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(4*R*,6*R*)-6-(Hydroxymethyl)-4-methyltetrahydro-2*H*-pyran-2-one in the Synthesis of Polyfunctional Compounds with the Methyl-Branched Carbon Skeleton

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Abstract—A simple and efficient asymmetrical synthesis was performed of a convenient bifunctional building block, methyl (R)-5,5-dimethoxy-3-methylpentanoate and its (*S*)-enantiomer. The possibility was shown of its application to the synthesis of insect pheromones.

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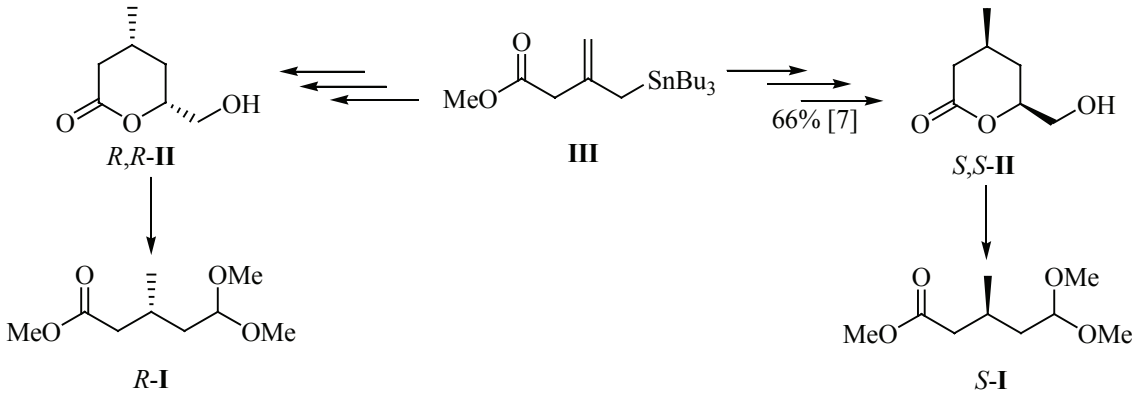
The presence of several chiral centers and functional groups is characteristic of many polyfunctional biomolecules: carbohydrates, prostanoids, pheromones, macrolide antibiotics, and antitumor drugs. Therefore their synthesis is often performed with the use of versatile chiral blocks obtained frequently basing on monoterpenoids, amino acids, and oxyacids [1, 2]. The application of natural compounds is in some cases limited by the optical purity of the initial substances, multistage and complicate processes, the use of expensive reagents and enzymes, and also by the availability of a single optical isomer (antipode).

Especially important for the insect pheromones synthesis are the methods of preparation of bifunctional compounds capable of selective chemical transformations [3]. Therefore in this study an asymmetrical synthesis was developed of a convenient bifunctional building block, methyl (*R*)-5,5-dimethoxy-3-methylpentanoate *R*-(**I**), which had been previously obtained from natural chiral compounds with a methyl-branched carbon skeleton, (*R*)-(+)-pulegone [4] and *L*-(–)-menthol [5, 6]. Ester *R*-(**I**) was synthesized proceeding from (4*R*,6*R*)-6-(hydroxymethyl)-4-methyltetrahydro-2*H*-pyran-2-one (**II**) (Scheme 1), obtained by procedure [7]; at the stage of Keck asymmetric allylation methyl-3-[(tributylstannyl) methyl]but-3-enoate (**III**) was used [8] and (*R*)-1,1'-bi-2-naphthol (binol) as catalyst [9]. Also a number of useful intermediates was obtained that found application to the synthesis of biologically active compounds (Schemes 2–4).

