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Synthesis of Epothilones Molecule Fragment (15*R*)-C^{13}–C^{21} from D-Mannitol

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Abstract—Efficient synthesis of an epothilone molecules fragment (15*R*)-C^{13}–C^{21} was carried out from D-mannitol through its conversion into methyl 2,3-*O*-cyclohexylidene-D-glycerate followed by the cyclopropanation of the ester group with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide and the transformation of the obtained cyclopropanol into the corresponding 2-substituted allyl bromide. The coupling of the latter catalyzed by copper with 2-methylthiazolyl-4-magnesium bromide, the shift of a double carbon-carbon bond in the product obtained into the position, conjugated with the thiazole ring, and the common transformation of the protected 1,2-diol function afforded the target compound in 15% yield.

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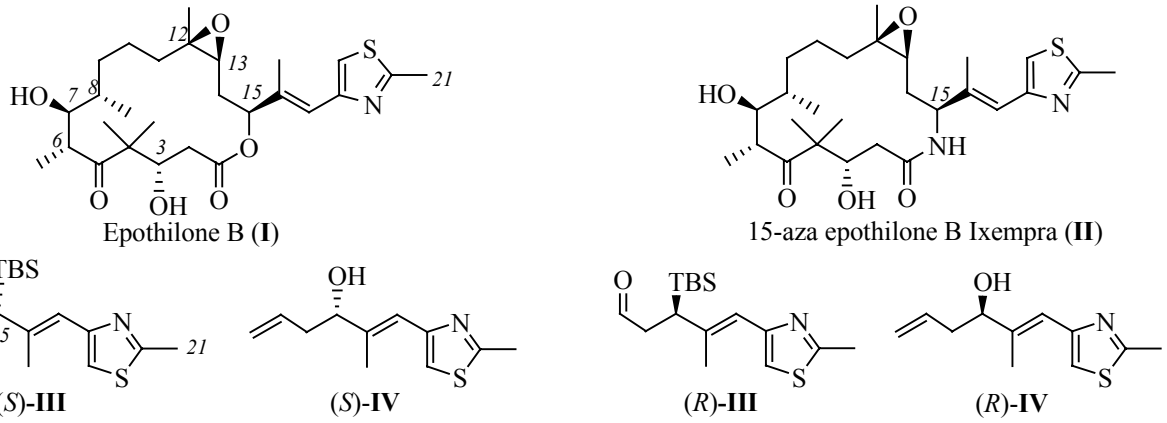
First compounds from the series of epothilones were isolated from extracts of mixobacterium *Sorangium cellulosum* [1], and they attracted a considerable attention as a promising initial material for developing antitumor agents [2]. Some of these compounds, among them epothilone B (**I**) at present is under clinical tests, and its 15-azaanalog **II** is the active substance of the antitumor drug with the commercial name Ixempra [3, 4]. The most efficient strategies of the synthesis of epothilones and their analogs are based on the macrocycle formation by lactonization or olefin metathesis and on the use as the key intermediates thiazole-containing C^{13}–C^{21} epothilone fragments (*S*)-(**III**) and (*S*)-(**IV**) [5, 6].

In the course of the development of cyclopropanol procedures for the syntheses of naturally existing biologically active compounds [7–9] we found efficient ways to the synthesis of compound (*S*)-(**III**) from L-malic acid [10], and compounds (*S*)-(**IV**) and (*R*)-(**IV**), from methyl 2,3-O-isopropylidene-D-glycerate prepared in its turn from D-mannitol [11]. Here we report on the conversion of the latter into the C^{13}–C^{21} epothilone fragment (*R*)-(**III**), a promising intermediate for the epothilone

Scheme 1.



