New Constrained Amines in a Bicyclo[2.2.1]Heptane Skeleton

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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 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 NaBH₄ 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 N₁,O₂- or O₂,O₄-substituted 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 N₆-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 EC₅₀ 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 [8,9] with antiviral activity against coxsackie viruses, most active being compound IV, with an EC₅₀ = 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 EC₅₀ 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 = NH₂), 3b (R = 6-(4-methoxy-phenethyl), 3c (R = phenylalaninol), and 13b (R = dimethylamino), 13g (R = 6-phenethylamino), 13j (R = N-methyl-piperazine), 13l (R = morpholine) (the number is from previous papers 4,3)](image)

![Fig. 1. Norbornane nucleoside analogues active against coxsackie viruses](image)

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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-cyclo-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 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 presented below.

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

The compound (1S,4S,5S,7R)-7-(((tert-butyldimethylsilyl)oxy)methyl)-5-chlorobicyclo[2.2.1]heptan-2-one, 3a was protected and recrystallized from 600 mL hexane and 50 mL ethyl acetate, resulting 30.95 g (in 3 fractions) (mother liquors were purified by low-pressure chromatography (LPC), resulting 30.95 g, total yield 95.5%).

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

Compound 2 (82, 0.475 mol) was dissolved in pyridine (220 mL) (or by adding also 220 mL toluene), and trityl chloride (158.9 g, 0.57 mol) 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, Rf = 0.37, Rf = 0.82; II, Rf = 0.15, Rf = 0.58). Pyridine was distilled under reduced pressure, the residue was taken up in toluene-hexane (1:2, 700 mL), poured under mechanical stirring on crushed ice and 20% KHCO3 (400 mL), stirred for 2h, the organic phase was washed with 20% KHCO3 (300 mL), brine (200 mL), dried (Na2SO4), 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)

#### 3. Synthesis of (1S,4S,5S,7R)-7-(((tert-butylidemethylsilyl)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 NaBH4 (22.7 g, 0.7 mol) in 0°C cooled water (250 mL) was dropwise added under mechanical stirring for 2.5 h. TLC (I, Rf = 0.72, Rf = 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 (tbp < 80°C) to about 1471m, 1255m, 833vs, 711vs, 721m, 1H-NMR (CDCl3, d ppm, / Hz): 4.01, (d, 1H, H-2, 3.9, 7.5), 4.01 (dd, 1H, H-3, 6.8, 10.8), 3.88 (dd, 1H, H-5, 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, 15.1), 7.30s, 9H, CH3-C), -0.05 (s, 6H, CH3-Si). 13C-NMR-300MHz (CDCl3, d ppm): 213.92 (C-S), 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 (CH3-C), 18.34 (CH3-C), -5.20, -5.26 (CH3-Si).

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

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

The compound 3b (148g, 0.357 mol) reduced similarly in THF (1.5 L) and methanol (1 L) with a solution of NaBH4 (20.28 g, 0.536 mol) in cooled water (250 mL); TLC (I, Rf = 0.42, Rf_{ab} = 0.20). The crude product was re-crystallized with warm ethyl acetate (1 L + 2 x 0.5 L), filtered off and the filtrate was concentrated until everything dissolved, then filtered and left to crystallize at r.t. in prisms, filtered again, resulting 78.69 g of pure diol 4b.

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

Compound 2 (100 g, 0.5726 mol) was dissolved in methanol (1 L), cooled to –50°C and reduced similarly with a solution of NaBH4 (23.8 g, ~0.63 mol) in water (300 mL) at r.t. in prisms, filtered again, resulting 80.5 g of pure diol 4b as prisms, mp 177.5-181.5°C, [α]D = –5.14, –5.19.

5b, 5d

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

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) was selectively tritylated in 100 mL pyridine with trityl chloride (29.27 g, 105 mmol) as in ex 2. TLC (I, Rf_{mg} = 0.12, Rf = 0.54; II, Rf_{mg} = 0.10, Rf_{ab} = 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: 1H-NMR-300MHz (CDCl3, δ ppm): 7.71-7.20 (m, 9H, 6H-α, 3H-β), 4.22 (m, 1H, H-5c, 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 (dd, 1H, H-1, 4.7), 2.12-2.03 (m, 1H, H-6-7), 1.53 (dt, 1H, H-3, 3.7, 14.5), 0.82 (dd, 1H, H-6, 2.9, 13.7), 13C-NMR-75 MHz (CDCl3, δ ppm): 144.31 (C), 128.74 (C-5), 127.70 (C-α), 126.90 (C-β), 86.35 (Cq-Tr), 70.36 (C-β), 61.31 (C-β), 60.39 (C-2), 49.39 (CH-C1), 48.27 (C-7), 45.50 (C-4), 39.81 (C-4), 32.52 (C-3).

