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Geminal Dimethyl-Substituted Functionalized C_4-Synthons from Pantolactone

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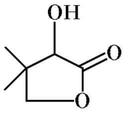
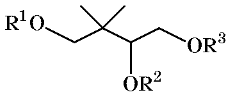
Abstract—Some geminal dimethyl-substituted functionalized C_4-synthons were prepared on the basis of (±)-pantolactone.

2-Hydroxy-3,3-dimethyl-4-butanolide (**I**, pantolactone) [1, 2] is commercially available in the enantiomerically pure forms. It possesses a structural fragment with geminal methyl groups which make it promising for synthesis of macrolide compounds exhibiting antitumor activity, such as Acutiphycin, Epothilones A and B, etc. [3–6]. We have studied some transformations of racemic pantolactone (**I**) with the goal of obtaining linear C_4-synthons **II** which contain various protective groups and are suitable for subsequent chemoselective transformations.

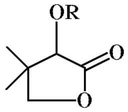


I



II

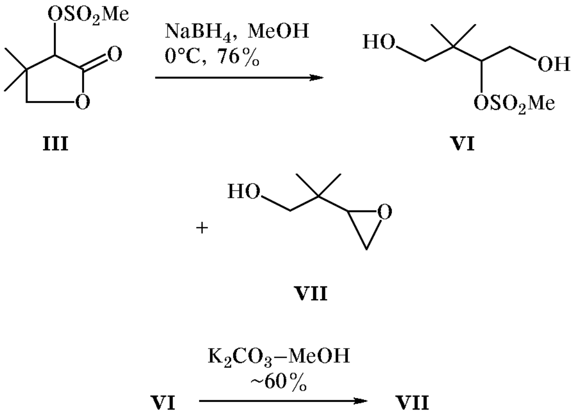
Initially, using standard procedures, we synthesized pantolactone derivatives with protected hydroxy group, in particular methanesulfonate **III**, methoxymethyl ether **IV**, and tetrahydrofuryl ether **V**. In the next stage we examined reactions of some protected pantolactone derivatives with metal hydrides. On treatment with $NaBH_4$ in MeOH the lactone carbonyl group in methanesulfonate **III** is reduced to hydroxy with opening of the lactone ring. The reaction was accompanied by formation of epoxy derivative **VII** (Scheme 1).



III–V

III, R = $MeSO_2$ (yield 95%); **IV**, R = $MeOCH_2$ (96%); **V**, α-tetrahydrofuryl (91%).

Scheme 1.



Pure methanesulfonate **VI** can be converted into epoxide **VII** in 60% yield by the action of K_2CO_3 in MeOH. Compound **VII** can be used to extend carbon chain at both ends through nucleophilic opening of the oxirane ring (**VII** → **IX**) or transformation into the corresponding epoxy aldehyde **X** with subsequent 1,2-addition of nucleophiles at more electrophilic carbonyl group. However, the Collins oxidation of **VII** gave not aldehyde **X** but compound **XI** as a result of the Tishchenko–Cannizzaro reaction (Scheme 2).

In order to obtain compound **XII**, pantolactone derivatives **IV** and **V** were first reduced to diols **XIII** and **XIV**, respectively, by the action of $LiAlH_4$. The third hydroxy group in **XIII** and **XIV** was deprotected using a catalytic amount of *p*-toluenesulfonic acid in