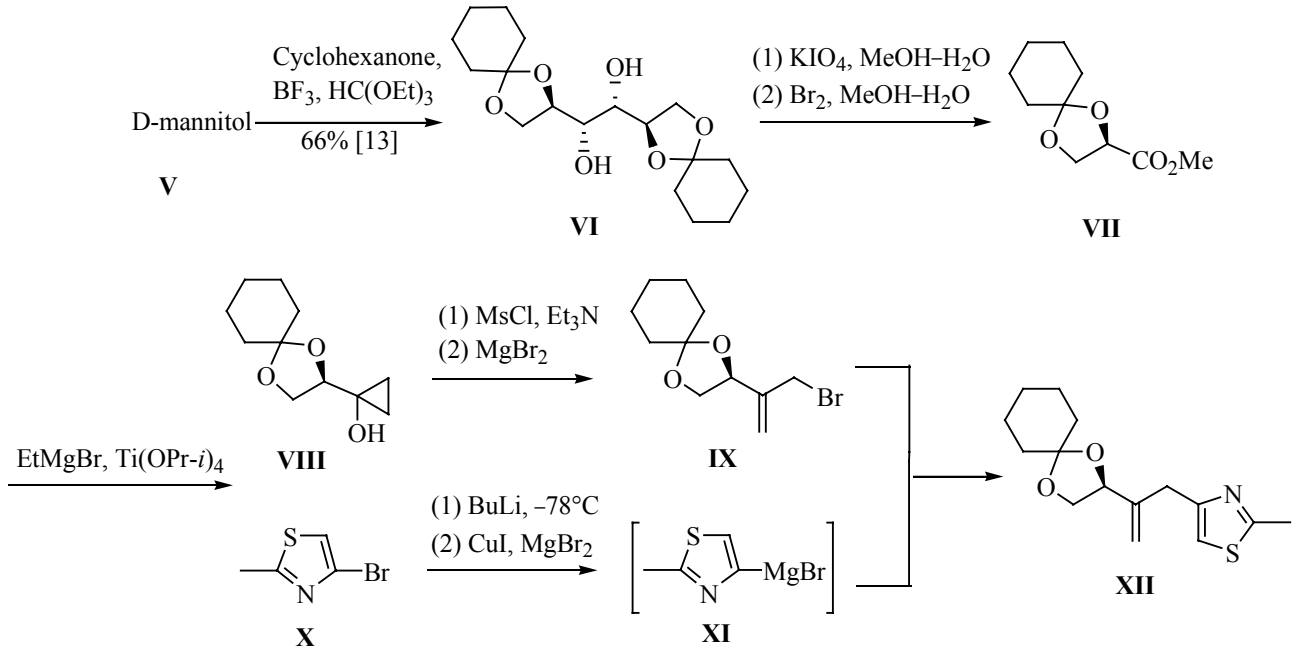
synthesis through the stage of the hydroxy group substitution with the reversal of the streochemical configuration of the atom C^{15} [12] (Scheme 1).

D-Mannitol was by the known procedure converted into biscyclohexylidene derivative **VI** [13], whose vicinal diol fragment was subjected to destructive oxidation by the method used with the corresponding isopropylidene analog [14] to obtain the known methyl 2,3-*O*-cyclohexylidene-D-glycerate (**VII**) (Scheme 2) that had been previously prepared from compound **VI** through its oxidation into the corresponding aldehyde [15]. The reaction of ester **VII** with ethylmagnesium bromide in the presence of an equimolar amount of titanium(IV) isopropoxide resulted in a good yield of cyclopropanol **VIII**, whereas the yield of the cyclopropanation product from the isopropylidene derivative of the D-methyl glycerate under similar conditions did not exceed 60% [11]. The attempts to carry out the cyclopropanation of compound **VII** in the presence of catalytic quantities of titanium(IV) isopropoxide led to significantly lower yields of compound **VIII**.

Analogously to the previously described protocol of the synthesis of the fragments C^{13}–C^{21} of the epothilone molecules (*S*)-(**III**), (*S*)-(**IV**), and (*R*)-(**IV**) [10, 11] the substituted cyclopropanol **VIII** was further converted into the corresponding methanesufonate which was transformed into 2-substituted allyl bromide **IX** through the cationic cyclopropyl-allyl rearrangement induced by magnesium bromide [16]. The coupling catalyzed with copper of allyl bromide **IX** with 2-methylthiazolyl-4-magnesium bromide (**XI**) prepared from 4-bromo-2-methylthiazole (**X**) [10] proceeded cleanly to yield compound **XII** (Scheme 2). The published procedure of preparation of compound **X** by methylation with dimethyl sulfate of 4-bromothiazolyl-2-lithium obtained by the reaction of halogen-lithium exchange [17] from the available 2,4-dibromothiazole was essentially improved by the workup of the reaction mixture with aqueous ammonia and the purification of the monomethylated product **X** by the distillation in a vacuum. The use of the described in the original procedure treatment of the reaction mixture with water did not completely eliminate the excess of the methylating agent, and the purification of 4-bromo-2-methylthiazole (**X**) by column chromatography on silica gel did not separate the target product from the simultaneously formed 2,5-dimethylthiazol due to the similar chromatographic mobility of these substances.

