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Article

Enantioselective Syntheses of the Linden Ethers

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Neste trabalho descrevemos as primeiras sínteses enantiosseletivas de ambos os enantiômeros do éter Linden **(1)**, um monoterpeno natural isolado na forma racêmica a partir do mel e das flores da *Tilia cordata*. Nossa abordagem sintética envolve a α-bromação da isopulegona **(2)**, as ciclizações aos intermediários **(6a)** e **(6b)** mediante sais de tálio (III) e, finalmente, desidratações regiosseletivas.

We describe the enantioselective syntheses of both enantiomers of the Linden ethers **(1)**, a natural monoterpene racemate isolated from the honey and blossoms of the linden lime tree *Tilia cordata*. Our synthetic approach involves α-bromination of isopulegone **(2)**, cyclizations to the intermediates **(6a)** and **(6b)** with thallium (III) salts, and finally regioselective dehydrations, thus providing the first reported syntheses of these unsaturated cyclic ethers.

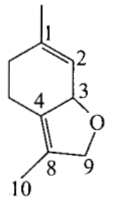
Keywords: *Linden ether, enantioselective syntheses, isopulegone*

Introduction

Linden ether **(1)** is a natural monoterpene racemate isolated from the honey and blossoms of the linden lime tree *Tilia cordata*[1], having a flowery and mint-like smell and thus proposed as an identification indicator for linden honey.

The general structure **(1)** of this monoterpene was proposed by Blank and co-workers[2] based on two dimensional NMR spectroscopy, high resolution MS, as well as hydrogenation experiments, and the nature of the racemic mixture on the basis of GC experiments on achiral and chiral stationary phases.

In connection with our continuing interest in developing methodologies for the construction of α-methylene-γ-butyrolactones and analogues[3a-c], we decided to investigate the enantioselective syntheses of both enantiomers of the linden ethers **(1)**. At the same time these syntheses should lead to versatile intermediates for the construction of both α-methylene-γ-butyrolactones and their endocyclic analogues, which are encountered in a wide variety of natural products with interesting biological activities[4a-e]. As far as we are aware this report presents the first syntheses of the Linden ether enantiomers.



(1)

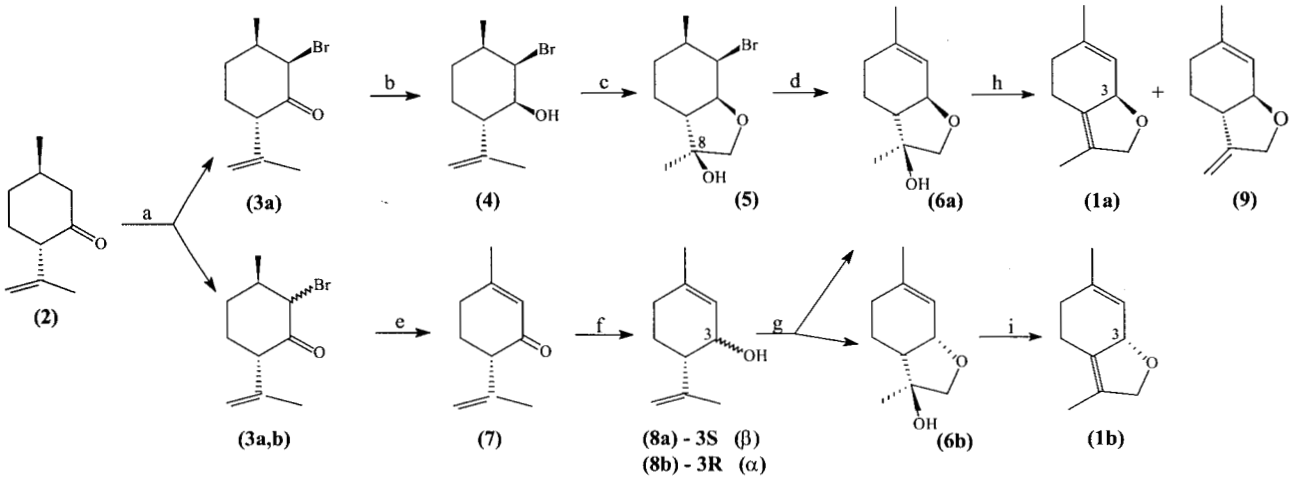
Figure 1. Linden ethers.

