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Synthesis-Freindly Chiral α-Hydroxymethyl Ketones from (–)-Carvone

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Abstract—Reactions were studied of ozonolysis and periodate cleavage catalyzed by $RuCl_3$ of a double bond in (1R,5R)-5-(1-methyl-1-chloroethyl)-2-cyclohexen-1-ol and its acetate. The ozonolysis of the unsaturated alcohol led to the formation of cyclic anomeric methoxyspiranes, and its acetate depending on the conditions and oxidant reagent provided the corresponding α, ω-aldehydes, α, ω-ketoacetals, and α, ω-ketoacids.

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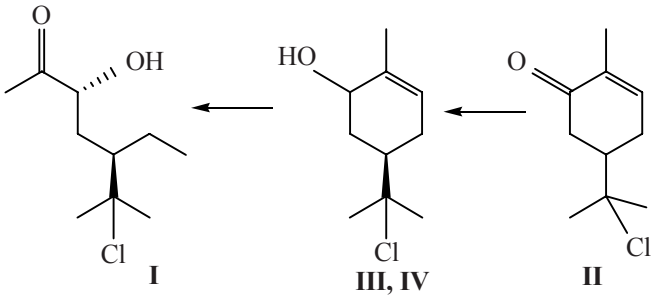
A chiral subunit of α-hydroxyketone appears in the structure of many naturally occurring substances [1–4], chiral α-hydroxyketones are widely used in the purposeful synthesis, in particular, in building up the thiazole-containing fragment of epothiolones [5, 6]. The known versions of asymmetric synthesis of α-hydroxyketones, in particular, of α-hydroxymethyl ketones, are based on application of electrophilic hydroxylation of enolates of appropriate ketones where the asymmetrical induction occurs both by the assistance of the optically active oxidants and by the presence of chiral groups in the ketone or the enolate [7]. An efficient α-hydroxylation of prochiral ketone enolates was performed with the use of chiral oxaziridines [8]; enantioselective oxidations of enol ethers was carried out applying asymmetric dihydroxylation by Sharpless [9] and catalyzed oxidation with chiral Jacobsen reagent Salen-Mn(III) [10], trimethylsilyl ethers were oxidized with a chiral dioxirane obtained from fructose [11]. At the same time the available chiral initial compounds (sugars, amino acids, monoterpenes etc.) often utilized in enantioselective syntheses of natural substances were seldom used for designing chiral α-hydroxymethyl ketones [12].

In the present study aiming at the preparation of a desired configuration of ω-functionalized α-hydroxymethyl ketones **I** we prepared from (–)-carvone chloroderivative **II** alcohol **III** and its acetate **IV** and investigated their oxidative cleavage.



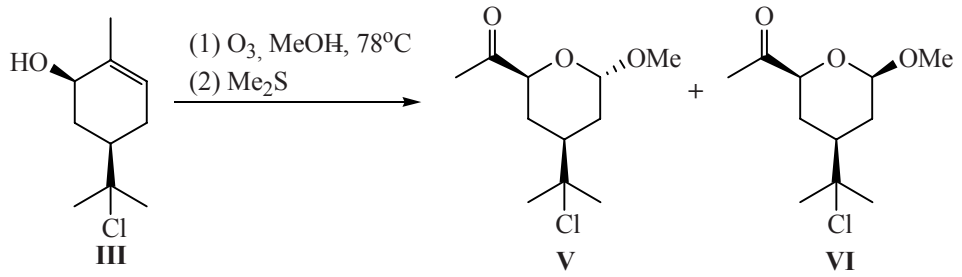
I **III, IV** **II**

R is a functional group in **I**, R = H (**III**), Ac (**IV**).

