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Synthesis of novel *C*-nucleosides with potential applications in combinatorial and parallel synthesis

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Abstract

Novel di-substituted pyrimidinyl *C*-nucleosides have been synthesised using a flexible synthetic methodology. This methodology conveniently allows the synthesis of alpha and beta nucleosides, both of which are of biological interest. Reactive acetylenic ketones, derived from 2-deoxyribose, can be reacted with substituted amidines to give new families of *C*-nucleoside natural product analogues.

We recently reported the use of an acetylenic ketone as a reactive motif for the synthesis of heterocyclic substituted amino acids.[1,2] We now wish to report extension of this methodology to the carbohydrate area. *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] Although most biologically active nucleosides are of the β-configuration,[4] there is growing interest in those of the α-configuration, which show biological activity.[5] Therefore, we set out to develop a flexible synthetic methodology which would allow the synthesis of pyrimidinyl *C*-nucleosides of both anomeric configurations. It would be preferable if we could install this feature at a late synthetic stage.

Naturally occurring *C*-nucleosides are based around either a ribose or 2-deoxyribose core. As *C*-nucleosides of 2-deoxyribose are reportedly not as well known in the literature as traditional 2-deoxyribonucleosides we chose the synthetic challenge posed by preparing 2-deoxyribose *C*-nucleosides.[6] It can be envisaged that reaction of a carbohydrate-substituted acetylenic ketone with substituted amidines would give a family of novel di-substituted pyrimidinyl *C*-nucleosides (Fig. 1).[7]

Choice of protecting group is important since it must permit both the formation of the acetylenic ketone **2**, and be easily removed without destroying the final *C*-nucleoside targets. Deprotection must also take into account the benzylic nature of the C1-oxygen bond in the tetrahydrofuran ring. After other alternatives were eliminated, benzyl protection and BCl_3 deprotection proved optimal.

3,5-Di-*O*-benzyl-2-deoxy-α-D-ribofuranosyl cyanide **5**, was synthesised from protected 2-deoxyribose[8,9] using literature precedent (Scheme 1).[10] This reaction gave an 81% yield of the

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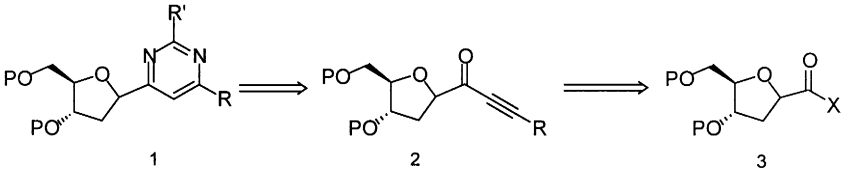
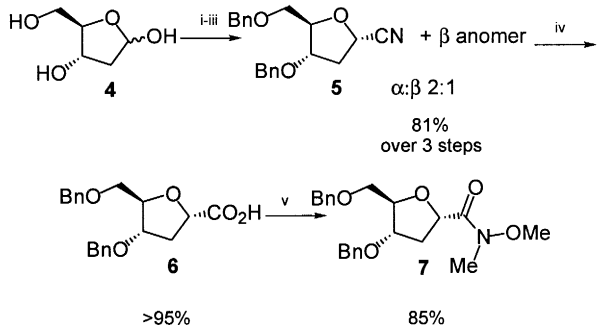


Fig. 1.

nitrile with predominantly the α stereochemistry (2:1 α:β ratio) at the anomeric centre.[11] Only the α anomer was used in subsequent synthetic steps. Hydrolysis of the nitrile **5**, under acidic conditions, gave the acid **6** in quantitative crude yield. Formation of the Weinreb amide **7** was similarly successful, so giving the intermediate for the crucial ketone formation step in gram quantities.[8,12]



