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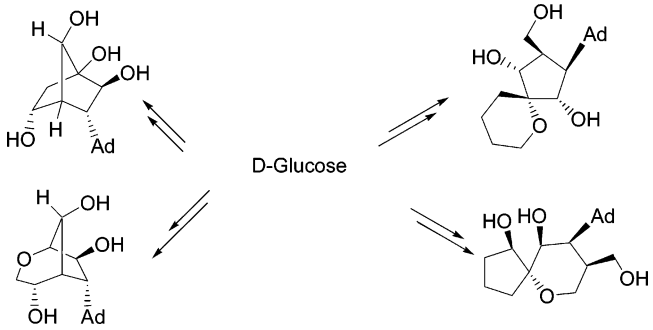
# Sequential Ring-Closing Metathesis and Nitrone Cycloaddition on Glucose-Derived Substrates: A Divergent Approach to Analogues of Spiroannulated Carbanucleosides and Conformationally Locked Nucleosides

Sk. Sahabuddin,[†] Ashim Roy,[†] Michael G. B. Drew,[‡] Biswajit Gopal Roy,[†] Basudeb Achari,[†] and Sukhendu B. Mandal*[,†]

*Department of Chemistry, Indian Institute of Chemical Biology, Jadavpur, 4, Raja S. C. Mullick Road, Kolkata 700 032, India, and Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, U.K.*

*sbmandal@iicb.res.in*

*Received March 27, 2006*




The carbohydrate-derived substrate 3-*C*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose was judiciously manipulated for preparing suitable synthons, which could be converted to a variety of isoxazolidino-spirocycles and -tricycles through the application of ring-closing metathesis (RCM) and intramolecular nitrone cycloaddition (INC) reactions. Cleavage of the isoxazolidine rings of some of these derivatives by tranfer hydrogenolysis followed by coupling of the generated amino functionalities with 5-amino-4,6-dichloropyrimidine furnished the corresponding chloropyrimidine nucleosides, which were elaborated to spiroannulated carbanucleosides and conformationally locked bicyclo[2.2.1]heptane/oxa-bicyclo[3.2.1]-octane nucleosides. However, use of higher temperature for the cyclization of one of the chloropyrimidines led to the dimethylaminopurine analogue as a sole product, formed via nucleophilic displacement of the chloro group by dimethylamine generated from DMF.

Various synthetic strategies have been reported in recent years to generate nucleoside analogues, particularly in search of effective and nontoxic antiviral and antitumor agents. The discovery of the natural carbanucleosides aristeromycin,[1] neplanocin A,[2] and neplanocin C[3] (conformationally rigid bicyclic nucleoside) having antibiotic and antitumor properties prompted the development of a number of synthetic carbanucleoside analogues endowed with important therapeutic properties.[4,5] Even though these analogues are resistant to the cleavage of the glycosidic linkage by phosphorylases and hydrolases,[6] they are often less effective than their furanose counterparts. The reduced activity may be due to the conformational flexibility of the cyclopentane ring as compared to furanose in the context

* Corresponding author. Fax: +91 (33) 24735197.
[†] Indian Institute of Chemical Biology.
[‡] University of Reading.

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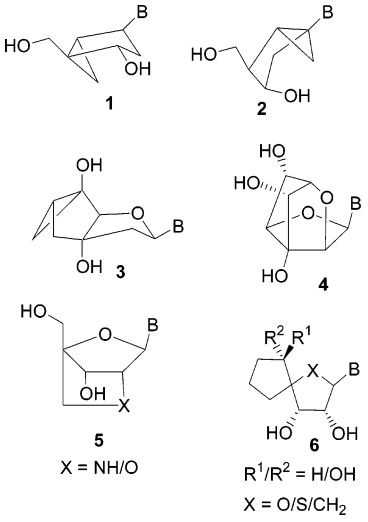
10.1021/jo0606554 CCC: $33.50 
Published on Web 06/30/2006

of pseudorotational cycle.[7] Thus, to confer metabolic stability as well as conformational rigidity in either furanose or cyclopentane ring, much attention has been given to the structural modifications of nucleosides, leading to a plethora of conformationally restricted nucleosides. These include, among others,[8] the bicyclo[3.1.0]hexane-derived carbanucleosides **1** and **2** prepared by the Altman[9] and Marquez[10] groups, Leumann's[11] and Nielsen's[12] tricyclic sugar derivatives **3** and **4**, and Wengel's locked system **5**.[13]




In addition, any bulky substituent fused to the pentose/cyclopentane ring of the nucleosides in a spirocyclic manner would be expected to confer conformational rigidity to the nucleosides. In this connection, the laboratories of Miyasaka[14] and Paquette,[15] in addition to others,[16−20] have reported the synthesis of C1′-spiro,[14,16] C2′-spiro,[18] C3′-spiro,[19] and C4′-spironucleosides,[15] which included 5/5 and 6/5 spironucleosides[17,20] as conformationally restricted or biased analogues with usual/unusual bases. The added advantage of the spiro structure at C4′ in the normal nucleosides[21] is that the free radical-induced degradation of the ribose ring of nucleosides or nucleotides by C-4′-H abstraction can be prevented, although this does not concern the carbanucleosides. Thus, synthesis of nucleosides of the type **6** has also been receiving attention in recent years.[22]

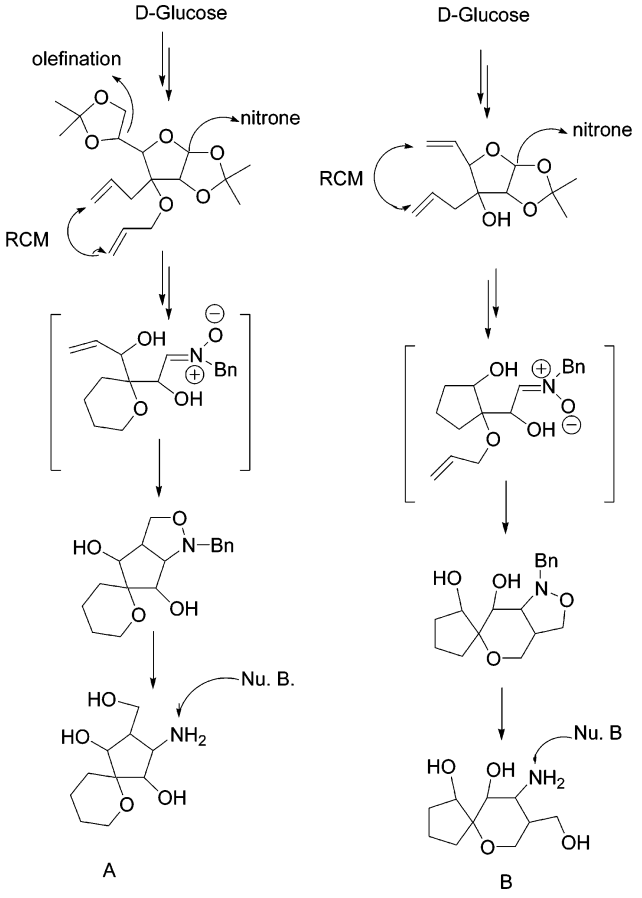



**FIGURE 1.** A strategy for the synthesis of spirofused carbocyclic nucleosides.

On the basis of these literature reports, we embarked upon the synthesis of a new family of spiroannulated carbocyclic nucleosides and conformationally locked bicyclic nucleoside analogues from sugar-based substrates. Toward this endeavor, we envisioned two approaches for the construction of 5/6- and 5/5-spirorings on a carbohydrate backbone. In the first (Figure 1A), ring-closing metathesis (RCM) of an appropriate glucose-derived precursor possessing olefin functionalities (*C*-allyl and