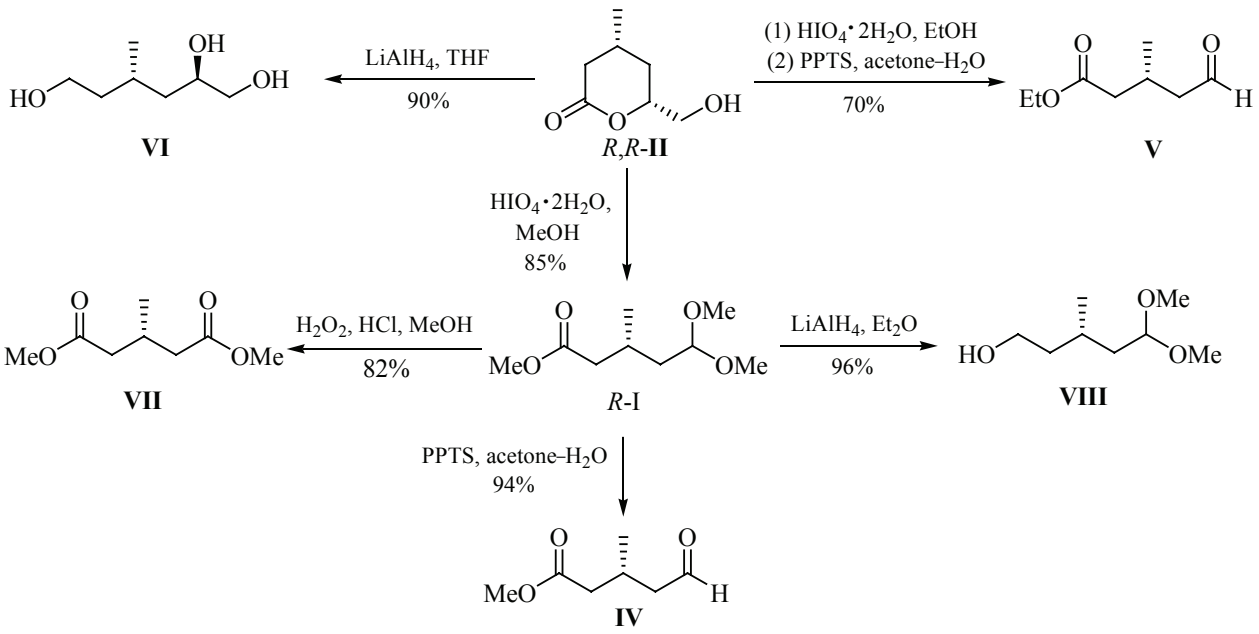
Scheme 1.



R,*R*-**II** **III** *S*,*S*-**II**

R-**I** *S*-**I**

Scheme 2.



Lactones *S*,*S*- and *R*,*R*-(**II**) we obtained with the optical purity >99% in 17% yield with respect to 8 preparative stages calculated on easily available initial ethyl 3,3-diethoxypropionate [7]**.** With respect to the C_5-allyl synthetic building block, methyl-3-[(tributylstannyl) methyl]but-3-enoate (**III**), the yield in 3 stages was 66%.

