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Stereoselective synthesis of (6*R*)- and (6*S*)-diosphenol and Ψ-diosphenol

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Abstract—Methods are discussed for the stereoselective synthesis of the (*R*)-and (*S*)-enantiomers of the diosphenols (**5**)–(**8**) by utilizing the commercially available stereoisomers (**9**), (**12**), (**23**) and (**25**) of carvone and limonene, respectively, as chiral starting materials. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

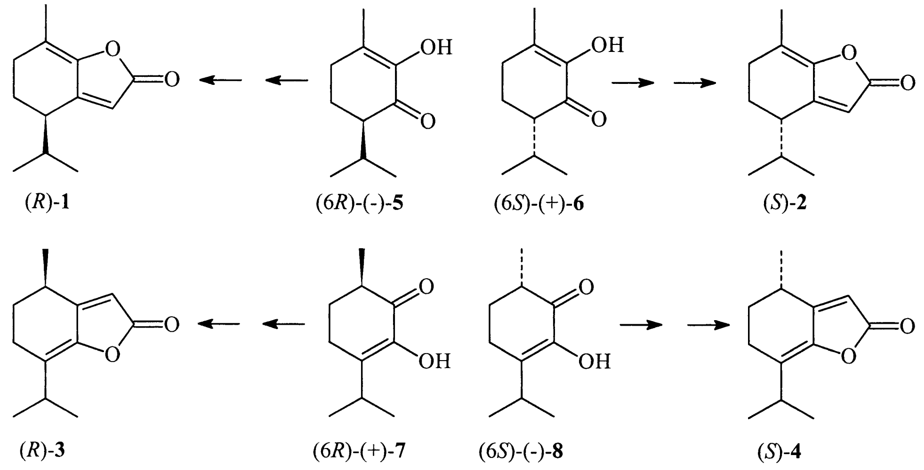
As part of a research program directed at the stereoselective synthesis of the annulated 5-alkylidene butenolides (**1**)–(**4**), the synthesis of the diosphenols (6*R*)-(**5**), (6*S*)-(**6**), (6*R*)-(**7**) and (6*S*)-(**8**) as chiral starting materials became necessary (Scheme 1).

2. Results and discussion

We initially elected to utilize commercially available (5*S*)-(+)-carvone (**9**) ($[\alpha]_D^{20}=+56.0$, neat) and (5*R*)-(−)-carvone (**12**) ($[\alpha]_D^{20}=-61.0$, neat) as potential chiral precursors for the stereoselective synthesis of the two enantiomers (**5**) and (**6**) of diosphenol. Our envisioned synthetic plan comprised the selective reduction of (**9**) to yield an expected mixture of the (2*R*,5*S*)-(**10**) and (2*S*,5*S*)-(**11**) diastereomers of carvomenthone, followed by bromination and alkaline hydrolysis[1,2] of the diastereomeric carvomenthones to produce the desired (6*R*)-diosphenol (**5**) (Scheme 2).

The synthesis of (6*S*)-diosphenol (**6**) may be conducted in a similar fashion via the intermediacy of the diastereomeric carvomenthones (**13**) and (**14**) by utilizing (5*R*)-carvone (**12**) as starting material.

Various authors have studied the selective reduction of racemic carvone to produce either carvotanacetone,[3] dihydrocarvone[4,5] or carvomenthone[6] depending on the reaction conditions employed. Petrier and Luche[7] published



Scheme 1.

Keywords: terpenoids; stereoselection; reduction; regioselection.

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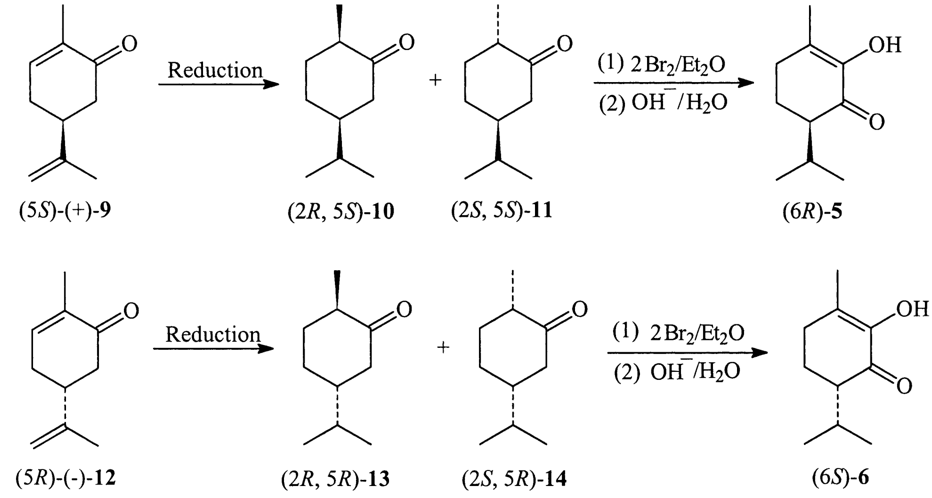
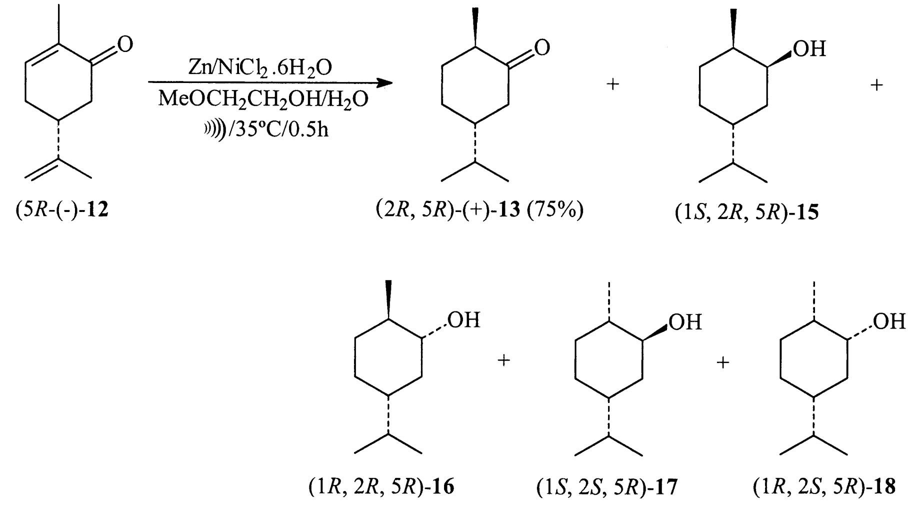


