Application of Intramolecular Nitrone Cycloaddition Reaction: Synthesis of Chiral Aminocarbocycles and Carbocyclic Nucleosides from Carbohydrate Precursors

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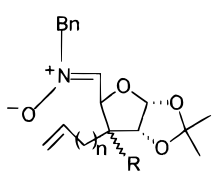
Intramolecular olefin−nitrone cycloaddition (INC) reaction constitutes a simple and promising method for the construction of carbocycles of different ring-sizes by varying the mode of cyclization and judicious manipulation of the substituents in the substrates.[1] In recent years, much effort has been expended in exploring carbohydrate derived enose−nitrone cycloaddition methodology toward the synthesis of chiral aminocarbocycles, many of which exhibit glycosidase inhibitory activity.[2] In addition, this class of compounds is an attractive precursor for carbocyclic nucleoside analogues,[3] often possessing enhanced activity with better resistance to most of the phosphorylase enzymes[3i] in comparison to their furanose counterparts. As a carbohydrate precursor, D-glucose is very useful due to its easy accessibility, and it has been possible to synthesize enantiomerically pure target molecules[4] by utilizing the carbon skeleton and the resident chirality of D-glucose.[5] An added attraction is the possibility of synthesizing both the pure enantiomers of a product from a common intermediate through INC reaction, by generating aldehyde precursors of nitrones at the appropriate end.[6] In this paper, we report the details of our work undertaken to investigate the scope and feasibility of such a strategy for developing chiral aminocarbocycles of different ring-sizes and varying stereochemistry based upon the respective D-glucose derived intermediates, leading to the synthesis of the isoxazolidinocarbocyclic derivatives **2a**−**f**, **3a**, **4**, **7**, and **8**. As an example, a simple and convenient transformation of **2e** to a carbocyclic nucleoside analogue **11** has also been presented.



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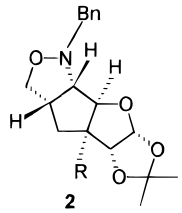
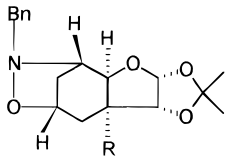


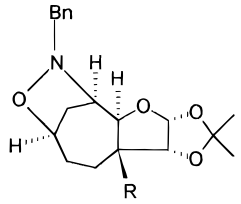
2

a, R = α - OH, n = 1
b, R = α - OMe, n = 1
c, R = α - OBn, n =1
d, R = α - Oallyl, n = 1
e, R = β - OH, n = 2
f, R = β - OBn, n = 2

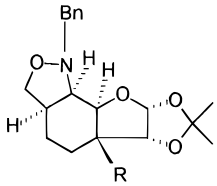
a, R = OH
b, R = OMe
c, R = OBn
d, R = Oallyl



3a, R = OH



2e, R = OH



2f, R = OBn

Results and Discussions

Preparation of Carbocyclic Derivatives of Different Ring Sizes. To understand the role of a 3-oxy substituent on the cyclization mode, enose−nitrone substrates **1b**−**d**,**f** were prepared and subjected to cyclization as follows. 1,2:5,6-Di-*O*-isopropylidene 3-allyl or 3-homoallyl furanose derivatives[7] were converted to their 3-alkoxy derivatives via reaction with the appropriate alkyl halides (BnBr, allyl bromide, CH_3I) under phase transfer reaction condition. Treatment with aqueous HOAc followed by $NaIO_4$ afforded the 6-nor aldehydes which were converted to the nitrones with benzyl hydroxylamine in alcohol. In situ cyclization afforded the corresponding products **2b**−**d** and **2f** in 50−60% overall yield.

Comparison of the results of cyclization with those reported by us[7] for 3-hydroxy substituents **1a** and **1e** shows that isomeric cyclization products differing in ring-sizes can be constructed by taking advantage of the profound influence of a hydroxy substituent at C-3 over the course of the cyclization. Thus, **1e** formed a seven-membered ring product **2e** exclusively, but **1f** bearing an alkoxy substituent gave a six-membered ring product **2f**. Similarly, **1a** carrying a hydroxyl group yielded a mixture of **2a** and **3a** upon cyclization, but only the five-membered products **2b**−**d** could be isolated[8] with the alkoxy bearing substrates **1b**−**d**.

Synthesis of Enantiomeric and Diastereomeric Carbocyclic Derivatives. The transformation of allyl diisopropylidene allofuranose intermediate **5** to the enan-

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(8) It appears plausible that the C-3 hydroxyl substituent with its hydrogen bonding ability to the nitrone oxygen suitably alters the transition state leading to different cyclization products.