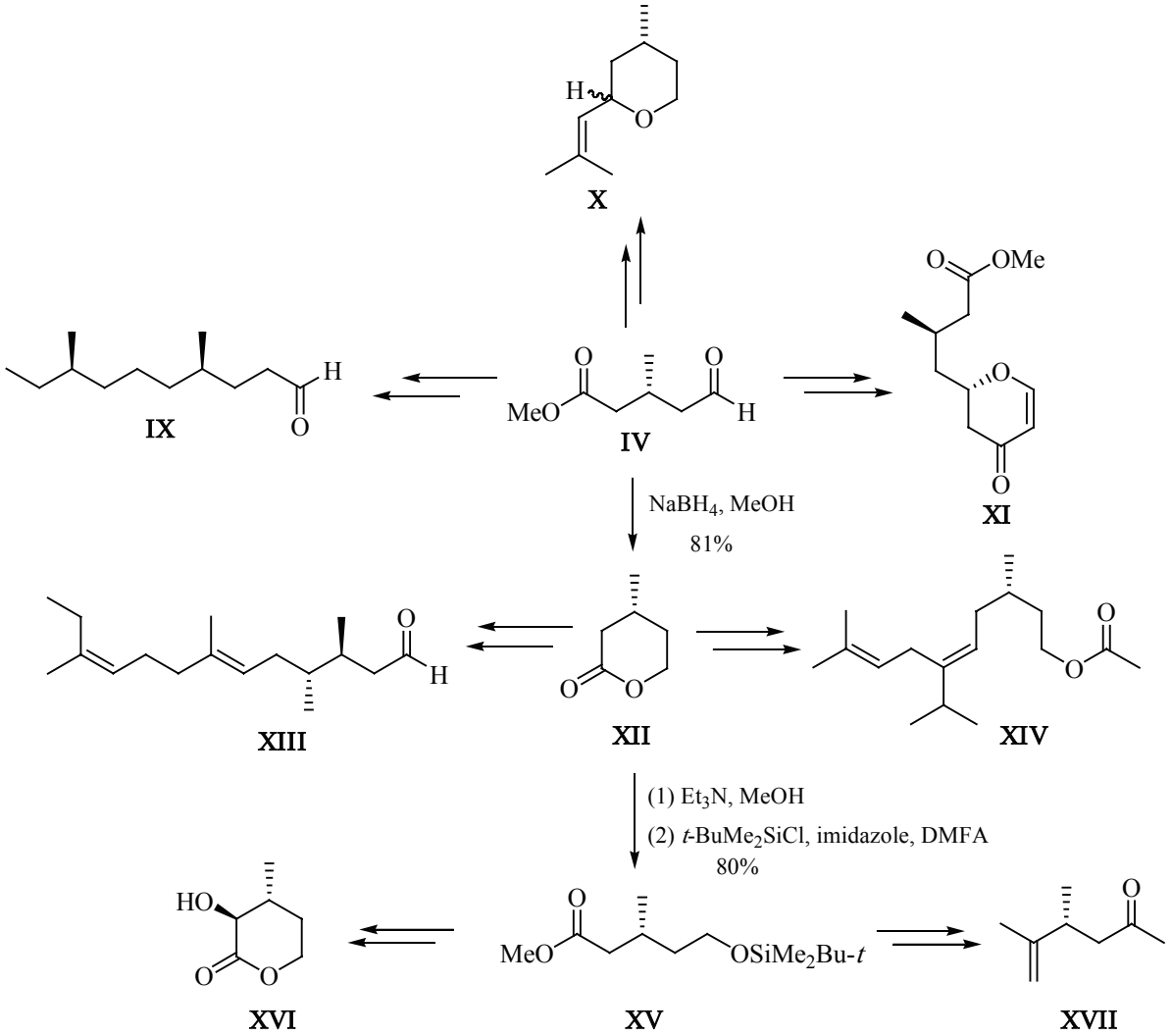
The target ester *R*-(**I**) was obtained after cleavage of lactone *R*,*R*-(**II**) with periodic acid in methanol and maintaining the reaction mixture for 12 h in order to complete the dimethylacetal protection (Scheme 2). The subsequent hydrolysis under mild conditions furnished aldehyde **IV** in a high yield. The oxidation of lactone *R*,*R*-(**II**) in ethanol proceeded slower and gave a mixture of products that was subjected to hydrolysis without purification to provide a bifunctional block **V** which had been used previously in the synthesis of the antitumor drug (–)-laulimalide [10, 11]**.** The reduction of compound *R*,*R*-(**II**) with lithium aluminum hydride in tetrahydrofuran occurred without complications affording triol **VI** that also had been utilized in the synthesis of the fragment C_{15}–C_{20} of aplyronines A, C, C, antitumor drugs from the seaweeds of Sea of Japan *Aplysia kurodai* [12, 13]. Ester *R*-(**I**) was selectively oxidized to alcohol **VII** and reduced to diether **VIII** in high yields; both compounds were also convenient bifunctional building blocks (Scheme 2).

Aldehyde **IV** also found application to the synthesis of several biologically active substances (Scheme 3). In particular it was used in the synthesis of all four isomers of 4,8-dimethyldecanal (**IX**), aggregation pheromone of dangerous cereal pests flour beetle (*Tribolium confusum)* and red flour beetle (*Tribolium castaneum)* [14], of isoprenoid (4*R*)-rose oxide (**X**) [15], of C_5–C_{12} block of a cytostatic drug (–)-laulimalide (**XI**) [16–18].

