Pergamon

Tetrahedron Letters, Vol. 35, No. 18, pp. 2937-2940, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0421-S

Synthesis of Novel 3',4'-Seco Analogues of Didehydro Dideoxy Nucleosides as Potential Antiviral Agents

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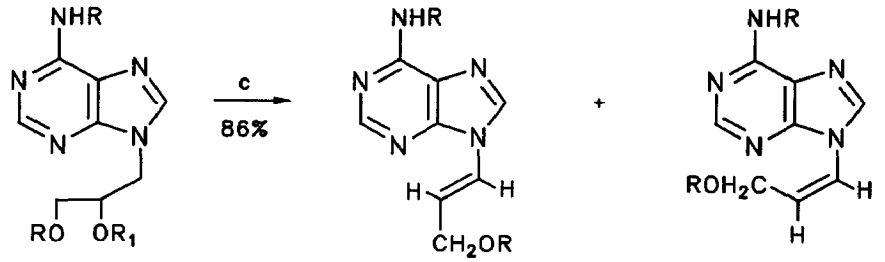
Abstract: Novel acyclo analogues (13,14) of didehydro dideoxy adenosine (d4A) lacking C-3'-C-4' bond were synthesized as potential anti-HIV agents. The key step involves the bromination of unsaturated isomer **6** with NBS in mono protected ethylene glycol leading to 3',4'-seco-2'-bromo-3'-hydroxy compound **11a**. Activation of 3'-hydroxy group and reductive elimination of vicinal bromo tosylate gave **13** which on deprotection was converted into the target molecule **14**.

In the recent years, the enormous efforts have been made to discover superior nucleoside or acyclonucleoside based therapeutic agents for treatment of viral infections, especially AIDS. Among compounds which were tested as anti-HIV agents 2',3'-dideoxynucleosides have been the most successful. Besides AZT (3'-azido-3'-deoxythimydine), ddI (2',3'-dideoxyinosine) and ddC (2',3'-dideoxycytidine) being the only approved drugs for the clinical treatment of AIDS[1], some very recently prepared unsaturated analogues such as d4T (2',3'- didehydro-3'-deoxythymidine) and its cytidine counterpart d4C (2',3'-didehydro-2',3'--dideoxycytidine) show very promising anti-HIV activity and selectivity. In addition d4T and d4C are less toxic than AZT in cell culture and d4T have gone through at last preliminary clinical trials[2]. The unsaturated adenosine analogue (d4A) does not display potent but moderate anti-HIV activity and its phosphonate derivative, was found recently, to exhibit activity comparable to that of d4T. Furthermore, the latter was superior to d4T in inhibiting replication of Rauscher-murine Leukemia retrovirus (R-MuLV)[3]. More recently, it was also reported that various 6-substituted acyclic pyrimidine nucleoside analogues related to acyclovir, 9-[(2-hydroxyethoxy)methyl] guanine, such as HEPT, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine, are selective inhibitors of HIV[1b,d].

Regarding the aforementioned, in this communication we report on the synthesis of a new acyclonucleoside analogue of d4A, (±)-9-[1-(2-hydroxyethoxy)allyl] adenine (**14**), lacking C-3'-C-4' bond[4]. The synthesis of acyclic thymidine analogue of d4T is currently under investigation. In the initial steps (**Scheme 1**) the primary hydroxyl group of 9-(2,3-dihydroxypropyl)adenine[5] (**1**) was selectively tritylated[6] followed by mesylation[7] of remaining secondary one to give the required 2'-mesyloxy-3'-trityloxy compound **3**[8]. Heating **3** (110-120°C) in the presence of an excess of DBU (1,8-diazabicyclo[5.4.0.] undec-7-ene) gave as the consequence of C-1'-C-2' elimination the mixture of (E)-9-(3-trityloxyprop-1-enyl)adenine (**4**)

and (Z)-isomer **5** in 65% and 21% yield, respectively. The exclusive formation of prop-1'-enyl and not prop-2'-enyl isomers results presumably from the greater acidity of 1'-proton compared to 3'-proton. On the other hand, the formation of (E)-**4** and (Z)-**5** in ~3:1 ratio, respectively, may be explained by the bulkiness of 3'-trityloxy group being *cis*- to adenine in **5**. The structures of olefins **4** and **5** were established by spectral data (^{1}H and ^{13}C NMR, IR, UV) and microanalytical results. In particular, the *trans*- and *cis*-

Scheme 1



a: TrCl,py,60-65°C,2 days; b: MsCl,py,5°C,overnight;
c: DBU,110-120°C,1h; d: 80% HOAc,10 min.

