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Prostanoids: LXXXV.* Synthesis 9-Oxo Derivatives of 9-LO Thromboxans

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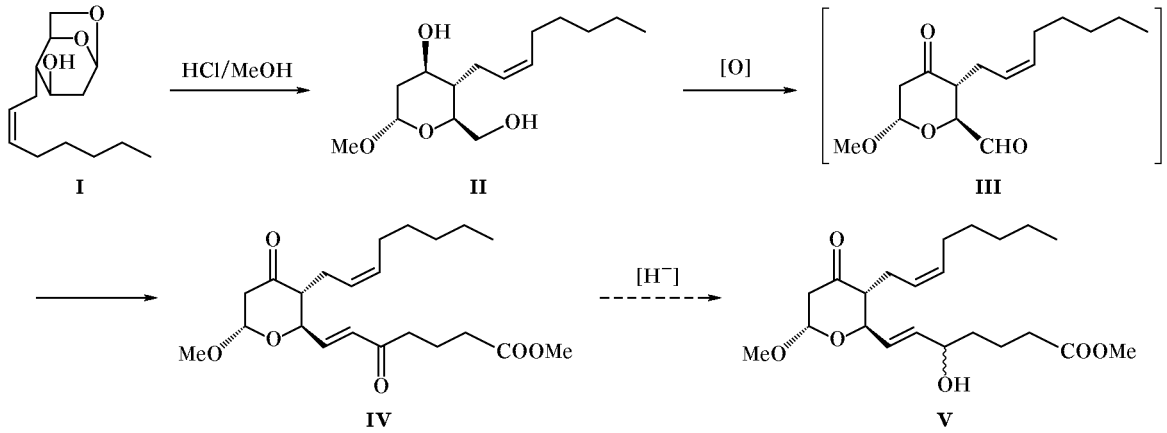
Abstract—Starting from levoglucosan, 1,6-anhydro-2,4-dideoxy-4-*C*-(2*Z*-octenyl)-β-D-*arabino*-hexopyranose was synthesized and converted into 9-oxo-9-LO thromboxan δ-lactone.

In the recent publication [2] we described the transformation sequence **I** → **IV** and planned to convert compound **IV** into **V** [3] (Scheme 1). The latter may be a useful model for studying the structure–activity relations in the series of 9-LO thromboxans (for 9-LO prostaglandins, see [4–6]).

The optimal version of the transformation **IV** → **V** seemed to be that involving regioselective reduction of the side-chain keto group in **IV**. However, our attempt to use for this purpose $(i\text{-Bu})_3Al$ (CH_2Cl_2, –78°C), which showed good results in the chemoselective reduction of the 15-keto group in 9,15-diketoprostenoic acid esters [7], was unsuccessful. We also failed to reduce both ketone groups in **IV** using *L*-Selectride, $NaBH_4$, and $Zn(BH_4)_2$. In all cases, unusual fragmentation of molecule **IV** occurred [8]. We also tried to approach compound **V** through 9-hydroxy derivatives (thromban nomenclature) which could be prepared from bis(triethylsilyl) ether **VI**. By analogy with the data of [9, 10], we used the system oxalyl chloride–DMSO (Swern's reagent [11]) to effect direct oxidation of the primary triethylsiloxy group in **VI**. Unfortunately, ether **VI** failed to react for unknown reason (Scheme 2).

It was more promising to use protected derivatives of alcohol **I**. We examined methanolysis of the corresponding acetate, methoxymethyl ether, and benzoate **VII**. Under these conditions, the acetate and methoxymethyl ether of **III** readily underwent hydrolysis to diol **II**, whereas the benzoate protection turned out

Scheme 1.



I **II** **III** **IV** **V**

* For communication LXXXIV, see [1].

