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Intramolecular Nitrone Cycloaddition Reaction on Carbohydrate-Based Precursors: Application in the Synthesis of Spironucleosides and Spirobisnucleosides

Kaushik Singha, Atanu Roy, Pradeep K. Dutta, Subhankar Tripathi, Sk. Sahabuddin, Basudeb Achari, and Sukhendu B. Mandal*

Division of Medicinal Chemistry, Indian Institute of Chemical Biology, Jadavpur, Kolkata 700 032, India

sbmandal@iicb.res.in

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Abstract: A simple synthesis of chiral spironucleosides and spirobisnucleosides is described. Intramolecular 1,3-dipolar nitrone cycloaddition reaction of D-glucose-derived precursors having olefin at C-3 and nitrone at C-5, C-1, or C-2 (in nor-series) furnished bisisoxazolidinospirocycles **4**−**7**, **11**, and **12** in good yields. Reductive ring opening of the isoxazolidine moieties in **4**−**6** followed by construction of a nucleoside base upon the generated amino groups smoothly yielded spirobisnucleosides **17** and **18** and spironucleosides **20** and **21**.

Synthesis of enantiomerically pure carbocyclic amino alcohols en route to carbocyclic nucleosides,[1−4] many of which are of interest in search of therapeutic agents for dreaded diseases such as HIV, HSV, and cancer, remains a cherished goal of synthetic organic chemists. Since the discovery of the nucleoside hydantocidin[5] possessing a spirocyclic ring at the anomeric center, the area of synthetic spirocyclic nucleosides also started to develop. Besides notable contributions from Miyasaka's laboratory[6] and others,[7] the field has been enriched by publications of Paquette's group[8] on the synthesis of nucleosides bearing a spiro ring juncture at the anomeric center, as well as of other carbaspironucleosides. Syntheses of 5/5 and 6/5 spironucleosides with unusual heterocycles spirofused to the ribose ring has also been reported by Gasch et al.[9] However, development of newer and versatile synthetic routes to enantiomerically pure products with structural variations, starting from the readily available chiral pool constituted by sugars, remains a relevant task.

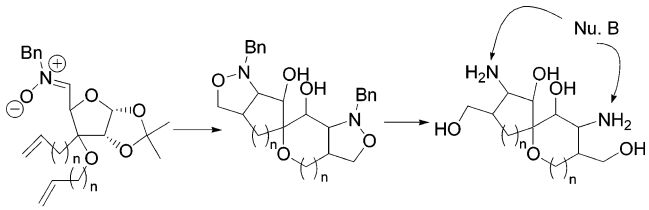

FIGURE 1. A general scheme for the synthesis of spirocyclic nucleosides.

We have recently demonstrated the applicability of intramolecular nitrone cycloaddition (INC) reaction on glucose-derived enose-nitrones for enantioselective as well as enantiodirecting synthesis of carbocyclic nucleosides of varying ring sizes.[10] We reasoned that if a *C*-allyl as well as an *O*-allyl group could be introduced at C-3 of the glucose ring, consecutive INC reactions (Figure 1) involving the olefins with a C-1 aldehyde and an aldehyde generated at C-5 through simple functional group manipulations should lead to optically active and structurally unique spirocyclic nucleosides. The present communication deals with the results derived from such studies.

Compound **1**, generated[10c] from a D-glucose-derived substrate through INC reaction of C-5 nitrone with C-3 allyl function, could be converted to the masked aldehyde **2**, which in turn afforded the nor-aldehyde **3** via periodate cleavage. INC reaction of **2** with BnNHOH afforded the tetracyclic spirocycles **4** (43%) and **5** (27%), and similar treatment of **3** furnished **6** (65%) and **7** (4%), presumably through a nonisolable enose-nitrone (Scheme 1). The gross structures of the products[11] were evident from their mass spectra, which showed an identical molecular ion peak for **4** and **5** (at *m*/*z* 438) and for **6** and **7** (at *m*/*z* 408). Further, the stereochemistry for the A/B rings of the spirocycles, as also for C-7 of **4** and **5**, should be the same as for the corresponding centers in **1**. Only those of the newly formed stereocenters (C/D ring juncture) remained to be determined. The *cis* geometry assumed

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(11) The alternative bridged ring structures could be easily excluded from NMR evidence (absence of upfield signals for the methylene bridge).

