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# Stereoselective free radical phenylsulfenylation of a nonactivated δ-carbon atom

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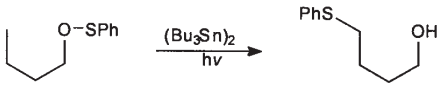
*Abstract*: A stereoselective free radical introduction of a phenylthio group onto a nonactivated methyl group in the δ-position, adjacent to a prochiral carbon atom, was achieved by photolysis of (-)-menthyl benzenesulfenate in the presence of hexabutylditin and (1*R*, 3*R*, 4*S*, 8*S*)-9-phenylthiomenthol (**4**) was obtained with 91 % optical purity. High stereoselectivity of the reaction was calculated (*ab initio* MP2/6-31G**) to be the consequence of the difference in the transition state eneregies ($\Delta\Delta G^{\#}$ = 5.08 kJ/mol) favouring **4** relative to (1*R*,3*R*,4*S*,8*R*)-9-phenylthiomenthol (**5**). The absolute configuration of a the new chiral carbon atom was confirmed by its correlation with the corresponding menthane-3,9-diol of known stereochemistry.

*Keywords*: radical reactions, stereoselective reactions, C-H activation, absolute configurations, *ab initio* calculations, menthyl benzenesulfenate, 9-phenylthiomenthol.

## INTRODUCTION

A recently discovered, free radical rearrangement of alkyl benzenesulfenates **1** into δ-phenylthio alcohols **2**, could have valuable synthetic applications (Eq. (1)).[1] The δ-carbon atom adjacent to sulfur functional groups may be transformed into different functional groups and also be useful for carbon-carbon bond forming reactions.[2] The introduction of a phenylthio group onto a nonactivated δ-carbon atom was achieved by irradiation of alkyl benzenesulfenates in the presence of hexabutylditin and involves alkoxyl and δ-carbon radical intermediates.[1]




**1** **2** (1)

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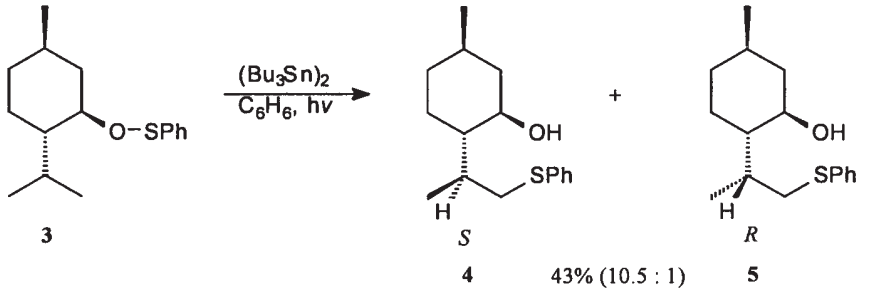
## RESULTS AND DISCUSSION

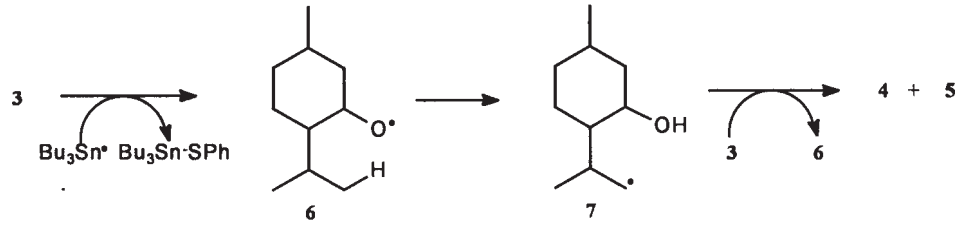
The reaction of δ-phenylsulfenylation of a nonactivated carbon atom was applied to (–)-menthol, in order to introduce the phenylthio group onto the methyl group of the side isopropyl group. (–)-Menthol was converted to (–)-menthyl benzenesulfenate (**3**), as a good alkoxyl radical precursor, by reaction with benzenesulfenyl chloride in the presence of thiethylamine.[1,3] The reaction of (–)-menthyl benzenesulfenate with hexabutylditin (15 % mol) was carried out under irradiation conditions and 9-phenylthiomenthol was obtained in 43 % yield (Eq. (2)).[1]




**3** *S* **4** 43% (10.5 : 1) *R* **5** (2)

The mixture of the two diastereoisomeric (1*R*,3*R*,4*S*,8*S*)-9-phenylthiomenthol (**4**) and (1*R*,3*R*,4*S*,8*R*)-9-phenylthiomenthol (**5**) was separated by chromatography on a silica gel column, using petroleum ether/acetone (95 : 5) as the eluent whereby the stereoisomer **4** was isolated in 39.3 % yield. On rechromatography of the residue after isolation of isomer **4**, using toluene/ethyl acetate (95 : 5), the diastereoisomer **5** was isolated (3.7 % yield).

