Russian Journal of Organic Chemistry, Vol. 38, No. 3, 2002, pp. 365–369. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 3, 2002, pp. 387–391.

Prostanoids: LXXXII.* Synthesis of Key Precursors of 9-LO Thromboxans**

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Received February 7, 2001

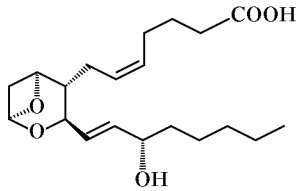
Abstract—Starting from levoglucosan, methyl 2,4-dideoxy-3-*O*-mesyl-4-*C*-[(2*Z*)-octenyl]-α-D-*arabino*-hexopyranoside and (+)-2α-methoxy-6β-[6-methoxycarbonyl-3-oxo-(1*E*)-hexenyl]-5α-[(2*Z*)-octenyl]pyran-3-one were synthesized as potential building blocks for preparation of 9-LO thromboxanes.

In continuation of our studies on the synthesis of 9-LO prostanoids (9-LO PG) [2–4] the present communication describes a new approach to thromboxanes on the basis of accessible 1,6-anhydro sugar, levoglucosan. Natural thromboxane A_2 (**I**, TXA_2) is the most powerful proaggregant and vasoconstrictor; it is a very unstable compound; under physiological conditions, its half-conversion period $\tau_{1/2}$ is 30 min [5, 6]. Thromboxane A_2 undergoes fast hydrolysis in neutral and weakly acid aqueous solutions to give more stable but low-active TXB_2 (**II**). Bhagwat *et al.* [7] were the only to describe the synthesis of TXA_2 as a relatively stable sodium salt (–20°C, 1 week without loss of activity) by alkaline hydrolysis of macrolactone **III** (Scheme 1). A considerable number of publications deal with the synthesis of chemically more stable analogs TXA_2 and TXB_2 [8–10].

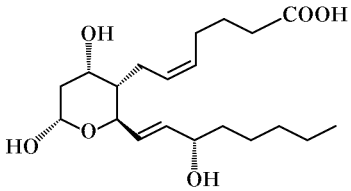
Our complete project on the synthesis of 9-LO thromboxane derivatives includes design of structures **IV**–**VI** (Scheme 2). These compounds attract interest due to the possibility of varying the character of biological activity of thromboxanes and enhancing their chemical stability as compared to TXA_2 and TXB_2. In the present article we describe synthetic routes to universal block-synthons **VII** and **VIII** for the above thromboxane analogs, starting from levoglucosan. The latter was selected as a chiral initial compound for the following reason. By known consecutive reactions involving functionalization of C^4 and deoxygenation of C^2 [11–14] levoglucosan can be converted with a sufficient chemoselectivity into compound **IX** which is suitable for synthesis of blocks **VII** and **VIII** (Scheme 3).

Analogs of compound **IX** were synthesized starting from *p*-toluenesulfonate **X** which can readily be obtained from levoglucosan in three steps [11]. Treatment of **X** with sodium methoxide in methanol gave epoxy derivative **XI** in high yield (Scheme 4). The

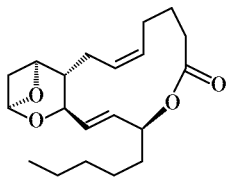
Scheme 1.



I, TxA_1



II, TxB_2



III

* For communication LXXXI, see [1].