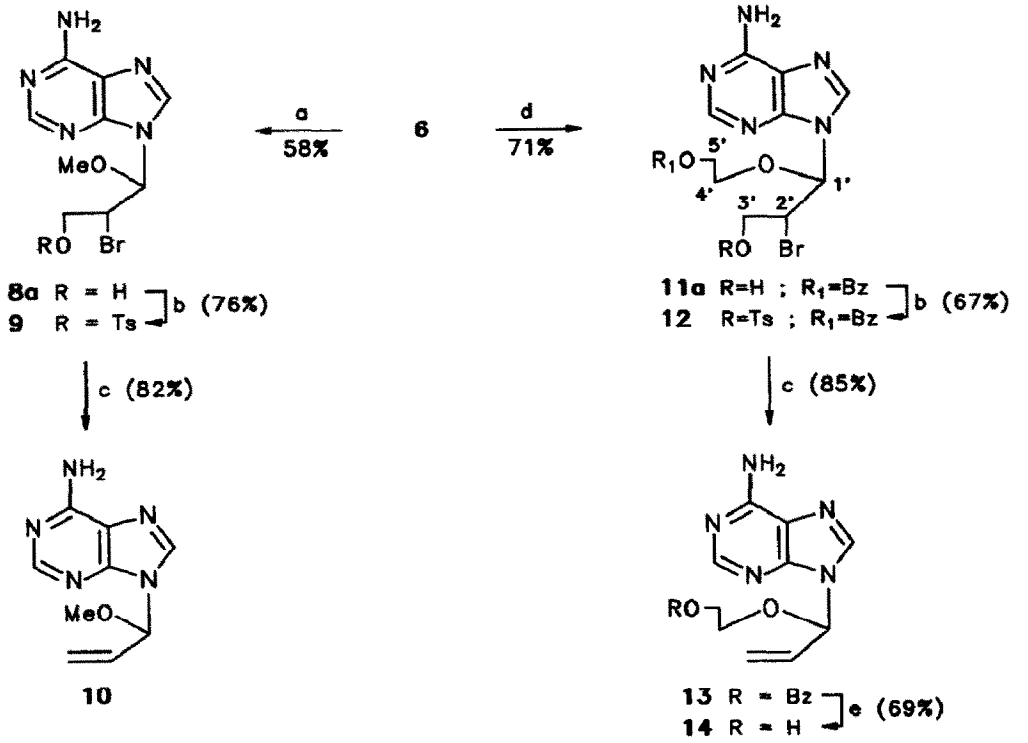
-relation of the 1'- and 2'-protons was supported by the values of the coupling constants ($^3J_{trans}$=14.5 and $^3J_{cis}$=9 Hz). Subsequent detritylation of (E)-**4** and (Z)-**5**, under acidic conditions, afforded (E)-9-(3--hydroxyprop-1-enyl)adenine (**6**) and (Z)-olefin **7**, respectively, in nearly quantitative yields[9]. According to the report of J. Zemlicka and coworkers, analogous (E)- and (Z)-9-(4-hydroxybut-1-enyl)adenine are good substrates for adenosine deaminase[10].

The synthesis of the hitherto unknown 9-(1-methoxyallyl)adenine (**10**) (**Scheme 2**) started with bromo-methoxylation of unsaturated **6** by the efficient procedure described recently[7] to give racemic *erythro*-1'-methoxy-2'-bromide **8a**[11]. Similarly, the reaction of (Z)-isomer **7** with Br_2 / MeOH, under identical reaction conditions, furnished (±)-*threo*-1'-methoxy-2'-bromo compound **8b**[11] in 65% yield. Further tosylation of **8a** under standard conditions provided the (±)-*erythro*-tosylate **9**. Reductive elimination[12] of the vicinal bromo tosylate **9** was readily accomplished with freshly prepared zinc-copper couple under acidic conditions in DMF to give acyclic unsaturated analogue **10**[13].

