Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4805–4815

TETRAHEDRON: *ASYMMETRY*

Synthesis and characterization of all stereoisomers of 8-phenylmenthol

Franco Fernández,[a] Xerardo García-Mera,[a,*] Carmen López,[a] Gonzalo Rodríguez[b] and José Enrique Rodríguez-Borges[a,†]

[a]*Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, E-15706 Santiago de Compostela, Spain*

[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, E-28048 Madrid, Spain*

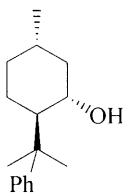
Received 7 November 2000; accepted 15 November 2000

Abstract

New, improved and/or specific syntheses of the diastereoisomers of (−)-8-phenylmenthol are described. The configurations of these products, usable as chiral auxiliaries, were confirmed by X-ray diffractometry of their 3,5-dinitrobenzoates.

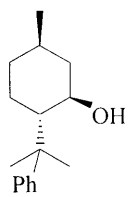
1. Introduction

Since 1975, when Corey[1] used (+)-8-phenylmenthol **1** for the enantioselective synthesis of prostaglandins, this compound and its enantiomer, **2**, have ranked among the most versatile chiral auxiliaries in the armamentarium of asymmetric organic synthesis, being especially useful for face-differentiation.



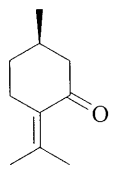
1

(1*S*,2*R*,5*S*)-8-phenylmenthol
(+)-8-phenylmenthol



2

(1*R*,2*S*,5*R*)-8-phenylmenthol
(-)-8-phenylmenthol



3

* Corresponding author. Fax: +00 34 981 59 49 12; e-mail: qoxgmera@usc.es

† Present address: Departamento de Química da Faculdade de Ciências do Porto, Rua do Campo Alegre, 687-4169007 Porto, Portugal.

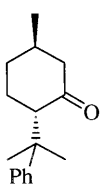
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00454-7

For example, in view of the excellent stereoselectivity of [4+2] cycloaddition reactions of 8-phenylmenthyl enoates, **2** was used to direct intramolecular ene reactions;[2] and this use was later extended by other authors to intermolecular ene reactions between 8-phenylmenthyl glyoxylates and simple alkenes[3] and related cycloadditions.[4]

Oppolzer[5] was the first to describe BF_3-mediated Michael addition of organocopper reagents to enoates of **2**. Likewise in the 1980s, conjugated addition of amines to 8-phenylmenthyl crotonates was achieved with high yield and diastereoselectivity,[6] and excellent stereoselectivity was reported for the addition of Grignard reagents to 8-phenylmenthyl glyoxylates[7a] and their imino derivatives.[7b]

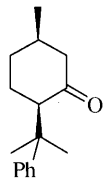
In the 1990s, the use of **2** as a chiral auxiliary was further extended to stereoselective addition of hydride to glyoxylates,[8] addition of organomagnesium reagents to salts of 1-(8-phenylmenthyloxycarbonyl)pyridinium en route to chiral 2-alkyl-2,3-dihydro-4-pyridones,[9] aza-Darzens condensation reactions,[10] asymmetric Horner–Wadsworth–Emmons reactions,[11] [3+2] photocycloaddition of esters to alkenes,[12] stereoselective Birch reduction of pyrroles,[13] and enantioselective aza-Diels–Alder reactions of imines of glyoxylates.[14]

Corey's[1] original syntheses of **1** and **2** involved copper(I)-mediated conjugated addition of phenylmagnesium bromide to the pulegone with the appropriate configuration (e.g. **3** for **2**), treatment of the resulting *trans*/*cis* mixture of ketones with alkaline medium to shift the equilibrium towards the *trans* form (obtaining, for example, 85:15 **4**/**5**), and final reduction with Na/Pr^{i}OH to obtain, as the major product, the equatorial alcohol **2**, which was then purified by chromatography on silica gel,[1] by preparative HPLC,[15] or by fractionated crystallization of its chloroacetate followed by saponification.[16]



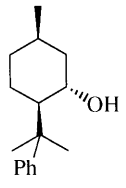
4

(2*S*,5*R*)-8-phenylmenthone
(-)-8-phenylmenthone



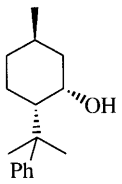
5

(2*R*,5*R*)-8-phenylmenthone
(+)-8-phenyl*iso*menthone



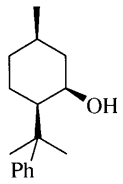
6

(1*S*,2*R*,5*R*)-8-phenylmenthol
(+)-8-phenyl*iso*menthol



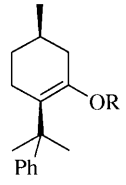
7

(1*S*,2*S*,5*R*)-8-phenylmenthol
(+)-8-phenyl*neo*menthol



8

(1*R*,2*R*,5*R*)-8-phenylmenthol
(-)-8-phenyl*isoneo*menthol



9

a (R = TMS)
b (R = Ac)

Because of the ease of preparation and low cost of (*R*)-(+)-pulegone **3**, use of **2** rapidly became widespread; for example, **2** was the 8-phenylmenthol used in almost all the studies mentioned above. By contrast, use of **1** was hindered by the almost prohibitively high cost of

(*S*)-(−)-pulegone. Seeking to redress the imbalance, Corey[17] also synthesized **1** enantiodivergently from **3**, but this involves seven steps and affords only a 42% overall yield.