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*O*-allyl) at C-3 would be followed by didehydroxylation to introduce unsaturation between C-5 and C-6. Intramolecular nitrone cycloaddition (INC) reaction thereafter between the nitrone at C-1 and the olefin moiety at C-5 would generate a fused isoxazolidine derivative. Subsequent hydrogenolytic fission of the isoxazolidine ring would form a tricyclic 5/6-spirofused ring, which could be utilized to install nucleoside bases on the amino group of the spirocycle. In an alternative method, we hoped to build a 6/5-spirofused bicyclic compound from a 3-*C*-allyl-5,6-didehydroxy intermediate (D-glucose derived) through appropriate RCM, double bond reduction, and INC reaction (Figure 1B), and elaborate the spirocycle to the corresponding spirofused carbocyclic nucleoside. If, however, the double bond in the RCM product is not reduced, it could itself be submitted to INC reaction with a nitrone generated at C-1 (Figure 2A), leading to structurally novel tricyclic compounds en route to confomationally locked bicyclic nucleosides. Another approach could be to utilize (Figure 2B) the 3-*O*-allyl-5,6-didehydroxy glucose/allose derivative for RCM reaction, which has been known to furnish dihydropyran derivatives. INC reaction of the ring double bond of these with the C-1 nitrone could give dihydropyran fused tricyclic products for the generation of locked bicyclic nucleosides. The present article deals with the results on the generation of spirocyclic carbanucleosides and locked nucleosides with bicyclo[2.2.1] heptane and oxa-bicyclo[3.2.1] octane ring systems.

## Results and Discussion

**Synthesis of Spirocycles 11, 14, 19, 20, 23, and 24.** Diallylated compound **8**, generated from the D-glucose-derived substrate **7**[23] through *O*-allylation, furnished (Scheme 1) the spirocycle **9** upon ring-closing metathesis reaction[24] using the first generation Grubbs catalyst. Selective deprotection of the 5,6-*O*-isopropylidene ring with dilute HOAc and subsequent olefination between C-5 and C-6 (glucose numbering) by treatment with triphenyl phosphine-imidazole-iodine in refluxing toluene[25] yielded **10**. Removal of 1,2-acetonide protection followed by reaction of the latent aldehyde with *N*-benzyl hydroxylamine in ethanol smoothly afforded the isoxazolidinospirocycle **11** through a nonisolable nitrone intermediate at C-1. However, hydrogenation of the double bond in **11** with Pd/C (10%) in EtOH failed to afford the corresponding dihydro compound in good yield. Attempted cleavage of the isoxazolidine ring[26] with simultaneous reduction of the olefin moiety

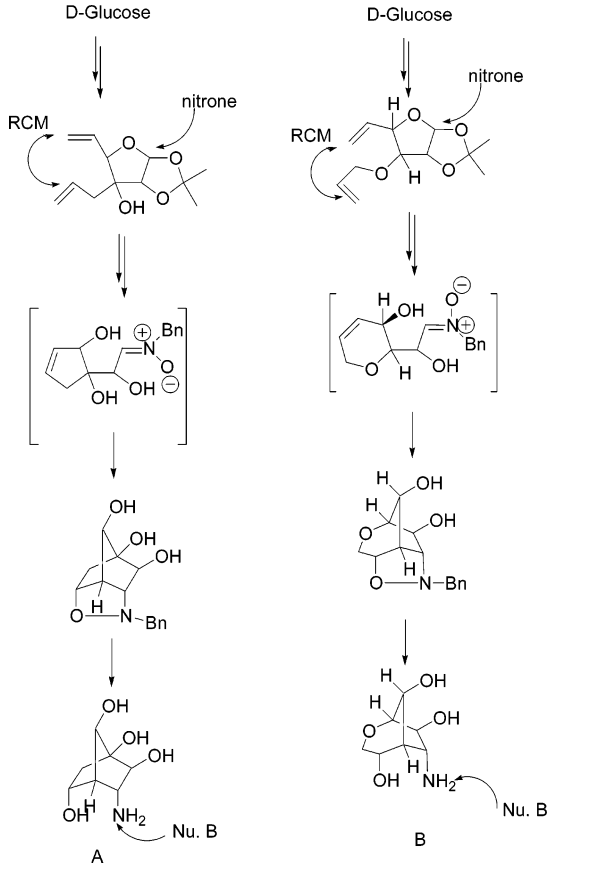
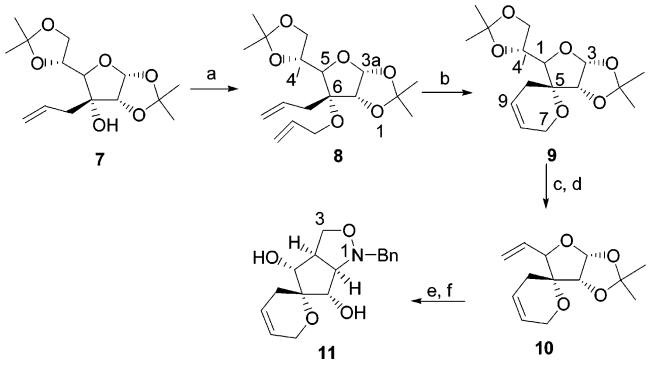



**FIGURE 2.** A strategy for the synthesis of conformationally locked nucleosides.

**SCHEME 1**[a]




[a] Reagents and conditions: (a) NaH, allyl bromide, THF, reflux, 4 h; (b) $[Cl_2(Pcy_3)_2Ru{=}CHPh]$, $CH_2Cl_2$, rt, 6 h, $N_2$; (c) HOAc−$H_2O$ (3:1), rt, overnight; (d) $Ph_3P$, imidazole, $I_2$, toluene, reflux, 6 h; (e) 4% $H_2SO_4$, $CH_3CN-H_2O$ (3:1), rt, 24 h; (f) BnNHOH, dry EtOH, reflux, 4 h, $N_2$.