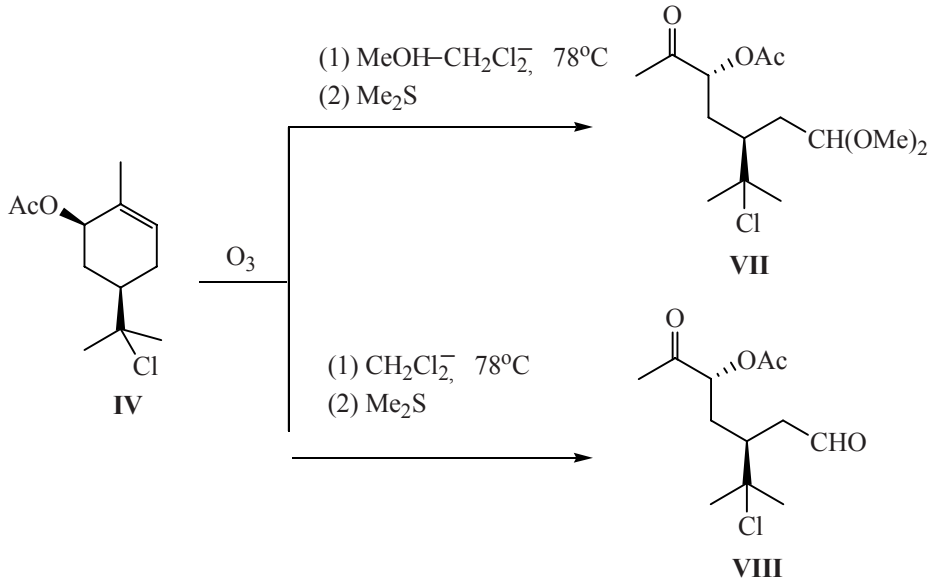
First alcohol **III** and its acetate **IV** were subjected to ozonolyzis. Through the solution of alcohol **III** in MeOH at –78°C was passed excess O_3, the ozonides were treated with dimethyl sulfide to obtain an anomeric mixture of methoxypyranes **V** and **VI** in the ratio 3:1 with an overall yield 60% after column chromatographic purification on SiO_2. The formation of cyclic pyrans **V** and **VI** in the course of the oxonolysis of compound **III** might occur both in the stage of ozonides generation (by intramolecular stabilization of the zwitter ion) and by subsequent cyclization of acyclic precursors (aldehyde and dimethoxyacetal). The stereochemical assignments of the substituted pyrans **V** and **VI** were performed with the use of the data of ^{13}C NMR spectra where the more sterically loaded minor *cis,cis*-isomer **VI** gave rise to more upfield signals of the ring atoms C^2, C^4, and C^5 (Scheme 1).

Acyclic derivatives of α-hydroxymethyl ketones **VII** and **VIII** were obtained in good yield and selectivity by

Scheme 1.

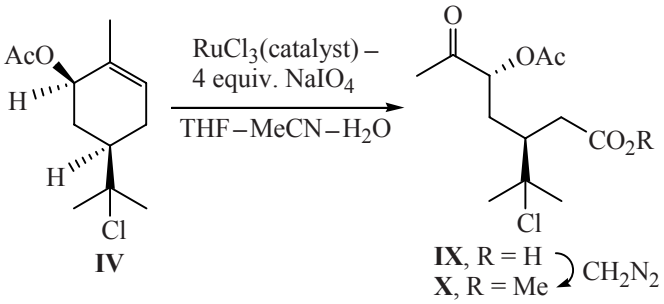


Scheme 2.

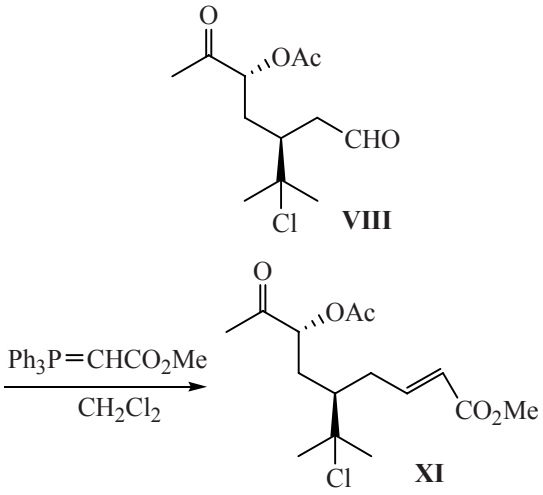


ozonolysis of acetate **IV** dissolved in MeOH–CH_2Cl_2, 1 : 1, and CH_2Cl_2 respectively (Scheme 2).

