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A crystal structure of the tritylated product of 3-hydroxymethyl-bicyclo[3.3.1]nonan-2-on-7-ol ethylene acetal cyclization

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General information

All reaction temperatures correspond to internal temperatures unless otherwise noted. Solvents for extraction and chromatography were technical grade and distilled from indicated drying agents: petroleum ether (P_2O_5); ethyl acetate (K_2CO_3); methylene chloride and chloroform (P_2O_5); toluene and benzene (sodium); tetrahydrofuran and diethyl ether (sodium, benzophenone). Flash and column chromatography were performed on silica gel Acros (40-60 μm). Reaction control was carried out by thin-layer chromatography on "Silufol" plates. If otherwise was not stated ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz correspondingly. Spectra are referenced to residual $CHCl_3$ (δ 7.26 ppm ^{1}H; δ 77.0ppm ^{13}C). Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet). Electron impact mass spectra were obtained with typical voltage of 70 eV. Elemental analysis of synthesised compounds was performed on CNH analyser "Carlo-Erba" ER-20. Infrared spectra (IR) were registered on UR-20 apparatus (thin layer in liquid paraffin) and reported in cm^{-1}. Melting points were measured in block with sealed capillaries and are uncorrected. Crystallographic data for structures **13** and **15a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 291898 and 626665 correspondingly. Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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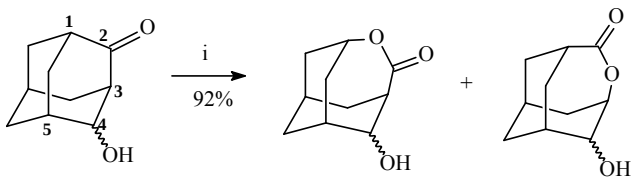
endo,endo-7-(Hydroxymethyl)bicyclo[3.3.1]nonane-1,3-diol (**2**).

To a stirred suspension of $LiAlH_4$ (0.15 g) in 20 ml of diethyl ether was added etheral solution of lactone **1**[1] (1.0 g, 5.5 mmol). After being stirred for 3 h under reflux, the reaction mixture was quenched with water (1 ml), the organic layer was decanted and solid residue was washed with hot tetrahydrofuran (5x15 ml). Organic fractions were combined, dried with anhydrous Na_2SO_4 and evaporated in vacuum and flash chromatographed (ethyl acetate – petroleum ether 1:3, then 3:1) to give title compound **1** (0.85 g, 83%) as white crystals. M.p. 83-86 ^oC. Anal. Calcd for $C_{10}H_{18}O_3*H_2O$: C, 58.82; H, 9.80. Found: C, 59.14; H, 9.71. ^1H NMR (DMSO-d_6, δ): 1,13-1.16 (m, 2H), 1.50-1.81 (m, 6H), 1.92 (m, 2H), 2.12 (m, 2H), 2.73-2.50 (m, 3H), 3.22 - 3,38 (two m, 2H, C<u>H</u>$_2$OH), 4.03 (m, 1H, C<u>H</u>OH). ^{13}C NMR (DMSO-d_6, δ): 26.73, 29.49, 37.09, 37.35, 40.50, 47.14, 48.80, 66.54, 67.33, 75.99. IR (ν_{max}): 3320-3510 (OH).

Methyl 7-*endo*-1,7-dihydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylate (**3**).

Lactone **1** (1 g, 5.5 mmol) was refluxed in 30 % NaOH water-methanol (1:3) solution. In 26 h methanol was evaporated in vacuum and residue diluted with ice water (20 ml) and extracted with CH_2Cl_2 (2x30 ml) to remove unreacted lactone. Water solution was neutralised by HCl (conc.) up to pH ~ 3-4 and extracted with CH_2Cl_2 (6x30 ml). Organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved in methanol (20 ml) and Et_2O*BF_3 (1 ml) were added to the solution. The reaction mass was refluxed for 4 h, then evaporated in vacuum and redissolved in $CHCl_3$, washed with 0.1N solution of HCl, (2x15 ml), saturated solution of $NaHCO_3$ (15 ml) and water (15 ml). Organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. Column chromatography of residue (ethyl acetate – petroleum ether 1:3, then 2:1) resulted in compound **3** (0.35 g, 30%) as colourless oil. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.52. Found: C, 61.66; H, 8.47. ^1H NMR (δ): 1.34-2.01 (m, 12H), 2.34 (m, 1H, C<u>H</u>CO_2Me), 3.46 (s, 1H, OH), 3.65 (s, 3H, CH_3), 4.18 (m, 1H, C<u>H</u>OH). IR (ν_{max}): 1730 (C=O), 3450 (OH).