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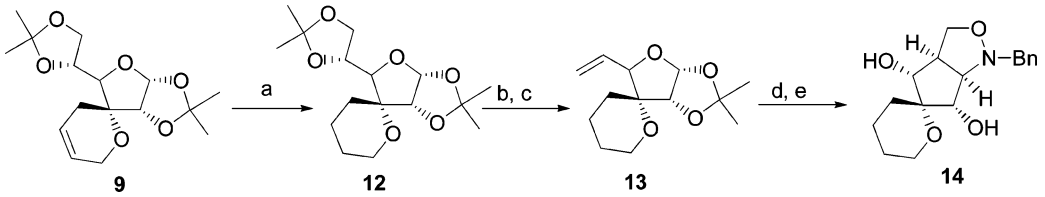
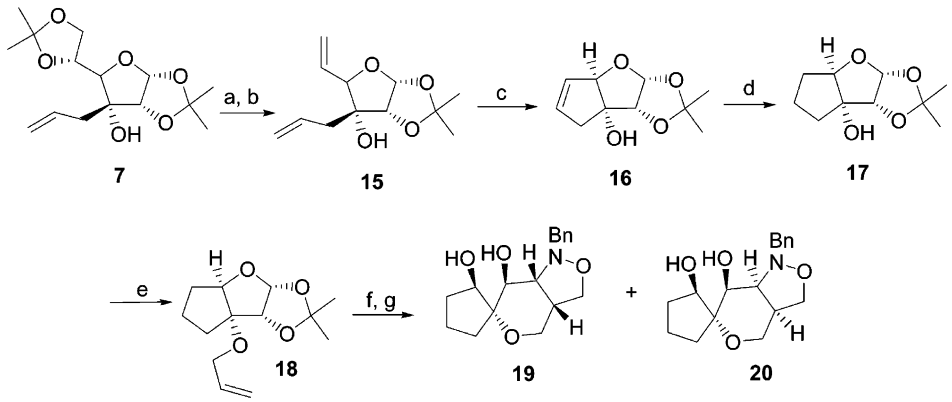
**SCHEME 2**[a]




[a] Reagents and conditions: (a) $H_2$–Pd/C (10%), EtOH, rt, 4 h; (b) HOAc−$H_2O$ (3:1), rt, 14 h; (c) $Ph_3P$, imidazole, $I_2$, toluene, reflux; 6 h; (d) 4% $H_2SO_4$, $CH_3CN$−$H_2O$ (3:1), rt, 24 h; (e) BnNHOH, EtOH, reflux, 4 h, $N_2$.

**SCHEME 3**[a]




[a] Reagents and conditions: (a) HOAc−$H_2O$ (3:1), rt, overnight; (b) $Ph_3P$, imidazole, $I_2$, toluene, reflux, 6 h; (c) [$Cl_2(Pcy_3)_2Ru$═CHPh], $CH_2Cl_2$, rt, 6 h, $N_2$; (d) $H_2$–Pd/C (10%), EtOH, rt; (e) NaH, allyl bromide, THF, reflux, 5 h, $N_2$; (f) 4% $H_2SO_4$, $CH_3CN$−$H_2O$ (3:1), rt, 24 h; (g) BnNHOH, dry EtOH, rt, 20 h.

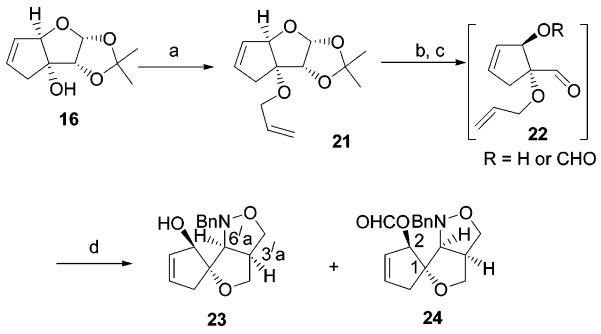
using cyclohexene and Pd/C was also found to be unsuccessful; a mixture of several uncharacterized products was obtained.

Next, we altered our sequence to reduce the double bond of **9** before proceeding to the subsequent steps. Thus, the spirocycle **9** was hydrogenated with Pd/C (10%) in EtOH (Scheme 2) to produce the dihydro derivative **12**, which on selective deprotection of the 5,6-acetonide moiety and olefination as described above furnished **13**. When the spirocycle **13** was subjected to sequential removal of protection from 1,2 hydroxyl groups followed by INC reaction involving the masked aldehyde generated at C-1 and the olefin function at C-5, the reaction went off smoothly, yielding the desired product **14**.

The other approach en route to 6/5-spirocycles involved the introduction of an olefin moiety in **7** by didehydroxylation to produce **15** (Scheme 3). Ring-closing metathesis reaction between the olefins in **15** furnished **16**, which on hydrogenation to **17** followed by allylation of the tertiary hydroxyl group afforded **18**. Deprotection of its 1,2 hydroxyl groups with diluted $H_2SO_4$ followed by nitrone formation at the hemiacetal center with *N*-benzyl hydroxylamine set in motion spontaneous cyclization, affording two isomeric spiro compounds **19** (45%) and **20** (33%).

When *O*-allylation of **16** was performed without reducing the cyclic double bond, **21** could be isolated (Scheme 4). Deprotection of the 1,2 hydroxyl groups and subsequent treatment with an aqueous solution of $NaIO_4$ produced a nor aldehyde **22**. INC reaction with BnNHOH now preferentially involved the allyl group, generating the spirocycle **23** accompanied by its formate **24**, retaining C-1 of sugar. Compound **24** could be converted to **23** by hydrolysis with dilute alkali solution.

**SCHEME 4**[a]




[a] Reagents and conditions: (a) NaH, allyl bromide, THF, reflux, 5 h, $N_2$; (b) 4% $H_2SO_4$, $CH_3CN$−$H_2O$ (3:1), rt, 24 h; (c) $NaIO_4$ (aqueous), MeOH, 10 °C, 45 min; (d) BnNHOH, dry EtOH, rt, 20 h.

The structures of the products were deduced from spectral analyses (IR, $^1$H NMR, $^{13}$C NMR, MS). The appearance of a two-proton multiplet at $\delta$ 5.84 in the $^1$H NMR spectrum of **9** testified to the formation of a dihydro pyran ring. The $^1$H NMR spectrum of **10** exhibited signals for ═$CH_2$ protons along with three more olefinic proton (methine) signals. The gross structure of **11** was deduced from the appearance of one double doublet at $\delta$ 3.64 for C*H*NBn together with two doublets at $\delta$ 3.66 and 3.73 for two C*H*OH in its $^1$H NMR spectrum. The absence of the olefinic proton signal and appearance instead of upfield methylene signals in the $^1$H NMR spectrum of **12** confirmed the absence of the double bond. However, appropriate signals for vinyl protons were present in the $^1$H NMR spectrum of **13**. The absence of olefinic proton and carbon signals in the $^1$H and $^{13}$C NMR spectra of **14** clearly suggested its gross structure. The $^{13}$C NMR as well as mass spectra of these products were also in good agreement with the proposed structures. The cis

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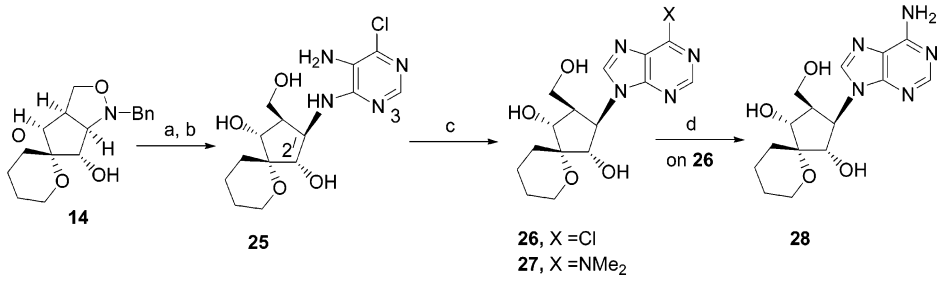
**SCHEME 5**[a]




[a] Reagents and conditions: (a) Pd/C (10%), cyclohexene, EtOH, reflux, 5 h; (b) 5-amino-4,6-dichloropyrimidine, *n*-butanol, $Et_3N$, reflux, 30 h; (c) $HC(OEt)_3$, *p*-TSA, DMF, 10 °C, 16 h; (d) MeOH, $NH_3$, sealed tube, 100 °C, 40 h.

stereochemistry of the ring juncture in **14** was confirmed by its X-ray crystal structure analysis.[27] Similar ring juncture stereochemistry in **11** as indicated was thus suggested.