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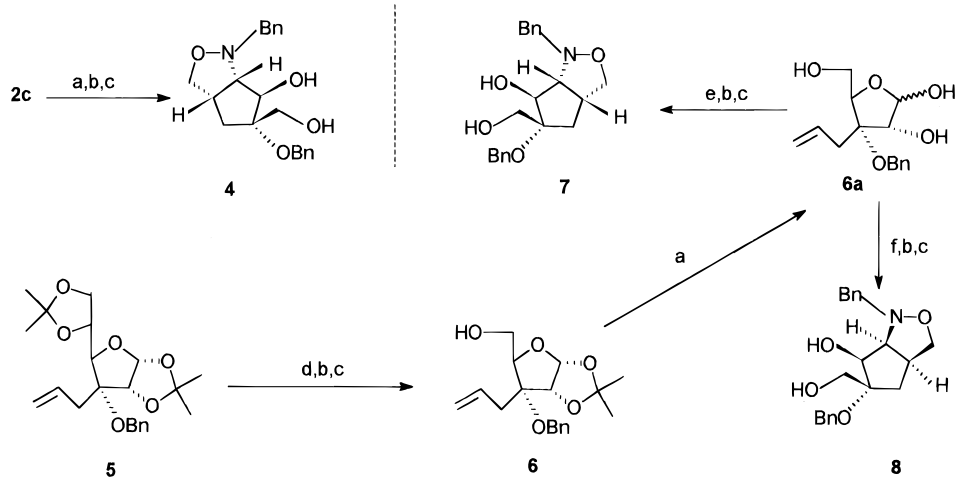
Scheme 1[a]



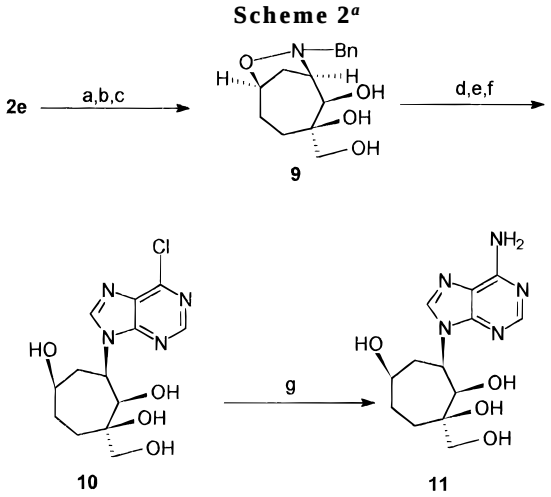
[a]Key: (a) 4% H_2SO_4, MeCN, H_2O; (b) $NaIO_4$, EtOH, H_2O; (C) $NaBH_4$, MeOH; (d) HOAc : H_2O (3:2); (e) BnNHOH, DMF, 50°C; (f) BnNHOH, toluene, reflux.

tiomerically pure isoxazolidinocarbocycles **4** and **7** could be realized by subjecting the C-3 allyl group to undergo cyclization with the nitrones generated from the respective C-5 and C-1 aldehydes (Scheme 1). Thus, the treatment of **5** with 60% HOAc and subsequent diol cleavage gave an aldehyde which on treatment with benzyl hydroxylamine led to the addition product **2c**. Acid-induced opening of the isopropylidene ring of **2c** followed successively by diol cleavage with $NaIO_4$ and $NaBH_4$ reduction afforded **4** in 80% yield. On the other hand **7** in its pure enantiomeric form could be obtained in good yield by INC reaction (in DMF or DMSO at 50 °C) of the nitrone generated in situ from the hemiacetal **6a** with benzyl hydroxylamine. This masked aldehyde in turn was readily obtained from the respective alcohol **6**, which was prepared from **5** by selective cleavage of the 5,6-isopropylidene group, followed by vicinal diol cleavage with $NaIO_4$ and $NaBH_4$ reduction. The two products **4** and **7** had identical melting points, superimposable IR as well as ^1H NMR, and optical rotations of equal magnitude but opposite signs.

The cyclization of the nitrone derived from **6a**, however, was strongly dependent on the nature of the solvent. Thus, the reaction proceeded smoothly in polar aprotic solvents such as DMF and DMSO leading to the desired product **7**. However, no reaction occurred in protic solvents such as EtOH, MeOH, or *n*-BuOH. The cyclization reaction also failed in benzene under reflux; however, a different mode of cyclization[9] took place in boiling toluene or xylene resulting exclusively in the product **8**. The compound **8** differed significantly from **7** in its ^1H NMR, ^{13}C NMR, and IR spectra. Since bicyclo[3.3.0]-octanes[10] prefer a *cis*-ring juncture, the diastereomeric structure **8** was assigned to it.