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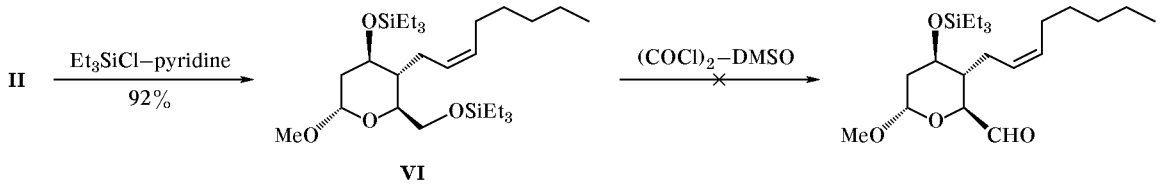
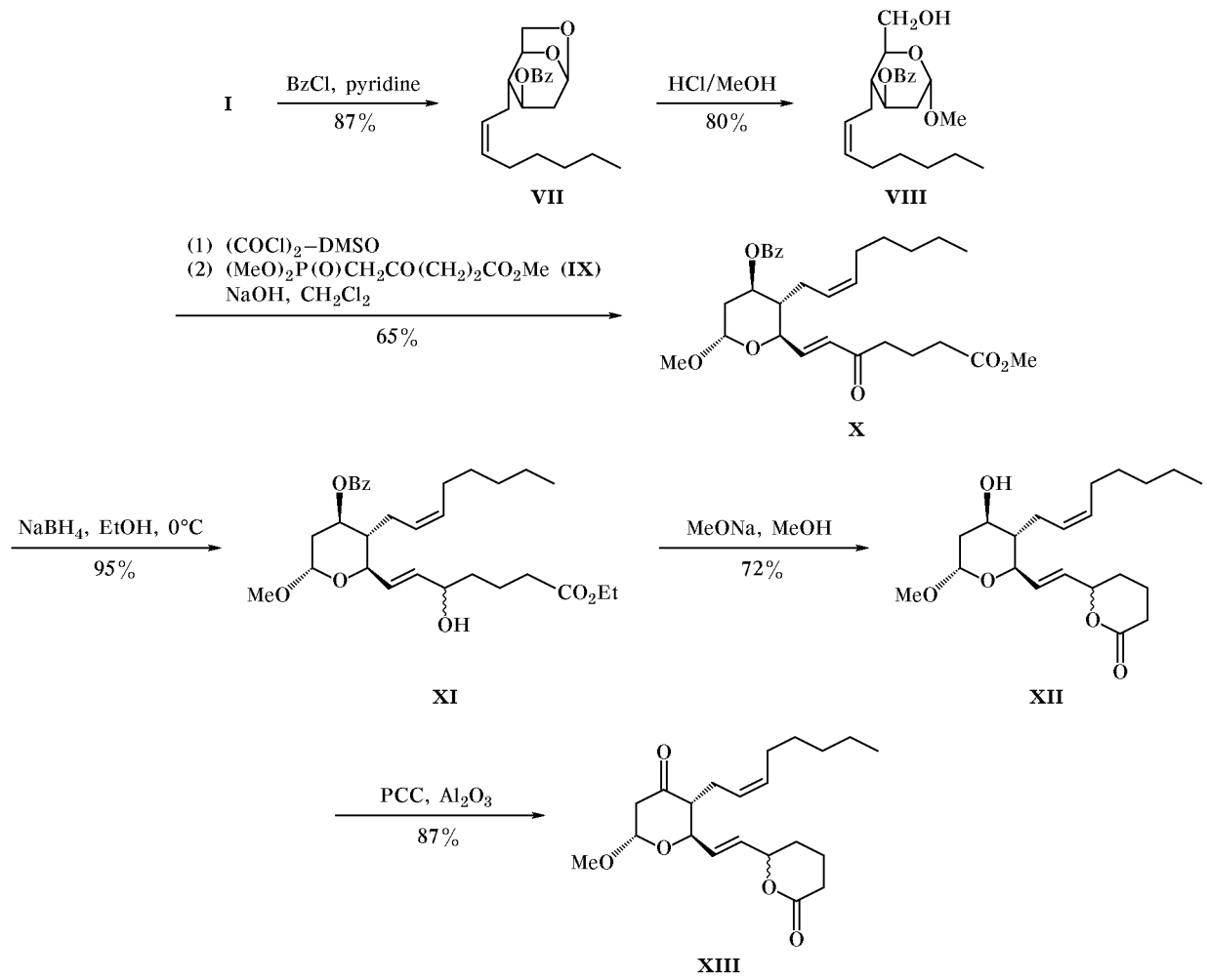
Scheme 2.



to be resistant to the system 10% HCl–MeOH (20°C, 0.5 h), and α-anomer **VIII** was obtained in a high yield. The corresponding β-glycoside was formed in an amount not exceeding 2–3% (according to the ^{1}H NMR data). It should be noted that prolonged keeping of compound **VII** in the system 1% HCl–MeOH (20°C, 10 h) leads to formation of an equilibrium (~1 : 1) mixture of the α- and β-anomers of **VIII**.