** This study was financially supported by the Russian Foundation for Basic Research (project no. 99-03-32916a).

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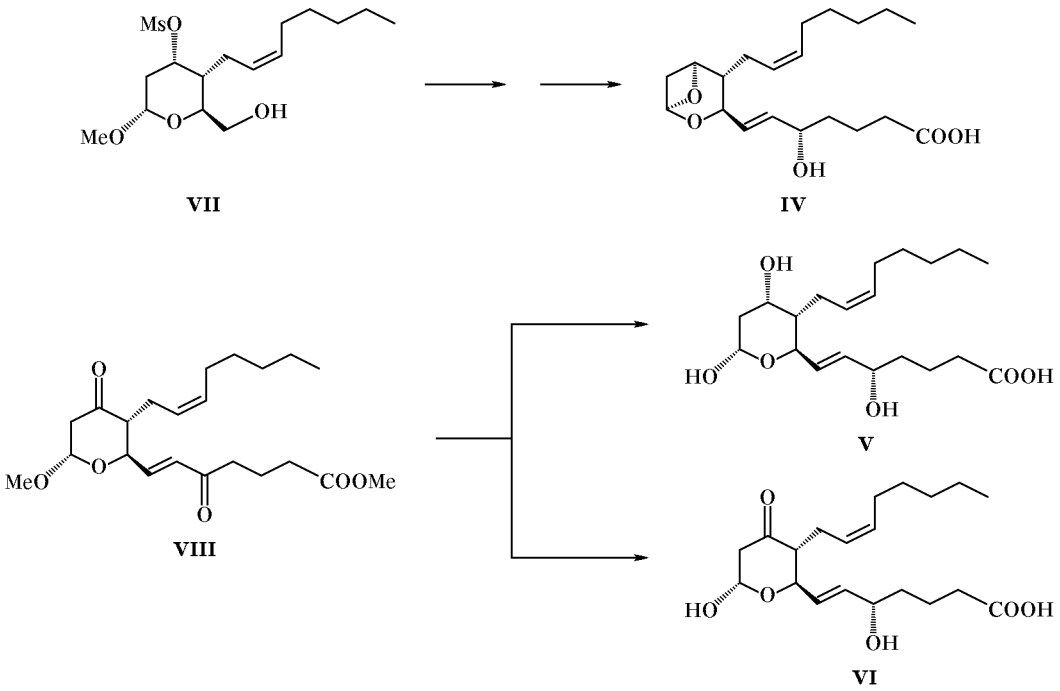
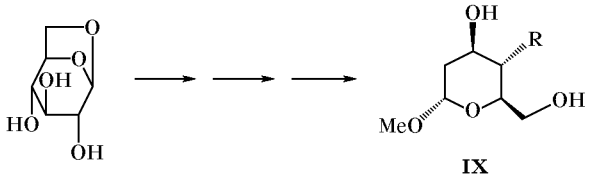
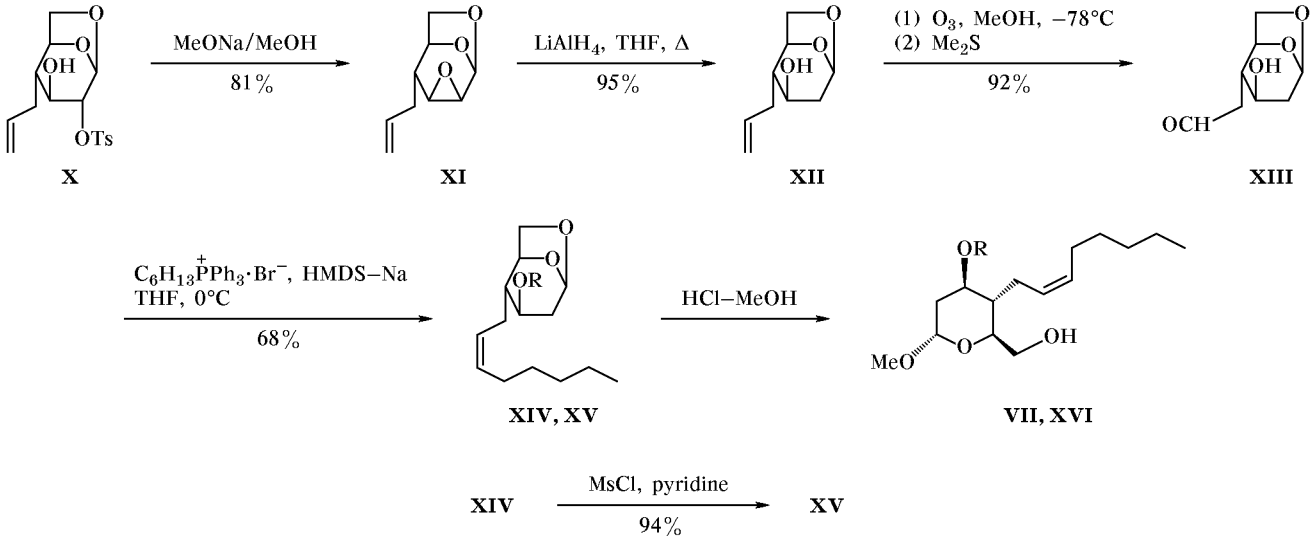
Scheme 2.



Scheme 3.

