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TETRAHEDRON

A Case of Unusual Sterically Driven C-Tritylation Reaction of Tricyclic Analogues of Acyclovir

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Abstract: 3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine (**1**) and its silylated derivative (**2**) when tritylated under conditions suitable for regioselective N-5 alkylation underwent instead C-substitution to give 7-trityl (**12, 3**) and 7-(4-benzhydrylphenyl) (**13, 4**) derivatives as major and minor products, respectively. Substrates lacking 6-Me group (**5, 6**) yielded 5-tritylated (**10, 7**) and 5,7-ditritylated (**11, 8**) major products and 7-tritylated (**9**) minor product. The regioselectivity of the reaction seems to be driven mainly by steric hindrance of the 6-Me substituent.
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INTRODUCTION

It has been previously found that transformation of the guanine moiety of the potent antiherpetic drug acyclovir, 9-[(2-hydroxyethoxy)methyl]guanine, into the tricyclic 3,9-dihydro-9-oxo-6R-5*H*-imidazo[1,2-*a*]-purine system allows to modify physical and biological properties of the parent compound. 6-Substitution (R = alkyl or aryl) is indispensable to obtain more selective or fluorescent active analogues.[1-3]

When we turned to extending this study onto 6,7-disubstituted analogues, one of our approaches to the synthesis of these compounds was a direct modification of already preformed tricyclic system of 6-methyl derivative **1**. It required protection of N-5-H endoamino group with an acid-labile e.g. triphenylmethyl (trityl) blockade. Earlier studies have pointed to the N-1 nitrogen as the major site of protonation because regioselective N-1 methylation with MeX reagents has been observed under neutral conditions.[4,5] Acidic N-5-H hydrogen has easily been abstracted by bases e.g. solid potassium carbonate, and a new nucleophilic centre, more reactive than N-1, has been generated. That centre, once formed, reacted with alkylating agents to give exclusively high yields of N-5 substituted **1**.[6]

RESULTS AND DISCUSSION

Similarly we treated silylated compound **2** with triethylamine in anhydrous dichloromethane followed by chlorotriphenylmethane (Scheme 1). Surprisingly, instead of N-5 tritylation, C-7 tritylation was observed.

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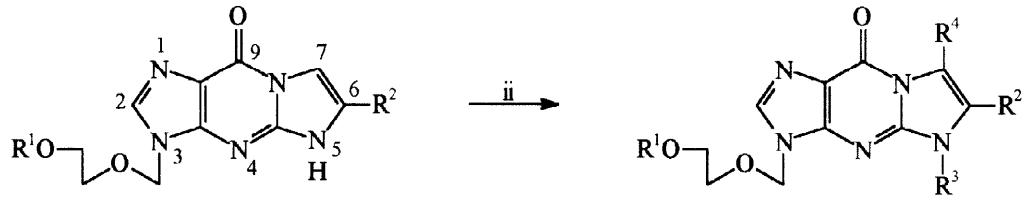
The only stable products: 7-trityl-6-methyl **3** and 7-(4-benzhydrylphenyl)-6-methyl **4** were isolated in respective yields of 59% and 9%. According to mass spectra both compounds appeared to be isomers. Their structures were elucidated on the basis of comparison of their ^{1}H and ^{13}C spectra with those of substrate **2** (Tables 1, 2). The N-5 tritylation was excluded by the maintenance of N-5 exchangeable proton at approx. 12.5 ppm in both products **3** and **4**. Characteristic doublet of H-7 occuring in parent compound at 7.39 ppm was not diagnostic due to its overlapping with complex patterns of aromatic substituents introduced by tritylation. Nevertheless C-7 as the site of substitution was clearly indicated by ^{13}C spectra showing for that carbon in products **3** and **4** a significant downfield shift (from 103.26 ppm in **2** to 122.98 and 118.38 respectively) as well as corresponding changes in the C-H coupling patterns. The C-7 substituent of **3** was an expected trityl group appearing in ^{1}H NMR as a fifteen-proton multiplet centered at 7.23 and in ^{13}C NMR as four signals of aromatic carbons and one signal of tetrasubstituted carbon. In the case of product **4** the C-7 group resonated in ^{1}H NMR as two multiplets and a doublet centered at 7.36, 7.23 and 7.15 respectively corresponding to fourteen protons and a singlet of one proton at 5.70 ppm. These data, together with ^{13}C spectrum in which signals of eight aromatic carbons and of trisubstituted aliphatic one appeared, were consistent with the 7-(4-benzhydrylphenyl) structure of the substituent. The different steric arrangements of the discussed C-7 substituents were manifested by an upfield shift of the signal of the adjacent 6-methyl group - conspicuous (1ppm) in **3** and small (0.14 ppm) in **4**.

We examined also other conditions of the reaction as described in the aforementioned literature (solid K_2CO_3/DMF and NaH/DMF). However, the reactions again led to a mixture of **3** and **4** as major and minor products respectively. When pyridine was applied as base and solvent, **2** reacted in 10% and only C-7 tritylation occurred after prolonged heating at 75°C. Based on that observation, abstraction of N-5-H proton seems to be essential for further substitution with a trityl or benzhydrylphenyl group.

An ambident ion of **2** (Scheme 2, I), resulting from N-5-H abstraction, stabilized by mesomeric effect, underwent only C-substitution. This effect could be ascribed to steric hindrance which may be due to the presence of bulky substituents: 6-methyl group in the appended ring and *tert*-butyldimethylsilyl group in the aliphatic chain.