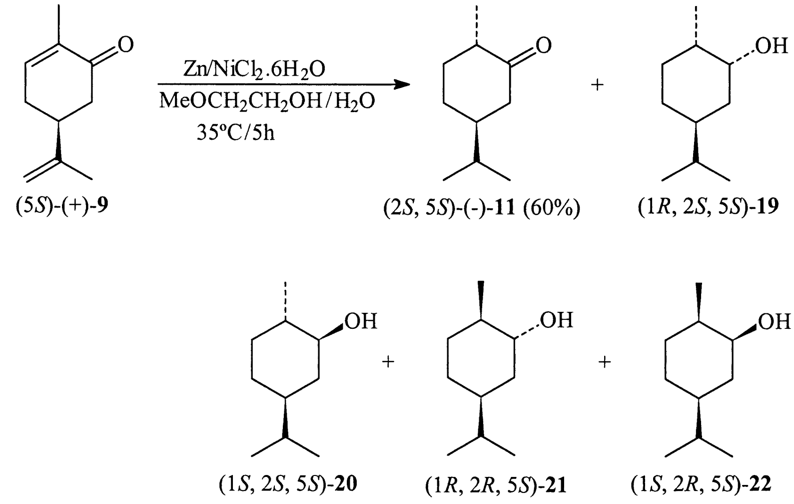
Scheme 2.

an efficient procedure for the selective reduction of (5*R*)-(**12**) by a mixture of zinc dust and nickel chloride hexahydrate in aqueous medium to produce carvomenthone of unspecified stereoisomeric composition and purity in 96% isolated yield. These authors also found that the reduction process could substantially be accelerated by sonication of the reaction mixture.[7,8] Application of this method to the selective reduction of (5*R*)-carvone (**12**) led in our hands to somewhat different results and a detailed investigation was consequently conducted to determine the optimum reaction conditions. In contrast to the published data[7] we found that repetition of the reduction of (**12**) under similar reaction conditions, yielded a reaction product which comprised a mixture of (2*R*,5*R*)-(**13**) (70%) and the four diastereomeric carvomenthols (**15**)–(**18**) in a combined yield of 9% according to gas chromatographic analysis. The reduction was also significantly accelerated by applying pulsed ultrasonic energy at different vibrational amplitudes to the reaction mixture from a tunable 300 W Vibracell high intensity ultrasonic processor. Optimum conditions for the selective reduction of (5*R*)-carvone (**12**) to (2*R*,5*R*)-(**13**)(75%) were eventually found to be pulsed ultrasonic irradiation (60% pulse, amplitude 4) of the reaction mixture for only 30 min. Although separation of the initially expected diastereomeric mixture of carvomenthones (**13**) and (**14**) as reduction products could not be achieved under the gas chromatographic conditions employed, the ^{13}C NMR spectrum of the reduction product (**13**), however, exhibited only 10 sharp lines which demonstrated the stereoisomeric homogeneity of the isolated (2*R*,5*R*)-carvomenthone (**13**). Since the specific rotation of the synthesized carvomenthone ($[\alpha]_D^{20}=+11.1$, neat) is in reasonable agreement with published values for (2*R*,5*R*)-(+)-carvomenthone (**13**) ($[\alpha]_D^{20}=+13.3$),[9,10] it can be concluded that the reduction of (5*R*)-(−)-carvone (**12**) with zinc dust and nickel chloride hexahydrate proceeded in a highly stereoselective fashion to yield (**13**) as the sole stereoisomer of carvomenthone (Scheme 3).

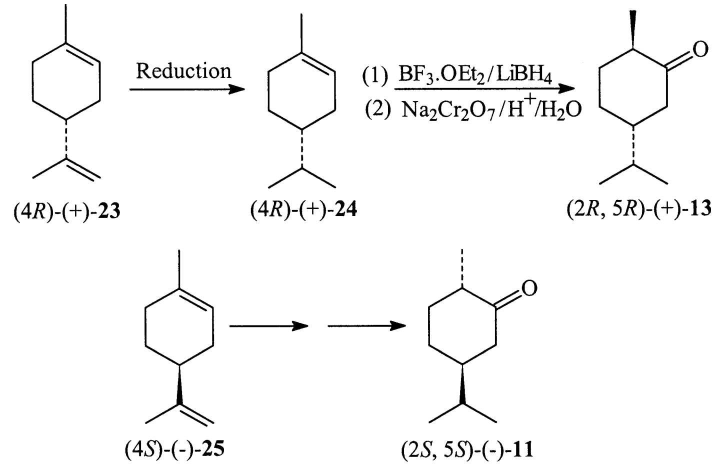
Reduction of (5*S*)-carvone (**9**) with zinc dust and nickel chloride hexahydrate again proceeded stereoselectively to yield after column chromatographic separation (2*S*,5*S*)-(−)-carvomenthone (**11**) (60%, $[\alpha]_D^{20}=-8.9$, neat), and a mixture of the four diastereomeric carvomenthols (**19**)–(**22**) in a combined yield of 21% according to gas chromatographic and ^{13}C NMR analysis. In order to eliminate the



Scheme 3.



Scheme 4.



Scheme 5.

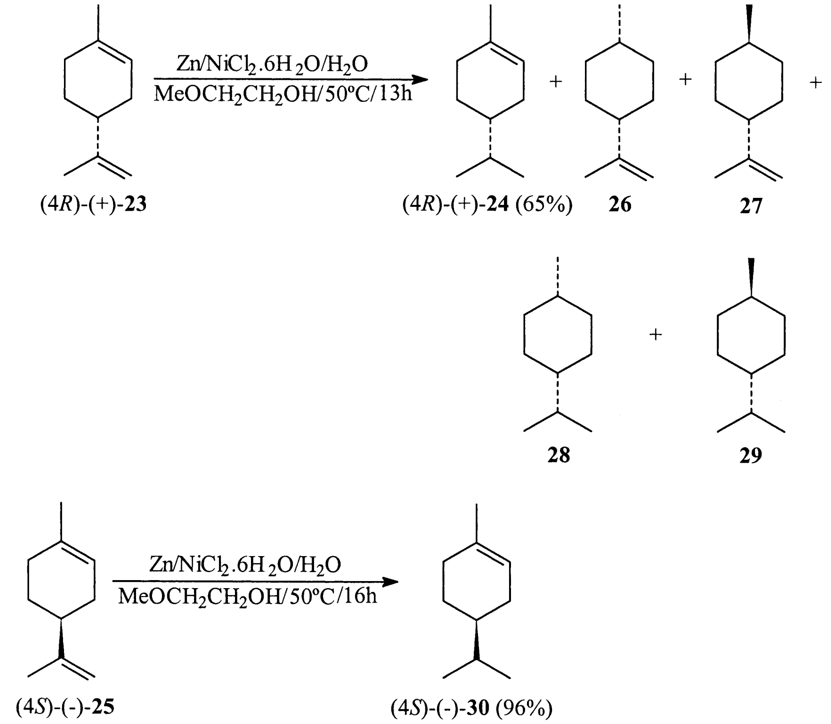
cumbersome column chromatographic separation which we had to adopt to purify the synthetic carvomenthones (**11**) and (**13**) from small amounts of carvomenthols as contaminants, we eventually resorted to commercially available (4*R*)- and (4*S*)-limonene (**23**) and (**25**), respectively, as starting materials for the synthesis of the desired carvomenthones (Schemes 4 and 5).

