SYNTHESIS AND REACTIONS OF CHIRAL CYCLIC NITRONES DERIVED FROM D-RIBOSE

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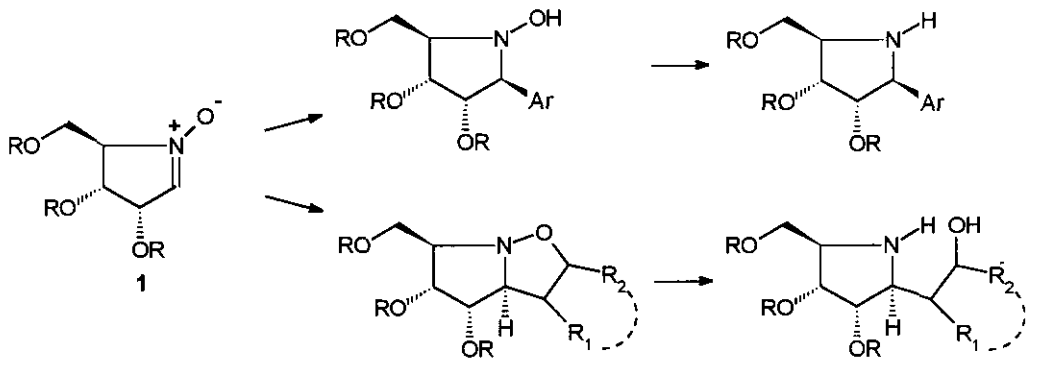
Abstract- A facile route to chiral cyclic nitrones derived from D-ribose is described. Their versatility as substrates for 1,3-dipolar cycloadditions and nucleophilic additions is demonstrated.

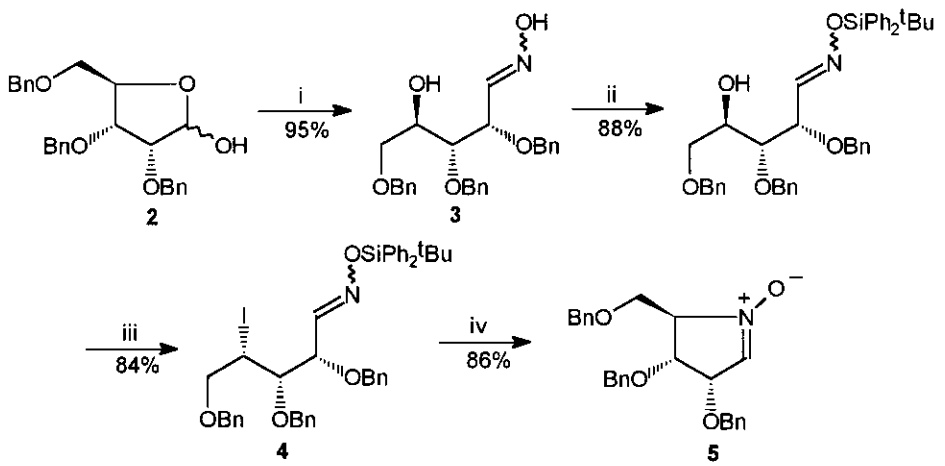
In the search for effective, non-toxic, antiviral agents a variety of modified nucleoside analogues are currently being developed.[1] Carbonucleosides,[2] thionucleosides[3] and diheterosubstituted nucleosides[4] have received much attention. As part of an ongoing investigation in our laboratories into the synthesis of analogues of biologically active compounds,[5] we were interested in synthesising the aza analogues of β-*C*-nucleosides and β-*C*-glycosides.[6] Our strategy involves the synthesis of a carbohydrate derived chiral cyclic nitrone (**1**) as the key synthon (Scheme 1). The rich chemistry displayed by these 1,3-dipoles[7] makes them attractive targets, but the preparative methods for chiral cyclic nitrones of type (**1**) remain limited.



