

A new procedure for the synthesis of C-glycosides of nojirimycin

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Received (in Cambridge) 15th May 2000, Accepted 30th May 2000

Published on the Web 26th June 2000

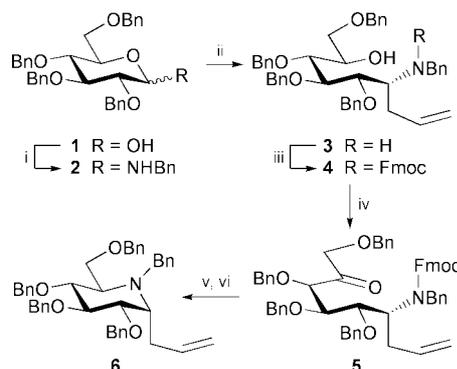
Reaction with allylmagnesium bromide of *N*,2,3,4,6-penta-benzyl- β -D-glucopyranosylamine **2**, obtained from tetrabenzylglucose and benzylamine, afforded stereoselectively the open chain amino alcohol **3**, which was converted into the C-glycoside of nojirimycin **6** by full protection of the amino function by Fmoc, oxidation of the free hydroxy group, hydrolysis of the Fmoc group and final intramolecular reductive amination with $\text{NaBH}(\text{OAc})_3$; compound **6** was also converted into methyl ketone **7**, by manipulation of the allylic appendage.

Deoxynojirimycin (1,5-dideoxy-1,5-imino-D-glucitol, DNJ) is a sugar-like plant alkaloid with inhibitory activity of a variety of glucosidases.¹ In particular, the capacity of deoxynojirimycin to inhibit trimming glucosidase I and II, interfering in N-linked oligosaccharide processing,² makes this molecule particularly attractive as a potential drug. It is well established that many pathological processes such as viral infections³ and adhesion of tumour metastasis to endothelial cells,⁴ involve complex N-linked oligosaccharides. Furthermore, inhibitors of glucosidases can find application in regulation of carbohydrate metabolic disorders.⁵ In view of current interest in anti-HIV activity, the synthesis of DNJ derivatives and their analogues, which can reduce replication and infectivity of HIV, has attracted particular attention. Homologues,⁶ deoxygenated,⁷ N-alkylated,^{7,9} O-glycosylated⁷ and other DNJ derivatives have been synthesised by chemical⁸ and enzymatic⁹ methods. Investigation of their activity led to the interesting observation that short lipophylic appendages, e.g. a butyl group, at the N atom, strongly enhance the biological response.¹⁰

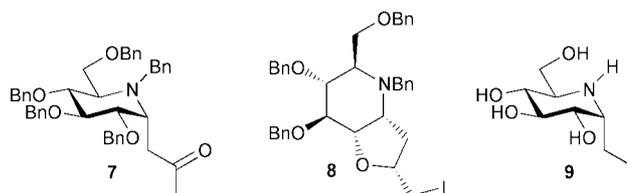
We wanted to find an efficient method for the introduction of a lipophylic substituent at position 1 of protected DNJ instead of at the N atom, particularly one affording stereoselectively the α -derivative, since the trimming α -glucosidases are the most interesting enzymes to be inhibited. We identified the allyl group as the substituent of choice, since its transformation into other functional groups, and its exploitation in the synthesis of neoglycoconjugates and C-disaccharides is widely described.¹¹

Protected α -1-allyl-1-deoxynojirimycin has already been synthesised¹² from glucose through the key intermediate 1-fluoro-1-deoxynojirimycin, using a complex multistep sequence. We herein report an efficient approach allowing the stereoselective synthesis of protected α -1-allyl-1-deoxynojirimycin in 6 steps and 36% overall yield, using tetrabenzylglucose (**1**) as commercially available starting material (Scheme 1). This requires first the introduction of the amino function, secondly of the allylic appendage and finally the cyclisation to the desired piperidine derivative. From a stereochemical point of view, the allylation reaction and the cyclization are crucial to the effectiveness of the synthesis, and must be highly stereoselective. The amino group was introduced by reaction of **1** with benzylamine in CH_2Cl_2 , in the presence of 4 Å molecular sieves and 1 equiv. of toluene-*p*-sulfonic acid. The resulting glycosylamine **2** (80% yield) was then treated with allylmagnesium bromide (10 equiv., Et_2O), in order to introduce stereoselectively the allylic appendage. The Grignard reaction occurs at the imino function, in equilibrium with the glycosylamine, via a Cram-chelated intermediate,