The introduction of the phenylthio group onto the nonactivated methyl group (in position 9) involves the intermediary menthyloxy radical **6**, which after subsequent 1,5-hydrogen transfer, generates the carbon radical **7** (Scheme 1). 9-Phenylthiomenthol is formed by a free radical substitution reaction of the carbon radical **7** in which the phenylthio group from the starting (–)-menthyl benzenesulfenate **3** is abstracted and the new alkoxyl radical **6** is generated.[1,4]



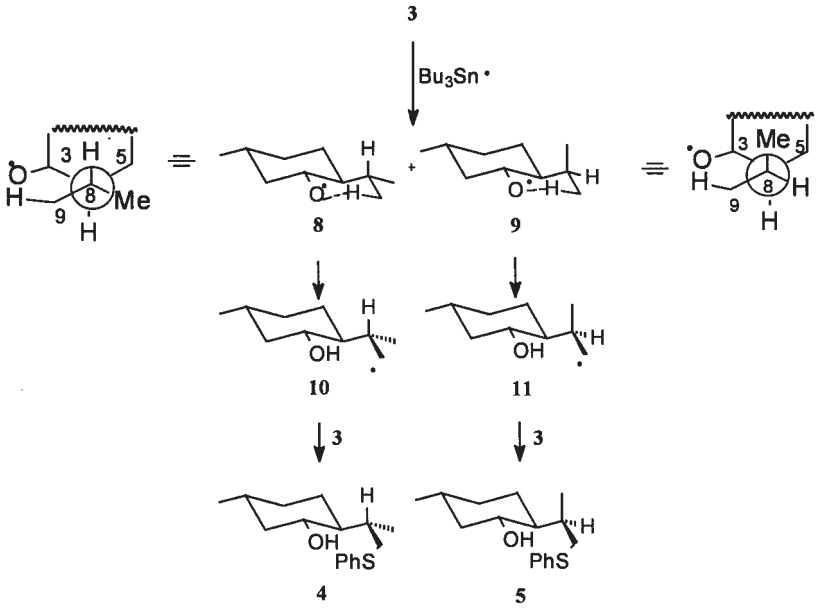

**6** **7**

Scheme 1.

It would be expected that the two nonactivated methyl groups which could be attacked by the alkoxyl radical **6** are equivalent for hydrogen abstraction and subsequent introduction of the phenylthio group, since the rotational barrier of the isopropyl group is relatively low. However, it was found that the phenylsulfenylation reaction proceeds stereoselectively and the two stereoisomers (8*S*)-9-phenylthiomenthol (**4**) and (8*R*)-9-phenylthiomenthol (**5**) were obtained in the ratio 91 : 9 (Eq. (2)).[1c] The formation of the

(8*S*)-diastereoisomer **4** in considerable excess may be explained by the different stereochemical interactions in the transition states **8** and **9**, necessary for 1,5-hydrogen abstraction at the intermediary alkoxyl radicals, and thus two diastereoisomeric carbon radicals **10** and **11** were generated (Scheme 2).

Similar results have also been obtained in the 1,5-hydrogen transfer from one of the diastereotopic methyl groups by a vinyl radical.[5]




Scheme 2.

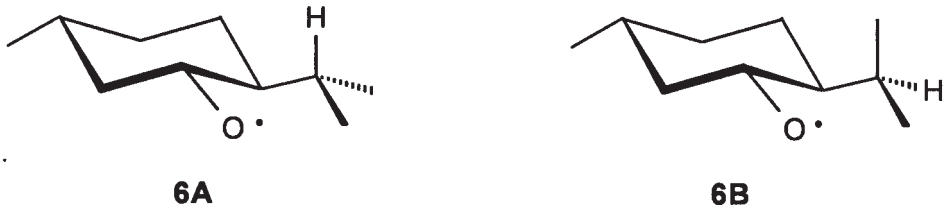
Calculations at the molecular mechanics and *ab initio* quantum chemical level were performed on the two starting radical conformations, **6A** and **6B** (Scheme 3), leading to the transition states **8** and **9** as well as on transition states. The structures of the radical **6** conformations, **6A** and **6B**, were built and initially optimized using MM+ force field.[6] They were fully optimized using the UHF/3-21G[6] method, followed by optimization at the UHF/6-31G* level. Single point calculations were carried out at the MP2/6-31G**[7,8] level. In all cases the **6B** conformation was more stable, Table I.

The transistion structures of **8** and **9** were located (UHF/3-21G followed by UHF/6-31G* and single point MP2/6-31G**). The activation enthalpy for the conversion of **6A** to **4**, *via* **8** is 9.00 kJ/mol lower than the one for the conversion of **6B** to **5**, *via* **9**. However, since the two starting radical conformations (**6A** and **6B**) interconvert with relatively low (~12 kJ/mol) barrier, the ratio of the products **4** and **5** will depend solely on the free energy difference $\Delta\Delta G^{\#}$ of the corresponding transition states. The entropies of the reactant conformations and transition structures were computed from the calculated geometries and frequencies at the 3-21G level. The entropy of mixing was *R*ln2 for each transition state to account for the existence of an enantiomeric transition state. The entropies of mixing of the

TABLE I. Energies and entropies of the starting radicals and the transition states.

| Radical | $E$/(kJ/mol) | | | | $\Delta E^{\#}$ kJ/mol | $H$ | $\Delta H^{\#}$ | $S$ | $\Delta S^{\#}$ | $-T\Delta S^{\#}$ kJ/mol | $\Delta G^{\#}$ kJ/mol |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | kJ/mol | | kJ/mol K | | | |
| | MM+ | UHF/3-21G | UHF/6-31G* | MP26-31G** | MP2/6-31G** | | | | | | |
| **6A** | 53.55 | –1213042.2 | –1219742.5 | –1224000.58 | 0.0 | –1223194.7 | 0.0 | 402.2 | 0.0 | 0.0 | 0.0 |
| **8** | | –1212912.7 | –1219604.5 | –1223954.85 | 45.73 | –1223167.7 | 27.0 | 376.5 | –25.73 | 7.66 | 34.68 |
| **6B** | 51.63 | –1213046.8 | –1219744.5 | –1224001.67 | 0.0 | –1223199.1 | 0.0 | 401.4 | 0.0 | 0.0 | 0.0 |
| **9** | | –1212908.2 | –1219598.3 | –1223950.58 | 51.09 | –1223163.1 | 36,0 | 374.9 | –26.57 | 7.91 | 43.93 |

$E$ - total energies. $H$, enthalpies, were calculated from MP2 energies by correcting for zero point energies, $RT$ and other $C_pT$ terms at 298.15 K.