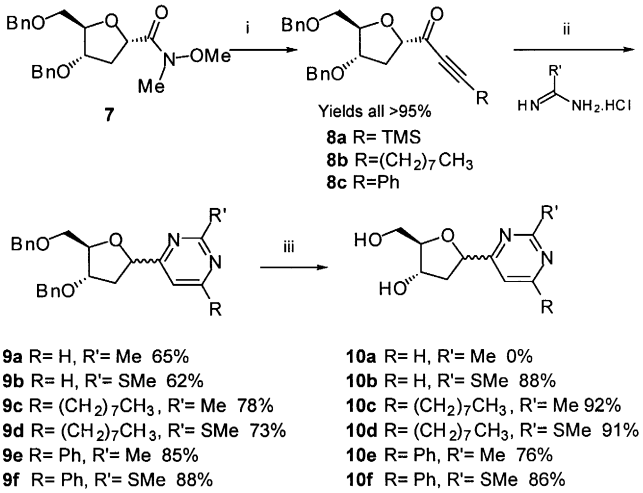
Scheme 1. *Reagent and conditions*: (i) MeOH, AcCl, rt, 7 min then Ag_2CO_3; (ii) BnBr, NaH, Bu_4NI, DMF, −30°C to rt, 24 h; (iii) TMSOTf, TMSCN, DCM, 24 h, rt, then chromatography [silica gel, (5:1) petroleum ether:Et_2O]; (iv) HCl, 1,4-dioxan, 100°C, 4 h; (v) α,α-dichloromethylmethyl ether, DCM, reflux, 5 h, then Me(OMe)NH·HCl, NEt_3, DCM, rt, 24 h

The Weinreb amide **7** was reacted with a variety of lithium acetylides (LiCCR) which, after mild acidic work up, yielded ketones **8(a–c)** in near quantitative yield (Scheme 2). The acetylenic ketones were highly sensitive to oxygen and were used without purification in the following cyclisation reaction. Cyclisation of the ketones, in strictly deoxygenated solvents, with substituted amidines, resulted in the formation of the desired protected *C*-nucleosides **9(a–f)** in good yields, as the anomeric mixture in a 1:1 α:β ratio. Where R is TMS, **8a**, the silicon group was hydrolytically cleaved during reaction to give the parent compounds, **9a** and **9b**, R=H. All compounds were purified by column chromatography on silica gel. After considerable investigation an optimised protocol using BCl_3 in DCM for up to 24 hours at room temperature, was found to smoothly deprotect all compounds (except **9a**) giving **10**(**b–f**). All compounds **10**(**b–f**) were isolated and purified by column chromatography on silica gel.

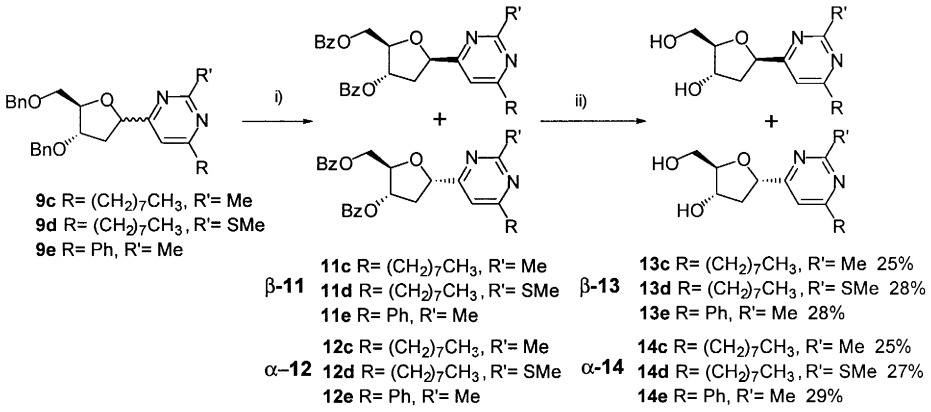
In a separate study the separated α and β anomers of **9**(**b–f**) epimerised under the deprotection protocol to give product mixtures **10**(**b–f**) in a 1:1 α:β ratio.