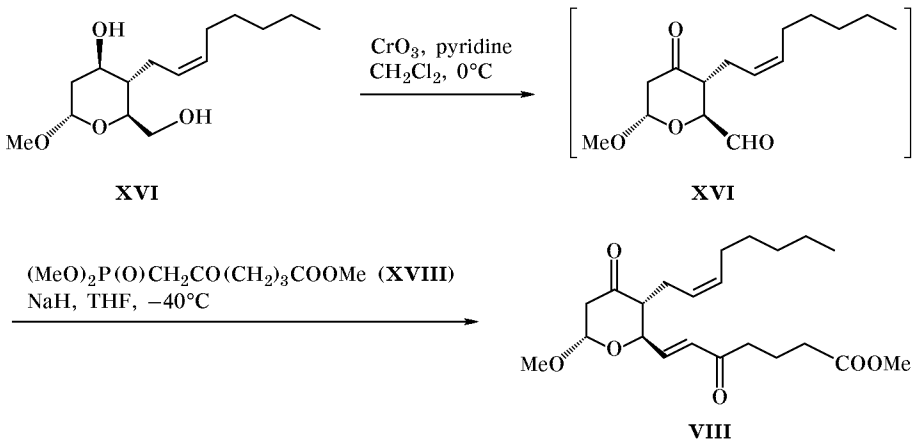


Scheme 4.



VII, R = Ms (yield 77%); **XIV**, R = H; **XV**, R = Ms; **XVI**, R = H (yield 82%).

Scheme 5.



reduction of **XI** with $LiAlH_4$ in THF was regioselective; as a result, alcohol **XII** was obtained. Ozonolysis of the terminal double bond in **XII** afforded labile aldehyde **XIII** as a necessary carbonyl component of the Wittig reaction (addition of *Z*-alkene chain). After purification, aldehyde **XIII** was brought into reaction with hexylidenetriphenylphosphorane generated *in situ* from hexyltriphenylphosphonium bromide. The yield of *Z* isomer **XIV** was 68%, and the fraction of the corresponding *E* isomer did not exceed 3–5% (according to the ^1H NMR spectrum of methanesulfonate **XV** which gives different signals from the CH_3SO_2 groups of the *E* and *Z* isomers).

Methanolysis of alcohol **XIV** and methanesulfonate **XV** derived therefrom was not accompanied by side processes, and α-anomeric pyran derivatives **XVI** and **VII**, respectively, were smoothly formed in good yields. According to the GLC data, the fraction of the corresponding β-anomer was no more than ~5–7%. Their structures were assigned on the basis of the ^{13}C NMR spectra, where α-anomers give more upfield signal from the C^1 atom [15]. Methyl pyranoside **VII** seemed to be suitable for the synthesis of 9-LO TXA_2 (**IV**). Using diol **XVI** as starting compound, we have developed a short scheme for preparation of compound **VIII** through ketoaldehyde **XVII** (Scheme 5). Some difficulties appeared at the stage of oxidation of diol **XVI**. The oxidation of **XVI** with Collins' reagent was nonselective; as a result, labile products were formed, which were impossible to identify by spectral methods and purify. Therefore, the oxidation products (presumably, dimers or trimers of **XVII**) without purification were brought into the subsequent Emmons–Horner olefination with phosphonate **XVIII** [4]. The reaction gave a readily detectable (by TLC) and fairly stable compound which was isolated in the pure state by column chromatography on silica gel. Its spectral parameters were in agreement with the structure of expected enedione **VIII**, whose overall yield was more than 45% (calculated on diol **XVI**).

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from samples prepared as thin films or dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively; $CDCl_3$ was used as solvent, and TMS, as internal reference. The optical rotations were measured on a Perkin–Elmer polarimeter in chloroform. GLC analysis was performed on a Chrom-5 chromatograph equipped with a flame-ionization detector; column length 1.2 and 3.7 m; stationary phase SE-30 (5%) on Chromaton N-AW-DMCS (0.20–0.25 mm); oven temperature 50–300°C; carrier gas helium. Silufol UV-254:366 plates were used for TLC; spots were visualized with iodine vapor or by treatment with a solution of *p*-methoxybenzaldehyde and sulfuric acid in ethanol (ratio 1:0.5:10), followed by heating to 120–150°C.

