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Synthesis and Organoleptic Properties of *p*-Menthane Lactones

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Abstract—The stereoselective synthesis and organoleptic properties of *p*-menthane lactones **7a**–**h** are described. Apart from correcting the published data concerning these compounds, this work has also allowed an unambiguous identification of **7a**, **7b** and **7g** in Italo Mitcham black peppermint oil (*Mentha piperita*). In addition, these lactones are of considerable interest to the perfume industry, due to their exceptional odor intensity and typical coumarin-like note.

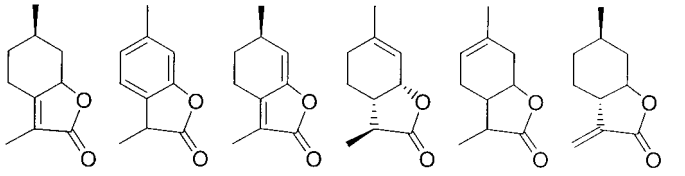
Introduction

The family of *p*-menthane lactones is a very interesting class of compounds for a variety of reasons. For example, (−)-mintlactone **1a**, (+)-isomintlactone **1b** and lactones **2**, **3** have been identified as minor components from the essential oil of black peppermint oil (*Mentha piperita*).[1] **1a**,**b** are used as commercial flavoring ingredients, and numerous syntheses of these natural lactones have been reported.[2,3] Lactone **4**, named wine lactone, has been detected in several white wines and appears to be an important flavor compound, possessing a sweet coconut odor and a particularly low threshold (10^{-5} ng/l of air).[4] In addition, Southwell has isolated lactone **5** from the metabolized essential oil of eucalyptus leaves (*Eucalyptus punctata*).[5]

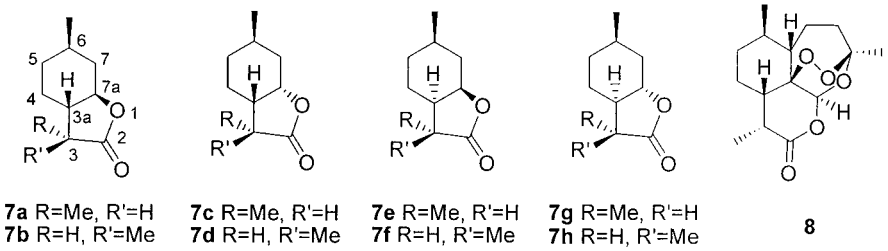
Moreover, the isolation of many natural biologically active mono and sesquiterpenoid α-methylene-γ-butyrolactones has resulted in the synthesis of compounds **6a** and **6b**[6] (Scheme 1).

These lactones, except **3** and **5**, are fully characterized in the literature.

On the other hand, the saturated analogs **7a**–**h** (Scheme 2), are reported to be insect repellents.[7] They have also been



Scheme 1.



Scheme 2.

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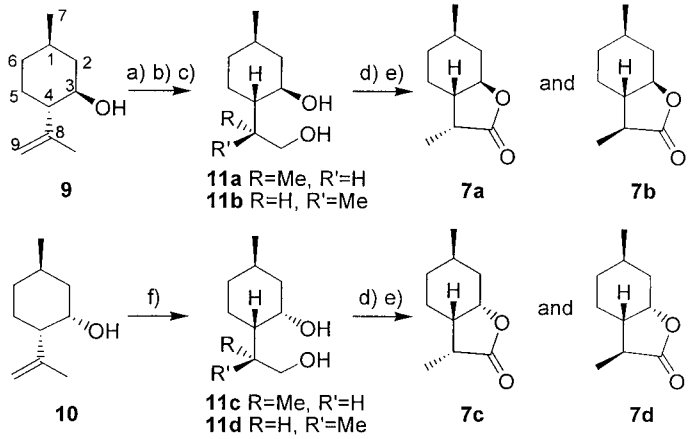


Scheme 3. (a) *m*CPBA/CH_2Cl_2 (88%); (b) LDA/THF (74%); (c) H_2/Pd–C (70%); (d) crystallization; (e) $KMnO_4$ (76%); (f) B_2H_6/NaOH (94%).

used as key intermediates in a synthesis of Pseudopterosins[8] and in the synthesis of the promising anti-malaria active principle **8**, isolated from the plant *Artemisia annua*.[9] Five of these stereoisomers are specifically cited in the literature[3,6d,7,8,1,10–14] but are sometimes only partially characterized, often as a result of synthesis using non stereoselective routes.[3e,7,10,11] It is evident that, due to the similarity of their spectral data, unambiguous structural elucidation of the individual isomers is difficult and leads to errors in stereochemical assignments.

Our interest in **7a**–**h** results primarily from their powerful coumarin-like odor properties,[15] and we now present the stereoselective syntheses and full spectral characterization of all eight stereoisomers, together with a description of their individual organoleptic properties.

Results and Discussion

Synthesis of (7a–h)

Starting from (−)-isopulegol **9** and (+)-neoisopulegol **10** (e.e.≥99%), isomers **7a-d** were synthesized according to known procedures[16–18] (Scheme 3).