Synthesis of Carbocyclic Nucleosides. To demonstrate the feasibility and scope of the present methodology for synthetic entry to carbocyclic nucleoside analogues with varying ring-sizes or stereochemistry, the isoxazolidinofuranocarbocyclic derivative **2e** was subjected to the sequence of transformations shown in Scheme 2. Thus, trimming of the furanose ring involving deprotection with acid, diol cleavage with $NaIO_4$ and reduction of aldehyde with $NaBH_4$ converted **2e** to isoxazolidinocycloheptane derivative **9**. Further cleavage of the isoxazolidine ring in **9** by catalytic transfer hydrogenation (Pd/C, cyclohexene)[11] followed by reaction with 5-amino-4,6-dichloropyrimidine, and ring closure by treatment with triethyl orthoformate afforded the chloronucleoside **10**. This was finally converted to the seven-

Scheme 2[a]



[a]Key: (a) 4% H_2SO_4, MeCN, H_2O; (b) $NaIO_4$, EtOH, H_2O; (c) $NaBH_4$, MeOH, 0 -10°C; (d) 10% Pd/C, cyclohexene, EtOH; (e) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux, 24 h; (g) NH_3, MeOH, 100°C, sealed tube, 60 h.

(9) We believe that the possibility of dipole−dipole interaction between the nitrone and solvents such as DMSO or DMF favors the formation of the transition state intermediate, and cyclization occurs to give the product **7**. In apolar solvents such as toluene or xylene the dihydroxy-bearing group and the nitrone come closer, away from the solvent, and cyclization is arrested. However, at elevated temperature (refluxing temperature) the existing arrangement breaks down; the nitrone group moves about and comes closer to the allyl group when cyclization occurs, giving rise to the product **8**. In protic solvents, e.g. EtOH, MeOH or *n*-BuOH the formation of nitrone is prevented, as evident from the recovery of the starting material from the reaction mixture.

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membered carbocyclic nucleoside analogue **11** through ammonolysis.[12]

In conclusion, the present investigation offers simple and flexible strategies to synthesize different functionalized carbocycles and chiral carbocyclic nucleoside analogues varying in ring-sizes and stereochemistry.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were measured on a 100 MHz or a 300 MHz spectrometer using TMS as internal standard. Mass spectra were recorded under electron impact at 70 eV. Reagents and solvents were of analytical grade or were purified by standard procedures prior to use. Merck silica gel 60 F_{254} (thickness 0.2 mm) was used for TLC visualization of nucleosides.

Preparation of Nitrones 1b−d and 1f, and Their Conversion to 1-Benzyl-5:6-*O*-isopropylidene-4a-methoxy-perhydrofuro[2′,3′:2,1]cyclopent[3,4-*c*]isoxazole (2b), 1-Benzyl-5,6-*O*-isopropylidene-4a-(benzyloxy)-perhydrofuro[2′,3′:2,1]cyclopent[3,4-*c*]isoxazole (2c), 1-Benzyl-5,6-*O*-isopropylidene-4a-(allyloxy)-perhydrofuro[2′,3′:2,1]cyclopent[3,4-*c*]isoxazole (2d), and 1-Benzyl-6,7-*O*-isopropylidene-5a-(benzyloxy)-perhydrofuro[2′,3′:2,1]cyclohex[3,4-*c*]isoxazole (2f). Oil free NaH (72 mg, 3 mmol) was added to a stirred and ice-cooled solution of 1,2:5,6-di-*O*-isopropylidene-3-prop-1-enyl-α-D-allofuranose[7] (450 mg, 1.5 mmol) in diethyl ether (50 mL). After 30 min the solution was heated at reflux under N_2, MeI (1 mL) was added dropwise to it, and heating was continued for 5 h. Excess NaH was decomposed with cold H_2O (1 mL). The ethereal solution was washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and evaporated to a crude residue (405 mg) which, without further purification, was treated with HOAc−H_2O (3:2) mixture (30 mL) at 70 °C for 50 min to remove 1,2-isopropylidene group. The solvent was evaporated to afford a dihydroxy compound (340 mg). To the cooled ethanolic solution (20 mL) of it was added an aqueous solution (20 mL) of $NaIO_4$ (200 mg) dropwise, and the mixture was stirred for 1 h and then filtered. The filtrate was evaporated, the residue was dissolved in $CHCl_3$ (30 mL), and the $CHCl_3$ solution was washed with H_2O (2 × 10 mL) and dried (Na_2SO_4). Evaporation of the solvent afforded the crude aldehyde (285 mg). The aldehyde was dissolved in EtOH (15 mL) and treated with BnNHOH (185 mg, 1.5 mmol) to obtain a crude oil (via in situ cyclization of the nonisolable nitrone **1b**). The oily mixture was purified by column chromatography on silica gel eluting with petroleum ether−$CHCl_3$ (1:1) to furnish **2b** (260 mg, 50%). **2b**: oil; $[\alpha]^{26}_D$ −12.4° (*c* 0.31, $CHCl_3$); IR (neat) 1608, 1497, 1374, 735, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H), 1.53 (s, 3H), 1.68 (dd, 1H, J = 8, 14 Hz), 2.19 (d, 1H, J = 14 Hz), 3.29 (m, 1H), 3.42 (s, 3H), 3.54 (d, 1H, J = 8 Hz), 3.72 (dd, 1H, J = 7, 8 Hz), 3.95 (d, 1H, J = 13.5 Hz), 4.08 (d, 1H, J = 13.5 Hz), 4.15 (t, 1H, J = 8 Hz), 4.38 (s, 1H), 4.48 (d, 1H, J = 3.7 Hz), 5.72 (d, 1H, J = 3.7 Hz), 7.32 (m, 5H); FABMS, *m/z*: 347 (M^+ + 1).

