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Synthesis of Brassinolide and Its Biosynthetic Precursors Using Methyl 3-Hydroxy-2-Methylpropionate

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Abstract—Formal synthesis of plant hormones that belong to the group of 24α-methylbrassinosteroids, including brassinolide and its biosynthetic precursors with one hydroxyl group in their side chain, was performed. Stereochemistry of a methyl group at the C24 atom was provided by the choice of the desired enanthiomer of methyl-3-hydroxy-2-methylpropionate and by the sequence of its conversions into the chiral intermediate that was necessary for the formation of the C23-C28 fragment of the side chain. The (22*R*,23*R*)-diol group was introduced by the Sharpless asymmetric dihydroxylation of the intermediate Δ^{22}-steroids, the products of consecutive reactions of attachment of a low-molecular sulfone to the steroid C22-aldehyde, acetylation, and reductive desulfurization of the intermediate β-acetoxysulfones. Reduction of 22-acetoxy-23,25-disulfones was shown to proceed with the preservation of the functional group at atom C22.

Key words: steroids, brassinolide, sulfones, olefination

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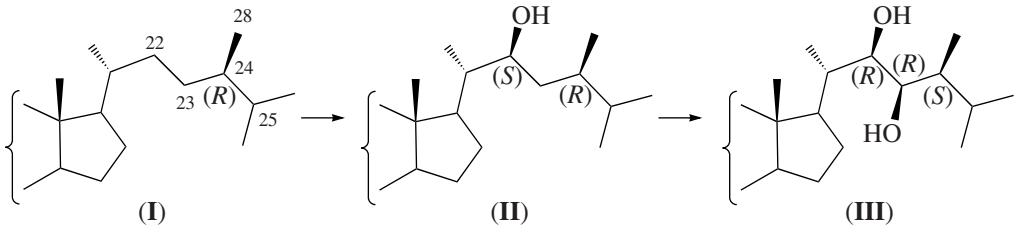
INTRODUCTION

The side chain of brassinosteroids is the structural element [1] that significantly affects their biological activity [2–4].[2] Organic chemists consider this element to be the most difficult in the preparative synthesis of such compounds, especially in the case of brassinolide and its analogues.

Brassinolide forms in plants as a result of the transformations (mainly oxidative) of campesterol. The side chain of compound (**I**) begins to form from (22*S*)-alcohols (**II**) by the action of the CYP90B1 enzyme (EC 1.14.13) from the cytochrome P-450 family. This enzyme catalyzes hydroxylation of the C22 atom of campesterol and its derivatives with the oxidized cyclic part [5] (Scheme 1). Further C-23 hydroxylation with participation of the CYP90A1 cytochrome (EC 1.14) results in (22*R*,23*R*)-diols (**III**). Chemical methods for synthesis of all the compounds of probable biosynthetic chain are obligatory for systematic study of biosynthetic pathways of brassinosteroids. Although, a number of papers devoted to the preparation of both 22-mono- and 22,23-dihydroxyderivatives of campesterol are published now [6–9], a universal synthetic method is still not proposed.



(**I**) (**II**) (**III**)

Scheme 1.

The goal of this study is elaboration of the approach to preparation of brassinosteroids which contain a partially or completely formed side chain of brassinolide using available starting compounds and common intermediates. Molecules of the target compounds contain the asymmetric C24 atom, and suitable chiral synthetic block will be useful for the preparation of the terminal fragment of their side chain. We decided to study the possibilities for the use of commercially available (2*S*)-3-hydroxy-2-methylpropionate (**IV**) in addition to our previously described variations of synthesis of C28-

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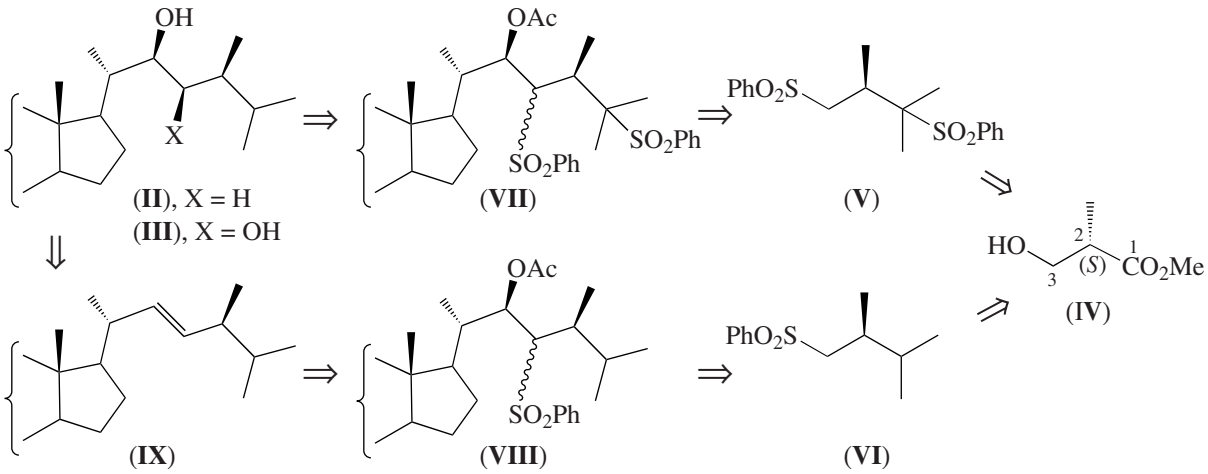
[2] Abbreviations: Alk, alkyl; Bn, benzyl; DHP, dihydropyran; Thp, tetrahydropyranyl; Ts, toluenesulfonyl; mCPBA, *m*-chloroperbenzoic acid.

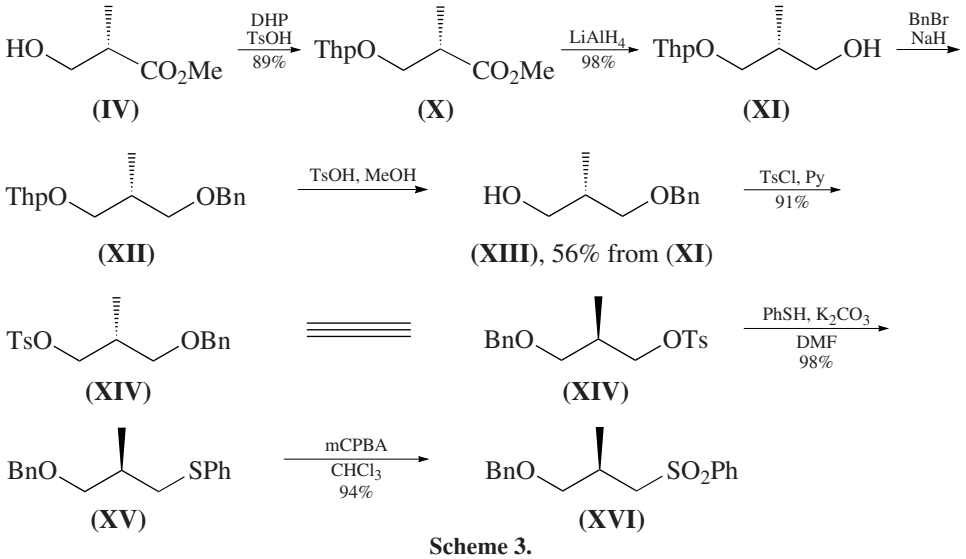
brassinosteroids [8, 10, 11]. We planned to use the attachment of disulfone (**V**) or sulfone (**VI**) (Scheme 2) to the corresponding C22-steroid aldehydes as a key reaction for synthesis of all the target brassinosteroids. Synthesis of both the natural hormone (**III**) itself, its monohydroxylated analogue (**II**), and their sterol precursor (**IX**) would be performed by further conversions according to the given retrosynthetic scheme.



