New Constrained Amines in a Bicyclo[2.2.1]Heptane Skeleton

CONSTANTIN I. TANASE[1]*, CONSTANTIN DRAGHICI[2], CATALINA NEGUT[1], LUCIA PINTILIE[1]

[1] National Institute for Chemical-Pharmaceutical Research and Development, 112 Vitan Av., 031299 Bucharest, Romania

[2] Organic Chemistry Center C.D.Nenitescu, 202 B Splaiul Independentei, 060023, Bucharest, Romania

*In this paper we present an efficient procedure for obtaining ether-protected bicyclo[2.2.1]heptane amines in six steps, from an optically active keto-alcohol norbornane compound, for building the heterocyclic bases of pyrimidine and purine constrained nucleosides. Trityl as protecting group makes it possible to isolate 5-endo-compounds in pure form by selective crystallization, and to isolate the intermediates in the next 3 steps of the reaction by crystallization. With TBDMS, all compounds were obtained as oil. The direct selective reduction of the keto-alcohol norbornane compound gave the pure 5-endo-diol **4d** in high yield, which was then selectively protected at the primary hydroxyl with a trityl group; the next steps are similar for obtaining the trityl-protected bicyclo[2.2.1]heptane amine. The azide intermediates are valuable intermediates for click chemistry.*

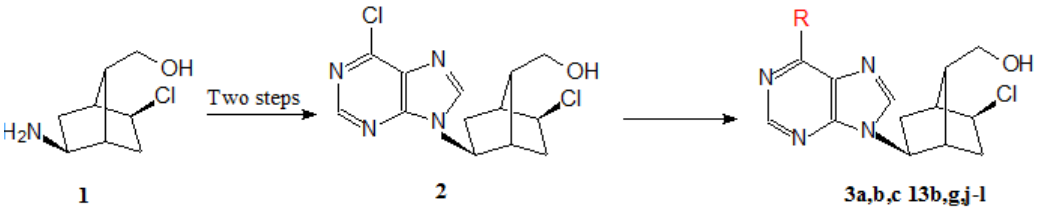
Keywords: selective $NaBH_4$ reduction; bicyclo[2.2.1]heptane amines; bicyclo[2.2.1]heptane azides; mesyl substitution; azide reduction

In the previous papers [1,2] we presented the synthesis of new constrained carbocyclic nucleosides based on a hydroxyl-functionalized bicyclo[2.2.1]heptane skeleton as sugar moiety and pyrimidines as heterocyclic bases which were tested for their anticancer activity [1]. During our studies we obtained also N^1,O^2- or O^2,O^4-nucleoside analogues by Mitsunobu reaction with the same bicyclo[2.2.1]heptane fragment and two O-alkylated nucleosides with thymine and 5-fluorouracil, which exhibited mainly a cytostatic activity in Jurkat lymphoblasts and U937 monocytic blasts [5]. Then we synthesized new N^6-substituted adenine nucleosides [3,4] and pyrimidine nucleosides [4] by building the purine and pyrimidine ring on an optically active 5-*exo*-amine bicyclo[2.2.1]heptane intermediate, **1**, followed in the adenine analogues, by substitution of the 6-chloro purine with selected amines (scheme 1). Some of the analogues were tested at the National Cancer Institute, Bethesda-USA at a single high dose (10^{-5} M) in the full NCI 60 human tumor cell screen panel, and a few nucleoside analogues proved to have anticancer activity: compound **3b** [4] [with 6-(4-methoxy-phenethyl)amino group] was more active, with a growth inhibition of ~ 66% on breast cancer-47D and 56.7% on Non-Small Cell Lung Cancer NCI-H522 cell lines, followed by 6-phenethyl analogue, **13g** [3].

All compounds were tested for their anti-viral activity against clinically important viruses: influenza viruses, herpesviruses, enteroviruses and coxsackievirus B4, compounds **13a** and **13d** being *the most prospective for their antiviral activity against influenza virus due to their low toxicity and high activity* [4] and *compound **3c** against coxsackievirus B4, due to its impressive EC_{50} of 0.6μg/mL and of its selectivity index SI of 141* [4].

A norbornane skeleton as sugar moiety was used for obtaining new constrained nucleoside analogues of type **I** [6], **II** [7], **III**[X], **IV** [8,9] with antiviral activity against coxsackie viruses, most active being compound **IV**, with an EC_{50} = 0.8 ÷ 5.4μM [8] against coxsackievirus CVB3 (Compound **IV** also has antileukemic activity [9]) (fig. 1).

The results obtained, especially for our compound **3c** with an EC_{50} close to that of most active compounds with a norbornane skeleton as sugar moiety, motivated us to



Scheme 1. Synthesis from amine **1** of carbocyclic nucleoside analogues: **3a** (R = NH_2), **3b** (R = 6-(4-methoxy-phenethyl), **3c** (R = phenyl-alaninol), and **13b** (R = dimethylamino), **13g** (R = 6-phenethylamino), **13j** (R = N-methyl-piperazine), **13l** (R = morpholine) (the number is from previous papers 4,3])

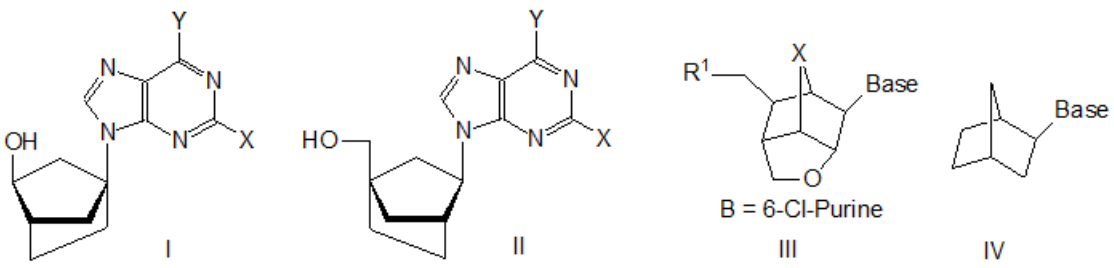


Fig.. 1. Norbornane nucleoside analogues active against coxsackie viruses

* email: cvtanase@gmail.com.: Phone: +40-21-321.21.17

continue the studies in the field and to obtain the starting optically active 5-*exo*-amine bicyclo[2.2.1]heptane intermediate, **1** (scheme 1), not only with the free hydroxy-methyl group, but also protected with an ether type protected group. Having an ether type protected group makes some steps of the reaction chain easier to conduct and simplifies the work-up for the isolation of the compounds, which in turn are also easier to deprotect in the final steps.