The $^1$H NMR spectrum of **15** showed characteristic signals assignable to the olefinic protons. Besides, appropriate signals were detected in its $^{13}$C NMR spectrum for olefinic methylene and methine carbons, respectively. The mass spectrum exhibited a pseudomolecular ion at *m*/*z* 249 $(MNa)^+$, confirming the structure of the compound. The appearance of two signals (multiplets) for olefinic protons in the $^1$H NMR spectrum of **16**, and the disappearance of olefinic protons signals in the corresponding spectrum of **17**, among other evidence, suggested their structures as shown. The presence of an allyl group in **18** was evident from the characteristic olefinic proton signals at the appropriate region in its $^1$H NMR spectrum. However, the spectra for **19** and **20** proved less helpful for deducing the structures, as signals for many of the protons overlapped with each other. Only the absence of olefinic proton signals and the presence of aromatic proton signals in their $^1$H NMR spectra, coupled with the location of a peak at 328 $(MNa)^+$ in the mass spectra for both of the compounds, proved helpful in deducing their gross isomeric structures. Finally, the structures and relative stereochemistries of the spirocycles were deduced from the X-ray analyses.[27] For the crystals of **19**, there are two molecules in the asymmetric unit with equivalent geometries.

The five olefinic proton signals and two methyl signals in the $^1$H NMR spectrum of **21** were indicative of the structure. Although the INC reaction of the aldehyde **22** could have afforded either a six-membered or a five-membered isoxazolidine (or a mixture of the two) depending upon the mode of cyclization, the gross structure **23** (for the major product) was evident from the presence of two methylene carbon signals at ~70 ppm in the $^{13}$C NMR spectrum, indicating the presence of two $-CH_2O-$ linkages. The involvement of the double bond of the allyl group in **22** during the INC reaction was also confirmed by the absence of the characteristic signals for the olefinic protons of the allyl group in the $^1$H NMR spectra of both **23** and **24**.

For **23** and **24**, the stereochemistry of the spirocyclic carbon and the carbon bearing OH/OCHO must be the same as that of the corresponding carbons in D-glucose, because these centers were not disturbed during the reaction sequence. The cis ring juncture is energetically favored in case of bicyclo[3.3.0]octane system, and thus the H's at the ring juncture of both these spirocycles could have been either in α or in *β* orientation. Yet the distinction between the two could not be made from the NOESY spectrum of **23**. The observed *J* value (8.4 Hz) for $H_{3'a}-H_{6'a}$ proved more helpful, suggesting the indicated structure based on the calculated dihedral angles for the $H-C_{3'a}-C_{6'a}-H$ unit [15° for α-Hs and 1° for *β*-Hs in the energy minimized structures obtained using Chem Office, version 6.0]. The appearance of one singlet at *δ* 7.61 and the downfield shift of H-1 signal in the $^1$H NMR spectrum of **24** indicated the presence of a formate ester, which could be converted to **23** by base hydrolysis.

**Synthesis of Spirofused Carbocyclic Nucleosides 26−28, 30, 31, and 33.** The successful synthesis of the tricyclic spirocycle **14** by the application of RCM and INC reactions on appropriate glucose-derived substrates prompted us to attempt the synthesis of [5/6]-spirofused carbocyclic nucleosides. Thus, transfer hydrogenolysis of **14** (Pd/C, cyclohexane, EtOH) was performed to cleave the isoxazolidine ring (Scheme 5). The product, a trihydroxy aminospirocycle, was directly coupled with 5-amino-4,6-dichloropyrimidine to obtain the pyrimidinyl spirocycle **25** (50%). Construction of a purine ring from the pyrimidine ring in **25** was achieved by the treatment of triethyl orthoformate in acidic medium. This furnished both the chloropurine-spironucleoside **26** (32%) and the dimethylaminopurine-spironucleoside **27** (~7%). The chloronucleoside **26** on ammonolysis with a saturated solution of ammonia in methanol furnished **28** in good yield. The formation of **27** could be rationalized via nucleophilic displacement of the chloro group by dimethylamine generated in the reaction medium from DMF.[28]

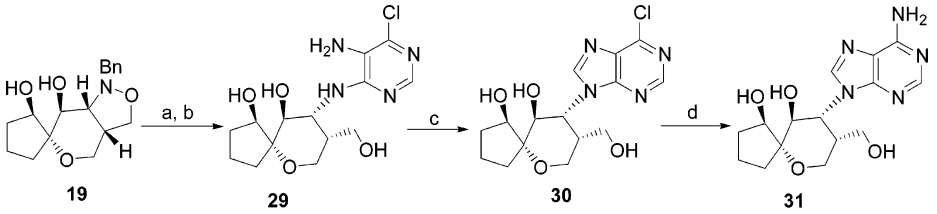
Similarly, hydrogenolysis of **19** followed by coupling of the generated amino derivative with 5-amino-4,6-dichloropyrimidine furnished (Scheme 6) the pyrimidine nucleoside **29** (76%), which was converted to the purine nucleoside **30** (80%). The target nucleoside derivative **31** became available by simple substitution of the chloro group of **30** with amino group.

On the other hand, although the spirocycle **20** could be transformed (Scheme 7) into the pyrimidine nucleoside **32** (44%), further cyclization using triethyl orthoformate failed to furnish the corresponding chloropurine nucleoside, when the reaction was carried out at the usual temperature (10 °C). Attributing the reluctance to steric hindrance faced by the amino substituent, which should be oriented in axial direction and facing 1,3-diaxial interaction with a cyclopentane ring residue, we attempted to carry out the reaction at a raised temperature (25 °C). The cyclization did occur under this condition, but the product was the dimethylaminopurine nucleoside **33** isolated in poor yield.

(27) ORTEP diagram(s) are given in the Supporting Information.

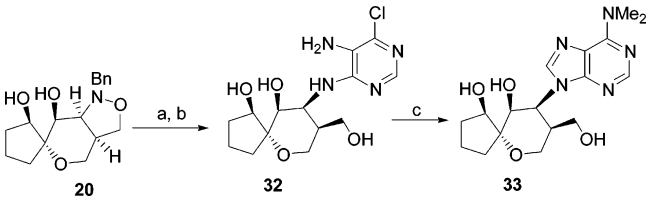
(28) Roy, A.; Chakrabarty, K.; Dutta, P. K.; Bar, N. C.; Basu, N.; Achari, B.; Mandal S. B. *J. Org. Chem.* **1999**, *64*, 2304.

**SCHEME 6**[a]




[a] Reagents and conditions: (a) Pd/C (10%), cyclohexene, EtOH, reflux, 5 h; (b) 5-amino-4,6-dichloropyrimidine, *n*-butanol, $Et_3N$, reflux, 30 h; (c) $HC(OEt)_3$, *p*-TSA, DMF, 10 °C, 16 h; (d) $NH_3$, MeOH, sealed tube, 100 °C, 40 h.

