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# Synthesis and Some Transformations of (–)-Carveol

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**Abstract**—Reduction of the oxo group in (–)-carvone with $LiAlH_4$, $NaBH_4$, and $(i\text{-Bu})_2AlH$ was performed. It was found that the reduction with the system $CeCl_3 \cdot 7H_2O$–$NaBH_4$ in methanol at 20°C is the most practical procedure for the synthesis of (–)-carveol. Solvolysis of (–)-carvyl methanesulfonate gave products of $S_N2$ and $S_N2'$ replacement of the methylsulfonyloxy group, the latter slightly prevailing. Overman rearrangement of (–)-carveol resulted in the formation of the corresponding trichloroacetamide derivative, and intramolecular iodoetherification of the title compound afforded 6-iodomethyl-2,6-dimethyl-7-oxabicyclo[3.2.1]oct-2-ene.

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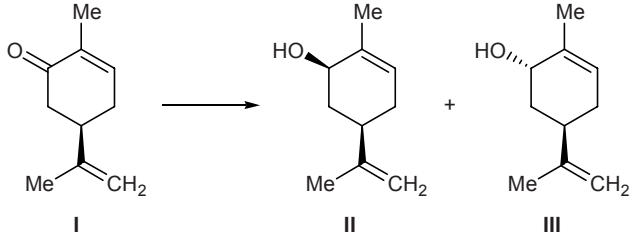
Commercially available and cheap monoterpene (*R*)-(–)-carvone (**I**) is widely used in organic synthesis as chiral template [1–5]. In the present work we examined some aspects of selective transformations of (–)-carvone into building blocks that are more suitable for subsequent target-oriented syntheses. Initially, we planned to obtain (–)-carveol (**II**) by reduction of **I** with lithium tetrahydridoaluminate in diethyl ether at –78°C [6]. According to the GLC data, the purity of compound **II** synthesized in this way was 95%, and the concentration of minor (–)-carveol (**III**) reached 5%. The best results (from the viewpoint of stereoselectivity) were obtained using Luche's reagent ($NaBH_4$–$CeCl_3 \cdot 7H_2O$) [7]. In this case, the reduction of (–)-carvone (**I**) in methanol at room temperature gave (–)-carveol (**II**) in 90% yield, and its purity was 98% (after chromatographic purification on silica gel; cf. [8–10]) (Scheme 1). In the reduction of **I** with Luche's reagent in THF the yield of (–)-**II** was 96%, and the reduction with $(i\text{-Bu})_2AlH$ in $CH_2Cl_2$ at –78°C gave 80% of (–)-**II**. From the preparative viewpoint, it is convenient to perform reduction of (–)-**I** in methanol with subsequent purification of the product by vacuum distillation, although in this case the yield of (–)-**II** is somewhat lower (~80%).

