



First synthesis of 1-deazacytidine, the C-nucleoside analogue of cytidine

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Abstract—The synthesis of 1-deazacytidine, the C-nucleoside analogue of cytidine, is described. It involves coupling of a protected 2-amino-5-bromopyridine with perbenzylated ribonolactone and transformation of the pyridine ring into the desired substituted pyridone. This synthesis completes the family of C-nucleosidic analogues of natural nucleosides. © 2002 Elsevier Science Ltd. All rights reserved.

Nucleoside analogues that are only minimally altered with respect to the corresponding natural nucleosides are valuable tools in structure activity studies.^{1,2} A very simple alteration is the replacement of the nitrogen linking the base to the sugar by a carbon, forming C-nucleosidic analogues of the natural nucleosides. In the case of the pyrimidines, but not the purines, this changes the hydrogen bond recognition properties of the base (Fig. 1). An attractive feature of these ana-

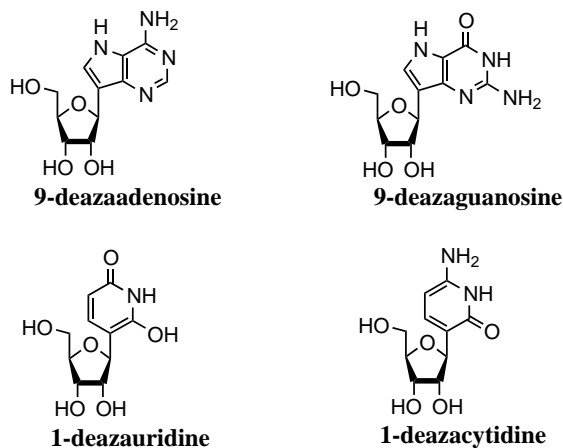


Figure 1.

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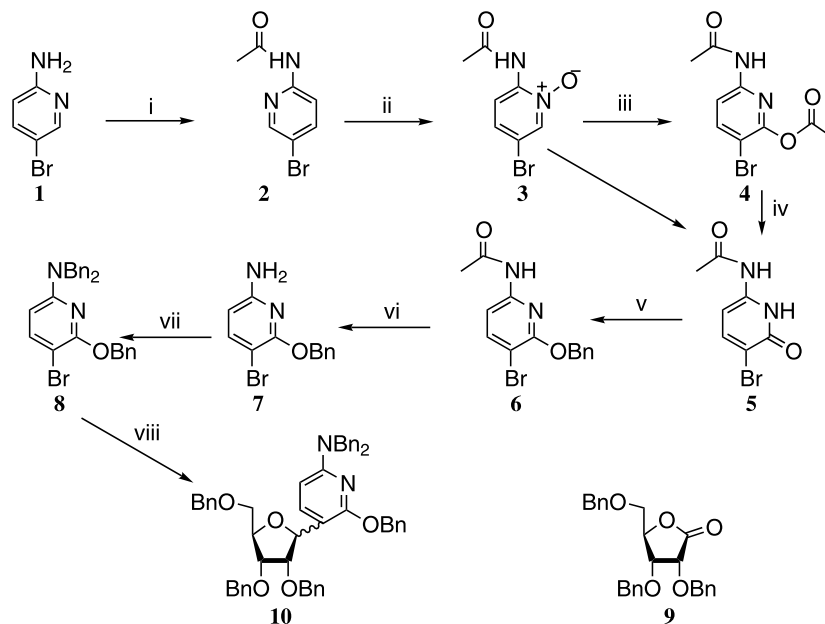
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logues is the stability of the bond between base and sugar towards both chemical and enzymatic hydrolysis. Furthermore, C-nucleosides, such as showdomycin,³ show a broad spectrum of biological activity and so have stimulated considerable interest as potential anti-tumour, anti-bacterial and anti-cancer agents.⁴

C-Nucleosidic analogues of adenosine (9-dezaadenosine)⁵ and guanosine (9-deazaguanosine)⁶ have been synthesised and studied. 1-Dezaauridine⁷ was synthesised some time ago but the authors encountered problems with its stability. To the best of our knowledge 1-deazacytidine has never been synthesised.

As synthetic targets, C-glycosides have received much attention⁸ and amongst them C-nucleosides have been widely studied.⁹ The synthesis of C-nucleosides bearing functionalised pyridine rings has mainly been approached by two methods: Heck-type coupling to a glycol^{10,11} or nucleophilic attack on a lactone followed by dehydroxylation.^{1,12,13} We decided to use the latter because it allowed more flexibility and was potentially higher yielding.