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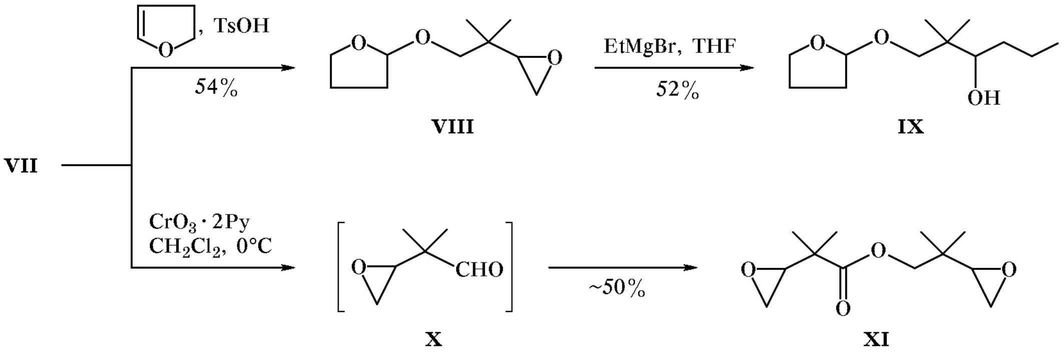
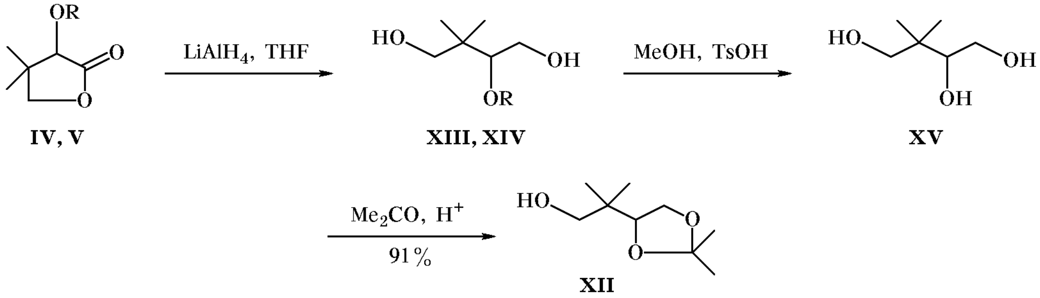
Scheme 2.



Scheme 3.



methanol. In the series of transformations (**IV, V**) → (**XIII**, **XIV**) the yield of the products in both stages was greater with methoxymethyl derivative **IV**. Triol **XV** was treated with acetone in the presence of *p*-toluenesulfonic acid to obtain the target product **XII** (Scheme 3).

Thus, using racemic pantolactone as an example, we have demonstrated the possibility for synthesizing C_4-blocks containing two geminal methyl groups (compounds **VII**, **VIII**, and **XII**). Pure stereoisomers of these compounds may be useful for preparation of the above-noted macrolides.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal reference.

3,3-Dimethyl-2-methylsulfonyloxy-4-butanolide (III) was synthesized from 1 g (7.8 mmol) of pantolactone (**I**), 1 ml (11.8 mmol) of methanesulfonyl chloride, and 1.23 g (11.8 mmol) of triethylamine in 20 ml of dry methylene chloride at –5°C. Yield 1.76 g (92%), yellow oily substance. IR spectrum, ν, cm^{-1}: 830, 870, 1000, 1180, 1315, 1365, 1480, 1785, 1810. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 s and 1.25 s (6H, CH_3), 3.25 s (3H, SO_2CH_3), 4.05 d (1H, *J* = 9.13 Hz) and 4.10 d (1H, OCH_2, *J* = 9.13 Hz), 4.98 s (1H, OCH).

3,3-Dimethyl-2-methoxymethoxy-4-butanolide (IV). To a solution of 1 g (7.8 mmol) of compound **I** in 20 ml of anhydrous dichloroethane we added with stirring at room temperature 0.8 ml (10.2 mmol) of methoxymethyl chloride and 1.4 ml (10.2 mmol) of ethyldiisopropylamine in 5 ml of dichloroethane. The mixture was stirred for 24 h at 40°C, washed in succession with cold water and a saturated solution of NaCl, dried over $MgSO_4$, and evaporated. We isolated 1.3 g (96%) of compound **IV** as a yellow oily substance. IR spectrum, ν, cm^{-1}: 840, 940, 1130, 1290, 1310, 1390, 1785, 1810. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 s and 1.05 s (6H, CH_3), 3.27 s (3H, OCH_3), 3.79 s (1H) and 3.82 s (1H, OCH_2), 3.94 s (1H, OCH), 4.56 d (1H, *J* = 6.73 Hz) and 4.81 d (1H, OCH_2O, *J* = 6.72 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.93 and 22.42 (CH_3), 39.69 (C^3), 55.32 (OCH_3), 75.51 (C^4), 77.91 (C^2), 95.58 (OCH_2O), 174.73 (C=O).