Thus, epoxidation of **9** in CH_2Cl_2[18] (88%), followed by treatment with LDA in THF (2.2° mol equiv.)[17] (74%) and catalytic hydrogenation of the resulting allylic alcohol (70%) afforded diols **11a/11b**. Separation by crystallization and subsequent oxidation with potassium permanganate[16] gave the lactones **7a** and **7b**.

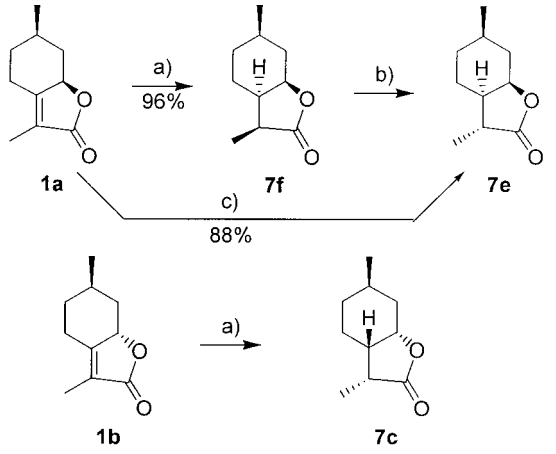
An alternative and more direct approach was used to synthesize **7c** and **7d**, starting from (+)-neoisopulegol **10**. Thus, hydroboration gave a mixture of diols **11c/11d** (20/80) in 94% yield.[17] These crude diols were then oxidized with potassium permanganate to afford **7c/7d** (20/80) in 76% yield. Recrystallization directly afforded pure **7c**, whereas **7d** was isolated from the mother liquor by preparative GC. This route was also repeated with **9** as starting material, allowing a more efficient access to **7a/7b**.

Lactones **7e** and **7f** were synthesized from (−)-mintlactone **1a** (e.e. 97%) as shown in Scheme 4.

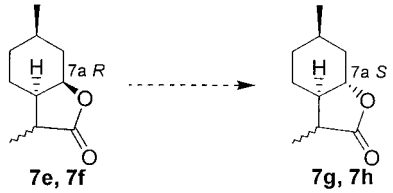
Thus, stereoselective catalytic reduction of (−)-mintlactone **1a** using Raney nickel under 40 atmospheres of hydrogen afforded **7f** (96%), which underwent ready base-catalyzed epimerization (MeONa/MeOH) to the thermodynamically more stable **7e**. This equilibration is fully in favor of **7e** (see later). Similarly, reduction of (+)-isomintlactone **1b** gave the already mentioned **7c**. It is interesting to note that the reduction of (−)-mintlactone **1a** by magnesium in methanol[19] provided **7e** (88%) directly with high diastereoselectivity.

In order to synthesize the final two isomers **7g** and **7h**, it was necessary to inverse the stereochemistry at the C(7a) position (Scheme 5).

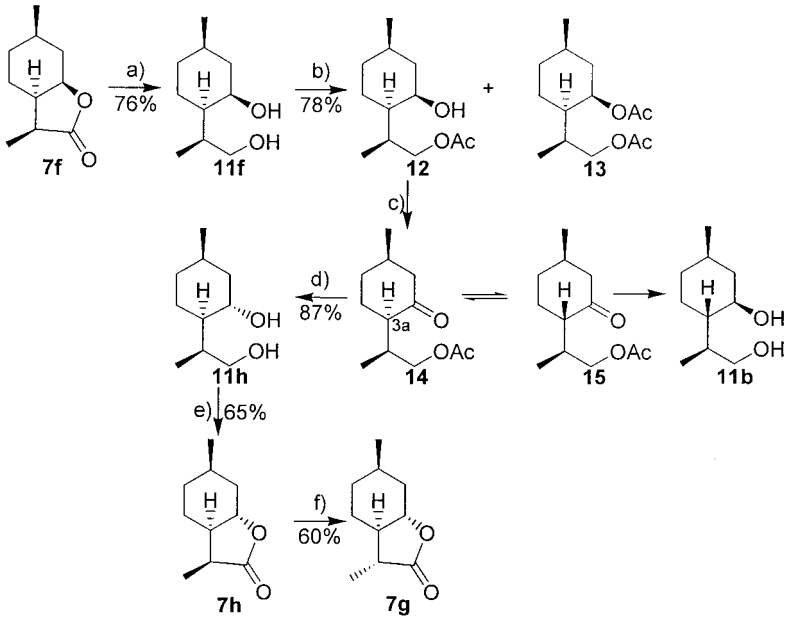
To carry out this synthetic transformation, we opted for a



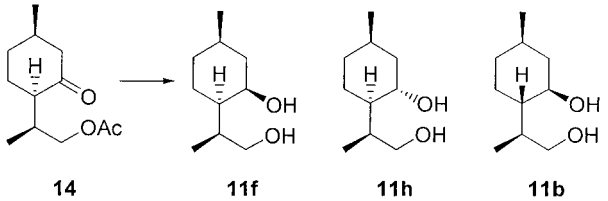
Scheme 4. (a) H_2/Raney Ni; (b) MeOH; (c) Mg/MeOH.