The preparation of **1c** from **5** was carried out following a procedure similar to that described for **1b**. Compound **5** (1.17 g, 3 mmol) was treated with aqueous HOAc to cleave 1,2-*O*-isopropylidene protection. Usual workup followed by $NaIO_4$ (600 mg) afforded the crude aldehyde (680 mg). The ethanolic solution (40 mL) of the aldehyde, on reaction with BnNHOH (310 mg, 2.5 mmol), furnished the nonisolable nitrone **1c** which was immediately cyclized to afford **2c**. The impure compound **2c** was purified by column chromatography on silica gel eluting with the same solvent as used for **1b** to give pure **2c** (760 mg, 60%). **2c**: mp 95−96°; $[\alpha]^{26}_D$ −21.9° (*c* 0.75, $CHCl_3$); IR (KBr) 1607, 1498, 1374, 1042, 734, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.56 (s, 3H), 1.64 (m, 1H), 2.17 (d, 1H, J = 14.6 Hz), 3.32 (app quintet, 1H, J = 7.5 Hz), 3.57 (d, 1H, J = 8.2 Hz), 3.76 (dd, 1H, J = 6.4, 8.1 Hz), 3.97 (d, 1H, J = 13.3 Hz), 4.05 (d, 1H, J = 13.3 Hz), 4.12 (t, 1H, J = 8.4 Hz), 4.51 (merged 1×s and 1×d), 4.78 (2×d, 1H each, J = 10.6 Hz), 5.74 (d, 1H, J = 3.8 Hz), 7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9 (q), 27.1 (q), 36.5 (t), 47.8 (d), 61.5 (t), 67.7 (t), 72.2 (t), 75.6 (d), 82.6 (d), 87.1 (d), 93.7 (s), 105.2 (d), 113.0 (s), 127.3 (d), 127.4 (d), 127.7 (d), 128.2 (d), 128.3 (d), 129.0 (d) 137.2 (s), 138.7 (s); EIMS, *m/z*: 422 (M^+ − 1), 408 (M^+ − 15), 346, 317, 230, 217, 91. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.69; H, 7.12; N, 3.19.

For the preparation of **1d**, 1,2:5,6-di-*O*-isopropylidene-3-prop-1-enyl-α-D-allofuranose[7] (885 mg, 2.6 mmol) was allylated with allyl bromide (3 × 1 mL) following the procedure adopted for **5**. The crude diallylated compound thus obtained was then converted to the nonisolable **1d** according to the method as described for **1b**. The nitrone **1d** on in situ cyclization afforded a crude material which was purified on silica gel using the same solvent as used for **1b** to furnish **2d** (550 mg, 57%). **2d**: mp 82−83 °C; $[\alpha]^{27}_D$ −5.8° (*c* 0.31, $CHCl_3$); IR (KBr) 1653, 1498, 1250, 929, 878 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.32 (s, 3H), 1.52 (s, 3H), 2.12 (d, 1H, J = 14 Hz), 3.28 (app quintet, 1H, J = 8 Hz), 3.56 (d, 1H, J = 8 Hz), 3.76 (dd, 1H, J = 6, 8 Hz), 3.92 (d, 1H, J = 14 Hz), 4.06 (d, 1H, J = 14 Hz), 4.08 (t-like, 1H, J = 8 Hz), 4.22 (m, 2H), 4.40 (s, 1H), 4.42 (d, 1H, J = 4 Hz), 5.04−5.48 (m, 2H), 5.72 (d, 1H, J = 4 Hz), 5.80−6.20 (m, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 26.7 (q), 26.9 (q), 36.0 (t), 47.6 (d), 61.2 (t), 66.6 (t), 71.9 (t), 75.3 (d), 82.2 (d), 87.4 (d), 93.3 (s), 104.9 (d), 112.7 (s), 115.7 (t), 127.1 (d), 128.1 (d), 128.2 (d), 134.9 (d), 137.0 (s); EIMS, *m/z*: 373 (M^+), 358 (M^+ − 15), 216, 123, 91. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.51; H, 7.21; N, 3.39.