3,3-Dimethyl-2-(2-tetrahydrofuryloxy)-4-butanolide (V) was synthesized from 1 g (7.88 mmol) of compound **I** and 1.32 g (15.75 mmol) of dihydrofuran in 20 ml of dry methylene chloride containing 10 mg of *p*-toluenesulfonic acid at 0°C. Yield 1.5 g (91%). The product was isolated as a mixture of diastereoisomers at a ratio of 1 : 2. IR spectrum, ν, cm^{-1}: 745, 940, 1085, 1140, 1390, 1460, 1480, 1800, 2380. Found, %: C 59.88; H 7.90. $C_{10}H_{16}O_4$. Calculated, %: C 60.00; H 8.00. ^1H NMR spectrum ($CDCl_3$), δ, ppm: major isomer: 0.99 s and 1.11 s (6H, CH_3), 1.77–2.04 m (4H, CH_2), 3.79–3.98 m (4H, OCH_2) and 4.06 s (1H, OCH), 5.51 d (1H, OCHO, *J* = 4.23 Hz); minor isomer: 1.01 s and 1.16 s (6H, CH_3), 1.77–2.04 m (4H, CH_2), 3.79–3.98 m (4H, OCH_2) and 4.15 s (1H, OCH), 5.21 d (1H, OCHO, *J* = 4.18 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: major isomer: 19.39 and 22.80 (CH_3), 23.08 and 32.13 (CH_2, THF), 39.89 (C^3), 67.19 (OCH_2, THF), 76.21 (C^4), 77.45 (C^2), 103.07 (OCHO), 175.68 (C=O); minor isomer: 19.39 and 23.38 (CH_3), 22.76 and 32.30 (CH_2, THF), 40.21 (C^3), 67.36 (OCH_2, THF), 75.57 (C^4), 77.87 (C^2), 104.07 (OCHO), 175.05 (C=O).

3,3-Dimethyl-2-methylsulfonyloxy-1,4-butanediol (VI) and 2,2-dimethyl-3,4-epoxy-1-butanol (VII). To a suspension of 2.05 g (53.5 mmol) of $NaBH_4$ in 30 ml of anhydrous MeOH at 0°C we added dropwise a solution of 1 g (5.1 mmol) of compound **III** in 3 ml of MeOH. The mixture was stirred for 4 h at that temperature, excess $NaBH_4$ was decomposed with a small amount of a saturated solution of NH_4Cl, methanol was distilled off, and the products were extracted into ethyl acetate (3 × 20 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated, and the residue was subjected to column chromatography on silica gel using ethyl acetate–benzene (1 : 1) as eluent. We isolated 0.4 g (38%) of compound **VI** and 0.25 g (42%) of epoxy derivative **VII**.

Compound **VI**. IR spectrum, ν, cm^{-1}: 830, 870, 940, 1075, 1180, 1345, 2905, 3380–3540 (OH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 s and 0.98 s (6H, CH_3), 3.15 s (3H, SO_2CH_3), 3.17 br.s (2H, OH), 3.31 d (1H, *J* = 11.54 Hz) and 3.47 d (1H, OCH_2, ^2J = 11.54 Hz), 3.79 d.d (1H, *J* = 7.00, 12.60 Hz) and 3.92 d.d (1H, OCH_2, *J* = 2.8, 12.60 Hz), 4.66 d.d (1H, OCH, *J* = 2.80, 7.08 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.17 and 21.82 (CH_3), 38.65 (SO_2CH_3), 38.98 (C^3), 61.48 (C^1), 68.23 (C^4), 88.51 (C^2).