We tried to evaluate the importance of both groups by carrying out tritylation experiments on further appropriate substrates **1,5** and **6** (Scheme 1). Compound **6** pretreated with Et_3N reacted readily with trityl chloride. The reaction resulted in two products: the desired N-5-trityl **7** and 5,7-ditrityl **8**, obtained in 1:1 ratio regardless of the applied excess of base and TrCl (35% yield at equimolar amounts, 45% if Et_3N and TrCl were used in 100% excess). In that experiment compound **6** manifested two reactivities: N-nucleophilic and C-nucleophilic (Scheme 2). The structures of both **7** and **8** were established by means of mass spectra and NMR spectroscopy. The absence of N-5-H signal and presence of a multiplet centered at 7.28 ppm corresponding to 15 protons indicated N-5 of compound **7** as a position substituted with a trityl group. This assignment was supported by two doublets at 7.75 and 7.16 ppm attributable to H-6 and H-7 and a significant

Scheme 1



1, 2, 5, 6 **3, 4, 7-15**

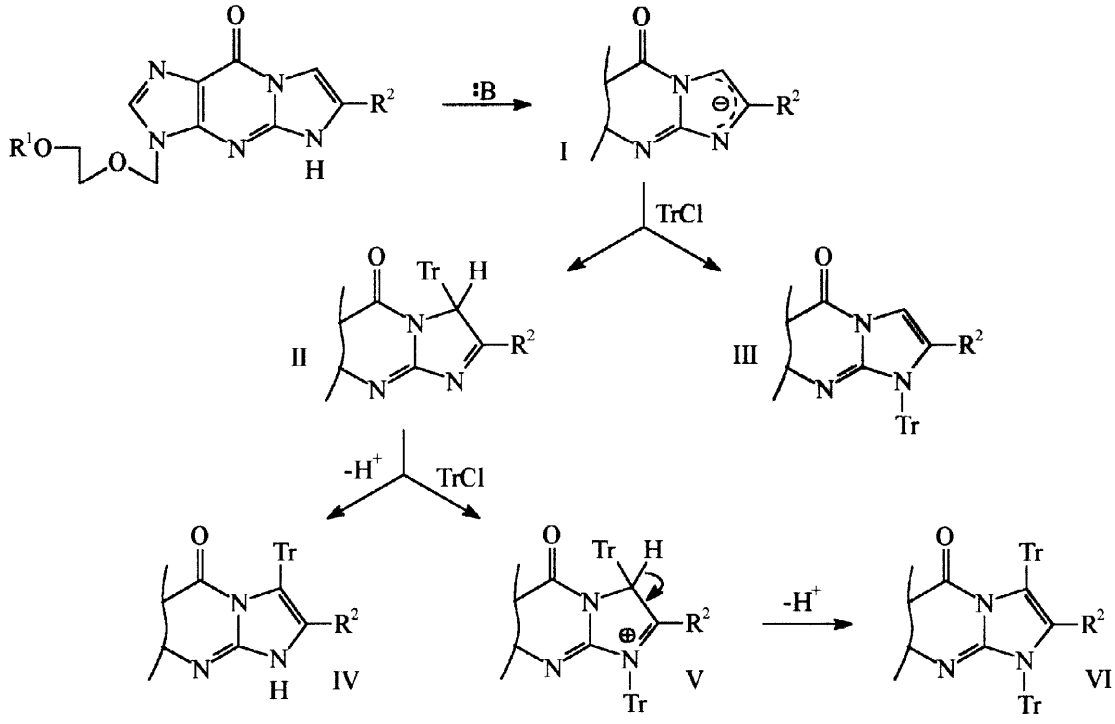
1. $R^1 = H$ $R^2 = Me$
2. $R^1 = TBDMS$ $R^2 = Me$
3. $R^1 = TBDMS$ $R^2 = Me$ $R^3 = H$ $R^4 = Tr$
4. $R^1 = TBDMS$ $R^2 = Me$ $R^3 = H$ $R^4 = BzhPh$
5. $R^1 = R^2 = H$
6. $R^1 = TBDMS$ $R^2 = H$
7. $R^1 = TBDMS$ $R^2 = R^4 = H$ $R^3 = Tr$
8. $R^1 = TBDMS$ $R^2 = H$ $R^3 = R^4 = Tr$
9. $R^1 = R^2 = R^3 = H$ $R^4 = Tr$
10. $R^1 = R^2 = H$ $R^3 = Tr$ $R^4 = H$
11. $R^1 = R^2 = H$ $R^3 = R^4 = Tr$
12. $R^1 = R^3 = H$ $R^2 = Me$ $R^4 = Tr$
13. $R^1 = R^3 = H$ $R^2 = Me$ $R^4 = BzhPh$
14. $R^1 = H$ $R^2 = Me$ $R^3 = Tr$ $R^4 = BzhPh$
15. $R^1 = H$ $R^2 = Me$ $R^3 = Tr$ $R^4 = H$

$C(C_6H_5)_3 = Tr$ $(C_6H_5)_2CHC_6H_4 = BzhPh$ $(CH_3)_3CSi(CH_3)_2 = TBDMS$

1 $\xrightarrow{i}$ **2** 91% **5** $\xrightarrow{i}$ **6** 88% **8** $\xrightarrow{iii}$ **9** 77% **3** $\xrightarrow{iii}$ **12** 90%

i/ Py, TBDMSCl /*ii*/ Et_3N, $C(C_6H_5)_3Cl$, CH_2Cl_2 or K_2CO_3,$C(C_6H_5)_3Cl$, DMF /*iii*/ 80% AcOH