The generation of the nonisolable nitrone **1f** and its corresponding cyclization product **2f** (234 mg, 54%) was similarly carried out from 1,2:5,6-di-*O*-isopropylidene-3-prop-1-enyl-α-D-allofuranose[7] (405 mg, 1 mmol). Benzylation was done with benzyl bromide (3 × 0.3 mL), according to the procedure as adopted for **5**. The rest of the reactions were performed following the method as described for **1b**. **2f**: mp 78−80 °C; $[\alpha]^{26}_D$ +53.5° (*c* 0.18, $CHCl_3$); IR (KBr) 1605, 1495, 1375, 731, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H), 1.54 (s, 3H), 1.83 (m, 3H), 2.11 (m, 1H), 3.11 (m, 1H), 3.48 (t, 1H, J = 8.1 Hz), 3.56 (brt, 1H, J = 8.6 Hz), 3.95 (d, 1H, J = 14 Hz), 4.05 (d, 1H, J = 8.7 Hz), 4.06 (d, 1H, J = 13.8 Hz), 4.16 (t, 1H, J = 8.5 Hz), 5.55 (ABq, 2H, J = 12 Hz overlapping an 1H signal), 5.98 (d, 1H, J = 3.7 Hz), 7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8 (t), 21.0 (t), 26.2 (q), 26.8 (q), 39.8 (d), 60.7 (t), 64.2 (t), 65.2 (d), 70.2 (t), 79.7 (d, 2C), 84.9 (s), 105.9 (d), 112.2 (s), 126.5 (d, 2C), 127.0 (d), 127.5 (d), 128.2 (d, 2C), 128.4 (d, 2C), 128.9 (d, 2C), 137.9 (s), 138.3 (s); FABMS, *m/z*: 437 (M^+ + 1). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.12; H, 7.02; N, 3.13.

(3*aS*,5*S*,6*R*,6*aS*)-1-Benzyl-5-(benzyloxy)-5-(hydroxymethyl)-6-hydroxycyclopent[*c*]isoxazole (4). Compound **2c** (1.75 g, 4.13 mmol) was treated with 4% H_2SO_4 in CH_3CN−H_2O (30 mL) at rt for 24 h. The solution was neutralized with solid $CaCO_3$ and filtered, and the solvent was evaporated in vacuo to obtain a crude material (1.50 g). To this material dissolved in EtOH (20 mL) and cooled to 10 °C was added an aqueous solution (20 mL) of $NaIO_4$ (1.08 g, 5 mmol, 1.2 eq) dropwise with stirring. After stirring at rt for 40 min, the mixture was filtered, the solvent was evaporated, and the residue was dissolved in $CHCl_3$ (80 mL). The solution was washed with H_2O (2 × 20 mL) and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the crude aldehyde (1.60 g) (IR: 1740 cm^{-1}).

To the aldehyde in MeOH (35 mL) at 0 °C was added $NaBH_4$ (240 mg) portionwise and the mixture was kept at ice temperature for 14 h. The solvent was evaporated, and the residue was taken up in H_2O (30 mL), and was extracted with $CHCl_3$ (2 × 45 mL). The $CHCl_3$ solution was washed with H_2O (1 × 30 mL), dried (Na_2SO_4), and evaporated to give a residue which was purified by column chromatography, eluting with $CHCl_3$ to afford **4** (1.12 g, 80%): mp 130−132 °C; $[\alpha]^{26}_D$ −30.8° (*c* 0.5, $CHCl_3$); IR (KBr) 3346, 1451, 724, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67 (dd, 1H, J = 8.2, 13.4 Hz), 2.15 (dd,1H, J = 9.2, 13.3 Hz), 3.00 (quintet of doublets, 1H, J = 9, 9, 9, 9, 3 Hz), 3.46 (brt, 1H, J = 8 Hz), 3.60 (dd, 1H, J = 3.5, 8.8 Hz), 3.76 (d, 2H, J = 13 Hz), 3.93 (d, 1H, J = 12.2 Hz), 4.03 (d, 1H, J = 13 Hz), 4.09 (t, 1H, J = 8 Hz), 4.27 (brd, 1H, J = 6.6 Hz), 4.48 and 4.64 (2×d, 1H each, J = 11.2 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.7 (t), 41.1 (d), 59.9 (t), 63.4 (t), 65.7 (t), 72.1 (t), 75.4 (d), 81.0 (d), 84.9 (s), 127.6 (d), 128.4 (d), 128.5 (d), 129.0 (d), 136.8 (s), 138.7 (s); EIMS, *m/z*: 355 (M^+), 252, 232, 174, 161, 91. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.48; H, 7.02; N, 3.62.