The boiling of the solution of disubstituted olefin **XII** in *tert*-butanol in the presence of potassium *tert*-butylate led to the shift of the disubstituted double bond into the position conjugated with the thiazole ring and to the formation with a high stereoselectivity of trisubstituted (*E*)-olefin **XIII** [10]. In the latter the acid hydrolysis of the acetal moiety followed by selective tosylation of the

Scheme 2.



primary hydroxy group in the arising 1,2-diol gave monosulfonate **XIV** that by the treatment with sodium cyanide in dimethyl sulfoxide was converted into β-hydroxynitrile **XV**. In the course of the latter process in the reaction mixture alongside substrate **XIV** and compound **XV** was also detected oxirane derivative **XVI**, probably the direct precursor of nitrile **XV**.

The optical purity of secondary alcohol **XV** was estimated from the ^{1}H NMR spectrum of the product of its acylation with Mosher's (*S*)-acid [18]. In the ^{1}H NMR spectrum of Mosher ester **XVII** the signal of the methine proton was observed at δ 5.68 ppm, the proton signals from methoxy and methyl groups, at δ 3.65 and 1.98 ppm. No signals were detected from the minor diastereomer at δ 5.76, 3.53, and 2.17ppm indicating that compound **XV** was obtained with *ee* >99%. The expected chemical shifts of the proton signals belonging to the minor diastereomer were determined from the ^{1}H NMR spectrum of the ester prepared from the secondary alcohol **XV** and racemic Mosher's acid. The silylation of compound **XV** followed by the reduction of the formed product with diisobutylalumunum hydride resulted in the target aldehyde (*R*)-(**III**) in the yield 15% with respect to D-mannitol (**V**) (Scheme 3).

The protocol of the synthesis of the fragment C^{13}–C^{21} of epothilones molecule (*R*)-(**III**) is distinguished from the previously developed procedures for preparation of the fragment C^{13}–C^{21} of epothilones molecules (*S*)-(**III**), (*S*)-(**IV**) and (*R*)-(**IV**) from the derivatives of chiral α-hydroxycarboxylic acids [10, 11] by the lesser number of stages and larger overall yield of the target compound.