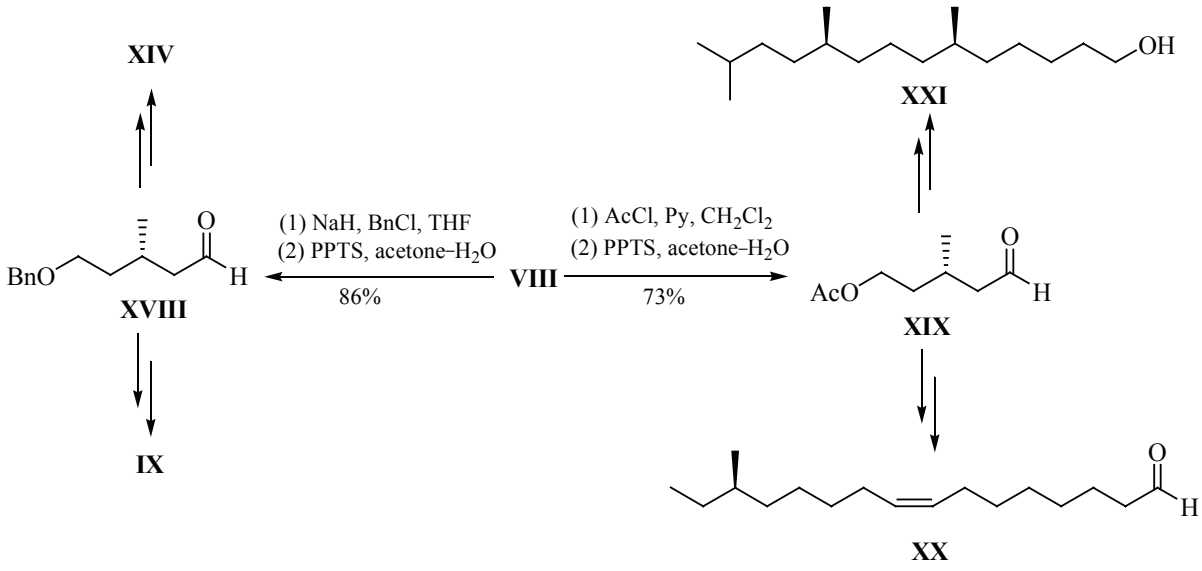
The reduction of aldehyde **IV** with sodium borohydride in methanol was accompanied with the lactonization with the formation of compound **XII** that had been previously used in the synthesis of (+)-faranal (**XIII**), the pheromone of the Pharaoh's ant *Monomorium pharaonis*, a dangerous infection carrier in hospitals and food stores [19, 20], of (*R*)- and (*S*)-enantiomers of (*E*)-6-isopropyl-3,9-dimethyl-5,8-decadienyl acetate (**XIV**), the pheromone of yellow scale *Aonidiella citrina* (*Coquillett*) [21]. After transesterification into a methyl ether lactone **XII** was converted into silyl ether **XV** that could serve as a convenient methyl-branched block in the preparation of the key fragment of the verrucarinic acid **XVI** [22] and a fragment of a cytotoxic macrolide amphidinolide H2 (**XVII**) [23, 24].

Alcohol **VIII** in several preparative stages was converted into functionalized aldehydes **XVIII, XIX** in moderate yields (Scheme 4). Convenient methods are published describing conversion of these aldehydes into insect pheromones. For instance, compound **XVIII** was used in one protocol of the synthesis of the pheromone

Scheme 3.



Scheme 4.



of yellow scale **XIV**, a dangerous pest of citrus plants [21], and of flour beetles **IX** [1]. In its turn aldehyde **XIX** proved to be a promising building block in the preparation of (*R*)- and (*S*)-isomers of (*Z*)-14-methylhexadec-8-enal (trogodermal) (**XX**), aggregation pheromone of Kharpa beetle *Trogoderma granarium* [25], of stereoisomers of 6,10,13-trimethyl-1-tetradecanol (**XXI**), aggregation pheromone of anchor stink bug *Stiretrus anchorago* [26].