Scheme 2



upfield shift (0.5 ppm) of O-CH_2-N group. ^{13}C NMR spectrum of **7** confirmed the presence of N-trityl group as its aliphatic carbon atom linked with N-5 absorbed at the field 75.80 ppm, lower than that found for C-trityl of **3** (60.13 ppm). In proton spectrum of **8** a strong multiplet centered at 7.26 ppm corresponding to 25 protons, a broad small one at 7.05 ppm (3 protons) and a broad doublet at 6.77 ppm (2 protons) were found. The abovementioned signals were ascribed to two trityl groups N-5 and C-7, as neither N-5-H signal nor characteristic doublets of H-6 and H-7 were observed. ^{13}C NMR of **8** confirmed the presence of C-7 and N-5 trityl substituents but demonstrated additional signals of aromatic carbons, three more than eight aromatic signals routinely expected from both groups. In order to unequivocally assign C-7 as a site of C-tritylation both TBDMS and N-5-trityl groups of compound **8** were removed by treatment with acid and the structure of resulting **9** was assigned by NMR. ^1H spectrum presented the characteristic pattern of two multiplets at 7.22 and 6.84 ppm corresponding to 15 protons indicating a trityl group. Besides, a coupling (J=2.1 Hz) was found between N-5-H (δ_H 12.48 ppm) and the proton absorbing at 6.34 ppm thus showing that the latter signal is due to H-6. Finally, ^1H NOE difference spectra of **9** (Table 1) confirmed all the assignments.

The major effect of steric hindrance exerted by 6-Me group was the most spectacular when the reaction was performed on the unprotected **1** and **5**. Compound **5**, treated with solid K_2CO_3 or triethylamine in anhydrous DMF, followed by TrCl was transformed mainly into N-5 trityl derivative **10** (60%) and minor products: 5,7-ditrityl **11** (25%) and 7-trityl **9** (5%). **10** and **11** spectroscopically resembled compounds 7 and **8**, respectively. However, tritylation of **1** in the presence of triethylamine in DMF led to a mixture of C-substituted products: 7-trityl-6-methyl **12** (27%) and 7-(4-benzhydrylphenyl)-6-methyl **13** (13%) spectroscopically analogous to compounds **3** and **4**. Compound **12** was identical in all respects with a sample obtained by deprotection of **3** either with acetic acid or fluoride ions. Interestingly, two byproducts less polar than **12** and **13** resulted from tritylation of **1**: 7-(4-benzhydrylphenyl)-6-methyl-5-trityl **14** (5%) and 6-methyl-5-trityl **15** (minute amount, 0.5%), our original target. The structure of **14** was easily assigned owing to prior determination of the characteristic features of both substituents in ^1H and ^{13}C NMR. Unlike **8** or **11**, almost 40% of **14** underwent spontaneous N-detritylation during routine reaction with D_2O in DMSO-d_6 solution carried out to check the presence of exchangeable protons. In the case of N-trityl derivatives (**8**,**10**,**14**) LR mass spectra were of diagnostic value due to the observed 100% intensity of liberated trityl cations (m/z 243). Based on that we assigned the structure of product **15** as N-5-trityl isomer of both **12** and **13**.

On scheme 2 we propose the possible sequence of events which may explain this unusual C-7 nucleophilic reactivity of 3,9-dihydro-9-oxo-5*H*-imidazo[1,2-*a*]purine system. N-tritylation of ambident ion I seems to proceed first. Substrates lacking 6-Me substituents (**5**,**6**) are quickly transformed into stable final products III (**10**,**7**). After C-tritylation of I, N-5 nucleophile II readily reacts yielding disubstituted products VI. 6-Me substituted substrates (**1**,**2**) however, could form N-5-trityl derivatives sensitive to solvolysis.

Table 1. Selected ^{1}H NMR Data.

Cmpd	N-5-R	6-R	7-R	O-CH_2-N
2	12.43 s, 1, ex[a]	2.29 d, 3 $J_{7,6\text{-Me}}$ = 1.0 Hz	7.39 d, 1	5.52 s, 2
6	12.53 s, 1, ex	7.65, d, 1 7.43, d, 1 $J_{6,7}$ = 3.0 Hz		5.52 s, 2
3	12.33 s, 1, ex	1.28 s, 3	7.23 m, 15	5.42 s, 2
4	12.60 s, 1, ex	2.15 s, 3	7.36, m, 6 7.23, m, 6 7.15, d, 2 5.70, s, 1	5.50 s, 2
7	7.28 m, 15	7.75, d, 1 7.16, d, 1 $J_{6,7}$ = 3.0 Hz		5.00 s, 2
8	7.26, m, 25 7.05, br m, 3 6.77, br d, 2	6.32 s, 1	b	4.92 s, 2
9[c]	12.48 d, 1, ex $J_{5,6}$ = 2.1 Hz	6.34 d, 1	7.22, m, 13 6.84, m, 2	5.43 s, 2
14	7.45, m, 5 7.22, m, 24 5.68, s, 1	1.54 s, 3	b	4.89 s, 2

a. Deuterium exchangeable - ex

b. Data for both N-5-R and 7-R substituents given under heading N-5-R.

c. ^{1}H NOE difference spectra of **9**: 2.8% NOE effect observed for H-6 when N-5-H irradiated. When H-6 irradiated enhancement of N-5-H and both trityl signals (δ 7.22, 6.84) observed.

The above may be an explanation for the trace amounts of such products as **15** found in the reaction mixture together with considerable amounts of the starting material **1** and C-7 substituted isomeric products **12**,**13**.