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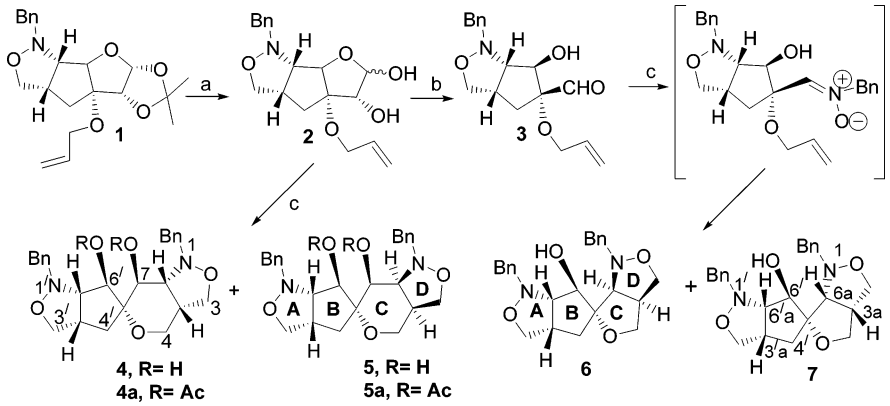
SCHEME 1. Synthesis of Bisisoxazolidinospirocycles 4−7 Using INC Reaction[a]



[a] Reagents and conditions: (a) 4% H_2SO_4, MeCN, H_2O; (b) $NaIO_4$, EtOH, H_2O; (c) BnNHOH, EtOH, rt, 24 h, then 60 °C, 1 h.

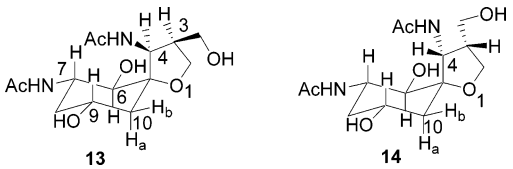
in all of the cases was fully supported by extensive ^{1}H NMR spectral analyses (COSY, TOCSY, and NOESY experiments) of the compounds or their derivatives as discussed below.

The ^{1}H NMR spectra of **4** and **5**, however, failed to afford any conclusive evidence for the structures, as signals for many of the protons overlapped with each other. The compounds were, therefore, acetylated to afford the derivatives **4a** and **5a**.[12] The TOCSY spectrum of **4a**, in conjunction with the COSY spectrum, showed the presence of two seven-proton spin systems: (a) δ 5.42 d (H-6′)−4.02 unresolved−3.72 unresolved−3.22 dd (H-6′a)−3.08 m (H-3′a)−2.18 dd (H-4′α)−1.85 dd (partly overlapped, H-4′β) and (b) δ 5.17 d (H-7)−4.09 t−3.89 unresolved−3.80 dd−3.71 unresolved−3.13 t (partly overlapped, H-7a)−2.92 m (H-3a). The former system having the most upfield signal (δ 1.85) was assigned to the 5/5-ring moiety, while the latter must belong to the 6/5-ring moiety. Similarly, in the ^{1}H NMR spectrum of **5a** the two spin systems consisted of signals at (i) δ 5.30 d (H-6′)−4.08 t−3.69 unresolved−3.27 dd (H-6′a)−3.17 m (H-3′a)−3.05 dd (H-4′α)−1.82 dd (H-4′β) and (ii) δ 5.20 d (H-7)−4.00 unresolved−3.88 t−3.67 unresolved−3.59 dd−3.44 dd (H-7a)−2.90 m (H-3a). In the NOESY spectrum of **4a**, the signal for H-7 (δ 5.17) showed no cross-peak with the signal for H-3a (δ 2.92), while the corresponding proton signals of **5a** (δ 5.20 for H-7 and δ 2.90 for H-3a) showed distinct cross-peaks, clearly indicating *trans* relationship of the protons in **4a** and *cis* relationship in **5a**.