Scheme 1

Van den Broek[8] has described the synthesis of cyclic nitrones *via* the oxidation of 1-deoxynojirimycin using 2,2-dimethyldioxirane. The oxidation was not regiospecific and separation of the isomers proved

to be tedious. Recently, the synthesis of pyrrolidine[9] and piperidine based nitrones[10] derived from carbohydrates was reported. The nitrone functionality was obtained by intramolecular conjugate addition of an oxime.[11] In both cases the nitrones were isolated as a mixture of diastereoisomers. Clearly, a stereospecific synthesis of these highly versatile intermediates is lacking. Herein we wish to report a facile route towards cyclic nitrones starting from suitably protected hemiacetals of D-ribofuranose. Readily available tri-*O*-benzyl-D-ribofuranose[12] was allowed to react with hydroxylamine hydrochloride to afford acyclic (**3**). Selective silylation followed by iodonation at C-5 (with inversion of configuration) furnished the cyclisation precursor (**4**). Anhydrous TBAF-mediated desilylation and subsequent intramolecular nucleophilic attack[13] afforded the cyclic nitrone (**5**)[14] in an isolated yield of 86% (Scheme 2).

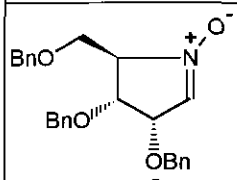
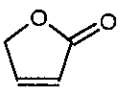
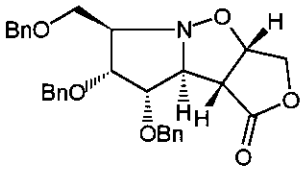
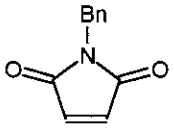
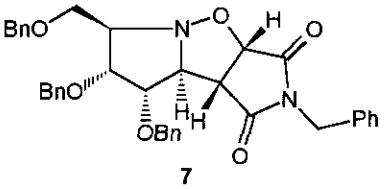
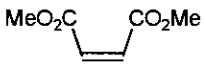
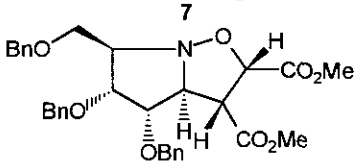
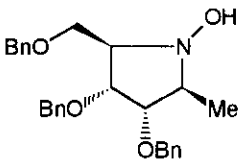
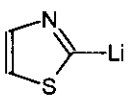
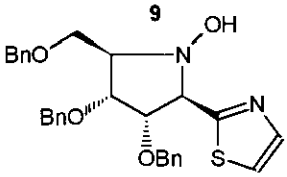
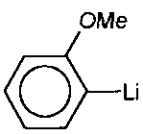
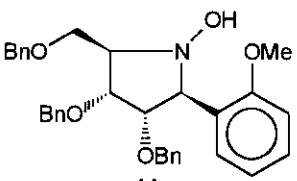
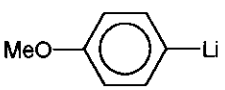
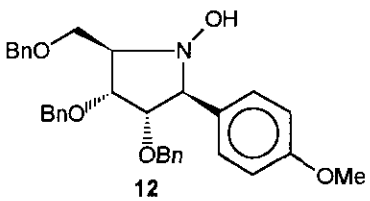


Reagents: i) $NH_2OH{\cdot}HCl$ / pyridine / rt / 3 h ii) $^tBuPh_2SiCl$ / pyridine / rt / 12 h iii) PPh_3 / imidazole / I_2 / toluene / reflux / 0.5 h iv) TBAF anhydrous / benzene / reflux / 0.5 h

Scheme 2

The 1,3-dipolar cycloaddition reaction of a nitrone to an alkene is an extremely powerful synthetic method for the creation of complex heterocyclic structures.[15] For example, the labile nature of the N-O bond under mild reducing conditions in the formed isoxazolidines, makes them suitable precursors of 1,3-amino alcohols. Reaction of nitrone (**5**) with α,β-unsaturated carbonyl compounds furnished the corresponding cycloadducts (**6**, **7** and **8**)[16] in good diastereomeric excess (Table 1). The *exo*-product was isolated as the major isomer in each case. The structures of all products were confirmed by NMR and MS analysis, and the stereochemistries by means of ROESY-spectra. The high diastereofacial selectivities observed were comparable to results reported by Ishikawa *et al.*[9] for a different cyclic nitrone. The reaction of a variety of carbon nucleophiles, including a Grignard reagent, with **5** (Table 1) led to the formation of interesting β-*C*-glycoside analogues (**9**, **10**, **11** and **12**).[17] The nitrone (**5**) was converted into the thymine *C*- nucleoside