Another interesting observation is the appearance of unexpected products with 4-benzhydrylphenyl groups at 7 position (**4**,**13**,**14**). Those products could be the final result of a reaction of C-nucleophile I with

Table 2. Selected ^{13}C NMR Data.

Cmpd	C-4a	C-6	C-7	N-5-R	6-R	7-R
2	145.79 Sd[a]	125.94 Sdq	103.26 Dq		10.45 Q	
6	145.98 Sdd	116.38 Dd	106.82 Dd			
3	146.49 Ss	124.88 Sm	122.98 Sm		11.89 Q	146.69 Sbrm[b] 60.13 Sm
4	145.91 Ss	123.61 Sq	118.38 Sm		9.70 Q	143.71 Spq 142.57 Spq[b] 55.60 Dm
7	144.87 Sdd	118.98 Dd	106.63 Dd	140.88 St[b] 75.80 Sm		
8	147.00 Sd	121.39 Ds	128.34 S[c]	140.57 St[b] 75.88 Ss		147.14 Sbrs 143.54 Sm[b] 60.12 Ss
9	148.31 Sd	118.14 Ds	129.06 Sd			147.59 Sm 144.17 St[b] 59.98 S[c]
14	145.87 Ss	125.97 S[c]	120.72 Sq	141.95 St[b] 76.37 Sm	13.73 Q	143.64 Spq 142.96 Spq[b] 55.51 Dm

a. Capital letters refer to the pattern resulting from directly bonded ^{13}C-^{1}H couplings and lower-case letters to those from ^{13}C-^{1}H couplings over more than one bond; br broad due to unresolved couplings; pq - pseudoquartet.

b. Data of other quaternary and tertiary aromatic carbon given in experimental part.

c. Overlapped with other signals.

trityl cation which leads first to 7-(4-benzhydrylidene-cyclohexa-2,5-dien-1-yl) derivatives.[7] 4-Benzhydryl-phenyl group in comparison with triphenylmethyl one reduces the steric congestion around positions 6 and 7 thus providing additional evidence that this unusual C-7 tritylation reaction is highly influenced by the steric hindrance caused by 6-Me substituent. Once introduced into N-5 position as in the case of **7** and **10**, the trityl group may play a protecting-directing role.[8] Therefore we are applying it at present in the synthesis of 7-substituted tricyclic derivatives of acyclovir.

Examples of C-tritylation of heterocycles such as pyrrole, indole under basic conditions[8,9] and of N-tritylation[10] of imidazole derivatives described in the literature are very different from the present reaction. Interestingly, search through Beilstein[11] for heterocycles substituted with 4-benzhydrylphenyl group resulted in few examples only. Either N-[12] or C-substitution[13] with this group were accomplished using different experimental approaches.

EXPERIMENTAL SECTION

General: Melting points were determined on MEL-TEMP II capillary melting point apparatus and are uncorrected. UV spectra were recorded on a Beckman DU-65 spectrophotometer in methanol solutions. LR and HR mass spectra were measured on a AMD-604 mass spectrometer by LSIMS method with glycerol or m-nitrobenzyl alcohol as matrices. Elemental analyses were performed by Microanalytical Laboratories of Institute of Organic Chemistry Polish Academy of Sciences in Warsaw. ^{1}H and ^{13}C NMR spectra were recorded in hexadeuteriodimethyl sulfoxide on a Unity 300 Varian spectrometer operating at 299.95 MHz and 75.43 MHz respectively. Tetramethylsilane was used as the internal standard and the chemical shifts are reported in ppm (δ scale). Thin-layer chromatography (TLC) was performed on Merck precoated 60 F_{254} silica gel plates. Short column chromatography was carried out on Merck silica gel 60H (5-40 μm or 40-63 μm). Anhydrous dichloromethane was distilled over P_2O_5 immediately prior to tritylation experiments. Anhydrous pyridine and dimethylformamide were dried over molecular sieves 4 A. 3,9-Dihydro-3-[(2-hydroxyethoxy) methyl]-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine **1** and 3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-5*H*-imidazo[1,2-*a*]purine **5** were prepared as described previously.[1,2]

3,9-Dihydro-3[(2-tert-butyldimethylsilyloxyethoxy)methyl]-6-methyl-9-oxo-5H-imidazo[1,2-a]purine (2).

To a suspension of **1** (0.200 g, 0.76 mmol) in pyridine (5 ml) was added *tert*-butyldimethylchlorosilane[14] (0.140 g, 0.9 mmol). The reaction mixture was stirred for 24 h at room temperature. The solvent was removed under vacuum and the residue was purified on a silica gel column with 5% methanol in dichloromethane. Yield: 0.260 g (91%), mp195°C dec. UV (MeOH): λ_{max} 284 nm (ε 12800). MS: calcd for $(M+H)^+$ 378. 1961, found 378.1930. ^{1}H NMR (DMSO-d_6): 12.43 (s, 1H, ex, N-5-H), 8.04 (s, 1H, H-2), 7.39 (d, 1H, H-7), 5.52 (s, 2H, OCH_2N), 3.66, 3.60 (2m, 4H, 2xCH_2), 2.29 (d, 3H, 6-CH_3), 0.82 (s, 9H, *tert*-butyl), 0.01 (s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): 151.07 (C-9), 150.07 (C-3a), 145.79 (C-4a), 138.96 (C-2), 125.94 (C-6), 115.25 (C-9a), 103.26 (C-7), 72.26 (OCH_2N), 70.30 (CH_2O), 61.83 (CH_2OSi), 25.64, 17.82 (*tert*-butyl), 10.45 (6-CH_3), 5.42 (2xCH_3-Si).