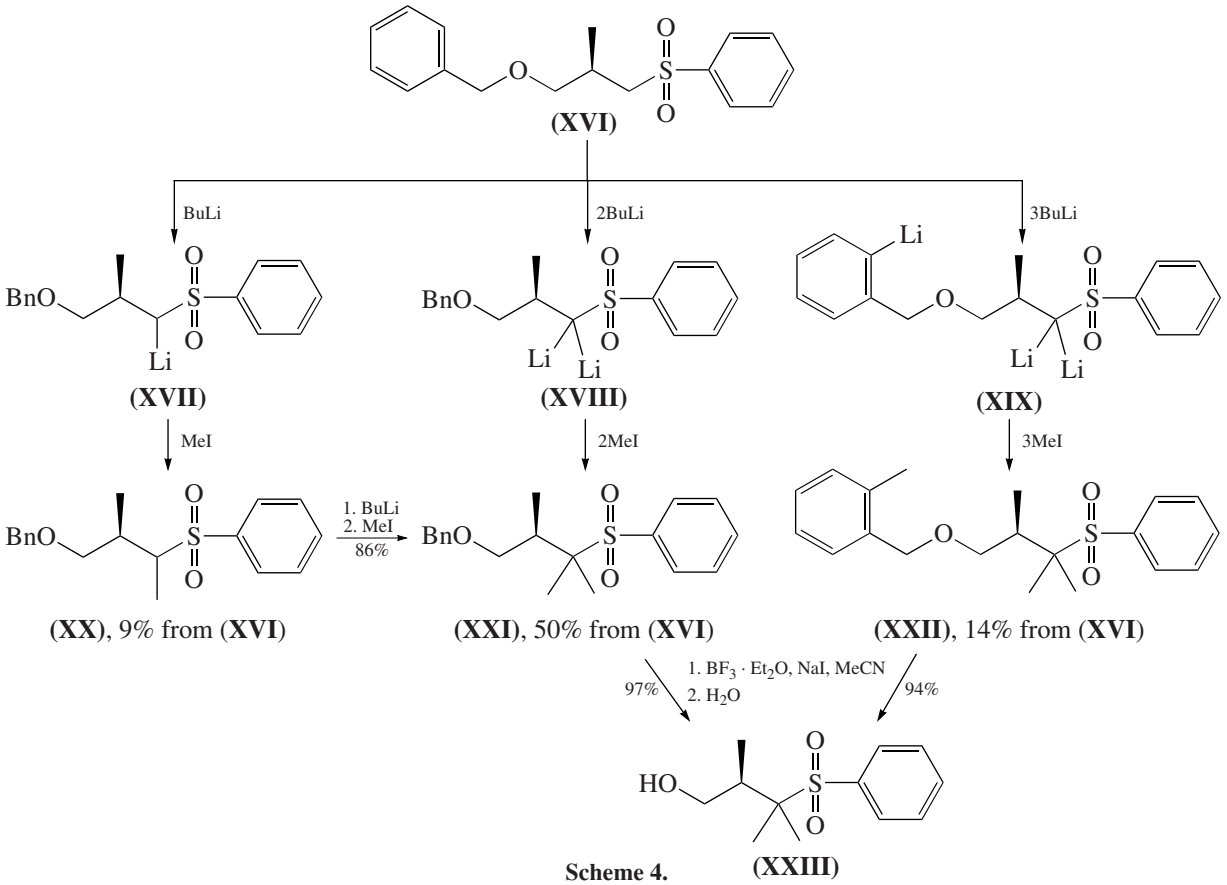
Scheme 2.

RESULTS AND DISCUSON

Both commercially available enanthiomers (*R* and *S*) of 3-hydroxy-2-methylpropionate can theoretically be applied to the formation of the 24α-methylsterol side chain typical for brassinolide and its biosynthetic precursors. The desired stereochemistry of the C24 asymmetric center can be achieved in the case of the application of methyl-(2*S*)-3-hydroxy-2-methylpropionate (**IV**) only under the condition of the final conversion of the C1 atom of this compound into the C23 atom of the side chain. We solve this problem as follows from scheme 3. The treatment of alcohol (**IV**) with dihydropropionate, the hydride reduction of ester (**X**), and the benzylation of alcohol (**XI**) gave disubstituted ester (**XII**). Protective groups of this compound were introduced according to the principle of orthogonal stability [12], i.e., every of them could be separately removed in the presence of the others. For example, the treatment of compound (**XII**) with toluenesulfonic acid in methanol resulted in selective removal of tetrahydropyranyl protection and the formation of alcohol (**XIII**).



Scheme 3.



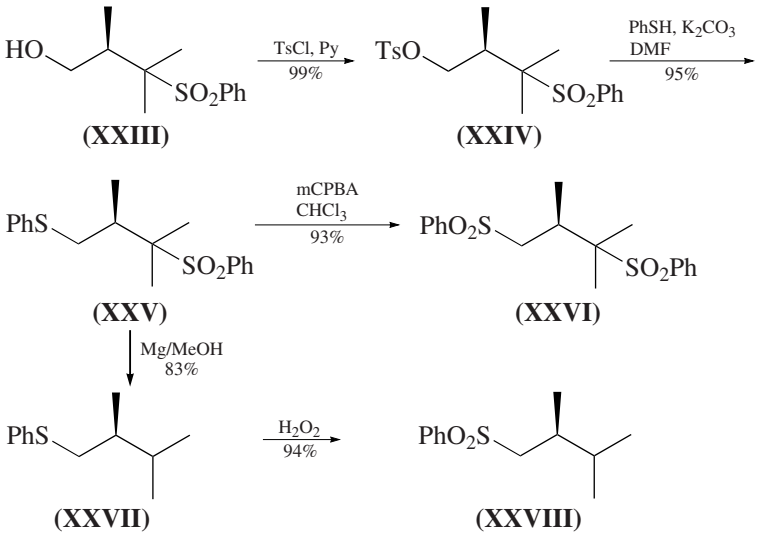
Scheme 4.

The introduction of two methyl groups in the low molecular fragment (the terminal methyl groups of the side chain of the target steroids) was aimed at the preparation of an intermediate with the substituent which could effectively stabilize the carbanion center at the C1 atom. Further, this substituent should easily be removed on the corresponding stage of the synthesis. The Phenylsulfonyl group was chosen as such substituent. It was introduced by the tosylation of alcohol (**XIII**), the nucleophilic substitution of the phenylsulfoxide anion for tosylate (**XIV**), and the oxidation of sulfide (**XV**). All o these reactions proceeded with the yields closed to quantitative.

Investigations demonstrated that methylation of sulfone (**XVI**) was a stepwise process that was accompanied by side reactions (Scheme 4). The interaction of sulfone (**XVI**) with 1 equivalent of butyl lithium resulted in the formation of lithium salt (**XVII**). Further, it can react with methyl iodide with the formation of a product of monoalkylation (**XX**). The treatment of sulfone (**XVI**) with the excess of a base gave dilithium salt (**XVIII**). It reacts with two equivalents of methyl iodide and forms an alkylation product (**XXI**). In addition, *o*-attachment of lithium to aromatic cycles is possible under the reaction conditions [13]. The isolation of compound (**XXII**) demonstrated that benzyl residue is mainly involved in this attachment in the case of sulfone (**XVI**). Note that significant amounts of both the monoalkyl product (**XX**) and trialkyl product (**XXIII**) were present in the reaction mixture under the reaction conditions optimized for the preparation of the dimethyl derivative (**XXI**). Both side products were used for the preparation of sulfone (**XXIII**). Repetitive methylation of sulfone (**XX**) gave compound (**XXI**), whereas a product of trialkylation (**XXII**) and a product of dialkylation (**XXI**) formed the target sulfone (**XXIII**) after the treatment with boron trifluoride etherate.