**SCHEME 7**[a]



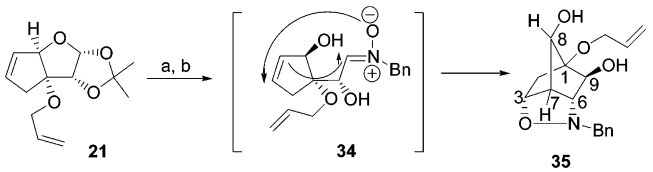

[a] Reagents and conditions: (a) Pd/C (10%), cyclohexene, EtOH, reflux, 5 h; (b) 5-amino-4,6-dichloropyrimidine, *n*-butanol, $Et_3N$, reflux, 30 h; (c) $HC(OEt)_3$, *p*-TSA, DMF, 25 °C, 8 h.

In contrast to the 5/6-spirocyclic systems, the synthesis of nucleosides with 5/5-spirocyclic ring, beginning with the spirocycle **23**, failed to occur. This appears likely to be due to steric hindrance offered by the neighboring spirocyclic ring,[20] as the amino function generated would be located next to the central carbon atom.

The indicated structure of **25** was derived from the observation of a one-proton signal assignable to aromatic H-2 in its $^1$H NMR spectrum, and of four aromatic carbon signals along with one for the spirocyclic carbon at $\delta$ 77.5 in the $^{13}$C NMR spectrum. Also, the FAB mass spectrum for **25** showed peaks for the $(MH)^+$ ion and for the $(MNa)^+$ ion as expected for the assigned structure. Transformation of the pyrimidine ring to a purine moiety (in **26**) could be ascertained by the appearance of two aromatic proton singlets in the $^1$H NMR spectrum and of five aromatic carbon signals in the $^{13}$C NMR spectrum. Compound **27** exhibited an extra proton signal at $\delta$ 3.29 as a singlet (6H), pointing to the presence of $NMe_2$. This compound showed expected pseudomolecular ion peaks in the ESI mass spectrum. The structures of other nucleosides **29**−**33** were similarly determined by spectral analyses.

**Synthesis of Tricyclic Compounds 35 and 36: Conversion of 36 to Conformationally Locked Bicyclic Nucleosides 38 and 39.** We have demonstrated with **21** that deprotection of the 1,2-acetonide moiety, conversion to the lower homologue aldehyde, and subsequent treatment with *N*-benzyl hydroxylamine furnished spirocycles **23** and **24** only, the INC reaction occurring exclusively through involvement of the allyl group. The endocyclic double bond perhaps refrained from participating in the cyclization, as the expected tricyclic product would have a four-membered ring. This constraint would not be there if the $NaIO_4$ treatment is avoided. It therefore seemed interesting to us to see the results of the INC reaction under this condition. Thus, compound **21** was subjected to 1,2-acetonide deprotection and then treatment with *N*-benzyl hydroxylamine for in situ generation of the nitrone **34** (Scheme 8). Subsequent cyclization was indeed observed to involve exclusively the cyclopentene olefin moiety to afford **35**; no product derived from the participation of the other olefin was isolated.

**SCHEME 8**[a]




[a] Reagents: (a) Diluted $H_2SO_4$ (4%), $CH_3CN-H_2O$ (3:1); (b) BnNHOH, EtOH.

The $^1$H−$^1$H COSY spectrum of **35** clearly identified most of the signals, including those of all ring juncture protons. The stereochemistries for C-8, C-1, and C-9 of this compound are the same as for the corresponding centers in **21**. Those of the newly formed stereocenters (C-6, C-3, and C-7) follow from the constraints of the fused ring system.

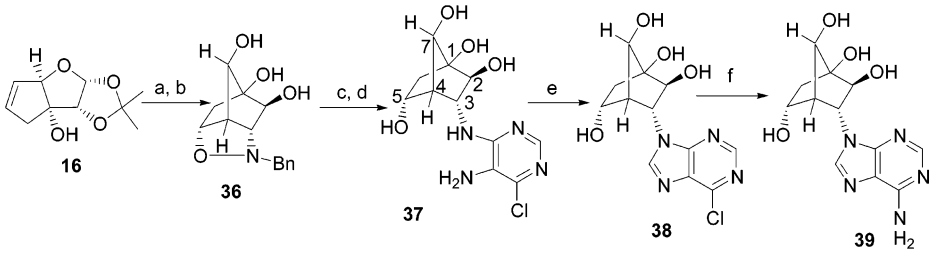
When **16** (of which **21** is the *O*-allyl ether) was subjected to a similar INC reaction after deprotection of 1,2 hydroxyl groups (Scheme 9), it generated the tricyclic product **36** (50% overall yield). Cleavage of the isoxazolidine moiety of **36** and subsequent coupling with 5-amino-4,6-dichloropyrimidine furnished **37** (50%), converted uneventfully to the chloropurine nucleoside **38** (70%) and subsequently to **39** under usual reaction conditions.

The structures of **36**−**39** were also elucidated from spectral analyses. The striking feature in the $^1$H NMR spectrum of **36** was the absence of the olefinic proton signals, which were present in the similar spectrum of **16** along with the presence of signals characteristic of benzylic protons in it. The observation of a one-proton singlet at $\delta$ 7.80 in the $^1$H NMR spectrum as well as of four carbon signals for the pyrimidine ring in the $^{13}$C NMR spectrum of **37** indicated its structure. The appearance of two one-proton singlets in the $^1$H NMR spectrum and five carbon signals in the aromatic region in the $^{13}$C NMR spectrum of **38** confirmed the formation of the purine ring. Mass spectral analysis detected the presence of chlorine atom in **37** and **38**, but its absence in **39**.

**Synthesis of the Tricyclic Compound 42 and Its Conversion to Conformationally Constrained Nucleosides 44 and 45.** The successful involvement of the cyclopentene double bond of **16** in undergoing INC reaction with a nitrone generated at C-1 suggested its possible extension to other related compounds with the hope of generating new ring systems. Thus, the substrate **40**[29] was subjected to deprotection of the 1,2-isopropylidene moiety by treatment with diluted $H_2SO_4$ and subsequent INC reaction with *N*-benzyl hydroxylamine. This smoothly yielded **42** in 80% yield (Scheme 10). The structure and relative stereochemistry of **42** was confirmed by an X-ray crystal structure analysis.[27]

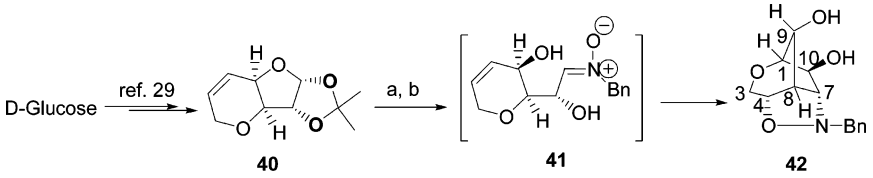
(29) Haque, A.; Panda, J.; Ghosh, S. *Indian J. Chem.* **1999**, *38B*, 8.