3,9-Dihydro-3[(2-tert-butyldimethylsilyloxyethoxy)methyl]-9-oxo-5H-imidazo[1,2-a]purine (6).

5 (0.150 g, 0.6 mmol) was suspended in pyridine (4 ml) and treated with *tert*-butyldimethylchlorosilane[14] (0.110 g, 0.72 mmol). The reaction mixture was stirred for 24 h at room temperature. The solvent was removed under vacuum and the residue was purified on a silica gel column with 5-10% methanol in dichloromethane. Yield 0.194 g (88%), mp 232°C dec. MS: calcd for $(M+H)^+$ 364.1804, found 364.1804. UV (MeOH): sh 272 nm (ε 10400), λ_{max} 285 nm (ε 11960). ^{1}H NMR (DMSO-d_6): 12.53 (s, 1H, ex, N-5-H), 8.06 (s, 1H, H-2), 7.65, 7.43 (2d, 2H, H-6, H-7), 5.52 (s, 2H, OCH_2N), 3.64, 3.58 (2m, 4H, 2xCH_2), 0.78 (s, 9H, *tert*-butyl), 0.03 (s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): 151.23 (C-9), 150.50 (C-3a), 145.98 (C-4a),

139.18 (C-2), 116.38 (C-6), 115.12 (C-9a), 106.82 (C-7), 72.12 (OCH_2N), 70.26 (CH_2O), 61.79 (CH_2OSi), 25.50, 17.78 (*tert*-butyl), -5.46 ($2xCH_3$-Si).

Tritylation of 2.

Method A. ***In dichloromethane in the presence of triethylamine.*** **2** (0.436 g, 1.16 mmol) was suspended in dichloromethane (9 ml) and treated with triethylamine (0.140 g, 1.39 mmol). Chlorotriphenylmethane (0.387 g, 1.39 mmol) was added in 5 min; the reaction mixture turned black immediately, then turned brown in 5 min. and this colour persisted. TLC indicated that after 1.5 hour reaction did not go further. The reaction mixture was applied on a silica gel short-column protected from light. The elution of products was conducted with dichloromethane containing 0-2% methanol. Two products: **3** and **4** were isolated.

3,9-Dihydro-3-[(2-tert-butyldimethylsilyloxyethoxy)methyl]-6-methyl-9-oxo-7-triphenylmethyl-5H-imidazo[1,2-a]purine (3): 0.424 g (59%). Analytical sample cryst. from CH_3CN mp 199°C dec. UV (MeOH): λ_{max} 285 nm (ε 14800). MS: m/z 620 $(M+H)^+$, 100%. Anal. for $C_{39}H_{41}N_5O_3Si \cdot 1/2\ H_2O$: calcd C 68.76, H 6.73, N 11.14; found C 68.84, H 6.56, N 11.52. ^1H NMR (DMSO-d_6): 12.33 (s, 1H, ex, N-5-H), 7.83 (s, 1H, H-2), 7.23 (m, 15H, Ph), 5.42 (s, 2H, OCH_2N), 3.66, 3.58 (2m, 4H, $2xCH_2$), 1.28 (s, 3H, 6-CH_3), 0.83 (s, 9H, *tert*-butyl), 0.02 (s, 6H, $2xCH_3$). ^{13}C (DMSO-d_6): 151.66 (C-9), 148.69 (C-3a), 146.49 (C-4a), 146.39 (Ph), 138.11 (C-2), 130.05, 127.11, 125.75 (Ph), 124.88 (C-6), 122.98 (C-7), 116.00 (C-9a), 72.09 (OCH_2N), 70.22 (CH_2O), 61.79 (CH_2OSi), 60.13 (CPh_3), 25.64, 17.81 (*tert*-butyl), 11.89 (6-CH_3), -5.43 ($2xCH_3$).

7-(4-benzhydrylphenyl)-3,9-dihydro-3-[(2-tert-butyldimethylsilyloxyethoxy)methyl]-6-methyl-9-oxo-5H-imidazo[1,2-a]purine (4): 0.065 g (9%), yellow foam. UV (MeOH): λ_{max} 292 nm (ε 19300). MS: calcd for $(M+H)^+$ 620.3057, found 620.3068. ^1H NMR (DMSO-d_6): 12.60 (s, 1H, ex, N-5-H), 7.98 (s, 1H, H-2), 7.36, 7.23 (2m, 12H, Ph), 7.15 (d, J=8.40, Hz, 2H, Ph), 5.70 (s, 1H, $CHPh_2$), 5.50 (s, 2H, OCH_2N), 3.66, 3.59 (2m, 4H, $2xCH_2$), 2.15 (s, 3H, 6-CH_3), 0.82 (s, 9H, *tert*-butyl), 0.01 (s, 6H, $2xCH_3$). ^{13}C NMR (DMSO-d_6): 152.52 (C-9), 149.30 (C-3a), 145.91 (C-4a), 143.71, 142.57 (Ph), 138.74 (C-2), 130.69, 129.01, 128.32, 127.49, 127.27, 126.24 (Ph), 123.61 (C-6), 118.38 (C-7), 115.78 (C-9a), 72.21 (OCH_2N), 70.26 (CH_2O), 61.83 (CH_2OSi), 55.60 ($CHPh_2$), 25.65, 17.83 (*tert*-butyl), 9.70 (6-CH_3), -5.40 ($2xCH_3$).