Selective reduction of (4*R*)-limonene (**23**) followed by hydroboration and oxidation[11] may produce (2*R*,5*R*)-carvomenthone (**13**), while utilization of (4*S*)-limonene (**25**) may likewise yield (2*S*,5*S*)-carvomenthone (**11**).

In order to evaluate the applicability of the zinc dust and nickel chloride hexahydrate combination for the regioselective reduction of both the enantiomers (**23**) and (**25**), a systematic study was accordingly undertaken to optimize yields and reaction conditions. It was eventually found that the selective reduction of (**23**) proceeded very efficiently when vigorous stirring of the reaction mixture was maintained for 13 h at 50°C, and a second portion of activated zinc dust and nickel chloride hexahydrate was introduced to the reaction flask after 9 h. Gas chromatographic analysis of the reaction product obtained under these conditions revealed the presence of desired (4*R*)-*p*-menthene (**24**), as well as four additional peaks in the chromatogram of very low intensity and with slightly shorter retention times than (**24**). These four peaks may be attributed to the presence of diastereomeric mixtures of partially hydrogenated and fully saturated minor reaction products (**26**)–(**29**) (Scheme 6).

The corresponding (4*S*)-enantiomer (**30**) of *p*-menthene was similarly synthesized by utilizing (4*S*)-limonene (**25**) as chiral starting material. Examination of the gas chromatogram of the reaction product again revealed the presence of four additional peaks of very low intensity, which may likewise be ascribed to the formation of the corresponding two pairs of (4*S*)-diastereomers in very small quantities as a result of further reduction of (4*S*)-*p*-menthene (**30**) under the reaction conditions employed.

Hydroboration of (4*R*)-*p*-menthene (**24**) and subsequent oxidation of the intermediate organoborane produced a

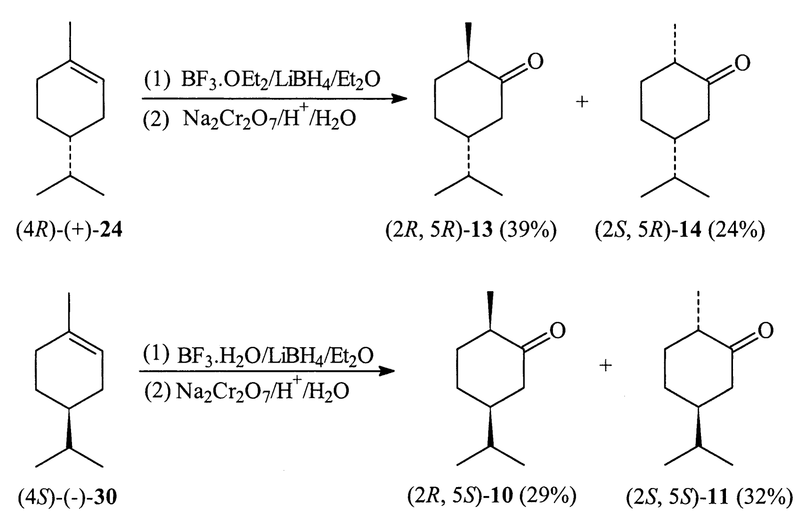


Scheme 6.

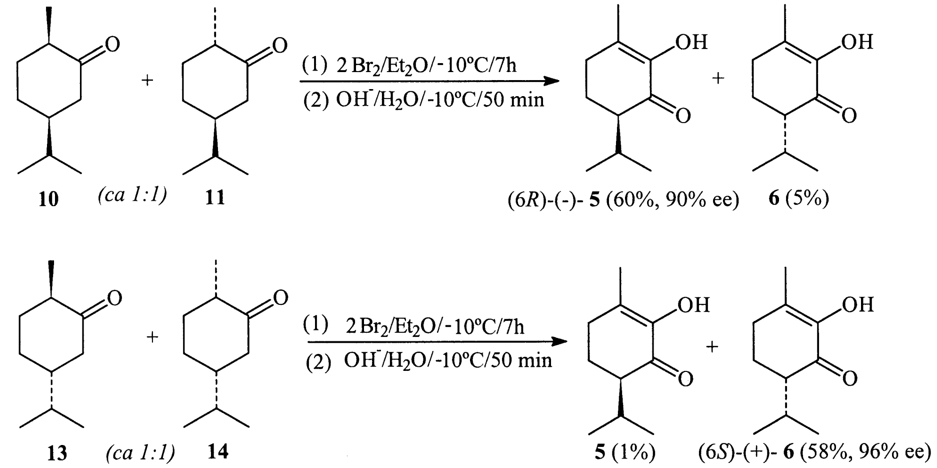
mixture of the desired diastereomers (**13**) and (**14**) of carvomenthone which could be purified and isolated in reasonable yield. Similar treatment of (4*S*)-*p*-menthene (**30**) gave a mixture of the expected diastereomers (**10**) and (**11**) of carvomenthone. The diastereomeric composition of the reaction products could accurately by determined from the relative intensities of the resonance lines of the respective carbonyl groups in the ^{13}C NMR spectra of the diastereomeric mixtures, as a consequence of the equal relaxation times of the similar carbonyl functionalities. The validity of this ^{13}C NMR analytical method was furthermore confirmed by gas chromatographic analysis of the diastereomeric mixtures on a chiral TM-β-CD OV 1701-OH column (Scheme 7).

In the final step of our planned stereoselective synthesis of the (*R*)-enantiomer (**5**) of diosphenol, a mixture of the diastereomers (**10**) and (**11**) of carvomenthone was brominated and subsequently hydrolyzed with aqueous alkali under carefully controlled conditions. This experimental procedure led to the formation of (6*R*)-diosphenol (**5**) ($[\alpha]_D^{20}=-52.9$, $c=10$, EtOH) with 90% ee (Scheme 8).