1,2:5,6-Di-*O*-isopropylidene-3-prop-1-enyl-3-*O*-benzyl-α-D-allofuranose (5). Benzyl bromide (3 × 0.5 mL) was added

to a stirred, refluxing mixture of 1,2:5,6-di-*O*-isopropylidene-3-prop-1-enyl-α-D-allofuranose[7] (600 mg, 2 mmol), tetrabutylammonium bromide (80 mg, 0.25 mmol), NaOH solution (50%, 15 mL), and benzene (20 mL) over 20 h. The benzene solution was separated, and the aqueous layer was extracted with benzene (2 × 20 mL). The combined benzene extract was washed with H_2O (3 × 30 mL) and dried (Na_2SO_4), and the solvent was evaporated to give a material which was purified by column chromatography on silica gel, eluting with petroleum ether−$CHCl_3$ (7:3) to afford a solid which was recrystallized from petroleum ether to furnish **5** (688 mg, 88%) as colorless crystals: mp 95−96 °C; $[\alpha]^{26}_D$ +51.9° (*c* 0.62, $CHCl_3$); IR (KBr) 1638, 1373, 852, 726 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.34, 1.38, 1.58 (3×s, 12H), 2.56 (2×brdd, 1H each, *J* = 7, 14 Hz), 3.90−4.30 (m, 4H), 4.50 (d, 1H, *J* = 4 Hz), 4.80 (2×d, 1H each, *J* = 12 Hz), 5.18 (m, 2H), 5.64 (d, 1H, *J* = 4 Hz), 6.04 (m, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 25.3, 26.5, 26.6, 26.9, 35.8, 66.9, 68.0, 73.0, 81.3, 83.0, 83.6, 103.4, 109.5, 112.6, 118.5, 127.0, 127.9, 132.6, 139.2; EIMS, *m*/*z*: 375 ($M^+ - 15$), 360, 216, 91. Anal. Calcd for $C_{22}H_{30}0_6$: C, 67.67; H, 7.74. Found: C, 67.63; H, 7.75.

1,2-*O*-Isopropylidene-3-prop-1-enyl-3-*O*-benzyl-α-D-allofuranose (6). The diisopropylidene compound **5** (1.17 g, 3 mmol) was left in HOAc−H_2O (3:2) mixture (50 mL) at 60 °C for 40 min. The solvent was evaporated, and the crude residue was extracted with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ solution was washed with H_2O (2 × 20 mL) and dried (Na_2SO_4), and the solvent was evaporated to afford a dihydroxy material. This was subsequently cleaved by $NaIO_4$ and reduced with $NaBH_4$ according to the protocol described with **4** to afford a thick gum which was purified by column chromatography on silica gel. Elution with petroleum ether−$CHCl_3$ (1:4) furnished **6** (537 mg, 56%): oil; $[\alpha]^{26}_D$ +35.2° (*c* 0.51, $CHCl_3$); IR (neat) 3420, 1645, 1603, 1375, 734, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (s, 3H), 1.56 (s, 3H), 2.44 (m, 2H), 3.82 (d, 2H, *J* = 6 Hz), 4.30 (t, 1H, *J* = 6 Hz), 4.42 (d, 1H, *J* = 4 Hz), 4.68 (s, 2H), 5.08−5.32 (m, 2H), 5.72 (d, 1H, *J* = 4 Hz), 5.92 (m, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 26.8, 27.1, 36.0, 66.7, 73.2, 81.4, 83.0, 83.8, 103.3, 112.8, 118.8, 127.5, 128.8, 132.3, 136.8; FABMS, *m*/*z*: 321 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found C, 67.23; H, 7.63.