affording stereoselectively the *threo* isomer **3** (81% yield, 90% de).¹³ The cyclisation of **3** to the 'allyl- α -C-glycoside' of **6**, was accomplished by oxidation followed by reductive amination,¹⁴ which turned out to be troublesome. Oxidation of the free -OH group of **3** with PCC resulted in over-oxidation and partial degradation of the product.¹⁵ Swern oxidation with $\text{DMSO}-\text{Ac}_2\text{O}$ provided the desired ketone with concomitant acetylation of the amine, and failed when Ac_2O was replaced with P_2O_5 or oxalyl chloride. These results clearly suggested that the amino group must be fully protected in order to perform a successful oxidation, and then deprotected to afford the cyclic azasugar by reductive amination. Both the protection/deprotection and the reductive amination reactions were difficult. Different protecting groups and reducing agents were tested. In terms of yields and stereoselection, the best results were obtained as follows: **3** was protected as **4** (FmocCl, Na_2CO_3 , dioxane- H_2O , 89% yield), oxidised with PCC (CH_2Cl_2 , 4 Å molecular sieves, 90% yield) to ketone **5**, then the amino group of **5** was deprotected with piperidine in DMF. Reductive amination of the crude product with $\text{Na}(\text{OAc})_3\text{BH}$ (AcOH, dry Na_2SO_4 , 1,2-dichloroethane, -35°C) afforded **6**,[†] the protected allyl- α -C-glycoside of nojirimycin, in 78% yield and 90% de.[‡] As an example of manipulation of the allylic appendage, **6** was treated with catalytic Na_2PdCl_4 (0.3 equiv.) and CuCl_2 (1 equiv.) in DMF-THF- H_2O (8/5/1) affording **7**§ in 50% yield. Alternatively, the allylic appendage can undergo a 5-*exo* iodocyclization-debenzylation, involving the benzyloxy group in the γ position.¹⁶ Treatment of **6** with NIS in THF, afforded stereoselectively the bicyclic compound **8**¶ (2'*R*, determined by NOE experiments, as the only detected isomer) in 42% yield. Deprotection of **6** by



Scheme 1 Reagents and conditions: i, PhCH_2NH_2 10 equiv., PTSA 1 equiv., CH_2Cl_2 , 4 Å m.s., 80% yield, 5 days; ii, $\text{CH}_2=\text{CHCH}_2\text{MgBr}$ 10 equiv., dry Et_2O , 81% yield, 90% de; iii, FmocCl, dioxane-10% aq. Na_2CO_3 , 89% yield; iv, PCC 3 equiv., CH_2Cl_2 , 4 Å m.s., 90% yield; v, piperidine, DMF; vi, $\text{NaBH}(\text{OAc})_3$, AcOH, dry Na_2SO_4 , 1,2-dichloroethane, -35°C , 78% yield, 90% de.



hydrogenolysis [H_2 , $\text{Pd}(\text{OH})_2$, AcOH , AcOEt-EtOH 1:1] afforded **9**¹² in quantitative yield.

The procedure herein reported allows the synthesis of protected allyl- α -C-glycoside of nojirimycin through a highly stereoselective (80% de) and high yielding procedure (36%, 6 steps), from commercially available tetrabenzylglucose. The manipulation of the allylic appendage, widely reported in C-glycosides and to some extent also in iminosugars, allows the synthesis of a variety of functional groups and derivatives. The reported approach will be exploited in future projects devoted to the synthesis of imino-C-disaccharides.

We thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support and Paolo Petroni for contributing to the experimental work.

Notes and references

† Selected data for **6**: oil, $[\alpha]_{\text{D}} + 21.4$ (c 1, CHCl_3); δ_{H} (500 MHz, C_6D_6): 2.39 (dt, 1H, J 14.0, 8.1, H-1'a), 2.53 (dt, 1H, J 14.0, 5.8, H-1'b), 3.11 (ddd, 1H, J 9.5, 4.9, 2.1, H-5), 3.16 (dt, 1H, J 8.6, 5.4, H-1), 3.63 (dd, 1H, J 10.3, 2.1, H-6a), 3.75–3.83 (m, 2H, H-2, H-6b), 3.84–3.90 (m, 3H, PhCHN, H-3, H-4), 4.04 (d, 1H, J 14.0, PhCHN), 4.14, 4.20 (ABq, 2H, J 11.9, PhCH₂O), 4.34 (s, 2H, PhCH₂O), 4.65, 5.04 (ABq, 2H, J 11.4, PhCH₂O), 4.84, 5.03 (ABq, 2H, J 11.2, PhCH₂O), 4.98–5.13 (m, 2H, H-3'), 5.78–5.92 (m, 1H, H-2'), 7.00–7.41 (m, 25H, Ph-H); δ_{C} (75.43 MHz, CDCl_3 , aromatic C omitted) 29.11 (t, C-1'), 52.95 (t, NCH₂Ph), 57.19 and 57.53 (2d, C-1 and C-5), 68.57 (t, C-6), 72.17, 72.90, 75.09 and 75.38 (4t, OCH₂Ph), 78.72, 79.31, 83.99 (3d, C-2, C-3, C-4), 115.30 (t, C-3'), 137.76 (d, C-2'). Anal. Calcd. for $\text{C}_{44}\text{H}_{47}\text{NO}_4$: C 80.82, H 7.25, N 2.14%; Found C 80.77, H 7.28, N 2.11%.