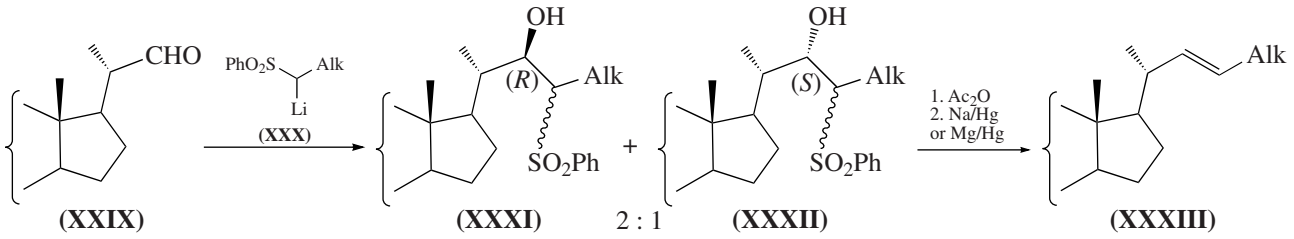
The second sulfonyl group was introduced into alcohol (**XXIII**) by the sequence of reactions described above, including tosylation, the nucleophilic substitution of phenylsulfide group for tosyl group of compound (**XXIV**), and the oxidation of sulfide (**XXV**) with *m*-chloroperbenzoic acid (Scheme 5). The sulfone group in compound (**XXV**) was selectively removed by magnesium reduction in methanol. Sulfide (**XXVII**) was oxidized by treatment with hydrogen peroxide. Note that this method of the conversion of sulfides into sulfones proved to be effective for the studied compounds as well as the use of *m*-chloroperbenzoic acid according to the yield of the target product. Moreover, it was more convenient in practice.

The Sharpless asymmetric hydroxylation of Δ^{22}-steroids is a standard method for the introduction of a 22*R*,23*R*-diol group in the synthesis of brassinosteroids



(XXIII) **(XXIV)** **(XXV)** **(XXVI)** **(XXVII)** **(XXVIII)**

Scheme 5.



(XXIX) **(XXX)** **(XXXI)** 2 : 1 **(XXXII)** **(XXXIII)**

Scheme 6.

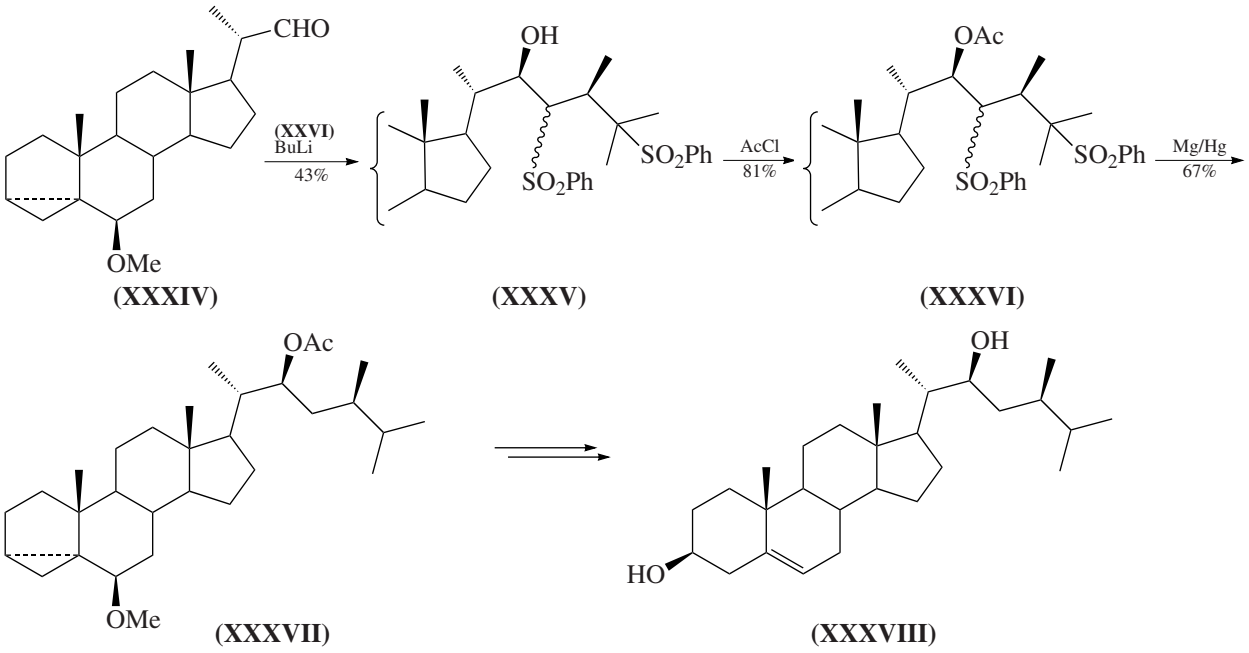
[1]. Many of these compounds were synthesized by the interaction of α-sulfonylcarbanions, which were generated from the corresponding sulfones, with C22-aldehydes [14]. This process is a special case of the Julia-Lythgoe olefination [15] that predominantly or exclusively gives *trans*-olefins. The attachment of the lithium salt of sulfones (**XXX**) to steroid aldehydes (**XXIX**) proceeds with the formation of the mixture of all four possible β-hydroxysulfones with predominance of 22*R*-isomers (**XXXI**) (Scheme 6). Isolation of such individual isomers was reported [16], although the mixture of isomers (**XXXI**) and (**XXXII**) is acetylated. The intermediate acetoxysulfones are further treated with sodium or magnesium amalgam, and *trans*-Δ^{22}-steroids (**XXXIII**) are prepared.

The desulfurization of β-hydroxysulfones (**XXXI**) in the synthesis of brassinosteroids with preservation of the functional group at the C22 atom is also of interest, but no one has successfully performed this reaction until now. We demonstrated that the introduction of an additional phenylsulfonyl group in the δ-position to hydroxyl group changed the direction of this reaction and gave 22-alcohols instead of the usual olefination products.