Results and Discussions

Our synthetic approach starts from the *p*-menthane monoterpene isopulegone **(2)**, obtained by oxidation[5] of readily available isopulegol, and involves the α-bromination[6,7] of **(2)** and cyclization of intermediates **(4)** and **(8a,b)** with thallium (III) salts[8] (Scheme 1). The key stereoselectivity necessary for generating both enantiomers of linden ether, is obtained either by 3-keto reduction of **(3a)** or in the thallium (III) salt cyclization of **(8a,b)**. Subsequent dehydrations then furnish the desired endocyclic tetrahydrofuran linden ether enantiomers **(1a)** and **(1b)**.

Kinetic deprotonation of **(2)** (LDA, THF, -78 °C) and treatment of the resulting enolate with bromine (1 equiv.)[6,7] in THF provided a mixture of the epimeric α-bromo-ketones, which after separation by column chromatography on silica gel, furnished a 59% yield of the axial bromide **(3a)**, as a yellow oil unstable at room temperature, and a 33% yield of the equatorial bromide **(3b)**, as a white solid also unstable at room temperature.

In the route to linden ether enantiomer **(1a)**, reduction of pure α-bromo-ketone **(3a)** with $NaBH_4$ in MeOH at 0 °C gave a 67% yield of the equatorial α-bromo-alcohol **(4)**, a colourless oil unstable at room temperature, with no trace

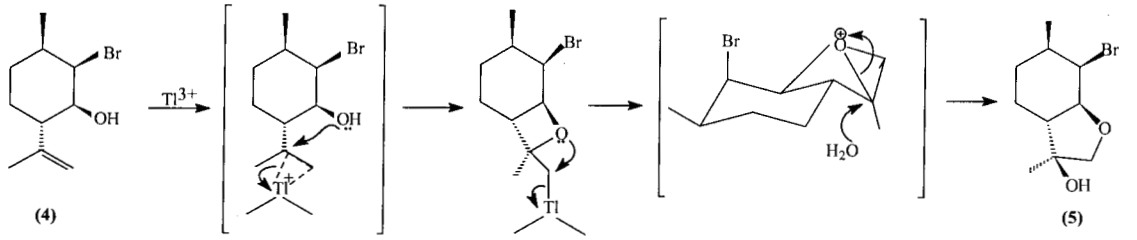


Scheme 1. Reaction conditions: a) LDA, Br_2, THF, -78 °C, 59%(3a), 33%(3b); b) $NaBH_4$, MeOH, 0 °C, 67%; c) $Tl(NO_3)_3$, $AcOH/H_2O$ (1:1), rt, 82%; d) t-BuOK, DMSO, 60 °C, 2 h, 74%; e) Li_2CO_3, LiBr, DMF, rt→85 °C (2 h) → rt (11 h), 65%; f) $LiAlH_4$, Et_2O, 0 °C, 84%; g) $Tl(NO_3)_3$, THF/H_2O(1:1), 0 °C, 3 min, 17% (6a), 26% (6b); h) $SOCl_2$, py, 0 °C, 35 min, 16% (9) and (1a); i) $SOCl_2$, Et_2O, $1\,^1/_2$ h, 28%.

of the stereoisomeric axial α-bromo-alcohol detected by spectroscopy and GC analysis. Thus having established the desired (S) configuration at C-3, cyclization of **(4)** was effected by thallium (III) nitrate trihydrate (TTN) in $AcOH:H_2O$ (1:1, vol/vol) at room temperature[8] leading exclusively in 82% yield to the β-hydroxy-tetrahydrofuran **(5)**, an interesting intermediate with five contiguous stereogenic centres. The (R) configuration at C-8 was proposed on the basis of the cyclization mechanism[8,9], involving initial 4-exo-trig[10] formation of a four membered cyclic oxythallated adduct and dethallation with concomitant oxygen migration (Scheme 2).

Elimination of the axial secondary bromide from **(5)** with $KOBu^t$ in DMSO[11] furnished the unsaturated ether **(6a)** as a colourless oil in 74% yield. Several procedures are available for dehydrating tertiary hydroxyl groups into olefins, as required for transforming **(6a)** into **(1a)**. In our first attempts, **(6a)** was treated with TsOH on SiO_2 in CH_2Cl_2 [12a,b], and while the column chromatography mode gave only starting material, direct contact for three hours furnished a complex mixture. We also tried $SOCl_2$ in Et_2O at room temperature, a specific and efficient methodology for eliminating tertiary hydroxyl groups of β-hydroxy-tetrahydrofuran systems[13]. However these conditions gave only a mixture of products difficult to identify. The dehydration was finally performed with $SOCl_2$ in pyridine[14] at 0 °C for 35 min, affording a mixture of **(1a)** and the isomeric exo-β-methylene-tetrahydrofuran **(9)**. After purification by column chromatography, a mixture of the exo and endo tetrahydrofurans (3:1) was obtained in 16% yield. The structure of **(1a)** was deduced from its ^{1}H-NMR spectrum, and by comparison with the literature values[2], whereas the structure of **(9)** was confirmed by comparison of ^{1}H-NMR spectra with authentic samples of exo-β-methylene-tetrahydrofurans prepared in our laboratory[15].