The oxidative cleavage of lactone *S*,*S*-(**II**) afforded the corresponding isomeric ester *S*-(**I**) (Scheme 1) with a high yield and a high enantiomeric purity demonstrating the universality of the developed protocol.

Thus a simple convenient protocol is described for the synthesis of several chiral building blocks with the methyl-branched carbon skeleton proceeding from easily available lactone *R*-(**II**) and wide opportunities were demonstrated of the application of these compounds to the synthesis of versatile biologically active substances, in particular, of the pure stereoisomers of pheromones of insect pests.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered from solutions of compounds in deuterochloroform on a spectrometer Bruker AC 400 at operating frequencies 400 and 100 MHz respectively. IR spectra were recorded on a spectrophotometer Bruker Vertex 70 from solutions in tetrachloromethane. The chromatographic isolation of individual compounds was performed with the use of silica gel (70–230 mesh). All solvents before use were dried by usual methods and distilled.

Methyl (*R*)-5,5-dimethoxy-3-methylpentanoate (I). To a solution of 2 g (13.9 mmol) of lactone *R*,*R*-(**II**) in 20 ml of anhydrous methanol was added 3.5 g (18.1 mmol) of $HIO_4 \cdot 2H_2O$, and the mixture was stirred for 12 h. The reaction mixture was diluted with 50 ml of ethyl ether and was treated at vigorous stirring with a saturated water solution of $NaHCO_3$ (50 ml). The organic layer was separated, the reaction product was extracted from the water layer with ethyl ether (3 × 30 ml), the combined organic solutions were washed with brine (50 ml) and dried with $MgSO_4$. The solvent was removed at a reduced pressure, the reaction product was isolated by chromatography (eluent petroleum ether–ethyl acetate, 80 : 1). Yield 2.24 g (85%), $[\alpha]_D$ –1.5° (*c* 2.4, $CHCl_3$). The spectra of compound obtained were consistent with those published in [4, 5].

Methyl (3*R*)-3-methyl-5-oxopentanoate (IV). To a solution of 0.89 g(4.7 mmol) of ester *R*-(**I**) in a mixture of 10 ml of acetone and 3 ml of water was added 0.08 g (0.3 mmol) of pyridine-*p*-toluenesulfonate (PPTS), and the mixture was stirred at boiling over 3 h till the completion of the reaction (TLC monitoring). After distilling off the solvent at a reduced pressure the residue was dissolved in 40 ml of $CHCl_3$, washed with saturated water solution of $NaHCO_3$ (25 ml), and dried with $MgSO_4$. The solvent was removed at a reduced pressure, the reaction product was isolated by chromatography (eluent petroleum ether–ethyl acetate, 60 : 1). Yield 0.63 g (94%). The spectra and optical rotation of compound obtained were consistent with those published in [27].

Ethyl (3*R*)-3-methyl-5-oxopentanoate (V). To a solution of 0.9 g (6.3 mmol) of lactone *R*,*R*-(**II**) in 10 ml of anhydrous ethanol was added 1.73 g (7.6 mmol) of $HIO_4 \cdot 2H_2O$, and the mixture was stirred for 24 h. The alcohol was removed at a reduced pressure, the reaction mixture was diluted with 15 ml of acetone and 2 ml of water, 0.08 g (0.3 mmol) of PPTS was added, and the solution was stirred at boiling for 4 h till the completion of the reaction (TLC monitoring). On removing the solvent at a reduced pressure the residue was dissolved in 40 ml of $CHCl_3$, washed with saturated water solution of $NaHCO_3$ (25 ml), and dried with $MgSO_4$. The solvent was removed at a reduced pressure, the reaction product was isolated by chromatography (eluent petroleum ether–ethyl acetate, 50 : 1). Yield 0.69 g (70%), $[\alpha]_D$ –5.4° (*c*2.5, $CHCl_3$). IR spectrum, cm^{-1}: 1730, 1713, 1415, 1360, 1238, 1182. ^{1}H NMR spectrum, δ, ppm: 1.05 q (3H, CH_3, *J* 7.2 Hz), 1.22 t (3H, $C\underline{H}_3CH_2O$, *J* 7.5 Hz), 2.19–2.80 m (5H, $CO\underline{CH}_2CHCH_3$, $C\underline{H}CH_3$, $C\underline{H}_2CHO$), 4.25 q (2H, $CH_3C\underline{H}_2O$, *J* 7.5 Hz), 9.80 br.s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: 14.6, 20.4, 25.7, 41.4, 50.4, 60.8, 168.2, 204.0. Found, %: C60.88; H 8.84. $C_8H_{14}O_3$. Calculated, %: C60.74; H 8.92.