In the previous paper [3] we obtained amine **1** by an efficient procedure starting from the optically active compound **2** (scheme 2), a by-product in the sequence for the synthesis of prostaglandins with the natural configuration, by using a benzoate group for the protection of the *exo*-cyclic hydroxy-methyl group and in the final step of the sequence we deprotect this group to amine **1**.

We find it more convenient to have an ether type group for the protection of all intermediates and of amine **1** with TBDMS and trityl groups, obtained from cheap reagents and with high yields, instead of the benzoate group which we previously used, and our results in this new direction are presented below.

Experimental part

IR spectra were recorded on a FT-IR-100 Perkin Elmer spectrometer, in solid phase by ATR and frequencies are expressed in cm^{-1}, with the following abbreviations: w = weak, m = medium, s = strong, v = very, br = broad. ^{1}H-NMR and ^{13}CNMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C), chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D-NMR and decoupling were done for correct assignment of NMR signals. The numbering of the atoms in the compounds is presented in scheme 1. Progress of the reaction was monitored by TLC on Merck silica gel 60 plates (Merck) eluted with the solvent systems: Ethyl acetate-hexane-acetic acid, 5:4:0.1 (I), hexane-ethyl acetate- acetic acid, 5:2:0.1 (II), dichloromethane-methanol, 9:1 (III), benzene (IV), dichloromethane-methanol, 95:5 (V). Spots were developed with iodine, sulfuric acid (15% in ethanol) or 2,4-dinitrophenylhydrazine reagent. In the present paper, the pure enantiomer compound **2** was used.

1.Synthesis of (1S,4S,5S,7R)-7-(((tert- butyldimethyl-silyl)oxy)methyl)-5-chlorobicyclo [2.2.1]heptan-2-one 3a

The compound **2**, (1S,4S,5S,7R)-5-chloro-7-(hydroxy-methyl)bicyclo[2.2.1]heptan-2-one, (116.5 g, 0.667 mol) with $[\alpha]_D$ = -40.5 °(1% in MeOH) [2] and imidazole (90.8 g, 1.334 mol) were dissolved in anh. THF (1L), *tert*-butyldimethylsilyl chloride (TBDMSCl) (110.6 g, 0.7337 mol) was added at room temperature (r.t.) in portions during 45 min. The reaction mixture was stirred for an additional 2h, monitoring the reaction by TLC (I, $R_{f\,2}$ = 0.35, $R_{f\,3a}$ = 0.72). The imidazolium hydrochloride was filtered off, washed in portions with THF (400 mL), the filtrate was concentrated under reduced pressure, the residue taken up in toluene (800 mL), the solution washed with 5% oxalic acid (500 mL), 10% $KHCO_3$ (500 mL), brine (400 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure, resulting 208 g of crude product **3a** as an oil, which crystallized in time in the refrigerator. The compound was recrystallized from 600 mL hexane and 50 mL ethyl acetate, resulting 153.06 g (in 3 fractions) (mother liquors were purified by low-pressure chromatography (LPC), resulting 30.95 g **3a**; total yield 95.5%) (1R,4R,5R,7R)-7-(((tert-butyldimethyl-silyl)oxy)methyl)-5-chlorobicyclo[2.2.1]heptan-2-one, $[\alpha]_D$ = -35.3 °(1% in $CHCl_3$), $[\alpha]_D$ = -40.7°(1% in THF), IR: 1741s, 1471m, 1255m, 1070vs, 833vs, 771vs, 721m, ^{1}H-NMR ($CDCl_3$, *d* ppm, *J* Hz): 4.01, (d, 1H, H-2, 3.9, 7.5), 4.01 (dd, 1H, H-8, 6.8, 10.8), 3.88 (dd, 1H, H-8, 5.8, 10.8), 2.79 (d, 1H, H-1, 5.0), 2.73 (m, 1H, H-4), 2.30-2.26 (m, 4H, 2H-3, H-6, H-7), 1.85 (d, 1H, H-6, 18.3), 0.88 (s, 9H, CH_3C), -0.05 (s, 6H, CH_3Si), ^{13}C-NMR-300MHz ($CDCl_3$, δ ppm): 213.92 (C-5), 60.28 (C-8), 57.29 (C-2), 52.60 (C-1), 51.91 (C-7), 46.52 (C-4), 45.97 (C-6), 34.37 (C-3), 25.94 (CH_3C), 18.34 (CH_3C), -5.20, -5.26 (CH_3Si).

2.Synthesis of (1S,4S,5S,7R)-5-chloro-7((trityloxy) methyl)bicycl[2.2.1]heptan-2-one, 3b

Compound **2** (82 g, 0.475 mol) was dissolved in pyridine (220 mL) (or by adding also 220 mL toluene), and trityl chloride (158.9 g, 0.57mol) was added under stirring at room temperature (r.t.) for 2 h, stirred over weekend, while monitoring the end of the reaction by TLC (I, $R_{f\,2}$ = 0.37, $R_{f\,3b}$ = 0.75; II, $R_{f\,2}$ = 0.15, $R_{f\,3b}$ = 0.58). Pyridine was distilled under reduced pressure, the residue was taken up in toluene-hexane (2:1, 700 mL), poured under mechanical stirring on crushed ice and 20% $KHCO_3$ (400 mL), stirred for 1h, the organic phase was washed with 20% $KHCO_3$ (300 mL), brine (200 mL), dried (Na_2SO_4), filtered and concentrated to dryness (Aqueous phases were extracted with 300 mL solvent system). The crude product was dissolved in methanol (500 mL) and crystallized overnight to obtain 83.4 g of pure product **3b**, mp (softens at 96.9 °C) 112.8-114.9°C, $[\alpha]_D$ = - 38.6° (1% in $CHCl_3$), IR: 3083w, 3058w, 3023w, 2938w, 2883w, 1750vs, 1489m, 1445m, 1399w, 1316w, 1277w, 1179w, 1147w, 1122w, 1089w, 1063m, 1029w, 971w, 899w, 755s, 701s, 633m, ^{1}H-NMR ($CDCl_3$, *d* ppm, *J* Hz): 7.28 (d, 6H, H-*o*, 7.2), 7.33-7.20 (m, 9H, 6H-*m*, 3H-*p*), 3.88 (dd, 1H, H-2, 4.1, 7.6), 3.53 (t, 1H, H-8, 9.7), 3.41 (dd, 1H, H-8, 5.0, 9.7), 2.77 (d, 1H, H-1, 3.9), 2.70 (δ, 1H, H-4, 4.2), 2.43 (dd, 1H, H-7, 5.0, 8.9), 2.21 (dd, 1H, H-6, 4.7, 18.1), 2.10 (dd, 1H, H-3, 8.0, 15.0), 1.84 (d, 1H, H-6, 18.1), 1.79 (dt, 1H, H-3, 4.2, 15.0), ^{13}C-NMR-300MHz ($CDCl_3$, δ ppm): 213.62 (C-5), 144.04 (C_q), 128.73 (C-*m*), 127.90 (C-*o*), 127.13 (C-*p*), 86.69 (Cq-Tr), 60.61 (C-8), 57.71 (C-2), 53.51 (C-1), 49.29 (C-7), 46.93 (C-4), 45.91 (C-6), 34.16 (C-3). By concentration of the mother liquors in 3 portions, 80 g of pure product (total yield 83.2%) crystallized. The mother liquors from other batches were purified by pressure chromatography (hexane-ethyl acetate, 5:2).