**6A** **6B**

Scheme 3.

starting conformers included contributions of all the conformations with a chair cyclohexane ring. The conformational energies were estimated by the force field method.[6]

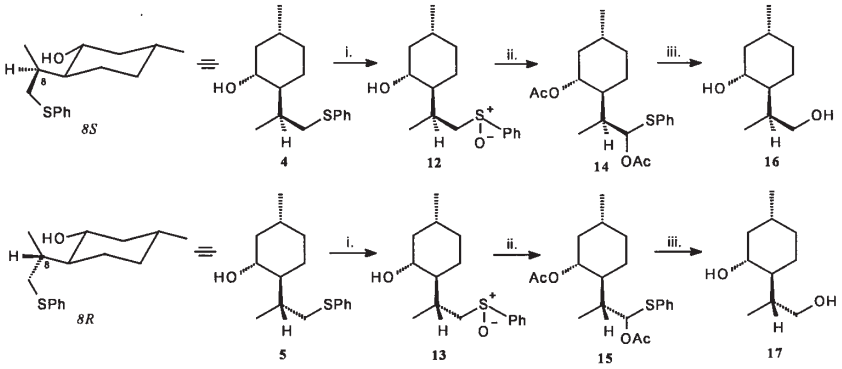
Both transition state structures, **8** and **9** have an "envelope" shape with a long C ... O "bond", equal 2.45 Å and 2.46 Å, respectively, and an O – H – C angle of 152.8 and 153.7 degrees, respectively, as expected.[9] Contrary to the starting radical conformations, **6A** and **6B**, the corresponding transition states **8** and **9** differ considerably in energy (Table II). The enthalpy difference of 4.60 kJ/mol favors the transition state **8** and the formation of product **4**. The transition state **8** is further stabilized by an entropy difference of 1.6 J/mol K (Table II). Finally, the $\Delta\Delta G^{\#}$, equal to 5.08 kJ/mol at room temperature, corresponds to a product ratio 89:11, which is very close to the experimentally determined ratio of 91:9 for the formation of products **4** and **5**. The unexpected low energy of **6B** is due to the fact that the isopropyl group in **6B** is twisted relieving one of the quasi *syn*-axial methyl-hydrogen interactions, as well as the oxygen-methyl interaction. This twist is not possible in the transition state and the energy of **9** is high.

TABLE II. Relative energies and entropies for the two transition states.

| Transition state | $\Delta\Delta E^{\#}$ kJ/mol | $\Delta\Delta H^{\#}$ kJ/mol | $\Delta\Delta S^{\#}$ J/mol K | $-T\Delta\Delta S^{\#}$ kJ/mol | $\Delta\Delta G^{\#}$ kJ/mol |
|---|---|---|---|---|---|
| **8** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **9** | 4.27 | 4.60 | –1.60 | 0.48 | 5.08 |

This hypothesis of the configuration of the new chiral carbon atom at position 8 was confirmed by transformation of the (8*S*)-9-phenylthiomenthol (**4**) and (8*R*)-9-phenylthiomenthol (**5**) into the corresponding diastereoisomeric (8*S*)-menthane-3,9-diol (**16**) and (8*R*)-menthane-3,9-diol (**17**), the stereochemistry of which were determined by Ohloff (Scheme 4).[10] The separated diastereoisomeric 9-phenylthiomenthols **4** and **5** were transformed into the corresponding menthane-3,9-diols **14** and **15**, respectively, by the following sequence of reactions: (*i*) oxidation by *m*-CPBA to the corresponding sulfoxides **12** and **13**,[2a,11] (*ii*) Pummerer rearrangement, induced by acetic anhydride and sodium acetate, affording the diastereoisomeric 9-acetoxy-9-phenylthiomenthyl acetates (**14**) and (**15**)[12] and (*iii*) by their reduction with $LiAlH_4$ whereby the corresponding (–) (1*R*, 3*R*, 4*S*, 8*S*)-menthane-3,9-diol (**16**) and (–) (1*R*, 3*R*, 4*S*, 8*R*)-menthane-3,9-diol (**17**) were obtained (Scheme 4).

The diastereoisomeric (–)-(8*S*)-menthane-3,9-diol (**16**), prepared by the described procedure (Scheme 4), has a m.p. of 90 ºC and an optical rotation of $[\alpha]_D^{21} = -42^{o}$, which



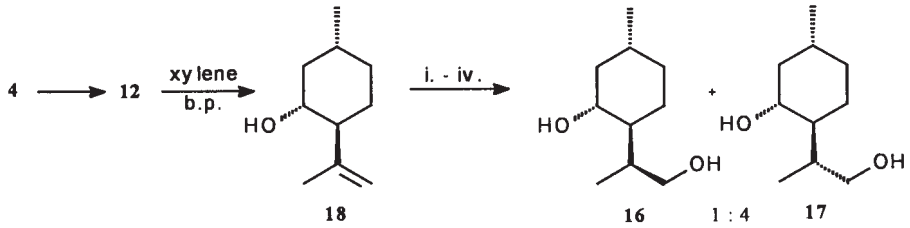

i. *m*CPBA, $CH_2Cl_2$, -78 °C; ii. $Ac_2O$, AcONa, heat; iii. $LiAlH_4$, $Et_2O$