7. Synthesis of (1S,2R,4S,5S,7R)-7-((tert-butyl dimethylsilyloxy)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, Rf = 0.65, Rf_{sa} = 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% KHCO3 soln. (300 mL) and crushed ice. The stirring was continued for 1 h, phases were separated, organic phase was washed with 20% KHCO3 soln. (250 mL) (the aqueous solutions were extracted with 250 mL toluene), dried (Na2SO4), 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 secective crystallizations of 6a, mp 51.5-52.6°C, [α]D = 10.7±1° (in THF), 1H-NMR-300MHz (CDCl3, δ ppm, J Hz): 4.93 (dddd, 1H, H-α, 1.6, 2.7, 4.4, 9.9), 3.97 (dd, 1H, H-8, 9.1, 10.7), 3.97 (dd, 1H, H-2, 1.1, 4.1, 8.0), 3.80 (dd, 1H, H-8, 5.5, 10.7), 2.99 (s, 3H, CH3), 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 (dd, 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, CH3), 0.01 -0.04 (s, 6H, CH2Si), 13C-NMR-75 MHz (CDCl3, δ ppm): 79.32 (CH-C5), 60.50 (C-8), 59.58 (C-2), 51.75 (C-4), 46.98 (C-1), 44.02 (C-4), 38.40 (SC6), 37.69 (C-6), 32.21 (C-3), 26.09 (CH2C1), 18.44 (CH2C1), -5.14, -5.19 (CH2Si).

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, 0.14 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 point by TLC (I, Rf_{ab} = 0.26, Rf_{sa} = 0.46). The reaction mixture was poured over 20% KHCO3 soln. (250 mL) with ice (400 g) (sometimes, the bulk of the product crystallized and was filtered off), organic phase was washed with 20% KHCO3 soln. (250 mL), brine (250 mL) (the aqueous phases were extracted with 3 200 mL solvents).
to 150 mL, and crystallized at r.t., resulting in 41.44 g (80.5%) of pure compound 6b, mp 96.9±0.7°C. [α]D = -2.8° (1% in THF), IR: 2935m, 2929m, 1409m, 1386m, 1341m, 1251m, 1173s, 1078s, 967v, 832v, 780s, 675s, 563s, 522s. 1H-NMR-300 MHz (CDCl3, δ ppm, J Hz): 7.46 (d, 6H, H-6), 7.4 (4H, H-8). 7.34-7.17 (m, 9H, 6H-p, 3H-m), 4.99 (ddd, 1H, H-5x, 1.4, 3.0, 4.9, 9.9), 3.84 (ddd, 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, CH3), 2.80 (t, 1H, H-4, 4.4), 2.52 (dd, 1H, H-3, 8.0, 15.1), 2.13 (br t, 1H, H-7, 7.5), 1.80 (m, 2H, H-6), 1.57 (dd, 1H, H-6, 7.6, 13.6), 1.50 (1H, H-6, 4.6, 13.6), 1.37 (1H, H-7, 7.6), 0.78 (1H, H-3, 13.6), 0.76 (3H, CH3). 13C-NMR-75MHz (CDCl3, δ ppm): 144.46 (C-Ar), 134.94 (C1-Ar), 130.28 (C-1), 129.34 (C-2), 113.81 (C-3), 44.38 (Cq-Tr), 43.24 (C1-Ar). 12. Deprotection of the trityl group of azide 8b to azide 8d.

Trypt amide 8b (1.22 g, 2.75 mmol) was dissolved in methanol (30 mL) and chloroform (30 mL), Dowex 50W x2 ion exchange resin was washed with methanol (0.55 g) was added and refluxed until the end of the reaction. 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-chloro-7-(((tert-butyl(dimethyl)silyl)oxy)methyl)bicyclo[2.2.1]heptan-2-amine, 9a TBDMS-azide 8a (5.61g, 17.7 mmol) was dissolved in methanol (100 mL), the catalyst (10-20% Pd(OH)2/C, 2.12 mg) was added and hydrogenation was done by bubbling hydrogen in the solution, under stirring, monitoring the end of the reaction by TLC (dichlormethane-methanol, 95:5, Rf = 0.76, Rf = 0.06). The catalyst was filtered off, washed with methanol, and the filtrate concentrated. The crude product was purified by PLC (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 hydrogen chloride salt, mp 202.0-205.3 (dec.)], [α]D = 10.2° (1% in THF), IR: 3229w, 2953w, 2929w, 2956w, 1406w, 1309w, 1234w, 1173s, 1063s, 987s, 850w, 775s. 1H-NMR-300 MHz (CDCl3, δ ppm, J Hz): 8.20 (NH3+, for hydrochloride), 3.95 (brt, 1H, 10.5, H-8), 3.89 (dd, 1H, 10.5, H-2), 3.14 (t, 1H, 5.8, H-5), 2.89 (m, 2H, H-1), 2.51 (br s, 1H, H-4), 2.45 (t, 1H, H-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-7, 6.6, 13.6), 1.50 (1H, H-6, 4.6, 13.6), 1.37 (1H, H-7, 7.6), 0.78 (1H, H-3, 13.6), 0.76 (3H, CH3). 13C-NMR-75MHz (CDCl3, δ ppm): 62.60 (C-8), 59.66 (C-2), 52.65 (C-5), 49.72 (C-4), 38.39 (C-Si), 37.66 (C-6), 32.96 (C-3). The melting points were determined by TLC (II, Rf = 0.65, Rf = 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].
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 form 7c, 5). deprotection of the benzoyl group to amine 1, an inversion of the last two steps, the deprotection of the benzoyl 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, 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 give 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 trietyl chloride (of course, a bulky silyl reagent, like TBDMS-, TBDPS-, TPhS-chloride, etc. reagents can also be 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.
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 compounds 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 liquor 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

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