Similar bromination and alkaline hydrolysis of a mixture of the diastereomers (**13**) and (**14**) yielded (6*S*)-diosphenol (**6**) ($[\alpha]_D^{20}=+56.4$, $c=10$, EtOH) with 96% ee. The enantiomeric composition of the reaction products was determined by separation on a Chiralcel OB-H HPLC column.



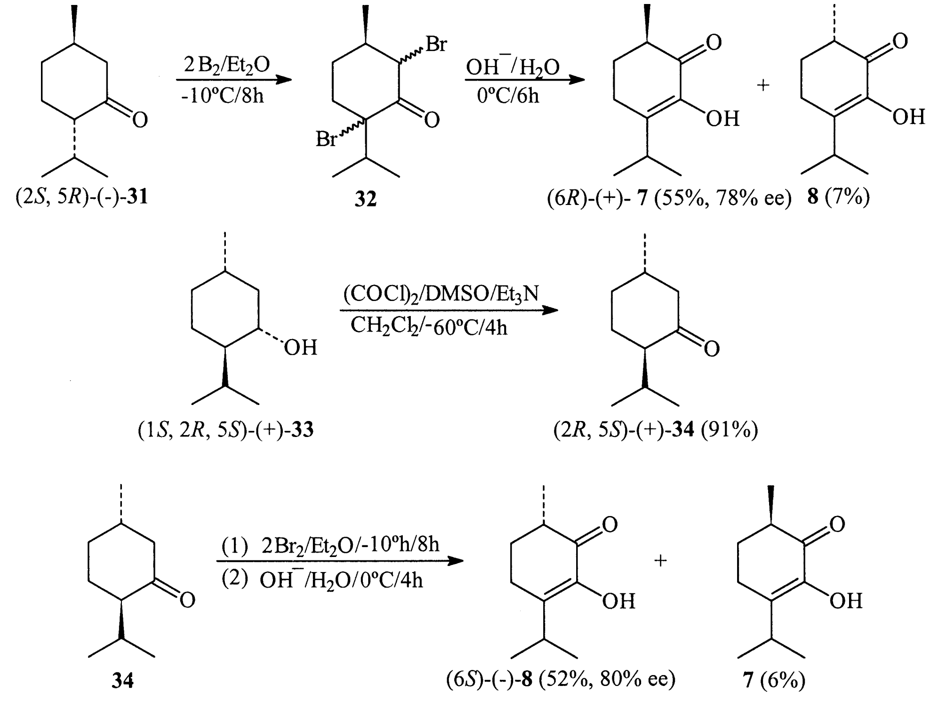
Scheme 7.



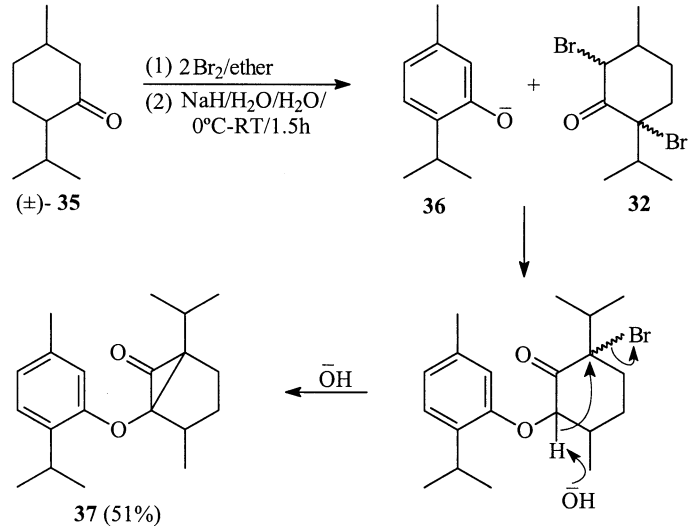
Scheme 8.

The stereoselective synthesis of (6*R*)-Ψ-diosphenol (**7**) was conducted by utilizing commercially available (2*S*,5*R*)-(−)-menthone (**31**) ($[\alpha]_D^{20}=-24$, neat)[12] as starting material, which contained 5% of the corresponding (2*R*,5*R*)-diastereomer, isomenthone ($[\alpha]_D^{20}=+93.8$, neat),[13] as an impurity. Bromination of (**31**), followed by alkaline hydrolysis of the intermediate dibromo compound (**32**) as before, led to the selective formation of (6*R*)-(**7**) ($[\alpha]_D^{25}=+106.5$, $c=1$, EtOH) with 78% ee. The presence of (2*R*,5*R*)-isomenthone as an optical impurity in the starting material (**31**), had of course no negative effect on the stereochemical outcome of the synthesis since the chiral centre at C2 is lost in the chemical transformation.

As the synthesis of (6*S*)-Ψ-diosphenol (**8**) required the use of commercially unavailable (2*R*,5*S*)-(+)-menthone (**34**), the latter was synthesized in high yield by the oxidation[14] of (1*S*,2*R*,5*S*)-(+)-menthol (**33**) ($[\alpha]_D^{23}=+48$, $c=10$, EtOH). Bromination of (**34**) and subsequent alkaline hydrolysis selectively yielded (6*S*)-(**8**) ($[\alpha]_D^{23}=-102.4$, $c=10$, EtOH) in 80% ee. The enantiomeric purity of the synthetic (6*R*)- and (6*S*)-Ψ-diosphenols (**7**) and (**8**) was once again accurately monitored by implementing the versatile Chiralcel OB-H HPLC column. In an effort to accelerate the reaction and in the process minimize contact time of the reaction product with alkali, the dibromo compound (**32**) derived from racemic menthone (**35**) was exposed to a highly active, finely divided suspension of sodium hydroxide, which was generated by treatment of oil-free sodium hydride in THF with an equivalent amount of water. Under these conditions the reaction took a completely different course and the cyclopropanone derivative (**37**) was produced instead. The formation of (**37**) under these reaction conditions most probably resulted from



Scheme 9.



Scheme 10.

nucleophilic coupling between the intermediately generated phenolate (**36**) and the dibromo compound (**32**), followed by a Favorskii-type elimination[15] (Schemes 9 and 10).

3. Experimental

3.1. General

All operations were carried out in an argon atmosphere. Merck silica gel 60 (particle size 0.063–0.200 mm) and 60PF 254 with calcium sulphate were used for column chromatography and separations on the chromatotron, respectively. NMR spectra were recorded in deuteriochloroform on a Varian VXR 300 instrument, while mass spectra were taken on a Varian MAT 311A spectrometer. COSY, HETCOR and DEPT experiments were performed to interpret more complex NMR spectra. Chiral compositions of reaction products were determined by GC and HPLC separations on chiral stationary phases.