The ^{1}H−^{1}H COSY spectra of both **6** and **7** clearly identified most of the signals, including those of all ring juncture protons, except for a few overlapping signals. In the NOESY spectrum of **7**, the most informative correlations were from C-6a H (δ 3.77) to C-3′a H (δ 2.71) and one of C-4′ H signals (δ 1.82), placing the three protons on the same face of the molecule and in close proximity in space. With **6** on the other hand, the C-6a H signal (δ 4.02) showed no cross-peaks with signals either of the C-4′ protons (δ 1.32 or δ 2.58) or of C-3′a H, suggesting their segregation; instead the C-6′a H signal (δ 2.34) showed a correlation with it, demonstrating their proximity. The above evidences showed that the isoxazolidine ring D in **6** was in the face opposite to that in **7**. As expected from the structures, C-6a H signal showed correlation with C-3a H signal and C-6′a H signal with C-3′a H signal, in both **6** and **7**.

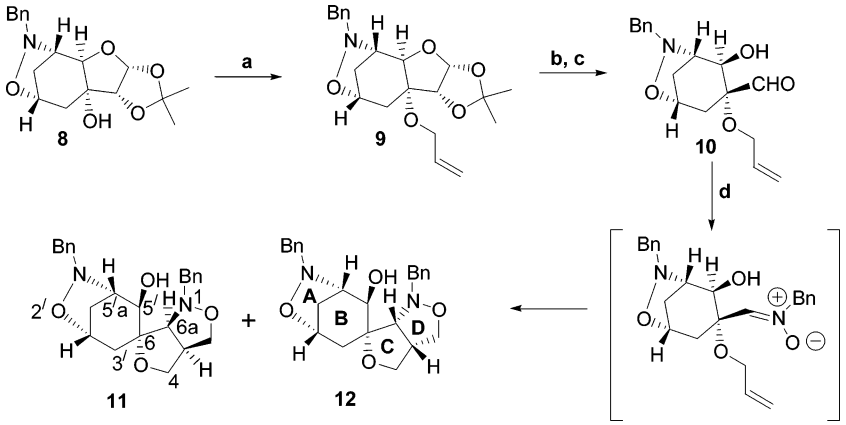
With the structure and stereochemistry of **4**−**7** satisfactorily established, we decided to test the applicability of the strategy with the bridged-ring product **8** synthesized[10d] earlier by INC reaction on a D-glucose-derived product. The olefinic moiety was inserted by allylation of the hydroxyl group of **8** to **9**. Subsequent deprotection of isopropylidene group and vicinal diol cleavage to the aldehyde **10** (IR at 1730 cm^{-1}, ^{1}H NMR peak at δ 9.82) and treatment with benzyl hydroxylamine spurred the desired INC reaction (Scheme 2), furnishing the spirocycles **11** (50%) and **12** (25%). Again, no product possessing bridged-ring structure could be isolated. The FAB mass spectra of both the products showed peaks at *m*/*z* 409 (MH^+) and 431 (MNa^+) for their pseudo molecular ions, indicating their isomeric relationship.

The ^{1}H NMR spectra of the compounds failed to provide any light on the stereochemistry of C/D ring juncture. They were thereafter subjected to transfer hydrogenolysis followed by selective acetylation of the newly generated amino functions to yield **13** and **14**, respectively. To our satisfaction, ^{1}H NMR analysis of the diamide derivatives provided the desired information on stereochemistry. The C-10 H_b signal (δ 2.90) showed NOE with the C-4 N*H*Ac signal (δ 8.88) in **13** but with the C-4 H signal (δ 5.69) instead in **14**. Additionally, C-4 H (δ 5.74) of **13** showed NOE with signals for C-9 H (δ 4.20) and C-7 H (δ 4.75), establishing the stereochemistry of C/D ring juncture in **11** and **12** as indicated.