3. Synthesis of (1S,2R,4S,5S,7R)-7-(((tert-butyldimethyl silyl)oxy)methyl)-5 chlorobicyclo[2.2.1]heptan-2-ol, 4a and 5a

Compound **3a** (181.6 g, ~0.594 mol) was dissolved in THF (1.5 L) and methanol (1.5 L) in a KPG, the solution was cooled to -60°C, after which a solution of $NaBH_4$ (22.7 g, 0.7 mol) in 0ÚC cooled water (250 mL) was dropwise added under mechanical stirring for 2.5 h. TLC (I, $R_{f\,3a}$ = 0.72, $R_{f\,4a\,+\,5a}$ = = 0.65) showed that the reaction ended and acetic acid (55 mL) was carefully added to decompose the hydride in excess. The KPG was removed from the cooling bath, the reaction mixture was stirred for 1 h, concentrated under reduced pressure (t_{bath} < 35°C) to about 300 mL, diluted with toluene (700 mL), washed with water (1.5 L), 20% $KHCO_3$ (500 mL), brine (500 mL) (the waters were extracted with 500 mL toluene), dried (Na_2SO_4), filtered, concentrated under reduced pressure, co-evaporated with toluene, resulting 185.1 g of crude product as an oil, as a mixture of *endo*-**4a** and *exo*-**5a** alcohols, in a ratio of **1**:**2** of >9:1 (determined by NMR), IR: 3333br w, 2954m, 2929m, 2857m, 1472m, 1255s, 1080s, 1004m, 836vs, 776s, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 4.12 (dddd, 1H, H-5-*exo*, 1.4, 3.0, 4.4, 9.6), 3.90 (ddd, 1H, H-2,

1.4, 4.9, 9.9), 3.90 (dd, 1H, H-8, 9.1, 10.4), 3.72 (dd, 1H, H-8, 5.5, 10.4), 2.66 (dd, 1H, H-6, 8.0, 14.3), 2.36 (t, 1H, H-4, 4.4), 2.25 (d, 1H, H-1, 4.9), 2.28 (+TFA, br s, 1H, H-7), 2.03 (ddd, 1H, H-6, 4.9, 9.9, 13.5), 1.84 (m, 1H, H-3), 1.83 (dt, 1H, H-6, 4.4, 14.3), 0.82 (s, 9H, CH_3C), -0.02 (s, 6H, CH_3Si), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 70.27 (C-5), 61.02 (C-8), 60.79 (C-2), 52.17 (C-7), 47.91 (C-1), 45.00 (C-4), 39.86 (C-6), 32.56 (C-3), 26.02 (CH_3C), 18.38 (CH_3C), -5.14, -5.19 (CH_3Si).

The alcohol isomers were used as so in the next mesylation reaction

4. Synthesis of (1S,2R,4S,5S,7R)-5-chloro-7-((trityloxy)methyl)bicyclo[2.2.1]heptan-2-ol, 4b

The compound **3b** (148g, 0.357 mol) was reduced similarly in THF (1.5 L) and methanol (1 L) with a solution of $NaBH_4$ (20.28 g, 0.536 mol) in cooled water (250 mL); TLC (I, $R_{f\,3b}$ = 0.42, $R_{f\,4b+5b}$ = 0.20). The crude product was extracted with warm ethyl acetate (1L + 2 x 0.5 L), filtered, concentrated until crystallization started, re-dissolved, filtered and crystallized, resulting 78.69 g **4b** as prisms, mp 177.5-181.5°C, $[\alpha]_D$ = -15.8 ° (1% in $CHCl_3$), IR: 3356brw, 2965m, 2159s, 2029m, 1977m, 1489m, 1448m, 1058s, 1031m, 1001m, 899m, 760m, 745s, 704vs, 695vs, 632s, ^{1}H-NMR-400MHz ($CDCl_3$, δ ppm, J Hz): 7.45 (d, 6H, H-*o*, 7.3), 7.31-7.18 (m, 9H, 6H-*m*, 3H-*p*), 4.20 (m, 1H, H-5-*exo*, 9.8), 3.84 (dd, 1H, H-2, 4.1, 8.0), 3.47 (t, 1H, H-8, 9.6), 3.28 (dd, 1H, H-8, 4.9, 9.6), 2.58 (dd, 1H, H-3, 8.0, 14.5), 2.49 (t, 1H, H-4, 4.1), 2.26 (d, 1H, H-1, 5.2), 2.05 (dd, 1H, H-7, 4.9, 9.9), 2.08 (ddd, 1H, H-6, 5.2, 9.9, 13.7), 1.52 (dt, 1H, H-3, 3.7, 14.5), 0.81 (dd, 1H, H-6, 2.9, 13.7), ^{13}C-NMR-75 MHz ($CDCl_3$, δppm): 144.40 (C_q), 128.84 (C-*m*), 127.83 (C-*o*), 127.02 (C-*p*), 86.43 (Cq-Tr), 70.45 (C-5), 61.40 (C-8), 60.51 (C-2), 49.46 (C-**7**), 48.36 (C-**1**), 45.58 (C-**4**), 39.87 (C-**6**), 32.43 (C-**3**).