Scheme 4.

are identical with the same diastereoisomeric (8*S*)-menthane-3,9-diol independently prepared from (–)-isopulegol by the procedure described by Ohloff and also the same as the physical constants given in the literature.[10] Physical characteristics of the other (8*R*)-menthane-3,9-diol (**17**), m.p. 107 ºC and $[\alpha]_D^{21} = -16.2^o$, were also in full agreement with stereoisomer prepared from (–)-isopulegol and data given in the literature.[10]

These results strongly support the assumption that the absolute configuration of C-8 in the 9-phenylthiomenthol (**4**), obtained by the free radical phenylsulfenylation reaction, is *S* and the other diastereoisomer **5** has the *R* absolute configuration of chiral carbon atom in the 8-position.

Additional proof of the configuration of the chiral carbon atom in position 8 was obtained by conversion of the separated diastereoisomeric 9-phenylthiomenthol **4** into (–)-isopulegol by heating of phenyl 9-menthyl sulfoxide (**12**) in boiling xylene.[13] The (–)-isopulegol (**18**) prepared by this method was transformed into the mixture of diastereoisomeric (1*R*,3*R*,4*S*,8*S*)-menthane-3,9-diol (**16**) and (1*R*,3*R*,4*S*,8*R*)-menthane-3,9-diol **17**, by the procedure described by Ohloff,[10] involving the following sequence of reaction: (*i*) methoxymethylation by methoxymethyl chloride in the presence of dimethylaniline,[14] (*ii*) hydroboration, (*iii*) oxidation with hydrogen peroxide in the presence of sodium hy-




i. $CH_3OCH_2Cl$, dimethyl aniline; ii. $B_2H_6$, THF; iii. $H_2O_2$, NaOH; iv. MeOH (HCl, traces).

Scheme 5

droxide to give a mixture of (8*S*)-9-hydroxy-3-*O*-(methoxymethyl)menthol and the 8*R* diastereoisomer in the ratio of 1 : 4,[10] and (*iv*) the mixture of diastereoisomeric 9-hydroxy-3-*O*-(methoxymethyl)menthol was hydrolysed to give a mixture of diastereoisomeric 8*S*-**16** and 8*R*-menthane-3,9-diol **17** (Scheme 5). The mixture of stereoisomers was separated by chromatography and pure stereoisomers showed identical physical constants and spectral characteristics as the diastereoisomer obtained from 9-phenylthiomenthol by the procedure described in Scheme 4.

## EXPERIMENTAL

Solvents used in all of the experiments wee purified by distillation before use (benzene distilled over calcium hydride and dichloromethane over phosphorus pentoxide). Purifications and separations of the reaction products were carried out by distillation and column chromatography using silica gel 100–200 mesh (60 Å) and by dry flash chromatography using silica gel (60 Å). The reactions were monitored by TLC using silica gel (TLC 60 Å) or by GC (Varian 3400, column OV-101 1 % on Chromosorb W-AW). The IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded on a Perkin-Elmer 457 grating instrument. The $^1$H-NMR spectra (ppm in δ-values, coupling constants, *J*, in Hz) were recorded (in $CDCl_3$) at 200 MHz using a Varian Gemini 200 instrument. The $^{13}$C-NMR spectra were recorded on the same instrument at 50 MHz. Mass spectra were recorded on a Finnigan ITDS 700 instrument.

*(1*R,*2*S,*5*R*)-2-Isopropyl-5-methylcyclohexyl benzenesulfenate* [*(–)-menthyl benzenesulfenate)*] (**3**)[1,3]

To a solution of (–)-menthol (3.0 g, 19.2 mmol) and triethylamine (4.75 g, 0.05 mol) in dichloromethane (150 ml), cooled to –78 ºC under an argon atmosphere, was added benzenesulfenyl chloride (3.3 g, 23.0 mmol) during 10 min at –78 ºC and left to reach r.t. The mixture was diluted with 400 mL of dichlorometane and washed successively with 50 ml of 2 M hydrochloric acid, 50 mL of saturated aqueous sodium bicarbonate and water. The solution was dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residual oil distilled on a short path under reduced pressure. Menthyl benzenesulfenate was obtained (4.4 g, 87 % yield) as a colourless oil, bp 108–110 ºC / 0.07 mm Hg. Elemental analysis was not performed because the compound decomposes with explosion in the Pregl apparatus, $[\alpha]_D^{22}$ –256.7 (*c* = 1 in $CHCl_3$) of 92 % purity of compound (determined by $^1$H-NMR spectrum). IR: 3062, 1583, 1477, 1455, 1440, 1387, 1370, 1345, 1097, 1024, 1004, 981, 959, 914, 851, 778, 738, 690. $^1$H-NMR: 0.62 *d*, 3 H, *J* = 7.0; 0.87 *d*, 3 H, *J* = 7.2; 0.88 *d*, 3 H, *J* = 7.2; 0.72–1.00 *m*, 3 H; 1.20–1.38 *m*, 2 H; 1.54–1.66 *m*, 2 H; 2.18–2.38 *m*, 2 H; 3.37 *td*, 1 H, $J_1$ = 10.7, $J_2$ = 4.4; 7.10–7.40 *m*, 5 H. $^{13}$C-NMR: 141.29, 128.52, 126.65, 125.37, 87.01, 48.62, 40.88, 34.10, 31.50, 25.06, 22.93, 22.03, 20.87, 15.59.

