Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2961–2964

Synthesis of the enantiomer of nelarabine

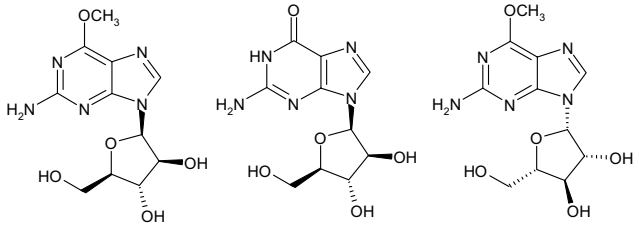
Karim Herbal,* John Kitteringham, Martyn Voyle and Andrew J. Whitehead

Synthetic Chemistry, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

Received 20 January 2005; revised 1 March 2005; accepted 8 March 2005
Available online 22 March 2005

Abstract—A synthesis of the enantiomer of nelarabine is described. Subtle changes in the protecting group strategy allow for an efficient inversion of the C-2′ stereocentre.

The nucleoside nelarabine **1** is a novel water soluble prodrug of arabinosylguanine **2**, which is currently being developed for the treatment of acute lymphoblastic leukaemia.[1,2]



1 **2** **3**

The synthesis of nelarabine is depicted in Scheme 1.[3] The key step in the synthesis is an enzyme catalysed *trans*-glycosylation reaction between 2-amino-6-methoxy-9*H*-purine **4** and 1-β-D-arabinosyl uracil **5** using a combination of purine nucleoside phosphorylase and uridine phosphorylase.[3] This enzymatic process is totally regio- and stereoselective as none of the alpha anomer or the *N*-7 regioisomer are observed. Furthermore, this transformation is totally stereospecific as the 1-β-L-arabinosyl uracil does not react.

To support the development program of nelarabine, the enantiomer **3** was required. Clearly the enzymatic approach used in the synthesis of nelarabine was unsuitable and therefore an alternative procedure was pursued.

One preferred method for the construction of nucleoside derivatives is via the use of the Vorbrüggen reaction.[4] In this case, however, a Vorbrüggen reaction on 1,2,3,5-tetra-*O*-acetyl-L-arabinose derivative **6** would lead predominantly to the undesired α-anomer **7** of the protected nucleoside derivative and not the desired β-substituted nucleoside[5] (Scheme 2).

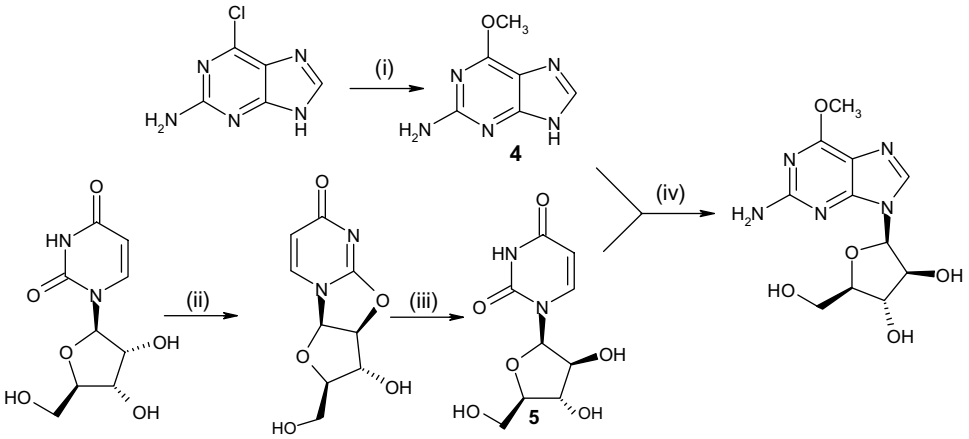
Our preferred strategy was to invert the C-2′ stereocentre of a nucleoside, which in turn would be prepared via a Vorbrüggen reaction between a suitably functionalised L-ribose derivative and a purine as depicted in Scheme 3.