Method B. ***In DMF / K_2CO_3.*** **2** (0.038 g, 0.1 mmol) was dried by coevaporation with DMF (2x5 ml) dissolved in DMF (1.5 ml) and treated with anh. K_2CO_3 (0.019 g, 0.13 mmol). The suspension was vigorously stirred at room temperature until became homogeneous. Then chlorotriphenylmethane (0.032 g, 0.12 mmol) was added; the reaction mixture turned black immediately and slowly turned brown. According to TLC after 1 hour **3** and **4** were formed as a main product and byproduct respectively. Small amounts of decomposition products along with unreacted **2** were also observed. **2** itself turned out to be stable in the presence of K_2CO_3 in DMF for 24 hours.

Method C. ***In DMF / NaH.*** **2** (0.038 g, 0.1 mmol) was dried by coevaporation with DMF (2x5 ml) dissolved in DMF (1.5 ml) and treated with NaH (0.029 g, 0.12 mmol). The mixture was stirred for 30 min. until clear

solution was obtained. Then chlorotriphenylmethane (0.032 g, 0.12 mmol) was added and the characteristic sequence of colour changes were noticed. TLC revealed that the same products **3** and **4** were formed as in afore-mentioned reactions. Partially unreacted **2** could be detected in the mixture after 1 hour of the reaction.

Method D. ***In pyridine.*** **2** (0.019 g, 0.05 mmol) dried by coevaporation with anh.pyridine (2x5 ml) was dissolved in pyridine (0.8 ml). Chlorotriphenylmethane (0.017 g, 0.06 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. According to TLC no reaction was observed. The temperature was raised up to 70°C at which in the next 24 hours **2** was transformed into **3** in approx. 10%.

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-7-triphenylmethyl-9-oxo-5H-imidazo-[1,2-a]purine (12). Method A[14] : **3** (0.150 g, 0.24 mmol) was stirred with 80% aqueous acetic acid (10 ml) at ambient temperature overnight. The volatiles were removed under vacuum, the residue was purified on a silica gel column with 10% methanol in chloroform. Yield: 0.109 g (90%) of crystalline product. **12** was recrystallized from methanol: mp 201°C dec. UV (MeOH): λ_{max} 285 nm (ε 19200). MS: calcd for $(M+H)^+$ 506.2192, found 506.2193. Anal. for $C_{30}H_{27}N_5O_3 \cdot 1/3\ H_2O$ (according to ^1H NMR): calcd C 70.43, H 5.45, N 13.69, found C 70.58, H 5.49, N 13.04. ^1H NMR (DMSO-d_6): 12.32 (s, 1H, ex, N-5-H), 7.82 (s, 1H, H-2), 7.22 (m, 15H, Ph), 5.40 (s, 2H, OCH_2N), 4.69 (t, 1H, ex, OH), 3.49 (m, 4H, 2xCH_2), 1.25 (6-CH_3). ^{13}C NMR (DMSO-d_6): 151.75 (C-9), 148.80 (C-3a), 146.57 (C-4a), 146.46 (Ph), 138.26 (C-2), 130.14, 127.20, 125.82 (Ph), 125.01 (C-6), 123.08 (C-7), 115.97 (C-9a), 70.06 (OCH_2N), 70.48 (CH_2O), 60.20 (CPh_3), 59.90 (CH_2OH), 12.00 (6-CH_3).

Method B[15] : A solution of **3** (0.102 g, 0.16 mmol) and ammonium fluoride (0.030 g, 0.8 mmol) in anhydrous methanol (3 ml) was stirred at 50°C overnight. After cooling **12** crystallized: 0.070 g (85%), mp 198°C dec.

Tritylation of 6 in the presence of triethylamine. **6** (0.436 g, 1.2 mmol) suspended in dichloromethane (19 ml) was stirred with triethylamine (0.243 g, 2.4 mmol) for 15 min. Chlorotriphenylmethane (0.669 g, 2.4 mmol) was added and the reaction was over in 1 hour to give two products **7** and **8** and no traces of unreacted **6**. The solution was diluted with dichloromethane (15 ml), cooled and treated with sat. $NaHCO_3$ solution (25 ml). Organic layer was separated, washed with water and dried over sodium sulfate. After evaporation **7** and **8** were separated on a silica gel column with 0-2% ethanol in dichloromethane.

3,9-Dihydro-3-[(2-tert-butyldimethylsilyloxyethoxy)methyl]-9-oxo-5-triphenylmethylimidazo[1,2-a]purine (7): 0.327 g (45%) as a colourless glass. UV (MeOH): λ_{max} 288 nm (ε 14500), 298 (ε 12600, sh). ^1H NMR (DMSO-d_6): 7.92 (s, 1H, H-2), 7.75 (d, 1H, H-7), 7.28 (br m, 15H, Ph), 7.16 (d, 1H, H-6), 5.00 (s, 2H, OCH_2N), 3.36, 3.03 (2m, 4H, 2xCH_2), 0.79 (s, 9H, *tert*-butyl), -0.02 (s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): 151.10 (C-9), 149.28 (C-3a), 144.87 (C-4a), 140.88 (Ph), 139.49 (C-2), 129.37, 127.83, 127.44 (Ph), 118.98 (C-6), 106.63 (C-7), 75.80 (CPh_3), 71.67 (OCH_2N), 71.08 (CH_2O), 61.75 (CH_2OSi), 25.73, 17.90 (*tert*-butyl), -5.34 (CH_3Si).