Oxidation of the hydroxy group in **VIII** with Swern's reagent, followed by Emmons–Horner olefination of unstable intermediate aldehyde with phosphonate **IX** [5] gave enone **X** in a good yield. Compound **X** was reduced with sodium tetrahydridoborate in EtOH at 0°C to obtain a mixture of diastereoisomeric diols **XI** (~1 : 1, according to the HLPC data) which could not be separated by chromatography on silica gel. Exhaustive alkaline hydrolysis of both ester groups (ethoxycarbonyl and benzoyloxy) in **XI** afforded the corresponding hydroxy acid which was converted into lactone **XII** during purification on silica gel. Lactone **XII** was oxidized with pyridinium chlorochromate on Al_2O_3 [12] to 9-oxo derivative

Scheme 3.



XIII (Scheme 3). The latter is a bioisoster of target compound **V**, which is suitable for biological testing both *per se* and as sodium salt readily obtainable via opening of the lactone ring.

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 ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent, and TMS as internal reference. HPLC analysis was performed with a Du Pont-8800 liquid chromatograph; 3 × 150-mm column packed with Separon SGX NH2 (5 μm); eluent hexane–*i*-PrOH–H_2O (90 : 9.5 : 0.5, by volume), flow rate 0.5 ml/min; pressure 5 MPa; UV detector (λ 254 nm). Thin-layer chromatography was performed on Silufol UV 254 : 366 plates; spots were visualized by treatment with iodine vapor, calcination, or spraying with a solution of *p*-methoxybenzaldehyde and sulfuric acid in ethanol (1 : 0.5 : 10) with subsequent heating at 120–150°C. The optical rotations were measured on a Perkin–Elmer 141 polarimeter.

Methyl 2,4-dideoxy-3,6-di-*O*-triethylsilyl-4-*C*-(2*Z*-octenyl)-α-D-*arabino*-hexopiranoside (VI). Chlorotriethylsilane, 1.37 g (9.1 mmol), was added dropwise with stirring to a solution of 1 g (3.6 mmol) of diol **II** in 20 ml of anhydrous pyridine. The mixture was kept for 1 h at room temperature, diluted with 100 ml of ethyl acetate, and washed with a saturated solution of sodium chloride (3 × 30 ml). The organic phase was dried over $MgSO_4$ and evaporated to obtain 1.27 g (92%) of bis-silyl ether **IV** as an oily substance. IR spectrum, ν, cm^{-1}: 1460, 1410, 1240. ^{13}C NMR spectrum, δ_C, ppm: 4.97 t ($SiCH_2$), 6.39 t ($SiCH_2$), 6.76 (Si**C**H_2CH_3), 14.03 (CH_3), 22.62 ($C^{7'}$), 27.53 ($C^{5'}$), 29.74 ($C^{1'}$), 31.64 ($C^{6'}$), 39.69 (C^2), 44.36 (C^4), 54.30 (OCH_3), 63.74 (CH_2), 66.97 (C^3), 72.45 (C^5), 98.58 (C^1), 126.62 and 130.85 (CH=CH).