Bayer-Villiger oxidation of 4-hydroxyadamantan-2-one **(4)**.



4 **4'** **4"**

Compound **4** (1 g, 6 mmol) was dissolved in acetic acid (10 ml) and under cooling on ice bath 30 % H_2O_2 (8 ml) was added dropwise. Reaction mixture was heated at 80ºC for 5 h, then the solvent was evaporated and the residue was redissolved in $CHCl_3$ (30 ml), washed with saturated $NaHCO_3$ solution (2*15 ml), brine (15ml), dried with anhydrous Na_2SO_4 and solvent was evaporated in vacuum. The residue was sublimed at 220 ºC (12 mm Hg) for 15 min to give white solid (1.0g, 92%). In composite ^{1}H NMR spectrum the signals of four isomers (two regio- and two OH-stereo isomers) were detected. Selected signals in ^{1}H NMR (δ): 3.02-3.09 (CHC(O), **4**'), 3.14 (CHC(O), **4**"), 43.93-3-97 (CHOH), 4.47-4.51 (CHOC(O)). The spectrometry ratio 4':4" is ca. 1.2:1. Oxidation with H_2O_2/SeO_2/t-BuOH (see preparation of **6**) gave the same ratio of products.

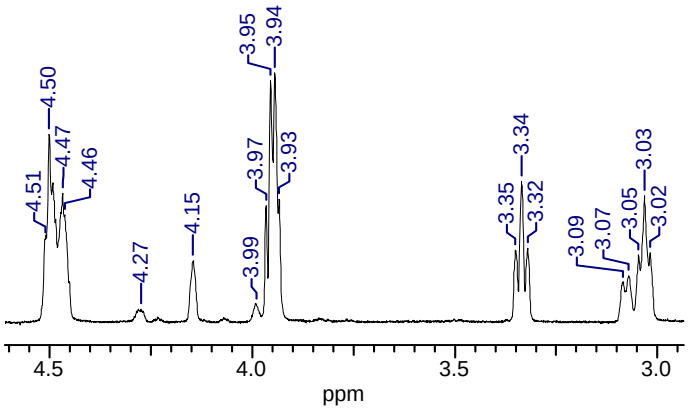


Figure **1**. Fragment of ^{1}H NMR spectrum of the mixture **4'** and **4''**.

4-(Benzyloxy)adamantan-2-one **(5)**.

To DMF (3 ml) solution of compound **4**[2] (0.7 g, 4.2 mmol) sodium hydride (0.22 g 60% in mineral oil, 5.5 mmol) and in 15 min benzyl chloride (0.65 ml, 5.4 mmol) were added portionwise. The reaction mixture was stirred for 1 h and poured onto ice (15 g). Water solution was extracted by CH_2Cl_2 (4x10 ml), the organic layer was washed with 10% solution of HCl (1x 20 ml), saturated solution of $NaHCO_3$ (20 ml), then with water (20 ml), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (ethyl acetate – petroleum ether 1:5) to yield white solid (1,03 g, 97%). M.p. 165-166 ^{o}C (subl). ^{1}H NMR (δ): 1.56 – 2.50 (m, 11H), 2.82 and 2.87 (two s 1:2, 1H, C^{3}H), 3.61 and 3.90 (two m, 1:1.5, J^{eq} = 3.17 Hz, J^{ax} = 5.08 Hz, 1H, C^{4}H), 4.44-4.60 (m, 2H, CH_2O), 7,25-7.34 (m, 5H, arom.).

