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Chiral Cyclohexene Block from *R*-(–)-Carvone

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Abstract—The oxidation with SeO_2 of a methyl group linked to an sp^2-hybridized carbon in the product of the intramolecular iodoetherification of *cis*-carveol afforded (1*R*,5*R*,7*S*)-7-iodomethyl-7-methyl-6-oxabicyclo[3.2.1]-oct-3-en-4-carbaldehyde and [(1*R*,5*R*,7*S*)-7-iodomethyl-7-methyl-6-oxabicyclo[3.2.1]oct-3-en-4-yl]methanol that were oxidized to methyl (1*R*,5*R*,7*S*)-7-iodomethyl-7-methyl-6-oxabicyclo[3.2.1]oct-3-en-4-carboxylate. The latter by the Zn-promoted opening of the γ-oxide ring was converted into the target chiral block, methyl (4*R*,6*R*)-6-hydroxy-4-(prop-1-en-2-yl)cyclohex-1-encarboxylate.

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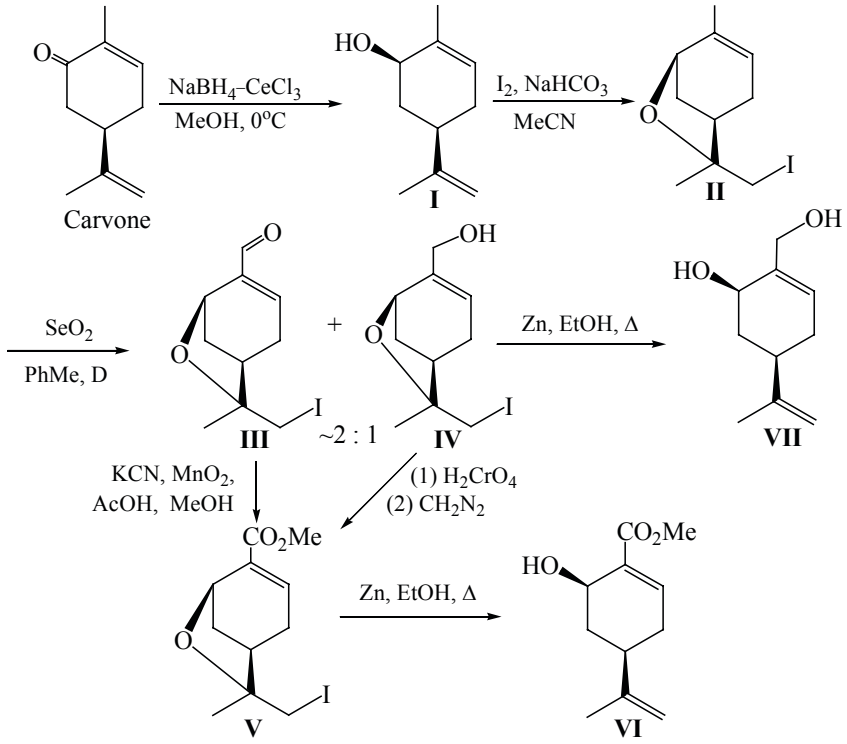
Commercially available and cheap *R*-(–)-carvone is extensively used in the targeted synthesis as a chiral matrix [1]. In this study aiming at the preparation of the functionalized α,β-unsaturated cyclohexenecarbonic blocks oxidation was studied with the help of SeO_2 of *cis*-carveol **I** [2] and its bicyclic derivative **II** [3].

The reactions were carried out by boiling in toluene equimolar amounts of the substrate and the reagent. In



the case of *cis*-carveol a complex mixture of compounds was obtained, but the reaction of compound **II** with SeO_2 proceeded cleanly and gave aldehyde **III** and primary alcohol **IV**. Both these products were isolated in the individual state by column chromatography on SiO_2. In the final stage aldehyde **III** was by Corey method [4] converted into methyl ester **V**. The same compound was obtained from alcohol **IV** by the oxidation with Jones reagent followed by the methylation of the acid obtained with diazomethane. The Zn-promoted opening of the γ-oxide ring to generate the isopropenyl function was first carried out on iodoalcohol **IV** and then on ester **V** in order to prepare compound **VI**, the key substance in the synthesis of analogs of the antiviral drug Tamiflu [5].