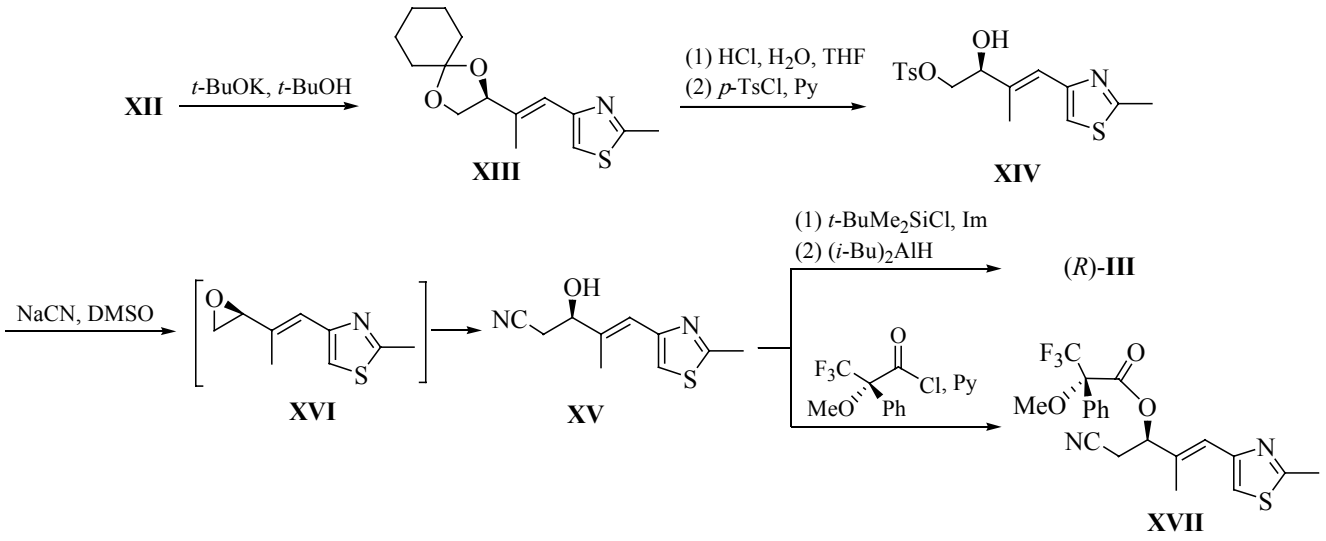
EXPERIMENTAL

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

Methyl 2,3-O-cyclohexylidene-D-glycerate (VII). To a solution of 40.0 g (0.116 mol) of cyclohexylidene derivatives of D-mannitol **VI** [13] in 300 ml of methanol was added at vigorous stirring 750 ml of water, 2.0 g (0.02 mol) of $KHCO_3$, and 32.0 g (0.14 mol) of KIO_4. The mixture was stirred for 3 h at room temperature, thereafter 50.0 g (0.59 mol) of $NaHCO_3$ was added and then dropwise 14.8 ml (0.29 mol) of bromine was added. Then the reaction mixture was treated with saturated water solution of Na_2SO_3, filtered, the precipitate was washed with dichloromethane (2×100 ml), water layer was extracted with the same solvent (3×100 ml). The combined organic solutions were dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was distilled in a vacuum [bp 82–83°C (1 mm Hg)]. Yield 35.3 g (76%), $[\alpha]_D$ 19.5° (*c* 6.8, $CHCl_3$) {$[\alpha]_D$ 18.99° (*c*1.0, MeOH) [15]}. The spectral characteristics of compound obtained were consistent with the published data [15].

1-{(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl}cyclopropanol

Scheme 3.



(VIII). To a solution of 35.3 g (0.176 mol) of ester **VII** and 50.0 g (0.176 mol) of titanium(IV) isoropoxide in 250 ml of THF under an argon atmosphere was added within 3 h while stirring a solution of ethylmagnesium bromide prepared from 20.5 g (0.84 mol) of magnesium and 87.0 g (0.80mol) of ethyl bromide in 500 ml of THF. The solvent was distilled off at a reduced pressure, the reaction mixture was diluted with 300 ml of dichloromethane, and it was treated at cooling with 100 ml of saturated water solution of NH_4Cl. The precipitate was filtered off, washed with dichloromethane (3 × 150 ml), the filtrate was dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was distilled in a vacuum [bp 86–88°C (1 mm Hg)]. Yield 25.0 g (72%), $[\alpha]_D$ 4.0° (*c*5.5, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3584 (OH), 3091 (CH cyclopropane). ^{1}H NMR spectrum, δ, ppm: 0.48–0.45 m (1H, CH_2 cyclopropane), 0.59–0.69 m (1H, CH_2 cyclopropane), 0.81–0.91 m (2H, CH_2 cyclopropane), 1.27–1.71 m [10H, $(CH_2)_5$], 2.48 br.s (1H, OH), 3.69–3.73 m (1H, OCH), 3.98–4.05 m (2H, OCH_2). ^{13}C NMR spectrum, δ, ppm: 9.4 (CH_2), 12.5 (CH_2), 23.7 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 34.9 (CH_2), 36.0 (CH_2), 53.9(C), 65.4 (CH_2), 80.4 (CH), 109.8 (C). Found, %: C 66.80; H 9.23. $C_{11}H_{18}O_3$. Calculated, %: C66.64; H 9.15.

