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Article

Cohalogenation of Limonene, Carvomenthene and Related Unsaturated Monoterpenic Alcohols

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A coalogenação de (*R*)-limoneno e (*R*)-carvomenteno com $I_2/H_2O/Cu(OAc)_2 \cdot H_2O$ em dioxano aquoso seguida por tratamento em meio básico produz estereoespecificamente os *trans*-epóxidos correspondentes. Já essa mesma metodologia de coalogenação aplicada a álcoois monoterpênicos insaturados estruturalmente relacionados produz derivados do pinol [a partir de (5*R*)-*cis*-carveol e (*S*)-α-terpineol] ou então iodoidrinas [a partir de (*S*)-álcool perílico e (5*R*)-*trans*-carveol].

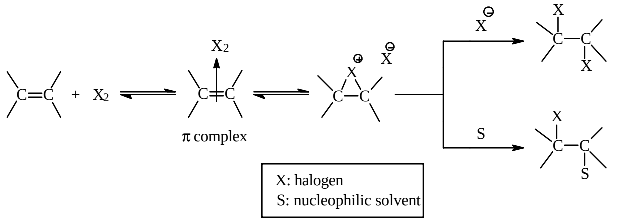
Cohalogenation of (*R*)-limonene and (*R*)-carvomenthene with $I_2/H_2O/Cu(OAc)_2 \cdot H_2O$ in aqueous dioxane followed by base treatment produced stereospecifically the corresponding *trans*-epoxides. Same methodology of cohalogenation applied to related monoterpenic unsaturated alcohols produced pinol derivatives [from (5*R*)-*cis*-carveol and (*S*)-α-terpineol] or iodohydrins [from (*S*)-perillyl alcohol and (5*R*)-*trans*-carveol].

Keywords: cyclisation, halohydrins, terpenes and terpenoids, electrophilic addition reaction

Introduction

Electrophilic halogenation of alkenes to produce vicinal dihaloalkanes is a well-known reaction in organic chemistry[1]. A proposed mechanism for it goes through a π complex among alkene and halogen, followed by decomposition to a bridged halonium ion intermediate and then a nucleophilic opening by the halide ion[2]. However, when the halogenation of the alkene is carried out in a nucleophilic solvent (water, alcohols, carboxylic acids, nitriles, etc), a competition between the halide ion and the solvent for opening of the halonium ion can occur and difunctionalized products are obtained[2]. This process, termed 'cohalogenation', proved to be useful for diverse synthetic applications[2,3] (Scheme 1).

Recently, we published an efficient coiodination of simple alkenes with oxygenated nucleophiles promoted by $Cu(OAc)_2 \cdot H_2O$ and other metal salts[4] or by 2 mol equiv. of iodine in place of the metal salt[5]. Thus, using this simple methodology, iodohydrins[4,6] and β-iodoethers[5] were effectively prepared in good yields and high purity when the iodination of alkenes was performed in water or alcohols, respectively.



Scheme 1.

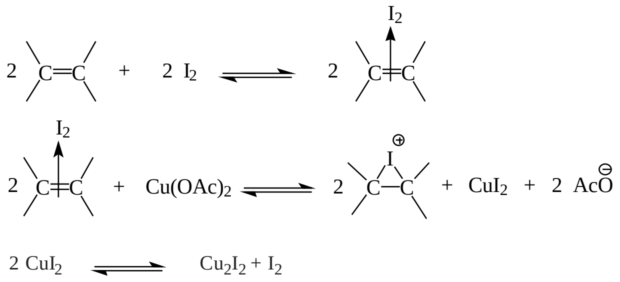
The role of the metal salt or of the second equivalent of iodine in the coiodination reactions is to decompose the π complex formed among alkene and iodine to the bridged iodonium ion[5,7]. In the case of $Cu(OAc)_2$, cupric iodide is formed followed by disproportionation to cuprous iodide and iodine[7] (Scheme 2). As iodine is formed from CuI_2, less than 1 mol equiv. of it is required for these reactions. On the other hand, in the absence of the metal salt (or without excess iodine), low conversion and poor yields of products are observed[4,7].