Scheme 5.



Scheme 6. (a) $LiAlH_4$; (b) Ac_2O; (d) Jones reagent; (d) Li/liq $NH_3/Et_2O/NH_4Cl$; (e) $KMnO_4$; (f) MeONa/MeOH.



Entry	Conditions				Yield
1	Li/NH_3 liq/Et_2O/NH_4Cl	16%	84%	-	87%
2	Na/NH_3 liq/EtOH	-	33%	67%	76%
3	$LiAlH_4/Et_2O$	100%	trace	-	95%

Scheme 7.

method published by Garcia-Granados et al. to convert 6α-lactones into 6β-lactones in the eudesmane series.[20]

Accordingly, hydride reduction of **7f** (76%) to diol **11f** was followed by chemoselective mono-acetylation to the desired product **12** (78%), which was separated from the diacetate **13** (8%) by column chromatography (Scheme 6).

Oxidation of **12** with Jones reagent gave quantitatively the ketone **14**.

Stereoselective reduction of **14** to **11h**, with the C(7a) hydroxyl group in the thermodynamically more stable position, was achieved by treatment with Li in liquid NH_3, in the presence of NH_4Cl as proton donor.[21,22] Under these conditions, the epimeric **11f**, possessing an axial hydroxyl group, was formed in 16% yield (Scheme 7, Entry 1). It should be noted that treatment of **14** with Na in liquid NH_3, in the presence of MeOH, a weaker proton donor, was less satisfactory, resulting in a partial isomerization at C(3a) and a reversal of selectivity (**11b/11h** 2/1) (Scheme 7, Entry 2). Not unexpectedly, $LiAlH_4$ reduction of **14** furnished **11f** exclusively and only trace amounts of **11h** were detected (Scheme 7, Entry 3). Completion of the synthesis (Scheme 6) was effected by chemoselective oxidation of the primary hydroxyl group of **11h** with $KMnO_4$ and

Table 1. ^{13}C NMR chemical shifts (δ [ppm]) of lactones **7a–h** in $CDCl_3$

Lactones	C(6)	C(7)	C(7a)	C(3a)	C(4)	C(5)	Me–C(6)	C(3)	C(2)	Me–C(3)
7a	31.3	38.8	81.5	47.2	23.8	34.2	22.0	38.8	180.4	9.6
7b	31.4	38.2	82.5	51.5	26.7	34.2	22.0	41.4	179.5	12.6
7c	26.2	36.2	78.2	39.1	23.2	32.1	22.0	42.3	179.8	9.1
7d	26.0	36.0	77.4	41.3	27.3	31.6	21.5	44.1	180.5	14.1
7e	29.5	37.8	77.5	41.7	24.0	28.7	22.0	35.3	179.6	13.3
7f	25.3	33.1	77.9	38.8	17.4	28.9	19.8	41.3	179.7	9.7
7g	28.2	35.7	79.3	52.5	23.0	31.0	19.2	41.5	179.5	12.5
7h	28.1	36.1	78.2	48.1	20.2	31.0	19.2	38.9	180.3	12.5

Table 2. ^{1}H NMR chemical shifts (δ [ppm]) of lactones **7a**–**h** in $CDCl_3$ (360 MHz)

H	Lactones							
	7a	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**
H–C(6)	1.60	1.63	1.57	1.80	1.40	1.88	2.30	2.30
	m	m	m	m	m	m	m	m
H–C(7)	1.24	1.22	1.21	1.25	0.98	1.90	1.70	1.72
	ddd(11,11,11)	m	m	m	m	m	dd(12,5)	dd(12,5)
H′–C(7)	2.25	2.22	2.22	2.17	2.08	1.90	2.16	2.10
	ddd(11,4,4)	m	m	dm(14)	m	m	ddd(12,3,3)	ddd(12,3,3)
H–C(7a)	4.00	3.76	4.44	4.69	4.49	4.52	3.99	4.23
	ddd(11,11,4)	ddd(13,13,4)	m	dd(4,4)	ddd(12,7,7)	dd(5,5)	ddd(11,9,4)	ddd(12,12,4)
H–C(3a)	1.93	1.47	2.22	1.95	2.22	2.32	1.48	1.94
	m	dddd(13,13,13,4)	m	m	m	m	m	m
H–C(4)	1.34	1.26	1.11	1.25	1.67	1.33	1.48	1.4–1.7
	m	m	m	m	m	m	m	m
H′–C(4)	1.77	1.94	1.67	1.80	1.86	1.50	1.80	1.4–1.7
	m	ddd(13,5,3)	m	m	dm(14)	m	m	m
H–C(5)	1.11	1.03	0.90	0.94	0.98	1.50	1.62	1.62
	m	m	m	m	m	m	m	m
H′–C(5)	1.82	1.82	1.67	1.80	1.56	1.50	1.62	1.62
	m	dm(13)	m	m	dm(13)	m	m	m
Me–C(6)	1.02	1.02	0.92	0.93	0.96	1.02	1.07	1.07
	d(7)	d(7)	d(7)	d(7)	d(7)	d(7)	d(7)	d(7)
H–C(3)	2.64	2.24	2.79	2.36	2.48	2.77	2.30	2.65
	dq(7,7)	m	dq(7,7)	q(7)	dq(14,7)	dq(7,7)	m	dq(7,7)
Me–C(3)	1.15	1.22	1.16	1.27	1.21	1.18	1.23	1.17
	d(7)	d(7)	d(7)	d(7)	d(7)	d(7)	d(7)	d(7)

concomitant lactonization of the intermediate hydroxy acid to **7h** (65%).