3-Bromo-2-{(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl}-prop-1-ene (IX). To a solution of 24.5 g (0.124 mol) of tertiary cyclopropanol **VIII** and 42.0 ml (0.30 mol) of triethylamine in 200 ml of ethyl ether was added at stirring and cooling with ice a solution of 15.5 ml (0.20 mol) of methanesulfonyl chloride in 50 ml of ether. The reaction mixture was warmed to room temperature within 2 h, it was treated with 150 ml of saturated water solution of $NaHCO_3$, the organic layer was separated, the water layer was extracted with ether (3×50 ml), the combined organic solvents were washed with brine and dried with Na_2SO_4. The solvent was distilled off at a reduced pressure, to the residue was added 250 ml of chloroform and a solution of magnesium bromide prepared from 11.0 g (0.45 mol) of magnesium and 81.0 g (0.43 mol) of dibromoethane in 250 ml of ether. The mixture was boiled at stirring for 2.5–3 h, cooled, washed with 300 ml of saturated water solution of $NaHCO_3$, the organic layer was separated, the water layer was extracted with ether (2×100 ml). The combined organic solvents were washed with brine and dried with Na_2SO_4. The solvent was distilled off at a reduced pressure, the residue was distilled in a vacuum [bp 90–93°C (1mm Hg)]. Yield 23.5 g (73%), $[\alpha]_D$ 14.3° (*c* 4.2, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3095 (CH olefin), 1645 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.38–1.68 m [10H, $(CH_2)_5$], 3.74–3.78 m (1H, OCH_2), 3.90–4.06 m (2H, CH_2Br), 4.21 d.d (1H, OCH_2, J_1 8.2, J_2 6.4 Hz), 4.64–4.68 m (1H, OCH), 5.35 br.s (1H, CH_2=), 5.40 br.s (1H, CH_2=). ^{13}C NMR spectrum, δ, ppm: 23.8 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 31.9 (CH_2), 35.2 (CH_2), 35.9 (CH_2), 68.9 (CH_2), 76.3 (CH), 109.9 (C), 117.0 (CH_2), 143.3 (C). Found, %: C 50.75; H 6.60. $C_{11}H_{17}BrO_2$. Calculated, %: C50.59; H 6.56.

4-Bromo-2-methylthiazole (X). To a solution of 30.0 g (0.123 mol) of 2,4-dibromothiazole in 400 ml of ether at –78°C under argon was added dropwise 115 ml (133 mmol) of 1.16 M solution of butyllithium in hexane. The mixture was stirred for 1 h at –78°C, then 35 ml (0.37 mol) of dimethyl sulfate in 30 ml of ether was added, the mixture was stirred for 0.5 h at –78°C and warmed to room temperature withinj 2 h. To the reaction mixture 200 ml of 20% water solution of ammonia was added, and the two-phase system was vigorously stirred for 1 h. The organic layer was separated, the water layer was extracted with ether (3×50 ml), the combined organic solvents were washed with brine, dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was distilled in a vacuum [bp 88–89°C (16mm Hg)]. Yield 17.5 g (80%). The spectral characteristics of compound obtained were consistent with the published data [17].

4-(2-{(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl}prop-2-en-1-yl)-2-methylthiazole (XII). To a solution of 17.6 g (99 mmol) of 4-bromo-2-methylthiazole (**X**) in 100 ml of ether at –78°C under argon was added dropwise while stirring 80 ml (93 mmol) of 1.16 M solution of butyllithium in hexane. The mixture was stirred for 1 h at –78°C, then 0.35 g (1.83 mmol) of copper iodide was added, the mixture was warmed to –40°C, and an ether solution was added of magnesium bromide prepared from 3.10 g (128 mmol) of magnesium and 22.6 g (120 mmol) of dibromoethane in 90 ml of ether. The mixture was warmed at stirring to 0°C, then 17.6 g (67 mmol) of 2-substituted allyl bromide **IX** in 80 ml of ether was added, and the mixture was warmed to the room temperature. The reaction mixture was treated with 150 ml of the saturated water solution of NH_4Cl, the organic layer was separated, the water layer was extracted with ether (3×75 ml). The combined organic solvents were washed with saturated solution of $NaHCO_3$ and with brine, dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was distilled in a vacuum [bp 132–134°C (1mm Hg)]. Yield 17.3 г (92%), $[\alpha]_D$ 11.3° (*c* 5.5, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3090 (CH olefin),

1651 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.37–1.69 m [10H, $(CH_2)_5$], 2.67 s (3H, CH_3 thiazole), 3.43–3.55 m (2H, $C\underline{H}_2C=CH_2$), 3.58–3.62 m (1H, OCH_2), 4.00 d.d (1H, OCH_2, J_1 8.1, J_2 6.5 Hz), 4.53–4.57 m (1H, OCH), 4.90 br.s (1H, $CH_2C=C\underline{H}_2$), 5.28 br.s (1H, $CH_2C=C\underline{H}_2$), 6.79 s (1H, CH thiazole). ^{13}C NMR spectrum, δ, ppm: 19.1 (CH_3), 23.8 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 34.3 (CH_2), 35.2 (CH_2), 35.9 (CH_2), 68.5 (CH_2), 77.9 (CH), 109.8 (C), 113.3 (CH_2), 114.2 (CH), 144.6 (C), 153.7 (C), 165.6 (C). Found, %: C64.61; H 7.50. $C_{15}H_{21}NO_2S$. Calculated, %: C64.48; H 7.58.