In the route to linden ether enantiomer **(1b)** the synthesis was carried out with the diastereoisomeric mixture of bromoketones **(3a,b)**. Thus dehydrobromination of **(3a,b)** with a mixture of LiBr and Li_2CO_3 in DMF[16] gave the enone **(7)** in 64% yield after purification by column chromatography. This well known procedure was modified by addition of the lithium salts at room temperature to a solution of **(3a,b)** in DMF, and then the resulting mixture was slowly warmed to 80-90 °C and stirred for 1 h. The mixture was cooled to room temperature and stirred for an additional period of 11 h before isolation.



Scheme 2.

Reduction of enone **(7)** with $LiAlH_4$ in Et_2O at 0 °C led to an 84% yield of pseudo-equatorial alcohol **(8a)** and pseudo-axial alcohol **(8b)** in a 6:4 ratio as proposed by GC and ^{1}H-NMR spectroscopy. All attempts to separate the diastereomers by column chromatography on silica gel were unsuccessful, so the cyclization with thallium salts was carried out on the mixture of **(8a,b)**. Our first attempt to transform **(8a,b)** into **(6b)** was performed using the same conditions employed for the cyclization of α-bromo alcohol **(4)** [1.2equiv TTN in aqueous AcOH (50% vol/vol) at room temperature)]. Under these conditions the yield was only 7% of the unsaturated ether **(6b),** isolated after several purifications. A similar result was obtained when the mixture **(8a,b)** was treated with thallium triacetate (TTA)[8], and therefore we decided to undertake a more complete study of this cyclization and our results are summarized in Table 1.

In all the conditions employed the yields for the cyclization of **(8a,b)** were much lower than those obtained for the bromo-alcohol **(4)**. This fact can be rationalized on the basis of the presence of the C1-C2 double bond in **(8a,b)**, which causes more rigidity thus inhibiting an efficient cyclization. Chromatographic separation of the two β-hydroxy tetrahydrofurans **(6a)** and **(6b)**, as formed in entry 4 in Table 1, permitted definition of their structures based upon the starting material used **(8a,b)** and comparisons with **(6a)** obtained in the sequence leading to **(1a)**. It was possible to compare directly the optical activity, GC behaviour, mass spectra and ^{1}H-NMR spectra of samples from the first route with samples obtained in this route, and convincely show that one product is **(6a)** and therfore the other product must be **(6b)**.

The cyclization reaction and separation thus guarantee the (R) configuration at C-3 in **(6b)** and now requires only the transformation into **(1b)**. Our first approach was to use $TsOH/SiO_2$ in CH_2Cl_2 at room temperature[12] but only a complex mixture of products was obtained. However dehydration of **(6b)** with $SOCl_2$ in Et_2O at room temperature[13] over a period of $1^1/_2$ h gave, after several column chromatography purifications, the desired product **(1b)** in 28% yield. The structure of **(1b)** was confirmed on the basis of the data obtained from the ^{1}H-NMR spectrum, and comparison with the literature values[2].

Conclusion

The syntheses of both enantiomers of the linden ethers **(1a)** and **(1b)** have been effected starting from (-)-isopulegone **(2)**. The absolute configuration at C-1 was transposed to the new stereogenic centre at C-3 by appropriate reductions of the 3-keto function, and the cyclic ether was generated by thallium (III) induced electrophilic attack at the isopropenyl group double bond. Finally, elimination reactions produced the double bonds at C-1 and C-4(8). The syntheses were adversely affected by the instability and volatility of many intermediates, which caused low yields in some of the key reactions. This represents the first reported syntheses of the enantiomers of the linden ethers **(1a)** and **(1b)**, and further work will investigate the optimization of the lower yielding reactions.