**Scheme 1.**

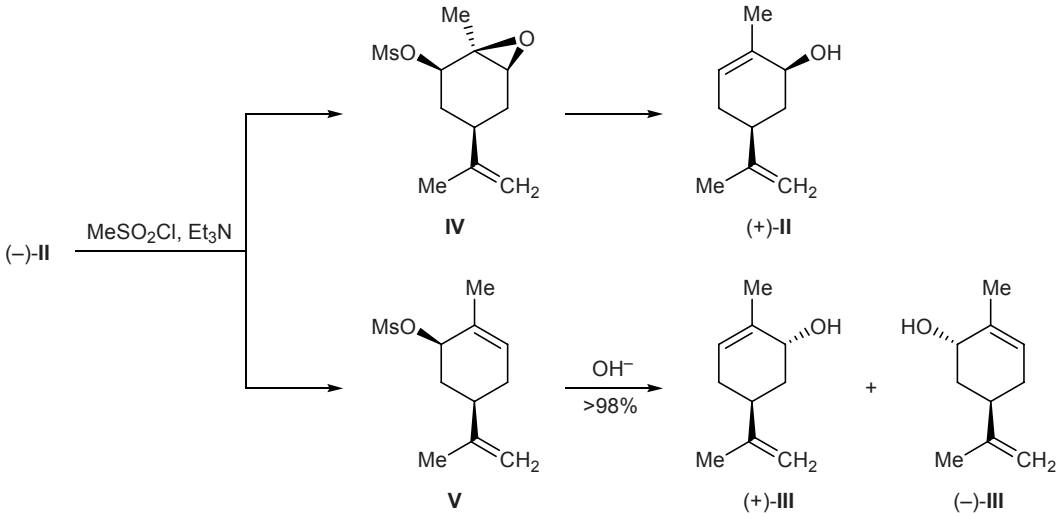



**I** **II** **III**

We made an attempt to convert (–)-carveol (**II**) into its enantiomer. The known procedure for the transformation of (–)-**II** into (+)-**II** includes initial preparation of epoxy derivative, mesylation, and reductive fragmentation of methanesulfonate **IV** with "dissolved metal" (Scheme 2). The yield of (+)-carveol (+)-**II** in the latter step was moderate (57%) [11]. We tried a shorter way of converting carveol enantiomers into each other via solvolysis of allylic methanesulfonates, which follows $S_N2'$ mechanism. For this purpose, (–)-carveol (**II**) was treated with methanesulfonyl chloride in the presence of triethylamine, and methanesulfonate **V** thus obtained was heated for 1 h at 60°C in a mixture of DMSO and 10% aqueous sodium hydroxide (1 : 1 by volume). The subsequent chromatographic purification on silica gel gave pure (according to the GLC data) carveol (**III**, $[\alpha]_D^{20} = +17^o$).

In our case, the initial (–)-carveol (**II**) had $[\alpha]_D^{20} = -25.4°$ {published data: $[\alpha]_D^{20} = -25.8$ [6], –23.9 [12], –23.0 ($c$ = 5.6, EtOH, *ee* 100%) [11]}; (–)-**III**: $[\alpha]_D^{20} = -213.8$ [12]. Obviously, the observed optical rotation of solvolysis product **III** results from the presence of a small excess of enantiomeric (+)-carveol (**III**) which is formed according to the $S_N2'$ mechanism. Taking into account that racemization is hardly probable under the above conditions (alkaline medium), (–)-carveol (**III**) is likely to be formed via $S_N2$ substitution of the

**Scheme 2.**




methylsulfonyloxy group in (–)-(**V**) by hydroxy group. We can conclude that the solvolysis of methanesulfonate **V** is not regioselective and that it follows both possible paths, $S_N2$ and $S_N2'$, though each of these paths is stereoselective [only (+)- or (–)-carveol (**III**) is formed].

With a view to obtain nitrogen-containing chiral building blocks, (–)-carveol (**II**) was subjected to Overman rearrangement [13]. Treatment of (–)-**II** with trichloroacetonitrile in methylene chloride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0°C gave trichloroacetimidate **VI** which was converted into trichloroacetamide **VII** by heating in boiling xylene (Scheme 3). It is known that this [3,3]-sigmatropic rearrangement is suprafacial and stereospecific.

(–)-Carveol (**II**) was then subjected to intramolecular iodoetherification. *cis* Arrangement of the isopropenyl and hydroxy groups in its molecule favored iodine-initiated intramolecular cyclization with preferential formation of sterically less hindered bicyclic product **VIII** (Scheme 4). Minor stereoisomer **IX** was formed in trace amounts (3–5%) and was detected by downfield signals from the $C^6$Me group in the $^{13}C$ NMR spectrum.

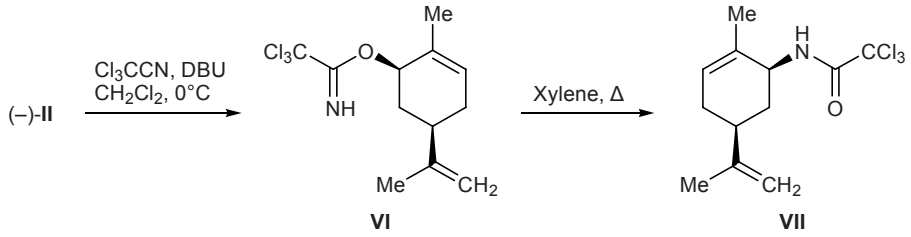
Thus we proposed a highly stereoselective and practical procedure for the reduction of (–)-carvone to (–)-carveol using the system $NaBH_4$–$CeCl_3 \cdot 7H_2O$ and studied solvolysis of the corresponding methanesulfonate. (–)-Carveol (**II**) was converted into *N*-carvyltrichloroacetamide via Overman rearrangement, and intramolecular iodoetherification of (–)-**II** gave iodomethyl-substituted bicyclic ether.