Subsequent base-catalyzed epimerization allowed access to its thermodynamically more stable epimer **7g** (60%).

Spectral and thermodynamic properties of (7a–h)

On the basis of ^{1}H, ^{13}C and COSY NMR spectra, together with nOe experiments, all protons and all carbons of **7a**–**h** were unambiguously assigned. The data are summarized in Tables 1 and 2.

The mass spectra of **7a**–**h** have similar fragmentation patterns, although there is a large difference with regard to the relative peak intensities. Five of them (**7a**, **7b**, **7e**, **7g**, **7h**) have an identical mass spectrum (base peak at *m*/*z* 81), while **7c**, **7d** and **7f** show a second type of spectrum with a base peak at *m*/*z* 95.

The MM2 energies of **7a**–**h** were calculated using *MacroModel* program (version 5.5)[23] and were consistent with equilibration experiments (MeONa in MeOH or THF) (Table 3).

Table 3. MM2 energies of lactones **7a**–**h** and results of some epimerization experiments

Lactones	MM2 Energy (kcal/mol)	Energy difference (kcal/mol)	Theoretical equilibrium at 300 K	Experimental equilibrium at 300 K
7a	44.34			
7b	42.95	1.39	9/91	10/90
7c	42.82			
7d	42.89	0.07	54/47	57/43
7e	42.14			
7f	44.88	2.74	99/1	97/3
7g	44.83			
7h	46.15	1.32	90/10	75/25

GC separation of (7a–h)

Lactones **7a**–**h** were conveniently separated on a 60 m *Supelcowax* capillary column; conditions and retention times are described in Fig. 1.

This separation technique has allowed an unambiguous identification of **7a**, **7b** and **7g** as components of Italo Mitcham black peppermint oil (*Mentha piperita*).[1d] This is the first time that stereoisomers of **7** have been found in nature.

Organoleptic properties of (7a–h)

The odor evaluation has been done by *Firmenich*'s perfumers using neat compound on smelling stips. Lactones **7a**–**h** possess very interesting olfactive properties (Table 4). In general, their odors are more coumarin-like and less lactonic than the odor of mintlactone **1**. They have the typical hay character of coumarin, which is lacking in **1**.[15] The stereoisomers **7a** and **7b** are particularly powerful and exhibit an exceptional tenacity on cloth.

Table 4.

Lactones	Odor description
7a	Lactonic
7b	Coumarinic, lactonic, tonka, hay, flouve
7c	Coumarinic, fatty, weak
7d	Coumarinic, lactonic, weak
7e	Weak, without character
7f	Weak, vaguely lactonic
7g	Flouve, coumarinic, sulfury, hay
7h	Coumarinic, flouve

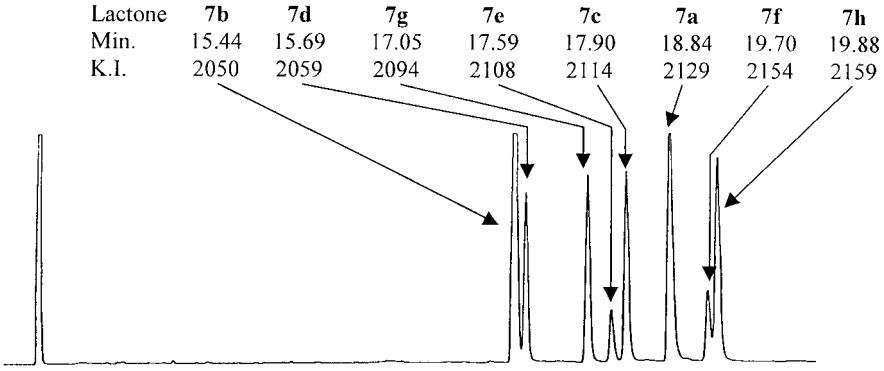


Figure 1. Retention times in min and *Kováts* indices of lactones **7a**–**h** on *Supelcowax* 10 column (60 m×0.25 nm), 160°C isotherm.

Conclusion

The stereoselective synthesis of *p*-menthane lactones **7a**–**h** has been effected and their individual organoleptic properties have been investigated. This work has thus clarified and rectified the published data concerning some of these compounds, and also allowed an unambiguous identification of **7a**, **7b** and **7g** as trace components in Italo Mitcham black peppermint oil (*Mentha piperita*).[1d] These compounds, in spite of their very low concentration, make an important contribution to the organoleptic quality of this mint oil. In addition, they are of considerable interest to the perfume industry, due to their exceptional odor intensity and typical coumarinic-note (in particular **7a** and **7b**).[15]

Further work on other *p*-menthane derivatives is in progress and will be reported in due course.