3.1.1. Partial reduction of (5*R*)-(−)-carvone (12). A suspension of zinc dust (5.04 g, 77.1 mmol), nickel chloride hexahydrate (2.12 g, 8.9 mmol) and (5*R*)-(−)-carvone (**12**) (2.0 g, 13.3 mmol) in a mixture of water (15 cm^3) and 2-methoxyethanol (15 cm^3) was subjected to pulsed ultrasonic irradiation (tunable Vibracell high intensity ultrasonic processor, 60% pulse, amplitude 4, 120 W, 20 kHz) for 30 min at 35°C in a specially designed thick wall glass container. The reaction mixture was then filtered, diluted with saturated, aqueous ammonium chloride (40 cm^3) and extracted with ether (3×20 cm^3). After repetition of the preceding synthetic procedure, gas chromatographic analysis (7% Carbowax on Chromosorb B, temp. prog. 150–170°C at the rate of 1.5°C/min, inlet pressure 100 kPa N_2) of the residue from the combined ether extracts revealed the presence of (2*R*,5*R*)-(+)-carvomenthone (**13**) (3.06 g, 75%), and a small quantity of the four diastereomeric carvomenthols (**15**)–(**18**) (0.2 g, 5%). Column chromatographic separation of the reaction product on silica gel yielded upon elution with ether–petroleum ether (2:3) pure *(2R,5R)-(+)-carvomenthone* (**13**) (2.29 g, 56%) as a light yellow oil, bp 40°C (air-bath temp.)/0.24 mmHg (lit.[16] 218–219°C/705 mmHg); $[\alpha]_D^{20}=+11.1$(neat);[9,10] δ_H 0.89 (d, J=6.5 Hz, 3H, CH_3), 0.90 (d, J=6.5 Hz, 3H, CH_3), 1.01 (d, J=6.5 Hz, 3H, CH_3), 1.30 (‘qd’, J=12.7 and 3.3 Hz, 1H, CH_aH_b), 1.44 (qdd, J=12.4, 3.1 and 1.2 Hz, 1H, CH_aH_b), 1.49–1.62 (m, 2H, $CHCH_aH_b$), 1.86 (‘d quint.’, J=11.9 and 2.6 Hz, 1H, CH_aH_b), 2.04–2.14 (m, 2H, $CHCH_aH_b$), 2.33 (d sept. J=1.4 and 6.5 Hz, 1H, $CH(CH_3)_2$), 2.40 (ddd, J=12.9, 3.1 and 2.3 Hz, 1H, CH_aH_b); δ_C 14.37 (q, CH_3), 19.36 (q, CH_3), 19.62 (q, CH_3), 28.93 (t, CH_2), 32.78 (d, CH), 35.13 (t, CH_2), 44.92 (d, CH), 45.41 (t, CH_2), 46.61 (d, CH), 213.59 (s, >C=O); M^+, 154.1356. Calcd for $C_{10}H_{18}O$: M, 154.1357.

Elution with ether–petroleum ether (1:1) subsequently afforded a mixture of the four diastereomeric carvomenthols (**15**)–(**18**) (0.15 g, 4%), bp 75°C (air-bath temp.)/0.32 mmHg; δ_C 10.57 (q, CH_3), 17.54 (q, CH_3), 18.33 (q, 2×CH_3), 18.38 (q, CH_3), 19.59 (q, 2×CH_3), 19.75 (q, 3×CH_3), 19.91 (q, 2×CH_3), 22.58 (t, CH_2), 25.17 (t, CH_2), 27.37 (t, CH_2), 28.22 (t, CH_2), 29.12 (t, CH_2), 29.17 (t, CH_2), 30.69 (t, CH_2), 32.44 (t, CH_2), 32.50 (d, CH), 32.62 (d, CH), 33.33 (t, CH_2), 33.88 (d, CH), 34.15 (t, CH_2), 36.40 (d, CH), 36.51 (d, 2×CH), 37.03 (t, CH_2), 38.97 (t, CH_2), 40.32 (d, CH), 43.18 (d, CH), 71.27 (d, CH), 72.36 (d, CH), 73.10 (d, CH), 76.80 (d, CH); M^+, 156.1514. Calcd for $C_{10}H_{20}O$: M, 156.1514.

3.1.2. Partial reduction of (5*S*)-(+)-carvone (9). To a stirred suspension of zinc dust (7.56 g, 115.6 mmol) and nickel chloride hexahydrate (3.15 g, 13.3 mmol) in a mixture of water (25 cm^3) and 2-methoxyethanol (25 cm^3) was added (5*S*)-(+)-carvone (**9**) (3.0 g, 20.0 mmol) and the resulting mixture stirred for 5 h at 35°C. The reaction mixture was then worked up and extracted as in Section 3.1.1 and the residue from the ether extract chromatographed on silica gel. Elution with ether–petroleum ether (1:4) yielded pure *(2S,5S)-(−)-carvomenthone* (**11**) (1.85 g, 60%) as a light yellow oil, bp 110°C (air-bath temp.)/15 mmHg (lit.[12] 219°C/705 mmHg); $[\alpha]_D^{20}=-8.9$ (neat);[9,12] δ_H 0.89 (d, J=6.5 Hz, 3H, CH_3), 0.90 (d, J=6.5 Hz, 3H, CH_3), 1.01 (d, J=6.5 Hz, 3H, CH_3), 1.30 (qd, J=12.7 and 3.3 Hz, 1H,

$\mathrm{CH_aH_b}$), 1.44 (qdd, J=12.4, 3.1 and 1.2 Hz, 1H, $\mathrm{CH_aH_b}$), 1.49–1.62 (m, 2H, $\mathrm{CHCH_aH_b}$), 1.86 ('d quint.', J=11.9 and 2.6 Hz, 1H, $\mathrm{CH_aH_b}$), 2.04–2.14 (m, 2H, $\mathrm{CHCH_aH_b}$), 2.33 (d sept., J=1.1 and 6.5 Hz 1.4 Hz, 1H, $\mathrm{CH(CH_3)_2}$), 2.40 (ddd, J=12.9, 3.1 and 2.3 Hz, 1H, $\mathrm{CH_aH_b}$); δ_{C} 14.37 (q, $\mathrm{CH_3}$), 19.36 (q, $\mathrm{CH_3}$), 19.62 (q, $\mathrm{CH_3}$), 28.93 (t, $\mathrm{CH_2}$), 32.78 (d, CH), 35.13 (t, $\mathrm{CH_2}$), 44.92 (d, CH), 45.41 (t, $\mathrm{CH_2}$), 46.61 (d, CH), 213.59 (s, >C=O); $\mathrm{M^+}$, 154.1356. Calcd for $\mathrm{C_{10}H_{18}O}$: M, 154.1357. Elution with ether–petroleum ether (2:3) subsequently produced a mixture of the four diastereomeric carvomenthols (**19**)–(**22**) (0.65 g, 21%), bp 115°C (air-bath temp.)/15 mmHg, with similar gas chromatographic retention times and ^{13}C NMR spectra as the antipodal set of diastereomers (**15**)–(**18**). The mass spectral data of the diasteomers (**19**)–(**22**) were also in total agreement with those exhibited by the carvomenthols (**15**)–(**18**) as depicted in Section 3.1.1.