(2*R*,4*S*)-4-Methylhexane-1,2,6-triol (VI). At cooling to 0°C to a slurry of 0.4 g (10 mmol) of $LiAlH_4$ in 10 ml of THF was added a solution of 0.72 g (5 mmol) of lactone *R*,*R*-(**II**) in 5 ml of THF, and a vigorous stirring was continued for 12 h. The mixture was diluted with 30 ml of ethyl ether, and 0.2 ml of water was added at cooling. The reaction mixture was filtered through a thin bed of silica gel, and the solvent was removed at a reduced pressure. Yield 0.67 g (90%), $[\alpha]_D$ +10.1° (*c*1.0, $CHCl_3$). The spectra of compound obtained were in agreement with published data [13].

Dimethyl 3-methylpentanedioate (VII). To a solution of 0.95 g (5 mmol) of compound *R*-(**I**) in 10 ml of methanol cooled to 0°C was added 0.7 ml of concn. HCl, then 0.9 ml of 33% H_2O_2, and the mixture was stirred for 1 h and later heated at 50–55°C for 5 h. The large part of methanol was removed at a reduced pressure, the residue was diluted with ethyl acetate (30 ml) and neutralized with sodium hydrogen carbonate, the organic layer was separated and dried with Na_2SO_4. The solvent was removed at a reduced pressure. Yield 0.71 g (82%). The spectra of compound obtained were consistent with those published in [28].

(3*S*)-5,5-Dimethoxy-3-methylpentan-1-ol (VIII). To a slurry of 0.76 g (5 mmol) of $LiAlH_4$ in 20 ml of anhydrous ethyl ether was added a solution of 1.33 g (7 mmol) of ester *R*-**(I)** in 3 ml of anhydrous ethyl ether at uniform stirring while boiling. After 2 h the mixture was diluted with 20 ml of ethyl ether and at cooling 1 ml of water was added. The reaction mixture was filtered through a thin bed of silica gel, and the solvent was removed at a reduced pressure. Yield 1.09 g (96%), $[\alpha]_D$ +5.7° (*c* 1.9, $CHCl_3$). The spectra of compound obtained were consistent with those published in [4].

(4*R*)-4-Methyltetrahydro-2*H*-pyran-2-one (XII). To a solution of 1.15 g (8 mmol) of aldehyde **IV** in 20 ml of methanol was added 0.38 g (10 mmol) of $NaBH_4$, and the mixture was stirred for 12 h. The reaction mixture was treated with 20 ml of saturated water solution of NH_4Cl. The reaction product was extracted into ethyl ether (4 × 10 ml), the combined organic solutions were dried with Na_2SO_4. On removing the solvent at a reduced pressure compound **XII** was isolated by chromatography (eluent petroleum ether–ethyl acetate, 15 : 1). Yield 0.74 g (81%). The spectra and optical rotation of compound obtained were consistent with those published in [20, 27].

Methyl (3*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylpentanoate (XV). To a solution of 1.2 g (10.5 mmol) of lactone **XII** in 10 ml of anhydrous methanol was added 5 ml of Et_3N, and the mixture was kept for 48 h. On removing the mixture of solvents at a reduced pressure the residue was dissolved in 5 ml of DMF, in one portion was added 0.95 g (14 mmol) of imidazole and 1.96 g (13 mmol) of *tert*-butyldimethylchlorosilane (*t*-$BuMe_2SiCl$). The reaction mixture was treated with 15 ml of saturated water solution of NH_4Cl. The reaction product was extracted into ethyl ether (4×10 ml), the combined organic solutions were dried with Na_2SO_4. On removing the solvent at a reduced pressure the reaction product was isolated by chromatography (eluent petroleum ether–ethyl acetate, 70:1). Yield 2.07 g (80%). The spectra of compound obtained were consistent with those published in [23].

