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Efficient stereocontrolled synthesis of 2-benzimidazolyl- and 2-indolyl-*C*-nucleosides

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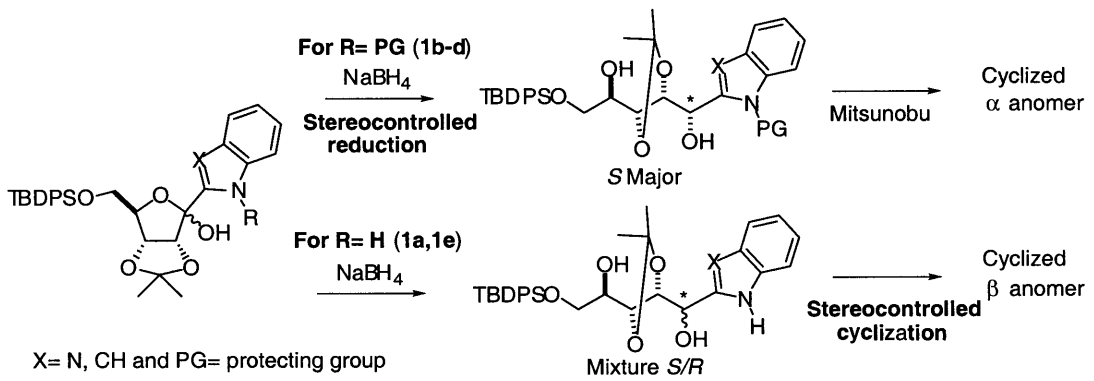
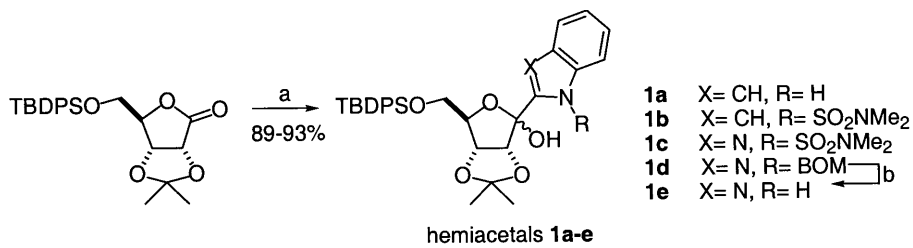
Abstract—We report herein the synthesis of β-2-benzimidazolyl- and β-2-indolyl-*C*-nucleosides and their α-anomers in a stereoselective way. The stereocontrol was observed either in the reduction step (hemiacetal to diol) of the protected heterocycles (**1b–d**), or in the intramolecular Mitsunobu cyclisation of the free heterocyclic diols obtained from the hemiacetals **1a** and **1e**.

Natural *C*-nucleosides such as showdomycin, bredinin, pyrazofurin, have received great attention since this class of molecules is well known for its potent biological activity.[1] Therefore, much effort has been undertaken in the synthesis of natural and modified *C*-nucleosides for their biological evaluation and for their potential use in nucleic acid studies.[2] Recently, several *C*-nucleosides have been synthesised by addition



Scheme 1. Synthetic strategy.



Scheme 2. Reagents and conditions: (a) heterocycles (1.5 equiv.), THF, LDA (1.5 equiv.), −78°C (for X=CH) or −50°C (for X=N); (b) H_2 (60 psi), Pd/C, MeOH/THF, 95%.

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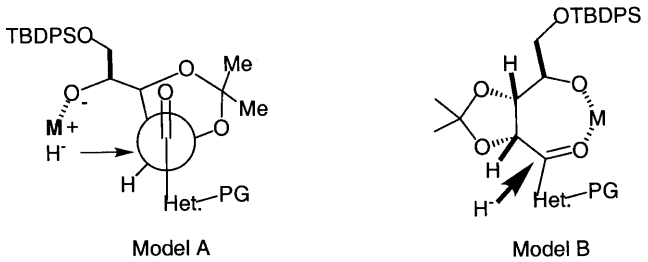


Figure 1. Felkin–Anh model (A) and the chelated transition state (B).

of an organometallic reagent to a ribonolactone derivative followed by Lewis acid induced hemiacetal deoxygenation.[3] However, the direct deoxygenation led, in many cases, to poor yields and/or diastereoselectivity and chemical modifications are sometimes required to overcome this difficulty.[3] To our knowledge, only a few convergent and stereocontrolled syntheses of both anomers have been reported, particularly when the reactive centre of the heterocyclic moiety is adjacent to a protected or functionalised position.[4]

Here, we describe the stereocontrolled synthesis of 2-indolyl- and 2-benzimidazolyl-*C*-nucleosides as either their α- or β-anomer, starting from the same type of intermediate (Scheme 1).