1,6-Anhydro-3-*O*-benzoyl-2,4-dideoxy-4-*C*-(2*Z*-octenyl)-β-D-*arabino*-hexopyranose (VII). Freshly distilled benzoyl chloride, 0.68 g (4.79 mmol), was added dropwise over a period of 5 min to a solution of 1 g (4.17 mmol) of alcohol **I** in 10 ml of anhydrous pyridine under stirring at 0°C. The mixture was stirred for about 30 min at room temperature, treated with 30 ml of a saturated solution of $NaHCO_3$, and extracted with chloroform (3 × 10 ml). The combined extracts were washed with several portions of water and with a saturated solution of sodium chloride and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel to isolate 1.25 g (87%) of compound **VII** as an oily substance. R_f 0.34 (heptane–ethyl acetate, 4 : 1); $[\alpha]_D^{20}$ = –39° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3040, 1760, 1690, 1684, 1568. ^{1}H NMR spectrum, δ, ppm: 0.65 t (3H, CH_3, *J* = 7.4 Hz), 1.00–1.30 m (6H, $3CH_2$), 1.60–2.40 m (7H, 4-H, $3CH_2$), 3.75 d.d (1H, *exo*-6-H, *J* = 5.2, 6.8 Hz), 4.10 d (1H, *endo*-6-H, *J* = 6.8 Hz), 4.20 d (1H, 5-H, *J* = 5.2 Hz), 4.87 d (1H, 3-H, *J* = 5.2 Hz), 5.30–5.60 m (2H, CH=CH), 5.54 s (1H, 1-H), 7.30–7.65 m (3H) and 7.95–8.20 m (2H) (H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.08 (CH_3), 22.61 ($C^{7'}$), 27.39 ($C^{5'}$), 28.67 ($C^{4'}$), 29.33 ($C^{1'}$), 31.58 ($C^{6'}$), 33.67 (C^2), 43.46 (C^4), 67.90 (C^6), 70.03 (C^3), 74.17 (C^5), 100.22 (C^1), 126.26 ($C^{3'}$), 128.93, 129.05, 130.62 (C_{arom}), 133.18 ($C^{2'}$), 165.93 (CO_2).

Methyl 2,4-dideoxy-3-*O*-benzoyl-4-*C*-(2*Z*-octenyl)-α-D-*arabino*-hexopyranoside (VIII). A solution of 0.4 g (1.16 mmol) of benzoate **VII** in 5 ml of a 10% solution of HCl in methanol was stirred for 1 h, neutralized with $NaHCO_3$, and filtered, and the filtrate was evaporated to obtain 0.35 g (0.93 mmol, 80%) of compound **VIII** containing ~3% of the corresponding β-anomer. Oily substance, $[\alpha]_D^{20}$ = +16° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1600, 1620, 1740, 3500. ^{1}H NMR spectrum, δ, ppm: 0.80 t (3H, CH_3, *J* = 8.0 Hz), 1.05–1.35 m (6H), 1.70–2.40 m (8H), 3.35 s (3H, OCH_3), 3.60–3.90 m (3H, CH_2O, 5-H), 4.90 br.s (1H, 1-H), 5.30–5.50 m (3H, CH=CH, 3-H), 7.45 m (2H), 7.55 m (1H), 8.05 m (2H) (H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.05 (CH_3), 22.50 ($C^{7'}$), 24.72 ($C^{5'}$), 27.38 ($C^{4'}$), 29.17 ($C^{1'}$), 31.54 ($C^{6'}$), 35.95 (C^2), 41.40 (C^4), 54.85 (OCH_3), 63.32 (CH_2O), 69.89 (C^3), 71.44 (C^5), 98.61 (C^1), 124.98 and 132.48 (CH=CH), 128.40, 128.55, 129.66, 130.25 (C_{arom}), 165.60 (CO_2).

Methyl (2*R*,3*S*,4*R*,6*S*)-7-[3-(2*Z*-octenyl)-4-benzoyloxy-6-methoxytetrahydropyran-2-yl]-5-oxo-6*E*-heptenoate (X). A solution of 2.59 g (33.11 mmol) of DMSO in 5 ml of dry methylene chloride was added dropwise under argon to a solution of 1.19 g (15.05 mmol) of oxalyl chloride in 20 ml of dry methylene chloride on stirring at –60°C. The mixture was stirred for 30 min at –70°C, and a solution of 1.13 g (3.01 mmol) of methyl pyranoside **VIII** in 5 ml of methylene chloride was added, maintaining the temperature below –60°C. The mixture was stirred for 30 min at –70°C, and 3.76 g (63.67 mmol, 5.6 ml) of triethylamine was added. The mixture was allowed to warm up to room temperature, diluted with 15 ml of water, and stirred for 10 min. The organic phase was separated, the aqueous phase was extracted with