(3*S*)-5-Benzyloxy-3-methylpentanal (XVIII). To a slurry of 0.12 g (5 mmol) of NaH in 15 ml of THF was added 0.64 g of alcohol **VIII**, and the mixture was stirred for 20 min. Then a solution of 0.63 g (5 mmol) of benzyl chloride in 3 ml of THF was added, and the reaction mixture was stirred at 50°C over 8 h. The reaction mixture was treated with 45 ml of saturated water solution of NH_4Cl. The reaction product was extracted into ethyl ether (4 × 10 ml), the combined organic solutions were dried with Na_2SO_4. The solvent was removed at a reduced pressure. The residue was diluted with 25 ml of acetone and 3 ml of water, 0.16 g (0.6 mmol) of PPTS was added, and the mixture was stirred at boiling for 4 h till the completion of the reaction. The solvent was removed at a reduced pressure. The residue was dissolved in 40 ml of $CHCl_3$, washed with saturated water solution of $NaHCO_3$ (25 ml), and dried with $MgSO_4$. The solvent was removed at a reduced pressure, the reaction product was isolated by chromatography (eluent petroleum ether–ethyl acetate, 60 : 1). Yield 0.71 g (86%), $[\alpha]_D$ –4.2° (*c* 1.5, $CHCl_3$). IR spectrum, cm^{-1}: 1708, 1454, 1408, 1277, 1178, 1096, 1027. ^1H NMR spectrum, δ, ppm: 0.97 q (3H, CH_3, *J* 6.8 Hz), 1.23–1.34 m (1H, C<u>H</u>$_2$CH), 1.38–1.45 m (1H, C<u>H</u>$_2$CH), 2.02–2.09 m (C<u>H</u>CH_3), 2.19–2.24 m (1H, C<u>H</u>$_2$CHO), 2.35–2.41 m (1H, C<u>H</u>$_2$CHO), 3.42 t (2H, CH_2C<u>H</u>$_2$O, *J* 6.8 Hz), 4.46 s (2H, OC<u>H</u>$_2$Ph), 7.18–7.31 m (5H, Ph), 9.71 br.s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: 19.5, 26.8, 32.9, 50.5, 69.9, 72.5, 127.1, 127.2, 127.9, 138.2, 202.2. Found, %: C75.73; H 8.72. $C_{13}H_{18}O_2$. Calculated, %: C75.69; H 8.80.

(3*S*)-5-Methyl-5-oxopentyl acetate (XIX). To a solution of 0.64 g (4 mmol) of alcohol **VIII** in 10 ml of anhydrous CH_2Cl_2 was added at cooling in succession 0.8 g (10 mmol) of pyridine and 0.47 g (6 mmol) of acetyl chloride in 2 ml of CH_2Cl_2 , and the mixture was stirred for 12 h. The reaction mixture was treated with 40 ml of saturated water solution of $NaHCO_3$. The reaction product was extracted into CH_2Cl_2 (2 × 10 ml), the combined organic solutions were dried with Na_2SO_4. The solvent was removed at a reduced pressure. The residue was diluted with 25 ml of acetone and 3 ml of water, 0.16 g (0.6 mmol) of PPTS was added, and the mixture was stirred at boiling for 3 h till the completion of the reaction. The solvent was removed at a reduced pressure. The residue was dissolved in 40 ml of $CHCl_3$, washed

with saturated water solution of $NaHCO_3$ (25 ml), and dried with (eluent petroleum ether–ethyl acetate, 60 : 1). Yield 0.46 g (73%). The spectra and optical rotation of compound obtained were consistent with those published in [26].

Methyl (*S*)-5,5-dimethoxy-3-methylpentanoate (I) was obtained similarly to the *R*-enantiomer. Yield 2.18 g (83%), $[\alpha]_D$ +1.5° (*c*1.6, $CHCl_3$). The spectral characteristics of compound obtained were consistent with those of compound *R*-(***I***).

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