Experimental

Melting points were determined on a Micro Química model APF-301 and are uncorrected. Optical rotations were taken on a Perkin-Elmer polarimeter model 241. GC analyses were obtained on a Shimadzu GC-17A chromatograph, equipped with a DB-1 capillary column (0.25 mm i.d. x 30 m), using a 1.5 mL/min H_2 carrier gas flow and a temperature programme from 70 °C (for 1 min) to 250 °C (for 10 min) at 8 °C/min. Column chromatography was performed on silica gel 60 (70-230 mesh ASTM Merck) and flash silica gel 60 (230-400 mesh ASTM Merck). Infrared spectra were recorded with a Bomem Michelson model 102 FTIR spectrophotometer. Low resolution mass spectra (MS) were measured on a Shimadzu GC/MS QP-5000 spectrometer operating at 70 eV. Hydrogen nuclear magnetic resonance spectra (^{1}H-NMR) were recorded in $CDCl_3$ with TMS as an internal standard at 400 MHz on a Bruker ARX-400 spectrometer. The chemical shifts are reported on the δ scale (ppm) downfield from TMS. Carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded in $CDCl_3$ with TMS as an internal standard at 100 MHz on a Bruker ARX-400 spectrometer. The chemical

Table 1. Reaction conditions employed for the cyclization of (8a,b) to (6a,b).

Entry	Reagent/excess	Solvent	Temperature	Time (min)	Yield (%)*	
					(6a)	**(6b)**
1	TTN/20%	$AcOH/H_2O$	r.t	10	---	7
2	TTA/20%	$AcOH/H_2O$	r.t	22	---	4
3	TTN/20%	$AcOH/H_2O$	0 °C	7	9	19
4	TTN/0%	$AcOH/H_2O$	0 °C	5	3	24
5	TTN/0%	THF/H_2O	0 °C	2-3	26	17

*yields after separation by column chromatography.

shifts (ppm) are reported relative to the centre line of the triplet at 77.0 ppm for $CDCl_3$.

*(1R,2R,4S) and (1R,2S,4S)-2-Bromo-8-*p*-Menthenone-3 (**3a,b**)*

Dry THF (7.40 mL) and freshly distilled diisopropylamine (0.34 mL, 2.4 mmol) were placed into a 25 mL two-neck round-bottom flask under nitrogen, cooled to -78 °C, and then n-BuLi (1.64 mL, 2.4 mmol, 1.47 M in hexane) was added with continuous stirring. After 30 min, a solution of isopulegone **(2)** (0.306 g, 2.0 mmol) in dry THF (0.81 mL) was added dropwise (10 min). The reaction mixture was stirred at -78 °C for 30 min, then a solution of bromine (0.1 mL, 2.0 mmol) in dry THF (1.47 mL) at 0 °C was rapidly added to the enolate solution (immediate decolourization). The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and stirred over a period of 15 min. The resulting mixture was washed with saturated NaCl solution (2 x 15 mL) and dried over anhydrous $MgSO_4$. The yellow oil obtained was immediately purified by column chromatography [hexane:ethyl acetate (9:1)] to afford 0.275 g of **(3a)** as a yellow oil (yield: 59%) and 0.153 g of **(3b)** as a white solid (yield: 33%). Both compounds are unstable at room temperature. **(3a)** $[\alpha]_D^{18}$ -25.02° [c. 3.66, $CHCl_3$]; IR (cm^{-1}): 2963, 2929, 1700, 1622, 1449, 1374, 1212, 1109, 1028, 900, 667; MS; *m/z* (rel intensity) 232 (4), 230 (4), 151 (11), 123 (12), 109 (100), 82 (9), 81 (41), 67 (50); ^{1}H-NMR, ($CDCl_3$, 400 MHz) δ 1.12 (d, 3H, J = 6.4 Hz), 1.65-1.69 (m, 1H), 1.76 (s, 3H), 1.78-1.95 (m, 3H), 1.99-2.04 (m, 1H), 3.91 (dd, 1H, J = 12.4, 5.6 Hz), 4.28 (dd, 1H, J = 3.2, 1.2 Hz), 4.78-4.80 (m, 1H), 4.99-5.0 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.54, 21.26, 27.75, 30.57, 38.38, 50.53, 61.66, 113.35, 142.35, 203.93. **(3b)** $[\alpha]_D^{23}$ -0.20° [c. 1.74, $CHCl_3$]; IR (cm^{-1}): 2941, 2869, 1715, 1650, 1449, 1374, 1154, 1030, 898 , 670 ; MS; *m/z* (rel intensity) 232 (1), 230 (2), 151 (10), 123 (9), 109 (100), 82 (8), 81 (35), 67 (50); ^{1}H-NMR, ($CDCl_3$, 400 MHz) δ 1.29 (d, 3H, 6.0 Hz), 1.61-1.65 (m, 1H), 1.77 (s, 3H), 1.82 (dd, 1H, J = 13.4, 3.2 Hz), 2.04-2.12 (m, 3H), 3.08 (dd, 1H, J = 13.2, 5.2 Hz), 4.34 (d, 1H, J = 11.8 Hz), 4.74 (sl, 1H), 4.95 (sl, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.02, 21.13, 30.55, 33.85, 44.36, 57.22, 66.02, 113.30, 142.32, 199.98.