Herein we communicate our results on the cohalogenation of limonene, carvomenthene and related unsaturated monoterpenic alcohols, namely carveols, α-terpineol, and perillyl alcohol[8].

Results and Discussion

The reaction of (*R*)-limonene (**1**) with iodine in aque-

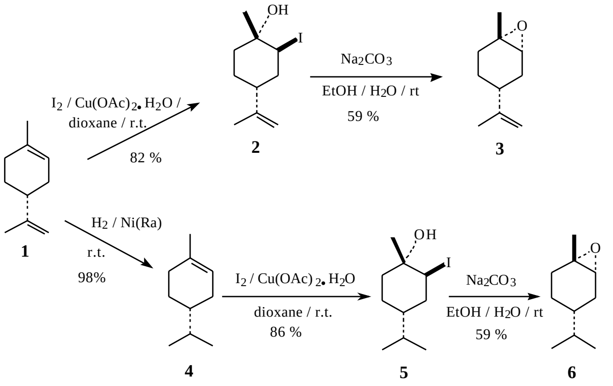
Dedicated to our teacher and mentor W. Bruce Kover, who taught us to find the beauty of each reaction.



Scheme 2.

ous dioxane in the presence of Cu(OAc)$_2$·H$_2$O was carried out at room temperature (rt) stirring together 1 mol equiv. of **1**, 0.5 mol equiv. of Cu(II) salt and addition of 0.75 mol equiv. of iodine. After NaBH$_4$ reduction of the remaining excess of iodine and work up, HRGC (high-resolution gas chromatography) analysis of the crude material showed the unstable iodohydrin **2** (82 %) along with recovered substrate (*ca.* 15 %). Several attempts to purify **2** were unsuccessful and only dark products and intense gas evolution were obtained. Treatment of **2** with Na$_2$CO$_3$ in aqueous ethanol produced pure trans-1,2-epoxylimonene[9,10] (**3**) in 59 % isolated yield.

Catalytic hydrogenation of (*R*)-limonene to (*R*)-carvomenthene (**4**) and similar cohalogenation led to the iodohydrin **5** in 86 % crude yield (*ca.* 8 % recovered substrate). Base treatment of **5** produced *trans*-epoxycarvomenthene[11] (**6**) in 59 % yield. Scheme 3 summarizes all results.



Scheme 3.

The characterization of **3** and **6** were made by comparison of their spectral data with those previously reported[10,11] and by the ^{13}C NMR values of chemical shift for the γ-carbon of the epoxides and the parent alkenes, assuming that there is no significant difference if the epoxide ring is *trans* to the γ-carbon hydrogen[12] (see Figure 1).

The results on the cohalogenation of limonene are important because electrophilic additions to it lack stereo and chemoselectivity[13]. The *trans*-epoxides were obtained stereospecifically and usual oxidation (peracids and related oxidants) of limonene and carvomenthene produced both a 1:1 mixture of *cis*- and *trans*-epoxides[14], useful intermediates in synthesis of natural products[15]. Although the separation of both *cis*- and *trans*-1,2-epoxylimonene can be achieved by careful spinning-band distillation[16], this is a difficult and slow task and more practical methods of obtaining the pure *trans*-epoxide involve selective chemical transformation of the 1:1 mixture of isomers[10] or reaction of limonene with NBS/H$_2$O followed by base treatment[17]. Moreover, *trans*-1,2-epoxylimonene is more reactive than *cis* and so it is selectively opened on nucleophilic additions to the mixture of *cis*- and *trans*-1,2-epoxylimonene[18].