Compound **VII**. IR spectrum, ν, cm^{-1}: 864, 1072, 1156, 1212, 1368, 1456, 3448, 3600. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 s and 0.91 s (6H, CH_3), 2.65 d (2H, OCH_2, *J* = 3.30 Hz), 2.80 br.s (1H, OH), 2.84 t (1H, OCH, *J* = 3.30 Hz), 3.29 d (1H, *J* = 11.0 Hz), 3.39 d (1H, CH_2O, *J* = 11.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.85 and 20.75 (CH_3), 35.19 (C^2), 43.85 (C^4), 58.12 (C^3), 69.59 (C^1).

2,2-Dimethyl-1-(2-tetrahydrofuryloxy)-3,4-epoxybutane (VIII) was synthesized as described above for compound **V** from 0.12 g (1.03 mmol) of epoxy derivative **VII** and 0.14 g (2.06 mmol) of dihydrofuran in 5 ml of dry methylene chloride containing 3 mg of *p*-toluenesulfonic acid. Product **VIII** was isolated as a mixture of diastereoisomers by column chromatography on silica gel. Yield 0.1 g (54%). IR spectrum, ν, cm^{-1}: 880, 940, 1005, 1070, 1135, 1215, 1380, 1480. Found, %: C 63.90; H 9.90. $C_{10}H_{18}O_3$. Calculated, %: C 64.52; H 9.68. ^1H NMR spectrum ($CDCl_3$), δ, ppm: major isomer: 0.82 s and 0.83 s (6H, CH_3), 1.70–2.00 (4H, CH_2), 2.59 d (2H, OCH_2, *J* = 3.50 Hz), 2.85 t (1H, OCH, *J* = 3.50 Hz), 3.42 d (1H, *J* = 9.2 Hz) and 3.48 d (1H, OCH_2, *J* = 9.2 Hz), 3.82 t (2H, OCH_2, THF, *J* = 6.60 Hz), 5.04 d.d (1H, OCHO, *J* = 2.5, 5.3 Hz); minor isomer: 0.83 s and 0.85 s (6H, $2CH_3$), 1.70–2.00 (4H, CH_2), 2.61 d (2H, CH_2O, *J* = 3.50 Hz), 2.82 t (1H, OCH, *J* = 3.50 Hz), 3.09 d.d (1H, *J* = 9.3 Hz) and 3.12 d (1H, OCH_2, *J* = 9.3 Hz), 3.82 t (2H, OCH_2, THF, *J* = 6.60 Hz), 5.39 d (1H, *J* = 4.58 Hz, OCHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: major isomer: 20.34 and 20.46 (CH_3), 23.47 and 32.24 (CH_2, THF), 34.68 (C^2), 43.97 (C^4), 57.40 (C^3), 66.75 (C^1), 73.49 (OCH_2, THF), 103.96 (OCHO); minor isomer: 20.22 and 20.63 (CH_3), 23.41 and 32.24 (CH_2, THF), 34.68 (C^2), 44.03 (C^4), 57.22 (C^3), 66.99 (C^1), 73.59 (OCH_2, THF), 103.79 (OCHO).

2,2-Dimethyl-1-(2-tetrahydrofuryloxy)hexan-3-ol (IX). To a solution of 0.1 g (0.56 mmol) of compound **VIII** in 10 ml of anhydrous THF at 0°C we added dropwise 0.7 ml of a 2.9 N solution of EtMgBr (2 mmol) in THF. The mixture was stirred for 30 min at 0°C and for 3 h at 45–50°C (TLC monitoring). It was decomposed with a saturated solution of NH_4Cl, tetrahydrofuran was distilled off, the residue was extracted with ethyl acetate (3 × 10 ml), and the extract was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 1) as eluent to isolate 0.06 g (52%) of compound **IX** as an oily substance. IR spectrum, ν, cm^{-1}: 1125, 1285, 1325, 1380, 1465, 1670. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 s and 1.04 s (6H, CH_3), 0.87 t (3H, CH_3, *J* = 7.80 Hz), 1.26 m (2H, CH_2), 1.70–1.86 m (4H, CH_2), 1.91 br.s (1H, OH), 3.29 t (1H, OCH, *J* = 10.28 Hz), 3.39 d (1H, *J* = 11.2 Hz), 3.55 d (1H, OCH_2, *J* = 11.2 Hz), 3.69 t (2H, OCH_2, THF, *J* = 6.01 Hz), 4.61 d.d (1H, OCHO, *J* = 4.22, 4.80 Hz).