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer IR Prestige-21 Shimadzu from thin films. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 and 75.47 MHz respectively, internal reference TMS. The optical rotation was measured on a Perkin Elmer-341instrument. Mass spectra were taken on an instrument Thermo Finnigan MAT 95XP, ionizing electrons energy 70 eV. The temperature of the ionization chamber 200°C, sample admission at 5–270°C, heating rate 22 deg/min. The reaction progress was monitored by TLC on Sorbfil plates (Russia), development by the ethanol solution of anisaldehyde acidified with sulfuric acid with subsequent heating at 120–150°C. The synthesized products were isolated by column chromatography on silica gel (30–60 g of sorbent per 1 g of substance), as eluents freshly distilled solvents were used.

Reaction of compound II with SeO_2. To the boiling solution of 0.5 g (3.30 mmol) of compound **II** in 15 ml of anhydrous toluene under argon was added by small portions 0.75 g (6.60 mmol) of SeO_2 within 60 min. The reaction mixture was boiled for 1.5 h, cooled to room temperature, and filtered. Then the red-brown solution was cooled to 0°C, and *m*-chloroperbenzoic acid was added till the solution became light-yellow (~0.6 g). The reaction mixture was stirred for 5 min at 0°C, then it was poured into K_2CO_3 and extracted first with toluene (2 × 20 ml), and afterwards with $CHCl_3$ (3 × 20 ml). The combined organic extracts were washed with the saturated K_2CO_3 solution, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 2). Yield 0.28 g (~45%) of compound **III** and and 0.1 g (~15%) of compound **IV**.

(1*R*,5*R*,7*S*)-7-Iodomethyl-7-methyl-6-oxabicyclo[3.2.1]oct-3-en-4-carbaldehyde (III). Colorless crystals, mp 98–99°C, $[\alpha]_D^{20}$ –89.3° (*c* 1.685, $CHCl_3$). IR spectrum, cm^{-1}: 2953, 2924, 2870, 2851, 2357, 1670, 1657, 1629, 1448, 1420, 1373, 1184, 1157, 1132, 1037, 1028, 1001, 957, 935, 906, 830, 787, 719, 607, 595. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.42 s (3H, CH_3), 1.76 d (1H, H^8, *J* 11.3 Hz), 2.38–2.48 m (2H, CH, H^8), 2.60 d.t (1H, H^2, *J* 3.4 and 21.5 Hz), 2.92 d.d (1H, H^2, *J* 3.6 and 21.5 Hz), 3.01 d (1H, CH_2I, *J* 9.9 Hz), 3.26 d (1H, CH_2I, *J* 9.9 Hz), 4.97 d (1H, OCH, *J* 4.9 Hz), 6.67 s (1H, =CH), 9.35 s (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.82 (CH_2I), 27.37 (CH_3), 31.14 (C^8), 34.20 (C^2), 41.00 (C^1), 68.50 (C^5), 84.94 (C^7), 146.19 (C^4), 149.28 (C^3), 190.44 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 292 $[M]^+$ (6), 277 $[M - CH_3]^+$ (18), 185 (5), 169 (7), 151 (74), 107 (100), 79 (80), 77 (29), 43 (25). Found $[M]^+$ 291.992. $C_{10}H_{13}IO_2$. Calculated *M* 291.996.

[(1*R*,5*R*,7*S*)-7-Iodomethyl-7-methyl-6-oxabicyclo-[3.2.1]oct-3-en-4-yl]methanol (IV). Oily substance, $[\alpha]_D^{20}$ –40.6° (*c* 2.452, $CHCl_3$). IR spectrum, cm^{-1}: 3408, 3396, 2970, 2947, 1448, 1419, 1373, 1290, 1224, 1201, 1153, 1136, 1086, 1037, 1025, 1003, 957, 943, 905, 823, 785, 597. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (3H, CH_3), 1.96 d (1H, H^8, *J* 10.61 Hz), 2.37 t (1H, H^2, *J* 4.60 Hz), 2.41–2.44 m (2H, CH, CH_2), 2.59–2.66 m (1H, CH_2), 3.26 d (1H, CH_2I, *J* 9.8 Hz), 3.38 d (1H, CH_2I, *J* 9.6 Hz), 4.08 c (2H, OCH_2), 4.39 d (1H, OCH, *J* 4.9 Hz), 5.57 br.s (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.88 (CH_2I), 27.85 (CH_3), 29.52 (C^8), 35.03 (C^2), 41.03 (C^1), 64.80 (OCH_2), 73.89 (C^5), 84.41 (C^7), 122.63 (C^3), 143.27 (C^4). Mass spectrum, *m/z* (I_{rel}, %): 294 $[M]^+$ (25), 261 $[M - CH_3OH]^+$ (20), 185 (3), 169 (18), 153 $[M - CH_2I]^+$ (35), 149 (20), 135 (40), 110 (19), 93 (35), 91 (100), 79 (90), 77 (30), 57 (18), 43 (35). Found $[M]^+$ 294.008. $C_{10}H_{15}IO_2$. Calculated *M* 294.0116.