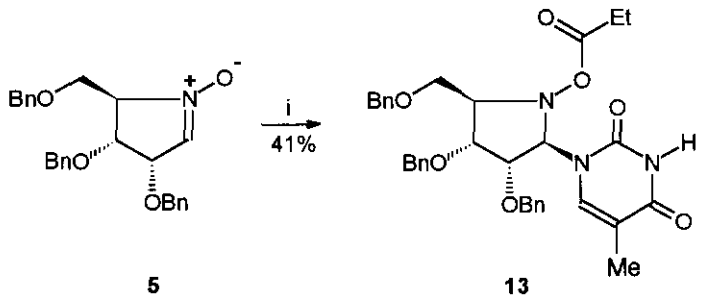
Table 1: Reactions of **5** with dipolarophiles and carbon nucleophiles.

Nitrone	Reagent	Major Product	Yield[a]
 **5**		 **6**	**92%**[b] (78% de)
		 **7**	**95%**[b] (65% de)
		 **8**	**86%**[b] (60% de)
MeMgI		 **9**	**83%**[c]
		 **10**	**59%**[d]
		 **11**	**75%**[d]
		 **12**	**73%**[d]

a) Total cycloadduct yield. b) Alkene (2 mmol) and nitrone (1 mmol) in dry benzene (2 mL) were reacted at 60°C for 3 h c) Grignard reagent (1.1 mmol) and nitrone (1 mmol) in dry THF (2 mL) were reacted at 0°C for 10 min.

d) Lithiated species (1.1 mmol) and nitrone (1 mmol) in dry THF (2 mL) were reacted at -30°C for 1 h.

analogue (**13**) using a method reported by Tronchet and co-workers[18] (Scheme 3).

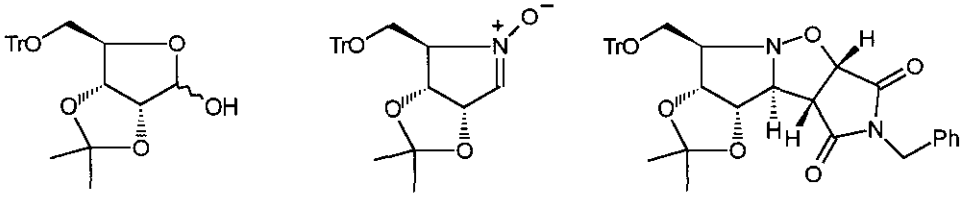


5 **13**

Reagents: i) a: $(EtCO)_2O$ / H^+ b: Thymine / HMDS / TMSCl / $SnCl_4$

Scheme 3

Following the same protocol as for the synthesis of **5**, 2,3-isopropylidene-5-*O*-trityl-D-ribofuranose (**14**)[19] was converted to the corresponding nitrone (**15**).[20] The reaction of **15** with *N* -benzylmaleimide afforded cycloadduct (**16**)[21] in a yield of 95% (diastereomeric excess 83%).



14 **15** **16**

This work clearly shows that the construction of chiral cyclic nitrones from D-ribose derivatives is an extremely efficient and simple procedure. Furthermore, 1,3-dipolar cycloadditions of the nitrones to appropiate olefins proceed smoothly in high yielding diastereoselective reactions.

ACKNOWLEDGEMENTS

We thank the FRD (South Africa), AECI and SASOL for funding.

