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New Orthogonally Functionalized Synthetic Blocks from *R*-(–)-Carvone

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Abstract—The intramolecular cyclization of (–)-*cis*-carveol under iodine treatment afforded (1*R*,5*R*,6*S*)-6-iodomethyl-2,6-dimethyl-7-oxabicyclo[3.2.1]oct-2-ene that was subjected to allyl oxydation with the complex CrO_3DMP giving a synthetically valuable building block, (1*R*,5*R*,6*S*)-6-iodomethyl-2,6-dimethyl-7-oxabicyclo[3.2.1]oct-2-ene-4-one. In the latter the double bond was cleaved by ozonization to obtain the expected trioxo derivative, and the subsequent ozonolysis of its enol form provided a multiple functionalized tetrahydrofuran derivative.

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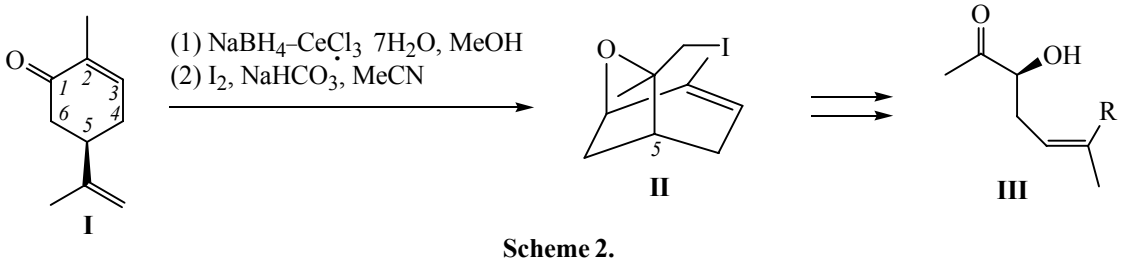
Recently available and cheap *R*-(–)-carvone (**I**) found extensive application as a chiral matrix to the targeted synthesis of complex structures [1–10]. In the course of development of the transition from the bicyclic compound **II** [11] to unsaturated α-hydroxyketone **III** we obtained several synthons **IV–VIII** of the general synthetic interest and found an uncommon SiO_2-promoted case of the enolization of the α-ketoaldehyde fragment of compound **VI**.

In keeping with the planned design of preparation of hydroxyketone **III** a problem arose of the oxidative cleavage of the double bond in compound **II** with the oxidative "removal" of its two-carbon C^3–C^4. To this end we first of all subjected compound **II** to allyl oxidation with the complex CrO_3·DMP (DMP is 1,5-dimethylpyrazole) [12] and obtained cyclohexenone **IV**.

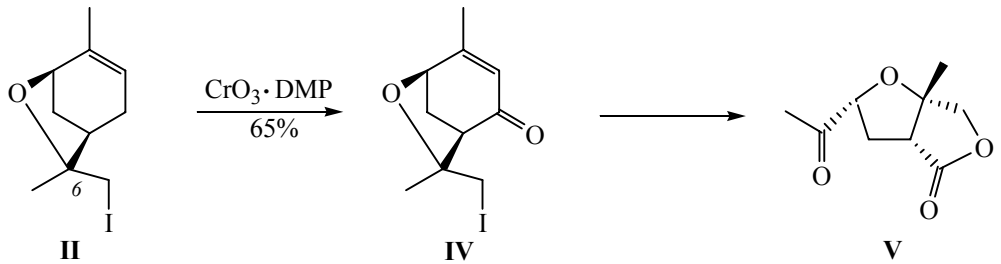
Cyclohexenone **IV** apart from the possibility to use it in the main path of the designed synthesis is synthetically

Scheme 1.



I **II** **III**

Scheme 2.



II **IV** **V**

attractive also as a inherently protected and stable 4-oxo derivative of *cis*-carveol. We also used compound **IV** for proving the structure of the basis bicycle **II**. The *S*-configuration of the chiral center C^6 in compound **II** shown on the scheme was assumed on the grounds of the data of chemical correlation with the preparation from compound **IV** of lactone **V** by periodate cleavage catalyzed with $RuCl_3$. The latter process will be published elsewhere.