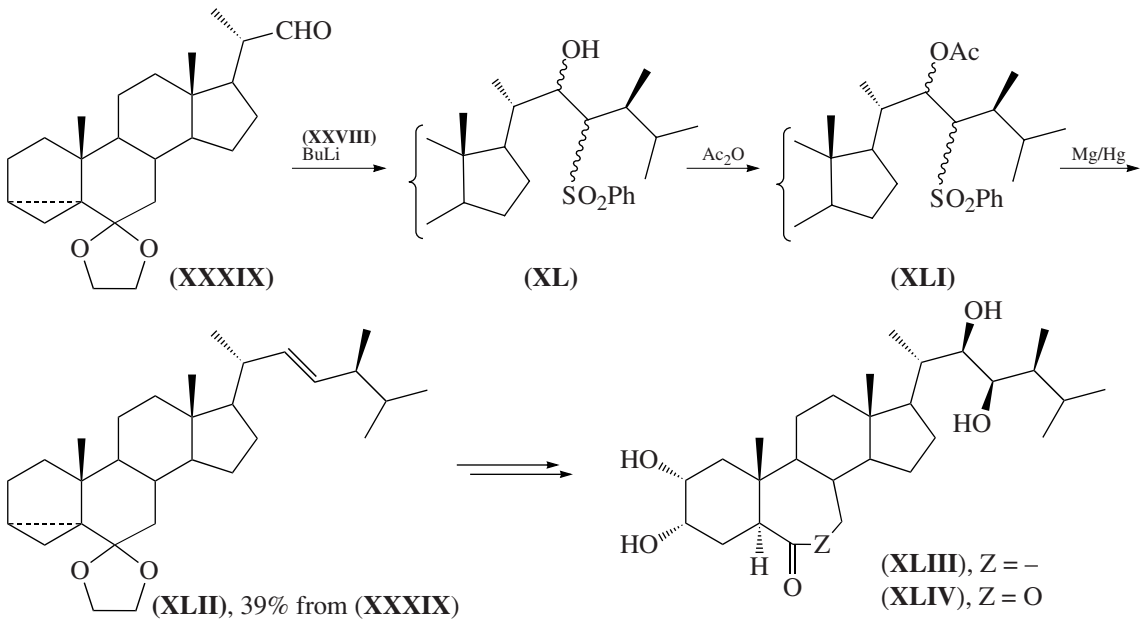
The attachment of the lithium salt of sulfone (**XXVI**) to aldehyde (**XXXIV**), which was prepared from stigmasterol by a three-step synthesis [17, 18], with the subsequent chromatographic fractionation yielded β-hydroxysulfone (**XXXV**) (Scheme 7). Its acetylation resulted in acetate (**XXXVI**) that was treated with magnesium amalgam in methanol with the formation of 22-acetate (**XXXVII**). The structure of this compound was confirmed by the comparison of its spectral characteristics with those of the [26,27-$^2H_6$]-analogue of (**XXXVII**), which were previously prepared by us through another method [11]. Diol (**XXXVIII**) can be prepared from acetate (**XXXVII**) in two stages [11].

Synthesis of (22*R*,23*R*)-dihydroxyderivatives can be performed using sulfone (**XXVIII**) (Scheme 8). The interaction of lithium salt of this sulfone with aldehyde (**XXXIX**) [19] gave a mixture of β-hydroxysulfones (**XL**) that was acetylated without any additional treatment. The mixture of β-acetoxysulfones (**XLI**) was reduced with magnesium amalgam. The obtained Δ^{22}-olefin (**XLII**) is a known intermediate in the synthesis of castasterone (**XLIII**) and brassinolide (**XLIV**) [10].

Thus, the described synthetic scheme used methyl (*S*)-3-hydroxy-2-methylpropionate (**IV**) as a chiral part for the creation of the C23-C28-fragment of the side chain, and allowed synthesis of a number of 24α-methylbrassinosteroids beginning from the first representative of biosynthetic sequence, (22*S*)-hydroxycampesterol (**XXXVIII**).



Scheme 7.



Scheme 8.

EXPERIMENTAL

The following reagents were used in this study: methyl (2*S*)-3-hydroxy-2-methylpropionate, toluenesulfonyl chloride, benzyl bromide, *m*-chloroperbenzoic acid, thiophenol, methyl iodide, and butyl lithium (Aldrich, United States). NMR spectra (δ, ppm; *J*, Hz) were recorded on a Bruker Avance 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C, Germany) in a solution of $CDCl_3$ (if another solvent is not indicated). Chemical shifts were determined according to the resonance of chloroform that was present in deuterochloroform as an impurity (δ 7.26 ppm for proton resonances and δ 77 ppm for resonances from carbon atoms). Melting points were determined on a Kofler block (Germany). The reactions were monitored by TLC on DC-alufolien Kieselgel 60 F_{254} plates (VWR, Art. 5715). A column chromatography was performed on a Kieselgel 60 silica gel (VWR, Art. 7734).

Methyl (2*S*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propionate (X). Dihydropyran (1.00 ml,

10.4 mmol) and TsOH · H_2O (92 mg, 0.49 mmol) were added to the solution of methyl methylpropionate (**IV**) (0.99 ml, 1.06 g, 8.9 mmol) in anhydrous CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature for 2.5 h, mixed with pyridine (0.1 ml), and the solvent was evaporated. The residue was fractionated on a column with silica gel eluted with the mixture of ether and CH_2Cl_2 (from 20 : 1 to 1 : 10). Ester (**X**) was isolated as an oil with the yield of 1.62 g (89%). The spectrum of ^{1}H NMR: 1.17 (1.5 H, dd, *J* 7.0, 2-Me), 1.18 (1.5 H, dd, *J* 7.0, 2-Me), 1.47–1.62 (4 H, m, CH_2 of Thp), 1.65–1.70 (1 H, m, CH_2 of Thp), 1.74–1.83 (1 H, m, CH_2 of Thp), 2.74–2.81 (1 H, m, H2), 3.44 (0.5 H, dd, *J* 5.9, 9.6, H3), 3.47–3.52 (1 H, m, H3), 3.58 (0.5 H, dd, *J* 7.5, 9.6, H3), 3.683 (1.5 H, s, $CO_2\underline{Me}$), 3.686 (1.5 H, s, $CO_2\underline{Me}$), 3.75 (0.5 H, dd, *J* 6.0, 9.6, CH_2 of Thp), 3.78–3.86 (1 H, m, CH_2 of Thp), 3.90 (0.5 H, dd, *J* 7.4, 9.6, CH_2 of Thp), 4.60 (1 H, m, CH of Thp). The spectrum of ^{13}C NMR: 14.01,19.09, 19.31, 25.40, 30.40, 30.47, 40.01, 40.19, 51.62, 61.78, 62.09, 69.00, 69.35, 98.40, 99.03, 175.29, 175.38.

(2*R*)-2-Methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propane-1-ol (XI). Ester (**X**) (1.62 g, 8.03 mmol) was dissolved in ether (20 ml) and cooled by ice. $LiAlH_4$ (0.97 g, 25.6 mmol) was added in small portions to the solution during the cooling. The reaction mixture was stirred for 2 h at room temperature; water (1.0 ml), 15% aqueous solution of NaOH (1.0 ml), and water (3 ml) again were added dropwise. The precipitate was filtered and washed with ether. The filtrate was evaporated. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 10 : 1 to 2 : 1). Alcohol (**XI**) was prepared as an oil with a yield of 1.37 g (98%). The spectrum of ^{1}H NMR: 0.87 (1.5 H, dd, *J* 6.8, 2-Me), 0.89 (1.5 H, dd, *J* 6.8, 2-Me), 1.46–1.61 (4 H, m, CH_2 of Thp), 1.66–1.82 (2 H, m, CH_2 of Thp), 1.98–2.06 (1 H, m, H2), 2.77 (1 H, broadened s, OH), 3.30–3.90 (6 H, m, H1, H3, and CH_2 of Thp), 4.56 (1 H, m, CH of Thp). The spectrum of ^{13}C NMR: 13.42, 13.53, 19.57, 25.25, 25.28, 30.50, 30.55, 35.34, 35.59, 62.43, 62.49, 67.23, 67.27, 71.98, 72.08, 76.75, 77.00, 77.25, 99.02, 99.30.