*(–)-(1*R,*2*S,*5*R,*1'*S*)-5-Methyl-2-(1-methyl-2-phenylthioethyl)cyclohexanol*
[*(–)-(1*R,*3*R,*4*S,*8*S*)-9-phenylthiomenthol*] (**4**)

A solution of menthyl benzenesulfenate (0.26 g, 1 mmol) and hexabutylditin (58 mg, 0.1 mmol) in 4 ml of benzene was irradiated at room temperature, under an argon atmosphere, with a 125 W high pressure mercury lamp during 15 min. The benzene was removed by evaporation and the reaction products were separated from the oily residue by chromatography on silica gel column using petroleum ether/acetone 95 : 5 or 90 : 10. (–) - (1*R*, 3*R*, 4*S*, 8*S*)-9-Phenylthiomenthol (**4**) was obtained (0.103 g, 39 % yield) as a white crystalline compound, m.p. 49 ºC, $[\alpha]_D^{21}$ –29.4 (*c* = 1 in $CHCl_3$). Elemental analysis: calculated for $C_{16}H_{24}OS$: C, 72.67 %; H, 9.15 %; S, 12.13 %; found: C, 72.72 %; H, 9.33 %; S, 12.41 %. IR: 3392, 1584, 1480, 1455, 1439, 1377, 1312, 1263, 1147, 1091, 1049, 1026, 991, 965, 922, 885, 846, 737, 691. $^1$H-NMR: 0.91 *d*, 3 H, *J* = 6.2; 0.94 *d*, 3 H, *J* = 6.4; 0.82–1.14 *m*, 2 H; 1.25–1.71 *m*, 5 H; 1.92–2.03 *m*, 1 H; 2.34 *sext*, 1 H, $J_1$ = 7.4, $J_2$ = 2.8; 2.80–2.95 *m*, 2 H; 3.40 *td*, 1 H, $J_{aa}$ = 10.4, $J_{ae}$ = 4.2; 7.10–7.36 *m*, 5 H. $^{13}$C-NMR: 137.24, 128.81, 125.61, 71.04, 47.58, 45.01, 39.36, 34.19, 31.52, 30.99, 23.18, 22.09, 13.88. MS (CI): 265 ($M^+ + 1$) 60 %, 247 [($M^+ + 1$) – $H_2O$] 100 %.

*(–)-(1*R,*2*S,*5*R,*1'*R*)-5-Methyl-2-(1-methyl-2-phenylthioethyl)cyclohexanol [(1*R,*3*R,*4*S,*8*R)-9-phenylthiomenthol)]* (**5**)

This compound was isolated by rechromatography of the residue after isolation of the isomer **4** using toluene/ethyl acetate 95 : 5 as the eluent. Stereoisomer **5** was isolated (9.8 mg, 3.7 %) as a colorless oil, $[\alpha]_D^{22}$ –44.0 (*c* = 1 in $CHCl_3$). Elemental analysis: calculated for $C_{16}H_{24}OS$: C, 72.67 %; H, 9.15 %; S 12.13 %; found: C, 72.33 %; H, 9.15 %; S, 12.22 %. IR: 3364, 1583, 1476, 1449, 1376, 1304, 1258, 1223, 1170, 1090, 1022, 969, 922, 891, 847, 740, 694. $^1$H-NMR: 0.90 *d*, 3 H, *J* = 6.6; 1.07 *d*, 3 H, *J* = 6.9; 0.81–1.14 *m*, 3 H; 1.26–1.45 *m*, 2 H; 1.57–1.70 *m*, 2 H; 1.87–1.98 *m*, 1 H; 2.05–2.25 *m*, 1 H; 2.70 *dd*, 1 H, $J_{gem}$ = 12.6, $J_{vic}$ = 9.1; 3.15 *dd*, 1 H, $J_{gem}$ = 12.6, $J_{vic}$ = 4.9; 3.50 *td*, 1 H, $J_{aa}$ = 10.4, $J_{ae}$ = 4.2; 7.10–7.38 *m*, 5 H. $^{13}$C-NMR: 137.29, 128.80, 128.77, 125.60, 71.05, 49.19, 45.05, 37.56, 34.42, 33.02, 31.46, 25.77, 22.02, 17.09.

*(–)-(1*R,*3*R,*4*S,*8*S)-9-Phenylsulfinyl-menthol* (**12**)[2a,11]