Experimental

GLC: Hewlett-Packard—6890 instrument equipped with a flame-ionization detector.

Flash chromatography (FC)

Silica gel 60, Merck, 230–400 mesh. MS: Finnigan 4021 C, 70 eV, *m/z*, intensities in % relative to the base peak. HR-MS: GC mate JEOL −30 eV-EI resolution 5000. NMR: Bruker WH-360, Bruker AMX-360; ^{1}H at 360 and ^{13}C at 90.5 MHz, in $CDCl_3$; chemical shifts δ in ppm; tetramethylsilane as internal standard, d=0.00 ppm; coupling constants J in Hz.

Optical rotation

Perkin–Elmer 241 Polarimeter, in $CHCl_3$ at 20°C, *c*: concentration in %. IR: GC-FTIR Hewlett Packard 5890. Calculations were carried out on a Silicon Graphics Iris 4D/35 computer system with the program *MacroModel* (version 5.5).[23] The Monte Carlo method was used for conformational searching from an energy-minimized (MM2) starting conformation by using the automatic set-up from the *MacroModel* program.

(1*R*,3*R*,4*S*,8*R*)-3,9-*p*-Menthanediol (11a) and (1*R*,3*R*,4*S*,8*S*)-3,9-*p*-menthanediol (11b) 64.5 g (317 mmol) of *m*-chloroperbenzoic acid were added to 40.7 g (264 mmol) of (−)-isopulegol (Fluka, e.e.≥99%) in CH_2Cl_2 (130 ml). The reaction mixture was stirred for 4 h at room temperature and then filtered, washed with saturated $NaHSO_3$ solution, water and brine. The organic layer was dried, concentrated and the crude product was distilled to give 39.5 g (88%) of pure epoxide. It should be noted that the method with H_2O_2/MeCN[18a] gave exactly the same yield. 16.15 g (95 mmol) of this epoxide in THF (30 ml) were slowly added to 295 mmol of LDA in 170 ml of THF at 0°C. Then the reaction was heated for 1 h at 45°C and cooled to room temperature. The reaction mixture was poured on ice and extracted with ether. The organic layer was washed with brine, dried and concentrated to give 14 g of crude material. It was recrystallized from hexane and afforded 11.96 g (74%) of pure diol. 15 g (88 mmol) of this diol were hydrogenated with 0.15 g of 10% palladium on charcoal in ethyl acetate (150 ml) under atmospheric pressure of hydrogen. 15.7 g of crude oil were distilled, which gave 10.6 g (70%) of diols **11a** and **11b**. Both diols were separated by crystallization in hexane.

11a. MS: 172(1, $M^{+\cdot}$), 154(3), 139(7), 124(18), 112(28), 95(33), 81(100), 71(62), 55(65), 41(35); ^{13}C NMR: 12.0(q), 22.1(q), 29.5(t), 31.5(d), 34.7(t), 38.6(d), 44.6(t), 48.6(d), 67.0(t), 70.1(d); ^{1}H NMR: 0.93(d, J=7 Hz, 3H), 0.97(d, J=7 Hz, 3H), 0.8–1.0(m, 2H), 1.24(dddd, J_1=11 Hz, J_2=11 Hz, J_3=11 Hz, J_4=3 Hz, 1H), 1.35(dm, J=11 Hz, 1H), 1.42(m, 1H), 1.56(dm, J=13 Hz, 1H), 1.64(dm, J=13 Hz, 1H), 1.84(m, 1H), 1.97(dm, J=13 Hz, 1H), 3.44(ddd, J_1=10 Hz, J_2=10 Hz, J_3=4 Hz, 1H), 3.58(dd, J_1=11 Hz, J_2=3 Hz, 1H), 3.65(dd, J_1=11 Hz, J_2=5 Hz, 1H); $[\alpha]_D$=−22.5° (c=1.2); mp: 100–101°C.

11b. MS: 172(1, $M^{+\cdot}$), 154(3), 139(6), 123(16), 112(16), 95(38), 81(100), 71(63), 55(57), 41(32); ^{13}C NMR: 12.6(q), 22.2(q), 25.3(t), 31.6(d), 34.4(t), 35.6(d), 45.2(t), 45.6(d), 66.6(t), 71.7(d); ^{1}H NMR: 0.85(d, J=7 Hz, 3H); 0.89(m, 1H); 0.92(d, J=6 Hz, 3H); 0.98(m, 2H); 1.35(m, 1H); 1.41(m, 1H); 1.63(m, 2H); 1.99(dm, J=13 Hz, 1H); 2.07(m, 1H); 3.42(ddd, J_1=11 Hz, J_2=4 Hz, J_3=4 Hz, 1H); 3.48(dd, J_1=11 Hz, J_2=7 Hz, 1H); 3.56(dd, J_1=11 Hz, J_2=5 Hz, 1H); $[\alpha]_D$=−28.5° (c=0.9); mp: 89–91°C.