3.1.3. Regioselective reduction of (4*R*)-(+)-limonene (23). Zinc dust (100 g, 1.53 mol) was activated by stirring with two aliquots of aqueous hydrochloric acid (10%, 2×50 cm^3), filtered, successively washed with water and acetone, dried under vacuum and used instantly. To an efficiently stirred suspension of activated zinc dust (12.0 g, 183.6 mmol) and nickel chloride hexahydrate (10.0 g, 42.1 mmol) in a mixture of water (30 cm^3) and 2-methoxyethanol (30 cm^3), (4*R*)-(+)-limonene (**23**) (5.10 g, 37.4 mmol) was added and the resulting reaction mixture stirred for 9 h at 50°C. The reaction mixture was then filtered, diluted with saturated ammonium chloride (50 cm^3), extracted with ether (2×40 cm^3) and the residue from the dried ($\mathrm{MgSO_4}$) ether extract treated with a second, freshly prepared portion of the reducing agent as above for an additional 4 h at 50°C. The reaction mixture was worked up as above and the residue from the ether extract fractionally distilled to yield *(4R)-(+)-p-menthene* (**24**) (3.36 g, 65%) as a colourless oil, bp 60°C/22 mmHg (lit.[16] 174–176°C); $[\alpha]_{\mathrm{D}}^{20}$=+74 ($c$=10, EtOH);[6] δ_{H} 0.87 (d, J=4.1 Hz, 3H, $\mathrm{CH_3}$), 0.89 (d, J=4.1 Hz, 3H, $\mathrm{CH_3}$), 1.19–1.26 (m, 2H, $\mathrm{CH_2}$), 1.36–1.49 (m, 2H, 2×CH), 1.63 (ddd, J=3.3, 2.6 and 1.3 Hz, 3H, $\mathrm{CH_3}$), 1.65–1.77 (m, 2H, $\mathrm{CH_2}$), 1.78–2.03 (m, 2H, $\mathrm{CH_2}$), 5.38 (tq, J=4.3 and 1.3 Hz, 1H, =CH); δ_{C} 19.71 (q, $\mathrm{CH_3}$), 20.02 (q, $\mathrm{CH_3}$), 23.48 (q, $\mathrm{CH_3}$), 26.53 (t, $\mathrm{CH_2}$), 28.00 (t, $\mathrm{CH_2}$), 30.85 (t, $\mathrm{CH_2}$), 32.31 (d, CH), 40.05 (d, CH), 120.00 (s, =C<), 133.94 (s, =C<). Gas chromatographic analysis (7% Carbowax on Chromosorb B, column temp. 100°C, inlet pressure 80 kPa $\mathrm{N_2}$) of the distillate revealed the presence of very small quantities of a 1:1 diastereomeric mixture of *cis-* and *trans-4-isopropenyl-1-methylcyclohexane* (**26**) and (**27**) (80 mg, 1.5%) as well as *cis-* and *trans-p-menthane* (**28**) and (**29**) (81 mg, 1.5%).

3.1.4. Regioselective reduction of (4*S*)-limonene (25). To an efficiently stirred suspension of activiated zinc dust (12.0 g, 183.6 mmol) and nickel chloride hexahydrate (10.0 g, 42.1 mmol) in a mixture of water (30 cm^3) and 2-methoxyethanol (30 cm^3), (4*S*)-(−)-limonene (**25**) (5.10 g, 7.4 mmol) was added and the resulting reaction mixture stirred for 5 h at 50°C. The reaction mixture was then worked up, the product treated with an additional portion of the reducing agent as above and finally extracted as in Section 3.1.3. Fractional distillation of the residue from the ether extract yielded (4*S*)-(−)-*p*-menthene (**30**) (3.76 g, 73%) as a colourless oil, bp 65°C/20 mmHg (lit.[17] 177°C/732 mmHg); $[\alpha]_{\mathrm{D}}^{20}$=−60.3 ($c$=10, $\mathrm{CHCl_3}$);[17] δ_{H} 0.87 (d, J=4.1 Hz, 3H, $\mathrm{CH_3}$), 0.89 (d, J=4.1 Hz, 3H, $\mathrm{CH_3}$), 1.19–1.26 (m, 2H, $\mathrm{CH_2}$), 1.36–1.49 (m, 2H, 2×CH), 1.63 (ddd, J=3.3, 2.6 and 1.3 Hz, 3H, $\mathrm{CH_3}$), 1.65–1.77 (m, 2H, $\mathrm{CH_2}$), 1.78–2.03 (m, 2H, $\mathrm{CH_2}$), 5.38 (tq, J=4.3 and 1.3 Hz, 1H, =CH); δ_{C} 19.71 (q, $\mathrm{CH_3}$), 20.02 (q, $\mathrm{CH_3}$), 23.48 (q, $\mathrm{CH_3}$), 26.53 (t, $\mathrm{CH_2}$), 28.00 (t, $\mathrm{CH_2}$), 30.85 (t, $\mathrm{CH_2}$), 32.31 (d, CH), 40.05 (d, CH), 120.00 (s, =C<), 133.94 (s, =C<). Gas chromatographic analysis of the distillate as in Section 3.1.3 likewise revealed the presence of trace quantities of the corresponding 4*S*-diastereomers of *cis-* and *trans-4-isopropenyl-1-methylcyclohexane* as well as *cis-* and *trans-p-*menthane.