**SCHEME 9**[a]



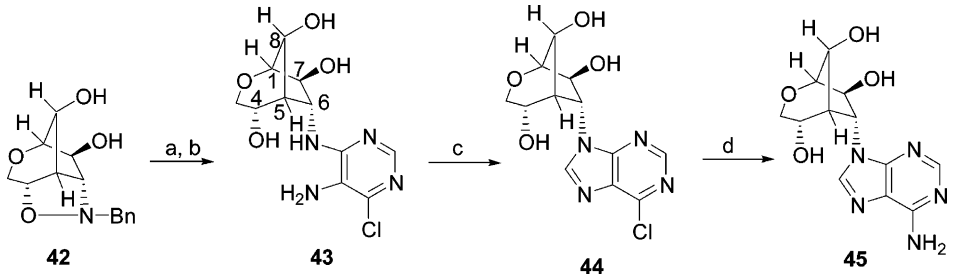

[a] Reagents: (a) Diluted $H_2SO4$, $CH_3CN-H_2O$ (3:1); (b) BnNHOH, EtOH; (c) Pd/C (10%), cyclohexene, EtOH; (d) 5-amino-4,6-dichloropyrimidine, *n*-butanol, $Et_3N$; (e) $HC(OEt)_3$, *p*-TSA, DMF; (f) $NH_3$, MeOH.

**SCHEME 10**[a]



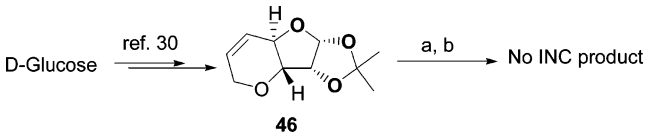

[a] Reagents and conditions: (a) 4% $H_2SO_4$, $CH_3CN-H_2O$ (3:1), rt, 24 h; (b) BnNHOH, reflux, EtOH, 4 h, $N_2$.

**SCHEME 11**[a]




[a] Reagents and conditions: (a) Pd/C (10%), cyclohexene, EtOH, reflux, 5 h; (b) 5-amino-4,6-dichloropyrimidine, *n*-butanol, $Et_3N$, reflux, 30 h; (c) $HC(OEt)_3$, *p*-TSA, DMF, 10 °C, 16 h; (d) $NH_3$, MeOH, sealed tube, 100 °C, 40 h.

**SCHEME 12**[a]




[a] Reagents and conditions: (a) 4% $H_2SO_4$, $CH_3CN-H_2O$ (3:1), rt, 24 h; (b) BnNHOH, dry EtOH, reflux, 4 h, $N_2$.

Opening of the isoxazolidine moiety of **42** (Scheme 11) followed by reaction with 5-amino-4,6-dichloropyrimidine generated **43** (41% yield). Construction of the purine ring furnished chloropurine nucleoside **44** (73%). Transformation of **44** to **45** was smoothly accomplished by ammonia treatment. The structures of **43**−**45** were elucidated from spectral analyses in the usual way.

The bicyclic compound **46**,[30] an isomer of **40**, however, failed to afford any cyclized product (Scheme 12) upon deprotection of the acetonide function followed by reaction with *N*-benzyl hydroxylamine. Model studies reveal that this requires both of the substituents of the dihydropyran ring to assume axial orientation, which is energetically unfavorable. In the cis-series, however, the hydroxyl group may remain in equatorial orientation with the other substituent in axial disposition, which is quite likely to occur, and this favors the cyclization process.

In conclusion, judicious applications of ring-closing metathesis (RCM) and intramolecular 1,3-dipolar cycloaddition (INC) reactions on D-glucose-derived substrates have permitted entry to new classes of spiroannulated carbanucleosides and conformationally locked bicyclic nucleosides. The precursor assembly for RCM as well as INC reactions appears simple, making the strategy an attractive one. X-ray crystal structure determinations on some of the products have conclusively established the structures. The scope of the strategy to synthesize other ring systems is under study.

## Experimental Section

**(3a*R*,4′*R*,5*R*,6*R*,6a*R*)-6-Allyl-6-allyloxy-5-(2,2-dimethyl[1,3]-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (8).** To a refluxing mixture of **7** (200 mg, 0.7 mmol), tetrabutylammonium bromide (27 mg, 0.08 mmol), NaOH solution (50%, 10 mL), and benzene (10 mL) was added allyl bromide (3 × 0.3 mL) over 10 h. The mixture was cooled, washed with $H_2O$, dried ($Na_2SO_4$), and evaporated to give a material, which was purified by column chromatography on silica gel. Elution with $CHCl_3$−petroleum ether (3:7) afforded a solid, which was recrystallized from petroleum ether to furnish **8** (190 mg, 80%) as a semisolid mass.

**8.** $[\alpha]^{27}_D$ +48.7 (*c* 0.72, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.32, 1.36, 1.43, 1.57 (4 × 3H s), 2.32 (dd, 1H, $J$ = 7.5, 15 Hz), 2.65 (dd, 1H, $J$ = 6.6, 15 Hz), 3.93 (m, 1H), 4.08−4.21 (m, 4H),

(30) Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; van der Marcel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253.

4.30 (brdd, 1H, $J$ = 5.0, 12.0 Hz), 4.41 (d, 1H, $J$ = 3.6 Hz), 5.09−5.33 (m, 4H), 5.58 (d, 1H, $J$ = 3.6 Hz), 5.87−6.04 (m, 2H). ESIMS, $m/z$: 363 $(MNa)^+$. Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.30; H, 8.28.

**(1*R*,3*R*,4*R*,4′*R*,5*R*)-3,4-Isopropylidenedioxy-1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,6-dioxa-spiro[4.5]dec-8-ene (9).** To a solution of **8** (0.50 g, 1.47 mmol) in dry distilled $CH_2Cl_2$ (250 mL), degassed by $N_2$ gas, was added Grubbs catalyst (0.69 g, 5 mol %), and the mixture was stirred at room temperature for 6 h under $N_2$ atmosphere. The solvent was evaporated in a rotary evaporator to a blackish gummy residue, which was purified by column chromatography on silica gel. Elution with EtOAc−petroleum ether (1:24) furnished **9** (0.40 g, 87%) as a gum.

**9.** $[\alpha]^{27}_D$ +106.7 ($c$ 0.85, $CHCl_3$). IR (neat): $\nu_{max}$ 1635, 1598, 1455, 1377, 1248, 1217, 1076, 1010 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.34, 1.35, 1.45, 1.60 (4 × 3H s), 1.67 (m, 1H), 2.50 (m, 1H), 3.95 (dd, 1H, $J$ = 6.0, 8.3 Hz), 4.04−4.09 (m, 2H), 4.14 (t, 1H, $J$ = 6.0 Hz), 4.26 (brd, 1H, $J$ = 16.5 Hz), 4.41 (d, 1H, $J$ = 3.6 Hz, including a merged signal, 1H), 5.65 (d, 1H, $J$ = 3.6 Hz), 5.84 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 25.7 ($CH_3$), 26.9 ($CH_2$ + $CH_3$), 27.0 ($CH_3$), 27.4 ($CH_3$), 64.1 ($CH_2$), 67.7 ($CH_2$), 74.0 (CH), 80.2 (C), 81.6 (CH), 82.6 (CH), 104.1 (CH), 110.0 (C), 113.4 (C), 121.4 (CH), 127.8 (CH). EIMS, $m/z$: 311 $(M - 1)^+$, 297 $(M - 15)^+$. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.38; H, 7.72.