To a solution of 9-phenylthiomenthol (**4**) (0.88 g, 3.33 mmol) in $CH_2Cl_2$ (20 ml), cooled to –78 ºC in an argon atmosphere was added a solution of *m*-CPBA (0.57 g, 3.33 mmol) in $CH_2Cl_2$ (54 ml) during 10 min. The mixture was then stirred for 30 min at –78 ºC and then left to reach r.t. The resulting mixture was successively washed with 10 % aqueous $Na_2SO_3$, saturated $NaHCO_3$ and water. The solution was dried and solvent evaporated to give an oily residue which was purified by chromatography on silica gel using successively petroleum ether/acetone 95 : 5, 90 : 10 and 80 : 20 as an eluent. The title sulfoxide **12** was obtained as a colorless oil (0.87 mg, 93 % yield). Elemental analysis: calculated for $C_{16}H_{24}O_2S$: C, 68.53 %; H, 8.63 %; S, 11.43 %; found: C, 68.39 %; H, 8.87 %; S, 11.15 %. IR: 3399, 1449, 1405, 1379, 1267, 1227, 1142, 1090, 1048, 1023, 1000, 921, 750, 693. $^1$H-NMR: 0.89 *d*, 1.5 H, *J* = 6.4; 0.91 *d*, 1.5 H, *J* = 6.6; 0.98 *d*, 1.5 H, *J* = 6.4; 1.07 *d*, 1.5 H, *J* = 6.6; 0.73–1.16 *m*, 3 H; 1.20–1.74 *m*, 5 H; 1.94–2.08 *m*, 1 H; 2.55 *dd*, 0.5 H, $J_{gem}$ = 12.0, $J_{vic}$ = 9.4; 2.67–2.94 *m*, 1.5 H; 2.96–3.08 *broad s*, 1 H 3.41 *td*, 1 H, $J_{aa}$ = 10.4, $J_{ae}$ = 4.2; 7.48–7.57 *m*, 3 H; 7.60–7.68 *m*, 2 H. $^{13}$C-NMR: 144.49, 144.14, 130.92, 130.85, 129.18, 123.99, 123.91, 70.72, 65.20, 63.71, 48.99, 47.39, 44.97, 44.77, 34.08, 31.44, 27.49, 27.42, 24.09, 23.74, 21.99, 14.60, 13.82.

*(–)-(1*R,*3*R,*4*S,*8*R)-9-Phenylsulfinylmenthol* (**13**)

This compound was obtained as a white crystalline compound (92 % yield) according to the above procedure but using stereoisomer **5** as the starting compound. Elemental analysis: calculated for $C_{16}H_{24}O_2S$: C, 68.53 %; H, 8.63 %; S, 11.43 %; found: C, 68.22 %; H, 8.79 %; S, 11.66 %. IR: 3365, 1451, 1378, 1311, 1226, 1169, 1133, 1090, 1014, 925, 750, 692, 641. $^1$H-NMR: 0.73 *d*, 1.5 H, *J* = 6.7; 0.89 *d*, 1.5 H, *J* = 6.5; 0.91 *d*, 1.5 H, *J* = 6.4; 1.20 *d*, 1.5 H, *J* = 6.5; 0.81–1.08 *m*, 3 H; 1.25–1.52 *m*, 2.5 H; 1.59–1.75 *m*, 2 H; 1.90 –2.10 *m*, 1 H; 2.45 *m*, 0.5 H; 2.47 *dd*, 0.5 H, $J_{gem}$ = 12.6, $J_{vic}$ = 9.8; 2.58–2.71 *m*, 0.5 H; 2.98 *dd*, 0.5 H, $J_{gem}$ = 12.6, $J_{vic}$ = 5.8; 3.17–3.29 *m*, 0.5 H; 3.22–3.45 *m*, 1 H; 7.49–7.52 *m*, 3 H; 7.55–7.68 *m*, 2 H. $^{13}$C-NMR: 144.28, 142.40, 130.98, 130.86, 129.28, 129.11, 124.17, 123.85, 70.34, 70.10, 62.93, 58.14, 49.29, 49.16, 44.33, 43.82, 34.25, 31.54, 31.47, 28.82, 25.69, 24.88, 22.06, 22.00, 18.91, 16.97.

*(–)-(1*R,*3*R,*4*S,*8*S)-9-Acetoxy-9-phenylthiomenthyl acetate* (**14**)[12]

A mixture of sulfoxide **12** (59 mg, 0.21 mmol), anhydr. NaOAc (0.208 g, 2.55 mmol) and acetic anhydride (4.0 ml) was heated at 165 ºC during 2.5 h. Dichloromethane (10 ml) was added to the reaction mixture and then poured into a 1 M aqueous NaOH solution (10 ml). The separated $CH_2Cl_2$ solution was washed with 1 M aqueous NaOH solution and water. The resulting solution was dried and solvent was removed by evaporation to give an only residue. The crude product was purified by chromatography on silica gel column using petroleum ether/acetone 100 : 1 and 100 : 2 as an eluent. The title compound **14** was obtained as a colorless oil (39 mg, 53 % yield), containing two diastereoisomers. IR: 1738, 1581, 1447, 1373, 1230, 1224, 1078, 1022, 978, 902, 847, 745, 695. $^1$H-NMR: 0.83 *d,* 1.5 H, *J* = 6.9; 0.88 *d*, 1.5 H, *J* = 5.8; 0.91 *d*, 1.5 H, *J* = 6.0; 0.94 *d*, 1.5 H, *J* = 6.9; 0.75–1.28 *m*, 3 H; 1.35–1.57 *m*, 1 H; 1.60–1.80 *m*, 3 H; 1.89 *s*, 1.5 H; 1.91 *s*, 1.5 H; 2.03 *s*, 1.5 H; 2.05 *s*, 1.5 H; 1.94–2.15 *m*, 2 H; 4.64 *td*, 1 H, $J_{aa}$ = 10.6, $J_{ae}$ = 4.2; 6.00 *d*, 0.5 H, *J* = 9.1; 6.01 *d*, 0.5 H, *J* = 9.5; 7.25–7.38 *m*, 3 H; 7.43–7.58 *m*, 2 H. $^{13}$C-NMR: 170.55, 169.74, 169.59, 134.77, 134.19, 134.15, 131.52, 131.41, 128.81, 128.27, 83.38, 83.28, 73.22, 72.98, 42.55, 41.69, 40.69, 35.35, 33.90, 33.76, 31.08, 23.69, 21.83, 21.00, 20.93, 11.13, 10.52.