(1*R*,3*S*,4*S*,8*S*)-3,9-*p*-Menthanediol (11d). 21.3 g (150 mmol)

of boron trifluoride ethyl etherate were added dropwise, within 1 h at −10 to 0°C, to an ice cooled solution of 30.8 g (200 mmol) of (+)-neoisopulegol **10** (e.e.≥99%), 4.18 g (110 mmol) of sodium borohydride in THF (80 ml) under nitrogen. After complete addition, the reaction was stirred at 0°C for 3 h. Then 30 ml of water were added slowly (15 min) and the reaction was stirred for 15 min 80 g of a 12% KOH solution in ethanol and after 20 min, 22 g (460 mmol) of hydrogen peroxide (70% solution in water) were added always at 0°C (exothermic). After complete addition, the reaction was stirred at 20°C for 2 additional hours. Then, the THF was removed and the crude material was extracted with ether and washed with brine. The organic mixture was dried and concentrated to afford 32 g (94%) of oily crude material constituted by diols **11c** and **11d** (20/80), which were used without further purification. Pure **11d** was obtained for analysis from 1 g of this crude oil by flash chromatography (eluent: pentane/ether=1/2).

11d. MS: 172(2, $M^{+\cdot}$), 154(8), 139(13), 123(25), 112(40), 95(63), 81(100), 71(78), 55(88), 41(67); ^{13}C NMR: 15.9(q), 22.4(q), 25.5(t), 26.2(d), 35.4(t), 38.2(d), 42.4(t), 46.0(d), 66.1(t), 66.6(d); ^{1}H NMR: 0.88(d, J=7 Hz, 3H); 1.00(d, J=7 Hz, 3H); 1.13(m, 1H); 1.23(m, 1H); 1.47(m, 1H); 1.57(m, 1H); 1.65(m, 1H); 1.7–1.9(m, 4H); 3.55(m, 1H); 3.70(dd, J_1=11 Hz, J_2=3 Hz, 1H); 4.34(m, 1H); $[\alpha]_D$=+19.8° (c=1.20).

(3*R*,3a*S*,6*R*,7a*S*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7c) and (3*S*,3a*S*,6*R*,7a*S*)-perhydro-3,6-dimethyl-2-benzo[b]furanone (7d). 6.88 g (40 mmol) of crude diols **11c** and **11d** in solution with 20 ml of ethyl acetate were added dropwise within 10 min to 15.15 g (96 mmol) of potassium permanganate in 50 ml of ethyl acetate. The reaction mixture was stirred at room temperature overnight, then hydrolyzed by addition of saturated sodium bisulfite solution, until complete fading. The white precipitate was filtered, the organic layer was washed with brine until pH 7, dried and concentrated to afford 6.34 g of a 20/80 mixture of lactones **7c** and **7d**, from which lactone **7c** was recrystallized in hexane. The lactone **7d** was isolated in pure form from the mother liquor by preparative GC.

7c. NMR: see Tables 1 and 2; MS: 167(1), 139(1), 124(12), 109(18), 95(100), 81(38), 67(70), 55(27), 41(35); IR: 2938, 1806, 1158, 962; e.e.≥99%; $[\alpha]_D$=∓31.3° (c=0.95); mp: 47–48°C.

7d. NMR: see Tables 1 and 2; MS: 167(1), 139(1), 124(13), 109(19), 95(100), 81(55), 67(72), 55(30), 41(38); IR: 2937, 1804, 1161, 969; e.e.≥99%; $[\alpha]_D$=−67.9° (c=1.07); mp: 52–53°C.

The same method was applied on *p*-menthanediol **11a** to give the lactone **7a** and on the diol **11b** to give the lactone **7b**.

(3*R*,3a*S*,6*R*,7a*R*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7a). Oil NMR: see Tables 1 and 2; MS: 167(1), 139(1), 124(4), 109(18), 95(27), 81(100), 67(73), 55(24), 41(30); IR: 2940, 2883, 1808, 1158, 962; e.e.≥99%; $[\alpha]_D$=+121.0° (c=0.7).

(3*S*,3a*S*,6*R*,7a*R*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7b). NMR: see Tables 1 and 2; MS: 167(1), 139(1), 124(6), 109(16), 95(27), 81(100), 67(62), 55(18), 41(17); IR: 2939, 2884, 1809, 1175, 1093, 1006; e.e.≥99%; $[\alpha]_D$=+19.5° (c=1.25); mp: 54–55°C.

(3*R*,3a*R*,6*R*,7a*R*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7e). 1.70 g (70 mmol) of magnesium were added by portions to a solution of 0.83 g (5 mmol) of (−)-mintlactone **1a** (e.e. 97%) in THF (50 ml). The exothermic reaction was maintained near room temperature with a water bath and stirred overnight. Then the reaction mixture was hydrolyzed by a 10% HCl solution and extracted with ether. The organic layer was washed with brine, dried and evaporated. The residue was purified by flash chromatography, which gave 743 mg (88%) of product **7e**.