7-benzyloxy-4-oxatricyclo[4.3.1.1^{3,8}]undecane-5-one **(6)**. Ketone **5** (1 g, 3.9 mmol) was added to the stirred solution 50% H_2O_2 (1,5 ml) and 0.15 g SeO_2 in 10 ml of t-BuOH at 80ºC. After 1.5 h at this temperature the reaction mixture was diluted with cold brine solution (20 ml) and extracted with $CHCl_3$ (3x30 ml). The organic layer was washed with water (10 ml), dried over anhydrous Na_2SO_4 and evaporated to dryness. Flash chromatography (ethyl acetate – petroleum ether 1:3) of the residue gave compound **6** (1.0 g, 94%) as colourless oil. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.83; H, 7.62. ^{1}H NMR (δ): 1.22 - 1.39 (m, 2H), 1.61-1.79 (m, 3H), 1.88-1.96 (m, 3H), 2.10-2.17 (m, 2H), 2.49 (m, 1H), 3.23 and 3.58 (two m, 1:2, 1H, C^{7}H), 4.40-4.73 (m, 3H, C^{3}H and CH2O), 7,25-7.34 (m, 5H, arom.). ^{13}C NMR (δ): 25.14-35.84 (skeletal); 45.79 and 46.69 (C^6), 69.60 and 70.66(C^4), 72.52 and 72.90 (CH_2Ph), 75.00 and 75.53 (CHOBn), 127.19-138.01 (arom.), 175.42 and 175.71 (C=O). IR (ν_{max}): 1380, 1450, 1470, 1735.

2-*endo*-(Benzyloxy)-7-*endo*-hydroxybicyclo[3.3.1]nonan-3-*exo*-carboxylic acid **(7)**. The title compound was prepared from lactone **6** (0.57 g, 2.1 mmol) by the method used for alkaline hydrolysis of **1**. Chromatographic purification (ethyl acetate – petroleum ether 1:9) yielded compound (0.5 g, 83%) as colourless oil. ^{1}H NMR (δ): 1.20-2.22 (m, 12H), 2.43 (m, 1H, CHCO_2H), 3.54 (m, 1H, CHOH), 4.09 (m, 1H, CHOBn), 4.67 (m, 2H, OCH_2Ph), 7,27-7.55 (m, 6H, arom). ^{13}C NMR (δ): 25.46, 28.70, 30.72, 33.66, 36.62, 41.00, 63.70 ($C_{(3)}$), 70.57(PhCH_2O), 80.19 ($C_{(7)}$), 127.94-139.82 (arom.). IR (ν_{max}): 178,86 (C=O).

Methyl 2-*endo*-(benzyloxy)-7-*endo*-hydroxybicyclo[3.3.1]nonan-3-*exo*-carboxylate **(8)**. Compound **7** (0.5 g), p-TSA (0.03 g) in $CHCl_3$ (50 ml) and methanol (5 ml) were refluxed with Dean-Stark trap for 6 h. The reaction solution was washed with water (2x10 ml), dried with anhydrous Na_2SO_4 and evaporated to dryness. Column chromatography of residue (diethyl ether – petroleum ether 1:2) ester **8** (0.41 g, 37% from **6**) as white solid. M.p. 60-62^{o}C. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.95; H, 7.83. ^{1}H NMR (δ): 1.18 – 2.21 (m, 11H), 2.40 (m, J_{H2H3}=8.5 Hz, 1H, CHCO_2Me), 3.64 (s, 3H, OCH_3), 3.70 (s, 1H, CHOH), 3.94 (m, J_{H3H2}=8.5 Hz, 1H, CHOBn), 4.42 and 4.53 (two d, J=12.7 Hz, 2H, OCH_2Ph), 7.23-7.32 (5H, arom.). ^{13}C NMR (δ) 25.51-42.16 (7C, skeletal), 51.54 (CH_3), 63.77 (CHOH), 70.62 (OCH_2Ph), 80.48 (CHOBn), 73.67 (CHOH), 127.55, 128.13 and 138.68 (arom.), 176.39 (CO_2).

2,2-Ethylenedioxyadamantan-4-ol.