Methyl [(1*R*,5*R*,7*S*)-7-iodomethyl-7-methyl-6-oxabicyclo[3.2.1]oct-3-en-4-carboxylate (V). *a.* To a solution of 0.1 g (0.34 mmol) of aldehyde **III** in 20 ml of methanol at room temperature was added while stirring in one portion 0.085 g (1.30 mmol) of KCN, 0.59 g (6.8 mmol) of MnO_2, 0.03 g (0.51 mmol) of AcOH. The reaction mixture was filtered, methanol was distilled off, the residue was dissolved in $CHCl_3$, washed with brine, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent

EtOAc–petroleum ether, 1 : 5). Yield 0.04 g (47%) of ester **V**. Besides 0.02 g of initial aldehyde was recovered.

b. To a solution of 0.08 g (0.27 mmol) of compound **IV** in 10 ml of acetone at 0°C while stirring was added dropwise 0.53 ml (1.37 mmol) of 2.67 M solution of Jones reagent. After a complete consumption of the initial compound (TLC monitoring) to the reaction mixture *i*-PrOH was added dropwise till the reaction mixture got green. Acetone was distilled off, the residue was dissolved in EtOAc, the precipitate was filtered off. The filtrate was washed with brine, dried with $MgSO_4$, and evaporated to obtain 0.060 g (75%) of (1*R*,5*R*,7*S*)-7-iodomethyl-7-methyl-6-oxabicyclo[3.2.1]oct-3-en-4-carboxylic acid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.48 s (3H, CH_3), 1.87 d (1H, H^8, *J* 10.7 Hz), 2.47 m (2H, CH, H^8), 2.55 d (1H, H^2, *J* 21.1 Hz), 2.88 d.d (1H, H^2, *J* 3.5, 21.1 Hz), 3.09 d (1H, CH_2I, *J* 10.2 Hz), 3.34 d (1H, CH_2I, *J* 9.9 Hz), 5.01 d (1H, OCH, *J* 2.8 Hz), 6.72 s (1H, =CH), 10.53 br.s (1H, CO_2H). The reaction product without further purification was brought into the next methylation stage.

To a solution of 0.06 g (0.19 mmol) of acid in 5 ml of ethyl ether was added at room temperature while stirring an ethereal solution of diazomethane till the appearance of the stable light-yellow color of the solution. Excess CH_2N_2 was removed by adding several drops of AcOH. The reaction mixture was washed with brine, dried with $MgSO_4$, and evaporated to obtain 0.06 g (93%) of ester **V**.

Compound V. Oily substance, $[\alpha]_D^{20}$ –63.4° (*c* 1.395, $CHCl_3$). IR spectrum, cm^{-1}: 2970, 2924, 1772, 1705, 1697, 1454, 1443, 1375, 1250, 1247, 1080, 1026, 1001, 962, 930, 910, 800, 759, 600. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.52 s (3H, CH_3), 1.92 d (1H, H^8, *J* 10.7 Hz), 2.49 d (1H, H^8, *J* 10.7 Hz), 2.48 m (1H, CH), 2.58 d (1H, H^2, *J* 20.8 Hz), 2.88 d.d (1H, H^2, *J* 20.8, 4.4 Hz), 3.16 d (1H, CH_2I, *J* 9.9 Hz), 3.38 d (1H, CH_2I, *J* 9.9 Hz), 3.80 s (3H, CO_2Me), 5.08 d (1H, OCH, *J* 4.2 Hz), 6.88 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.04 (CH_2I), 27.37 (CH_3), 30.45 (C^8), 34.54 (C^2), 40.43 (C^1), 51.83 (CO_2Me), 71.78 (C^5), 84.97 (C^7), 136.21 (C^4), 143.02 (C^3), 165.69 (CO_2). Found, %: C 40.88; H 4.87; I 40.06. $C_{11}H_{15}IO_3$. Calculated, %: C 41.01; H 4.69; I 39.39.