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14. **5**: colourless oil; $[\alpha]_D$ +8.21° (c=2.1, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.27 (15H, m), 6.91 (1H, s), 4.69-4.36 (7H, m), 4.43 (1H, t, *J*=5.4 Hz), 4.12 (1H, dd, *J*=10.7 and 2.5 Hz), 4.08 (1H, m), 3.61 (1H, dd, *J*=10.7 and 2.1 Hz), ^{13}C NMR (300 MHz, $CDCl_3$): δ 137.61, 137.41, 137.23, 133.43, 128.63, 128.16, 128.11, 127.86, 127.68, 76.34, 75.35, 74.46, 73.41, 72.41, 72.06, 64.72, MS: m/z 418 (M^{+1}).
15. For review, see: M. Frederickson, *Tetrahedron*, 1997, **53**, 403.
16. **6**: mp 63-64°C (ethyl acetate/hexane); $[\alpha]_D$ +0.58° (c=2.4, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.27 (15H, m), 4.87 (1H, dt, *J*=5.7 and 2.0 Hz), 4.68-4.46 (6H, m), 4.34 (2H, d, *J*=2.1 Hz), 4.23 (1H, dd, *J*=6.3 and 2.4 Hz), 4.11 (1H, dd, *J*=6.3 and 4.5 Hz), 3.94 (1H, dd, *J*=6.0 and 2.4 Hz), 3.85 (1H, t, *J*=4.2 Hz), 3.56-3.41 (3H, m), ^{13}C NMR (300 MHz, $CDCl_3$): δ 177.47, 137.91, 137.72, 137.56, 128.51, 128.47, 128.42, 127.96, 127.89, 127.81, 78.66, 78.32, 76.68, 73.44, 72.74, 72.56, 71.14, 70.75, 69.92, 69.77, 50.57, MS: m/z 501 (M^+).

17. **11**: mp 84-85°C (ethyl acetate/hexane); $[\alpha]_D$ +5.93° (c=1.8, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (1H, dd, J=7.5 and 1.8 Hz), 7.31-7.26 (16H, m), 6.88 (2H, m), 5.29 (1H, br s) 4.68 (1H, d, *J*=4.8 Hz) 4.65-4.43 (6H, m), 3.91 (1H, dd, *J*=7.5 and 5.7 Hz), 3.81 (1H, t, *J*=5.5 Hz), 3.77 (3H, s), 3.76 (1H, dd, *J*=10.2 and 3.9 Hz), 3.67 (1H, dd, *J*=10.2 and 4.2 Hz), 3.61 (1H, m), ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.49, 138.48, 138.36, 138.23, 128.32, 128.25, 128.17, 127.99, 127.83, 127.59, 120.66, 110.63, 80.05, 75.29, 73.21, 71.62, 71.13, 71.04, 70.35, 69.11, 55.29, MS: m/z 525 (M^+).

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20. **15**: colourless oil; $[\alpha]_D$ +2.22° (c=2.6, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.24 (15H, m), 7.09 (1H, s), 5.34 (1H, d, *J*=6.3 Hz), 4.52 (1H, d, *J*=6.3 Hz), 4.07 (1H, dd, *J*=10.2 and 2.7 Hz), 4.02 (1H, m), 3.13 (1H, dd, *J*=10.2 and 2.1 Hz), 1.42 (3H, s), 1.31 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 143.26, 133.31, 128.46, 128.11, 127.43, 111.79, 86.99, 79.19, 79.14, 77.32, 59.48, 27.26, 25.81, MS: m/z 430 (M^{+1}).

21. **16**: colourless oil; $[\alpha]_D$ +0.45° (c=1.2, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.21 (20H, m), 4.81, (1H, t, *J*=5.1 Hz), 4.73 (2H, s), 4.70 (1H, d, *J*=7.5 Hz), 4.69 (1H, d, *J*=5.1 Hz), 4.19 (1H, d, *J*=5.1 Hz), 3.94 (2H, m), 3.24 (1H, dd, *J*=9.9 and 4.2 Hz), 3.14 (1H, dd, *J*=9.9 and 4.2 Hz), 1.42 (3H, s), 1.26 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.82, 175.11, 143.35, 135.27, 128.78, 128.59, 128.53, 127.99, 127.26, 113.08, 87.47, 85.94, 82.86, 75.68, 72.84, 71.59, 63.53, 50.24, 42.55, 26.31, 24.06., MS: m/z 616 (M^+).

Received, 9th March, 1998