4-*C*-Allyl-1,6:2,3-dianhydro-4-deoxy-β-D-*manno*-pyranose (XI). A solution of 0.88 g (22 mmol) of MeONa in 10 ml of MeOH was added over a period of 1 h to a solution of 5 g (14.7 mmol) of *p*-toluenesulfonate **X** in 10 ml of CH_2Cl_2, stirred at room temperature. When the reaction was complete (TLC), 10 ml of water was added, the mixture was extracted with chloroform (3 × 25 ml), and the combined extracts were washed with water and a saturated aqueous solution of NaCl, dried over $MgSO_4$, and evaporated to obtain 2 g (81%) of epoxy derivative **XI**. R_f 0.42 (ethyl acetate–hexane, 1:1). mp 128°C, $[\alpha]_D^{20}$ –38° (*c* = 0.8, $CHCl_3$). ^1H NMR spectrum, δ,

ppm: 1.90–2.00 m (1H, 4-H), 2.10–2.35 m (1H, CH_2), 2.90 br.s (1H, 3-H), 3.31 m (1H, 2-H), 3.67 m (2H, 6-H), 4.19 m (1H, 5-H), 5.00–5.15 m (2H, $=CH_2$), 5.61 d (1H, 1-H, $J_{1,2}$ = 3.2 Hz), 5.70–5.90 m (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 34.89 (CH_2), 38.68 (C^4), 50.11 (C^3), 53.37 (C^2), 68.26 (C^6), 70.70 (C^5), 97.79 (C^1), 118.16 ($CH_2=$), 135.09 (CH=).

4-*C*-Allyl-1,6-anhydro-2,4-dideoxy-β-D-*arabino*-hexopyranose (XII). Lithium aluminum hydride, 0.1 g (2.7 mmol), was added to a solution of 0.5 g (3 mmol) of epoxy derivative **XI** in 5 ml of THF, the mixture was refluxed for 30 min and cooled, 15 ml of diethyl ether and 1 ml of a 10% solution of KOH were added, and the mixture was stirred for 10 min. The organic phase was separated, and the solvent was removed to obtain 0.48 g (95%) of alcohol **XII** as an oily substance. R_f 0.15 (ethyl acetate–hexane, 1:1). $[\alpha]_D^{20}$ –67° (*c* = 0.6, $CHCl_3$). IR spectrum: ν 3500 cm^{-1}. ^1H NMR spectrum, δ, ppm: 1.70–1.80 m (2H), 1.90–1.95 m (1H), 2.05–2.30 m (2H), 3.14 br.s (1H, OH), 3.60–3.75 m (2H, *exo*-6-H, 3-H), 4.24 d (1H, *endo*-6-H, *J* = 7.0 Hz), 4.32 d (1H, 5-H, *J* = 5.0 Hz), 4.95–5.10 m (2H, $CH_2=$), 5.49 s (1H, 1-H), 5.67–5.85 m (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 35.17 (CH_2), 35.73 (C^4), 44.45 (C^2), 67.35 (C^3), 67.58 (C^7), 74.40 (C^1), 100.02 (C^5), 116.92 ($CH_2=$), 135.87 (CH=).

1,6-Anhydro-2,4-dideoxy-4-*C*-formylmethyl-β-D-*arabino*-hexopyranose (XIII). A solution of 1 g (5.55 mmol) of olefin **XII** and 0.01 g of $NaHCO_3$ (to prevent acetalization of the aldehyde formed) in 20 ml of CH_2Cl_2 and 10 ml of MeOH was saturated at –78°C with an ozone–oxygen mixture (~8 min, efficiency of the reactor 45 mmol/h). The mixture was purged with argon, 1.2 ml of dimethyl sulfide was added, and the mixture was allowed to warm up to room temperature, kept for 4 h, and evaporated. The residue was subjected to column chromatography on silica gel (eluent ethyl acetate, R_f 0.21) to obtain 0.93 g (92%) of aldehyde **XIII**. IR spectrum, ν, cm^{-1}: 1725, 3400. ^1H NMR spectrum, δ, ppm: 1.50–2.90 m (4H), 3.30–3.85 m (4H), 4.20–4.40 m (2H), 5.49 s (1H, 1-H), 9.74 d (1H, CHO, *J* = 3.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 35.74 (C^2), 39.21 (C^4), 45.18 (CH_2), 67.96 (C^6), 68.27 (C^3), 74.82 (C^5), 100.73 (C^1), 200.78 (CHO).