A mixture of **4** (2.2 g; 13,3 mmol) in 60 ml of toluene and 1.8 ml of dry ethylene glycol in the presence of catalytic amount p-toluenesulfonic acid (p-TSA) was refluxed with Dean-Stark trap for 6 h. Whereupon the mixture was cooled, washed with saturated solution of $NaHCO_3$ (3x20 ml) and water (3x20 ml). The organic layer was dried with anhydrous Na_2SO_4 and toluene was evaporated in vacuum. Purificatiopn of the residue by column chromatography (ethyl acetate – petroleum ether 1:5) gave protected title ketone (2.5 g, 89%). ^{1}H NMR (δ): 1.57 – 2.05 (m, 13 H), 3.71 – 4.05 (m, 5 H, OH, - CH_2CH_2 -). IR (ν_{max}): 34 br (OH), 1110 (COC).

2,2-Ethylenedioxyadamantan-4-one (**9**).

A solution of 2,2-ethylenedioxyadamantan-4-ol (2.5 g, 11.9 mmol) in 100 ml of benzene was treated with pyridinium chlorochromate (PCC) on Al_2O_3 (13g, with PCC content 1 mmol for 1 g). After 12 h of vigorous stirring at room temperature the reaction mixture was filtered, the sediment was washed with benzene (2x20 ml), combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate – petroleum ether 1:9) to give ketone **9** (2.2 g, 90%) as white solid. M.p. 56 ºC. ^{1}H NMR (δ): 1,7 - 2,1 (m, 8H), 2,14 – 2,17 (m, 1H), 2,3 (m, 1H, C^5H), 2,50 - 2,56 (two m, 2H, C^1H, C^3H), 3,97 (m, 4H, - CH_2CH_2 -). ^{13}C NMR (δ): 26.20, 32.08, 33.74, 36.26, 37.41, 38.85, 45,42 (C^1), 56,13 (C^3), 64.53 (OCH_2), 64,79 (OCH_2), 111.88 (O-C-O), 214.24 (C=O). IR (ν_{max}): 1710 (C=O), 1110 (COC).

7,7-ethylenedioxy-4-oxatricyclo[4.3.1.1^{3,8}]undecane-5-one (**10**).

A solution of compound **9** (1g, 4.8 mmol), m-chloroperoxybenzoic acid (m-CPBA) (2.5 g of 50% mixture with m-chlorobenzoic acid) and $NaHCO_3$ (0.2 g) in 40 ml of $CHCl_3$ was refluxed for 24 h. The reaction mixture was washed with water (3x20 ml), dried over anhydrous Na_2SO_4 and evaporated to dryness. Column chromatography of residue (ethyl acetate – petroleum ether 1:9, then 1:5) gave initial ketone **9** (0.27 g, 26%) and lactone **10** (0.77 g, 72%) as colourless oil. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.21. ^{1}H NMR (δ): 1.72 – 2.46 (m, 10H), 3.10 (d, 1H, C^6H), 3.96-4.14 (m, 4H, OCH_2CH_2O), 4.46 (m, 1H, C^3H). ^{13}C NMR (δ): 25.13, 29.75, 31.64, 31.85, 35.67, 35.97, 51.41, 64.73, 64.88 (2C, OCH_2CH_2O), 72.84 (C^3), 112.61 (C^7), 172.80 (C^5). IR (ν_{max}): 1730 (C=O).

(+/-)-(*1R**,*3S**,*6R**,*8S**)-3-methoxy-2-oxatricyclo[4.3.1.$0^{3,8}$]decane (**11**). The title compound was synthesised from lactone **10** (1 g, 5.4 mmol) by the same method as used for **3**. Column chromatography (ethyl acetate – petroleum ether 1:9) resulted in compound **11** (0.81 g, 70%) as colourless oil. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.12. ^{1}H NMR (δ): 0.98- 2.11 (m, 10H), 2.25 (m, J_{HaHa} = 11.20 Hz, J_{HaHe} = 5.60 Гц , 1H, C$\underline{H}_2$CO$_2$), 3.37 (s, 3H, OCH_3), 4.41 (t, J_{HaHa} = 9.33 Hz, J_{HaHe} = 4.77 Hz, 1H, C$^2\underline{H}$O). ^{13}C NMR (δ): 26.75, 27.46, 28.23, 31.94, 38.18, 40.45, 41.27, 49.08 (OCH_3), 76.53 (C^{1}HO), 108.41 (C^{7a}).