## EXPERIMENTAL

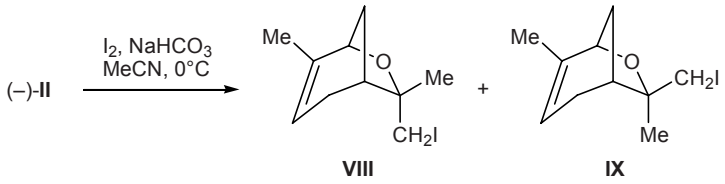
The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films. The $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. Thin-layer chromatography was performed on Silufol plates. The optical rotations were measured on a Perkin–Elmer 241 MS polarimeter. The purity of the initial compounds was checked by GLC on a Chrom 5 chromatograph.

**Reduction of (*R*)-(–)-carvone with $LiAlH_4$.** A solution of 5 g (33 mmol) of (*R*)-(–)-carvone in 10 ml of diethyl ether was added dropwise to a suspension of

**Scheme 3.**



**Scheme 4.**




**VIII** **IX**

0.32 g (8.3 mmol) of $LiAlH_4$ in 30 ml of diethyl ether under stirring at –78°C in a stream of argon. The mixture was stirred for ~1.5 h until the initial ketone disappeared (TLC). Excess $LiAlH_4$ was decomposed by carefully adding 10% sulfuric acid at 0°C to pH ~7. The organic phase was separated, the aqueous phase was extracted with ethyl acetate (3×15 ml), and the extracts were combined with the organic phase, washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:3) as eluent. We isolated 4.8 g (95%) of a mixture of stereoisomers (–)-**II** and (–)-**III** at a ratio of 95:5 (according to the GLC data). Light yellow oily liquid, $[\alpha]_D^{20}$ = –25.4° (*c* = 2.1, EtOH); published data [6]: $[\alpha]_D^{20}$ = –25.8° (ee 97%).

**(1*R*,5*R*)-5-Isopropenyl-2-methylcyclohex-2-en-1-ol (II).** IR spectrum, ν, $cm^{-1}$: 3331 (OH), 3082 (=C–H), 1645 (C=C). $^1H$ NMR spectrum, δ, ppm: 1.47–1.52 m (1H, 6-H), 1.72 s (3H, $CH_3$), 1.74 d (3H, $CH_3$, *J* = 2 Hz), 1.85–2.30 m (5H, 4-H, 5-H, 6-H, OH), 4.17 br.s (1H, 1-H), 4.71 s (2H, $=CH_2$), 5.44 m (1H, 3-H).

**Reduction of (–)-carvone (I) with $NaBH_4$–$CeCl_3\cdot 7H_2O$.** *a*. Sodium tetrahydridoborate, 0.025 g (0.67 mmol), was added at 20°C to a solution of 0.1 g (0.67 mmol) of (–)-carvone (**I**) and 0.25 g (0.67 mmol) of $CeCl_3\cdot 7H_2O$ in 10 ml of methanol. The mixture was stirred for 5 min, 20 ml of diethyl ether and 20 ml of water were added, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×10 ml). The extracts were combined with the organic phase, dried over $Na_2SO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:5) to isolate 0.09 g (90%) of (–)-carveol (**II**).

*b*. Likewise, the reduction of (–)-**I** with $CeCl_3\cdot 7H_2O$–$NaBH_4$ in THF at 0°C gave 90% of (–)-**II** with a purity of 98% (according to the GLC data).

**Reduction of (–)-carvone (I) with $(i\text{-Bu})_2AlH$.** A solution of 2.7 mmol of $(i\text{-Bu})_2AlH$ in 5 ml of anhydrous methylene chloride was added dropwise under stirring to a solution of 0.1 g (0.67 mmol) of (–)-**I** in 20 ml of anhydrous methylene chloride, cooled to –70°C. The mixture was stirred for 1 h at that temperature, 0.17 ml of water was slowly added dropwise, the mixture was allowed to warm up to 25°C, the solvent was distilled off under reduced pressure, and the powder-like residue was extracted with hot methanol (3×10 ml). The extract was evaporated, and the residue was dried with benzene (azeotropic distillation). We thus isolated 0.08 g (80%) of a mixture of stereoisomers (–)-**II** and (–)-**III** at a ratio of 4:1 (according to the $^1H$ NMR data).