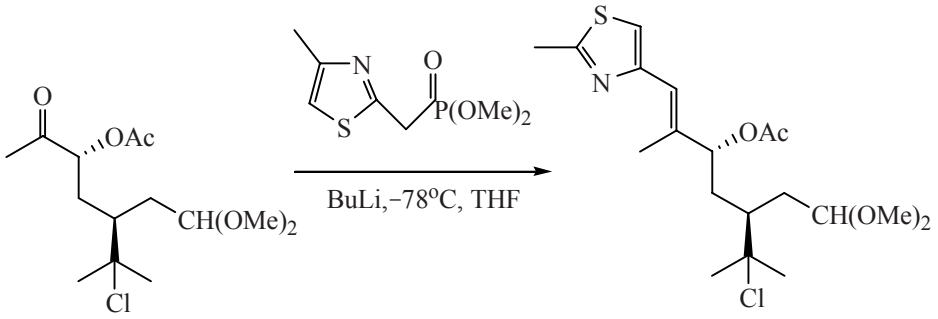
To obtain more deeply oxidized products, we examined the reaction of periodate cleavage of acetate **IV** catalyzed by $RuCl_3$. Under standard oxidation conditions using 2 equiv of $NaIO_4$ [14] exclusively formed aldehyde **VIII**, and compound **IV** was completely converted into the corresponding ketoacid **IX** only after consumption of 4 equiv of $NaIO_4$. The yield of ketoacid **IX** was 50%, on treatment with diazomethane methyl ester **X** was obtained.



As seen from the structures, the derivatives of α-hydroxymethyl ketone with the blocked OH group **V–X** containing two chiral centers of a known configuration are suitable for multipurpose application in the directional sysnthesis. For instance, based on compounds **VII**



Scheme 3.



VII **XII**

and **VIII** we prepared blocks **XI** and **XII** for the synthesis of dimethylcarbaanalogs of epothiolones [15].

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord-80 from thin films or mulls in mineral oil. ^{1}H 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. Optical rotation was measured on a Perkin Elmer-341 instrument.

(1*R*,5*R*)-2-Methyl-5-(1-methyl-1-chloroethyl)-2-cyclohexen-1-ol (III). To a dispersion of 0.4 g (10.53 mmol) of $LiAlH_4$ in 10 ml of anhydrous ethyl ether at –40...–50°C was added dropwise 1 g (5.33 mmol) of ketone **II** in 5 ml of ether. The reaction mixture was warmed to room temperature and stirred for 1.5 h (TLC monitoring). Then the reaction mixture was quenched with 10% aqueous HCl, extracted with ether (3 × 10 ml), the combined extracts were dried with $MgSO_4$, and evaporated. The residue was purified by column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:3). Yield 0.68 g (~68%), $[\alpha]_D^{20}$ –12.9° (*C* 1.0, $CHCl_3$). IR spectrum, cm^{-1} : 3250–3500, 1465, 1380, 1045, 930. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 q (1H, *J* 10.4 Hz) and 2.37 m (1H, C^6H_2), 1.54 s and 1.58 s (3H each, *gem*-CH_3), 1.76 s (3H, C^2CH_3), 1.79 m (1H) and 2.12 m (1H, C^4H_2), 1.92 m (1H, H^5), 1.96 m (1H, OH), 4.19 m (1H, H^1), 5.47 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.57 and 29.60 (*gem*-CH_3), 27.66 (C^4), 30.47 (CH_3), 35.15 (C^6), 45.60 (C^5), 70.92 (C^1), 73.33 (CCl), 123.10 (C^3), 136.47 (C^2).

(1*R*,5*R*)-2-Methyl-5-(1-methyl-1-chloroethyl)-2-cyclohexen-1-yl acetate (IV). To a stirred solution of 0.6 g (3.2 mmol) of alcohol **III** in 5 ml of anhydrous pyridine was added 1.63 g (16.0 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 48 h, then 5 ml of ice water was added, the reaction products were extracted into chloroform (3×20 ml), the extract was washed with a saturated NaCl solution, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:7), yield 0.55 g (74%), $[\alpha]_D^{20}$ –30.0° (*C* 1.02, $CHCl_3$). IR spectrum, cm^{-1}: 1740, 1710, 1465, 1380, 1275, 1040. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.44 s and 1.47 s (3H each, *gem*-CH_3), 1.52 s (3H, CH_3), 1.34 m (1H) and 2.23 m (1H, C^6H_2), 1.98 s (3H, CH_3CO), 1.73 m (1H) and 2.05 m (1H, C^4H_2), 1.99 m (1H, H^5), 5.34 m (1H, H^1), 5.47 m (1H, =CH, *J* 1.77 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.53 and 23.86 (*gem*-CH_3), 27.29 (C^4), 30.04 and 30.49 (CH_3, CH_3CO), 30.96 (C^6), 45.23 (C^5), 72.93 (C^1), 73.62 (CCl), 125.09 (C^3), 135.78 (C^2), 170.87 (CH_3CO). Found, %: C 62.73; H 8.52; Cl 15.69. $C_{12}H_{19}ClO_2$. Calculated, %: C 62.47; H 8.30; Cl 15.37.