Mother liquors were concentrated, purified by LPC, resulting 14.64 g of compound **4b** (III, $R_{f\,3b}$ = 0.43) and 17.59 g as mixture of **4b** and **5b** (III, $R_{f\,3b}$ = 0.35)

5. The reduction of ketoalcohol 2 to diol 4d, (1S, 2R, 4S, 5S,7R)-5-chloro-7-(hydroxymethyl) bicyclo[2.2.1]heptan-2-ol

Compound **2** (100 g, 0.5726mol) was dissolved in methanol (1L), cooled to –50°C and reduced similarly with a solution of $NaBH_4$ (23.8 g, ~0.63 mol) in water (300 mL) in 90 min., TLC (I, $R_{f\,1}$ = 0.42, $R_{f\,3+4}$ = 0.20). AcOH (55 mL) was added dropwise, stirred for 30 min., then solid Na_2CO_3 (30 g, 0.283 mol) was added in portions to pH 7-7.5, methanol was distilled under reduced pressure and the concentrate extracted with warm (60°C) ethyl acetate (1 L + 2 x 0.5 L), filtered off and the filtrate was concentrated until the diol began to crystallize. The product was warmed until everything dissolved, then filtered and left to crystallize at r.t. in prisms, filtered again, resulting 78.69 g of pure diol **4d** ($R_{f\,4d}$ = 0.43 in system I), mp 115.2-117.3°C, $[\alpha]_D$ = 12.8 Ú(1% in acetone), $[\alpha]_D$ = 11.4°(1% in MeOH), IR: 3650w, 3240w, 2518m, 1348m, 1305m, 1080s, 1001s, 874s, 679s, ^{1}H-NMR-300MHz (DMSO-d6, δppm, *J* Hz): 4.69 (d, 1H, OH, 3.8), 4.43 (t, 1H, OH, 8-OH, 5.2), 4.00 (dd, 1H, H-5, 3.8, 8.0), 3.94 (dd, 1H, H-2, 4.1, 8.0), 3.71 (ddd, 1H, H-8, 5.2, 9.1, 11.0), 3.56 (dt, 1H, H-8, 5.2, 11.0), 2.63 (dd, 1H, H-3, 8.0, 14.0), 2.26 (t, 1H, H-4, 4.1), 2.20 (d, 1H, H-1, 5.2), 1.97 (ddd, 1H, H-6, 5.2, 8.0, 13.2), 1.76 (dd, 1H, H-7, 5.2, 9.1), 1.75 (dt, 1H, H-3, 4.1, 14.0), 0.75 (dd, 1H, H-6, 3.2, 13.2), ^{13}C-NMR-75 MHz (DMSO-d6, δppm): 68.66 (C-5), 61.68 (C-2), 59.15 (C-8), 51.76 (C-**7**), 47.69 (C-**1**), 44.81 (C-**4**), 39.45 (C-**6**), 32.65 (C-**3**).

The mother liquors were concentrated and purified by LPC, resulting 13.64 g of pure diol **4d** (total yield 91.3%) and a fraction (9.1 g) containing alcohol **4d** and alcohol **5d** ($R_{f\,5d}$ = 0.35).

6. Synthesis of (1S,2R,4S,5S,7R)-5-chloro-7-((trityloxy) methyl)bicyclo[2.2.1]heptan-2-ol, 4b, from diol 4d

Diol **4d** (12.22 g, 70 mmol) wa selectively tritylated in 100 mL pyridine with trityl chloride (29.27 g, 105 mmol) as in ex. 2 [TLC (I, $R_{f\,4d}$ = 0.12, $R_{f\,4b}$ = 0.54; II, $R_{f\,4d}$ = 0.10, $R_{f\,4d}$ = 0.43). The crude product was purified by LPC (hexanes-ethyl acetate, 5:2), resulting 28.94 g of pure **4d** as an oil, which in time became glassy, with the same NMR: ^{1}H-NMR-300MHz ($CDCl_3$, δppm, *J* Hz): 7.44 (d, 6H, H-*o*, 7.4), 7.31-7.20 (m, 9H, 6H-*m*, 3H-*p*), 4.22 (m, 1H, H-5α, 9.8), 3.84 (dd, 1H, H-2, 3.7, 7.8), 3.48 (t, 1H, H-8, 9.6), 3.29 (dd, 1H, H-8, 5.1, 9.6), 2.58 (dd, 1H, H-3, 8.0, 14.5), 2.49 (t, 1H, H-4, 3.9), 2.26 (d, 1H, H-1, 4.7), 2.12-2.03 (m, 2H, H-6-7), 1.53 (dt, 1H, H-3, 3.7, 14.5), 0.82 (dd, 1H, H-6, 2.9, 13.7), ^{13}C-NMR-75 MHz ($CDCl_3$,δ ppm): 144.31 (C_q), 128.74 (C-*m*), 127.70 (C-*o*), 126.90 (C-*p*), 86.35 (Cq-Tr), 70.36 (C-5), 61.31 (C-8), 60.39 (C-2), 49.39 (CH, C-1), 48.27 (C-7), 45.50 (C-4), 39.81 (C-6), 32.52 (C-3).

7. Synthesis of (1S,2R,4S,5S,7R)-7-(((tert-butyl dimethylsilyl)oxy)methyl)-5-chlorobicyclo[2.2.1] heptan-2-yl methanesulfonate, 6a + 7b

A mixture of alcohols **4a** and **5a** (80.92 g, 0.278 mol), obtained above, was dissolved in pyridine (150 mL) and anh. toluene (300 mL), the solution was cooled on an ice-bath, methansulfonyl chloride (32.6 mL, 0.417 mol) was added dropwise for 1.5 h under stirring and after 2h TLC (I, $R_{f\,4a+5a}$ = 0.65, $R_{f\,6a+7a}$ = 0.71) still showed the presence of the starting alcohols. An additional methansulfonyl chloride (2.2 mL) was added, the mixture was stirred overnight and poured in portions, under efficient mechanical stirring, into 20% $KHCO_3$ soln. (300 mL) and crushed ice. The stirring was continued for 1h, phases were separated, organic phase was washed with 20% $KHCO_3$ soln. (250 mL) (the aqueous solutions were extracted with 250 mL toluene), dried (Na_2SO_4), filtered off, concentrated under reduced pressure, co-evaporated with toluene, to give 97.9 g of crude product as an oil. The compound was crystallized from hexanes, resulting 80.5 g (in 3 seccesive crystallizations) of **6a**, mp 51.5-52.6°C, $[\alpha]_D$= 10.7°(1% in THF), ^{1}H-NMR-300 MHz ($CDCl_3$, δppm, *J* Hz): 4.93 (dddd, 1H, H_5-*exo*, 1.6, 2.7, 4.4, 9.9), 3.97 (dd, 1H, H-8, 9.1, 10.7), 3.97 (ddd, 1H, H-2, 1.1, 4.1, 8.0), 3.80 (dd, 1H, H-8, 5.5, 10.7), 2.99 (s, 3H, CH_3), 2.74 (dt, 1H, H-4, 1.1, 4.4), 2.67 (dd, 1H, H-3, 8.0, 14.8), 2.41 (d, 1H, H-1, 4.9), 2.25 (ddd, 1H, H-6, 4.9, 9.9, 14.3), 2.02 (dt, 1H, H-3, 4.4, 14.8), 1.97 (dd, 1H, H-7, 5.5, 9.1), 1.26 (dd, 1H, H-6, 3.0, 14.3), 0.89 (s, 9H, CH_3C), 0.01, -0.04, (s, 6H, CH_3Si), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 79.32 (CH, C-5), 60.50 (C-8), 59.58 (C-2), 51.75 (C-7), 46.98 (C-1), 44.02 (C-4), 38.40 (S-CH_3), 37.69 (C-6), 32.21 (C-3), 26.09 (CH_3C), 18.44 (CH_3C), -5.14, -5.19 (CH_3Si).