(3*aR*,5*R*,6*S*,6*aR*)-1-Benzyl-5-(benzyloxy)-5-(hydroxymethyl)-6-hydroxycyclopent[*c*]isoxazole (7) and (3*aS*,5*R*,6*S*,6aS)-1-Benzyl-5-(benzyloxy)-5-(hydroxymethyl)-6-hydroxycyclopent[*c*]isoxazole (8). The 1,2-isopropylidene group in **6** (320 mg, 1 mmol) was cleaved by 4% H_2SO_4 according to the procedure described under the preparation of **4** to afford **6a** (280 mg). The trihydroxy compound **6a** (140 mg, 0.5 mmol) in DMF (5 mL) was treated with BnNHOH (74 mg, 0.6 mmol, 1.2 equiv), and the mixture was kept at 50 °C for 8 h. The solvent was evaporated, and the crude mixture on subsequent reaction with $NaIO_4$ and $NaBH_4$ according to the method described earlier (in the preparation of **4**) afforded a solid product which was purified by column chromatography on silica gel using $CHCl_3$ as the eluent to furnish **7** (80 mg, 45%); mp 129−130 °C; $[\alpha]^{26}_D$ +30.1° (*c* 0.5, $CHCl_3$). Compound **6a** (140 mg, 0.5 mmol) on reaction with BnNHOH (75 mg, 0.6 mmol) in refluxing toluene (10 mL) followed by cleavage with $NaIO_4$ and then reduction with $NaBH_4$ yielded a thick oily product which was purified by silica gel column chromatography to afford the product **8** (85 mg, 48%): gum; $[\alpha]^{26}_D$ −14.9° (*c* 0.47, $CHCl_3$); IR (neat) 3409, 1386, 708, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66 (dd, 1H, *J* = 9.8, 13.8 Hz), 2.05 (brdd, 1H, *J* = 7.9, 13.8 Hz), 3.20 (quintet of doublets, 1H, *J* = 7, 7, 7, 7, 2 Hz), 3.59 (dd, 1H, *J* = 2, 8.8 Hz), 3.68 (dd, 1H, *J* = 1,6 Hz), 3.77 (dd, 1H, *J* = 5.7, 8.7 Hz), 3.81−3.88 (m, 3H), 4.02 (dd, 1H, *J* = 6, 8.9 Hz), 4.16 (d, 1H, *J* = 11.4 Hz), 4.30 and 4.42 (2×d, 1H each, *J* = 11.4 Hz), 7.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.0 (t), 47.1 (d), 60.2 (t), 61.4 (t), 64.5 (t), 70.7 (t), 71.5 (d), 74.5 (d), 90.6 (s), 127.3 (d), 127.5 (d), 127.7 (d), 128.4 (d), 128.5 (d), 128.8 (d), 136.1 (s), 138.4 (s); EIMS, *m*/*z*: 355 (M^+), 264, 248, 163, 149, 135, 106, 91. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.83; H, 7.04; N, 3.83.

(1*R*,2*R*,5*R*,7*R*)-1,2-Dihydroxy-2-(hydroxymethyl)-8-benzyl-5,7-(epoxyimino)cycloheptane (9). Compound **2e**[7] (3.50 g, 10.1 mmol) was converted to **9** (1.86 g, 66%) by treatment with (i) 4% H_2SO_4, (ii) $NaIO_4$, and (iii) $NaBH_4$ following the procedure as described under the preparation of **4**. **9**: gum; $[\alpha]^{25}_D$ +59.2° (*c* 0.29, MeOH); IR (neat) 3412, 725, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.24−1.88 (m, 4H), 2.06 (d, 1H, *J* = 14 Hz), 2.44 (dt, 1H, *J* = 8, 8, 14 Hz), 3.28 (brs, 2H, becoming 1H doublet, *J* = 4 Hz on D_2O exchange), 3.42 (m, becoming t, 1H, *J* = 10 Hz on D_2O exchange), 3.58−3.68 (m, 2H), 3.77 (d, 1H, *J* = 14 Hz), 4.06 (d, 1H, *J* = 14 Hz), 4.68 (m, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 27.2 (t), 28.4 (t), 29.4 (t), 62.3 (t), 68.6 (d), 69.3 (t), 72.7 (d), 74.8 (s), 76.8 (d), 127.5 (d), 128.3 (d, 2C), 128.8 (d, 2C), 136.7 (s); EIMS, *m*/*z*: 279 (M^+), 159, 81. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.38; H, 7.53; N, 4.88.