1,6-Anhydro-2,4-dideoxy-4-*C*-[(2*Z*)-octenyl]-β-D-*arabino*-hexopyranose (XIV). A solution of 0.93 g (5.11 mmol) of aldehyde **XIII** in 3 ml of THF was added under argon to a suspension of phosphorus ylide, prepared from 5.46 g (12.77 mmol) of hexyltriphenylphosphonium bromide and 2.36 g (12.77 mmol) of sodium hexamethyldisilazide in 35 ml of THF and cooled to –20°C. The mixture was stirred for 1 h, diluted with 10 ml of water, and extracted with diethyl ether (4 × 40 ml). The combined extracts were washed with a saturated aqueous solution of NaCl (10 ml), dried over $MgSO_4$, and evaporated under reduced pressure at room temperature. The residue was subjected to column chronatography on silica gel using ethyl acetate–hexane (1:2) as eluent. Yield of **XIV** 0.84 g (68%). Oily substance, R_f 0.32, $[\alpha]_D^{20}$ –39° (*c* = 0.9, $CHCl_3$). IR spectrum: ν 3500 cm^{-1}. ^1H NMR spectrum, δ, ppm: 0.82 t (3H, Me, *J* = 7.0 Hz), 1.15–1.40 m (6H, $3CH_2$), 1.65–1.85 m (2H), 1.85–2.40 m (5H), 3.10 br.s (1H, OH), 3.65–3.75 m (2H, *exo*-6-H, 3-H), 4.26 d (1H, *endo*-6-H, *J* = 7.0 Hz), 4.33 d (1H, 5-H, *J* = 5.0 Hz), 5.25–5.50 m (2H, $2CH_2=$), 5.53 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 13.72 (Me), 22.21 ($C^{7'}$), 26.92 ($C^{5'}$), 28.48 ($C^{4'}$), 28.96 ($C^{1'}$), 31.08 ($C^{6'}$), 35.77 (C^4), 45.28 (C^2), 67.53 (C^3), 67.53 (C^6), 74.51 (C^5), 100.78 (C^1), 126.51 and 132.26 (CH=CH).

1,6-Anhydro-2,4-dideoxy-3-*O*-methylsulfonyl-4-*C*-[(2*Z*)-octenyl]-β-D-*arabino*-hexopyranose (XV). A solution of 0.4 ml of methanesulfonyl chloride in 5 ml of CH_2Cl_2 was added dropwise over a period of 15 min to a solution of 0.2 g (0.83 mmol) of hydroxy olefin **XIV** and 1.2 ml of triethylamine in 5 ml of CH_2Cl_2. When the reaction was complete (TLC), the mixture was diluted with 5 ml of a saturated solution of NaCl and was extracted with CH_2Cl_2 (3 × 15 ml). The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure to obtain 0.27 g (94%) of methanesulfonate **XV**. IR spectrum, ν, cm^{-1}: 1180, 1340, 1360. ^1H NMR spectrum, δ, ppm: 0.81 t (3H, Me, *J* = 7.0 Hz), 1.20–1.40 m (6H, $3CH_2$), 1.90–2.40 m (7H), 3.01 s (3H, OMe), 3.79 d.d (1H, *exo*-6-H, *J* = 5.4, 7.8 Hz), 4.22 d (1H, *endo*-6-H, *J* = 7.2 Hz), 4.37 d (1H, *J* = 5.4 Hz, 5-H), 4.71 m (1H, 3-H), 5.30–5.65 m (2H, 2CH=), 5.53 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 13.92 (Me), 22.41 ($C^{7'}$), 27.20 ($C^{1'}$), 28.24 ($C^{4'}$), 29.08 ($C^{6'}$), 31.39 ($C^{5'}$), 33.93 (C^2), 38.82 (OMe), 43.79 (C^4), 67.53 (C^6), 73.82 (C^5), 76.78 (C^3), 99.32 (C^1), 125.44 ($C^{2'}$), 134.63 ($C^{3'}$).

Methyl 2,4-dideoxy-4-*C*-[(2*Z*)-octenyl]-α-D-*arabino*-hexopyranoside (XVI). A mixture of 0.24 g of alcohol **XIV** and 5 ml of a 10% solution of HCl in methanol was stirred for 5 min, neutralized with $NaHCO_3$, filtered, and evaporated. We isolated 0.23 g (82%) of oily compound **XVI** containing 5–10% of the corresponding β-anomer. $[\alpha]_D^{20}$ +59° (*c* = 0.4, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 0.80 t (3H, Me,

J = 8.0 Hz), 2.50 br.s (2H, OH), 3.25 s (3H, OMe), 3.50–3.90 m (4H), 4.80 br.s (1H, 1-H), 5.40–5.50 m (2H, CH=CH). ^{13}C NMR spectrum, δ, ppm: 13.94 (Me), 21.39 ($C^{7'}$), 25.13 ($C^{5'}$), 27.33 ($C^{4'}$), 29.21 ($C^{1'}$), 31.92 ($C^{6'}$), 36.91 (C^{2}), 44.30 (C^{4}), 54.65 (OMe), 63.32 (CH_2O), 66.59 (C^{3}), 71.57 (C^{5}), 98.77 (C^{1}), 128.70 and 130.71 (CH=CH).