^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.22 (CH_3), 18.38 and 21.63 (C^2H_3), 27.17 and 31.49 (CH_2, THF), 29.78 and 31.64 (CH_2), 32.01 (C^2), 62.73 (C^1), 78.11 (OCH_2, THF), 85.33 (C^3), 102.69 (OCHO).

3,3,7,7-Tetramethyl-5-oxa-1,2 : 8,9-diepoxynonan-4-one (XI). Anhydrous chromium(VI) oxide, 1.31 g (13.1 mmol), was added to a solution of 1.69 g (21.38 mmol) of anhydrous pyridine in 20 ml of methylene chloride, stirred at 0°C under argon. The resulting Collins reagent was stirred for 5 min at 0°C and for 30 min at room temperature. It was then cooled to 0°C, and a solution of 0.2 g (1.72 mmol) of compound **VII** was quickly added under vigorous stirring. The mixture was stirred for 10 min at 0°C and for 30 min at room temperature and was filtered through a thin layer of silica gel. The filtrate was washed in succession with 5% hydrochloric acid, a 5% solution of $NaHCO_3$, and a saturated solution of NaCl, dried over $MgSO_4$, and evaporated to obtain 0.1 g (50%) of compound **XI** as an oily substance. IR spectrum, ν, cm^{-1}: 950, 980, 1070, 1100, 1160, 1200, 1250, 1385, 1480, 1740, 2790. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 s and 0.93 s (6H, CH_3), 1.14 s and 1.21 s (6H, CH_3), 2.62–2.74 m (4H, OC^1H_2, OC^9H_2), 2.85 br.s (1H, C^8H), 3.17 t (1H, C^2H, J = 2.77 Hz), 3.94–3.98 m (2H, OC^6H_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.04 and 20.16 (CH_3), 20.37 and 21.05 (CH_3), 34.59 (C^7), 42.66 (C^3), 43.69 and 43.88 (C^1, C^9), 56.26 (C^2), 56.81 (C^8), 70.63 (C^6), 175.43 (C=O).

2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methyl-1-propanol (XII). To a solution of 4.2 g (31.58 mmol) of triol **XV** in 40 ml of acetone we added 20 mg of *p*-toluenesulfonic acid, and the mixture was stirred for 12 h at room temperature. The solution was neutralized with solid $NaHCO_3$ and evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel. Yield 5 g (91%). IR spectrum, ν, cm^{-1}: 1125, 1280, 1325, 1380, 1465, 1670, 3300. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 s and 0.86 s (6H, CH_3), 1.29 s and 1.36 s (6H, C^5H_3), 2.87 br.s (1H, OH), 3.37 d (1H, J = 10.94 Hz) and 3.39 d (1H, $OC^{2'}H_2$, J = 10.94 Hz), 3.71 t (1H, OCH, J = 7.71 Hz), 3.89 d.d (1H, J = 6.50, 7.71 Hz) and 3.97 d.d (1H, OCH_2, J = 6.49, 7.71 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.70 and 21.35 (CH_3), 25.08 and 26.24 (C^5H_3), 36.69 ($C^{1'}$), 65.22 ($C^{2'}$), 70.74 (C^3), 81.75 (C^2), 108.84 (C^5). Found, %: C 62.50; H 10.70. $C_9H_{18}O_3$. Calculated, %: C 62.07; H 10.34.