It was pointed out by Whitesell[15] in 1986 that the configuration of **1** in the region responsible for chiral induction (C1 and C2) is the same as that of its diastereomer (+)-8-phenyl*iso*menthol **6**, and that **6** therefore ought to exhibit the same effects as **1** when used as a chiral auxiliary, a prediction he verified for Diels–Alder and ene reactions. Similarly, Quinkert[18] hypothesized that (+)-8-phenyl*neo*menthol **7** ought to behave like **1** in certain $S_{cN'}$ cyclopropanation reactions, and successfully used it to prepare a vinylcyclopropane with the configuration opposite to that afforded by the use of **2**, and hence to obtain enantiomerically pure (−)-jasmonate methyl ester. Surprisingly, in spite of **6** and **7** both being considerably less expensive than **1**, as far as we know there have been no further reports on the use of diastereomers of **2** as chiral auxiliaries.[19] This apparent lack of interest is doubtless due to the preparation methods published hitherto having involved the separation of mixtures of isomers by single- or double-stage HPLC (usually followed by Kugelrohr distillation), and to overall yields from commercially available starting materials being only moderate (47%[18] or 66%[19] for **7**; cf. 42% for Corey's[17] synthesis of **1** from **3**) or very low (6% for **6**,[15] 10% for (−)-8-phenyl*isoneo*menthol, **8**[19]).

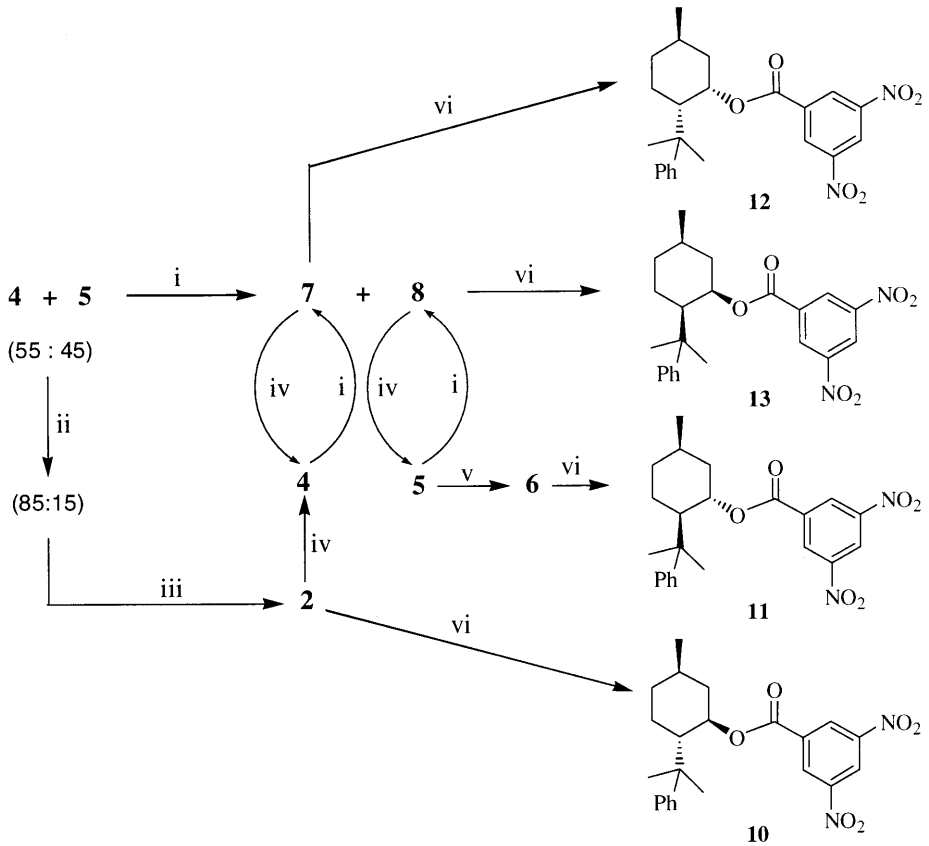
In view of this situation, we embarked on the development of procedures affording better yields of **6**, **7**, and **8**. At the same time, we decided to use X-ray diffraction analysis of crystalline derivatives to confirm the configurations of these compounds, which appear to have been inferred hitherto only on the most plausible but fallible basis of the identities of the starting ketone and the reducing system.

2. Results and discussion

(−)-8-Phenylmenthol **2**,[20] which we initially intended to use only for purposes of comparison, was easily prepared from (*R*)-(+)-pulegone by Ort's[16] modified version of Corey's[1] procedure.

Since reduction of 2-alkylcyclohexanones with L-Selectride affords the corresponding axial alcohols with almost no contaminating equatorial epimer,[19,21] we aimed to obtain **7** and **8** by L-Selectride reduction of (−)-8-phenylmenthone **4** and (+)-8-phenyl*iso*menthone **5**, respectively. All known syntheses of these intermediates start by conjugate addition of phenylmagnesium bromide to pulegone **3**, and give mixtures of **4** and **5** in proportions that depend on the method used to quench the resulting enolate.[15,16,22] The method reported[22] to afford the highest yield of the thermodynamically disfavored epimer, **5**, consists in quenching with trimethylsilyl chloride, isolation of the trimethylsilylenolether **9a**, and treatment of **9a** with 40% HF/MeCN. In our hands, however, this method did not give the reported[22] 50:50 mixture of **4** and **5**, but a 70:30 mixture. An even worse result was achieved when we tried using acetyl chloride instead of trimethylsilyl chloride and subjecting the resulting enol intermediate **9b** to alkaline saponification; this afforded **4** and **5** in 85:15 ratio, the same as is obtained when mixtures of **4** and **5** are equilibrated by treatment with KOH/EtOH. In view of these results, following Ort,[16] we finally quenched the enolate with 2N HCl, obtaining **4** and **5** in 55:45 ratio. Reduction of this mixture with L-Selectride afforded a mixture of the desired axial alcohols **7** and **8** which was cleanly resolved by column chromatography (SiO_2), both compounds being obtained in 40% yield with respect to the starting pulegone. For the low-melting solid **8** this is a considerable improvement over the 10% achieved by the only other published synthesis.[19]