4-[(1*E*)-2-{(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl}-prop-1-en-1-yl]-2-methylthiazole (XIII). A solution of 15.8 g (56.6 mmol) of compound **XII** and 9.0 g (80 mmol) of potassium *tert*-butylate in 300 ml of *tert*-butanol was boiled for 1 h. The solvent was distilled off at a reduced pressure, the residue was diluted with water, the reaction products were extracted into ether (5×80 ml). The combined organic solutions were washed with the saturated water solution of $NaHCO_3$, dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was subjected to column chromatography (silica gel, eluent petroleum ether–ethyl acetate, 10:1). Yield 14.8 g (94%), $[\alpha]_D$ 2.0° (*c*5.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3113 (CH olefin), 1664 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.38–1.76 m [10H, $(CH_2)_5$], 2.03 s (3H, $C\underline{H}_3C=CH$), 2.70 s (3H, CH_3 thiazole), 3.68–3.72 m (1H, OCH_2), 4.14 d.d (1H, OCH_2, J_1 8.1, J_2 6.7 Hz), 4.59–4.63 m (1H, OCH), 6.62 br.s (1H, $CH_3C=C\underline{H}$), 6.96 s (1H, CH thiazole). ^{13}C NMR spectrum, δ, ppm: 14.1 (CH_3), 19.2 (CH_3), 23.8 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 35.1 (CH_2), 35.9 (CH_2), 68.2 (CH_2), 80.6 (CH), 110.2 (C), 115.9 (CH), 120.0 (CH), 136.9 (C), 152.6 (C), 164.5 (C). Found, %: C64.33; H 7.52. $C_{15}H_{21}NO_2S$. Calculated, %: C64.48; H 7.58.

(2*S*,3*E*)-2-Hydroxy-3-methyl-4-(2-methylthiazol-4-yl)but-3-enyl 4-methylphenylsulfonate (XIV). A mixture of 13.8 g (49.5 mmol) of compound **XIII**, 150 ml of THF, and 50 ml of 3 M hydrochloric acid was stirred for 4 h at room temperature. To the mixture solid K_2CO_3 was added to saturation, the organic layer was separated, the products were extracted from the water layer into THF (3×30 ml), the combined organic solutions were dried with K_2CO_3, filtered, and evaporated at a reduced pressure. The residue was dissolved in 80 ml of pyridine, cooled to 0°C, and to the solution was added 11.0 g (58 mmol) of *p*-toluenesulfonyl chloride. The mixture was kept for 5 h at 4–5°C, then diluted with 250 ml of ether and 100 ml oif saturated solution of $NaHCO_3$. The organic layer was separated, the water layer was extracted with ether (3 × 50 ml), the combined organic solutions were washed with brine, dried with Na_2SO_4. The solvent was distilled off at a reduced pressure, the residue was subjected to column chromatography on silica gel (eluent petroleum ether–ethyl acetate, 3 : 1). Yield 15.7 g (90%), $[\alpha]_D$ 6.4° (*c* 4.7, ethyl acetate). IR spectrum, ν, cm^{-1}: 3613 (OH), 1375 (SO_2), 1178 (SO_2). ^{1}H NMR spectrum, δ, ppm: 1.91 s (3H, $C\underline{H}_3C=CH$), 2.41 s (3H, $C\underline{H}_3C_6H_4$), 2.67 (3H, CH_3 thiazole), 3.96 d.d (1H, $C\underline{H}_2OTs$, J_1 10.2, J_2 7.6 Hz), 4.11 d.d (1H, $C\underline{H}_2OTs$, J_1 10.2, J_2 3.7 Hz), 4.20 br.s (1H, OH), 4.37 d.d (1H, $C\underline{H}OH$, J_1 7.6, J_2 3.7 Hz), 6.57 br.s (1H, $CH_3C=C\underline{H}$), 6.91 s (1H, CH thiazole), 7.28–7.30 m (2H, C_6H_4), 7.75–7.77 m (2H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 14.9 (CH_3), 18.9 (CH_3), 21.5 (CH_3), 72.3 (CH_2), 74.2 (CH), 116.2 (CH), 120.8 (CH), 127.9 (2CH), 129.8 (2CH), 132.7 (C), 136.8 (C), 144.8 (C), 152.0 (C), 164.9 (C). Found, %: C54.50; H 5.46. $C_{16}H_{19}NO_4S_2$. Calculated, %: C54.37; H 5.42.