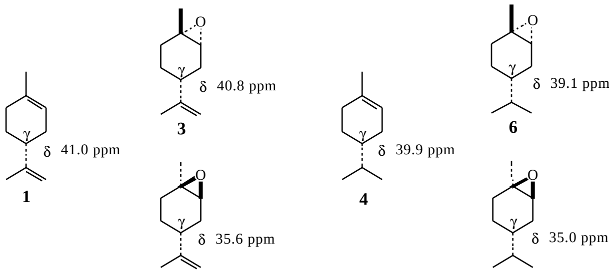
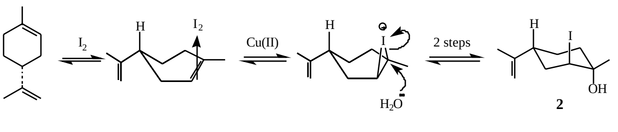


Figure 1. ^{13}C NMR chemical shifts (in CDCl$_3$, relative to TMS) of γ-carbon for limonene, carvomenthene and related 1,2-epoxides.

A proposed mechanistic scheme (Scheme 4) for the stereospecific formation of the iodohydrin **2** derived from limonene (and the analogue **5** from carvomenthene) assumes a π complex *anti* to the isopropenyl (or isopropyl) group, followed by its decomposition to the iodonium ion and an antiperiplanar opening by an axial[19] nucleophilic attack of water on the tertiary carbon to produce the *trans*-diaxial iodohydrin. Stereospecific formation of epoxides by base promoted cyclisation of halohydrins is vastly described in the literature[20].

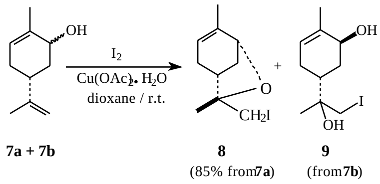


Scheme 4.

The above results led us to investigate the extension of this methodology of cohalogenation with unsaturated monoterpenic alcohols, as a possible route of cyclofunctionalization[21] to produce functionalized bicyclic ethers.

The reaction of (5*R*)-*carveols* **7** (1:1 mixture of *cis* **7a** and *trans* **7b** isomers by HRGC) with I$_2$/H$_2$O/Cu(OAc)$_2$·H$_2$O for

5 h led to an iodopinol derivative (**8**)[22] and an iodohydrin (**9**)[23], as shown in Scheme 5.



Scheme 5.

Control experiments showed that *cis*-carveol (**7a**) was completely converted to **8** (85 % isolated yield based on **7a**) in 1 h while **7b** was unchangeable. After that, *trans*-isomer (**7b**) was slowly and incompletely converted to the iodohydrin **9** among other unidentified products. The structure of **8** was determined by ^1H and ^{13}C NMR 1D and 2D NMR techniques[24] (COSY, HMQC, and HMBC) and its relative stereochemistry was established with the aid of NOESY experiment that showed the cross signals shown in Figure 2[25].

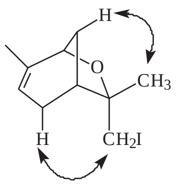
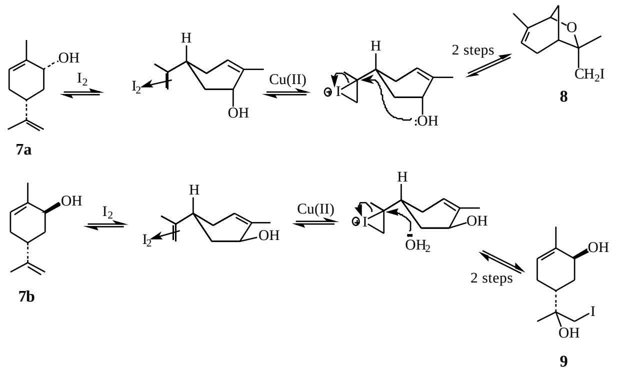


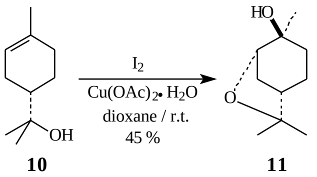
Figure 2. Essential NOE observed in NOESY spectra for determination of relative stereochemistry of **8**.