Further the oxidative cleavage of the double bond in enone **IV** was investigated. The ozonization was performed in MeOH at –78°C. In the process of chromato-0graphic purification of the reduced ozonization product ketoaldehyde **VI** detected in the reaction mixture by TLC transformed into enol **VII**. According to the spectral data enol **VII** is an isomerically pure compound, but we have not proved the configuration of its double bond, and the shown structure belongs to the preferred less hindered *E*-isomer.

The primary ozonization product **VI** was stirred in EtOAc with the dispersion of SiO_2 to convert it into enol **VII** and then the latter was subjected to ozonization. Under the conditions of the ozonization of enone **IV** (MeOH, –78°C) enol **VII** did not react with ozone. Therefore the enol ozonization was performed in MeOH at –40°C to obtain furanones **VIII** and **IX** in the 1:1 ratio (^{1}H NMR). These compounds appeared on TLC as a single spot, their chromatographic separation on SiO_2 failed due to the ready removal of the protective dimethylketal function in compound **IX**. Therefore the formed mixture of compounds **VIII** and **IX** was maintained in acid-water medium till ketal **IX** completely converted into ketone **VIII**.

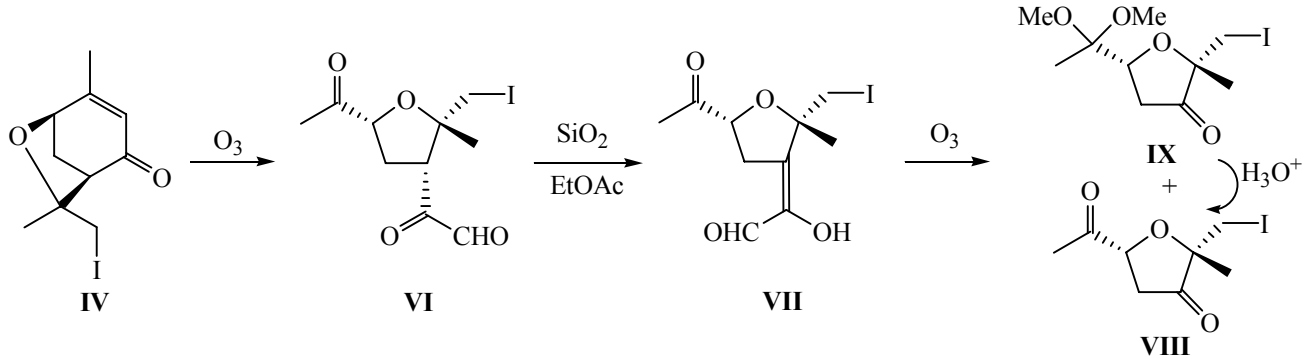
The tendency of α-ketoaldehyde **VI** to enolization is not quite understandable. One of probable reasons consists in the sterical overloading and the electrostatic repulsion of the *all-cis* oxo functions and the CH_2I-substituent in compound **VI**. The enolization in the α-ketoaldehyde fragment somewhat reduces the strain in the system and is the driving force of the conversion of ketone **VI** into enol **VII**.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from thin films. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 [300 (^{1}H), 75.47 MHz (^{13}C)] from solutions in $CDCl_3$, internal reference TMS. TLC analysis was performed on Silufol plates. Rotation angles were measured on an instrument Perkin-Elmer 241 MC. The purity of initial compounds was checked by GLC on a chromatograph Chrom 5.