The found regioselective reactions of **6** and **7** with Br_2 / MeOH giving 1'-methoxy-2'-bromo derivatives **8a** and **8b**, respectively, opened the possibility for preparation of (±)-*erythro*-9-[1-(2-benzoyloxy-ethoxy)-2-bromo-3-hydroxypropyl] adenine (**11a**)[14] as the key intermediate in the synthesis of (d4A) analog **14**. However, reacting **6** with bromine in dry 2-benzoyloxyethanol gave the 1:1 mixture of **11a** and racemic *erythro*-9-(1,2-dibromo-3-hydroxypropyl)adenine while in the same reaction with **7** the (±)-*threo*-

-9-[1-(2-benzoyloxyethoxy)-2-bromo-3-hydroxypropyl] adenine (**11b**)[14] and (±)-*threo*-1',2'-dibromide were obtained[15]. At variance to the above reactions with Br_2 / MeOH, both **6** and **7** in reactions with NBS / HO-C_2H_4-OBz gave single products **11a**(71% yield) and **11b** (70% yield), respectively.

Scheme 2



a: Br_2,MeOH; b: TsCl,py,5°C,2-3 days; c: Zn-Cu,HOAc,DMF,15 min;
d: NBS,HO-CH_2CH_2-OBz; e: NH_3,MeOH.

Conversion of **11a** to (±)-9-(1-[2-benzoyloxyethoxy] allyl)adenine (**13**)[16] was carried out in same manner as described for **10**. Deprotection of **13** by methanolic ammonia gave the target product **14**[16].
Further studies on the synthesis of the related compounds, particularly pyrimidine analogues, as well as the investigations of the biological activity are in due course.

Acknowledgement: This work was supported by Ministry of Science and Technology, Republic of Croatia, project no. 1-07-188.