Methyl (4*R*,6*R*)-6-hydroxy-4-(prop-1-en-2-yl)-cyclohex-1-enecarboxylate (VI). To 0.027 g (0.09 mmol) of compound **V** in anhydrous ethanol was added 0.055 g (0.87 mmol) of activated zinc. The reaction mixture was boiled at stirring for 5 h, then it was cooled to room temperature, filtered, the precipitate was washed with ethanol. The filtrate was evaporated and the residue was purified by flash-chromatography on a column packed with SiO_2 (eluent EtOAc–petroleum ether, 1:5). Yield 0.010 g (67%). Colorless crystals, mp 152–153°C, $[\alpha]_D^{20}$ –85.0° (*c* 0.574, $CHCl_3$). IR spectrum, cm^{-1}: 3527, 3466, 2947, 2924, 2856, 1715, 1701, 1689, 1647, 1437, 1400, 1375, 1358, 1294, 1259, 1207, 1118, 1090, 1047, 929, 894, 810, 764, 696, 613. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.55 d.d (1H, H^5, *J* 2.6, 12.5 Hz), 1.76 s (3H, CH_3), 2.17–2.30 m (4H, CH, CH_2), 3.78 s (3H, CO_2Me), 3.88 d (1H, OH, *J* 1.92 Hz), 4.66 m (1H, OCH), 4.78 m (2H, =CH_2), 7.05 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.36 (CH_3), 31.60 (C^5), 35.49 (C^3), 39.38 (C^4), 51.78 (OCH_3), 66.73 (C^6), 109.96 (=CH_2), 132.55 (C^1), 141.85 (C^2), 147.68 (C^1), 167.53 (CO_2). Mass spectrum, *m/z* (I_{rel}, %): 195 [*M* – H]$^+$ (2), 178 [*M* – H_2O]$^+$ (70), 165 (18), 164 (52), 163 (16), 153 (15), 152 (20), 137 (40), 128 (54), 119 (65), 100 (40), 96 (100), 91 (32), 84 (20), 79 (25), 68 (58), 67 (20), 59 (10), 53 (14). Found [*M*]$^+$ 196.10. $C_{11}H_{16}IO_3$. Calculated *M* 196.11.

(1*R*,5*R*)-2-Hydroxymethyl-5-isopropenyl-cyclohex-2-en-1-ol (VII) was obtained similarly to compound **VI** from 0.32 g (1.09 mmol) of compound **IV** at the addition of 0.715 g (10.94 mmol) of activated zinc. After the treatment the residue was purified by flash-chromatography on a column packed with SiO_2 (eluent EtOAc–petroleum ether, 1 : 5). Yield 0.18 g (86%), $[\alpha]_D^{20}$ –5.1° (*c* 0.751, $CHCl_3$). IR spectrum, cm^{-1}: 3392, 3373, 3356, 3080, 2966, 2937, 2920, 2879, 2862, 1645, 1448, 1437, 1375, 1273, 1201, 1153, 1095, 1076, 1060, 1020, 999, 945, 920, 891, 817. ^{1}H NMR spectrum, δ, ppm: 1.53–1.65 m (1H, H^6), 1.75 s (3H, CH_3), 2.04–2.34 m (5H, CH, CH_2, OH), 2.51 m (1H, OH), 4.24 s (2H, OCH_2), 4.53 m (1H, OCH), 4.76 s (2H, =CH_2), 5.77 m (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 20.36 (CH_3), 30.72 (C^6), 37.22 (C^4), 40.07 (C^5), 65.48 (CH_2O), 70.45 (C^1), 109.61 (=CH_2), 129.20 (C^3), 136.89 (C^1), 148.12 (C^2). Found, %: C 71.88; H 9.86. $C_{10}H_{16}O_2$. Calculated, %: C 71.39; H 9.59.

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