(2*S*)-3-Benzyloxy-2-methylpropane-1-ol (XIII). NaH (80% suspension in oil, 5.63 g, 0.188 mol) was added to the solution of alcohol (**XI**) (13.2 g, 75.9 mmol) in anhydrous tetrahydrofurane (500 ml) during intensive stirring. The reaction mixture was stirred for 10 min, and benzyl bromide (38.7 ml, 0.33 mol) and tetrabutylammonium iodide (39.9 g, 0.108 mol) were added. The reaction mixture was stirred for 4 days at room temperature. Ethanol (10 ml) and, then, NH_4Cl (15 g) were added. The reaction mixture was diluted with water (200 ml) and extracted with ethyl acetate (3 × 200 ml). The joined organic phase was dried over Na_2SO_4, and the filtrate was evaporated in a vacuum. The residue was filtered through a layer of silica gel and evaporated. The obtained product was dissolved in methanol (550 ml) and mixed with TsOH · H_2O (2.20 g, 11.6 mmol). The mixture was kept for 10 h at 40°C, mixed with pyridine (5 ml), and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 8 : 1 to 3 : 1). Ester (**XIII**) was prepared as an oil with a yield of 11.2 g (56%). The spectrum of ^{1}H NMR: 0.88 (3 H, d, *J* 7.0, 2-Me), 2.03–2.13 (1 H, m, H2), 2.64 (1 H, m, OH), 3.43 (1 H, dd, *J* 8.0, 9.1, H1 or H3), 3.50 (1 H, dd, *J* 9.1, 4.7, H1 or H3), 3.57–3.65 (2 H, m, H1 or H3), 4.52 (2 H, s, PhC$\underline{H_2}$O), 7.27–7.37 (5 H, m, Ph). The spectrum of ^{13}C NMR: 13.43, 35.52, 67.80, 73.35, 75.40, 127.57, 127.69, 128.42, 137.97.

(2*R*)-3-(Benzyloxy)-2-methylpropyl-4-methylbenzene sulfonate (XIV). Tosyl chloride (26.4 g, 138 mmol) was added to the solution of alcohol (**XIII**) (12.6 g, 69.9 mmol) in pyridine (150 ml). The excess of tosyl chloride was decomposed four hours later by the addition of water (5 ml) to the reaction mixture. Ten minutes later, the reaction mixture was diluted with water (200 ml) and extracted with chloroform (3 × 200 ml). The joined organic phase was dried over Na_2SO_4 and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 20 : 1 to 3 : 1). Tosylate (**XIV**) was prepared with a yield of 21.3 g (91%) mp 27–28°C (hexane). The spectrum of ^{1}H NMR: 0.94 (3 H, d, *J* 6.9, 2-Me), 2.07–2.16 (1 H, m, H2), 2.42 (3 H, s, OTs), 3.30–3.37 (2 H, m, H3), 3.99 (1 H, d, *J* 5.7, 9.4, H1), 4.04 (1 H, dd, *J* 5.7, 9.4, H1), 4.40 (2 H, s, PhC$\underline{H_2}$–O), 7.22–7.25 (2 H, m, Ar), 7.27–7.35 (5 H, m, Ar), 7.78 (2 H, d, *J* 8.3, Ar). The spectrum of ^{13}C NMR: 13.59, 21.59, 33.63, 71.04, 72.19, 73.02, 127.39, 127.53, 127.88, 128.30, 129.76, 132.95, 138.16, 144.62.

Benzyl-(2*R*)-methyl-3-phenylthiopropyl ester (XV). Potassium carbonate (13.3 g, 96.4 mmol) and thiophenol (8.85 ml, 10.6 g, 96.4 mmol) were added to the solution of tosylate (**XIV**) (21.3 g, 63.7 mmol) in dimethylformamide (210 ml). The reaction mixture was stirred for 2 h at room temperature, diluted with 5% aqueous solution of KOH (400 ml), and extracted with chloroform (3 × 100 ml). The joined organic phase was dried over Na_2SO_4 and the solvent was evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 100 : 1 to 10 : 1). Sulfide (**XV**) was prepared as an oil with a yield of 17.0 g (98%). The spectrum of ^{1}H NMR: 1.06 (3 H, d, *J* 6.8, 2-Me), 2.03–2.12 (1 H, m, H2), 2.79 (1 H, dd, *J* 13.0, 7.4, H1), 3.16 (1 H, dd, *J* 13.0, 5.7, H1), 3.40–3.45 (2 H, m, H3), 4.47 (2 H, s, O–C$\underline{H_2}$–Ph), 7.14 (1 H, t, *J* 7.4, Ph), 7.23–7.36 (9 H, m, Ph). The spectrum of ^{13}C NMR: 16.73, 33.78, 37.42, 72.99, 74.00, 125.56, 127.47, 128.31, 128.72, 128.79, 137.17, 138.49.

(2*R*)-3-(Benzyloxy)-2-methylpropylphenylsulfone (XVI). Sulfide (**XV**) (17.0 g, 62.4 mmol) was dissolved in chloroform (300 ml) and mCPBA (42.8 g, 77%, 0.191 mol) was added on ice-cooling. The reaction

mixture was stirred for 4 h at room temperature, alkalified to pH 7 with 25% NH_4OH, and diluted with water (400 ml). The organic phase was separated and water phase was washed with petroleum-ether (4 × 100 ml). The joined organic phase was dried over Na_2SO_4 and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of ether and ethyl acetate (from 10 : 1 to 3 : 1). Sulfone (**XVI**) was prepared as an oil with a yield of 17.9 g (94%). The spectrum of ^{1}H NMR: 1.12 (3 H, d, *J* 6.8, 2-Me), 2.35–2.44 (1 H, m, H2), 2.93 (1 H, dd, *J* 14.1, 8.0, H1), 3.31 (1 H, dd, *J* 9.3, 6.4, H1), 3.40–3.43 (2 H, m, H3), 4.38–4.44 (2 H, m, PhC$\underline{H}_2$–O), 7.23–7.35 (5 H, m, Ph), 7.53–7.57 (2 H, m, Ph), 7.62–7.66 (1 H, m, Ph), 7.90–7.93 (2 H, m, Ph). The spectrum of ^{13}C NMR: 17.16, 29.38, 59.23, 72.84, 73.51, 127.48, 127.61, 127.81, 128.33, 129.22, 133.51, 138.05, 140.01.

Methylation of sulfone (XVI). The 2.35 M solution of butyl lithium (36 ml, 84.5 mmol) in hexane was added to the solution of sulfone (**XVI**) (10.3 g, 33.8 mmol) in tetrahydrofurane (240 ml) in a two-necked flask (internal thermometer, septum) in an argon atmosphere during stirring at a temperature range of –70°C to –45°C. The solution of methyl iodide (5.5 ml, 12.5 g, 87.9 mmol) in tetrahydrofurane (30 ml) was added to the reaction mixture at a temperature range of –45°C to –30°C, 30 min later. After 15 min, the cooling bath was removed, and the temperature of the reaction mixture was allowed to rise to –10°C. NH_4Cl (5 g) was added, the reaction mixture was stirred for 5 min, filtered through a layer of silica gel, and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 20 : 1 to 3 : 1) and the following compounds were isolated in the course of elution:

(2*R*)-1,1,2-Trimethyl-3-[(2-methylbenzyl)oxy]propylphenylsulfone (XXII) as an oil with a yield of 1.69 g (14%). The spectrum of ^{1}H NMR: 1.22 (3 H, d, *J* 7.0, 2-Me), 1.29 (3 H, s), 1.31 (3 H, s), 2.42–2.47 (1 H, m, H2), 2.72 (3 H, s, C$\underline{H}_3$C$_6$H$_4$–), 4.49 (2 H, m, –OC$\underline{H}_2$C$_6$H$_4$CH$_3$), 7.28–7.90 (9 H, m, aromatic). The spectrum of ^{13}C NMR: 14.18, 19.85, 20.76, 21.30, 36.55, 67.18, 72.69, 73.09, 126.10, 127.50, 128.31, 130.39, 133.04, 133.21, 133.36, 134.58, 138.43, 140.40.