With **2**, **7**, and **8** in hand we found that their oxidation with CrO_3–pyridine afforded good yields of the corresponding ketones **4** and **5** with no contaminating epimer. As reported previously in a preliminary communication,[23] this allowed **7** to be obtained in 87% yield from pulegone **3** via **2** and **4** (Scheme 1), which is to date the most efficient known route to this product.



Scheme 1. Reagents: (i) L-Selectride. (ii) KOH/EtOH; Na, ^{i}PrOH. (iii) PhMgBr, CuCl; AcCl. (iv) CrO_3, py. (v) Na, ^{i}PrOH. (vi) 3,5-Dinitrobenzoyl chloride

As described above, the axial alcohol **8** is obtained without contaminating epimer by L-Selectride reduction of **5**. By contrast, all available methods for reducing **5** to the equatorial alcohol **6** without contamination by **8** involve conditions that induce the prior or competitive isomerization of **5** to the thermodynamically favored epimer **4**, which naturally results in yields of **6** being very poor. We have nevertheless somewhat improved the yield of **6** with respect to starting pulegone **3** from 6%[15] to 21% (calculated for pure **6** following chromatographic separation of a mixture of four 8-phenylmenthols) by reducing pure **5** with Na/Pr^{i}OH in boiling toluene.

The preparation of pure **4** and **5** allowed them to be characterized for the first time as pure compounds; in Section 3 we present their optical activities and IR and ^{1}H and ^{13}C NMR spectra. The 8-phenylmenthols **2**, **6**, **7**, and **8** were characterized not only in terms of their optical activities and IR and ^{1}H and ^{13}C NMR spectra, but also by studies of the respective 3,5-dinitrobenzoates **10**–**13**, including X-ray diffraction studies of **11**–**13** that confirmed the

iconfigurations of **6**–**8** (Figs. 1–3). In **11**–**13** the cyclohexane ring is a more or less distorted chair with the bulky $C(Me)_2Ph$ group equatorial, which makes the O equatorial and the C5 Me axial in **11** and **6**, the O axial and the C5 Me equatorial in **12** and **7**, and the O and C5 Me both axial n **13** and **8**. It is of interest that the ester and phenyl groups of **11** and **12** are close together,