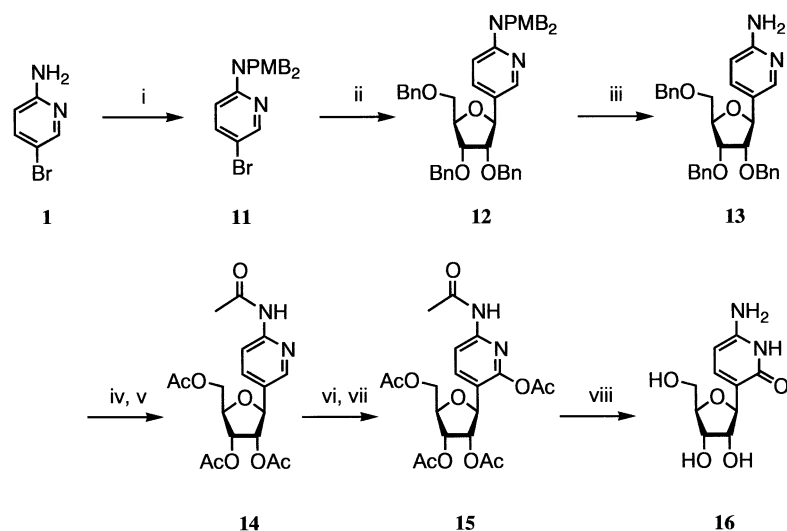
1-Deazacytidine is a 2-oxygenated pyridine, a family of compounds which is difficult to prepare.¹⁴ In an initial study (Scheme 1) we followed a known route¹⁵ to the pyridone **5**. Acetylation of 2-amino-5-bromo-pyridine **1** in the presence of acetic anhydride gave **2** in 97% yield, which was oxidised to the N-oxide **3** with *m*CPBA in 85% yield. Compound **3** underwent a rearrangement¹⁶ upon heating in acetic anhydride, and deacetylation of the resulting acetate **4** gave the pyridone **5**. This



Scheme 1. (i) Ac₂O, 80°C, 24 h, 97%; (ii) *m*CPBA (1.5 equiv.), CH₂Cl₂, rt, 12 h, 85%; (iii) Ac₂O, reflux, 1 h; (iv) NaOH, MeOH, rt, 2 h, 58% (two steps); (v) BnBr (2.5 equiv.), Ag₂CO₃ (0.6 equiv.), toluene, 60°C, 24 h, 41%; (vi) KOH, MeOH, pyr., H₂O, 110°C, 24 h, 94%; (vii) BnBr (3 equiv.), NaH (3 equiv.), DMF, rt, 12 h, 87%; (viii) (a) *n*BuLi (1 equiv.), -78°C, 3 h, (b) 9 (1 equiv.), -78°C, 2 h, 0°C, 3 h, (c) BF₃·OEt₂ (3 equiv.), Et₃SiH (3 equiv.), CH₂Cl₂, -78°C→rt, 12 h, 34%.

product was transformed into the fully benzyl-protected pyridine **8**¹⁷ by selective *O*-benzylation of the pyridone¹⁸ in the presence of silver carbonate (41%), followed by deacetylation with potassium hydroxide (94%) and final benzylation of the amino group (87%). Bromide–lithium exchange in **8** with *n*BuLi at -78°C and in situ reaction with lactone **9** furnished a mixture of hemiacetals that were subsequently reduced with excess of Et₃SiH/BF₃·OEt₂ to give **10** as a mixture of isomers in 34% yield.

Difficulties in deprotection of this compound and low yields encountered throughout the synthesis led us to strive for a more efficient route. In an alternative approach (Scheme 2) we decided to couple 2-amino-5-bromo-pyridine to the ribose moiety before transforming it to the pyridone. A previous synthesis of the 2-amino-pyridine *C*-nucleoside of ribose¹³ utilised the stabase protecting group, but in our hands PMB protected 2-amino-5-bromo-pyridine **11** was more efficient.



Scheme 2. (i) PMBCl (2.5 equiv.), NaH (2.5 equiv.), DMF, rt, 6 h, 64%; (ii) (a) *n*BuLi (1 equiv.), -78°C, 3 h, (b) 9 (1 equiv.), -78°C, 2 h, 0°C, 3 h; (c) BF₃·OEt₂ (3 equiv.), Et₃SiH (3 equiv.), CH₂Cl₂, -78°C→rt, 12 h, 64%; (iii) TFA, rt, 24 h, 88%; (iv) Ac₂O, pyr., rt, 2 h, 91%; (v) (a) BBr₃ (5 equiv.), CH₂Cl₂, -78°C, 4 h, (b) Ac₂O, pyr, rt, 1 h, 91%; (vi) *m*CPBA (1.5 equiv.), CH₂Cl₂, rt, 12 h, 89%; (vii) Ac₂O, 140°C, 30 min, 84%; (viii) conc. aq. NH₃, 60°C, 24 h (79%).