(2*S*,4*S*,6*S*)-1-[4-(1-Methyl-1-chloroethyl)-6-methoxytetrahydro-2*H*-pyran-2-yl]ethan-1-one (V) and its (6*R*)-epimer VI. Through a solution of 0.2 g (1.07 mmol) of compound **III** in 20 ml of anhydrous methanol at –70°C was passed at stirring the ozone-oxygen mixture till the solution turned blue. The excess ozone was flushed from the reaction mixture with argon flow, 5 ml of Me_2S was added, the mixture was stirred for 30 min at –60°C, then 6 h at room temperature. The reaction mixture was evaporated, the residue was dissolved in $CHCl_3$ and washed with a saturated NaCl solution, the organic layer was separated, dried over $MgSO_4$, and evaporated. After purification by chromatography on a column packed with SiO_2 (eluent EtOAc–petroleum ether, 1:2) we obtained 0.12 g (48%) of a mixture of compounds **V** and **VI**.

(6*S*)-Epimer **V**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.52 s and 1.53 s (3H each, *gem*-CH_3), 2.27 s (3H, CH_3),

3.55 s (3H, OCH_3), 3.80 d.d (1H, $H^{2'}$, *J* 2.4 and 11.9 Hz), 4.40 d.d (1H, $H^{6'}$, *J* 3.2 and 9.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.78 and 29.80 (*gem*-CH_3), 28.59 (C^3), 30.00 (CH_3), 32.48 (C^5), 46.18 (C^4), 56.21 (OMe), 71.97 (CCl), 79.77 (C^2), 102.81 (C^6), 208.10 (CO).

(6*R*)-Epimer **VI**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.51 s and 1.52 s (6H, *gem*-CH_3), 2.22 s (3H, CH_3), 3.50 s (3H, OCH_3), 4.13 d.d (1H, $H^{2'}$, *J* 2.6 and 12.3 Hz), 4.62 d.d ($H^{6'}$, *J* 3.6 and 9.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 26.13 and 29.73 (*gem*-CH_3), 26.13 (C^3), 30.09 (CH_3), 31.62 ($C^{5'}$), 42.02 ($C^{4'}$), 55.78 (OMe), 72.31 (CCl), 76.29 ($C^{2'}$), 99.85 ($C^{6'}$), 208.62 (CO).

(1*R*,3*S*)-1-Acetyl-3-(2,2-dimethoxyethyl)-4-methyl-4-chloropentyl acetate (VII) was obtained by the ozonolysis of 0.3 g (1.3 mmol) of compound **IV** in 20 ml of a mixture MeOH–CH_2Cl_2 similarly to compounds **V** and **VI**. Yield after column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:2) 0.24 g (75%), $[\alpha]_D^{20}$ +12.6° (*C* 1.1, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.54 s and 1.56 s (3H each, *gem*-CH_3), 2.10 s and 2.13 s (3H each, CH_3CO and CH_3COO), 3.29 s (6H, OMe), 4.38 t (1H, H^1, *J* 5.4 Hz), 5.11 d.d [1H, $CH(OMe)_2$, *J* 2.3 and 11.3 Hz]. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.45 and 25.85 (*gem*-CH_3), 30.42 and 30.87 (CH_3CO and CH_3COO), 32.84 (C^2), 35.31 ($C^{1'}$), 42.60 (C^3), 52.71 and 54.30 ($2OCH_3$), 74.20 (C^4), 77.12 (C^1), 104.29 (COO), 170.27 (CH_3COO), 205.30 (C=O). Found, %: C 54.88; H 8.31; Cl 11.79. $C_{14}H_{25}ClO_5$. Calculated, %: C 54.45; H 8.16; Cl 11.48.