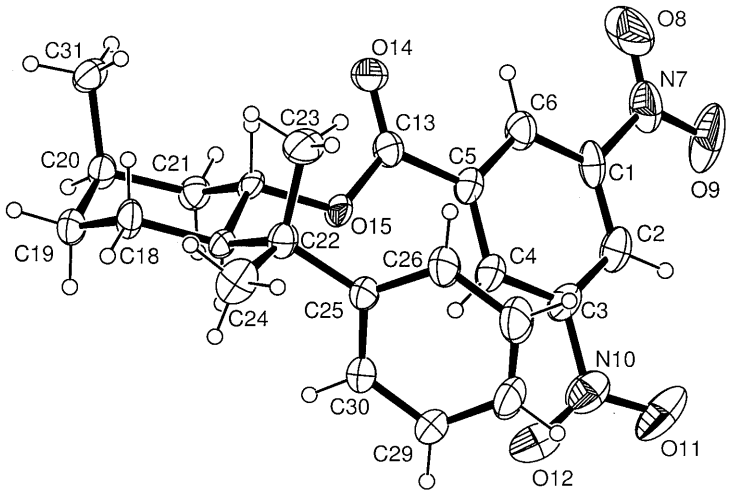


Figure 1. (+)-8-Phenyl*iso*menthol 3,5-dinitrobenzoate **11**

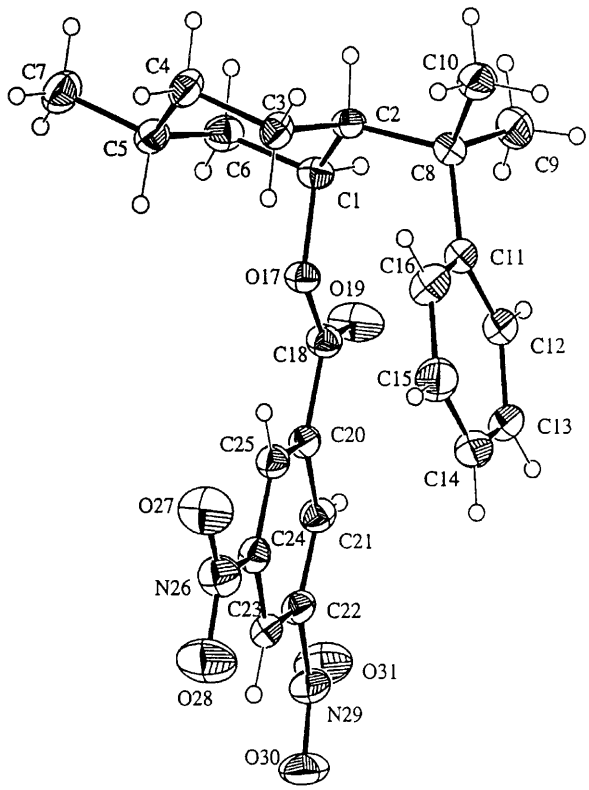


Figure 2. (+)-8-Phenyl*neo*menthol 3,5-dinitrobenzoate **12**

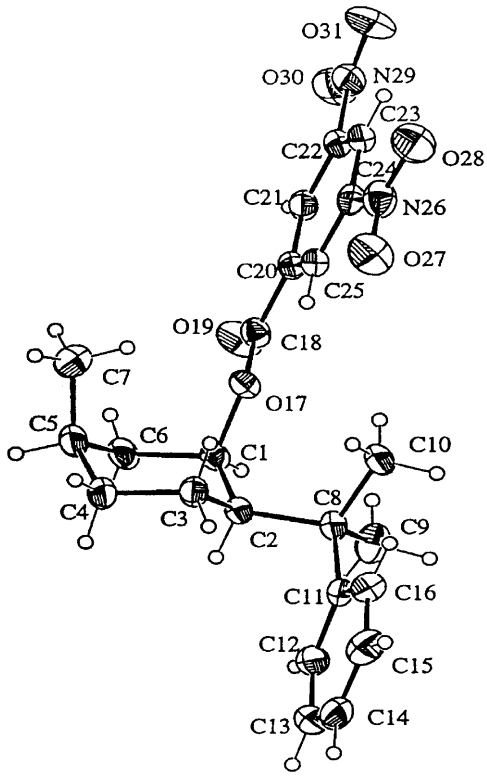


Figure 3. (–)-8-Phenyl*isoneo*menthol 3,5-dinitrobenzoate **13**

since if the same holds in the analogues used in chiral synthesis (e.g. the acrylate or glyoxylate derivatives of **6** and **7**) it would allow the π-stacking interactions that have often been invoked as responsible for the stereoselectivity of the reactions of 8-arylmenthols. By contrast, the phenyl and ester groups of **13** point in opposite directions, which would prevent π-stacking.

Although NMR data for the 8-phenylmenthols have already been published in the papers reporting their various syntheses, we present here data for **2**, **6**, **7**, and **8** that, having been obtained under identical conditions, allow more rigorous comparisons to be made. The salient features of the ^{1}H NMR spectra are the methyl and C1 proton signals. In those of **2** and **6**, in both of which the OH group is equatorial, the geminal methyls appear 0.12 ppm apart, a much greater difference than the 0.02 ppm found in the cases of **7** and **8**, in which OH is axial. Also, the C1 proton signal of **2** appears 0.21 ppm from that of **6**, whereas those of **7** and **8** appear at practically the same position. As expected, the C1 proton signals of **2** and **6** are triplets ($J \geq 10$ Hz) of doublets ($J \approx 4$ Hz) due to two *trans*-diaxial *anti* vicinal couplings and an axial–equatorial *gauche* vicinal coupling, whereas those of **7** and **8** appear as the envelope of an unresolved multiplet due to three *gauche* vicinal couplings (two equatorial–axial and one equatorial–equatorial). The C5 methyl protons are more shielded in **2**, in which this group is equatorial, than in **6**, in which it is axial; and are similarly more shielded in **7** than in **8**, although the strong deshielding in **8** is largely attributable to the 1,3-diaxial steric interaction between the methyl and the OH group.

3. Experimental

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. Observed rotations at the Na-D line were determined at 23°C in a Perkin–Elmer 241 polarimeter. Infrared spectra were recorded in a Perkin–Elmer 681 spectrophotometer. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded in a Bruker WM spectrometer, using TMS as the internal reference (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed in a Perkin–Elmer 240B element analyzer by the Microanalysis Service of the University of Santiago. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC data on pre-coated silica gel plates (Merck 60 F254, 0.25 mm). Crystallographic data were obtained with a Seifert XRD 3000S diffractometer.

*3.1. (1*S,*2*S,*5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol* **7** *and (1*R,*2*R,*5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexanol* **8**

A 55:45 mixture of diastereomers **4** and **5** of the crude product (8.00 g), obtained by copper(I)-catalyzed addition of PhMgBr to (*R*)-(+)-pulegone (5.13 g; 33.7 mmol),[16] was dissolved in dry THF and added dropwise with a syringe to an L-Selectride solution (52 mL, 1.0 M in THF; 52 mmol) at 0°C. The reaction mixture was stirred at 0°C for 4 h, at which point aqueous 3 M NaOH (18 mL; 54 mmol) was added dropwise followed by slow addition of 30% H_2O_2 (18 mL, 180 mmol). The solution was stirred for 30 min at room temperature and extracted with Et_2O (4×30 mL). The combined organic phases were washed with water (2×20 mL) and dried (Na_2SO_4). The solvent was removed, giving a mixture of **7** and **8** (7.68 g) as an oil that was resolved by flash chromatography (220 g SiO_2; 9:1 hexane:AcOEt). Compound **8** (3.13 g; 40%) was the first to elute, followed by **7** (3.11 g; 40%); both were colorless oils with no alien signals in their ^{1}H and ^{13}C NMR spectra. Compound **8** crystallized spontaneously upon standing for a few days at room temperature.