(3*S*,4*E*)-3-Hydroxy-4-methyl-5-(2-methylthiazol-4-yl)pent-4-enenitrile (XV) and 2-methyl-4-{(1*E*)-2-[(2*S*)-oxiran-2-yl]prop-1-en-1-yl}thiazol (XVI). A mixture of 10.0 g (28.3 mmol) of tosylate **XIV** and 10.0 g (0.20 mol) of NaCN in 70 ml of dimethyl sulfoxide was stirred for 10 h at 40°C. To the reaction mixture 100 ml of water was added, the reaction products were extracted into ethyl acetate (5 × 50 ml). The combined organic solutions were washed with brine, dried with Na_2SO_4. The solvent was distilled off at a reduced pressure, the residue was subjected to column chromatography on silica gel (eluent petroleum ether–ethyl acetate, 3 : 1–1 : 1). Yield of compound **XV** 5.10 g (87%), mp 92–94°C, $[\alpha]_D$ 13.8° (*c* 2.1, ethyl acetate). IR spectrum, ν, cm^{-1}: 3616 (OH), 2251 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.00 s (3H, $C\underline{H}_3C=CH$), 2.65 d (2H, CH_2CN, *J* 6.4 Hz), 2.71 s (3H, CH_3 thiazole), 4.47 t (1H, $C\underline{H}OH$, *J* 6.4 Hz), 4.62 br.s (1H, OH), 6.66 br.s (1H, $CH_3C=C\underline{H}$), 6.97 s (1H, CH thiazole). ^{13}C NMR spectrum, δ, ppm: 14.0 (CH_3), 18.9 (CH_3), 24.7 (CH_2), 72.6 (CH), 116.5 (CH), 117.7 (C), 120.2 (CH), 139.1 (C), 151.6 (C), 165.5 (C). Found, %: C57.86; H 5.85. $C_{10}H_{12}N_2OS$. Calculated, %: C57.67; H 5.81.

In the process carried out under the above described conditions when 0.50 g (1.41 mmol) of tosylate **XIV** and 0.5 g (10 mmol) of NaCN in 5 ml of DMSO were taken after 30 min at 40°C alongside nitrile **XV** [yield 0.05 g (17%)] oxirane **XVI** was obtained [yield 0.19 g (74%). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, $C\underline{H}_3C=CH$),

2.71 s (3H, CH_3 thiazole), 2.79 d.d (1H, CH_2 oxirane, J_1 5.2, J_2 2.5 Hz), 2.94 d.d (1H, CH_2 oxirane, J_1 5.2, J_2 4.2 Hz), 3.48 d.d (1H, CH oxirane, J_1 4.2, J_2 2.5 Hz), 6.66 br.s (1H, CH_3C=C<u>H</u>), 6.98 s (1H, CH thiazole). Found, %: C59.75; H 6.15. $C_9H_{11}NOS$. Calculated, %: C59.64; H 6.12.

Product of compound XV acylation with Mosher's (*S*)-acid (XVII). To a solution of 12 mg (0.058 mmol) of compound **XV** in 0.5 ml of dichloromethane was added 50 mg (0.62 mmol) of pyridine and 30 mg (0.12 mmol) of (*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride. The mixture was kept for 12 h at room temperature, then it was diluted with ether, washed with saturated water solution of $NaHCO_3$, dried with Na_2SO_4. The solvent was distilled off at a reduced pressure, the residue was subjected to column chromatography on silica gel. Yield of **(2*R*,3*E*)-3-methyl-4-(2-methylthiazol-4-yl)-1-cyanobut-3-en-2-yl] (1*S*)-2-methoxy-2-phenyl-3,3,3-fluoropropionate (XVII)** 20 mg (90%). ^{1}H NMR spectrum, δ, ppm: 1.98 s (3H, C<u>H</u>$_3$C=CH), 2.72 s (3H, CH_3 thiazole), 2.76 d.d (1H, CH_2CN, J_1 17.1, J_2 4.6 Hz), 2.86 d.d (1H, CH_2CN, J_1 17.1, J_2 8.4 Hz), 3.65 s (3H, CH_3O), 5.68 d.d [1H, $CF_3(OCH_3)(Ph)CCO_2C$<u>H</u>, J_1 8.4, J_2 4.6 Hz], 6.48 br.s (1H, CH_3C=C<u>H</u>), 6.93 s (1H, CH thiazole), 7.35–7.62 m (5H, C_6H_5).