(1*R*,5*R*,6*S*)-6-Iodomethyl-2,6-dimethyl-7-oxabicyclo[3.2.1]oct-2-ene (II). To a solution of 0.1 g (0.67 mmol) of *R*-(–)-carvone (**I**) and 0.25 g (0.67 mmol) of $CeCl_3 \cdot 7H_2O$ in 10 ml of MeOH was added at 20°C 0.025 g (0.67 mmol) of $NaBH_4$, and the reaction mixture was stirred for 5 min. The reaction mixture was diluted with 20 ml of ethyl ether and 20 ml of H_2O, the ether layer was separated, the products were extracted from the water layer with ether (3 × 10 ml), the combined ether extracts were dried with Na_2SO_4 and filtered. The filtrate was concentrated under a reduced pressure, the residue was purified by column chromatography on SiO_2 (petroleum ether–ethyl acetate, 5:1). Yield of (–)-*cis*-carveol 0.09 g (90%), $[\alpha]_D^{20}$ –23.6° (*C* 0.85, EtOH). IR spectrum, ν, cm^{-1}: 3331 (OH), 3082 (=CH), 1645 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.47–1.52 m (1H, H^6), 1.72 s (3H, CH_3), 1.74 d (3H, CH_3, *J* 2 Hz), 1.85–2.30 m (5H, $H^{4,5,6}$, OH), 4.17 br.s (1H, H^1), 4.71 s (2H, $=CH_2$), 5.44 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 18.71 (CH_3), 20.36 (CH_3), 30.72 (C^4), 37.60 (C^6), 40.11 (C^5), 70.61

Scheme 3.



(C^1), 108.86 (=CH_2), 123.59 (C^3), 135.84 (C^2), 148.69 (=C=).

To a solution of 0.5 g (3.3 mmol) of (–)-carveol in 20 ml of acetonitrile at 0°C while stirring was added in one portion 0.55 g (6.6 mmol) of $NaHCO_3$. The mixture was stirred for 15 min, then 0.84 g (3.3 mmol) of crystalline I_2 was added. The reaction mixture was stirred for 2 h at room temperature till the disappearance of the initial compound (TLC monitoring), the solution was evaporated, and 15 ml of saturated solution of $Na_2S_2O_3$ was added, the reaction products were extracted with EtOAc (3 × 10 ml). The combined organic solutions were dried with $MgSO_4$ and evaporated, the residue was subjected to column chromatography on SiO_2 (EtOAc–petroleum ether, 1:10). Yield of compound **II** 0.66 g (73%). Light yellow fluid, $[\alpha]_D^{20}$ –17.5° (*C* 5.0, EtOH). IR spectrum, ν, cm^{-1}: 1088 (C–O–C). ^1H NMR spectrum, δ, ppm: 1.45 s (3H, CH_3), 1.70–1.72 m (3H, CH_3), 1.91–1.95 m (1H, H^8), 2.23–2.38 m (3H, $H^{4,5,8}$), 2.49–2.50 m (1H, H^4), 3.30 d (1H, CH_2I, *J* 9 Hz), 3.37 d (1H, CH_2I, *J* 9 Hz), 4.13–4.15 m (1H, H^1), 5.25–5.27 m (1H, H^3). ^{13}C NMR spectrum, δ, 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).

(1*R*,5*R*,6*S*)-6-Iodomethyl-2,6-dimethyl-7-oxabicyclo[3.2.1]oct-2-ene-4-one (IV). To a solution of 5.4 g (54.0 mmol) of CrO_3 in 40 ml CH_2Cl_2 at –20°C was added in one portion at stirring 5.2 g (54.0 mmol) of 1,5-dimethylpyrazole. The mixture was stirred for 15 min, then 1 g (3.6 mmol) of compound **II** was added. The reaction mixture was stirred for 4 h at –15°C, 20 ml of 20% aqueous NaOH was added, and the stirring was continued for 1 h at 0°C. The organic layer was separated, washed with 50% HCl solution for removing 1,5-dimethylpyrazole, then with brine, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 ($CHCl_3$–MeOH, 40:1). Yield 0.68 g (65%), light-yellow fluid. $[\alpha]_D^{20}$ +350.3° (*C* 4.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1676 (C=O). ^1H NMR spectrum, δ, ppm: 1.55 s (3H, CH_3), 2.08 s (3H, CH_3), 2.36 d (1H, H^8, *J* 12 Hz), 2.46–2.50 m (1H, H^8), 3.10 m (1H, H^5), 3.12 d (1H, CH_2I, *J* 9 Hz), 3.22 d (1H, CH_2I, *J* 9 Hz), 4.47–4.49 m (1H, H^1), 5.78–5.79 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 13.71 (CH_2I), 22.16 (CH_3), 28.23 (CH_3), 39.96 (C^8), 58.44 (C^5), 78.27 (C^1), 81.39 (C^6), 125.70 (C^3), 165.39 (C^2), 199.02 (C=O). Mass spectrum (ACPI), *m/z* (I_{rel}, %): 293 ($[M+H]^+$, ^{127}I) (100), 165 ($[M – HI + H]^+$, ^{127}I) (42.4).