These results contrast with those obtained for limonene and carvomenthene, where the reaction occurred at the trisubstituted double bond. In the case of carveols, probably due to electronic reasons, the allylic hydroxyl group deactivates the trisubstituted double bond to an electrophilic attack[26] and the π complex of I_2 is formed with the disubstituted double bond. Furthermore, the relative position of the hydroxyl is crucial to the nature of the products. When the hydroxyl is *cis* to the isopropenyl group (as in *cis*-carveol **7a**) it can open the iodonium ion producing the iodo-bicyclic ether **8**. On the other hand, if the hydroxyl is *trans* to isopropenyl (*trans*-carveol **7b**), this intramolecular process is less favorable and water in the media slowly opens the iodonium ion producing the iodohydrin **9** (Scheme 6).

The reaction of (*S*)-α-terpineol (**10**) with iodine and water in the presence of cupric acetate led predominantly to *trans*-4-hydroxy-dihydropinol (**11**)[27] along with some unidentified minor products. From the reaction mixture, **11** was isolated in 45 % yield after radial chromatography (Scheme 7).



Scheme 6.



Scheme 7.

The structure of **11** was determined by ^1H NMR (that showed a sharp signal of a tertiary hydroxyl group upon changing the solvent from $CDCl_3$ to DMSO-d_6) along with ^1H and ^{13}C NMR 1D and 2D techniques[24], assuming the most stable conformation being a bridged chair form[28]. NOESY experiment showed the cross signals shown in Figure 3[25].

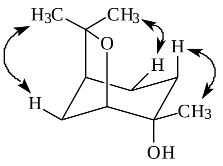
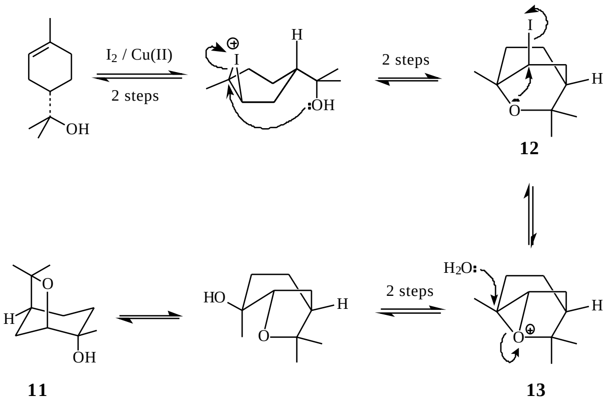


Figure 3. Essential NOE observed in NOESY spectra for determination of relative stereochemistry of **11**.

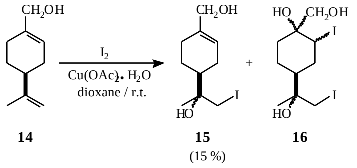
The formation of the dihydropinol derivative **11** by the cohalogenation methodology is an attractive alternative to the thallium(III)-induced cyclization of α-terpineol[29].

A proposed mechanistic scheme (Scheme 8) for the rationalization of the hydroxy-dihydropinol **11** could be the formation of an iodonium ion (similar in the case of limonene and carvomenthene) followed by intramolecular opening to the unstable β-iodoether intermediate **12** (detected by MS in the reaction media[30]). This kind of intermediate easily rearranges through a bridged oxonium ion (**13**) to dihydropinol derivatives[31]. Regiospecific opening of the oxonium ion by H_2O produced **11** in two further steps.



Scheme 8.

Reaction of (*S*)-perillyl alcohol (**14**) with $I_2/H_2O/Cu(OAc)_2{\cdot}H_2O$ was not completed after several hours and produced the diastereomeric iodohydrins **15** predominantly along with diiodohydrin[32] **16** (*ca.* 18:1 by HRGC) and several others minor products (epoxides, iodo-triols, etc) - Scheme 9. From this reaction mixture, **15** (a diastereomeric mixture) was isolated in 15 % yield after radial chromatography. Once more, no bicyclic products were formed because it would be necessary a bridgehead unsaturated seven-membered cyclic transition state. Attempts to improve the yield of **15**, lower the subproducts or increase the consumption of perillyl alcohol were unsuccessful. No significative changes in the crude reaction mixture were observed in HRGC analysis when the cohalogenation was performed with 2 mol equiv. I_2 in the place of cupric acetate[5].