8. Synthesis of (1S,2R,4S,5S,7R)-5-chloro-7-((trityloxy) methyl)bicyclo[2.2.1]heptan-2-yl methanesulfonate, 6b

The compound **4b** (43.36 g, 014 mol) with the minor isomer **5b** were mesylated, as previously shown, in pyridine (55 mL) and toluene (300 mL) with methansulfonyl chloride (12.1 mL, 17.9 g, 0.156 mol), monitoring the end of the reaction by TLC (IV, $R_{f\,4b+5b}$ = 0.26, $R_{f\,6b+7b}$ = 0.46). The reaction mixture was poured over 20% $KHCO_3$ soln. (250 mL) with ice (400 g) (sometimes, the bulk of the product crystallized and was filtered off), organic phase was washed with 20% $KHCO_3$ soln. (250 mL), brine (250 mL) (the aqueous phases were extracted with 3´200 mL

toluene), dried, concentrated to ~150 mL, and crystallized at r.t., resulting 41.44 g (80.5%) of pure compound **6b**, mp 96.9-97.9°C, $[\alpha]_D$ = - 2.8°(1% in THF), IR: 2953m, 2929m, 1881w, 2856w, 1471w, 1357s, 1341s, 1251m, 1173s, 1078vs, 967vs, 832vs, 780vs, 677s, 663s, 523vs, ^{1}H-NMR-300 MHz ($CDCl_3$, δ, ppm, *J* Hz): 7.46 (d, 6H, H-*o*, 7.4), 7.34-7.17 (m, 9H, 6H-*m*, 3H-*p*), 4.99 (dddd, 1H, H-5α, 1.4, 3.0, 4.9, 9.9), 3.84 (dd, 1H, H-2, 4.4, 8.0), 3.50 (t, 1H, H-8, 9.6), 3.35 (dd, 1H, H-8, 4.9, 9.6), 2.98 (s, 3H, CH_3), 2.80 (t, 1H, H-4, 4.4), 2.52 (dd, 1H, H-3, 8.0, 15.1), 2.37 (d, 1H, H-1, 4.9), 2.24 (ddd, 1H, H-6, 4.9, 9.9, 14.3), 2.09 (dd, 1H, H-7, 5.2, 9.6), 1.62 (dt, 1H, H-3, 4.4, 15.1), 1.23 (dd, 1H, H-6, 3.0, 14.3), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 144.18 (C_q), 128.79 (C-*m*), 127.91 (C-*o*), 127.13 (C-*p*), 86.64 (Cq-Tr), 79.28 (C-5), 60.75 (C-8), 59.19 (C-2), 48.97 (C-**7**), 47.34 (C-**1**), 44.46 (C-**4**), 38.39 (S-CH_3), 37.56 (C-**6**), 32.96 (C-**3**). The mother solutions were concentrated and purified by LPC.

9. Synthesis of (((1S,2S,4S,5S,7R)-2-azido-5-chloro-bicyclo[2.2.1]heptan-7-yl)methoxy)(tert-butyl) dimethylsilane, 8a

The crystallized compound 5-*endo*-O-Ms **6a** (22.14 g, 60 mmol) and NaN_3 (23.4 g, 0.36 mol) in anh. DMF (180 mL) were stirred at 120 ± 10°C on an oil bath for 24 h, monitoring the end of reaction by TLC (II, $R_{f\ 8a}$ ~ 0.60; An aliquot was diluted with ethyl acetate and washed with water, for TLC). DMF was distilled under reduced pressure, the residue taken in ethyl acetate (200 mL), the solution washed with water (200 mL), brine (200 mL) (the aqueous phases were extracted with 2 x 200 mL ethyl acetate), dried (Na_2SO_4), filtered off and concentrated under reduced pressure. The crude product (20.96 g) was purified by LPC (eluent, hexanes-ethyl acetate, 5:1), resulting 13.9 g of pure azide **8a** as an oil (73.3%), $[\alpha]_D$ = -13.4°(1% in THF), IR: 2954m, 2929m, 2856m, 2101s, 1472m, 1338w, 1252s, 1105s, 1079s, 838s, 777s, ^{1}H-NMR-300 MHz ($CDCl_3$, δppm, *J* Hz): 3.88 (dd, 1H, H-8, 8.7, 10.8), 3.80 (dd, 1H, H-8, 6.3, 10.8), 3.74 (ddd, 1H, H-2, 1.3, 4.2), 3.41 (dd, 1H, H-5, 3.7, 7.3), 2.38-2.37 (m, 2H, H-1, H-4), 2.13 (br t, 1H, H-7, 7.5), 2.01 (dt, 1H, H-3, 4.4, 15.2), 1.92 (dd, 1H, H-3, 8.4, 15.2), 1.57 (dd, 1H, H-6, 7.6, 13.6), 1.50 (1H, H-6, 4.6, 13.6), ^{13}C-NMR-75MHz ($CDCl_3$, δppm): 62.67 (C-2), 60.64 (C-8), 59.66 (C-5), 50.38 (C-7), 46.38 (C-1), 44.08 (C-4), 37.86 (C-3), 37.71 (C-6), 26.10 (CH_3C), 18.44 (C-CH_3), -5.04 (CH_3Si). and 2.3 g (19.0%) of pure un-protected azide, **8d**, with the same characteristic data as mentioned in the previous paper [4].