CH_2Cl_2 (2×15 ml), and the extracts were combined with the organic phase and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, a 1-g portion of the oily residue was dissolved in 20 ml of CH_2Cl_2 containing 0.93 g (3.67 mmol) of phosphonate **IX** and 3.5 mg of benzyltriethylammonium chloride, and 0.3 ml of 50% aqueous NaOH was added under vigorous stirring. When the reaction was complete (15–20 min, TLC), the mixture was diluted with 50 ml of CH_2Cl_2, acidified with 1 N hydrochloric acid to pH 5, and washed with a saturated aqueous solution of sodium chloride (3×15 ml). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure at room temperature, and the residue was subjected to chromatography on silica gel using ethyl acetate–hexane (2:1) as eluent to isolate 0.98 g of enone **X** (R_f 0.28). Yield 65% (calculated on compound **VIII**). $[\alpha]_D^{20}$ = +44° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1600, 1620, 1660, 1690, 1720, 1750, 3040. ^{1}H NMR spectrum, δ, ppm: 0.78 t (3H, CH_3, *J* = 7 Hz), 1.00–1.40 m (6H, $3CH_2$), 1.70–2.35 m (9H, $4CH_2$, CH), 2.37 t (2H, CH_2, *J* = 7.1 Hz), 2.65 t (2H, CH_2, *J* = 7 Hz), 3.33 s (3H, OCH_3), 3.66 s (3H, OCH_3), 4.29 d.d (1H, 2′-H, *J* = 10.1, 6.1 Hz), 4.89 s (1H, 6′-H), 5.30–5.50 m (3H, 4′-H, CH=CH), 6.38 d (1H, 6-H, *J* = 15.8 Hz), 6.86 d.d (1H, 7-H, *J* = 15.8, 6.1 Hz), 7.38–7.50 m (2H, *o*-H), 7.50–7.60 m (1H, *p*-H), 7.95–8.10 m (2H, *m*-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.87 (CH_3), 18.97 (C^3), 22.33 ($C^{7''}$), 24.89 ($C^{5''}$), 27.30 ($C^{4''}$), 28.99 ($C^{1''}$), 31.37 ($C^{6''}$), 32.98 (C^2), 35.70 ($C^{5'}$), 39.28 (C^4), 45.72 ($C^{3'}$), 51.44 (OCH_3), 69.54 ($C^{4'}$), 70.37 ($C^{2'}$), 98.60 ($C^{6'}$), 124.69 ($C^{2''}$), 128.27 (C^o), 129.50 ($C^{3''}$), 129.52 (C^m), 130.38 (C^p), 132.41 (C^i), 132.69 (C^6), 142.89 (C^7), 165.51 (CO_2), 173.45 (CO_2), 199.07 (C=O).