**5-Isopropenyl-2-methylcyclohex-2-en-1-ol (III).** Carvyl methanesulfonate (**IV**), 0.7 g (4.6 mmol), was added under stirring to 40 ml of a 1:1 mixture of DMSO with 5% aqueous sodium hydroxide. The mixture was stirred for 5 h at room temperature (until the initial compound disappeared according to the TLC data), neutralized with 5% hydrochloric acid, and extracted with methylene chloride (3×20 ml). The extracts were combined, dried over $MgSO_4$, and evaporated. After removal of DMSO under reduced pressure, the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:3) as eluent to isolate 0.45 g (99%) of compound **III** as a mixture of enantiomers, $[\alpha]_D^{20}$ = +17.2° (*c* = 0.85, EtOH). IR spectrum, ν, $cm^{-1}$: 3334 (OH), 3082, 1645. $^1H$ NMR spectrum, δ, ppm: 1.58–1.62 m (1H, 6-H), 1.76 s (3H, $CH_3$), 1.82 s (3H, $CH_3$), 1.92–1.97 m (3H, 4-H, 6-H), 2.13–2.34 m (2H, 5-H, OH), 4.04 m (1H, 1-H), 4.74–4.76 m (2H, $=CH_2$), 5.59–5.61 m (1H, 3-H). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 20.85 ($CH_3$), 20.91 ($CH_3$), 30.99 ($C^4$), 35.23 ($C^5$), 36.71 ($C^6$), 68.64 ($C^1$), 109.06 ($=CH_2$), 125.47 ($C^3$), 134.22 ($C^2$), 149.15 (**C**$=CH_2$).

**(1*R*,5*R*)-5-Isopropenyl-2-methylcyclohex-2-en-1-yl methanesulfonate (V).** Triethylamine, 1.3 g (13 mmol), was added under stirring in a stream of argon to a solution of 1.0 g (6.6 mmol) of (–)-carveol (**II**) prepared as described above (method *a*) in 20 ml of methylene chloride. The mixture was stirred for 15 min, a solution of 1.5 g (13 mmol) of methanesulfonyl chloride in 15 ml of methylene chloride was

slowly added dropwise, and the mixture was stirred for 4 h at 40°C, cooled, and neutralized to pH ~7 with 3% hydrochloric acid. The organic phase was separated, and the aqueous phase was extracted with methylene chloride (3×10 ml). The extracts were combined with the organic phase, dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography on silica gel using ethyl acetate–petroleum ether (1:5) as eluent. Yield 0.9 g (60%), light yellow oily liquid, $[\alpha]_D^{20}$ = –57.5° (*c* = 1.7, EtOH). IR spectrum, ν, $cm^{-1}$: 3082, 1645, 1440 ($SO_2$), 1379 (S–$CH_3$). $^1H$ NMR spectrum, δ, ppm: 1.56 m (1H, 6-H), 1.76 s (3H, $CH_3$), 1.83 s (3H, $CH_3$), 1.94–2.25 m (4H, 4-H, 5-H, 6-H), 2.15 s (3H, $SO_2CH_3$), 4.74 br.s (3H, =$CH_2$, 1-H), 5.52–5.54 m (1H, 3-H). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 20.93 ($CH_3$), 21.07 ($CH_3$), 30.76 ($C^4$), 34.86 ($C^5$ and $SO_2CH_3$), 37.14 ($C^6$), 60.67 ($C^1$), 109.26 (=$CH_2$), 126.53 ($C^3$), 133.15 ($C^2$), 148.45 (**C**=$CH_2$).