Scheme 9.

In summary, cohalogenation of limonene and carvomenthene with $I_2/Cu(OAc)_2{\cdot}H_2O$ in aqueous dioxane produce stereospecifically iodohydrins which upon base treatment are converted to the respective epoxides. On the other hand, when the cohalogenation is applied to related unsaturated monoterpenic alcohols, the nature of products is highly dependent on the structure of substrates. Thus, iodohydrins and bicyclic ethers are produced from inter- or intramolecular reactions, respectively.

Experimental

(*R*)-Limonene {$[\alpha]_D^{28}$ + 118.7 (neat)} and (*S*)-α-terpineol {$[\alpha]_D^{28}$ - 76.0 (c 1.0, $CHCl_3$)} were purchased from Dierberger, (5*R*)-carveols {$[\alpha]_D^{28}$ - 108.1 (c 1.1, $CHCl_3$), *ca.* 1:1 mixture of *cis*- and *trans*-isomers} and (*S*)-perillyl alcool {$[\alpha]_D^{28}$ - 91.0 (c 1.0, $CHCl_3$)} were purchased from Aldrich.

(*R*)-Carvomenthene {$[\alpha]_D^{28}$ + 78.5 (c 2.0, $CHCl_3$)} was prepared in 98 % yield (> 99 % purity) by catalytic hydrogenation of (*R*)-limonene, as described by Jackman *et al.*[33]

Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series FTIR (film in NaCl pellets). Analyses by HRGC were performed on a HP-5890-II gas chromatograph with FID by using a RTX-5 silica capillary column and H_2 (flowrate 50 cm/s) as carrier gas. Mass spectra (MS) were obtained on a Hewlett-Packard HP 5896-A (column: SE-54) or on a Hewlett-Packard HP 5937 (column: OV-1) HRGC-MS spectrometers using electron impact (70 eV). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were acquired on a Bruker spectrometer for $CDCl_3$ solutions with TMS as internal standard. Polarimetric analyses were performed on a Jasco DIP 370 polarimeter.

(1S,2S,4R)-2-Iodo-4-isopropenyl-1-methylcyclohexanol (**2**)

To a stirred solution of (*R*)-limonene (1.36 g, 10.00 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (1.00 g, 5.00 mmol) in dioxane (22 ml) and water (3 ml), was added I_2 (1.90 g, 7.50 mmol) in small lots at rt. After 4 h, Cu_2I_2 was filtered off and $CHCl_3$ (30 ml) was added to the filtrate. The resulting solution was treated with a suspension of $NaBH_4$ (1 g) in EtOH (50 ml) and then washed with water (3 × 20 ml). The organic layer was dried (Na_2SO_4) and filtered through a small silica gel column. The solvent was evaporated in a rotatory evaporator at reduced pressure and low heating to produce crude **2** (2.30 g, 8.21 mmol, 82 %), along with recovered limonene (15 %). $[\alpha]_D^{28}$ + 103.5 (c 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.00-2.00 (m, 7H), 1.37 (s, 3H), 1.44 (s, 3H), 2.85 (br s, 1H), 4.46 (d, 1H, J 8.5 Hz), 5.12 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 21.3 (CH_3), 26.1 (CH_2), 30.5 (CH_3), 33.5 (CH_2), 37.4 (CH_2), 40.0 (CH), 43.1 (CH), 70.4 (C), 109.4 (CH_2), 148.2 (C) ppm. MS: m/z (%): 280 (M^+, 1), 153 (42), 135 (62), 107 (46), 93 (50), 71 (58), 43 (100).