2,2-Ethylenedioxy-3-*endo*-(hydroxymethyl)bicyclo[3.3.1]nonan-7-*endo*-ol (**12**).
Lactone **10** (0.9 g, 4 mmol) was treated with $LiAlH_4$ (0.16 g) in 20 ml of diethyl ether analogously to the method for **2**. After evaporation of organic layer title compound **12** (0.83 g, 91%) was isolated as white crystals. M.p. 161-163 ^{o}C. ^{1}H NMR (δ): 1.19 – 2.41 (m, 12H), 3.55-3.82 (m, 6H, OCH_2CH_2O + CH_2OH), 4.09 (m, 1H, C$\underline{H}$OH), 4.67 (s, 1H, OH). ^{13}C NMR (δ): 23.22, 28.51, 30.28, 35.09, 38.68, 39.28,40.91, 62.68, 62.96, 65,20, 65.60, 113.94 (O-C-O). IR (ν_{max}): 3450 br (OH).

2,2-Ethylenedioxy-3-*endo*-(trityloxymethyl)bicyclo[3.3.1]nonan-7-*endo*-ol (**13**).
Solution of diol **12** (0.5 g, 2.7 mmol) with trityl chloride (0.84 g, 3 mmol) in DMF (2 ml) was mixed with DMAP (4-(dimethylamino)pyridine) (0.02 g) and triethylamine (0.41 g) and stirred at room temperature. In 8 h the reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3x15 ml). The organic layer was washed with brine (2x15 ml), dried with anhydrous Na_2SO_4 and evaporated to dryness. Column chromatography of the residue (ethyl acetate – petroleum ether 1:5) resulted in compound **13** (0.7 g, 55%) as white solid. M. p. 181-184 ^{o}C. ^{1}H NMR (δ): 1.28 – 2.39 (m, 11H), 2.91 (dd, J = 8.7, Hz 1H), 3.21 (dd, J = 8.7 Hz, 1H), 3.48 (m, 1H, C$\underline{H}$CH$_2$O), 3.46 – 3.87 (m, 4H), 4.00 (dd, J = 6.7 Hz, 1H, C$\underline{H}$OH), 7.18-7.43 (m, 15H, arom.). ^{13}C NMR (δ): 23.38-40.35 (skeletal), 63.91 (C^7), 65.22 and 65.61 (OCH_2CH_2O), 76.92 (CH_2OTr), 86.5 (CPh_3), 112.5 (C^2), 126.82-144.41 (arom.). IR (ν_{max}): 1450, 1470, 1600, 3450. MS (m/z, %): 260 (2), 243 (100), 227 (15), 209 (20), 165 (67), 149 (35), 105 (27), 99 (32).
Crystallographic data for ***13***: colorless, transparent crystals were obtained from methanol; $C_{31}H_{34}O_4$, *M* 470.58; space group P1, triclinic, *a* 9.022(2), *b* 9.902(2), *c* 14.799(3) E, *α*

72,46 (3), β 86.17(3), γ 78.30(3), V 1.234(4) Å^3, Z 2, d_{calc} 1.266 Mg/m^3, μ (MoK_α) 0.0820 см$^{-1}$

4-hydroxymethyl-3-(2-(trityloxy)ethoxy)-2-oxatricyclo[4.3.1.0^{3,8}]decane **(15a)** and 3-(2-hydroxyethoxy)-4-trityloxymethyl-2-oxatricyclo[4.3.1.0^{3,8}]decane **(15b)**.

A solution of compound **12** (0.8 g, 3.5 mmol) in diethyl ether (20 ml) was washed with 4N solution of HCl (2x10 ml), dried with anhydrous Na_2SO_4 and evaporated to dryness to give crude 2-{[7-(hydroxymethyl)hexahydro-2,5-methano-1-benzofuran-7a(2*H*)-yl]oxy}ethanol (**14**) (0.76 g, 95%). ^{1}H NMR (δ): 1.16 – 2.29 (m, 12H), 2.40 (m, 1H), 3.55-3.81 (m, 6H, OCH_2CH_2OH + CH_2OH), 4.52 (m, 1H, $C_{(2)}\underline{H}O$). IR (ν_{max}): 3450 br (OH).