2-Amino-5-bromo-pyridine **1** was protected using PMBCl and NaH yielding **11** (64%). Bromide–lithium exchange in PMB-protected **11** with *n*BuLi at -78°C and in situ reaction with lactone **9** furnished the hemiacetal that was subsequently reduced with excess of $\text{Et}_3\text{SiH}/\text{BF}_3\cdot\text{OEt}_2$ to provide **12** as a single isomer in 64% yield. PMB groups were removed with TFA to afford the known amine **13**¹³ confirming the stereoselectivity of the formation of **12**. The ^1H NMR spectrum of **13** was consistent with that reported in the literature.¹⁹ The primary amino group of **13** was acetylated and the benzyl groups were cleaved using BBr_3 and replaced with acetates (91%) to give **14**. It is also possible to debenzylate **13** and convert the fully deprotected nucleoside to **14** with acetic anhydride in pyridine, but this is lower yielding. The pyridine **14** was oxidised to the *N*-oxide with *m*CPBA and rearranged using Ac_2O at reflux to give the peracetylated pyridine derivative **15** in 75% yield over two steps. The final product **16**²⁰ was obtained (79%) as a foam by heating **15** in concentrated aqueous ammonia and removing the solvent under reduced pressure.

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References

- Matulic-Adamic, J.; Beigelman, L. *Tetrahedron Lett.* **1997**, *38*, 1667.
- Hsieh, H.-P.; McLaughlin, L. W. *J. Org. Chem.* **1995**, *60*, 5356.
- (a) Barton, D. H. R.; Ramesh, M. *J. Am. Chem. Soc.* **1990**, *112*, 891; (b) Kang, S. O.; Lee, S. B. *J. Chem. Soc., Chem. Commun.* **1995**, 1017.
- Review: Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223.
- Lim, M.-I.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25.
- Lim, M.-I.; Ren, W.-Y.; Brian, A. O.; Klein, R. S. *J. Org. Chem.* **1983**, *48*, 780.
- (a) Mertes, M. P.; Zielinski, J.; Pillar, C. *J. Med. Chem.* **1967**, *10*, 320; (b) Knackmuss, H.-J.; Briaire, J. *Liebigs Ann. Chem.* **1970**, *736*, 68.
- (a) Beau, J. M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1; (b) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55; (c) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545.
- (a) Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocyclic Chem.* **1997**, *68*, 223; (b) Nasr, A. Z. *Adv. Heterocyclic Chem.* **1998**, *70*, 163.
- Chen, J. J.; Walker, J. A., II; Liu, W.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1995**, *36*, 8363.
- Hsieh, H.-P.; McLaughlin, L. W. *J. Org. Chem.* **1995**, *60*, 5356.
- Piccirilli, J. A.; Krauch, T.; MacPherson, L. J.; Benner, S. A. *Helv. Chim. Acta* **1991**, *74*, 397.
- Hildbrand, S.; Blaser, A.; Parel, S. P.; Leumann, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 5499.
- Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* **1987**, *109*, 3789.
- Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263.
- Katada, M. *J. Pharm. Soc. Jpn.* **1947**, *67*, 51.
- Timpe, W.; Dax, K.; Weidmann, H. *Carbohydr. Res.* **1975**, *39*, 53.
- (a) Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040; (b) Shiao, M.-J.; Tarng, K.-Y. *Heterocycles* **1990**, *31*, 819.
- NMR data for **13**: ^1H NMR (300 MHz, CDCl_3) 3.58 (dd, $J=10.5, 3.9$ Hz, 1H), 3.63 (dd, $J=10.5, 4.2$ Hz, 1H), 3.79 (dd, $J=7.4, 5.2$ Hz, 1H), 4.01 (dd, $J=5.2, 3.3$ Hz, 1H), 4.31 (app.q, $J=4.1$ Hz, 1H), 4.41–4.62 (m, 6H), 4.90 (d, $J=7.4$ Hz, 1H), 6.42 (d, $J=8.5$ Hz, 1H), 7.20–7.38 (m, 15H), 7.45 (dd, $J=8.5, 2.2$ Hz, 1H), 8.07 (d, $J=2.2$ Hz, 1H). ^{13}C NMR (75.42 MHz, CDCl_3) 70.7, 72.1, 72.5, 73.6, 77.6, 80.6, 81.8, 83.4, 108.6, 125.6, 127.8–128.6 (15C), 136.4, 137.8, 138.0, 138.2, 146.8, 158.5.
- All compounds were fully characterised. Spectroscopic data for **16**: ^1H NMR (300 MHz, D_2O): δ 3.63 (t, $J=10.9$ Hz, 1H), 3.71 (dd, $J=5.5$ Hz, $J=10.5$ Hz, 1H), 3.88 (ddd, $J=3$ Hz, $J=5.5$ Hz, $J=10.5$ Hz, 1H), 3.94 (dd, $J=3$ Hz, $J=10.4$ Hz, 1H), 4.24 (t, $J=3$ Hz, 1H), 4.56 (d, $J=10.4$ Hz, 1H), 5.76 (d, $J=8.4$ Hz, 1H), 7.50 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O): δ 65.2, 67.1, 69.1, 71.2, 71.3, 91.9, 109.6, 144.4, 144.8, 162.7; MS/ES+: 243 (M+H)⁺. HRMS/ES+ *m/z* calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_5$ (MH⁺) 243.0982 found 243.0976.