*(1R,2R,3S,4S)-2-Bromo-8-*p*-Menthenol-3 (**4**)*

To a solution of bromo-ketone **(3a)** (0.917 g, 3.97 mmol) in MeOH (39.8 mL), cooled to 0 °C, was slowly added $NaBH_4$ (0.060 g, 1.60 mmol). The reaction mixture was stirred at 0 °C for 30 min. Then the solvent was evaporated in a rotatory evaporator and the residue was dissolved in Et_2O, washed with water, saturated NH_4Cl, saturated NaCl and dried over anhydrous $MgSO_4$. The ether extracts were concentrated and the residual oil was purified by column chromatography on silica gel eluting with hexane:ethyl acetate (9:1) leading to α-bromo-alcohol **(4)**, a colourless oil unstable at room temperature. Yield: 0.620 g (67%). $[\alpha]_D^{23}$ -3.70° [c. 1.85, $CHCl_3$]; IR (cm^{-1}): 3459, 2933, 2862, 1644, 1447, 1379, 1110, 1052, 890; MS; *m/z* (rel intensity) 234 (1), 232 (2), 152 (19), 135 (27), 123 (58), 109 (83), 93 (80), 67 (100); ^{1}H-NMR, ($CDCl_3$, 400 MHz) δ 1.08 (d, 3H, J = 6.4 Hz), 1.35-1.54 (m, 3H), 1.64-1.73 (m, 2H), 1.74 (s, 3H), 2.02 (d, 1H, J = 7.6 Hz), 2.49 (td, 1H, J = 11.2, 4.0 Hz), 3.42 (ddd, 1H, J = 11.2, 7.6, 2.8 Hz), 4.64 (m, 1H), 4.87-4.88 (m, 1H), 4.91 (m., 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.26, 20.65, 27.87, 29.69, 36.30, 47.80, 70.95, 72.29, 113.30, 145.62.

*(1R,2R,3S,4R,8R)-2-Bromo-3,9-Epoxy-*p*-Menthanol-8 (**5**)*

To a solution of the α-bromo-alcohol **(4)** (0.101 g, 0.43 mmol) in aqueous AcOH (1.3 mL, 50% vol/vol), thallium trinitrate trihydrate (0.230 g, 0.52 mmol) was added. A white precipitate was formed, and the mixture was stirred at room temperature for 20 min and then poured into a saturated solution of $NaHCO_3$. The resulting mixture was washed with EtOAc (5 x 20 mL). The organic layer was washed with water, then with saturated NH_4Cl solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude yellow product was purified by chromatography on silica gel, eluting with hexane:ethyl acetate (7:3) to give the β-hydroxy-tetrahydrofuran **(5)** as a white amorphous solid, which was recrystallized from cold hexane. Yield: 0.088 g. (82%). $[\alpha]_D^{23}$ -0.92° [c. 2.17; $CHCl_3$]); m.p.: 101.4-103.7 °C; IR (cm^{-1}): 3452, 2940, 2868, 1453, 1384, 1146, 1027, 955, 795, 648; MS; *m/z* (rel intensity) 248 (1), 169 (12), 151 (13), 109 (31), 95 (100), 81 (24),79 (27); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.08 (d, 3H, J = 6.40 Hz), 1.13-1.24 (m, 1H), 1.30 (s, 3H), 1.35-1.45 (m, 1H), 1.53 (dq, 1H, J = 12.4 Hz), 1.63-1.69 (m, 1H), 1.83 (dq, 1H, J = 12.0, 4.0 Hz), 2.26 (td,1H, J = 12.0, 4 Hz), 3.37 (dd, 1H, J = 12.0, 2.8 Hz), 3.78 (d, 1H, J = 9.20 Hz), 3.92 (d, 1H, J = 9.20 Hz), 4.58 (t, 1H, J = 2.80 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.05, 22.36, 22.50, 28.43, 35.11, 48.52, 63.22, 77.43, 81.06, 83.0.