Acylation of compound XV with racemic 2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride was carried out as described above. ^{1}H NMR spectrum, δ, ppm: 1.98 s (1.5H, C<u>H</u>$_3$C=CH), 2.17 s (1.5H, C<u>H</u>$_3$C=CH), 2.72 s (3H, CH_3 thiazole), 2.75–2.91 m (2H, CH_2CN), 3.53 s (1.5H, CH_3O), 3.65 s (1.5H, CH_3O), 5.68 d.d [0.5H, $CF_3(OCH_3)(Ph)CCO_2C$<u>H</u>, J_1 8.4, J_2 4.6 Hz], 5.76 d.d [0.5H, $CF_3(OCH_3)(Ph)CCO_2C$<u>H</u>, J_1 6.7, J_2 5.9 Hz], 6.48 br.s (1H, CH_3C=C<u>H</u>), 6.93 s (1H, CH thiazole), 7.35–7.62 m (5H, C_6H_5).

Silylation of compound XV with *tert*-butyldimethylchlorosilane. To a solution of 100 mg (0.48 mmol) of compound **XV** in 0.6 ml of DMF was added 51 mg (0.75 mmol) of imidazole and 100 mg (0.66 mmol) of *tert*-butyldimethylchlorosilane. The mixture was kept for 5 h at room temperature and diluted with 5 ml of ether and 2 ml of a saturated water solution of NH_4Cl, water layer was separated and extracted with ethyl ether (2 × 5 ml). The combined organic solutions were dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was subjected to column chromatography on silica gel (eluent petroleum ether–ethyl acetate, 15 : 1). Yield of **3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-enenitrile** 145 mg (94%), $[\alpha]_D$ 10.5° (*c*1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2252 (C≡N). ^{1}H NMR spectrum, δ, ppm: 0.05 s [3H, $(CH_3)_2Si$], 0.15 s [3H, $(CH_3)_2Si$], 0.92 s [9H, $(CH_3)_3CSi$], 2.06 s (3H, C<u>H</u>$_3$C=CH), 2.55 d.d (1H, CH_2CN, J_1 16.5, J_2 5.0 Hz), 2.61 d.d (1H, CH_2CN, J_1 16.5, J_2 7.5 Hz), 2.71 s (3H, CH_3 thiazole), 4.45 d.d (1H, CHOSi, J_1 7.5, J_2 5.0 Hz), 6.56 br.s (1H, CH_3C=C<u>H</u>), 6.98 s (1H, CH thiazole). ^{13}C NMR spectrum, δ, ppm: 4.8 (CH_3), 5.2 (CH_3), 13.5 (CH_3), 18.1 (C), 19.2 (CH_3), 25.6 ($3CH_3$) 26.2 (CH_2),74.5 (CH), 116.7 (CH), 117.6 (C), 120.5 (CH), 138.6 (C), 152.2 (C), 164.8 (C). Found, %: C59.41; H 8.15. $C_{16}H_{26}N_2OSSi$. Calculated, %: C59.58; H 8.12.

(3*R*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)pent-4-enal [(*R*)-III]. To a solution of 110 mg (0.34 mmol) silyl ether of compound **XV** in 5 ml of toluene at –78°C was added dropwise 100 mg (0.70 mmol) diisobutylaluminum hydride in 0.6 ml of toluene. The mixture was stirred for 2 h at –78°C, diluted with 0.5 ml methanol and 0.5 ml of 1 M water solution of HCl, warmed to room temperature, 5 ml of water was added, the organic layer was separated, the water layer was extracted with ether (2 × 5 ml). The combined organic solutions were dried with Na_2SO_4, the solvent was distilled off at a reduced pressure, the residue was subjected to column chromatography on silica gel (eluent petroleum ether–ethyl acetate, 20:1). Yield 100 mg (90%), $[\alpha]_D$ 20.5° (*c* 1.0, $CHCl_3$). The spectral characteristics of compound obtained were in agreement with those reported for the aldehyde (*S*)-(**III**) [5].

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