‡ Determined by ¹³C NMR of the crude reduction product, in comparison with the spectrum of the epimer at C-5 (ref. 8).

§ Selected data for **7**: oil, $[\alpha]_{\text{D}} + 9.6$ (c 1, CHCl_3); δ_{H} (300 MHz, C_6D_6): 1.76 (s, 3H, H-3'), 2.23 (dd, 1H, J 15.3, 5.0, H-1'a), 2.57 (dd, 1H, J 15.3, 7.1, H-1'b), 2.83–2.94 (m, 1H, H-5), 3.61 (dd, 1H, J 10.2, 1.6, H-6a), 3.64–3.82 (m, 5H, H-2, H-3, H-4, H-6b, PhCHN), 3.84–3.90 (m, 2H, H-1, PhCHN), 4.10, 4.15 (ABq, J 11.8, PhCH₂O), 4.24, 4.32 (ABq, J 11.8, PhCH₂O), 4.61, 5.02 (ABq, J 11.4, PhCH₂O), 4.84, 5.03 (ABq, J 11.2, PhCH₂O), 7.01–7.48 (m, 25H, Ph-H); Anal. Calcd. for $\text{C}_{44}\text{H}_{47}\text{NO}_5$: C 78.89, H 7.0, N 2.09%; Found C 78.92, H 7.08, N 2.06%.

¶ Selected data for **8**: yellow oil, $[\alpha]_{\text{D}} + 11$ (c 0.65, CHCl_3); δ_{H} (300 MHz, CDCl_3): 1.66 (bq, 1H, J 11.0, H-1'a), 2.24 (ddd, 1H, J 11.0, 5.7, 5.7, H-1'b), 2.98–3.03 (m, 1H, H-5), 3.21 (dd, 1H, J 9.9, 6.8, H-3'a), 3.30 (dd, 1H, J 9.9, 4.8, H-3'b), 3.55 (dd, 1H, J 8.1, 5.1, H-4), 3.60–3.72 (m, 4H, H-1, H-6a, H-6b, PhCHN), 3.86 (t, 1H, J 8.3, H-3), 3.90–3.97 (m, 2H, H-2', PhCHN), 4.15 (t, 1H, J 8.3, H-2), 4.41 (s, 2H, PhCH₂O), 4.43, 4.61 (ABq, J 11.0, PhCH₂O), 4.78, 4.97 (ABq, J 11.4, PhCH₂O); δ_{C} (75.43 MHz, CDCl_3 , aromatic C omitted) 9.92 (t, C-3'), 36.20 (t, C-1'), 59.34, 60.83 (2d, C-1 and C-5), 54.76 (t, NCH₂Ph), 67.02 (t, C-6), 72.84, 73.26 and 74.06 (3t, OCH₂Ph), 77.56, 80.00, 80.75 and 84.16 (4d, C-2, C-3, C-4 and C-2'); Calcd. for $\text{C}_{37}\text{H}_{40}\text{INO}_4$: C 64.44, H 5.85, I 18.40, N 2.03%; Found C 64.60, H 5.70, I 18.55, N 1.99%.