**(1*R*,3*R*,4*R*,5*R*)-3,4-Isopropylidenedioxy-1-vinyl-2,6-dioxa-spiro-[4.5]dec-8-ene (10).** Compound **9** (1.00 g, 3.20 mmol) was dissolved in a HOAc−$H_2O$ (3:1) mixture (20 mL), and the solution was stirred at room temperature overnight. The solvent was evaporated, and the last traces of HOAc were removed azeotropically using toluene (3 × 20 mL) to furnish the 5,6-dihydroxy spirocycle (0.70 g) as a thick gum, which was used in the next step after drying over $P_2O_5$ under vacuum. To a solution of the above gum (0.50 g, 1.84 mmol) in freshly distilled dry toluene (40 mL) were added $Ph_3P$ (1.80 g, 6.87 mmol) and imidazole (0.47 g, 6.87 mmol), and the mixture was heated slowly. When the solution started to reflux, iodine (0.70 g, 2.76 mmol) was added portionwise, and the heating was continued for 6 h under $N_2$ atmosphere. The solvent was evaporated, and the residue was extracted with toluene (2 × 30 mL). The combined extract was washed with sodium thiosulfate (2 × 20 mL) solution and water (2 × 20 mL), dried ($Na_2SO_4$), and evaporated to give a crude residue, which was purified by column chromatography on silica gel using EtOAc−petroleum ether (1:24) as eluent to furnish **10** (0.36 g, 47%).

**10.** mp 48−50 °C. $[\alpha]^{25}_D$ +129.4 ($c$ 0.91, $CHCl_3$). IR (KBr): $\nu_{max}$ 1647, 1436, 1378, 1255, 1216, 1105, 1066, 1014 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.35 (s, 3H, including a merged signal, 1H), 1.62 (s, 3H), 2.34 (m, 1H), 4.21 (dd, 1H, $J$ = 2.0, 16.0 Hz), 4.42 (d, 1H, $J$ = 3.6 Hz, including a merged signal, 1H), 4.56 (d, 1H, $J$ = 5.5 Hz), 5.30 (d, 1H, $J$ = 10.7 Hz, with fine splitting), 5.44 (d, 1H, $J$ = 17.3 Hz, with fine splitting), 5.72 (d, 1H, $J$ = 3.8 Hz), 5.76−5.87 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 26.7 ($CH_2$), 26.9 ($CH_3$), 27.2 ($CH_3$), 63.9 ($CH_2$), 80.5 (C), 81.6 (CH), 81.7 (CH), 104.2 (CH), 113.7 (C), 118.7 ($CH_2$), 121.9 (CH), 127.0 (CH), 132.7 (CH). EIMS, $m/z$: 223 $(M - 15)^+$. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.50; H, 7.54.

**(3a*R*,4R,5*R*,6*S*,6a*R*)-1-Benzyl-spiro[cyclopent[*d*]isoxazole-5.6′-(5,6-dihydro-2*H*-pyran)]-4,6-diol (11).** Compound **10** (1.50 g, 6.30 mmol) was dissolved in 40 mL of 4% $H_2SO_4$ in $CH_3CN-H_2O$ (3:1), and the solution was stirred at room temperature for 24 h. The solution was neutralized with solid $CaCO_3$ and filtered, and the solvent was evaporated under reduced pressure to obtain an anomeric mixture of the 1,2-dihydroxy compound (1.00 g), which was used in the next step without further purification. This material was dissolved in dry ethanol (30 mL), *N*-benzyl hydroxylamine (0.75 g, 6.06 mmol) was added to it, and the solution was heated at reflux for 4 h under $N_2$. TLC showed complete disappearance of the starting material. The solvent was evaporated, and the residue was extracted with $CHCl_3$ (3 × 20 mL) to furnish a yellowish mass. Column chromatography of this on silica gel using EtOAc−petroleum ether (3:22) as eluent yielded **11** (1.15 g, 60%).

**11.** mp 97−99 °C. $[\alpha]^{25}_D$ +34.6 ($c$ 1.25, $CHCl_3$). IR (KBr): $\nu_{max}$ 3384, 1607, 1496, 1433, 1348, 1100, 1079, 1024, 772, 734, 710 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + $D_2O$, 300 MHz): $\delta$ 2.33 (m, 2H), 3.20 (m, 1H), 3.64 (partially merged dd, 1H, $J$ = 5.0, 9.4 Hz), 3.66 (d, 1H, $J$ = 4.8 Hz), 3.73 (d, 1H, $J$ = 5.0 Hz), 3.74 (dd, 1H, $J$ = 3.3, 9.0 Hz), 3.82 (d, 1H, $J$ = 13.0 Hz), 4.01 (d, 1H, $J$ = 13.0 Hz), 4.16 (dd, 1H, $J$ = 8.0, 9.0 Hz), 4.39 (d, 1H, $J$ = 16.3 Hz, with further fine splitting), 4.53 (d, 1H, $J$ = 16.3 Hz with further fine splitting), 5.84 (m, 2H), 7.31 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 29.1 ($CH_2$), 53.3 (CH), 60.7 ($CH_2$), 64.8 ($CH_2$), 69.9 ($CH_2$), 75.9 (CH), 79.6 (C), 81.3 (CH), 82.4 (CH), 122.2 (CH), 126.5 (CH), 127.9 (CH), 129.9 (2 × CH), 129.3 (2 × CH), 137.4 (C). EIMS, $m/z$: 303 $(M^+)$, 190, 161, 91. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.28; H, 6.92; N, 4.38.

**(1*S*,3*R*,4*R*,4′*S*,5*R*)-3,4-*O*-Isopropylidene-1-(2,2-dimethyl[1,3]-dioxolan-4-yl)-2,6-dioxa-spiro[4.5]decane (12).** To a solution of **9** (0.60 g, 1.92 mmol) in dry ethanol (20 mL) was added Pd/C (10%, 0.15 g). Air was removed from the solution by applying suction, and then $H_2$ gas was passed through the reaction mixture from a balloon with stirring at room temperature for 4 h. The catalyst was filtered off, and the solvent was evaporated under reduced pressure to obtain a gummy material, which was purified by column chromatography on silica gel. Elution with EtOAc−petroleum ether (3:47) furnished **12** (0.513 g, 85%) as a white semisolid mass.

**12.** $[\alpha]^{28}_D$ +70.8 ($c$ 1.2, $CHCl_3$). IR (KBr): $\nu_{max}$ 1455, 1375, 1249, 1219, 1084, 1024, 876 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.36 (s, 6H), 1.44 (s, 3H), 1.60 (s, 3H), 1.64−1.86 (m, 6H), 3.67 (m, 1H), 3.91−3.96 (m, 2H), 3.99−4.05 (m, 2H), 4.16 (dd, 1H, $J$ = 6.0, 12.5 Hz), 4.61 (d, 1H, $J$ = 3.6 Hz), 5.68 (d, 1H, $J$ = 3.6 Hz). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 19.9 ($CH_2$), 25.7 ($CH_2$), 25.8 ($CH_3$), 26.9 (2 × $CH_3$), 27.1 ($CH_2$), 27.4 ($CH_3$), 65.2 ($CH_2$), 67.2 ($CH_2$), 74.0 (CH), 80.0 (CH), 81.2 (C), 82.3 (CH), 104.1 (CH), 109.5 (C), 113.1 (C). ESIMS, $m/z$: 337 $(MNa)^+$. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 60.90; H, 8.18.