Although the fully deprotected compounds **10**(**b–f**) can be isolated as anomeric mixtures and screened for biological activity, we also wished to isolate gram quantities of separated anomers. Thus, anomeric mixtures of compounds **10**(**c–e**) were benzoyl protected,[13] the anomers separated chromatographically, then deprotected under basic conditions, to yield the anomerically pure, fully deprotected *C*-nucleosides **13** and **14**(**c–e**) in 50–57% combined yield from **9**(**c–e**) (Scheme 3).[11,14]

To conclude, we have developed and extended a methodology for the synthesis of di-substituted pyrimidines to the carbohydrate field, giving access to a family of previously unknown *C*-nucleosides. They were formed in isolated parallel batches in good overall yield with minimal chromatography. Such compounds are likely to be predisposed to biological activity and we are presently determining that activity. Novel carbohydrate-substituted acetylenic ketones have been synthesised, as intermediates, by



Scheme 2. *Reagents and conditions*: (i) LiCCR (2 equiv.), THF, −78°C; 3 h, then NH_4Cl(aq), −78°C to rt; (ii) Na_2CO_3, MeCN, H_2O, 80°C, 24 h; (iii) BCl_3, (2.1 equiv.), DCM, rt, 2–24 h



Scheme 3. *Reagents and conditions*: (i) BCl_3, DCM, rt, 2–24 h then BzCl, DCM, DMAP, rt, 24 h; (ii) LiOH, THF, H_2O, rt

reaction of an activated carboxylic acid with lithiated acetylides, which upon cyclisation with substituted amidines, gave a family of *C*-nucleosides, as the anomeric mixture. Lewis acid catalysed deprotection was found to epimerise either α- or β-benzyl protected *C*-nucleosides **9**(**b**–**f**) to give both the α and β *C*-nucleosides as the 1:1 anomeric mixture. Potentially, this methodology allows other heterocyclic systems to be accessed by reaction of α,β unsaturated acetylenic ketones to give other novel *C*-nucleosides. Therefore, we have demonstrated that the parallel synthesis of heterocyclic natural products can be achieved by the reaction of 2-deoxyribose-derived acetylenic ketones and can thus be applied to the preparation of novel *C*-nucleosides.

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References

1. Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Catterick, D. *J. Chem. Soc., Perkin 1* **1999**, 855.
2. Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Catterick, D. *J. Chem. Soc., Chem. Commun.* **1997**, 1757
3. (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.
4. For reviews, see: Perigaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903.
5. Bernardo, S. D.; Weigele, M. *J. Org. Chem.* **1976**, *41*, 287.
6. Chaudhuri, N. C.; Ren, R. X.-F.; Kool, E. T. *Synlett* **1997**, 341
7. Fox has described related methodology as a route to pyrimidin-4-ones, see: Tam, S. Y.-K.; Heras, F. G. D. L.; Klein, R. S.; Fox, J. J. *Tetrahedron Lett.* **1975**, *38*, 3271.
8. Rolland, V.; Kotera, M.; Lhomme, J. *Synth Commun.* **1997**, *27*, 3505.
9. Brimacombe, J. S.; Fletcher, H. G. *Methods Carbohydr. Chem.* **1972**, *6*, 373
10. Jung, M. E.; Trifunovich, I.; Gardiner, J.; Clevenger, G. L. *J. Chem. Soc., Chem. Commun.* **1990**, 84.
11. Confirmed by NOE experiments on both epimers.The anomeric configuration of all anomers were confirmed by NOE experiments based on the known configuration of substituents at C3 and C4.
12. Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.
13. A more direct route to separate α and β anomers using only benzoyl-protecting groups was unsuccessful due to the failure to form an acetylenic ketone from the benzoyl analogue of **7**. Other routes using Lewis acid catalysed addition of trimethylsilyl acetylenes, and Stille cross-coupling reactions on stannyl acetylenes, all failed.
14. Yields of *C*-nucleosides, **13** and **14**(**c**–**e**) were calculated from the starting benzyl protected *C*-nucleosides, **9**(**c**–**e**). Deprotected *C*-nucleosides **13** and **14**(**c**–**e**) were purified by column chromatography on silica gel using an appropriate solvent system.