(1*R*,3*S*)-1-Acetyl-4-methyl-3-(2-oxoethyl)-4-chloropentyl acetate (VIII). To a solution of 0.3 g (1.3 mmol) of acetate **IV** in a mixture CCl_4–CH_3CN–H_2O, 2 : 2 : 3, was added at stirring 1.5 g (7.15 mmol) of $NaIO_4$, then to the mixture obtained 7 mg of $RuCl_3$ in 3 ml of water was added. The reaction mixture was stirred at room temperature for 2 h, then 5 ml of water was added, the reaction products were extracted into EtOAc, the combined extracts were dried with $MgSO_4$, and evaporated. After column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:2) yield 0.11 g (30%), $[\alpha]_D^{20}$ –40.8° (*C* 1.02, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.54 s and 1.58 s (6H, *gem*-CH_3), 1.70 m (1H), 2.50 m (1H) and 2.90–3.10 m (3H, CH, CH_2), 2.18 s (3H, CH_3), 2.20 s (3H, CH_3CO), 4.80 t (1H, C^1H, *J* 6.0 Hz), 9.80 t (1H, CHO, *J* 2.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.55 and 26.02 (*gem*-CH_3), 30.37 (CH_3), 31.40 (CH_3), 31.91 (C^2), 40.06 (C^3), 45.60 (CH_3CO), 73.18 (C^4), 76.40 (C^1), 170.47 (OAc), 200.04 (CHO), 205.02 (C=O).

(3*S*,5*R*)-5-Acetoxy-3-(1-methyl-1-chloroethyl)-6-oxoheptanoic acid (IX). To a mixture of CCl_4–CH_3CN–H_2O, 2 : 2 : 3, at vigorous stirring was added 1.0 g (4.34 mmol) of compound **IV**, then 2.78 g (6.52 mmol) of $NaIO_4$, and 10 mg of $RuCl_3$. The reaction mixture was vigorously stirred at room temperature for 8 h, then 10 ml of CH_2Cl_2 was added, the organic layer was separated. The water layer was diluted with 5 ml of water, the reaction products were extracted into CH_2Cl_2, the combined organic solutions were dried with $MgSO_4$, and evaporated. After column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:1) yield 0.5 g (54%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.51 s (6H, $2CH_3$), 1.56 m (1H) and 2.10 m (1H, CH_2), 2.15 s (3H, CH_3), 2.20 s (3H, CH_3), 2.30 m (2H) and 2.80 m (1H, CH, CH_2), 5.20 d.d (1H, H^5, *J* 2.8 and 11.1 Hz), 10.1 br.s (1H, CO_2H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.44 and 25.97 (*gem*-CH_3), 30.49 (CH_3), 31.02 (CH_3), 31.85 (C^2), 35.50 (C^4), 42.86 (C^3), 73.09 (CCl), 76.47 (C^5), 170.56 (OAc), 178.07 (C^1), 205.01 (C^6).

Methyl (3*S*,5*R*)-5-acetoxy-3-(1-methyl-1-chloroethyl)-6-oxoheptanoate (X). To a solution of 0.3 g (1.47 mmol) of acid **IX** was added at stirring a solution of CH_2N_2 in ether till the end of N_2 liberation, and the solution was stirred for 1 h more. Then 2 drops of glacial CH_3COOH was added, the reaction mixture was washed with a saturated NaCl solution, dried with $MgSO_4$, and evaporated. After column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:1) yield 0.27 g (84%), $[\alpha]_D^{20}$ +9.3° (*C* 0.98, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.56 s and 1.58 s (3H each, *gem*-CH_3), 1.75–1.83 m (1H) and 2.00–2.10 m (1H, CH_2), 2.15 s (3H, CH_3), 2.18 s (3H, CH_3), 2.30–2.40 m (2H) and 2.70–2.80 m (1H, CH, CH_2). ^{13}C ($CDCl_3$), δ, ppm: 20.49 and 25.93 (*gem*-CH_3), 30.63 (CH_3), 30.99 (CH_3), 31.82 (C^2), 35.40 (C^4), 43.10 (C^3), 51.90 (OCH_3), 73.15 (CCl), 76.47 (C^5), 170.46 (OAc), 172.98 (C^1), 204.92 (C^6). Found, %: C 53.76; H 7.31; Cl 11.78. $C_{14}H_{25}ClO_5$. Calculated, %: C 53.33; H 7.23; Cl 12.11.