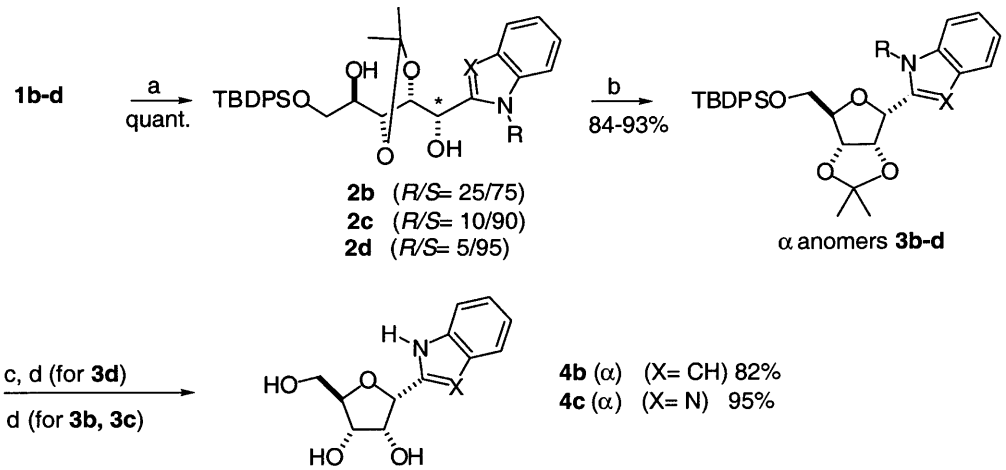
Hemiacetals **1a**[5]–**d** were first obtained by coupling 2-indolyl- or 2-benzimidazolyl-lithium to the known 5-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-D-γ-ribonol actone in high yield (89–93%). Hemiacetal **1e** was obtained from **1d** by catalytic hydrogenation (Scheme 2). We observed that the condensation step was very sensitive to steric factors. Thus, the utilisation of *N*-Boc or *N*-trityl protected indole and benzimidazole led to their corresponding hemiacetals in poor yields. We have verified that these protected heterocycles react satisfactorily with other electrophiles (cyclohexanone, hexachloroethane, Bu_3SnCl) to give the 2-substituted indoles and benzimidazoles derivatives.

The NMR spectra of each coupled product **1a–e** revealed the presence of three interconvertible species:[6] the hemiacetal diastereoisomers (major products) being in equilibrium with the carbonyl opened form (minor product). The chemical ratio of the three species depends on the concentration and NMR solvent.

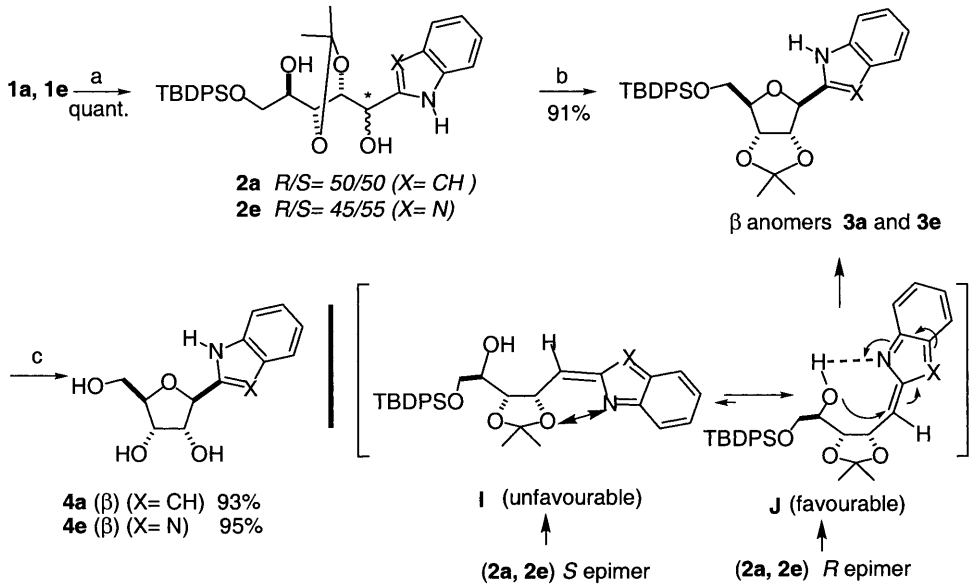
With derivatives **1b–d** in hand, we attempted the direct C_1-*OH* deoxygenation under Et_3SiH/Lewis acid reagent conditions ($BF_3{\cdot}Et_2O$, $ZnCl_2$, TMSOTf) but without success. The reaction did not occur at low temperature (−78 to −40°C) and only decomposition products were observed at room temperature or when using higher concentration of the reducing agent.