*3.1.1. (1*S,*2*S,*5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol* **7**

$[\alpha]_D^{23}$ +34.0 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3464, 3087, 3056, 2946, 1600, 1495, 1446, 1386, 1148, 1093, 1031, 1003, 964, 771, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.84 (d, 3H, J=6.18 Hz, 5-CH_3), 0.88–1.11 (m, 2H), 1.38 and 1.40 (2s, 6H, 8-$(CH_3)_2$), 1.43–1.76 (m, 6H), 3.86 (a.s., 1H, 1_{eq}-H), 7.16–7.21 (q, 1H, J=7.13, 5.92, 1.21 Hz, 4′-H), 7.26–7.33 (m, 2H, 3′-H+5′-H), 7.37–7.40 (m, 2H, 2′-H+6′-H). ^{13}C NMR ($CDCl_3$): 21.75 (C-3), 22.63 (C-7), 26.26 (C-9), 26.53 (C-5), 28.05 (C-10), 36.06 (C-4), 40.60 (C-8), 44.26 (C-6), 52.71 (C-2), 68.62 (C-1), 125.92 (C-4′), 126.59 (C-2′+C-6′), 128.42 (C-3′+C-5′), 150.31 (C-1′). Anal. calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41; found: C, 82.47; H, 10.69.

*3.1.2. (1*R,*2*R,*5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol* **8**

Mp 28–30°C. $[\alpha]_D^{23}$ −4.2 (*c* 0.5, $CHCl_3$). IR (film) ν_{max}: 3586, 3489, 2945, 2908, 1601, 1497, 1381, 1186, 1120, 1032, 959, 768, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.91 (a.s., 1H, $\omega_{1/2}$=7.7 Hz), 1.13 (d, 3H, J=7.41 Hz, 5-CH_3), 1.40 and 1.42 (2s, 6H, 8-$(CH_3)_2$), 1.35–1.64 (m, 6H), 1.72–1.81 (t×d, 1H, J_t=12.49 Hz, J_d=3.53 Hz), 1.86–1.90 (m, 1H), 3.85 (a.s., 1H, $\omega_{1/2}$=8.8 Hz, 1_{eq}-H), 7.17–7.22 (m, 1H, 4′-H), 7.29–7.34 (m, 2H, 3′-H+5′-H), 7.39–7.41 (m, 2H, 2′-H+6′-H). ^{13}C NMR ($CDCl_3$): 16.85 (C-3), 21.69 (C-7), 26.01 (C-9), 26.86 (C-5), 28.14 (C-10), 33.18 (C-4), 40.81

(C-8), 40.85 (C-6), 53.04 (C-2), 69.54 (C-1), 125.90 (C-4′), 126.62 (C-2′+C-6′), 128.40 (C-3′+C-5′), 150.27 (C-1′). Anal. calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41; found: C, 82.98; H, 10.71.

3.2. Preparation of 8-phenylmenthones by Sarett oxidation

3.2.1. (2S,5R)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanone **4**

To a solution of pyridine (24.9 g; 311 mmol) in CH_2Cl_2 (260 mL) at 0°C was added CrO_3 (15.48 g; 155 mmol; portionwise addition) followed by a solution of **2** (6.00 g; 25.8 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at 0°C for 45 min, filtered through Celite, and washed with Et_2O (4×90 mL). The pooled organic phases were concentrated to half volume, washed with water (100 mL) and brine (100 mL), and dried (Na_2SO_4). Evaporation of the remaining solvent left an oil (6.4 g) that was purified by column chromatography (210 g SiO_2; 9:1 hexane:AcOEt), giving **4** (5.47 g; yield 93%) as a colorless oil with no alien signals in its ^1H and ^{13}C NMR spectra. Application of the same procedure to **7** instead of **2** afforded a 91% yield of **4**. $[\alpha]_D^{23}$ −49.1 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 2953, 2870, 1709, 1600, 1446, 1364, 1205, 770 cm^{-1}. ^1H NMR ($CDCl_3$): 0.97 (d, 3H, $J=6.22$ Hz, 5-CH_3), 1.41 and 1.47 (2s, 6H, 8-$(CH_3)_2$), 1.50–1.89 (m, 5H), 1.91–2.06 (m, 1H, 6-H), 2.22–2.27 (m, 1H, 6-H), 2.61–2.70 (m, 1H, 2-H), 7.13–7.37 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$): 22.73, 24.43, 26.91, 29.45, 35.09, 36.69, 39.43 (C-8), 52.76, 59.94, 125.91 (C-4′), 126.16 (C-2′+C-6′), 128.38 (C-3′+C-5′), 150.31 (C-1′), 211.92 (C-1). Anal. calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63; found: C, 83.80; H, 9.33.

3.2.2. (2R,5R)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanone **5**

Application of the above procedure to **8** (6.00 g; 25.8 mmol) afforded **5** (5.71 g; 96%) as a colorless oil with no alien signals in its ^1H and ^{13}C NMR spectra. $[\alpha]_D^{23}$ +86.6 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 2953, 2870, 1709, 1600, 1446, 1364, 1205, 770 cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (d, 3H, $J=7.08$ Hz, 5-CH_3), 1.43 and 1.48 (2s, 6H, 8-$(CH_3)_2$), 1.50–2.25 (m, 7H), 2.44–2.52 (m, 1H, 2-H), 7.10–7.40 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$): 19.70, 24.28, 25.29, 27.61, 31.64, 32.63, 38.89 (C-8), 50.68, 60.08, 126.02 (C-4′), 126.31 (C-2′+C-6′), 128.41 (C-3′+C-5′), 149.78 (C-1′), 212.96 (C-1). Anal. calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63; found: C, 83.57; H, 9.42.