Methyl (5*S*,7*R*)-7-acetoxy-5-(1-methyl-1-chloroethyl)-8-oxonon-2-enoate (XI). To a solution of 0.04 g (0.15 mmol) of aldehyde **VIII** in 3 ml of anhydrous CH_2Cl_2 was added at stirring 0.076 g (0.23 mmol) of methoxycarbonylmethylenetriphenylphosphorane. The reaction mixture was stirred for 48 h, then 5 ml of CH_2Cl_2 was added, the reaction mixture was washed with a saturated NaCl solution, dried with $MgSO_4$, and evaporated. After column chromatography of the residue on SiO_2 (eluent EtOAc–petroleum ether, 1:2) yield 0.02 g

(41%), $[\alpha]_D^{20}$ +40° (*C* 1.38, $CHCl_3$). ^1H ($CDCl_3$), δ, ppm: 1.60 s (6H, *gem*-CH_3), 1.71–1.81 m (1H, C^4H_2) and 1.95–2.12 m (2H, C^6H_2), 2.15 s and 2.16 s (3H each, $COCH_3$), 2.34 q (1H, C^4H_2, *J* 7.80 Hz) and 2.69 m (1H, CH), 3.73 s (3H, CO_2Me), 4.96 d.d (1H, OCH, *J* 3.00 and 10.90 Hz), 5.90 d (1H, $=C^2H$, *J* 15.60 Hz), 6.97 d.d.d (1H, $=C^3H$, *J* 6.6, 7.90 and 15.60 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.53 and 25.99 (*gem*-CH_3), 30.98 (C^9), 31.61 (C^4), 33.80 (C^6), 45.89 (C^5), 51.55 (OCH_3), 73.46 (CCl), 76.83 (C^7), 122.53 (C^3), 147.30 (C^2) 166.45 (C^1), 170.35 (OAc), 204.69 (C^8). Found, %: C 56.78; H 7.33; Cl 11.80. $C_{15}H_{23}ClO_5$. Calculated, %: C 56.51; H 7.27; Cl 11.12.

(1*S*,3*R*)-3-(2,2-Dimethoxyethyl)-4-methyl-1-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)vinyl]-4-chloropentyl acetate (XII). To a solution of 0.1 g (0.45 mmol) of phosphonate **XIII** in 5 ml of anhydrous THF at –78°C under an argon atmosphere was added while stirring 0.12 ml of 2 M hexane solution of BuLi. The reaction mixture was stirred for 30 min, than at –78°C was added dropwise a solution of 0.09 g of ketone **VII** in 5 ml of THF. The reaction mixture was warmed to room temperature and stirred for 2 h more. Then a saturated NH_4Cl solution was added, THF was distilled off from the water layer, and the products were extracted into EtOAc (3 ×10 ml). The combined extracts were dried with $MgSO_4$, the residue was purified by column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 3). Yield 0.06 g (50%). Oily substance, $[\alpha]_D^{20}$ +14.8° (*C* 1.1, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.54 m (2H, CH_2), 1.58 s and 1.60 s (3H each, *gem*-CH_3), 2.03 m (1H, CH), 2.06 s (3H, CH_3), 2.07 s (3H, CH_3CO), 2.13 m (2H, CH_2), 2.68 s (3H, CH_3 of thiazole), 3.31 s and 3.33 s (3H each, OCH_3), 4.47 t (1H, OCHO, *J* 5.7 Hz), 5.3 d.d (1H, OCH, *J* 2.3 and 10.2 Hz), 6.52 s (1H, =CH), 6.95 s (1H, =CH of thiazole). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.98 (3H, CH_3 of thiazole), 19.06 and 21.11 (3H, *gem*-CH_3), 30.41 and 31.10 ($CH_3C=$ and CH_3CO), 35.74 and 36.70 (C^2 and C^1'), 42.89 (C^3), 52.71 and 53.75 (OCH_3), 74.78 (C^4), 77.21 (C^1), 104.06 (COO), 115.97 (CH=), 119.52 (C^5'' of thiazole), 138.64 (C^2'' of thiazole), 152.33 (C^4'' of thiazole), 164.58 ($CH_3C=$), 170.58 (CH_3CO). Found, %: C 56.87; H 7.56; Cl 9.33; N 3.18; S 7.77. $C_{19}H_{30}ClNO_4S$. Calculated, %: C 56.49; H 7.49; Cl 8.78; N 3.47; S 7.94.

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