(12) ^{1}H NMR ($CDCl_3$, 500 MHz). **4a**: δ 1.82 (s, 3 H), 1.85 (dd, 1 H, J = 6.0, 14.0 Hz), 2.02 (s, 3 H), 2.18 (dd, 1 H, J = 9.0, 14.0 Hz), 2.92 (m, 1 H), 3.08 (m, 1 H), 3.13 (t, 1H, J = 6.2 Hz), 3.22 (dd, 1 H, J = 3.0, 9.0 Hz), 3.71 and 3.72 (unresolved, 2 H), 3.80 (dd, 1 H, J = 5.5, 12.6 Hz), 3.89 and 3.90 (unresolved, 2 H), 3.95 (d, 1 H, J = 14.0 Hz), 4.00 and 4.02 (unresolved, 2 H), 4.09 (t, 1 H, J = 7.7 Hz), 4.15 (d, 1 H, J = 14.0 Hz), 5.17 (d, 1 H, J = 6.2 Hz), 5.42 (d, 1 H, J = 3.0 Hz), 7.22−7.36 (m, 10 H). **5a:** δ 1.79 (s, 3 H), 1.82 (dd, 1 H, J = 7.3, 13.4 Hz), 2.04 (s, 3 H), 2.90 (m, 1 H), 3.05 (dd, 1 H, J = 9.0, 13.4 Hz), 3.17 (m, 1 H), 3.27 (dd, 1 H, J = 5.0, 8.5 Hz), 3.44 (dd, 1 H, J = 4.5, 7.0 Hz), 3.59 (dd, 1 H, J = 4.2, 8.0 Hz), 3.67 and 3.69 (unresolved, 2 H), 3.83 (d, 1 H, J = 13.6 Hz), 3.85 and 3.88 (unresolved, 2 H), 3.92 (d, 1 H, J = 13.6 Hz), 3.98 and 4.00 (unresolved, 2 H), 4.08 (t, 1 H, J = 8.0 Hz), 5.20 (d, 1 H, J = 4.5 Hz), 5.30 (d, 1 H, J = 5.0 Hz), 7.23−7.33 (m, 10 H).

SCHEME 2. Synthesis of Bisisoxazolidinospirocycles 11 and 12 via INC Reaction[a]



[a] Reagents and conditions: (a) allyl Br, NaH, THF, reflux, 3 h; (b) 4% H_2SO_4, MeCN, H_2O; (c) $NaIO_4$, EtOH, H_2O; (d) BnNHOH, EtOH, rt, 20 h, then 60 °C, 1 h.

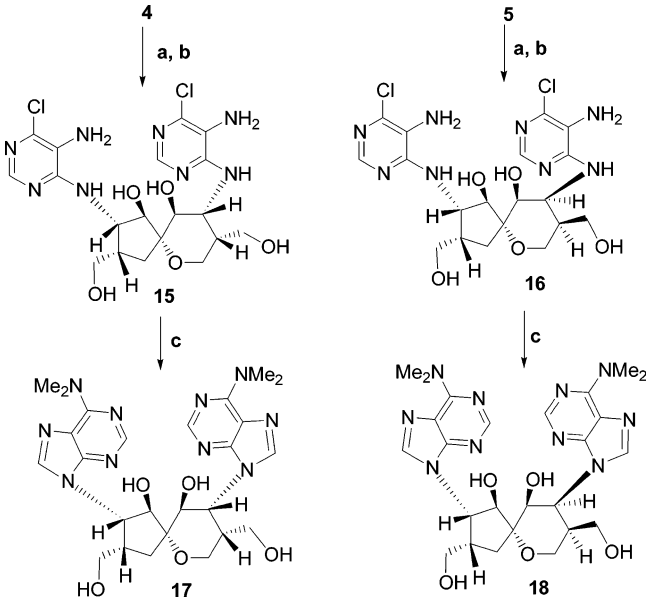
Having established the structure and stereochemistry of the spiro products, we next turned our attention to construct the purine nucleoside bases. Thus, transfer hydrogenolysis of **4** and **5** cleaved both of the isoxazolidine rings[13] to afford the respective trihydroxydiamino spirocycles, which were directly coupled with 5-amino-4,6-dichloropyrimidine (2.1 equiv) to obtain the bispyrimidinyl spirocycles **15** (59%) and **16** (55%), respectively (Scheme 3). Conversion of these pyrimidinyl spironucleoside derivatives to the corresponding 6-dimethylaminopurine spironucleosides **17** (38%) and **18** (35%) was accomplished[10b] by treatment with $HC(OEt)_3$/*p*-TSA in DMF followed by chromatographic purification (LiChroprep RP-18).