The crude diol **14** (0.76 g, 3.3 mmol) was mixed with a solution of trityl chloride (097 g, 3.5 mmol), DMAP (0.02 g) and triethylamine (0.76g, 0.35 mmol) in DMF (1.5 ml). After being stirred for 12 h at room temperature the reaction mixture was treated similarly to the method for compound **13**. Chromatographic purification (ethyl acetate – petroleum ether 1:7) yielded compounds **15a** (0.40 g, 26%) and **15b** (0.49 mg, 32%) as white crystals.

Data for **15a**: M.p. 156-157 ^{o}C. ^{1}H NMR (δ): 1.13 – 2.16 (m, 10H), 2.38 (m, 1H), 3.16-3.28 (m, 3H, CH_2+OH), 3.51(m, 2H), 3.81 (m, 2H), 4.46 (m, 1H, $C^2\underline{H}O$), 7.18-7.43 (m, 15H, arom.). ^{13}C NMR (δ): 27.90, 31.00, 32.05, 38.81, 39.86, 40.12, 40.54, 60.93, 63.11, 64.04, 76.68, 86.54 ($\underline{C}Ph_3$), 110.71 ($\underline{C}O(CH_2)_2$), 126.92, 127.78, 128.65, 143.98. IR (ν_{max}): 1450, 1475, 1600, br 3430. MS (ESI): $[M+Na]^{+\bullet}$ 503.

Data for **15b**: M.p. 124-126 ^{o}C. ^{1}H NMR (δ): 1.40 – 2.31 (m, 12H), 3.12 (m, 1H), 3.33 (m, 1H), 3.43-3.52 (m, 4H), 4.39 (m, 1H, $C^2\underline{H}O$), 7.18-7.43 (m, 15H, arom.). ^{13}C NMR (δ): 28.00, 32.02, 33.87, 38.33, 39.50, 40.08, 40.18; 62.04, 62.99, 65.23, 76.85, 87.02 ($\underline{C}Ph_3$), 108.57 ($\underline{C}O(CH_2)_2$), 126.77, 127.60, 128.59, 144.54. IR (ν_{max}): 1450, 1470, 1610, br 3430.

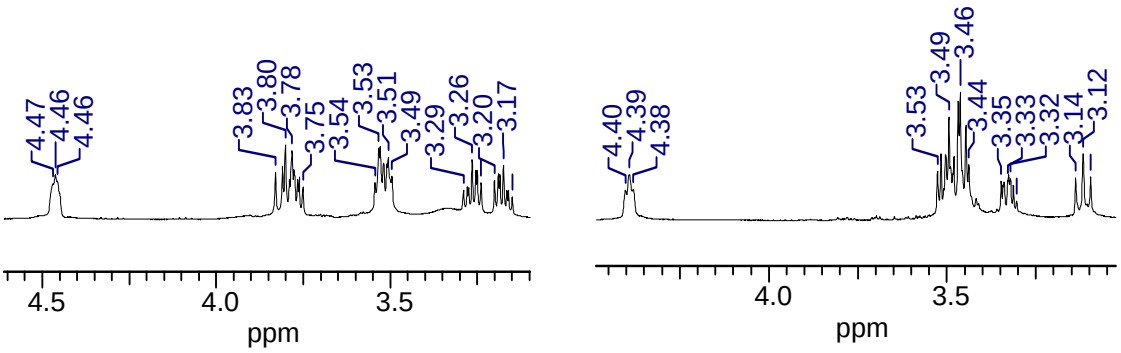


Figure 2. Fragments of ^{1}H NMR spectra of compounds **15a** and **15b**

For compound **15a** in ^{1}H NMR spectra with application of double resonance method the interaction of protons with signals at 3.49-3.54 ppm (2H) and 3.15-3.29 ppm (2H) (Fig. 19) was observed. Therefore these signals belong to protons of OCH_2CH_2O group. Evidently methylene fragment bound with trityl substitute has proton signals in stronger field (3.15-3.29 ppm).

In ^{1}H NMR spectra of compound **15b** signals at 3.12 and 3.33 ppm by analogy with compound **13** can be referred to geminal protons of $C\underline{H_2}OTr$ moiety.

1. J. Hlavaty, L. Vodicka and J. Triska, *Sb. Vscht Praze.*, 1984, **49**, 205.
2. J. G. Henkel and J. H. Spector, *J. Org. Chem.,* 1983, **48**, 3657.