3.3. Preparation of 8-phenylmenthols by reduction of pure 8-phenylmenthones with L-Selectride

3.3.1. (1S,2S,5R)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol **7**

Reduction of **4** (3.50 g; 15.2 mmol) with L-Selectride following the procedure described above in Section 3.1 afforded **7** (3.14 g; yield 89%), with the same spectral data as reported in Section 3.1.

3.3.2. (1R,2R,5R)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol **8**

Reduction of **5** with L-Selectride following the procedure described above in Section 3.1 afforded **8** (yield 92%) as a colorless oil that crystallized spontaneously upon standing. Spectral data as reported in Section 3.1.

3.4. Preparation of 8-phenylmenthols by reduction of pure 8-phenylmenthone **5** *with Na/Pr^{i}OH*

A solution of **5** (3.62 g; 15.7 mmol) in 2-propanol (3.6 mL, 2.83 g; 47 mmol) was added dropwise to a stirred suspension of Na (1.08 g; 47 mmol) in boiling toluene (140 mL). The

resulting mixture was stirred and refluxed until the Na dissolved (ca. 3 h), cooled to 0°C, and carefully treated with 2 M HCl (18 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (2×100 mL). The combined organic layers were washed with brine (2×100 mL) and dried (Na_2SO_4), and the solvent was removed leaving an oil (3.66 g), that upon column chromatography (130 g SiO_2; 9:1 hexane:Et_2O) successively afforded **8** (0.37 g; 10%), **7** (0.18 g; 5%), **2** (2.06 g; 56%) and **6** (0.76 g; 21%).

*3.4.1. (1*R,*2*S,*5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol* ***2***

$[\alpha]_D^{23}$ −25.3 (*c* 0.5, $CHCl_3$). IR (film) ν_{max}: 3561, 3412, 2951, 2918, 1599, 1494, 1456, 1387, 1370, 1095, 1055, 1030, 1001, 763, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.81–1.12 (m, 4H), 0.91 (d, 3H, $J=6.50$ Hz, 5-CH_3), 1.32 and 1.45 (2s, 6H, 8-$(CH_3)_2$), 1.34–1.50 (m, 1H), 1.62–1.77 (m, 3H), 1.87 (d×t, 1H, $J_d=12.4$ Hz, $J_t=3.74$ Hz, $J_d=2.35$ Hz), 3.55 (t×d, $J_t=11.94$ Hz, $J_d=3.61$ Hz, 1_{ax}-H), 7.18–7.23 (m, 1H, 4′-H), 7.31–7.44 (m, 4H, 2′-H+3′-H+5′-H+6′-H). ^{13}C NMR ($CDCl_3$): 22.46 (C-7), 25.01 (C-3), 26.97 (C-9), 28.94 (C-5), 31.96 (C-10), 35.34 (C-4), 40.26 (C-8), 45.58 (C-6), 54.59 (C-2), 73.35 (C-1), 126.19 (C-4′), 126.23 (C-2′+C-6′), 128.84 (C-3′+C-5′), 151.75 (C-1′). Anal. calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41; found: C, 82.35; H, 10.71.

*3.4.2. (1*S,*2*R,*5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol* ***6***

$[\alpha]_D^{23}$ +11.5 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3566, 3402, 3087, 3057, 2921, 1601, 1495, 1444, 1380, 1343, 1155, 1061, 1031, 1014, 972, 763, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.93 (d, 3H, $J=7.22$ Hz, 5-CH_3), 1.31 and 1.43 (2s, 6H, 8-$(CH_3)_2$), 1.20–1.55 (m, 5H), 1.61–1.77 (m, 2H), 1.97–2.05 (m, 1H), 3.72–3.80 (d×t, $J_t=9.70$ Hz, $J_d=4.32$ Hz, 1_{ax}-H), 7.15–7.21 (m, 1H, 4′-H), 7.29–7.34 (m, 2H, 3′-H+5′-H), 7.38–7.41 (m 2H, 2′-H+6′-H). ^{13}C NMR ($CDCl_3$): 19.08 (C-7), 21.65 (C-3), 24.91 (C-9), 28.06 (C-5), 28.83 (C-10), 31.88 (C-4), 40.30 (C-8), 42.24 (C-6), 55.39 (C-2), 69.18 (C-1), 126.18 (C-4′+C-2′+C-6′), 128.80 (C-3′+C-5′), 150.70 (C-1′). Anal. calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41; found: C, 83.03; H, 10.53.

3.5. Preparation of 8-phenylmenthyl 3,5-dinitrobenzoates: general procedure

A mixture of the appropriate 8-phenylmenthol (300 mg; 1.29 mmol), 3,5-dinitrobenzoyl chloride (320 mg; 1.39 mmol; freshly crystallized from CCl_4), dry Et_3N (0.20 mL, 145 mg; 1.43 mmol), DMAP (10 mg), and dry THF (20 mL) was refluxed for 5 h under argon, with stirring, cooled, and washed with saturated aqueous $NaHCO_3$ solution (3×50 mL) and brine (80 mL). The organic layer was drawn off and dried (Na_2SO_4), and removal of the solvent left an oil that was purified by column chromatography (SiO_2; 9:1 hexane:AcOEt).