- 1 *Carbohydrate Analogues as Glycosidase Inhibitors—Nojirimycin and Beyond*, ed A. Stütz, VCH, Weinheim, 1998; S. V. Evans, L. E. Fellows, T. K. M. Shing and G. W. Fleet, *Phytochemistry*, 1985, **24**, 1953.
- 2 A. D. Elbein, *FASEB J.*, 1991, **5**, 3055.
- 3 R. A. Gruters, J. J. Neeffjes, M. Tersmette, R. E. Y. De Goede, A. Tulp, H. G. Huisman, F. Miedema and H. L. Ploegh, *Nature*, 1987, **330**, 74.
- 4 See for example: R. J. Bernacki, M. J. Niedbala and W. Korytnyk, *Cancer Metastasis Rev.*, 1985, **4**, 81; R. Pili, J. Chang, R. A. Patris, R. A. Mueller, F. J. Chrest and A. Passaniti, *Cancer Res.*, 1995, **55**, 2920.
- 5 See for example: B. Junge, M. Matzke and J. Stoltefuss, *Handbook of Experimental Pharmacology*, 1996, **119**, 411.
- 6 G. C. Kite, L. E. Fellows, G. W. J. Fleet, P. S. Liu, A. M. Scofield and N. G. Smith, *Tetrahedron Lett.*, 1988, **29**, 6483; I. Bruce, G. W. Fleet, I. Cenci di Bello and B. Winchester, *Tetrahedron*, 1992, **48**, 183; K. E. Holt, F. J. Leeper and S. Handa, *J. Chem. Soc., Perkin Trans. I*, 1994, 231; C.-H. Wong, L. Provencher, J. A. Porco, Jr., S.-H. Jung, Y.-F. Wang, L. Chen, R. Wang and D. H. Steensma, *J. Org. Chem.*, 1995, **60**, 1492.
- 7 For a comprehensive review see: C. W. Eckhart, M. H. Fechter, P. Hadwiger, E. Mlaker, A. E. Stütz, A. Tauss and T. Wrodnigg in *Carbohydrate Analogues as Glycosidase Inhibitors—Nojirimycin and Beyond*, ed. A. Stütz, VCH, Weinheim, 1998, p. 254.
- 8 For a recent review of synthetic methods see: B. La Ferla and F. Nicotra in *Carbohydrate Analogues as Glycosidase Inhibitors—Nojirimycin and Beyond*, ed. A. Stütz, VCH, Weinheim, 1998, p. 68.
- 9 See for example: K. K.-C. Liu, T. Kajimoto, L. Chen, Z. Zhong, Y. Ichikawa and C.-H. Wong, *J. Org. Chem.*, 1991, **56**, 6280; T. Kajimoto, K. K.-C. Liu, R. L. Pederson, Z. Zhong, Y. Ichikawa, J. A. Porco, Jr. and C.-H. Wong, *J. Am. Chem. Soc.*, 1991, **113**, 6187.
- 10 See for example: A. Karpas, G. W. Fleet, R. A. Dwek, S. Petrusson, S. K. Namgoong, N. G. Ramsden, G. S. Jacob and T. W. Rademacher, *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 9229; A. Tan, L. van der Boek, S. van Bockel, H. Ploegh and J. Bolscher, *J. Biol. Chem.*, 1991, **266**, 14504; G. B. Karlsson, T. D. Butters, R. A. Dwek and F. M. Platt, *J. Biol. Chem.*, 1993, **268**, 570; F. M. Platt, G. R. Neises, R. A. Dwek and T. D. Butters, *J. Biol. Chem.*, 1994, **269**, 8362.
- 11 C. Bertozzi and M. Bednarski, *Carbohydr. Res.*, 1992, **223**, 243; K. H. Mortell, R. V. Weatherman and L. L. Kiessling, *J. Am. Chem. Soc.*, 1996, **118**, 2297; L. Lay, F. Nicotra, C. Pangrazio, L. Panza and G. Russo, *J. Chem. Soc., Perkin I*, 1994, 333; F. Peri, L. Cipolla, B. La Ferla, P. Dumy and F. Nicotra, *Glycoconjugates J.*, 1999, **16**, 399; L. Cipolla, F. Nicotra, E. Vismara and M. Guerrini, *Tetrahedron*, 1997, **53**, 6163.
- 12 T. Fuchss, H. Streicher and R. R. Schmidt, *Liebigs Ann. Rec.*, 1997, 1315.
- 13 L. Cipolla, L. Lay, F. Nicotra, C. Pangrazio and L. Panza, *Tetrahedron*, 1995, **51**, 4679.
- 14 H. S. Overkleeft, J. Van Wiltenburg and U. K. Pandit, *Tetrahedron*, 1994, **50**, 4215; R. Hoos, A. B. Naughton and A. Vasella, *Helv. Chim. Acta*, 1993, **76**, 2666.
- 15 L. Cipolla, F. Nicotra and C. Pangrazio, *Gazz. Chim. Ital.*, 1996, **126**, 663.
- 16 L. Cipolla, L. Lay and F. Nicotra, *J. Org. Chem.*, 1997, **62**, 6678.