Methyl 2,4-dideoxy-3-*O*-methylsulfonyl-4-*C*-[(2*Z*)-octenyl]-α-D-*arabino*-hexopyranoside (VII) was synthesized in a similar way from methanesulfonate **XV**. Yield 77%. $[\alpha]_D^{20}$ +36.5° (c = 0.3, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, Me, J = 6.9 Hz), 1.20–1.40 m (6H), 1.80–2.45 m (6H), 3.00 s (3H, SO_2Me), 3.30 s (3H, OMe), 3.60–3.80 m (3H, CH_2O, 5-H), 4.83 br.s (1H, 1-H), 4.95 d.d.d (1H, J = 5.0, 10.8, 15.7 Hz), 5.35–5.55 m (2H, CH=CH). ^{13}C NMR spectrum, δ_C, ppm: 14.04 (Me), 22.53 ($C^{7'}$), 24.32 ($C^{5'}$), 27.49 ($C^{4'}$), 29.06 ($C^{1'}$), 31.54 ($C^{6'}$), 37.31 (C^{2}), 38.72 (SO_2Me), 41.42 (C^{4}), 54.79 (OMe), 62.94 (CH_2O), 71.46 (C^{5}), 77.70 (C^{3}), 130.82 and 132.68 (CH=CH).

(+)-2α-Methoxy-6β-[6-methoxycarbonyl-3-oxo-(1*E*)-hexenyl]-5α-[(2*Z*)-octenyl]pyran-3-one (VIII). A solution of 0.23 g of diol **XVI** in 5 ml of CH_2Cl_2 was added with vigorous stirring under argon at 0°C to Collins' reagent prepared from 3.8 g CrO_3 and 6.6 ml of pyridine in 40 ml of CH_2Cl_2. After 15 min (TLC), the mixture was filtered through a small bed of silica gel, and the filtrate was evaporated under reduced pressure to obtain 0.18 g (0.67 mmol) of crude aldehyde **XVII**. The product was dissolved in 2 ml of THF, and the solution was added to a solution of phosphonate **XVIII** sodium salt (preliminarily prepared from 20 mg of NaH and 0.19 g of phosphonate **XVIII**; argon, 0°C, 1 h) in 2 ml of THF, cooled to –40°C. The mixture was stirred for 15 min and diluted with 5 ml of cold saturated aqueous NaCl, tetrahydrofuran was evaporated, and the product was extracted into ethyl acetate (3 × 10 ml). The combined extracts were dried over anhydrous $MgSO_4$, the solvent was removed, and the residue was purified by column chromatography on silica gel using hexane–ethyl acetate (1:1) as eluent. Yield of **VIII** 0.15 g (45%, calculated on diol **XVI**). R_f 0.5. $[\alpha]_D^{20}$ +6.5° (c = 0.4, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, J = 6.9 Hz), 1.20–1.40 m (6H), 1.90–2.00 m (4H), 2.40 m (4H), 2.70 (5H), 3.33 s (3H, OCH_3), 3.68 s (3H, OCH_3), 4.40 d.d (1H, 6-H, J = 6.0, 9.7 Hz), 5.15 d (1H, 9-H, J = 4.0 Hz), 5.25–5.50 m (2H, *cis*-CH=CH), 6.40 d (1H, J = 15.8 Hz) and 6.85 d.d (1H, J = 6.0, 15.8 Hz) (*trans*-CH=CH). ^{13}C NMR spectrum, δ, ppm: 14.50 (CH_3); 19.91, 22.84, 23.03, 27.90, 29.60, 32.02, 33.52, 40.02, 47.07 (CH_2); 52.02 (C^{5}); 55.18 (OMe); 55.56 (OMe); 72.25 (C^{6}); 100.40 (C^{2}); 126.32, 130.84, 132.51, 142.48 (CH=CH); 173.90 (CO_2); 199.43, 204.12 (CO).

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