7e. NMR: see Tables 1 and 2; MS: 169(1), 139(1), 124(3), 109(19), 95(44), 81(100), 67(65), 55(27), 41(32); IR: 2939, 1802, 1169, 1007; e.e.97%; e.e. 97%; $[\alpha]_D$=+45.7° (c=0.9); mp: 55–56°C.

(3*S*,3a*R*,6*R*,7a*R*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7f). 10 g (60 mmol) of (−)-mintlactone **1a** in methanol (40 ml) was hydrogenated with 3 g of Raney nickel under 50 atm. of hydrogen during 3 days at room temperature. An extraction with ether furnished 9.7 g (96%) of lactone **7f**, which was used without further purification.

7f. Oil NMR: see Tables 1 and 2; MS: 167(1), 139(1), 124(10), 109(21), 95(100), 81(55), 67(76), 55(35), 41(44); EI-HR-MS (30 eV): 139.0831 (M^+−29; $C_8H_{11}O_2$; calc 139.0759); IR: 2943, 1803, 1156, 972; e.e. 97%; $[\alpha]_D$=+9.2° (c=1.1).

(1*R*,3*R*,4*R*,8*S*)-3,9-*p*-Menthanediol (11f). 9.7 g (57.7 mmol) of lactone **7f** were added slowly to a cold (0°C) magnetically stirred suspension of 2.2 g (57 mmol) of lithium aluminum hydride in ether (200 ml). The exothermic reaction was maintained near 0°C with an ice bath. When the reaction was finished, it was diluted with ether and hydrolyzed by a small quantity of brine solution. Then the white granular solid was removed by filtration and rinsed with ether. The organic layer was filtered and evaporated to furnish 7.5 g (76%) of *p*-menthanediol **11f**.

11f. MS: 172(1, $M^{+\cdot}$), 154(4), 139(8), 123(28), 112(32), 95(69), 81(100), 71(80), 55(73), 41(44); ^{13}C NMR: 17.3(t); 17.6(q); 21.4(q); 27.4(d); 32.1(t); 38.5(d); 39.1(t); 46.4(d); 64.7(t); 71.3(d); ^{1}H NMR: 0.89(m, 2H); 0.95(d, J=7 Hz, 3H); 1.15(d, J=7 Hz, 3H); 1.30(ddd, J_1=13 Hz, J_2=9 Hz, J_3=4 Hz, 1H); 1.44(m, 1H); 1.53(m, 1H); 1.68(m, 2H); 1.85(m, 2H); 3.40(dd, J_1=8 Hz, J_2=4 Hz, 1H); 3.50(dd, J_1=11 Hz, J_2=8 Hz, 1H); 3.94(m, 1H).

(1*R*,3*R*,4*R*,8*S*)-3-Hydroxy-9-*p*-menthanyl acetate (12) and (1*R*,3*R*,4*R*,8*S*)-3,9-*p*-menthanediyl diacetate (13) 4.8 g of acetic anhydride were added at −5°C to a solution of 8 g (46.7 mmol) of diol **11f** in pyridine (50 ml). The reaction was then stirred overnight at room temperature. Ether was added and the ethereal solution was washed successively with a 10% HCl solution, water and brine, dried over magnesium sulfate and evaporated. The flash

chromatography (eluent: pentane/ether=5/1) of the mixture gave 7.8 g (78%) of acetate **12** and 0.9 g (8%) of diacetate **13**.

12. MS: 171(1), 154(9), 136(15), 121(13), 112(58), 97(52), 81(57), 69(58), 55(53), 43(100); EI-HR-MS (30 eV): 171.1412 (M^+-43; $C_{10}H_{19}O_2$; calc 171.1385); ^{13}C NMR:16.5(q), 21.0(q), 21.2(t), 21.4(q), 28.0(d), 31.1(t), 33.0(d), 39.2(t), 43.3(d), 68.3(t), 70.2(d), 171.5(s); ^1H NMR: 1.27(d, J=7 Hz, 3H), 1.30(d, J=7 Hz, 3H), 1.40(m, 3H), 1.50(m, 1H), 1.55–1.75(m, 3H), 1.82(m, 1H), 1.91(m, 1H), 2.07(s, 3H), 3.94(dd, J_1=11 Hz, J_2=7 Hz, 1H), 4.03(m, 1H), 4.20(dd, J_1=11 Hz, J_2=4 Hz, 1H).

13. MS: 213(<1), 153(12), 136(48), 121(40), 107(75), 93(72), 79(61), 67(27), 55(28), 43(100); ^{13}C NMR: 15.9(q), 20.6(q), 20.9(q), 21.4(q), 21.6(t), 27.5(d), 30.7(t), 33.1(d), 35.4(t), 41.6(d), 67.8(t), 72.3(d), 170.6(s), 171.3(s); ^1H NMR: 0.97(d, J=7 Hz, 3H), 1.02(d, J=7 Hz, 3H), 1.42–1.56(m, 4H), 1.65(m, 2H), 1.7–1.9(m, 3H), 2.04(s, 3H), 2.07(s, 3H), 3.94(dd, J_1=11 Hz, J_2=6 Hz, 1H), 4.15(dd, J_1=11 Hz, J_2=4 Hz, 1H), 5.18(m, 1H).