*3.5.1. (1′*R,*2′*S,*5′*R*)-2′-(1-Methyl-1-phenylethyl)-5′-methylcyclohexyl 3,5-dinitrobenzoate* ***10***

Yield 86%. Mp 116–119°C (cyclohexane–ether). $[\alpha]_D^{23}$ −175.2 (*c* 1.0, $CHCl_3$). IR (KBr) ν_{max}: 3111, 2958, 1725, 1654, 1627, 1544, 1495, 1458, 1342, 1276, 1173, 1074, 730, 720, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.93–0.95 (d, 3H, $J=6.47$ Hz, 5′-CH_3), 1.03–1.11 (m, 2H), 1.17 and 1.32 (2s, 6H, 8′-$(CH_3)_2$), 1.55–1.61 (m, 2H), 1.79–1.91 (m, 2H), 2.07–2.12 (m, 2H), 2.30–2.38 (m, 1H), 5.16–5.23 (d×t, 1H, $J_t=10.72$ Hz, $J_d=5.38$ Hz, $1'_{ax}$-H), 6.55–6.60 (m, 1H, 4″-H), 6.89–6.95 (m, 2H, 3″-H+5′-H), 7.19–7.22 (d, 2H, $J_d=8.03$ Hz, 2″-H+6″-H), 8.41–8.42 (d, 2H, $J=2.20$ Hz, 2-H+6-H), 9.05–9.07 (t, 1H, $J_t=4.28$ Hz, $J_d=2.20$ Hz, 4-H). ^{13}C NMR ($CDCl_3$): 21.43 (C-7′), 22.16 (C-5′), 26.44 (C-3′), 31.62 (C-9′), 31.79 (C-10′), 34.80 (C-4′), 39.70 (C-8′), 42.06 (C-6′), 50.69 (C-2′), 76.82 (C-1′), 122.15 (C-4), 124.68 (C-4″), 125.36 (C-2″+C-6″), 128.40 (C-3″+C-5″),

129.44 (C-2+C-6), 134.10 (C-1), 148.41 (C-1″), 152.65 (C-3+C-5), 161.65 (C(O)). Anal. calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15; N, 6.57; found: C, 64.56; H, 6.01; N, 6.39.

*3.5.2. (1′*S*,2′*R*,5′*R*)-2′-(1-Methyl-1-phenylethyl)-5′-methylcyclohexyl 3,5-dinitrobenzoate* ***11***

Yield 87%. Mp 126–128°C (cyclohexane–ether). $[\alpha]_D^{23}$ +164.0 (*c* 1.0, $CHCl_3$). IR (KBr ν_{max}: 3090, 2970, 1717, 1654, 1627, 1549, 1458, 1343, 1280, 1168, 1076, 730, 718, 705 cm^{-1}. ^1H NMR ($CDCl_3$): 1.06–1.08 (d, 3H, $J=7.28$ Hz, 5′-CH_3), 1.19 and 1.35 (2s, 6H, 8′-$(CH_3)_2$), 1.52–1.69 (m, 5H), 1.87–1.93 (m, 1H), 2.10–2.20 (m, 1H), 2.30–2.38 (m, 1H), 5.38–5.46 (d×t, 1H, $J_t=10.31$ Hz, $J_d=5.08$ Hz, $1'_{ax}$-H), 6.57–6.62 (m, 1H, 4″-H), 6.91–6.96 (m, 2H, 3″-H+5″-H), 7.21–7.25 (m, 2H, 2″-H+6″-H), 8.44–8.45 (d, 2H, $J=2.21$ Hz, 2-H+6-H), 9.18–9.19 (t, 1H, $J_t=4.25$ Hz, $J_d=2.18$ Hz, 4-H). ^{13}C NMR ($CDCl_3$): 18.54 (C-7′), 21.35 (C-3′), 21.77 (C-5′), 28.21 (C-9′), 31.24 (C-10′), 31.51 (C-4′), 39.01 (C-6′), 39.92 (C-8′), 51.47 (C-2′), 73.98 (C-1′), 122.14 (C-4), 124.77 (C-4″), 125.47 (C-2″+C-6″), 128.40 (C-3″+C-5″), 129.45 (C-2+C-6), 134.17 (C-1), 148.42 (C-1″), 152.39 (C-3+C-5), 161.61 (C(O)). Anal. calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15; N, 6.57; found: C, 64.98; H, 6.34; N, 6.70.

*3.5.3. (1′*S*,2′*S*,5′*R*)-2′-(1-Methyl-1-phenylethyl)-5′-methylcyclohexyl 3,5-dinitrobenzoate* ***12***