*(–)-(1*R,*3*T,*4*R,*8*R*)-9-Acetoxy-9-phenylthiomenthyl acetate (**15**)*

The acetate was obtained as a colorless oil containing two stereoisomers (34 mg, 32 % yield) from the sulfoxide **13** according to the above procedure. IR: 1737, 1582, 1456, 1373, 1240, 1091, 1022, 962, 904, 745, 695. $^1$H-NMR: 0.87 *d*, 2.25 H, *J* = 6.7; 0.91 *d*, 2.25 H, *J* = 6.0; 0.81–1.32 *m*, 4.5 H; 1.37–1.92 *m*, 4 H; 1.94 *s*, 0.75 H; 2.01 *s*, 2.25 H; 2.04 *s*, 2.25 H; 2.11 *s*, 0.75 H; 1.94–2.21 *m*, 2 H; 4.68 *td*, 1 H, $J_{aa}$ = 10.8, $J_{ae}$ = 4.2; 5.86 *d*, 0.25 H, *J* = 10.2; 6.37 *d*, 0.75 H, *J* = 9.5; 7.24–7.38 *m*, 3 H; 7.44–7.58 *m*, 2 H. $^{13}$C-NMR: 170.46, 169.73, 134.78, 134.28, 133.91, 133.30, 132.65, 132.03, 129.51, 129.04, 128.85, 128.79, 120.20, 83.84, 83.36, 74.07, 73.84, 43.42, 42.54, 40.68, 40.61, 40.48, 34.59, 34.32, 31.06, 30.93, 29.67, 21.91, 21.72, 21.33, 20.90, 13.97, 11.61, 10.73.

*(–)-(1*R,*3*R,*4*S,*8*S*)-Menthane-3,9-diol* (**16**)

A solution of the product of the Pummerer rearrangement **14** (37 mg, 1.01 mmol) in $Et_2O$ (2 ml) was added to a suspension of $LiAlH_4$ (38.5 mg, 1.01 mmol) in $Et_2O$ (1 ml). The mixture was stirred at r.t. for 30 min and after the standard work up procedure, the crude oily product was purified by dry flash chromatography using successively petroleum ether/acetone 95 : 5, 90 : 10 and 80 : 20 as eluents. The title diol **16** was obtained as a white crystalline compound (16 mg, 93 % yield), m.p. 90 ºC (lit. 90 ºC)[10], $[\alpha]_D^{22}$ = –48.6 (*c* = 1 in $CHCl_3$). IR: 3256, 3223, 1487, 1455, 1413, 1375, 1345, 1324, 1276, 1234, 1168, 1107, 1081, 1050, 1017, 1000, 954, 918, 883, 845, 744. $^1$H-NMR: 0.85 *d*, 3 H, *J* = 7.1; 0.91 *d*, 3 H, *J* = 6.6; 0.71–1.12 *m*, 3 H; 1.25–1.55 *m*, 2 H; 1.58–1.68 *m*, 2 H; 1.93–2.11 *m*, 2 H; 3.39 *broad s*, 2 H 3.43 *td*, 1 H, $J_{aa}$ = 10.6, $J_{ae}$ = 4.2; 3.48 *dd*, 1 H, $J_{gem}$ = 10.6 $J_{vic}$ = 7.6; 3.58 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 5.6. $^{13}$C-NMR: 71.59, 66.53, 45.50, 45.04, 35.52, 34.28, 31.48, 25.16, 22.12, 12.47.

The spectral characteristics and m.p. of diastereoisomer **16** are identical with the same isomer independently prepared from **4** (according to Scheme 5).

*(–)-(1*R,*3*R,*4*S,*8*R*)-Menthane-3,9-diol* (**17**)

This diol was prepared from stereoisomer **15** according to the previous procedure. M.p. 107 ºC (lit. 107 ºC)[10], $[\alpha]_D^{22}$ = –16.2 (*c* = 1 in $CHCl_3$). IR: 3251, 1487, 1455, 1372, 1337, 1309, 1272, 1218, 1171, 1150, 1103, 1043, 1018, 993, 951, 846, 698. $^1$H-NMR: 0.92 *d*, 3 H, *J* = 6.9; 0.96 *d*, 3 H, *J* = 7.6; 0.77–1.05 *m*, 2 H; 1.12–1.48 *m*, 3 H; 1.50–1.69 *m*, 2 H; 1.76–2.03 *m*, 2 H; 3.28 *broad s*, 2 H 3.45 *td*, 1 H, $J_{aa}$ = 10.4, $J_{ae}$ = 4.2; 3.58 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 3.5; 3.66 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 5.3. $^{13}$C-NMR: 70.06, 67.07, 48.49, 44.50, 38.56, 34.54, 31.39, 29.49, 22.01, 11.85.

The stereoisomer **17** had identical spectral characteristics and m.p. as the same isomer independently prepared from **5** (according to Scheme 5).

The correlation of the stereochemistry of **4** with **16** as well as **5** with **17** (Scheme 5) support the proposed configuration of the C-8 carbon atom in **4** (*S*-configuration) and **5** (*R*-configuration).