**2,2,2-Trichloro-1-[(1*R*,5*R*)-5-isopropenyl-2-methylcyclohexen-2-en-1-yloxy]ethan-1-imine (VI).** (–)-Carveol (**II**), 1 g (6.6 mmol), was dissolved in 20 ml of methylene chloride, 2 g (13 mmol) of DBU was added under stirring, the mixture was stirred for 15 min, and a solution of 1.9 g (13 mmol) of trichloroacetonitrile in 10 ml of methylene chloride was carefully added dropwise. The mixture was stirred for 6 h at room temperature until the initial compound disappeared (TLC), 10 ml of a saturated aqueous solution of ammonium chloride was added, the organic phase was separated, and the aqueous phase was extracted with methylene chloride (3×15 ml). The extracts were combined with the organic phase, washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:5) as eluent. Yield 1.45 g (74%), light yellow liquid, $[\alpha]_D^{20}$ = –19.4° (*c* = 1.25, EtOH). IR spectrum, ν, $cm^{-1}$: 3323 (N–H), 3082, 1680 (C=N), 1645. $^1H$ NMR spectrum, δ, ppm: 1.26–1.43 m (1H, 6-H), 1.73 s (3H, $CH_3$), 1.76 s (3H, $CH_3$), 1.81 m (1H, 6-H), 1.94–2.40 m (3H, 4-H, 5-H), 4.74 s (2H, =$CH_2$), 4.78 m (1H, 1-H), 5.62–5.64 m (1H, 3-H), 8.28 s (1H, NH). $^{13}C$ NMR spectrum (acetone-$d_6$), $\delta_C$, ppm: 20.58 ($CH_3$), 20.78 ($CH_3$), 29.41 ($C^4$), 29.67 ($C^6$), 35.97 ($C^5$), 75.86 ($C^1$), 108.67 ($CCl_3$), 108.86 (=$CH_2$), 123.98 ($C^3$), 133.97 ($C^2$), 150.03 (**C**=$CH_2$), 162.50 (C=NH).

**2,2,2-Trichloro-*N*-[(1*S*,5*S*)-5-isopropenyl-2-methylcyclohex-2-en-1-yl)acetamide (VII).** A solution of 1 g (3.37 mmol) of compound **VI** in 25 ml of xylene was heated for 7 h under reflux. When the initial compound disappeared, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as eluent. Yield 0.6 g (60%), colorless crystals, mp 90–90.5°C, $[\alpha]_D^{20}$ = –38.8° (*c* = 4.3, MeOH). IR spectrum, ν, $cm^{-1}$: 3298 (NH), 1692. $^1H$ NMR spectrum, δ, ppm: 1.60–1.65 m (1H, 6-H), 1.69 s (3H, $CH_3$), 1.76 s (3H, $CH_3$), 2.04 m (1H, 6-H), 2.13–2.33 m (3H, 4-H, 5-H), 4.52 m (1H, 1-H), 4.76 s (1H, =$CH_2$), 4.79 s (1H, =$CH_2$), 5.64–5.68 m (1H, 3-H), 6.68 br.s (1H, NH). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 19.64 ($CH_3$), 21.14 ($CH_3$), 30.13 ($C^4$), 34.02 ($C^6$), 39.25 ($C^5$), 51.34 ($C^1$), 92.88 ($CCl_3$), 109.87 (=$CH_2$), 125.96 ($C^3$), 132.03 ($C^2$), 148.42 (**C**=$CH_2$), 161.49 (C=O).

**(1*R*,5*R*,6*S*)-6-Iodomethyl-2,6-dimethyl-7-oxabicyclo[3.2.1]oct-2-ene (VIII).** A solution of 0.5 g (3.3 mmol) of (–)-carveol (**II**) in 20 ml of acetonitrile was cooled to 0°C, 0.55 g (6.6 mmol) of $NaHCO_3$ was added in one portion under stirring, the mixture was stirred for 15 min, and 0.84 g (3.3 mmol) of crystalline iodine was added. The mixture was stirred for 2 h at room temperature (until the initial compound disappeared according to the TLC data) and evaporated, 15 ml of a saturated solution of $Na_2S_2O_3$ was added to the residue, and the mixture was extracted with ethyl acetate (3×10 ml). The extracts were combined, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as eluent. Yield 0.66 g (73%), light yellow liquid, $[\alpha]_D^{20}$ = –17.5° (*c* = 5.0, EtOH). IR spectrum: ν 1088 $cm^{-1}$ (C–O–C). $^1H$ NMR spectrum, δ, ppm: 1.45 s (3H, $CH_3$), 1.50 m (1H, 8-H), 1.70–1.72 m (3H, $CH_3$), 1.91–1.95 m (1H, 8-H), 2.23–2.38 m (2H, 4-H, 5-H), 2.49–2.50 (1H, 4-H), 3.32 s (1H, $CH_2I$), 3.36 s (1H, $CH_2I$), 4.13–4.15 m (1H, 1-H), 5.25–5.27 m (1H, 3-H). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 14.22 ($CH_2I$), 21.41 ($CH_3$), 27.94 ($CH_3$), 29.76 ($C^4$), 35.10 ($C^8$), 40.77 ($C^5$), 77.53 ($C^1$), 84.03 ($C^6$), 120.72 ($C^3$), 139.80 ($C^2$).

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