Ethyl (2′*R*,3′*S*,4′*R*,6′*S*,5*RS*)-7-[4-benzoyloxy-6-methoxy-3-(2*Z*-octenyl)tetrahydropyran-2-yl]-5-hydroxy-6*E*-heptenoate (XI). A freshly prepared solution of 3.5 mg (0.94 mmol) of $NaBH_4$ in 1 ml of EtOH was added with stirring at 0°C to a solution of 0.2 g (0.4 mmol) of enone **X** in 3 ml of EtOH. The mixture was stirred for 30 min, acidified with 3% hydrochloric acid to pH 5, and extracted with ethyl acetate (3×5 ml). The extract was washed with an aqueous solution of sodium chloride (2×3 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel using ethyl acetate–hexane (1:1) as eluent to isolate 0.19 g (95%) of compound **XI** (R_f 0.39) as a mixture of epimers (1:1, HPLC); oily substance. The HPLC retention times were 8.7 and 9.3 min (for conditions, see above). IR spectrum, ν, cm^{-1}: 3500, 1740, 1720. ^{1}H NMR spectrum, δ, ppm: 0.75 t (3H, CH_3, *J* = 7.0 Hz), 1.00–1.30 m (8H), 1.25 t (3H, CH_3, *J* = 7.0 Hz), 1.50–2.30 (10H), 2.35 t (2H, CH_2), 3.33 s (3H, OCH_3), 4.12 q (2H, OCH_2, *J* = 6.8 Hz), 4.10–4.20 m (1H), 4.85 br.s (1H, 6′-H), 5.32 m (3H, CH=CH, 4′-H), 6.70–6.90 m (2H, CH=CH), 7.40 m (2H), 7.55 m (1H), 8.00 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.93 (CH_3), 14.18 (CH_3), 20.79 and 20.81 (C^3), 22.37 ($C^{7''}$), 25.09 and 25.16 ($C^{5''}$), 27.28 ($C^{4''}$), 29.07 ($C^{1''}$), 31.41 ($C^{6''}$), 33.96 (C^2), 35.80 ($C^{5'}$), 36.28 and 36.32 (C^4), 45.43 and 45.57 ($C^{2'}$), 54.77 (OCH_3), 60.27 (OCH_2), 69.79 and 69.87 (C^5), 71.40 ($C^{1'}$), 71.67 ($C^{4'}$), 98.57 ($C^{6'}$), 124.87 and 125.15 ($C^{3''}$), 128.24 (C^o), 128.80 and 129.04 ($C^{2''}$), 129.54 (C^m), 130.35 (C^i), 131.89 and 131.98 (C^7), 132.82 (C^p), 137.06 and 137.16 (C^6), 165.58 (CO_2), 173.49 and 173.53 (C^1).

(2′*R*,3′*S*,6′*S*,5*RS*)-7-[6-Methoxy-4-oxo-3-(2*Z*-octenyl)tetrahydropyran-2-yl]-6*E*-hepten-5-olide (XIII). A solution of 30 mg (0.6 mmol) of sodium methoxide in 1 ml of methanol was added under stirring at room temperature to a solution of 0.2 g (0.4 mmol) of benzoate **XI** in 2 ml of methanol. When the reaction was complete (TLC), the mixture was diluted with 5 ml of water and extracted with chloroform (3×5 ml). The combined extracts were washed with water and a saturated aqueous solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was subjected to chromatography on silica gel to isolate 0.11 g (72%) of lactone **XII**. R_f 0.1 (ethyl acetate–hexane, 1:1). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3, *J* = 7 Hz), 3.30 s (3H, OCH_3), 3.90 m (2H, 5-H, 4′-H), 4.80 m (2H, 6′-H, 5-H), 5.45 m (2H, CH=CH), 5.80 m (2H, CH=CH). A mixture of 0.1 g (0.27 mmol) of lactone **XII** and 0.8 g (~0.82 mmol) of pyridinium chlorochromate on aluminum oxide in 2 ml of methylene chloride was stirred for 12 h at room temperature. The mixture was filtered, the precipitate was washed with methylene chloride (5×2 ml) on a filter, and the filtrate was combined with the washings and evaporated to obtain 75 mg (76%) of compound **XII** as a 3:2 mixture of epimers at C^5. Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, *J* = 7 Hz), 1.19–1.40 m (6H, $3CH_2$), 1.60–2.70 m (13H), 3.33 s (3H, OCH_3), 4.22 m (1H, 2′-H), 4.86 m (1H, 5-H), 5.10 br.s (1H, 6′-H), 5.20–5.30 m (2H, CH=CH), 5.80–5.90 m (2H, CH=CH). ^{13}C NMR spectrum, δ_C, ppm: 14.10 (CH_3), 18.29 (C^3), 22.46 ($C^{7''}$), 22.59 ($C^{5''}$), 27.42 ($C^{4''}$), 28.12 ($C^{1''}$), 29.19 (C^4), 29.58 ($C^{6''}$), 31.59 (C^2),

46.78 ($C^{4'}$), 54.99 (OCH_3), 55.05 ($C^{3'}$), 72.89 and 73.05 ($C^{2'}$), 79.23 (C^5), 99.89 (C^6), 126.15 and 126.23 ($C^{3''}$), 130.29 and 130.55 (C^6), 131.48 and 131.63 ($C^{2''}$), 131.86 (C^7), 170.74 (CO_2), 204.44 (C=O).

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