3,3-Dimethyl-2-(methoxymethoxy)-1,4-butanediol (XIII). A solution of 2.7 g (15.7 mmol) of compound **IV** in 10 ml of dry diethyl ether was added dropwise with stirring at 0°C to a suspension of 0.9 g (23.62 mmol) of $LiAlH_4$ in 30 ml of dry diethyl ether. The mixture was stirred for 12 h at room temperature and cooled to 0°C, and 5 ml of H_2O and 2 ml of a 15% solution of NaOH were added with stirring. After 30 min, the mixture was filtered, the precipitate was washed on a filter with five 20-ml portions of THF, the filtrate was combined with the washings and dried over K_2CO_3, and the solvent was removed. We isolated 2.4 g (88%) of diol **XIII**. IR spectrum, ν, cm^{-1}: 920, 1036, 1080, 1104, 1128, 1144, 1208, 1364, 1412, 1468, 3392, 3600. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 s and 0.95 s (6H, $2CH_3$), 3.35 d (1H, J = 11.03 Hz) and 3.44 d (1H, OCH_2, J = 11.0 Hz), 3.39–3.42 m (4H, 2OH, OCH_2), 3.43 s (3H, OCH_3), 3.63 d.d (J = 6.54, 12.10 Hz) and 3.75 d.d (1H, OCH, J = 2.62, 12.17 Hz), 4.67 d (1H, J = 6.71 Hz) and 4.79 d (1H, OCH_2O, J = 6.71 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.48 (CH_3), 22.71 (CH_3), 38.77 (C^3), 56.01 (OCH_3), 62.17 (C^1), 69.34 (C^4), 88.07 (C^2), 98.30 (OCH_2O).

3,3-Dimethyl-2-(2-tetrahydrofuryloxy)-1,4-butanediol (XIV) was synthesized as described above for compound **XIII** from 0.55 g (3.1 mmol) of compound **V** and 0.18 g (4.73 mmol) of $LiAlH_4$. The product was a mixture of diastereoisomers, yield 54%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: major isomer: 0.72 s and 0.90 s (6H, CH_3), 1.78–2.04 m (4H, CH_2), 3.06 d (1H, J = 11.29 Hz) and 3.44 d (1H, OC^4H_2, J = 11.15 Hz), 3.51–3.83 m (4H, OCH_2), 3.90 m (1H, OCH), 5.40 t (1H, OCHO, J = 2.94 Hz); minor isomer: 0.81 s (3H) and 0.88 s (3H, $2CH_3$), 1.78–2.04 m (4H, CH_2), 3.28 d (1H, J = 10.94 Hz) and 3.35 d (1H, OC^4H_2, J = 10.90 Hz), 3.51–3.83 m (1H, J = 10.28 Hz), 3.90 m (1H, OCH), 5.13 t (1H, OCHO, J = 3.05 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: major isomer: 19.39 and 22.74 (CH_3), 24.04 and 32.43 (CH_2, THF), 38.46 (C^2), 61.91 (C^1), 67.68 (C^4), 69.19 (OCH_2, THF), 80.39 (C^2), 104.34 (OCHO); minor isomer: 20.60 and 22.37 (CH_3), 23.99 and 32.36 (CH_2, THF), 38.66 (C^2), 62.22 (C^1), 66.52 (C^4), 67.39 (OCH_2, THF), 81.40 (C^2), 103.79 (OCHO).

3,3-Dimethyl-1,2,4-butanetriol (XV). To a solution of 5.4 g (30.5 mmol) of diol **XIV** in 20 ml of methanol we added 15 mg of *p*-toluenesulfonic acid. The mixture was stirred for 12 h at room temperature, neutralized with solid $NaHCO_3$, and filtered. The filtrate was evaporated to obtain 4 g (98%) of triol **XV** with mp 55–57°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 816, 1008, 1036, 1128, 1144, 1184, 1376, 1460, 3120, 3176, 3368. ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.07 s (6H, CH_3), 3.58 d (2H, OCH_2, J = 3.96 Hz), 3.72 s (2H, OCH_2), 3.86 d (1H, OCH, J = 8.14 Hz), 4.42 br.s (3H, OH). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 19.47 and 21.06 (CH_3), 37.66 (C^3), 62.42 (C^1), 69.09 (C^4), 76.93 (C^2). Found, %: C 53.36; H 10.20. $C_6H_{14}O_3$. Calculated, %: C 53.73; H 10.44.

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