In contrast, the borohydride reduction of hemiacetals **1b–d** afforded the corresponding diols **2b–d** in quantitative yield. Good diastereoselectivity was observed in this reduction step with the protected heterocyclic hemiacetals giving the *S* epimer (major product).[7] This diastereoselectivity was expected, in agreement with the Felkin–Anh model[8] (model A) or the chelated transition state (model B), postulating the participation of the protecting group in the hydride stereofacial addition (Fig. 1). Subsequent intramolecular Mitsunobu cyclisation gave the α-protected nucleosides **3b** (indole) and **3c**,**d** (benzimidazole) (Scheme 3).

In contrast, the reduction of the hemiacetals **1a** and **1e** having an unprotected heterocyclic moiety under the same reaction conditions gave a mixture of diastereomeric diols **2a** (*R*,*S*) and **2e** (*R*,*S*) in nearly a 1/1 ratio. Treatment of free diols **2a** (*R*,*S*) and **2e** (*R*,*S*) under standard Mitsunobu conditions gave only the cyclised β-*C*-nucleosides **3a** and **3e** in high yield (Scheme 4). This stereocontrol may result from benzylic



Scheme 3. Reagents and conditions: (a) $NaBH_4$ (2.2 equiv.), MeOH; (b) (i) the small amount of minor diol was removed by flash chromatography, (ii) DEAD (1.5 equiv.), PPh_3 (1.5 equiv.), THF, 60°C; (c) H_2 (60 psi), Pd/C, THF/EtOH (1/1); (d) aq. TFA, 50°C.



Scheme 4. Reagents and conditions: (a) $NaBH_4$ (2.2 equiv.), MeOH; (b) DEAD (1.5 equiv.), PPh_3 (1.5 equiv.), THF, 60°C; (c) aq. TFA/MeOH. Proposed intermediates **I** and **J** for the stereocontrolled cyclisation.

elimination (Ph_3PO) and spontaneous cyclisation via a thermodynamically stable intermediate **J** (unfavourable doublet–doublet repulsion in intermediate **I** and possible favourable intramolecular hydrogen bond in **J**). We have verified that Ph_3P/DEAD treatment of separated pure diols **2a** (*R*) and **2a** (*S*) gave only the same cyclised β-anomer **3a**.[9] Interestingly, Kurihara[10] has reported a similar observation in the imidazole series but with the formation of a small amount of the α-anomer (α/β = 1/26).

The final deprotection of **3a–e** was achieved in good yield giving the free *C*-nucleosides **4a**, **4b**, **4c** and **4e** (Schemes 3 and 4).[11]

In the present work, we have shown the importance of introducing a protective group for the stereoselective borohydride reduction of hemiacetals **1b–d** and in the ring closure step of diols **2a** and **2e**. By this methodology, both α- and β-*C*-nucleoside anomers could be accessed in a stereoselective manner. The procedure is compatible with the presence of sensitive groups on the heterocyclic systems (halogens, amine function and protective groups)[12] and, therefore, could be applied for the derivatisation and synthesis of highly functionalised *C*-nucleosides.

Acknowledgements

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5. The carboxylate-indolyl lithium was prepared following the procedure of: Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935–5938.
6. For example: (^1H NMR, 300 MHz) δ $OH_{1'}$ (ppm) **1b**: 5.07 and 5.42; **1c**: 5.30 and 5.79. (^{13}C NMR, 75 MHz) δ $C_{1'}$ (ppm) **1b**: 100.76, 106.24 (hemiacetals) and 151.00 (C=O); **1c**: 100.80, 106.85 (hemiacetals) and 152.10 (C=O).

7. The stereochemistry of each diol was determined on the basis of their cyclised products in which the anomeric configuration was assigned by ^{1}H and 2D COSY–NOESY NMR.
8. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, *18*, 2199–2102. (b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145.
9. (a) This observation is in disagreement with the previously reported work by Yokoyama et al. (Yokoyama, M.; Toyoshima, A.; Akiba, T.; Togo, H. *Chem. Lett*. **1994**, 265–268) in which an unchanged ratio α versus β (1/8) was obtained from the starting indole–diol mixture (*R*/*S*: 8/1), suggesting an S_N2 process. (b) In our case, with the lithiated heterocycles, only poor yields were obtained in the condensation step with a protected ribose.
10. In this paper, the highly toxic reagent tetramethylazodicarboxylate (TMAD) was required for increasing the yields: Harusawa, S.; Murai, Y.; Moriyama, H.; Imazu, T.; Ohishi, H.; Yoneda, R.; Kurihara, T. *J. Org. Chem*. **1996**, *61*, 4405–4411.
11. All products gave satisfactory spectroscopic and microanalytical data.
12. The application of this strategy to other functionalised heterocycles is under investigation and will be described in a full paper.