Hence, commercially available L-ribose **8** was acetylated to give the 1,2,3,5-tetra-*O*-acetyl-L-ribofuranoside **9** according to the method reported by Guthrie and Smith.[6] Vorbrüggen reaction of **9** and 2-amino-6-methoxy-9*H*-purine **4** under standard conditions predominantly gave the *N*-7 adduct.[7] However, replacing 2-amino-6-methoxy-9*H*-purine **4** with 2-amino-6-chloropurine **10** gave exclusively the desired *N*-9 adduct **11**.[8] Tandem chloride displacement and deprotection of the ester functionalities was carried out using excess sodium methoxide in methanol and this afforded the desired nucleoside **12** (Scheme 4).[9]

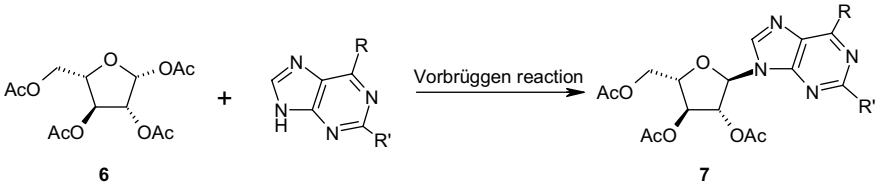
Selective protection of the C-3′ and C-5′ alcohol functionalities was achieved using di-*tert*-butyldichlorosilane to give the silyl ether[10] **13**, which was reacted with triflic anhydride to give the desired triflate **14**. Surprisingly, attempts to invert the C-2′ stereocentre with a range of nucleophiles proved unsuccessful as the C-2′ triflate did not react (Scheme 5).

Keywords: Nelarabine; Enantiomer; Nucleosides; Vorbrüggen.
* Corresponding author. Tel.: +44 14 38 76 8122; fax: +44 14 38 76 4869; e-mail: karim.9.herbal@gsk.com

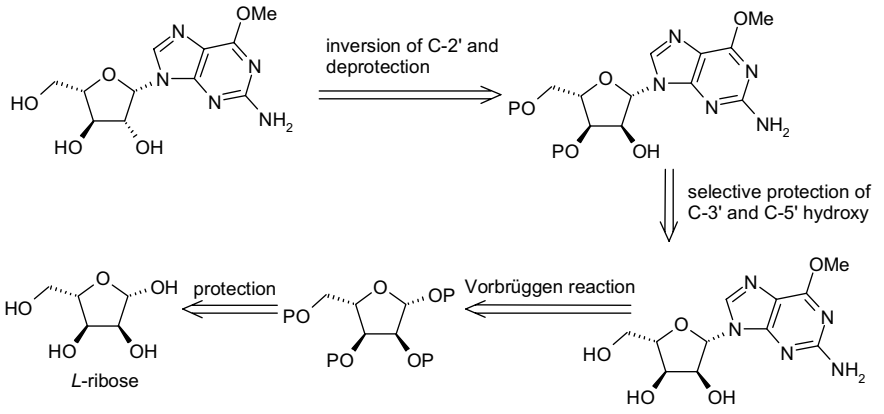
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.039