3,9-Dihydro-5,7-di-triphenylmethyl-3-[(2-tert-butyldimethylsilyloxyethoxy)methyl]-9-oxoimidazo[1,2-a]-purine (8): 0.478 g (47%) as a colourless glass. UV (MeOH): λ_{max} 296 nm (ε 16500), 285 (ε 16100, sh). MS: m/z 848 $(M+H)^+$ 8%, 243 $(CPh_3)^+$ 100%, calcd for $(M+H)^+$ 848.3996, found 848.3997. ^{1}H NMR (DMSO-d_6): 7.75 (s, 1H, H-2), 7.26 (m, 25H, Ph), 7.05 (br m, 3H, Ph), 6.77 (brd, 2H, Ph), 6.32 (s, 1H, H-6), 4.91 (s, 2H, OCH_2N), 3.39, 3.06 (2m, 4H, 2xCH_2), 0.84 (s, 9H, *tert*-butyl), 0.01 (s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): 151.25 (C-9), 147.71 (C-3a), 147.14 (Ph), 147.00 (C-4a), 143.54, 140.57 (Ph), 138.68 (C-2), 129.83, 129.44, 129.19 (Ph), 128.34 (C-7), 127.68, 127.28, 127.13, 126.27, 125.74 (Ph), 121.39 (C-6), 115.89 (C-9a), 75.88 (CPh_3), 71.48 (OCH_2N), 71.03 (CH_2O), 61.70 (CH_2OSi), 60.12 (CPh_3), 25.69, 17.86 (*tert*-butyl), -5.39 (CH_3Si).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-5-triphenylmethylimidazo[1,2-a]purine (10).

A suspension of **7** (0.133 g, 0.22 mmol), in 80% aqueous acetic acid (5 ml) was stirred at ambient temperature for 6 hours. The resulting solution was diluted with anhydrous toluene (25 ml) and evaporated under vacuum below 25°C. The residue was coevaporated with successive volumes of toluene (3x10 ml) to remove traces of acetic acid. **10** was then purified on a silica gel column with 5% methanol in dichloromethane to give 0.098 g (91%) of title compound as colourless oil. Analytical sample was crystallized from methanol mp 180°C dec. UV (MeOH): λ_{max} 287 nm (ε 20000), 296 (ε 16800, sh). MS: m/z 492 $(M+H)^+$ 20%, 243 $(CPh_3)^+$ 100%, calcd for $(M+H)^+$ 492.2035, found 492.2036. Anal. for $C_{29}H_{25}N_5O_3 \cdot 1/3\ CH_3OH$ (according to ^{1}H NMR): calcd C 70.15, H 5.28, N 13.94; found C 69.96, H 5.65, N 13.25. ^{1}H NMR (DMSO-d_6): 7.94 (s, 1H, H-2), 7.76 (d, 1H, H-7), 7.32 (m, 15H, Ph), 7.19 (d, 1H, H-6), 5.00 (s, 2H, OCH_2N), 4.53 (t, 1H, ex, OH), 3.24 (m, 2H, CH_2OH), 2.99 (m, 2H, CH_2O). ^{13}C NMR (DMSO-d_6): 151.04 (C-9), 149.27 (C-3a), 144.79 (C-4a), 140.82 (Ph), 139.50 (C-2), 129.30, 127.78, 127.37 (Ph), 118.92 (C-6), 114.99 (C-9a), 106.55 (C-7), 75.74 (CPh_3), 71.55 (OCH_2N), 71.29 (CH_2O), 59.64 (CH_2OH).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-7-triphenylmethyl-5H-imidazo[1,2-a]purine (9).

A suspension of **8** (0.237 g, 0.28 mmol) in 80% aqueous acetic acid (15 ml) was stirred at 55°C for 3 hours. According to TLC both O-TBDMS and N-5-Tr groups were removed. The solution was then coevaporated with toluene (3x20 ml) and the residue was purified on a silica gel column with 5-10% methanol in chloroform. It yielded 0.106 g (77%) of **9** as a white solid. Analytical sample was crystallized from methanol: soft. 186°C, mp 239°C dec. UV (MeOH): λ_{max} 285 nm (ε 24500). MS: calcd for $(M+H)^+$ 492.2036, found 492.2031. Anal. for $C_{29}H_{25}N_5O_3 \cdot 1/4\ CH_3OH$ (according to ^{1}H NMR): calcd C 70.32, H 5.25, N 14.02; found C 70.64, H 5.24, N 13.31. ^{1}H NMR (DMSO-d_6): 12.48 (d, 1H, ex, N-5-H), 7.88 (s, 1H, H-2), 7.22 (m, 13H, Ph), 6.84 (m, 2H, Ph), 6.34 (d, 1H, H-6), 5.43 (s, 2H, OCH_2N), 4.69 (t, 1H, ex, OH), 3.52 (m, 4H, 2xCH_2). ^{13}C NMR (DMSO-d_6): 151.49 (C-9), 149.19 (C-3a), 148.31 (C-4a), 147.59, 144.17 (Ph), 138.47 (C-2), 129.79 (Ph), 129.06 (C-7), 127.35, 127.05, 126.48, 125.65 (Ph), 118.14 (C-6), 115.88 (C-9a), 72.07 (OCH_2N), 70.44 (CH_2O), 59.98 (CPh_3), 59.85 (CH_2OH).

Tritylation of 5 in the presence of potassium carbonate in DMF. **3** (0.025 g, 0.1 mmol) dried by successive coevaporations with dimethylformamide (2x6 ml) was suspended in DMF (4 ml) and treated with powdered anhydrous K_2CO_3 (0.018 g, 0.13 mmol). The reaction mixture was vigorously stirred for 30 min. at room temperature and chlorotriphenylmethane (0.031 g, 0.11 mmol) was then added. The suspension darkened immediately. The reaction was completed in 1 hour. The volatiles were removed under vacuum. The residue contained three products which were separated on silica gel plates, and then eluted from silica gel with 8% methanol in dichloromethane to give: **10** (0.029 g, 60%), **11** (0.018 g, 25%) and **9** (0.002 g, 5%) respectively. The products were identical with samples obtained upon deprotection of **7** and **8**.