10. Synthesis of (1S,2S,4S,5S,7R)-2-azido-5-chloro-7-((trityloxy)methyl)bicyclo[2.2.1]heptane, 7b

The compound **6b (**24.85 g, 50 mmol) was reacted with NaN_3 (13 g, 200 mmol) in DMF (170 mL) as previously [120°C, 24 h, TLC (II, $R_{f\ 6b}$ = 0.36, $R_{f\ 8b}$ = 0.76), the extraction of the product was performed with toluene]. The crude product (20.5 g), crystallized in mass, was dissolved in hot toluene and a little isopropanol, decolorated with activated charcoal, and crystallized overnight, resulting 9.28 of pure product **8b** [the mother liquors were concentrated and purified by LPC (hexanes-ethyl acetate, 5:1), resulting a pure fraction of 9.5 g of **8b**, total yield, 83.9%], mp 118.3-119.8 °C, $[\alpha]_D$ = -21.8 °(1% in $CHCl_3$), $[\alpha]_D$ = -20.9 °(1% in THF), IR: 2974m, 2948m, 2895m, 2081vs (N_3), 1492m, 1446m, 1335m, 1268m, 1061s, 1034m, 972m, 755s, 696s, 633s, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.48 (d, 6H, H-*o*, 8.0), 7.32-7.22 (m, 9H, 6H-*m*, 3H-*p*), 3.64 (dd, 1H, H-2, 4.1, 8.0), 3.44-3.36 (m, 3H, 2H-8, H-5), 2.46 (d, 1H, H-4, 4.7), 2.37-2.32 (m, 2H, H-1, H-7), 1.80 (dd, 1H, H-3, 8.0, 14.8), 1.62 (dd, 1H, H-3, 4.4, 14.8), 1.60-1.56 (m, 2H, H-6), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 144.34 (C_1-Ar), 128.84 (C-*m*), 127.86 (C-*o*), 127.02 (C-*p*), 86.48 (Cq-Tr), 62.58 (C-5), 60.88 (C-8), 59.24 (C-2), 47.53 (C-7), 46.71 (C-1), 44.54 (C-4), 37.64, 37.54 (C-3, C-6).

11. Deprotection of the TBDMS group of azide 8a to azide 8d, ((1S,2S,4S,5S,7R)-2-azido-5-chlorobicyclo [2.2.1] heptan-7-yl)methanol

Azide **8a** (13.58 g, 43 mmol) in methanol (80 mL) and 48% HF (10 mL) was stirred at r.t overnight, monitoring the end of the reaction by TLC (II, $R_{f\ 8a}$ = 0.65, $R_{f\ 8d}$ = 0.32). The reaction mixture was neutralized with solid $NaHCO_3$, concentrated under reduced pressure and the residue was purified by LPC (eluent, hexanes-ethyl acetate, 5:1), resulting 8.06 g (93.0%) of pure azide **8d**.

12. Deprotection of the trityl group of azide 8b to azide 8d

Trityl azide 8b (1.22 g, 2.75 mmol) was dissolved in methanol (30 mL) and chloroform (30 mL), Dowex 50W x2 ion exchange resin (washed with methanol) (0.55 g) was added and refluxed until the end of the reaction was determined by TLC (II, $R_{f\ 8b}$ = 0.76, $R_{f\ 8d}$ = 0.32). The solution was cooled to r.t., the resin was filtered off, washed with methanol, the filtrate concentrated and purified as before, resulting 502 mg (90.5%) azide **8d** [4].

13. Synthesis of (1S,2S,4S,5S,7R)-5-cloro-7-(((ter-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]heptan-2-amine, 9aTBDMS-azide 8a (5.61g, 17.7 mmol) was dissolved in methanol (100 mL), the catalyst (10-20% $Pd(OH)_2$/C, 212 mg) was added and hydrogenation was done by bubbling hydrogen in the solution, under stirring, monitoring the endo of the reaction by TLC (dichlormetane-methanol, 95:5, $R_{f\ 9a}$ = 0.76, $R_{f\ 9a}$ = 0.06). The catalyst was filtered off, washed with methanol and the filtrate concentrated. The crude product was purified by LPC (eluent: heptane-ethyl acetate, 5:2, then dichloromethane-methanol, 9:1), resulting 3.5 g (68.2%) of pure amine **9a** as an oil [as hydrochloride salt, mp 202.0-205.3 (dec.)], $[\alpha]_D$ = 10.2°(1% in THF), IR: 3229w, 2953w, 2929w, 2956w, 1466w, 1279w, 1253w, 1110w, 1065m, 834s, 788s, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 8.20 (NH_3^+, for hydrochloride), 3.95 (brt, 1H, 10.5, H-8), 3.89 (dd, 1H, 10.5, 7.1 H-8), 3.80 (dd, 1H, 7.1, 4.4 H-2), 3.14 (t, 1H, 5.8, H-5), 2.60 (brs, m 1H, H-1), 2.51 (br s, 1H, H-4), 2.45 (t, 1H, H-7, 7.3), 2.09 (m, 2H, H-3), 1.80 (m, 2H, H-6), ^{13}C-NMR-75MHz ($CDCl_3$, δppm): 60.41 (C-8), 58.50 (C-2), 52.65 (C-5), 49.72 (C-7), 46.76 (C-1), 43.01 (C-4), 38.45 (C-3), 36.55 (C-6), 26.25 (CH_3C), 18.56 (CCH_3), -4.96 (CH_3Si), and 1.08 g (20.8%) unprotected amine **1**.

14.Synthesis of (1S,2S,4S,5S,7R)-5-chloro-7-((trityloxy) methyl)bicyclo[2.2.1]heptan-2-amine, 9b

Trityl-azide **8b** (2.25 g, 5 mmol) was disolved in pyridine (20 mL), Ph_3P (10 mmol, 2.62 g) was added and stirred at r.t. monitoring the end of the reaction by TLC (II, ($R_{f\ 8b}$ = 0.76, $R_{f\ 9b}$ = near start point). After 7 h, 25% ammonia (7 mL) was added and the solution stirred overnight [TLC (dichloromethane-methanol, 4:1, $R_{f\ 9b}$ = 0.39, comparatively, the amine **1** has $R_{f\ 1}$ = 0.08)]. The volatiles were distilled off under reduced pressure, the residue was purified by LPC (dichloromethane-methanol, 4:1), resulting 1.92 g (92%) amine **9b**, as an oil [the hydrochloride has mp 233.2-234.5°C(desc.)], $[\alpha]_D$ = -10.6°(1% in THF), IR: 3060w, 3024w, 2973w, 2948w, 2896w, 1445m, 1336m, 1267m, 1062s, 973m, 756s, 697vs, ^{1}H-NMR-300 MHz (DMSO-d_6, δ ppm, *J* Hz): 8.28 (NH_3^+, for hydrochloride),