(2*R*)-3-(Benzyloxy)-1,1,2-trimethylpropylphenylsulfone (XXI) with the yield of 5.62 g (50%); mp 86–87°C (hexane). The spectrum of ^{1}H NMR: 1.21 (3 H, d, *J* 6.9, 2-Me), 1.30 (3 H, s, 1-Me), 1.31 (3 H, s, 1-Me), 2.29–2.35 (1 H, m, H2), 3.48 (1 H, dd, *J* 9.4, 6.8, H3), 3.80 (1 H, dd, *J* 9.4, 3.5, H3), 4.45–4.51 (2 H, m, PhC$\underline{H}_2$–O), 7.26–7.36 (5 H, m, Ph), 7.52–7.56 (2 H, m, Ph), 7.62–7.66 (1 H, m, Ph), 7.84–7.87 (2 H, m, Ph). The spectrum of ^{13}C NMR: 14.06, 19.93, 20.70, 36.95, 65.78, 72.54, 73.08, 127.50, 128.31, 128.71, 130.39, 133.43, 136.36, 138.39.

(2*R*)-3-(Benzyloxy)-1,2-dimethylpropylphenylsulfone (XX). with the yield of 969 mg (9%) as an oil. The spectrum of ^{1}H NMR: 0.99 (1.8 H, d, *J* 9.3, 1-Me), 1.19 (3 H, dd, *J* 7.1, 2.2, 2-Me), 1.24 (1.2 H, d, *J* 9.3, 1-Me), 2.41–2.49 (0.4 H, m, H2), 2.66–2.74 (0.6 H, m, H2), 3.18–3.25 (1 H, m, H3), 3.34 (0.6 H, dd, *J* 9.8, 5.2, H1), 3.43–3.47 (1 H, m, H3), 3.78 (0.4 H, dd, *J* 9.3, 5.2, H1), 4.35–4.53 (2 H, m, PhC$\underline{H}_2$–O), 7.23–7.37 (5 H, m, Ph), 7.52–7.57 (2 H, m, Ph), 7.62–7.66 (1 H, m, Ph), 7.84–7.91 (2 H, m, Ph). The spectrum of ^{13}C NMR: 7.39, 11.00, 11.09, 15.85, 30.99, 33.93, 59.44, 62.32, 71.77, 72.40, 72.61, 73.10, 127.49, 127.59, 127.66, 128.24, 128.32, 128.36, 128.54, 128.62, 129.06, 130.39, 133.38, 133.42, 137.99, 138.54.

Methylation of sulfone (XX). The 2.3 M solution of butyl lithium (1.75 ml, 4.03 mmol) in hexane was added to the solution of sulfone (**XX**) (1.10 g, 3.54 mmol) in tetrahydrofurane (30 ml) in an argon atmosphere during stirring at the temperature range of –60°C to –45°C. The solution of methyl iodide (0.25 ml, 4.02 mmol) in tetrahydrofurane (0.75 ml) was added to the reaction mixture at a temperature interval of –45°C to –30°C, 20 min later. Cooling was stopped after 15 min, the reaction mixture was allowed to be heated to –10°C, and NH_4Cl (1.2 g) was added. The reaction mixture was stirred for 5 min, filtered through a layer of silica gel, and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 20 : 1 to 3 : 1). The oily product was isolated with a yield of 990 mg (86%). Its ^{1}H NMR and ^{13}C NMR spectra were identical to those of sulfone (**XXI**).

(2*R*)-2,3-Dimethyl-3-(phenylsulfonyl)butane-1-ol (XXIII) Sodium iodide (9.72 g, 64.8 mmol) was added to the solution of ester (**XXI**) (10.66 g, 32.07 mmol) in acetonitrile (215 ml). The solution of boron trifluoride etherate (12.2 ml) in acetonitrile (100 ml) was added to the reaction mixture drop-wise within 15 min during stirring and ice cooling. The reaction mixture was stirred for 30 min during ice cooling and for 6 h at room temperature, poured out in ice-water (250 ml), and extracted with methylene chloride (4 × 100 ml). The joined organic phase was dried over Na_2SO_4 and the solvent was evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of hexane and ethyl acetate (from 10 : 1 to 1 : 1). The alcohol (**XXIII**) was prepared with the yield of 7.53 g (97%); mp 78–82°C (hexane–ethyl acetate). The spectrum of ^{1}H NMR: 1.16 (3 H, d, *J* 7.1, 2-Me), 1.26 (3 H, s, H4 or 3-Me), 1.31 (3 H, s, H4 or 3-Me), 2.17-2.23 (1 H, m, H2), 2.38 (1 H, broadened s, OH), 3.70-3.76 (1 H, m, H1), 3.94-3.99 (1 H, m, H1), 7.54-7.57 (2 H, m, Ph), 7.63-7.67 (1 H, m, Ph), 7.86-7.89 (2 H, m, Ph). The spectrum of ^{13}C NMR: 13.64, 19.49, 22.18, 39.73, 64.75, 65.76, 128.77, 130.45, 133.61, 136.10.

Alcohol (**XXIII**) was prepared according to the analogous procedure from ester (**XXII**) with a yield of 94%.

(2*R*)-2,3-Dimethyl-3-(phenylsulfonyl)butyl-4-methylbenzenesulfonate (XXIV). Tosyl chloride (14.8 g, 77.8 mmol) was added to the solution of alcohol (**XXIII**) (8.58 g, 35.4 mmol) in pyridine (200 ml). Water (10 ml) was added to the reaction mixture dropwise 20 min later for the decomposition of the excess of tosyl chloride. After 10 min, the reaction mixture was diluted with water (200 ml) and extracted with chloroform (3 × 200 ml). The joined organic phase was dried over Na_2SO_4 and the solvent was evaporated in a vacuum. The residue was fractionated on a column with a silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 20 : 1 to 3 : 1). Tosylate (**XXIV**) was prepared with a yield of 13.9 g (99%) as an oil. The spectrum of ^{1}H NMR: 1.12 (3 H, d, *J* 6.9, 2-Me), 1.23 (3 H, s, H4 or 3-Me), 1.24 (3 H, s, H4 or 3-Me), 2.31-2.37 (1 H, m, H2), 2,45 (3 H, s, OTs), 4.06 (1 H, dd, *J* 9.9, 7.5, H1), 4.52 (1 H, dd, *J* 9.9, 3.5, H1), 7.36 (2 H, d, *J* 8.0, aromatic), 7.53 (2 H, t, *J* 7.5, aromatic), 7.63-7.67 (1 H, m, aromatic), 7.76-7.81 (4 H, m, aromatic). The spectrum of ^{13}C NMR: 13.25, 18.87, 21.64, 36.71, 64.96, 72.25, 127.93, 128.87, 129.91, 130.37, 132.72, 133.79, 135.57, 144.92.