*(3S,4R,8R)-3,9-Epoxy-1-*p*Menthenol-8 (**6a**)*

Potassium *tert*-butoxide (0.052 g, 0.44 mmol) was added portionwise over a period of 15 min to a solution of the bromide **(5)** (0.086 g, 0.37 mmol) in DMSO (1,63 mL) under nitrogen. The reaction mixture was slowly warmed to 60 °C and then stirred for an additional 1h. The mixture was cooled to room temperature and then quenched by the addition of saturated NH_4Cl solution (15 mL). The resulting mixture was extracted with Et_2O and EtOAc, and the organic layer was washed with water (20 mL), dried over anhydrous Na_2SO_4 and evaporated. The yellow residue was purified by flash chromatography [hexane:ethyl acetate (6:4)] to afford 0.046 g (74%) of the unsaturated ether **(6a)**,

as a colourless oil. $[\alpha]_D^{19}$ -0.94° (c. 4.76, $CHCl_3$); IR (cm^{-1}): 3396, 2911, 1655, 1446, 1378, 1153, 1025, 947, 825, 682; MS; *m/z* (rel intensity) 168 (3), 153(34), 134 (13), 119 (48), 91 (100), 79 (70); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 3H), 1.37-1.45 (m, 1H), 1.67 (s, 3H), 1.83 (ddd, 1H, J = 13.1, 10.5, 2.4 Hz), 1.92 (m,1H), 2.12-2.13 (m, 2H), 2.86 (sl, 1H), 3.76 (d, 1H, J = 9.2 Hz), 3.86-3.89 (m, 1H), 3.95 (d, 1H, J = 9,2 Hz), 5.68 (sl, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.29, 22.50, 22.82, 31.49, 54.19, 77.34, 80.08, 82.17, 122.38, 136.97.

*1,8-*p*-Menthadienone-3 (7)*

A mixture of bromo-ketones **(3a,b)** (0.400 g, 1.73 mmol), Li_2CO_3 (0.338 g, 4.58 mmol) and LiBr (0.258 g, 2.92 mmol) in anhydrous DMF (19 mL) was stirred at 85 °C for 1 h. The mixture was cooled to room temperature and then stirred for a period of 11 h. The reaction was quenched by the addition of saturated NH_4Cl solution (30 mL) and the mixture was extracted with Et_2O (6 x 30 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (4 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated to give a crude product, which was cromatographed on silica gel [hexane:ethyl acetate (9:1)] to give 0.166 g (64%) of **(7)** as a yellow oil. $[\alpha]_D^{24}$ +6.36° [c. 1.64, $CHCl_3$]); IR (cm^{-1}): 2926, 1665, 1438, 1377, 1315, 1198, 1093, 888; MS; *m/z* (rel intensity) 150 (16), 135 (28), 122 (6), 108 (3), 82 (100), 67 (10); 54 (52); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 1.96 (s, 3H), 2.01-2.12 (m, 2H), 2.33-2.34 (m, 2H), 2.96 (dd, 1H, J = 10.6, 5.0 Hz), 4.76 (sl, 1H), 4.95 (sl, 1H), 5.90 (sl, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.63, 24.19, 27.73, 30.35, 53.82, 113.43, 126.62, 143.40, 162.04, 199.14.

*(3R,4S) and (3S,4S)-1,8-*p*-Menthadienol-3 (**8a,b**)*

To a suspension of $LiAlH_4$ (0.626 g, 1.66 mmol) in dry ether (6.6 mL) cooled to 0 °C under nitrogen, was added dropwise during 15 min a solution of enone **(7)** (0.500 g, 3.33 mmol) in dry Et_2O (1.5 mL). Saturated NH_4Cl solution was then added and the resulting mixture was filtered through celite. The filtrate was extracted with Et_2O and the combined ether extracts were washed three times with water and dried over anhydrous $MgSO_4$. The solvent was removed on a rotatory evaporator and the crude product was analysed by gas chromatography and by ^{1}H-NMR spectrum. The ratio of the diastereomeric alcohols **(8a:8b)** is 6:4. The crude product was purified by chromatography on silica gel [hexane:ethyl acetate (9:1)] to give the diastereomeric mixture **(8a,b)** as a colourless oil. Yield: 0.422 g (84%). $[\alpha]_D^{26}$ +11.35° [c. 3.54, $CHCl_3$]; MS; *m/z* (rel intensity) major isomer 152 (1), 134 (37), 119 (44), 94 (4), 91 (100), 83 (20), 79 (21), 67 (11); minor isomer 152 (11), 134 (37), 119 (42), 94 (7), 91 (100), 83 (29), 79 (30), 67 (15); IR (cm^{-1}): 3389, 2908, 1645, 1440, 1242, 1155, 1023, 950, 891; ^{1}H-NMR, ($CDCl_3$, 400 MHz) δ 1.56-1.63 (m, 3H), 1.69 (m, 3H, of 8a), 1.71 (sl, 3H, of 8b), 1.72-1.73 (m, 3H, of 8a), 1.83 (sl, 3H, of 8b), 1.89 (sl, 2H), 1.94-1.95 (m, 1H, of 8a), 2.02-2.12 (m, 6H), 4.10 (m, 1H, of 8b), 4.13 (m, 1H, of 8a), 4.81 (sl, 1H, of 8b), 4.84-4.85 (m, 1H, of 8a), 4.88-4.89 (m, 1H, of 8a), 4.99-5.0 (m, 1H, of 8b), 5.44-5.45 (m, 1H, of 8a), 5.67-5.69 (m, 1H, of 8b); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.24, 22.42, 22.86, 23.24, 20.68, 26.08, 30.01, 30.96, 45.93, 50.63, 63.68, 68.51, 111.45, 112.01, 122.38, 124.36, 136.33, 139.34, 146.33.