Yield 77%. Mp 139–140°C (cyclohexane–ether). $[\alpha]_D^{23}$ +116.8 (*c* 1.0, $CHCl_3$). IR (KBr ν_{max}: 3112, 2954, 1719, 1654, 1629, 1548, 1497, 1457, 1342, 1276, 1170, 1119, 1072, 730, 718, 705 cm^{-1}. ^1H NMR ($CDCl_3$): 0.83–0.86 (d, 3H, $J=7.56$ Hz, 5′-CH_3), 1.02–1.25 (m, 2H), 1.36 and 1.41 (2s, 6H, 8′-$(CH_3)_2$), 1.58–1.99 (m, 6H), 5.45 (a.s., 1H, $1'_{eq}$-H), 6.88–6.93 (t, 1H, 4″-H), 7.08–7.13 (t, 2H, 3″-H+5′-H), 7.23–7.25 (d, 2H, $J=7.48$ Hz, 2″-H+6″-H), 8.82–8.83 (d, 2H, $J=2.12$ Hz, 2-H+6-H), 9.17–9.18 (t, 1H, $J_t=4.23$ Hz, $J_d=2.11$ Hz, 4-H). ^{13}C NMR ($CDCl_3$): 22.29 (C-3′), 23.26 (C-7′), 26.30 (C-5′), 27.51 (C-9′), 27.88 (C-10′), 35.65 (C-4′), 40.19 (C-6′), 40.34 (C-8′), 52.19 (C-2′), 74.27 (C-1′), 122.47 (C-4), 125.76 (C-4″), 126.63 (C-2″+C-6″), 128.40 (C-3″+C-5″), 129.52 (C-2+C-6), 134.80 (C-1), 148.40 (C-1″), 148.87 (C-3+C-5), 161.71 (C(O)). Anal. calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15; N, 6.57; found: C, 64.93; H, 6.19; N, 6.36.

*3.5.4. (1′*R*,2′*R*,5′*R*)-2′-(1-Methyl-1-phenylethyl)-5′-methylcyclohexyl 3,5-dinitrobenzoate* ***13***

Yield 74%. Mp 160–161°C (cyclohexane–ether). $[\alpha]_D^{23}$ −102.4 (*c* 1.0, $CHCl_3$). IR (KBr ν_{max}: 3093, 2981, 2953, 2905, 1721, 1631, 1598, 1542, 1497, 1458, 1382, 1343, 1274, 1172, 1115, 1072, 923, 730, 719, 703 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92–0.94 (d, 3H, $J=7.38$ Hz, 5′-CH_3), 1.37 and 1.42 (2s, 6H, 8′-$(CH_3)_2$), 1.58–2.07 (m, 8H), 5.40 (a.s., 1H, $1'_{eq}$-H), 6.90–6.95 (t, 1H, 4″-H), 7.08–7.13 (t, 2H, 3″-H+5′-H), 7.22–7.25 (d, 2H, 2″-H+6″-H), 8.83–8.84 (d, 2H, $J=2.18$ Hz, 2-H+6-H), 9.18–9.19 (t, 1H, $J_t=4.15$ Hz, $J_d=2.19$ Hz, 4-H). ^{13}C NMR ($CDCl_3$): 18.17 (C-3′), 21.16 (C-7′), 26.29 (C-5′), 27.72 (C-9′), 27.91 (C-10′), 32.40 (C-4′), 36.97 (C-6′), 40.34 (C-8′), 52.35 (C-2′), 74.75 (C-1′), 122.47 (C-4), 125.78 (C-4″), 126.63 (C-2″+C-6″), 128.39 (C-3″+C-5″), 129.52 (C-2+C-6), 134.73 (C-1), 148.39 (C-1″), 148.92 (C-3+C-5), 161.74 (C(O)). Anal. calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15; N, 6.57; found: C, 64.95; H, 6.41; N, 6.38.

Acknowledgements

The authors would like to thank the Spanish Ministry of Education and Science (MEC-DGICYT, PB94-0617) and the Xunta de Galicia (XUGA 20307B94) for financially supporting this work.

References

1. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
2. Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta* **1980**, *63*, 2015.
3. Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.
4. Binger, P.; Brinkmann, A.; Richter, W. J. *Tetrahedron Lett.* **1983**, *24*, 3599.
5. Oppolzer, W.; Loher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808.
6. D'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.
7. (a) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988; (b) Ermert, P.; Meyer, J.; Stucki, C.; Schnecbeli, J.; Obrecht, J. P. *Tetrahedron Lett.* **1988**, *29*, 1265.
8. Solladie-Cavallo, A.; Bencheqroun, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1165.
9. Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.
10. Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K.; Hiraga, Y.; Kojima, S.; Okhata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 689.
11. Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284.
12. Kubo, Y.; Yoshioka, M.; Nakajima, S.; Inamura, I. *Tetrahedron Lett.* **1999**, *40*, 2335.
13. Donohoe, T. J.; Guyo, P. M.; Helliwell, M. *Tetrahedron Lett.* **1999**, *40*, 435.
14. Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; López, C.; Rodríguez, G.; Rodríguez-Borges, J. E.; Rodríguez-Hergueta, A. *Tetrahedron Lett.* **1998**, *39*, 5663.
15. Whitesell, J. K.; Lin, C.-L.; Buchanan, C. M.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551.
16. Ort, O. *Org. Synth.* **1987**, *65*, 203.
17. Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610.
18. Quinkert, G.; Schwalz, H. G.; Dzierzynski, E. M.; Dürner, G.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 992.
19. Compound **7** has been used as a building block for preparation of the chiral ligand of an organometallic complex: Halterman, R. L.; Vollhardt, P. C. *Organometallics* **1988**, *7*, 883.
20. Compound **2** is now commercially available from Aldrich (Product Number 32,948-7) and Fluka (Product Number 78805).
21. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
22. Potin, D.; Dumas, F. *Synth. Commun.* **1990**, *20*, 2805.
23. Caamaño, O.; Fernández, F.; García-Mera, X.; Rodríguez-Borges, J. E. *Tetrahedron Lett.* **2000**, *41*, 4123.