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8. All spectral and analytical data for new compounds are in accordance with their structures.
9. Selected data for **6**: mp 226-227°C (MeOH), ^{1}H NMR (DMSO-d_6, **300 MHz**) δ 8.56 (s, 1H, H-8), 8.31 (s, 1H, H-2), 7.41 (br.s, 2H, NH_2-6) 7.33 (d, 1H, H-1', $^3J_{1',2'}$=14.45 Hz), 6.84 (dt, 1H, H-2', $^3J_{2',3'}$=5.15 Hz), 5.13 (t, 1H, HO-3', $^3J_{OH,3'}$=5.3 Hz), 4.29 - 4.26 (m, 2H, H-3'). For **7**: mp 196-197°C (MeOH), ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H, H-8), 8.18 (s, 1H, H-2), 7.39 (br.s, 2H, NH_2-6), 6.91 (dd, 1H, H-1', $^3J_{1',2'}$=9.0 Hz, $^4J_{1',3'}$=1.4 Hz), 5.78 (dt, 1H, H-2', $^3J_{2',3'}$=6.4 Hz), 5.11 (t, 1H, HO-3', $^3J_{OH,3'}$=5.45 Hz), 4.18 (ddd, 2H, H-3').
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11. **8a**: mp 209-210°C (MeOH), ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H, H-8), 8.27 (s, 1H, H-2), 7.44 (br.s, 2H, NH_2-6), 5.91 (d, 1H, H-1', $^3J_{1',2'}$=**9.1** Hz), 5.53 (t, 1H, HO-3', $^3J_{OH,3'}$=5.55 Hz), 5.20 (dt, 1H, H-2', $^3J_{2',3'}$=3.5 Hz), 4.10 - 3.97 (m, 2H, H-3'), 3.33 (s, 3H, CH_3O-1'). **8b**: oil, ^{1}H NMR (DMSO-d_6) δ 8.26 (s, 1H, H-8), 8.19 (s, 1H, H-2), 7.28 (br.s, 2H, NH_2-6), 5.91 (d, 1H, H-1', $^3J_{1',2'}$=**5.5** Hz), 5.40 (t, 1H, HO-3', $^3J_{OH,3'}$=5.65 Hz), 4.66 (ddd, 1H, H-2', $^3J_{2',3'a}$=5.5 Hz, $^3J_{2',3'b}$=5.7 Hz), 3.73 (ddd, 1H, H_a-3', $^2J_{3'a,3'b}$=11.85 Hz), 3.58 (ddd, 1H, H_b-3'), 3.33 (s, 3H, CH_3O-1').
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13. **10**: mp 150-151°C (MeOH), ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H, H-8), 7.95 (s, 1H, H-2), 6.17 (dd, 1H, H-1', $^3J_{1',2'}$=4.45 Hz), 6.11 (ddd, 1H, H-2', $^3J_{2',3'a}$=16.9 Hz, $^3J_{2',3'b}$=10.4 Hz), 6.00 (br.s, 2H, NH_2-6), 5.54 (ddd, 1H, H_a-3', $^2J_{3'a,3'b}$=3.4 Hz, $^4J_{3'a,1'}$=1.45 Hz), 5.46 (ddd, 1H, H_b-3', $^4J_{3'b,1'}$=1.45 Hz), 3.36 (s, 3H, CH_3O-1').
14. **11a**: ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H, H-8), 8.12 (s, 1H, H-2), 8.02 - 7.46 (m, 5H, Ar), 6.37 (br.s, 2H, NH_2-6), 6.22 (d, 1H, H-1', $^3J_{1',2'}$=**3.9** Hz), 4.66 (ddd, 1H, H-2', $^3J_{2',3'b}$=9.35 Hz, $^3J_{2',3'a}$=4.5 Hz), 4.58 (ddd, 1H, H_a-5', $^2J_{5'a,5'b}$=12.45 Hz, $^3J_{5'a,4'b}$=6.1 Hz, $^3J_{5'a,4'a}$=3.1 Hz), 4.47 (ddd, 1H, H_b-5', $^3J_{5'b,4'a}$=5.8 Hz, $^3J_{5'b,4'b}$=3.1 Hz), 3.97 (ddd, 1H, H_a-4', $^2J_{4'a,4'b}$=11.4 Hz), 3.93 - 3.86(m, 2H, H_b-4' and H_a-3'), 3.41 (dd, 1H, H_b-3', $^2J_{3'b,3'a}$=12.65 Hz). **11b**: ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H, H-8), 8.15 (s, 1H, H-2), 8.00 - 7.44 (m, 5H, Ar), 6.24 (br.s, 2H, NH_2-6), 6.16 (d, 1H, H-1', $^3J_{1',2'}$=**5.7** Hz), 4.59 (ddd, 1H, H_a-5', $^2J_{5'a,5'b}$=12.4 Hz, $^3J_{5'a,4'b}$=6.3 Hz, $^3J_{5'a,4'a}$=3.2 Hz), 4.47 (ddd, 1H, H_b-5', $^3J_{5'b,4'a}$=5.5 Hz, $^3J_{5'b,4'b}$=3.2 Hz), 4.37 (ddd, 1H, H-2', $^3J_{2',3'a}$=5.7 Hz, $^3J_{2',3'b}$=3.2 Hz), 3.99 (ddd, 1H, H_a-4', $^2J_{4'a,4'b}$=11.5 Hz), 3.94 - 3.87 (m, 1H, H_b-4'), 3.90 (dd, 1H, H_a-3', $^2J_{3'a,3'b}$=12.7 Hz), 3.76 (dd, 1H, H_b-3').
15. Full details of this reactions will be published in due course.
16. **13**: ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H, H-8), 7.97 (s, 1H, H-2), 7.99 - 7.44 (m, 5H, Ar), 6.37 (d, 1H, H-1', $^3J_{1',2'}$=4.2 Hz), 6.11 (ddd, 1H, H-2', $^3J_{2',3'a}$=17.0 Hz, $^3J_{2',3'b}$=10.6 Hz), 6.10 (br.s, 2H, NH_2-6), 5.59 (d, 1H, H_a-3'), 5.47 (d, 1H, H_b-3'), 4.5 (ddd, 1H, H_a-5', $^2J_{5'a,5'b}$=12.2 Hz, $^3J_{5'a,4'b}$=6.2 Hz, $^3J_{5'a,4'a}$=3.3 Hz), 4.42 (ddd, 1H, H_b-5', $^3J_{5'b,4'a}$=6.2 Hz, $^3J_{5'b,4'b}$=3.3 Hz), 3.99 (ddd, 1H, H_a-4', $^2J_{4'a,4'b}$=11.2 Hz), 3.78 (ddd, 1H, H_b-4'). **14**: ^{1}H NMR (DMSO-d_6) δ 8.45 (s, 1H, H-8), 8.20 (s, 1H, H-2), 7.35 (br.s, 2H, NH_2-6), 6.39 (d, 1H, H-1', $^3J_{1',2'}$=4.25 Hz), 6.12 (ddd, 1H, H-2', $^3J_{2',3'a}$=17.05 Hz, $^3J_{2',3'b}$=10.55 Hz), 5.62 (d, 1H, Ha-3'), 5.46 (d, 1H, Hb-3'), 5.15 (br.s, 1H, HO-5'), 3.71-3.32 (m, 4H, H-4' and H-5').

(*Received in UK* 20 *December* 1993; *accepted* 25 *February* 1994)