trans-1,2-Epoxy-(R)-limonene (**3**)

The crude iodohydrin **2** (2.30 g, 8.21 mmol) was treated with Na_2CO_3 (1.59 g, 15.00 mmol) in water (40 ml) and ethanol (10 ml). After stirring for 24 h at rt the reaction mixture was extracted with ether (3 x 10 ml) and the organic phase dried (Na_2SO_4). The solvent was evaporated in a rotatory evaporator at reduced pressure and the residue purified by column chromatography (SiO_2, hexane, chloroform) to give epoxide **3** (0.74 g, 4.87 mmol, 59 %). $[\alpha]_D^{28}$ + 78.0 (c 1.0, $CHCl_3$). IR: ν_{max} 3072, 2960, 2920, 2860, 1637, 1437, 1373, 920, 890, 838 cm^{-1}. ^1H NMR ($CDCl_3$):

δ 1.31-1.43 (m, 2H), 1.34 (s, 3H), 1.68 (s, 3H), 1.65-1.77 (m, 2H), 1.80-1.95 (m, 1H), 2.00-2.10 (m, 2H), 2.99 (d, 1 H, J 5.38 Hz), 4.66 (br s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ 18.1 (CH_3), 20.2 (CH_3), 23.1 (CH_2), 30.0 (CH_2), 30.8 (CH_2), 40.8 (CH), 53.4 (C), 57.5 (CH), 109.1 (CH_2), 149.2 (C) ppm. MS: m/z (%):152 ($M^{+\bullet}$, 2), 137 (4), 123 (5), 108 (42), 94 (62), 67 (62), 43 (100).

(1S,2S,4R)-2-Iodo-4-isopropyl-1-methylcyclohexanol (**5**)

(*R*)-Carvomenthene (1.38 g, 10.00 mmol) used instead of (*R*)-limonene, other reagents and conditions being as described for **2** above. After all, it was obtained 2.43 g (8.62 mmol, 86 %) of crude **5**, along with recovered carvomenthene (8 %). $[\alpha]_D^{28}$ + 64.3 (c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.90-2.02 (m, 8H), 1.37 (s, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 2.85 (br s, 1H), 4.40 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.1 (CH_3), 20.2 (CH_3), 24.6 (CH_2), 30.9 (CH_3), 31.6 (CH), 33.5 (CH_2), 36.5 (CH_2), 39.5 (CH), 43.1 (CH), 71.5 (C) ppm. MS: m/z (%): 267 ($M^{+\bullet}$ - Me, 2), 249 (2), 155 (75), 137 (80), 95 (71), 93 (50), 81 (90), 43 (100).

trans-Epoxy-(R)-carvomenthene (**6**)

The crude iodohydrin **5** (2.43 g, 8.62 mmol) was treated as described for **3** above to give epoxide **6** (0.78 g, 5.06 mmol, 59 %). $[\alpha]_D^{28}$ + 42.9 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 6H), 1.30-1.34 (m, 1H), 1.31 (s, 3H), 1.37-1.40 (m, 2H), 1.53-1.62 (m, 2H), 1.70 (m, 2H), 1.98 (m, 1H), 2.98 (d, 1 H, J 5.37 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 19.2 (CH_3), 19.5 (CH_3), 22.4 (CH_3), 23.0 (CH_2), 27.7 (CH_2), 30.8 (CH_2), 32.1 (CH), 39.1 (CH), 57.7 (C), 59.5 (CH) ppm. MS: m/z (%): 154 ($M^{+\bullet}$, 5), 139 (20), 125 (12), 111 (50), 95 (10), 83 (20), 69 (40), 43 (100).