7.43-7.26 (m, 15H, 6H-*o*, 6H-*m*, 3H-*p*), 3.90 (dd, 1H, H-2, 4.7, 8.0), 3.27 (t, 1H, H-8, 9.6), 3.18 (dd, 1H, H-8, 5.5, 9.6), 3.04 (m, 1H, H-5), 2.71 (brt, m 1H, H-7), 2.53 (m, 1H, H-4, in DMSO), 2.33 (d, 1H, H-1, 4.1), 1.99 (dd, 1H, H-3, 8.0, 14.6), 1.74 (dd, 1H, H-6, 8.0, 13.5), 1.53 (dt, 1H, H-6, 4.1, 13.5), 1.46 (dt, 1H, H-3, 4.7, 14.6), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 143.87 (C_1-Ar), 128.23 (C-*m*), 127.84 (C-*o*), 126.99 (C-*p*), 85.61 (Cq-Tr), 60.38 (C-8), 58.90 (C-2), 51.13 (C-5), 46.52 (C-4), 46.02 (C-7), 42.78 (C-1), 37.44 (C-3), 35.24 (C-6).

^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.47 (br d, 6H, H-o, 7.1), 7.31-7.22 (m, 9H, 6H-*m*, 3H-*p*), 3.66 (dd, 1H, H-2, 4.0, 8.0), 3.42 (dd, 1H, H-8, 4.4, 9.7), 3.37 (dd, 1H, H-8, 5.7, 9.7), 2,79 (dd, 1H, H-5, 4.0, 8.1), 2.30 (br d, 1H, H-7, 5.0), 2.13 (d, 1H, H-4, 4.0), 1.97 (d, 1H, H-1, 4.0), 1.80 (dd, 1H, H-6, 8.1, 14.1), 1.63 (dd, 1H, H-3, 8.0, 13.4), 1.58 (dt, 1H, H-6, 4.0, 14.1), 1.19 (dt, 1H, H-3, 4.0, 13.4), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 144.38 (C_1-Ar), 128.33 (C-*m*), 127.77 (C-*o*), 126.94 (C-*p*), 86.40 (Cq-Tr), 61.35 (C-8), 59.94 (C-2), 53.61 (C-5), 47.93 (C-4), 47.26 (C-7), 46.57 (C-1), 40.88 (C-3), 38.61 (C-6).

Results and discussions

We followed the previous efficient sequence for obtaining amine **1** (scheme 2) from the optically active keto-alcohol **2**, in the following 6 steps: *1*). protection of the hydroxyl group as benzoate, *2*). selective reduction of the ketone group to the 5-*endo*-OH compound **4c** (the minor 5-*exo*-OH isomer **5c** was obtained in ~6%) [2], *3*). mesylation of the secondary alcohols and isolation of the *endo*-isomer **6c** by simple crystallization, *4*). SN2 substitution of the mesyl group with a 5-*exo*-azide to compound **8c**, with the inversion of configuration, *5*) reduction of the azide group to amine **9c**, and *6*). deprotection of the benzoate group to amine **1**; an inversion of the last two steps, the deprotection of the benzoate group and the final reduction of the azide was also performed 3].

Because we used the unprotected amine **1** for building the pyrimidine and 6-substituted adenine analogues [4,5], we encountered some difficulties related to the isolation of the compounds and their yields. We have since decided to overcome these issues in our future works by obtaining amine **1** protected with an ether group, but while having in the sequence some crystallized intermediates useful for a similar selective isolation of the 5-*endo*-substituted isomer at the step of the mesylated compound, as for benzoate, or at any other subsequent step. We began with the TBDMS group, knowing by experience that it could result in crystallized compounds [10]. After silylation of compound **2**, the reduction, in the same conditions, was selective to the alcohol **3a** in a good ratio > 9:1 (**3a**/**4a**, determined by NMR), but in the next steps we obtained no crystallized compounds until amine **9a**.

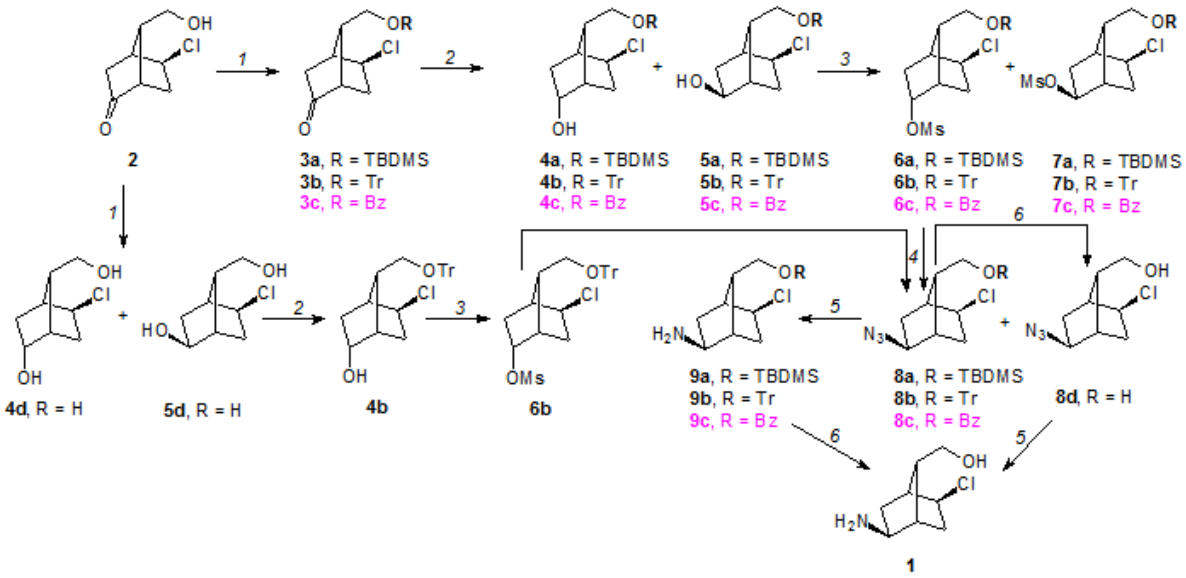
We then used a trityl protecting group and even alcohol **4b** was obtained by partial crystallization of the crude alcohols, but the *exo*-isomer **6b** was selectively separated from the mixture of the mesylated compounds **6b** and **7b**, as in the case of the benzoate protected compounds. In addition, the trityl azide **8b** was obtained crystallized, an advantage for the purification of the compound. The reduction of the azide group gave amine **9b**, as oil.