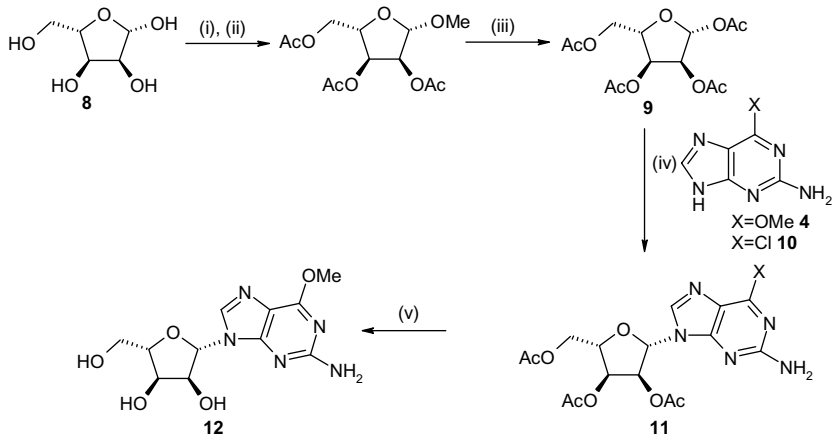
Scheme 1. Reagents and conditions: (i) NaOMe, MeOH; (ii) $(EtO)_2CO$, $NaHCO_3$; (iii) NaOH (aq); (iv) purine nucleoside phosphorylase, uridine phosphorylase, K_2HPO_4, KH_2PO_4.



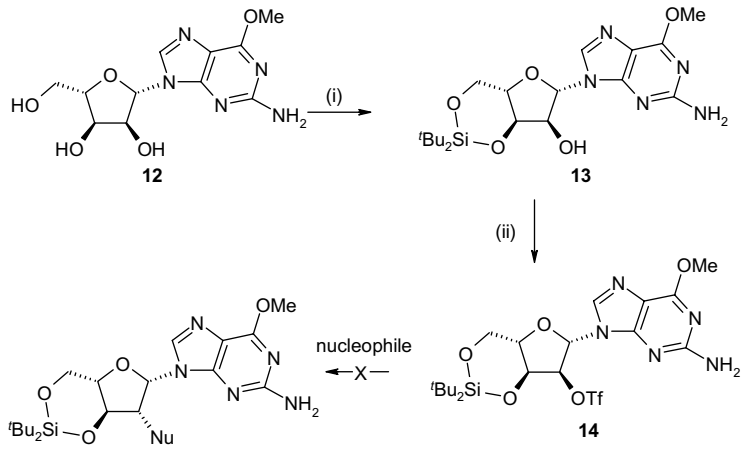
Scheme 2.



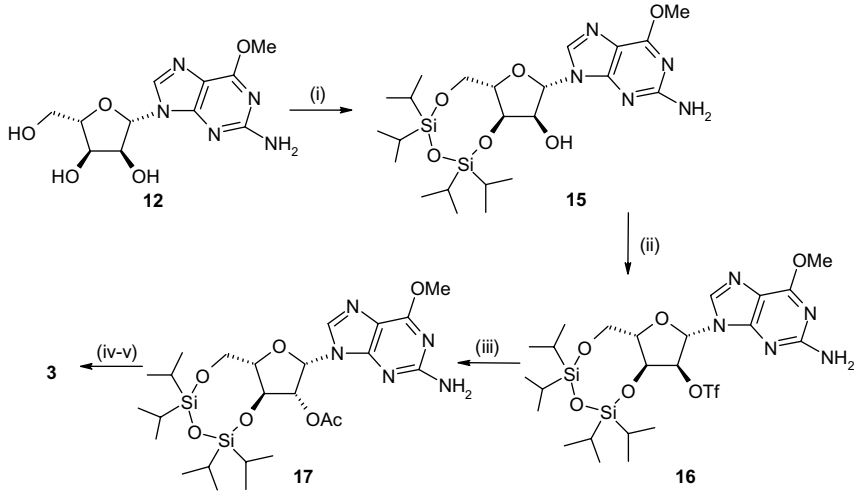
Scheme 3.



Scheme 4. Reagents and conditions: (i) MeOH, HCl; (ii) Ac_2O, pyridine; (iii) AcOH, Ac_2O, H_2SO_4; (iv) BSA, TMSOTf, MeCN, 75 °C; X = Cl, *N*-9 adduct 90%; X = OMe, *N*-7:*N*-9 1:1, 90%; (v) X = Cl, NaOMe, MeOH, *N*-7 adduct 60%; X = OMe, Na_2CO_3, MeOH–H_2O, *N*-9 adduct 97%.