(1*R*,2*R*,3*R*,5*R*)-9-[1,2,5-Trihydroxy-2-(hydroxymethyl)cycloheptyl]-6-chloroadenosine (10). To a solution of isoxazolidinocarbocycle **9** (1.54 g, 5.52 mmol) in dry EtOH (50 mL) was added Pd/C (10%, 200 mg) and cyclohexene (10 mL), and the mixture was heated at reflux under N_2 for 4 h. The Pd/C was filtered off, solvent was evaporated in vacuo, and the crude residue (800 mg) of free amino compound was used in the next step without further purification. To the crude amine in dry *n*-BuOH (25 mL) was added 4,6-dichloro-5-aminopyrimidine (1.03 g, 6.28 mmol, 1.34 equiv) and Et_3N (5 mL); the mixture was then heated at reflux for 22 h under N_2. The solvent was evaporated, and the residue was extracted with H_2O (3 × 30 mL). The aqueous part was washed with $CHCl_3$ (2 × 30 mL) [to remove free pyrimidine base] and evaporated to a gummy thick oil which turned into a foam (1.20 g) under vacuum over solid KOH. The material (1 g, 3.14 mmol) was dissolved in DMF (30 mL) and then *p*-TSA (896 mg, 4.70 mmol, 1.5 equiv) and $HC(OEt)_3$ (30 mL) were added to it, and the mixture was stirred at rt for 24 h under N_2. After neutralization of acid with Et_3N (2 mL), the solvent was evaporated in vacuo to a gummy dark brown material. The methanolic solution (10 mL) of it was passed through Dowex 1-OH^- resin. Elution with MeOH (4 × 20 mL) and evaporation of the solvent gave the partially purified chloronucleoside, which was again passed through Dowex 50W−H^+ resin. Aqueous-NH_3 (5%, 100 mL) eluted almost pure chloronucleoside (440 mg) which was further purified on silica gel using $CHCl_3$−MeOH (9:1) as the eluent to furnish pure carbocyclic chloronucleoside **10** (400 mg, 22%): mp 198−199 °C dec; $[\alpha]^{25}_D$ +32.5° (*c* 0.24, MeOH); IR (KBr) 3428, 1689, 1404, 1214, 1039 cm^{-1}; ^1H NMR (DMSO-d_6, 100 MHz) δ 1.68 (m, 5H), 3.38 (s, 1H), 3.44 (s, 2H), 3.70 (brd, 1H, *J* = 5 Hz, becoming s at 3.72 on D_2O exchange), 4.40 (s, 1H, exchangeable), 4.60−4.92 (m, 3H, including 2 exchangeable Hs), 5.32 (d, 1H, *J* = 5 Hz, exchangeable), 8.12 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 29.8, 30.1, 37.8, 52.0, 68.4, 70.1, 72.6, 73.5, 128.8, 138.1, 149.2, 151.4, 154.2; FABMS, *m*/*z*: 329 and 331 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{17}ClN_4O_4$: C, 47.50; H, 5.21; N, 17.04. Found: C, 47.39; H, 5.28; N, 16.88.

(1*R*,2*R*,3*R*,5*R*)-9-[1,3,5-Trihydroxy-2-(hydroxymethyl)cycloheptyl] adenine (11). Chloroadenosine derivative **10** (190 mg, 0.58 mmol) in dry methanolic ammonia (10 mL) was heated at 100 °C for 50 h in a sealed tube. The tube was cooled and opened up, and the reaction mixture was warmed on a water bath to remove ammonia. The solvent was removed under vacuo to obtain a crude product as a foam which was purified by flash column chromatography over silica gel (mesh size 230−400) using 8% MeOH in $CHCl_3$ as eluent to furnish **11** (168 mg, 94%): mp 240−242 °C dec; $[\alpha]^{25}_D$ +38.3° (*c* 0.12, MeOH); IR (KBr) 3418, 1667, 1397 cm^{-1}; ^1H NMR (DMSO-d_6, 100 MHz) δ 1.42−2.16 (m, 5H), 3.30 (s, 2H, seen after D_2O exchange), 3.74 (brs, 2H), 4.44 (brs, 1H, exchangeable), 4.60−5.04 (m, 3H changing to a brd, 1H, *J* = 10 Hz on D_2O exchange), 5.38 (d, 1H, *J* = 4 Hz, exchangeable), 7.22 (s, 2H, exchangeable), 8.12 (s, 1H), 8.20 (s, 1H); FABMS, *m*/*z*: 332 (M^+ + Na), 310 (M^+ + 1). Anal. Calcd for $C_{13}H_{19}N_5O_4 \cdot H_2O$: C, 47.70; H, 6.42; N, 21.39. Found: C, 47.69; H, 6.47; N, 21.31.

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