*(–)-Isopulegol* (**18**)

To a solution of sulfoxide **12** (0.61 g, 2.17 mmol) in xylene (20 ml) was added sodium bicarbonate (1.83 g, 2.17 mmol) and the resulting suspension was heated to reflux (160 ºC) during 18 h. To the cold reaction mixture, ether (100 ml) was added and the mixture washed with water (2 × 20 ml). The solution was dried over anhydrous sodium sulfate and then the solvents were removed by evaporation. The residual oil was purified by dry flash chromatography on silica gel column using petroleum ether, petroleum ether/acetone 100 : 3 and petroleum ether/acetone 100 : 5 as an eluents. The solvents were removed by evaporation and 0.31 g (93 % yield) of (–)-isolpulegol (**18**) was obtained. IR: 3414, 1705, 1645, 1452, 1374, 1346, 1285, 1220, 1166, 1125, 1095, 1052, 1028, 1000, 930, 889, 847. $^1$H-NMR: 0.95 *d*, 3 H, *J* = 6.6; 0.80–1.06 *m*, 2 H; 1.13–1.42 *m*, 1H; 1.44–1.59 *m*, 1 H; 1.61–1.66 *m*, 1 H; 1.71 *s*, 3 H; 1.82–1.95 *m*, 2 H; 1.98–2.09 *m*, 1 H; 3.46 *td*, 1 H, $J_{aa}$ = 10.4, $J_{ae}$ = 4.2; 4.84–4.87 *m*, 1 H; 4.88–4.92 *m*, 1 H. $^{13}$C-NMR: 146.62, 112.83, 70.30, 54.06, 42.57, 34.25, 31.37, 29.57, 22.16, 19.12.

*(–)-(1*R,*3*R,*4*S,*8*S*)-Menthane-3,9-diol* (**16**)

Diol **16** was prepared from **4**[10,13,14] M.p. 90 ºC (lit. 90 ºC),[10] $[\alpha]_D^{22}$ –48.6 (*c* = 1 in $CHCl_3$). IR: 3256, 3223, 1487, 1455, 1413, 1375, 1345, 1324, 1276, 1234, 1168, 1107, 1081, 1050, 1017, 1000, 954, 918, 883,

845, 744. $^1$H-NMR: 0.85 *d*, 3 H, *J* = 7.1; 0.91 *d*, 3 H, *J* = 6.6; 0.71–1.12 *m*, 3 H; 1.25–1.55 *m*, 2 H; 1.58–1.68 *m*, 2 H; 1.93–2.11 *m*, 2 H; 5.39 *broad s*, 2 H; 3.43 *td*, 1 H, $J_{aa}$ = 10.6, $J_{ae}$ = 4.2; 3.48 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 7.6; 3.58 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 5.6. $^{13}$C-NMR: 71.59, 66.53, 45.50, 45.04, 35.52, 34.28, 31.48, 25.16, 22.12, 12.47.

The spectral characteristics and m.p. of diastereoisomer **16** prepared from (–)-isopulegol were identical with the same isomer prepared from **4** (according to Scheme 4).

*(–)-(1*R,*3*R,*4*S,*8*R*)-Menthane-3,9-diol* (**17**)

Diol **17** was prepared from **5**. M.p. 107 ºC (lit. 107 ºC),[10] $[\alpha]_D^{22}$ –16.2 (*c* = 1 in $CHCl_3$). IR: 3251, 1487, 1455, 1372, 1337, 1309, 1272, 1218, 1171, 1150, 1103, 1043, 1018, 993, 951, 846, 698. $^1$H-NMR: 0.92 *d*, 3 H, *J* = 6.9; 0.96 *d*, 3 H, *J* = 7.6; 0.77–1.05 *m*, 2 H; 1.12–1.48 *m*, 3 H; 1.50–1.69 *m*, 2 H; 1.76–2.03 *m*, 2 H; 3.28 *s*, *broad*, 2 H; 3.45 *td*, 1 H, $J_{aa}$ = 10.4, $J_{ae}$ = 4.2; 3.58 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 3.5; 3.66 *dd*, 1 H, $J_{gem}$ = 10.6, $J_{vic}$ = 5.3. $^{13}$C-NMR: 70.06, 67.07, 48.49, 44.50, 38.56, 34.54, 31.39, 29.49, 22.01, 11.85.

The stereoisomer **17** independently prepared from (–)-isopulegol had identical spectral characteristics and m.p. as the same isomer prepared from **5** (according to Scheme 4).

## ИЗВОД

## СТЕРЕОСЕЛЕКТИВНО СЛОБОДНОРАДИКАЛСКО ФЕНИЛСУЛФЕНИЛОВАЊЕ НЕАКТИВИРАНОГ δ-УГЉЕНИКОВОГ АТОМА

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Фотолизом (–)-ментил-бензенсулфената у присуству хексабутил-дикалаја извршено је стереоселективно увођење фенилтио групе на неактивирану метил групу у δ-положају која је суседна прохиралном угљениковом атому и добивен је (1*R*, 3*R*, 4*S*, 8*S*)-9-фенилтио-ментол (**4**) са 91 % оптичке чистоће. Висока стереоселективност реакције, потврђена рачуном (ab initio MP2/6-21G**), последица је разлике у енергијама прелазних стања ($\Delta\Delta G^{\#}$ = 5.08 kJ/mol) која фаворизује настајање **4** у односу на (1*R*, 3*R*, 4*S*, 8*R*)-9-фенилтио-ментол (**5**). Апсолутна конфигурација новог хиралног угљениковог атома потврђена је корелацијом с одговарајућим ментан-3,9-диолом познате стереохемије.

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