3.2. Hydroboration/oxidation of (4*R*)-(+)-*p*-menthene (24)

Boron trifluoride etherate (1.06 g, 7.5 mmol) in ether (15 cm^3) was added dropwise to a stirred mixture of lithium borohydride (0.50 g, 23.0 mmol) and (4*R*)-(+)-*p*-menthene (**24**) (7.75 g, 56.2 mmol) in ether (50 cm^3) during 50 min at 20°C. Stirring was maintained for an additional 2 h whereupon the unreacted lithium borohydride was destroyed by the addition of water (5 cm^3). Aqueous chromic acid (46 cm^3), prepared from sodium dichromate dihydrate (11.0 g, 36.9 mmol), sulphuric acid (98%, 8 cm^3) and water, was then introduced to the reaction mixture during 15 min at room temperature and the resulting dark green mixture stirred for a further 110 min at 30°C. After separation of the ether layer, celite (10 g) was added to the aqueous layer, the resulting suspension filtered and the filtrate extracted with ether. The combined ether layers were washed with saturated, aqueous sodium chloride (2×40 cm^3) and the residue from the dried ($\mathrm{MgSO_4}$) ether extract fractionally distilled to yield a gas chromatographically determined 8:5 mixture of *(2R,5R)-(+)-carvomenthone* (**13**) (3.35 g, 39%) and *(2S,5R)-(+)-carvomenthone* (**14**) (2.07 g, 24%) as a colourless oil, bp 90°C/10 mmHg, with a specific optical rotation of $[\alpha]_{\mathrm{D}}^{20}$=+9.9 (neat) (chiral TM-β-CD OV 1701-OH column, temp. prog. 40–120°C at the rate of 1.7°C/min, flow rate 50 cm^3 $\mathrm{H_2}$/sec).

3.3. Hydroboration/oxidation of (4*S*)-(−)-*p*-menthene (30)

The hydroboration of (4*S*)-(−)-*p*-menthene (**30**) (6.63 g, 48.0 mmol) in ether (40 cm^3) was performed as in Section 3.2 by treatment with lithium borohydride (0.45 g, 20.7 mmol) and boron trifluoride etherate (1.20 g, 7.2 mmol) in ether (40 cm^3). The intermediate organoborane was oxidized by treatment with aqueous chromic acid (131 cm^3), prepared from sodium dichromate dihydrate (9.55 g, 32.05 mmol), sulphuric acid (98%, 7.0 cm^3) and water, during 15 min at room temp. After stirring for an additional 2 h at reflux the reaction mixture was worked up, fractionally distilled and gas chromatographically analyzed as in Section 3.2 to yield a 12:13 mixture of (2*R*,5*S*)-(−)-*carvomenthone* (**10**) (2.14 g, 29%) and *(2S,5S)-(−)-carvomenthone* (**11**) (2.34 g, 32%) as a colourless oil, bp 96°C/12 mmHg, with a specific optical rotation of $[\alpha]_{\mathrm{D}}^{20}$=−23.8 ($c$=10, EtOH).

3.4. Stereoselective synthesis of (6*R*)-(−)-diosphenol (5)

To a ca 1:1 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-carvomenthone (**10**) and (**11**) (3.10 g, 20.1 mmol) in ether (10 cm^3), bromine (6.44 g, 40.3 mmol) was added dropwise during 10 min at −10°C and the resulting reaction mixture stirred for 7 h at −10°C. After addition of ether (10 cm^3) the reaction mixture was consecutively washed with saturated, aqueous solutions of sodium chloride (30 cm^3), sodium hydrogen carbonate (2×30 cm^3) and sodium chloride (30 cm^3). The residue from the dried ($MgSO_4$) organic phase in THF (10 cm^3) was added dropwise to aqueous sodium hydroxide (10 M, 4 cm^3, 40 mmol) at −10°C and the mixture stirred for 50 min at −10°C. Neutralization of the reaction mixture with aqueous hydrochloric acid (10 M, 4 cm^3) at −10°C was followed by extraction with ethyl acetate (2×20 cm^3) and separation of the residue from the extract on a chromatotron (4 mm silica gel chromatodisc, activated at 120°C for 1 h). Elution with ether–petroleum ether (1:4) yielded white crystals of (6*R*)-(−)-*diosphenol* (**5**) (2.02 g, 60%), mp 83.7°C;[1,18] $[\alpha]_D^{20}=-52.9$ ($c=10$, EtOH), 90% ee, while the mother liquor comprised a 1:1 mixture of *(6R)-(+)-Ψ-diosphenol* (**7**) and *(6S)-(−)-Ψ-diosphenol* (**8**) (0.35 g, 12%). The enantiomeric composition of these reaction products was accurately determined by HPLC analysis on a Chiralcel OB-H column with hexane/2-propanol (9:1) as the mobile phase.

3.5. Stereoselective synthesis of (6*S*)-(+)-diosphenol (6)

A ca 1:1 mixture of (2*R*,5*R*)- and (2*S*,5*R*)-carvomenthone (**13**) and (**14**) (2.80 g, 18.2 mmol) in ether (10 cm^3) was treated with bromine (5.81 g, 36.4 mmol) at −10°C and the resulting reaction mixture worked up, hydrolyzed with aqueous sodium hydroxide (10 M, 3.61 cm^3, 36.0 mmol) and extracted as described in Section 3.4. The residue from the ethyl acetate extract was separated on a chromatotron as in Section 3.4 to yield white crystals of *(6S)-(+)-diosphenol* (**6**) (1.78 g, 58%), mp 83.1°C;[1,18] $[\alpha]_D^{20}=+56.4$ ($c=10$, EtOH), 96% ee, while the mother liquor comprised a 1:1 mixture of *(6R)-* and *(6S)-Ψ-diosphenol* (**7**) and (**8**) (0.50 g, 16.5%). The enantiomeric composition of these reaction products was determined by HPLC as in Section 3.4.

3.6. Stereoselective synthesis of (6*R*)-(+)-Ψ-diosphenol (7)

Commercially available (2*S*,5*R*)-(−)-menthone (**31**) (14.0 g, 90.8 mmol) in ether (30 cm^3) was treated with bromine (29.09 g, 181.8 mmol) at −10°C and the resulting reaction mixture worked up, hydrolyzed with aqueous sodium hydroxide (3.1 M, 400 cm^3) and extracted as described in **7**. The residue from the ethyl acetate extract was separated on a chromatotron as in Section 3.4 to afford an oily product which was crystallized from hexane to yield an 89:11 mixture of *(6R)-(+)-Ψ-diosphenol* (**7**) (8.34 g, 55%) and *(6S)-(−)-Ψ-diosphenol* (**8**) (1.04 g, 7%), mp 34.5°C;[1] $[\alpha]_D^{20}=+106.5$ ($c=10$, EtOH), 78% ee. Evaporation of the mother liquors yielded a residue which comprised a mixture of *racemic diosphenol* (**5**)/(**6**) (0.71 g, 4.7%) and *Ψ-diosphenol* (**7**)/(**8**) (1.32 g, 8.7%), determined by HPLC as in Section 3.4.