(2*R*)-1,1,2-Trimethyl-3-(phenylthio)propylphenyl sulfone (XXV). Potassium carbonate (7.22 g, 52.2 mmol) and thiophenol (5.37 ml, 6.43 g, 58.4 mmol) were added to the solution of tosylate (**XXIV**) (13.9 g, 35.1 mmol) in dimethylformamide (80 ml). The reaction mixture was stirred for 2.5 h at room temperature, diluted with 5% aqueous solution of KOH (300 ml), and extracted with chloroform (3 × 200 ml). The joined extract was dried over Na_2SO_4 and the solvent was evaporated in vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 20 : 1 to 3 : 1). Sulfonyl sulfide (**XXV**) was prepared as an oil with a yield of 10.9 g (95%). The spectrum of ^{1}H NMR: 1.21 (3 H, dd, *J* 0.7, 6.8, 2-Me), 1.23 (3 H, s, 1-Me), 1.33 (3 H, s, 1-Me), 2.15-2.22 (1 H, m, H2), 2.61 (1 H, dd, *J* 13.0, 11.1, H3), 3.88 (1 H, dd, *J* 0.8, 2.3, 12.9, 1.5, H3), 7.20-7.23 (1 H, m, Ph), 7.28-7.32 (2 H, m, Ph), 7.41-7.43 (2 H, m, Ph), 7.46-7.50 (2 H, m, Ph), 7.59-7.63 (1 H, m, Ph), 7.71-7.74 (2 H, m, Ph). The spectrum of ^{13}C NMR: 14.92, 18.00, 21.96, 37.42, 37.58, 66.18, 126.33, 128.74, 128.91, 130.22, 130.34, 133.47, 136.17.

(2*R*)-2,3-Dimethyl-1,3-bis(phenylsulfonyl)butane (XXVI). Sulfonyl sulfide (**XXV**) (822 mg, 2.46 mmol) was dissolved in chloroform (50 ml) and mCPBA (822 mg, 77%, 7.45 mmol) was added to the solution during ice cooling. The reaction mixture was stirred for 5 h at room temperature, neutralized with 25% aqueous solution of NH_4OH to pH 7, and diluted with water (40 ml). The organic phase was separated in a separating funnel, and the aqueous phase was washed with chloroform (4 × 20 ml). The joined organic extract was dried over Na_2SO_4 and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of toluene and ethyl acetate (from 50 : 1 to 5 : 1). Sulfone (**XXVI**) was prepared as an oil with a yield of 837 mg (93%). The spectrum of ^{1}H NMR: 1.17 (3 H, s, H4 or 3-Me), 1.27 (3 H, s, H4 or 3-Me), 1.31 (3 H, d, *J* 6.9, 2-Me), 2.64-2.71 (1 H, m, H2), 2.97 (1 H, dd, *J* 14.0, 10.4, H1), 4.31 (1 H, d, *J* 14.0, H1), 7.53-7.56 (2 H, m, Ph), 7.58-7.61 (2 H, m, Ph), 7.64-7.70 (2 H, m, Ph), 7.82-7.84 (2 H, m, Ph), 7.92-7.94 (2 H, m, Ph). The spectrum of ^{13}C NMR: 16.12, 17.06, 22.66, 32.65, 58.69, 64.89, 128.07, 128.90, 129.34, 130.54, 133.75, 133.87, 135.43, 139.85.

(2*S*)-2,3-Dimethylbutylphenylsulfide (XXVII). Magnesium (1.52 g, 63.0 mmol) was added to the solution of sulfonyl sulfide (**XXV**) (2.43 g, 7.26 mmol) in absolute methanol (150 ml) during intensive stirring. The reaction mixture was stirred for 3 h at 40°C. The precipitate was filtered off. The filtrate was neutralized with 3 N HCl to pH 7 and extracted with petroleum-ether (3 × 50 ml). The joined organic extract was dried over Na_2SO_4 and the solvent was evaporated in a vacuum. The residue was fractionated on a column with a silica gel eluted with the mixture of petroleum-ether and ethyl acetate (20 : 1). Sulfide (**XXVII**) was isolated as an oil with a yield of 1.18 g (83%). The spectrum of ^{1}H NMR: 0.85 (3 H, d, *J* 6.8), 0.90 (3 H, d, *J* 6.9), 0.96 (3 H, d, *J* 6.8), 1.57–1.66 (1 H, m, H3), 1.74–1.80 (1 H, m, H2), 2.70 (1 H, dd, *J* 8.5,12.4, H1), 3.03 (1 H, m, H1), 7.12–7.17 (2 H, m, Ph), 7.23–7.28 (1 H, m, Ph), 7.30–7.34 (2 H, m, Ph). The spectrum of ^{13}C NMR: 15.07, 17.68, 20.25, 31.38, 38.34, 38.80, 125.46, 128.66, 128.74, 128.90. The spectral characteristics of sulfide (**XXVII**) correlated with those published in the literature [20].

(2*S*)-2,3-Dimethylbutylphenylsulfone (XXVIII). The 30% hydrogen peroxide (60 ml) was added dropwise to the solution of sulfide (**XXVII**) (2.26 g, 11.6 mmol) in glacial acetic acid (60 ml) on stirring. The reaction mixture was stirred for 17 h at room temperature, diluted with water (50 ml), and extracted with petroleum-ether (3 × 50 ml). The joined organic phase was washed with the saturated solution of $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated to 1/3 of the initial volume; the residue was filtered through a layer of silica gel and evaporated. Sulfone (**XXVIII**) was prepared as an oil with a yield of 2.5 g (94%). The spectrum of ^{1}H NMR: 0.76 (3 H, d, *J* 6.8), 0.81 (3 H, d, *J* 6.8), 1.01 (3 H, d, *J* 6.9), 1.63–1.70 (1 H, m, H3), 1.97–2.05 (1 H, m, H2), 2.87 (1 H, dd, *J* 8.8, 14.1, H1), 3.08 (1 H, dd, *J* 3.3, 14.1, H1), 7.54–7.58 (2 H, m, Ph), 7.62–7.66 (1 H, m, Ph), 7.89–7.92 (2 H, m, Ph). The spectrum of ^{13}C NMR: 15.89, 17.81, 19.10, 32.37, 33.74, 60.45, 127.83, 129.22, 133.48, 140.06. The spectral characteristics of sulfone (**XXVIII**) correlated with those published in the literature [20].

(22*R*,24*R*)-23,25-Bis(phenylsulfonyl)-6β-methoxy-24-methyl-3α,5-cyclo-5α-cholestane-22-ol (XXXV). The 2.2 M solution of butyl lithium (0.8 ml, 0.65 mmol) in hexane was added to the solution of disulfone (**XXVI**) (128 mg, 0.35 mmol) in tetrahydrofurane

(4 ml) at –50°C in the argon atmosphere during stirring. The reaction mixture was stirred for 30 min at –50°C and cooled to –78°C, and the solution of aldehyde (**XXXIV**) (100 mg, 0.29 mmol, prepared according to the procedure {17, 18]) in tetrahydrofurane (1 ml) was added. The reaction mixture was stirred at –78°C for 3 h, the cooling was removed, and the reaction mixture was gradually brought up to room temperature and mixed with the saturated solution of NH_4Cl (5 ml). The aqueous phase was separated from the organic phase and washed with ethyl acetate (3 × 5 ml). The joined organic phase was dried over Na_2SO_4 and evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 15 : 1 to 3 : 1). Compound (**XXXV**) was prepared as an oil with a yield of 90 mg (43%). The spectrum of ^{1}H NMR: 0.60 (3 H, s, H18), 0.97 (3 H, s, H19), 1.51 (3 H, s, H26 or H27), 1.54 (3 H, d, *J* 7.3, H28), 1.65 (3 H, s, H26 or H27), 2.74 (1 H, t, *J* 2.8, H6), 3.30 (3 H, s, OMe), 3.84 (1 H, dd, *J* 2.6, 7.5, H22), 3.99 (1 H, s, H23), 7.55–7.63 (2 H, m, Ph), 7.65–7.70 (1 H, m, Ph), 7.91–7.96 (2 H, m, Ph). The spectrum of ^{13}C NMR: 12.43, 13.02, 14.11, 14.28, 15.02, 19.23, 21.22, 21.49, 21.63, 22.61, 24.44, 24.92, 27.43, 30.29, 33.29, 34.60, 34.84, 35.23, 39.79, 39.87, 43.29, 43.53, 47.77, 51.77, 55.98, 56.50, 65.58, 67.10, 73.63, 82.35, 128.37, 128.85, 129.39, 130.72, 133.77, 133.86, 136.25, 139.47.