Typical procedure for the cohalogenation of unsaturated monoterpenic alcohols

To a stirred a solution of appropriated unsaturated monoterpenic alcohol (5.00 mmol) and $Cu(OAc)_2 \cdot H_2O$ (1.00 g, 5.00 mmol) in dioxane (10 ml) and water (2 ml), was added I_2 (0.95 g, 3.75 mmol) in small portions at rt. After 16 h (1 h for carveols), the reaction media was filtered and $CHCl_3$ (15 ml) was added to the filtrate. The resulting solution was washed with a saturated solution of Na_2SO_3 (3 × 10 ml), the organic layer dried (Na_2SO_4) and filtered through a small silica gel column. The solvent was removed under reduced pressure and low heating and the crude product purified by radial chromatography using CH_2Cl_2 as eluent.

(1R,5R,6S)-2,6-dimethyl-6-iodomethyl-7-oxabicyclo[3.2.1]-oct-2-ene (**8**)

It was obtained 1.18 g [4.24 mmol, 85 % from (5*R*)-*cis*-carveol]. $[\alpha]_D^{28}$ - 17.8 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 3H), 1.72 (m, 3H), 1.94 (d, 1H, J 10.74 Hz), 2.34 (m, 3H), 2.52 (m, 1H), 3.36 (dd, 2H, J 22.61 Hz, 9.69 Hz), 4.15 (d, 1H, J 4.41 Hz), 5.26 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_2), 17.9 (CH_3), 27.9 (CH_3), 29.7 (CH_2), 35.1 (CH_2), 40.7 (CH), 77.6 (CH), 84.1 (C), 120.7 (CH), 139.8 (C) ppm.

(1S,2S,5S)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]-octan-2-ol (**11**)

It was obtained 0.38 g (2.24 mmol, 45 % from (*S*)-α-terpineol). $[\alpha]_D^{28}$ + 25.6 (c 10.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 3H), 1.24 (s, 3H), 1,38 (s, 3H), 1.43 (m, 2H), 1.66 (m, 2H), 1.84 (m, 2H), 2.17 (m, 2H), 3.81 (d, 1H, J 5.37 Hz) ppm. ^{1}H NMR (DMSO-D_6): δ 1.13 (s, 3H), 1.21 (s, 3H), 1.37 (s, 3H), 1.43 (m, 1H), 1.74 (m, 3H), 1.88 (m, 1H), 2.05 (m, 1H), 2.25 (d, 1H, J 11.55 Hz), 3.68 (d, 1H, J 6.33 Hz), 4.45 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.5 (CH_3), 24.3 (CH_2), 28.7 (CH_3), 30.2 (CH_3), 31.9 (CH_2), 33.1 (CH_2), 41.3 (CH), 72.1 (C), 82.3 (C), 82.5 (CH) ppm. MS: m/z (%) 170 ($M^{+\bullet}$, 5), 155 (2), 137 (1), 126 (23), 111 (10), 109 (16), 97 (18), 83 (10), 71 (45), 43 (100), 69 (27).

(1'S,2RS)-2-(4'-hydromethyl-3'-cyclohexenyl)-1-iodo-2-propanol (**15**)

It was obtained 0.22 g [0.74 mmol, diastereoisomeric mixture, 15 % from (*S*)-perillyl alcohol]. $[\alpha]_D^{28}$ - 32.1 (c 0.7, $CHCl_3$). IR: ν_{max} 3363, 1674, 1642, 1191, 1029 cm^{-1}. ^{1}H NMR: δ 1.25 (d, J 6.08 Hz), 1.82 (m), 2.15 (m), 3.45 (m), 4.05 (br s), 5.70 (m) ppm. ^{13}C NMR: δ 21.70 (CH_3), 22.7 (CH_2), 23.1 (CH_2), 23.3 (CH_2), 23.5 (CH_3), 24.1 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 42.2 (CH), 42.6 (CH), 66.9 (CH2), 67.0 (CH2), 72.1 (C), 72.2 (C), 121.5 (CH), 122.2 (CH), 137.3 (C), 137.9 (C) ppm. MS: m/z (%) 278 ($M^{+\bullet}$- H_2O, 4), 220 (2), 185 (63), 169 (8), 151 (18), 133 (65), 93 (75), 79 (100), 43 (37).

Acknowledgments

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