*(3S,4R,8R)-3,9-Epoxy-1-*p*-Menthenol-8 (**6a**) and (3R,4R, 8R)-3,9-Epoxy-1-*p*-Menthenol-8 (**6b**)*

To a solution of the allylic alcohols **(8a,b)** (0.200 g; 1.31 mmol) in aqueous THF (4 mL; 50% vol/vol) at 0 °C, thallium trinitrate trihydrate (0.582 g, 1.31 mmol) was slowly added. A white precipitate was formed and the solution turned green. The mixture was stirred at 0 °C for 3 min. and then poured into a saturated solution of $NaHCO_3$ (7 mL). The resulting mixture was extracted with EtOAc (5 x 10 mL). The organic layer was washed with water, then with saturated NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude yellow product was purified by chromatography on silica gel [hexane:ethyl acetate (7:3)] to give **(6a)** as a white amorphous solid and **(6b)** as a colourless oil. Yield: 0.038 g (17%) of **(6a)** and 0.058 g (26%) of **(6b)**. **(6a)** identical optical rotation and ^{1}H- and ^{13}C-NMR spectral data to those of **(6a)** previously obtained from **(5)**. **(6b)** $[\alpha]_D^{22}$ +5.81° (c. 1.30; $CHCl_3$); m.p.: 59.1-61.4 °C; IR (cm^{-1}) 3394, 2950, 2863, 1452, 1371, 1161, 1021, 924; MS; *m/z* (rel intensity) 168 (7), 134 (6), 119 (34), 91 (100), 79 (53); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 3H), 1.57-1.63 (m, 1H), 1.60 (sl, 2H), 1.75 (s, 3H) 1.77-1.83 (m, 2H), 1.90-1.95 (m, 2H), 2.10 (dt, 1H, J = 17.0, 4.8 Hz), 3.61 (d, 1H, J = 9.0 Hz), 3.78 (d, 1H, J = 9.0 Hz), 4.30 (sl, 1H), 5.59 (sl, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.50, 23.68, 25.49, 28.77, 45.86, 75.34, 78.21, 79.15, 120.20, 140.26.

*(3R)-3,9-Epoxy-1,4(8)-*p*-Menthadiene; (R)-Linden Ether (1a) and (3R,4R)-3,9-Epoxy-1,8(10)-*p*-Menthadiene (9)*

To a solution of unsaturated ether **(6a)** (0.245 g, 1.46 mmol) in dry pyridine (3.65 mL) at 0 °C under nitrogen, was slowly added $SOCl_2$ (5.60 mL, previously distilled from quinoline). The reaction mixture was stirred at 0 °C for 35 min, and then quenched by slow addition of ice-water (8 mL) followed by a saturated $NaHCO_3$ solution until pH 7 was obtained. The mixture was extracted with Et_2O (4 x 20 mL) and the combined organic layers were washed with 10% aqueous $CuSO_4$ solution (2 x 15 mL), distilled water (2 x 10 mL) and brine (2 x 20 mL), and then dried over anhydrous $MgSO_4$. After careful evaporation in a rotatory evaporator at ice-water temperature, the yellow residue was

purified by flash chromatography [hexane:ethyl acetate (9.5:0.5)]. Compounds **(9)** and **(1a)** were obtained as a mixture in a 3:1 ratio as determined by GC and ^{1}H-NMR spectroscopy Yield: 0.034 g (16%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 3H, of 1a), 1.55 (s, 3H, of 1a), 1.65 (s, 3H, of 9), 1.79-1.89 (m, 4H), 1.90-1.96 (m, 3H), 2.31-2.37 (m, 1H, of 1a), 2.36-2.40 (m, 1H, of 9), 4.05 (d, 1H, J = 10.05 Hz, of 9), 4.26 (d, 1H, J = 10 Hz, of 9), 4.57 (m, 1H, of 1a), 4,60 (m,1H, of 9) 4.68 (d, 1H, J = 10 Hz, of 1a), 4.74 (d, 1H, J = 2.8 Hz, of 9), 4.76 (d, 1H, J = 3.0 Hz, of 9), 5.25-5.29 (m, 1H, of 1a), 5.53 (sl, 1H, of 9), 5.81 (sl, 1H, of 1a).