(1*R*,4*R*,8*S*)-3-Oxo-9-*p*-menthanyl acetate (14). Jones' reagent was added dropwise to a solution of 7.44 g (34.8 mmol) of acetate **12** in acetone (100 ml), until the end of the oxidation (the reaction was followed by TLC). Then the reaction mixture was filtered on celite and evaporated. Ether was added and the solution was washed 3 times with water. Evaporation of ether gave 7.29 g (99%) of pure ketone **14**.

14. MS: 212(1, $M^{+\cdot}$), 169(1), 152(6), 137(11), 123(8), 112(100), 97(17), 69(29), 43(33); ^{13}C NMR: 15.5(q); 20.6(q), 20.9(q), 26.3(t), 29.9(t), 31.6(d), 33.4(d), 48.3(t), 52.7(d), 66.8(t), 171.1(s), 212.6(s); ^1H NMR (benzene): 0.70(d, J=7 Hz, 3H), 0.87(d, J=7 Hz, 3H), 1.15(m, 1H), 1.31(m, 1H), 1.43(m, 1H), 1.54(m, 1H), 1.72(m, 1H), 1.72(s, 3H), 1.87(dd, J_1=13 Hz, J_2=8 Hz, 1H), 2.03(m, 2H), 2.11(dd, J_1=13 Hz, J_2=5 Hz, 1H), 3.93(dd, J_1=10 Hz, J_2=5 Hz, 1H), 4.02(dd, J_1=10 Hz, J_2=4 Hz, 1H).

(1*R*,3*S*,4*R*,8*S*)-3,9-*p*-Menthanediol (11h). 2.9 g (415 mmol) of lithium were added in small portion during 2 h at −60°C into a solution containing 5.78 g (27.3 mmol) of ketone **14**, 33 g (620 mmol) of ammonium chloride in 300 ml of liquid NH_3 and 100 ml of ether. Then the liquid NH_3 was evaporated and 100 ml of ether and 100 ml of water were added. The organic layer was extracted with brine to afford 4.7 g of crude material, containing essentially diols **11f** and **11h** in a 16/84 ratio. The separation of both stereoisomers could be conveniently achieved by a flash chromatography (eluent pentane/ether=1/2) in 87% combined yield.

11h. Oil MS:154(6), 137(11), 123(25), 95(55), 81(100), 67(60), 55(65), 41(45); ^{13}C NMR:12.4(q), 18.7(q), 24.3(t), 28.1(d), 31.1(t), 38.4(d), 41.0(t), 48.8(d), 66.3(d), 66.9(t); ^1H NMR: 0.95(d, J=7 Hz, 3H), 0.98(d, J=7 Hz, 3H), 1.33–1.51(m, 6H), 1.78(m, 2H), 2.07(m, 1H), 3.57(dd, J_1=11 Hz, J_2=4 Hz, 1H), 3.65(dd, J_1=11 Hz, J_2=5 Hz, 1H), 3.70(ddd, J_1=9 Hz, J_2=4 Hz, J_3=4, 1H); $[\alpha]_D$= +8.7° (c=1.09).

(3*S*,3a*R*,6*R*,7a*S*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7h). 3.09 g (18 mmol) of diol **11h** in solution in 8 ml of ethyl acetate were added to 6.92 g (44 mmol) of potassium permanganate in 25 ml of ethyl acetate. The reaction mixture was stirred at room temperature overnight, then hydrolyzed by addition of saturated sodium bisulfite solution, until complete fading. The white precipitate was filtered and the organic layer was washed with brine until pH 7, dried and concentrated to afford 1.97 g of lactone **7h**.

7h. Oil NMR: see Tables 1 and 2; MS: 167(1), 124(3), 109(15), 95(22), 81(100), 67(57), 55(20), 41(15); IR: 2943, 1807, 1186, 989; e.e. 97%; $[\alpha]_D$=71.7° (c=0.8).

(3*R*,3a*R*,6*R*,7a*S*)-Perhydro-3,6-dimethyl-2-benzo[b]furanone (7g). A solution of 0.33 g (2 mmol) of lactone **7h**, 0.064 g (1.2 mmol) of anhydrous sodium methylate in THF (6 ml) was stirred for 4 h at room temperature, then quenched with a 10% HCl solution and extracted with ether. The organic layer was washed with brine, dried and concentrated to afford a 75/25 mixture of lactones **7g** and **7h** in 60% yield. Lactone **7g** was obtained in pure form by preparative GC. This reaction was realized only one time, so the thermodynamic equilibrium between lactones **7g** and **7h** might be slightly different.

7g. NMR: see Tables 1 and 2; MS: 147(1), 140(2), 133(1), 124(3), 109(12), 95(22), 81(100), 67(52), 55(23), 41(18); EI-HR-MS (30 eV): 124.1266 (M^+-44; C_9H_{16}; calc 124.1252); IR: 2940, 1809, 1171, 999; e.e. 97%; $[\alpha]_D$=−9.8° (c=0.92).

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