Regarding the structures of the nucleosides, the presence of two aromatic proton signals at δ 7.70 and 7.74 in **15** and at δ 7.74 and 7.76 in **16** in the ^{1}H NMR spectra indicated the introduction of two pyrimidinyl rings in each of them. On the other hand, the corresponding spectrum of **17** contained four aromatic singlets at δ 8.10, 8.17, 8.20, and 8.25. Besides, it showed a broad 12H singlet at δ 3.46 changing to a sharp signal at 60 °C, assignable to two NMe_2 groups. Similar proton signals were observed with **18**. The ^{13}C NMR spectra and the FAB mass spectra of **15**−**18** were also in conformity with the assigned structures.

Proceeding as with **4** and **5**, compound **6** was converted to **19** (52%); expected incorporation of the second chloropyrimidine moiety at the other amino group (in the tetrahydro furan ring) did not take place, possibly due to steric hindrance offered by the neighboring spirocyclic ring (Scheme 4). Cyclization reaction of **19** followed by chromatographic purification provided the 6-dimethylaminopurine nucleoside **20** (38%) and 6-methoxypurine nucleoside **21** (13%). No 6-chloro-purine nucleoside could be isolated; presumably, it is partly substituted by dimethylamine generated from DMF to afford **20** and partly by methanol during chromatography using $CHCl_3$/MeOH mixture to give the methoxy analogue **21**.

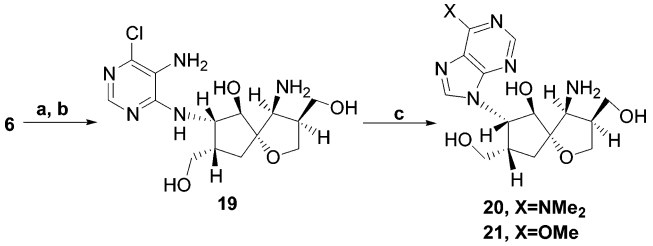
The product **19** showed a one-proton singlet at δ 7.72 (assigned to C-2 H) in its ^{1}H NMR spectrum and four aromatic carbon signals at δ 123.4, 136.8, 145.6, and 152.4 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum of **20** taken at 60 °C in DMSO-d_6 exhibited a sharp singlet (6H) at δ 3.45 (for NMe_2) and two discrete (1H) peaks at

SCHEME 3. Conversion of Spirocycles 4 and 5 to Spirobisnucleosides 17 and 18[a]



[a] Reagents and conditions: (a) Pd/C (10%), cyclohexene, EtOH, reflux, 4 h, N_2; (b) 5-amino-4,6-dichloropyrimidine, *n*-BuOH, Et_3N, reflux, 18 h; (c) $HC(OEt)_3$/*p*-TSA, DMF, rt, 30 h.

SCHEME 4. Conversion of Spirocycle 6 to Spironucleosides 20 and 21[a]



[a] Reagents and conditions: (a) Pd/C (10%), cyclohexene, EtOH, reflux, N_2; (b) 5-amino-4,6-dichloropyrimidine, *n*-BuOH, Et_3N, reflux, 18 h; (c) $HC(OEt)_3$/*p*-TSA, DMF, rt, 24 h.

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δ 8.11 and 8.18; that of **21** (in DMSO-d_6) showed a peak (3H) at δ 4.18 characteristic for OCH_3, in addition to 1H signals at δ 8.41 and 8.50.

In conclusion, the work has demonstrated successful application of INC reaction on appropriate D-glucose-derived enose-nitrones in generating spirocycles, which have been extended to the synthesis of complex spirocyclic nucleosides having carbocycles as well as oxygen heterocycles fused together in a spirocyclic manner.

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Supporting Information Available: Experimental procedures for the preparation and characterization of compounds and copies of ^1H and ^{13}C NMR spectra of **4**−**7**, **11**, **12**, **17**, **18**, **20**, and **21** including $^1H-^1H$ COSY, TOCSY, NOESY of **4a** and **5a** and $^1H-^1H$ COSY, NOESY of **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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