*(3S)-3,9-Epoxy-1,4(8)-*p*-Menthadiene; (S)-Linden Ether (**1b**)*

To a solution of unsaturated ether **(6b)** (0.015 g, 0.089 mmol) in dry Et_2O (0.25 mL) at 0 °C under nitrogen, was added dropwise $SOCl_2$ (0.012 mL, previously distilled from quinoline). The reaction mixture was stirred at room temperature for 1 1/2 h and then a saturated $NaHCO_3$ solution was slowly added until pH 7 was obtained. The resulting mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and carefully evaporated in a rotatory evaporator at ice-water temperature. The crude residue was purified by chromatography on silica gel [hexane:ethyl acetate (9.5:0.5)] to give **(1b)** as a yellow oil. Yield: 0.0036 g (28%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 3H), 1.55 (s, 3H), 1.79-1.87 (m, 2H), 1.92-1.95 (m, 1H), 2.31-2.37 (m, 1H), 4.57 (m, 1H), 4.69 (d, 1H, J = 10 Hz), 5.25-5.29 (m, 1H), 5.81 (sl, 1H).

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References

1. Blank, I.; Fischer, K.-H.; Grosch, W. *Z. Lebensm.-Unters.Forsch.* **1989**, *189*, 426.
2. Blank, I.; Grosch, W.; Eisenreich, W.; Bacher, A.; Firl, J. *Helv. Chim. Acta* **1990**, *73*, 1250.
3. (a) Brocksom, T.J.; Ferreira, J.T.B. *Synth.Commun.* **1981**, *11*, 1005. (b) Brocksom, T.J.; Santos, R.B.; Varanda, N.A.; Brocksom, U. *Synth.Commun.* **1988**, *18*, 1403. (c) Ferraz, H.M.C.; Brocksom, T.J.; Pinto, A.C.; Abla, M.A.; Zocher, D.H.T. *Tetrahedron Letters* **1986**, *27*, 811.
4. (a) Miles, D.H.; Lho, D.-S.; La Cruz, A.A.; Gomez, E.D.; Weeks, J.A.; Atwood, J.L. *J.Org.Chem.* **1987**, *52*, 2930. (b) Gören, N.; Bozok-Johansson, C.; Jakupovic, J.; Lin, L.-J.; Shieh, H.-L.; Cordell, G.A.; Çelik, N. *Phytochemistry* **1992**, *31*, 101. (c) Talwar, K.K.; Singh, I.P.; Kalsi, P.S. *Phytochemistry* **1992**, *31*, 336. (d) Ando, M.; Isogai, K.; Azami, H.; Hirata, N.; Yamazaki, H.; Yanagi, Y. *J. Nat. Prod.* **1992**, *55*, 1620. (e) Zhou, B.-N.; Bai, N.-S.; Lin, L.-Z.; Cordell, G.A. *Phytochemistry* **1994**, *36*, 721.
5. Corey, E.J.; Suggs, J.W. *Tetrahedron Letters* **1975**, 2647.
6. Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
7. Stotter, P.L.; Hill, K.A. *J. Org. Chem.* **1973**, *38*, 2576.
8. Ferraz, H.M.C.; Ribeiro, C.M.R.; Grazini, M.V.A.; Brocksom, T.J.; Brocksom, U. *Tetrahedron Letters* **1994**, *35*, 1497.
9. Michael, J.P.; Ting, P.C.; Bartlett, P.A. *J.Org.Chem.* **1985**, *50*, 2416.
10. Baldwin, J.E. *J.Org. Chem.* **1977**, *42*, 3846.
11. (a) Wood, N.F.; Chang, F.C. *J. Org. Chem.* 1965, *30*, 2054; (b) Tanida, H.; Irie, T. *J. Org. Chem.* **1987**, *52*, 5218.
12. (a) D'Onofrio, F.; Scettri, A. *Synthesis* **1985**, 1159; (b) Zarbin, P.H.G., personal communication.
13. Grazini, M.V.A. Ph.D Thesis, Universidade de São Paulo, 1996.
14. Schwartz, A.; Madan, P. *J. Org. Chem.* **1986**, *51*, 5463.
15. Zanotto, P.R.; Pereira, E.C.; Brocksom T.J.; Brocksom U. VII BMOS.
16. Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792.

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