3.6.1. (5*R*,5*S*)-(+)-Menthone (34). Dry dimethyl sulphoxide (6.58 g, 84.3 mmol) was added dropwise during 15 min to a stirred solution of oxalyl chloride (5.35 g, 42.2 mmol) in dry dichloromethane (100 cm^3) at −60°C. After stirring for an additional 30 min at −60°C, commercially available (1*S*,2*R*,5*S*)-(+)-menthol (**33**) (6.0 g, 38.4 mmol) in dry dichloromenthane (20 cm^3) was added during 5 min. Stirring was maintained for 3 h at −60°C, followed by the addition of dry triethylamine (19.50 g, 190 mmol) during 15 min whereupon the reaction mixture was allowed to reach room temperature, filtered and the residue from the filtrate subjected to column chromatographic separation on silica gel. Elution with ether–petroleum ether (1:3) yielded *(2R,5S)-(+)-menthone* (**34**) (11.88 g, 91%) as a colourless oil, bp 90°C (air-bath temp.)/7.1 mmHg; $[\alpha]_D^{20}=+19.0$ ($c=10$, EtOH); δ_H 0.85 (d, $J=6.8$ Hz, 3H, CH_3), 0.91 (d, $J=6.8$ Hz, 3H, CH_3), 1.01 (d, $J=6.2$ Hz, 3H, CH_3), 1.31–1.39 (m, 2H, CH_2), 1.80–2.08 (m, 5H, CH_2, $CHCH_2$), 2.13 (d sept., $J=5.2$ and 6.8 Hz, 1H, $CH(CH_3)_2$), 2.32–2.38 (m, 1H, CH); δ_C 18.73, (q, CH_3), 21.23 (q, CH_3), 22.30 (q, CH_3), 25.95 (d, CH), 27.92 (t, CH_2), 33.98 (t, CH_2), 35.49 (d, CH), 50.90 (t, CH_2), 55.94 (d, CH), 212.31 (s, >C=O); M^+, 154.1355. Calcd for $C_{10}H_{18}O$: M, 154.1356.

3.7. Stereoselective synthesis of (6*S*)-(−)-Ψ-diosphenol (8)

Bromine (15.58 g, 97.4 mmol) was added dropwise to (2*R*,5*S*)-(+)-menthone (**34**) (7.50 g, 48.6 mmol) in ether (25 cm^3) at −10°C and the resulting reaction mixture worked up, hydrolyzed with aqueous sodium hydroxide (3.13 M, 212 cm^3) and extracted as in Section 3.4. The residue from the ethyl acetate extract was separated on a chromatotron as in Section 3.4 to yield an oily product which was crystallized from hexane to afford a 9:1 mixture of *(6S)-(−)-Ψ-diosphenol* (**8**) (4.26 g, 52%) and *(6R)-(+)-Ψ-diosphenol* (**7**) (0.46 g, 6%), mp 34.5°C;[1] $[\alpha]_D^{20}=-102.4$ ($c=10$, EtOH), 80% ee. The residue from the mother liquors comprised a 1:3 mixture of *(±)-diosphenol* (**5**)/(**6**) (0.24 g, 3%) and *(±)-Ψ-diosphenol* (**7**)/(**8**) (0.73 g, 9%), determined by HPLC as in Section 3.4.

3.7.1. Bromination of (±)-menthone (35) and subsequent alkaline hydrolysis with a suspension of finely divided sodium hydroxide. (±)-Menthone (**35**) (7.0 g, 45.4 mmol) in ether (20 cm^3) was brominated by dropwise addition of bromine (14.52 g, 90.8 mmol) during 15 min at −10°C, whereupon the reaction mixture was stirred for an additional 7 h at −10°C. The reaction mixture was then worked up as in Section 3.4, the residue from the dried ($MgSO_4$) ether extract in THF (15 cm^3) added dropwise to a finely divided suspension of sodium hydroxide (9.07 g, 230 mmol), prepared by careful addition of water (4.14 g, 230 mmol) to a stirred suspension of oil-free sodium hydride (5.44 g, 230 mmol) in THF (30 cm^3), during 10 min at 0°C and the resulting mixture stirred for 1 h at 0°C and an additional 1.5 h at room temperature. Evaporation of the filtrate of the reaction mixture under vacuum produced a residue which was separated by column chromatography on silica gel. Elution with ether–petroleum ether (1:4) yielded *2-(2′-isopropyl-5′-methyl-1′-phenoxy)-6-isopropyl-3-methyl-1-oxybicyclo[3.1.0] cyclohexane* (**37**)

(6.97 g, 51%) as a colourless liquid, bp 144°C (air-bath temp.)/0.046 mmHg; ν_{max} (liquid film) 2910, 2822, 1695, 1592, 1440, 1432 cm^{-1}; δ_H 1.05 (d, J=6.9 Hz, 3H, CH_3), 1.07 (d, J=6.9 Hz, 3H, CH_3), 1.17 (d, J=6.6 Hz, 3H, CH_3), 1.20 (d, J=7.0 Hz, 3H, CH_3), 1.21 (d, J=6.7 Hz, 3H, CH_3), 2.09 (dddd, J=17.5, 9.2, 8.4 and 7.5 Hz, 1H, CH_aH_b), 2.09 (ddd, J=17.2, 8.4 and 4.7 Hz, 1H, CH_aH_b), 2.31 (s, 3H, CH_3), 2.58 (ddddd, J=17.6, 8.4, 7.5, 2.1 and 0.8 Hz, 1H, CH_aH_b), 3.00 (h, J=6.9 Hz, 1H, $CH(CH_3)_2$), 3.19 (dddd, J=8.4, 6.7, 2.1 and 1.0 Hz, 1H, CH), 3.68 (sept., J=6.9 Hz, 1H, $CH(CH_3)_2$), 4.45 (dddt, J=18.4, 9.1 and 5.0, 0.9 Hz, 1H, CH_aH_b), 6.84 (dd, J=1.8 and 0.7 Hz, 1H, ArH), 7.0 (dd, J=7.9 and 1.8 Hz, 1H, ArH), 7.20 (d, J=7.9 Hz, 1H, ArH); δ_C 20.14 (q, CH_3), 20.82 (q, CH_3), 20.83 (q, CH_3), 20.92 (q, CH_3), 22.83 (q, CH_3), 23.03 (q, CH_3), 27.13 (d, CH), 28.03 (d, CH), 30.63 (t, CH_2), 31.05 (t, CH_2), 40.77 (d, CH), 122.96 (d, $=$CH), 126.25 (d, $=$CH), 126.74 (d, $=$CH), 130.50 (s, $>$C–O), 136.39 (s, $=$C$<$), 137.21 (s, $=$C$<$), 147.98 (s, $=$C–O), 164.72 (s, $>$C$<$), 166.68 (s, $>$C$=$O), M$^+$, 300.2096. Calcd for $C_{20}H_{28}O_2$: M, 300.2089.

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