Scheme 5. Reagents and conditions: (i) $^{t}Bu_2SiCl_2$, $AgNO_3$, Et_3N, DMF, 92%; (ii) Tf_2O, DMAP, pyridine, DCM, 80%.



Scheme 6. Reagents and conditions: (i) $TIBDSCl_2$, pyridine, 98%; (ii) Tf_2O, DMAP, pyridine, DCM, 82%; (iii) Bu_4NOAc, toluene, 83%; (iv) Na_2CO_3, MeOH, 97%; (v) TBAF, AcOH, THF, 51%.

Protection of the C-3′ and C-5′ functionalities of **12** by reaction with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$), however, gave the disilyloxyl ether[11] **15**, which was reacted with triflic anhydride under standard conditions to gave the C-2′ triflate **16**. Exposure of the triflate **16** to tetrabutylammonium acetate in toluene led to complete inversion of the C-2′ stereocentre and the desired acetate **17** was isolated in 83% yield. Quantitative removal of the acetate protecting group with catalytic sodium carbonate in methanol and water, followed by desilylation of the 1,3-diol moiety with TBAF afforded the desired enantiomer **3** of nelarabine (Scheme 6).

A possible explanation for the lack of reactivity of the silyl ether **14** may be that the fused *trans* 6,5-ring system is highly constrained, so much so that a C-2′ triflate is so sterically encumbered that it will not react with a nucleophile. The 8,5 ring system of the disilyloxy ether **15** is much more flexible and steric effects may not play such an important role.

In conclusion, an efficient synthesis of the enantiomer of nelarabine is reported whereby subtle changes in the protecting group strategy allowed for a highly effective inversion of the C-2′ stereocentre.

References and notes

1. Averett, D. R.; Koszalka, G. W.; Fyfe, J. A.; Roberts, G. B.; Purifoy, D. J. M. *Antimicrob. Agents Chemother.* **1991**, *35*, 851–857.
2. Lambe, C. U.; Averett, D. R.; Paff, M. T.; Reardon, J. E.; Wilson, J. G.; Krenitsky, T. A. *Cancer Res.* **1991**, *55*, 3352–3356.
3. (a) Mahmoudian, M. *Focus Biotechnol.* **2001**, *1*, 249–265; (b) Krenitsky, T. A.; Koszalka, G. W; Jones, L. A.; Averett, D. R.; Moorman, A. R. Eur. Patent Appl. EP 294114 A2 1988120, 19887; *Chem. Abstr.* **1988**, *111*, 7760; (c) Krenitsky, T. A.; Koszalka, G. W; Wilson, J. D.; Chamberlain S. D.; Porter, D.; Wolberg, G.; Averett, D. R.; Moorman, A. R. PCT Int. Appl. WO 9201456 A1 19920206, 1992; *Chem. Abstr.* **1992**, *116*, 236100.

4. Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React.* **2000**, *55*, 1–630.
5. Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; John Wiley: New York, 2001.
6. Guthrie, R. D.; Smith, S. C. *Chem. Ind.* **1968**, 547–548.
7. (a) Zhong, M.; Robins, M. J. *Tetrahedron Lett.* **2003**, *44*, 9327–9330; (b) Geen, G. R.; Kincey, P. M.; Choudary, B. M. *Tetrahedron Lett.* **1992**, *33*, 4609–4612.
8. Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull.* **1979**, *27*, 2518–2521.
9. (a) Gerster, J. F.; Jones, J. W.; Robins, R. K. *J. Org. Chem.* **1963**, *28*, 945–948; (b) Nair, V.; Lyons, A. G. *Tetrahedron* **1990**, *46*, 7677–7692.
10. (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999–5002; (b) Saito, Y.; Nyilas, A.; Agrofoglio, L. A. *Carbohydr. Res.* **2001**, *331*, 83–90.
11. Markiewicz, W. T. *J. Chem. Res. (S)* **1979**, *24*, 181.