(22*R*,24*R*)-23,25-Bis(phenylsulfonyl)-22-acetoxy-6β-methoxy-24-methyl-3α,5-cyclo-5α-cholestane (XXXVI). The solution of pyridine (2.9 ml, 3.6 mmol) in CH_2Cl_2 (0.27 ml), the solution of acetyl chloride (2.5 ml, 3.5 mmol) in CH_2Cl_2 (0.24 ml), and 4-(dimethylamino)pyridine (0.5 mg) were added to the solution of hydroxysulfone (**XXXV**) (24 mg, 34 mmol) in CH_2Cl_2 (1 ml). The reaction mixture was kept for 24 at room temperature and diluted with water (2 ml). The organic phase was separated from the water phase, and the latter was extracted with CH_2Cl_2 (3 × 2 ml). The organic phases were dried over Na_2SO_4, and the solvent was evaporated. Acetate (**XXXVI**) was prepared as an oil with a yield of 20 mg (81%). The spectrum of ^{1}H NMR: 0.64 (3 H, s, H18), 0.74 (3 H, d, *J* 6.7, H21), 0.97 (3 H, s, H19), 1.47 (3 H, s, H26 or H27), 1.61 (3 H, d, *J* 7.3 H28), 1.63 (3 H, s, H26 or H27), 2.19 (3 H, s, OAc), 2.74 (3 H, T, *J* 2.8 H6), 3.30 (3 H, s, OMe), 4.08 (1 H, s, H23), 5.14 (1 H, d, *J* 7.7, H22), 7.54–7.62 (2 H, m, Ph), 7.63–7.71 (1 H, m, Ph), 7.92–7.98 (2 H, m, Ph). The spectrum of ^{13}C NMR: 11.87, 13.05, 14.41, 15.46, 19.20, 21.33, 21.42, 21.50, 22.14, 22.68, 24.77, 24.95, 28.27, 29.70, 30.36, 33.35, 34.93, 35.27, 39.95, 43.30, 43.85, 47.77, 51.87, 55.86, 56.50, 64.02, 67.04, 74.31, 82.36, 128.81, 129.12, 129.33, 130.83, 133.69, 133.77, 136.31, 139.58, 170.17.

(22*S*,24*R*)-22-Acetoxy-6β-methoxy-24-methyl-3α,5-cyclo-5α-cholestane (XXXVII). Magnesium (0.58 g, 23.6 mmol) and mercury (II) chloride (0.23 g, 0.86 mmol) were added to the solution of disulfone (**XXXVI**) (20 mg, 28 mmol) in absolute methanol (30 ml) cooled to 0°C during stirring. The reaction mixture was stirred for 1 h at 0°C and filtered through a layer of silica gel. The filtrate was diluted with water (15 ml) and extracted with petroleum-ether (3 × 10 ml). The organic extracts were dried over Na_2SO_4 and the solvent was evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (from 20 : 1 to 10 : 1). Acetate (**XXXVII**) was prepared as an oil with a yield of 9.0 mg (67%). The spectrum of ^{1}H NMR: 0.42 (1 H, dd, *J* 5.1, 7.9), 0.63 (1 H, dd, *J* 4.1, 4.7), 0.71 (3 H, s, H18), 0.87 (3 H, d, *J* 7.3), 0.88 (3 H, d, *J* 7.3), 0.95 (3 H, d, *J* 6.8), 1.06 (3 H, s, H19), 2.03 (3 H, s, OAc), 2.75 (1 H, t, *J* 2.7), 3.31 (3 h, s, OMe), 5.14 (1 H, m, H22). The spectrum of ^{13}C NMR: 12.00, 12.69, 13.01, 13.99, 19.26, 21.21, 21.48, 22.64, 22.76, 24.10, 24.93, 28.06, 28.18, 29.67, 30.48, 31.88, 33.33, 34.89, 35.27, 38.98, 40.21, 42.65, 43.32, 47.96, 52.66, 56.39, 56.54, 76.31, 82.35, 170.93.

(24*S*)-6-(1,3-Dioxolane-2-yl)-24-methyl-3α,5-cyclo-5α-cholest-22-ene (XLII). The solution of sulfone (**XXVIII**) (250 mg, 1.1 mmol) in anhydrous tetrahydrofurane (9 ml) was cooled to –60°C and mixed with 2.2 N solution of butyl lithium (0.6 ml, 1.32 mmol) in hexane in an argon atmosphere during stirring. The reaction mixture was stirred for 30 min at –60°C and cooled to –78°C, and aldehyde (**XXXIX**) (prepared according to the procedure [19], 345 mg, 0.93 mmol) in anhydrous tetrahydrofurane (5 ml) was added. The reaction mixture was stirred for 2 h at –78°C and monitored by TLC. After the disappearance of the starting aldehyde (**XXXIX**), acetic anhydride (0.3 ml, 3.2 mmol) was added at –78°C. The reaction mixture was gradually brought up to room temperature, kept under these conditions for 18 h, and diluted with the saturated solution of NH_4Cl (10 ml). The organic phase was separated, and the water phase was extracted with ethyl acetate. The joined organic phase was dried over Na_2SO_4, and the solvent was evaporated in a vacuum. The obtained acetoxysulfone (**XLI**) (0.64 g) was dissolved in absolute methanol (50 ml) and cooled to 0°C. Magnesium (0.5 g, 20.6 mmol) and $HgCl_2$ (0.2 g, 0.74 mmol) were added to the solution during intensive stirring. The reaction mixture was heated to room temperature, intensively stirred for 5.5 h, and filtered through a layer of silica gel. The filtrate was diluted with water (40 ml) and extracted with petroleum-ether (4 × 20 ml). The extracts were dried over Na_2SO_4, and the solvents were evaporated in a vacuum. The residue was fractionated on a column with silica gel eluted with the mixture of petroleum-ether and ethyl acetate (10 : 1). Olefin (**XLII**) was prepared as an oil with a yield of 166 mg (39%) relatively to aldehyde (**XXXIX**). The spectrum of ^{1}H NMR: 0.32 (1 H, t, *J* 4.2), 0.60 (1 H, dd, *J* 4.6, 8.1), 0.72 (3 H, s, H18), 0.81 (3 H, d, *J* 6.8), 0.82 (3 H, d, *J* 6.8), 0.90 (3 H, d, *J* 6.9), 0.99 (3 H, d, *J* 6.8), 1.00 (3 H, s, H19), 3.74 (1 H, q, *J* 6.4, dioxolan), 3.84 (1 H, dd, *J* 4.6, 12.4, dioxolan), 3.90 (1 H, td, *J* 6.4, 8.0, dioxolan), 4.02 (1 H, td, *J* 6.4,

7.7, dioxolan), 5.15 (2 H, m, H22 and H23). The spectrum of ^{13}C NMR: 7.25, 12.33, 18.02, 18.96, 19.63, 20.14, 20.96, 22.57, 23.03, 24.19, 24.89, 28.83, 33.19, 34.09, 39.23, 40.00, 40.17, 40.28, 42.70, 43.03, 45.59, 47.43, 56.02, 56.36, 64.60, 64.84, 109.89, 131.79, 136.04.

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