***3,9-Dihydro-5,7-di-triphenylmethyl-3-[(2-hydroxyethoxy)methyl]-9-oxoimidazo[1,2-a]*purine (11)**:
UV (MeOH): λ_{max} 296 nm (ε 16700), 285 (ε 15300, sh), ^{1}H NMR ($CDCl_3$): 7.45 (s, 1H, H-2), 7.25, 7.15 (2m, 25H, Ph), 6.99, 6.84 (2 brs, 5H, Ph), 6.28 (s, 1H, H-6), 4.89 (s, 2H, OCH_2N), 3.41 (m, 2H, CH_2OH), 3.02 (m, 2H, CH_2O), 1.71 (brs, 1H, ex, OH). **11** could be prepared upon deprotection of compound **8** with ammonium fluoride in methanol[15], as described for **12**. The reaction performed in the presence of triethylamine gave products **10**, **11** and **9** in the yields almost identical with above.

Tritylation of 1 in the presence of triethylamine. **1** (0.160 g, 0.61 mmol) dried by successive coevaporations with DMF (2x20 ml) was dissolved in DMF (8 ml) and treated with triethylamine (0.132 g, 1.3 mmol). Chlorotriphenylmethane (0.200 g, 0.73 mmol) was added in 5 min. and the solution turned black immediately. After three hours the reaction did not proceed further. According to TLC three products were observed in order of increasing polarity: **14**, **12**, **13** and considerable amount of substrate **1**. The volatiles were removed under vacuum. The residue was suspended in chloroform (20 ml) and washed with sat. $NaHCO_3$ solution (20 ml) then with water (20 ml). The layers were separated. Unreacted **1** remained in the aqueous solution and was isolated (0.064 g, 40%). The organic layer was dried over sodium sulfate and evaporated to dryness. The products were separated on a silica gel column with 5-8% ethanol in dichloromethane.

7-(4-Benzhydrylphenyl)-3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-9-oxo-5-triphenylmethyl-imidazo[1,2-a]purine (14). 0.022 g (5%) an off-white foam. UV (MeOH): λ_{max} 296 nm (ε 17500). MS: m/z 748 $(M+H)^+$ 8%, 243 $(CPh_3)^+$ 100%, calcd for $(M+H)^+$ 748.3287, found 748.3313. ^{1}H NMR (DMSO-d_6): 7.86 (s, 1H, H-2), 7.45, 7.22 (2m, 29H, Ph), 5.68 (s, 1H, $CHPh_2$), 4.89 (s, 2H, OCH_2N), 4.59 (t, 1H, ex, OH), 3.31 (m, 2H, CH_2OH), 3.03 (m, 2H, CH_2O), 1.54 (s, 3H, 6-CH_3). ^{13}C NMR (DMSO-d_6): 151.94 (C-9), 147.62 (C-3a), 145.87 (C-4a), 143.64, 142.96 ($CHPh_2$), 141.95 (CPh_3), 139.08 (C-2), 131.01, 129.56, 128.97, 128.28, 128.02, 127.06, 126.20 (Ph), 125.97 (C-6), 120.72 (C-7), 115.40 (C-9a), 76.37 (CPh_3), 71.29 (OCH_2N), 70.68 (CH_2O), 59.75 (CH_2OH), 55.51 ($CHPh_2$), 13.73 (6-CH_3).

12: 0.084 g (27%) an off-white solid, recrystallized from methanol afforded 0.051 g of crystals. The filtrate contained also traces of less polar byproduct ***3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-9-oxo-5-triphenylmethylimidazo[1,2-a]purine (15):*** 0.0015 g (0.5%) which was isolated by chromatography on TLC

plates with 7% ethanol in dichloromethane containing 0.2% of Et_3N. **15**, MS: m/z 506 $(M+H)^+$ 15%, 243 $(CPh_3)^+$ 100%, calcd for $(M+H)^+$ 506.2192, found 506.2153.

7-(4-Benzhydrylphenyl)-3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-9-oxo-5H-imidazo[1,2-a]-purine (13): 0.041 g (13%) a white foam. UV (MeOH): λ_{max} 291 nm (ε 10200). MS: calcd for $(M+H)^+$ 506.2192, found 506.2162. ^1H NMR (DMSO-d_6): 12.60 (s, 1H, ex, N-5-H), 7.97 (s, 1H, H-2), 7.34, 7.24 (2m, 12H, Ph), 7.14 (d, 2H, Ph), 5.69 (s, 1H, $CHPh_2$), 5.48 (s, 2H, OCH_2N), 4.69 (t, 1H, ex, OH), 3.49 (m, 4H, $2xCH_2$), 2.14 (s, 3H, 6-CH_3). ^{13}C NMR (DMSO-d_6): 152.50 (C-9), 149.30 (C-3a), 145.88 (C-4a), 143.69, 142.53 (Ph), 138.77 (C-2), 130.68, 128.98, 128.30, 127.44, 127.24, 126.21 (Ph), 123.60 (C-6), 118.37 (C-7), 115.70 (C-9a), 72.11 (OCH_2N), 70.46 (CH_2O), 59.83 (CH_2OH), 55.60 ($CHPh_2$), 9.67 (6-CH_3).

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