Finally, we reduced the unprotected keto-alcohol **2** to diole **4d** and successfully obtained the bulk of 5-*endo*-OH isomer **4d** in pure form by crystallization, which is really a great advantage of the sequence, because the key step of the whole sequence of reactions is the separation of the 5-*endo*-OH isomer **4d** from the 5-*exo*-OH isomer **5d** (R = H).

The next step is a selective protection of the primary hydroxyl group with a bulky ether forming reagent, like trityl chloride (of course, a bulky silyl reagent, like TBDMS-, TBDPS-, TPhS-chloride, etc. reagents can also be successful used) to the trityl protected compound **4b**, and the next steps are similar with those presented above.

We studied also the deprotection of the ether protecting group at the level of the azide compounds **8a** and **8b** and the amine compounds **9a** and **9b** and obtained azide **8d** and amine **1**, a proof for the versatility of the procedures.

Amines **9a-9c**, together with amine **1**, are important reagents for building of the pyrimidine and purine base moiety of constrained carbocyclic nucleoside analogues with a norbornane fragment in the sugar moiety. The alcohol intermediates **4a-4c** are valuable intermediates for the synthesis of nucleoside analogues by Mitsunobu reaction. In addition, azides **8a-8d** are starting compounds for click chemistry [11]. Therefore, the procedures presented above, together with the previously one presented, which use benzoate as protecting group, are very valuable for the efficient preparation of these compounds.



Scheme 2. The transformation of keto-alcohol **2** in the TBDMS and trityl substituted at the exocyclic hydroxy-methyl of azides **8a**, **8b**, and amines **8a** and **8b**, or unprotected azide **8c** and amine **1.**

Conclusions

An efficient procedure for obtaining ether-protecting amines **9a-9b**, as TBDMS and trityl, starting from an optically active by-product from the beginning stages of the prostaglandin synthesis sequence, was presented. The whole sequence with the TBDMS protecting group conducted to oily compounds, and the separation of the major 5-*endo*-isomer at the level of **4a**, **6a** from the minor 5-*exo* isomer, was difficult to do even by low pressure chromatography (LPC). With the trityl protecting group we obtained even the partial separation of the crystallized alcohol **4b**, but the efficient separation was realized at the level of the mesylated compunds **6b** and **7b**. Finally, the reduction of the keto-alcohol **2** made it possible to isolate the bulk of the 5-*endo*-OH compound **4d** (the isomer which remained in mother liquors was isolated by LPC) at the first step, the following step being the selective protection of the primary hydroxyl group with a bulky trityl group; the next steps are similar with the **4b**→**6b**→**8b**→**9b** steps discussed above. In conclusion, we obtained a number of protected and unprotected alcohols, azides and amines compounds, which represent useful key intermediates for obtaining constrained carbocyclic nucleoside analogues, in click chemistry and in fine organic chemistry.

References

1.TANASE, C., COCU, F. G., CAPROIU, M. T., DRAGHICI, C., NEAGOE, I., MANDA, G., Rev. Chim.(Bucharest) **58**, no. 8, 2007, p. 822.

2.TANASE, C., COCU, F. G., CAPROIU, M. T., NEAGU, M., MANDA, G., Rev. Chim.(Bucharest) **60**, no. 2, 2009, p. 147.

3.TANASE, C., COCU, F. G., CAPROIU, M. T., DRAGHICI, C., NEAGOE, I. V., ENACHE, C., NITA, S., Rev. Chim.(Bucharest) **61**, no. 2, 2010, p. 929.

4.TANASE, C., DRAGHICI, C., CAPROIU, M. T., SHOVA, S., MATHE, C., COCU, F. G., ENACHE, C., MAGANU, M., Bioorg. Med. Chem. **22**, no. 1, 2014, p. 513.

5.TANASE, C., DRAGHICI, C., COJOCARU, A., GALOCHKINA, A. V., ORSHANSKAYA, J. R., ZARUBAEV, V. V., SHOVA, S., ENACHE, C., MAGANU, M., Bioorg. Med. Chem. **23** no. 19, 2015, p. 6346.

6.DEJMEK, M., HREBABECKY, H., SALA, M., DRACINSKY, M., PROCHAZKOVA, E., LEYSSEN, P., NEYTS, J., BALZARINI, J., NENCKA, R., Bioorg. Med. Chem. **22**, no. 11, 2014, p. 2974.

7.DEJMEK, M., SALA, M., HREBABECKY, H., DRACINSKY, M., PROCHAZKOVA, E., CHALUPSKA, D., KLIMA, M., PLACKOVA, P., HAJEK, M., ANDREI, G., NAESENS, L., LEYSSEN, P., NEYTS, J., BALZARINI, J., BOURA, E., NENCKA, R., Bioorg. Med. Chem. **23**, no. 1, 2015, p. 184.

8.SALA, M., DE PALMA, A. M., HREBABECKY, H., DEJMEK, M., DRACINSKY, M., LEYSSEN, P., NEYTS, J., MERTLIKOVA-KAISEROVA, H., NENCKA, R., Bioorg. Med. Chem.Lett. **21**, 2011, p. 4271.

9.PLACKOVA, P., RAZUMOVA, N., HREBABECKY, H., SALA, M., NENCKA, R., ELBERT, T., DVORAKOVA, A., VOTRUBA, I., MERTLIKOVA-KAISEROVA, H., Antiviral Research **33**, 2013, p. 3163.

10.a) TANASE, C., DRAGHICI, C., Rev. Roum. Chim., **59**, no. 10, 2014, p. 845; b) TANASE, COCU, F., CAPROIU, M. T., DRAGHICI, C., RO129083B1, 2012.

11.For Click Chemistry: a) GONZALEZ-CALDERON, D., SANTILLAN-INIESTA, I., GONZALEZ-GONZALEZ, C. A., FUENTES-BENITES, A., GONZALEZ-ROMERO C., Tet. Letters, **56**, no. 3, 2015, p. 514; b) DHEER, D., SINGH, V., SHANKAR, R., Bioorg. Chem. **71**, 2017, p. 30; c) CUMMINGS, A. J., RAVALICO, F., KEGAN, I. S., et al., Nucleosides, Nucleotides & Nucleic Acids, **34**, 2015, p. 361.

Manuscript received: 20.11.2017