-2,8-dien-3-yl)pentylbenzene-1,3-diol [other name (–)-cannabidiol] (–)-(**26**)[9b]. Viscous pale yellow oil, $[\alpha]_D^{22}$ –107.1 (*c* 1.00, EtOH), $[\alpha]_D^{23}$ –69.4 (*c* 1.65, $CHCl_3$) (ref.[9b] gives $[\alpha]_D$ –126 (EtOH) for enantiopure **26**). ^{1}H NMR: 0.88 (t, 3 H, *J* = 6.6, MeC_4H_8); 1.29 (m, 4 H,

MeC**H**$_2$C**H**$_2$); 1.56 (m, 2 H); 1.65 (s, 3 H, 8′-Me); 1.79 (br s, 3 H, 1′-Me); 1.82 (m, 2 H); 2.12 (m, 2 H); 2.43 (m, 3 H); 3.85 (br d, 1 H, *J* = 8.8, 3′-H); 4.56 and 4.66 (2 × s, 2 × 1 H, 9′-CH_2); 5.57 (s, 1 H, 2′-H); 6.22 (br s, 2 H, 4-H and 5-H). ^{13}C NMR: 14.6 (Me), 20.8 (Me), 23.1 (CH_2), 24.3 (Me), 28.7 (CH_2), 30.8 (CH_2), 31.2 (CH_2), 31.9 (CH_2), 35.9 (CH_2), 37.4 (4′-CH), 45.6 (3′-CH), 108.2 and 110.0 (4.6-CH), 111.4 (9′-CH_2), 114.0 (C), 124.4 (2′-CH), 140.7 (C), 143.5 (C), 149.8 (C), 154.2 (C), 156.3 (C).

(–)-4-(p-Mentha-2,8-dien-3-yl)pentylbenzene-1,3-diol [other name (–)-abnormal cannabidiol] (–)-(**27**)[9b]. Viscous pale yellow oil, $[\alpha]_D^{22}$ –74.3 (*c* 2.12, $CHCl_3$) (ref.[9b] gives $[\alpha]_D$ –76 ($CHCl_3$) for enantiopure **27**). ^{1}H NMR: 0.89 (t, 3 H, *J* = 6.6, MeC_4H_8); 1.30 (m, 4 H, MeC**H**$_2$C**H**$_2$); 1.46 (m, 2 H); 1.53 (s, 3 H, 8′-Me); 1.78 (br s, 3 H, 1′-Me); 1.81 (m, 2 H); 2.22 (m, 3 H); 2.51 (m, 2 H); 3.53 (br d, 1 H, *J* = 8.8, 3′-H); 4.46 and 4.64 (2 × s, 2 × 1 H, 9′-CH_2); 5.52 (s, 1 H, 2′-H); 6.20 (s, 2 H, 2,6-H). ^{13}C NMR: 14.4 (Me), 21.7 (Me), 22.9 (CH_2), 24.0 (Me), 28.5 (CH_2), 30.7 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 34.4 (CH_2), 40.5 (4′-CH), 45.4 (3′-CH), 102.6 and 109.1 (2,6-CH), 111.8 (9′-CH_2), 120.3 (C), 125.1 (2′-CH), 140.2 (C), 144.4 (C), 148.1 (C), 155.0 (C), 156.8 (C).

(+)-(1*S*,4*R*)-*p*-Mentha-2,8-dien-1-ol (**21**)

This compound was prepared from a 1 : 1 mixture of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*R*)-limonene oxides **17** and **18** (1.22 g, 8 mmol) following the literature procedure[13]. The crude product was purified by column chromatography on silica gel (2 × 20 cm) with a 4 : 1 mixture of hexane–ethyl acetate as eluent to afford the title compound as a colorless oil (370 mg, 30%). **21**: $[\alpha]_D^{22}$ +68.2 (*c* 1.15, CH_2Cl_2) (ref.[17] gives $[\alpha]_D$ +73.6 or +76.0 (neat), and +73 (*c* 1.2, $CHCl_3$); ref.[13a] gives $[\alpha]_D$ +76.8 neat for enantiopure **21**). ^{1}H NMR: 1.29 (s, 3 H, 1-Me); 1.57–1.85 (m, 4 H, 5,6-CH_2); 1.74 (s, 3 H, 8-Me); 2.66 (m, 1 H, 4-H); 4.75 and 4.78 (2 × br s, 2 × 1 H, 9-CH_2); 5.67 (m, 2 H, 2,3-H).

(+)-(1*S*,4*R*)-*p*-Mentha-2,8-dien-1-yl Acetate (**22**)[13b]

Acetic anhydride (260 mg, 2.5 mmol) was added dropwise to a stirred solution of alcohol **21** (240 mg, 1.58 mmol), triethyl amine (303 mg, 3 mmol), and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in ether (25 ml) at room temperature. The mixture was stirred at room temperature for 4 h, then it was diluted with water (30 ml) and extracted with ether (3 × 20 ml). The combined ether extracts were dried over $MgSO_4$ and the ether was removed in a vacuum. The residue was passed through a silica gel column (2 × 10 cm) with a 9 : 1 mixture of hexane–ethyl acetate as eluent to afford the **22** as a colorless oil (260 mg, 85%). ^{1}H NMR: 1.46–1.76 and 2.13 (m, 4 H, 5,6-CH_2); 1.55 (s, 3 H, 1-Me); 1.71 (s, 3 H, 8-Me); 1.96 (s, 3 H, MeCO); 2.70 (m, 1 H, 4-H); 4.76 (br s, 2 H, 9-CH_2); 5.70 (dd, 1 H, *J* = 10.1 and 1.9, 3-H); 6.17 (dq, 1 H, *J* = 10.1 and 1.3, 2-H).

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8. The yield is calculated with respect of olivetol.
9. Crucial for the configurational assignment is the signal of the benzylic proton in the ^{1}H NMR spectrum, which appears as a broad singlet at 3.55 ppm for the *cis*-isomer and as a broad doublet at 3.20 ppm for the *trans*-isomer. For further discussion of the ^{1}H NMR characteristics, see: a) Taylor E. C., Lenard K., Shvo Y.: *J. Am. Chem. Soc.* **1966**, *88*, 367; b) Razdan R. K., Dalzell H. C., Handrick G. R.: *J. Am. Chem. Soc.* **1974**, *96*, 5860.
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16. Owing to the non-stereoselective epoxidation of limonene, the overall yield of **21** cannot exceed ≈50%.
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