(2*S*,5*R*)-5-Acetyl-2-iodomethyl-2-methyldihydrofuran-3-ylidenehydroxyacetaldehyde (VII). Through a solution of 0.75 g (2.6 mmol) of ketone **IV** in 20 ml of MeOH was passed O_3 at –78°C. When the solution turned blue it was flushed with argon, 1 ml of Me_2S was added, the mixture was warmed to room temperature and stirred for 3 h. Then the solvent was distilled off, the residue was dissolved in 20 ml of EtOAc, 3 g of SiO_2 was added, and the mixture was stirred for 6 h. Afterwards the solution was filtered, evaporated, and the residue was subjected to column chromatography on SiO_2 (EtOAc–petroleum ether, 2:1). Yield 0.82 g (98%), viscous light-yellow fluid, $[\alpha]_D^{20}$ +57.3° (*C* 2.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3412 (OH), 1716, 1658 (2C=O). ^1H NMR spectrum, δ, ppm: 1.64 s (3H, CH_3), 2.43 s (3H, CH_3), 2.99–3.08 m (1H, H^4), 3.27–3.35 m (1H, H^4), 3.56 d (1H, CH_2I, *J* 9 Hz), 3.93 d (1H, CH_2I, *J* 9 Hz), 4.45–4.51 m (1H, H^5), 6.04 br.s (1H, OH), 9.60 s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: 13.40 (CH_2I), 21.49 (CH_3), 26.58 (CH_3), 30.96 (C^4), 81.71 (C^5), 85.46 (C^2), 136.44 (C^3), 140.84 (=C=), 185.20 (CHO), 208.39 (C=O). Mass spectrum (ACPI), *m/z* (I_{rel}, %): 197 ($[M$ –HI + $H]^+$, ^{127}I) (100), 325 ($[M+H]^+$, ^{127}I) (1.25).

(2*S*,5*R*)-5-Acetyl-2-iodomethyl-2-methyldihydrofuran-3-one (VIII). Through a solution of 0.6 g (1.86 mmol) of enol **VII** in 20 ml of MeOH was passed O_3 at –40°C to the ratio 3 mmol of O_3 per 1 mmol of the substrate. Then the reaction mixture was flushed with argon, Me_2S was added, the mixture was warmed to room temperature, acidified with 10N water solution of HCl, and stirred for 6 h.The solvent was distilled off, and the residue was subjected to column chromatography on SiO_2 (EtOAc–petroleum ether, 2:1). Yield 0.31 g (60%), light-yellow fluid, $[\alpha]_D^{20}$ +105.5° (*C* 2.35, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 1761, 1716 (2C=O). ^1H NMR spectrum, δ, ppm: 1.39 s (3H, CH_3), 2.45 s (3H, CH_3), 2.72–2.75 m (2H, H^4), 3.26 d (1H, CH_2I, *J* 9 Hz), 3.35 d (1H, CH_2I, *J* 9 Hz), 4.60–4.65 m (1H, H^5). ^{13}C NMR spectrum, δ, ppm: 9.35 (CH_2I), 20.86 (CH_3), 26.47 (CH_3), 37.49 (C^4), 77.65 (C^5), 82.39 (C^2), 208.60 (2C=O).

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