**(1*R*,3*S*,4*R*,5*S*,6a*R*)-3,4-Isopropylidenedioxy-1-vinyl-2, 6-dioxa-spiro[4.5]decane (13).** Spirocycle **12** (1.20 g, 3.82 mmol) was dissolved in 30 mL of HOAc−$H_2O$ (3:1), and the solution was stirred at room temperature for 14 h. Evaporation of the solvent furnished a gummy residue. The last traces of HOAc were removed by coevaporation with toluene to give a crude gum (0.75 g), the toluene solution (50 mL) of which was treated with $Ph_3P$ (2.69 g, 10.27 mmol), imidazole (0.697 g, 10.27 mmol), and $I_2$ (1.04 g, 4.10 mmol) according to the procedure described for **10**. Usual workup and purification afforded **13** (0.60 g, 65%).

**13.** mp 45−46 °C. $[\alpha]^{28}_D$ +75.8 ($c$ 1.02, $CHCl_3$). IR (KBr): $\nu_{max}$ 1644, 1448, 1315, 1250, 1214, 1167, 1088, 1025, 994, 928, 877 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.38 (s, 3H), 1.59−1.80 (m, 6H, overlapping one s, 3H at $\delta$ 1.61), 3.66 (m, 1H), 3.91 (d, 1H, $J$ = 11.0 Hz), 4.44 (d, 1H, $J$ = 5.5 Hz), 4.64 (d, 1H, $J$ = 3.6 Hz), 5.29 (d, 1H, $J$ = 10.5 Hz, with further fine splitting), 5.40 (d, 1H, $J$ = 17.4 Hz, with further fine splitting), 5.73 (d, 1H, $J$ = 3.6 Hz, merged with a m, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 19.9 ($CH_2$), 25.8 ($CH_2$), 26.5 ($CH_2$), 26.8 ($CH_3$), 27.3 ($CH_3$), 65.4 ($CH_2$), 79.2 (CH), 81.8 (C), 82.4 (CH), 104.2 (CH), 113.0 (C), 118.5 ($CH_2$), 132.8 (CH). ESIMS, $m/z$: 263 $(MNa)^+$. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.69; H, 8.33.

**(3a*R*,4*R*,5*R*,6*S*)-1-Benzyl-spiro[cyclopent[*d*]isoxazole-5.2′-tetrahydropyran]-4,6-diol (14).** Compound **13** (0.50 g, 2.08 mmol) was dissolved in $H_2SO_4$ (4%) in $CH_3CN-H_2O$ (3:1, 25 mL), and the solution was kept at room temperature for 24 h. The solution was neutralized with solid $CaCO_3$ and filtered, and the solvent was evaporated under reduced pressure to obtain an anomeric mixture of the 1,2-dihydroxy compound (0.36 g) as a gum, which without purification was used in the next step. This material was dissolved in dry ethanol (30 mL), treated with *N*-benzyl hydroxylamine (0.265

g, 2.16 mmol), and the solution was heated at reflux for 4 h. The solvent was evaporated under reduced pressure to obtain a residue. The residue was extracted with $CHCl_3$ (2 × 25 mL), the $CHCl_3$ solution was dried ($Na_2SO_4$), and the solvent was evaporated to afford a crude product, which was purified by column chromatography using silica gel. Elution with EtOAc−petroleum ether (3:22) furnished **14** (0.46 g, 72%).

**14.** mp 140−142 °C. $[\alpha]^{28}_D$ +33.3 (*c* 0.92, $CHCl_3$). IR (KBr): $\nu_{max}$ 3388, 1025, 997, 824, 759 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + $D_2O$, 300 MHz): $\delta$ 1.53 (m, 2H), 1.69−1.84 (m, 4H), 3.15 (m, 1H), 3.58−3.64 (m, 2H), 3.69−3.74 (m, 2H), 3.80 (d, 1H, $J$ = 13.0 Hz), 3.88 (m, 1H), 4.00 (d, 1H, $J$ = 13.0 Hz), 4.02 (partially merged dd, 1H, $J$ = 6.0, 10.8 Hz), 4.16 (t, 1H, $J$ = 8.4 Hz), 7.31 (m, 5H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): $\delta$ 19.0 ($CH_2$), 25.4 ($CH_2$), 29.5 ($CH_2$), 51.4 (CH), 58.8 ($CH_2$), 63.8 ($CH_2$), 68.4 ($CH_2$), 74.7 (CH), 79.4 (C), 80.3 (CH), 81.6 (CH), 126.8 (CH), 127.9 (2 × CH), 128.8 (2 × CH), 138.2 (C). ESIMS, *m*/*z*: 306 $(MH)^+$, 328 $(MNa)^+$. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.56; H, 7.48; N, 4.30.

**(3a*R*,5*R*,6*R*,6a*R*)-6-Allyl-2,2-dimethyl-5-vinyl-tetrahydrofuro-[2,3-*d*][1,3]dioxol-6-ol (15).** Following the earlier procedure (as described for **10**), addition of $Ph_3P$ (1.89 g, 7.21 mmol), imidazole (0.49 g, 7.2 mmol), and $I_2$ (0.73 g, 2.89 mmol) to a solution of 5,6-dihydroxy derivative of **7** (0.5 g, 1.92 mmol) [obtained from **7** through removal of isopropylidene group by dilute HOAc] in dry distilled toluene (40 mL)) afforded **15** (260 mg, 60%) as a white crystalline solid after purification by column chromatography on silica gel using an EtOAc−petroleum ether (1:24) mixture as the eluent.

**15.** mp 97−98 °C. $[\alpha]^{27}_D$ +51.2 (*c* 1.48, $CHCl_3$). IR (KBr): $\nu_{max}$ 3467, 1643, 1381, 1108, 1076, 1003 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.36 (s, 3H), 1.59 (s, 3H), 2.07 (dd, 1H, $J$ = 8.4, 14.6 Hz), 2.39 (ddd, 1H, $J$ = 1.3, 6.0, 14.6 Hz), 2.67 (d, 1H, $J$ = 1.3 Hz), 4.29 (d, 1H, $J$ = 5.6 Hz), 4.34 (d, 1H, $J$ = 3.9 Hz), 5.12 (brd, 1H, $J$ = 17.0 Hz), 5.17 (brd, 1H, $J$ = 9.3 Hz), 5.31 (td, 1H, $J$ = 1.4, 1.4, 10.8 Hz), 5.41 (td, 1H, $J$ = 1.5, 1.5, 17.0 Hz), 5.75 (d, 1H, $J$ = 3.9 Hz), 5.78−5.96 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 26.9 (2 × $CH_3$), 36.8 ($CH_2$), 79.7 (C), 81.0 (CH), 83.6 (CH), 103.8 (CH), 112.6 (C), 118.7 ($CH_2$), 119.2 ($CH_2$), 131.8 (CH), 133.1 (CH). ESIMS, *m*/*z*: 249 $(MNa)^+$. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.48; H, 7.80.

**(3a*R*,4a*R*,7a*R*,7b*R*)-2,2-Dimethyl-3a,4a,7,7b-tetrahydrocyclopenta[4,5]furo[2,3-*d*][1,3]dioxol-7a-ol (16).** To a solution of **15** (500 mg, 2.21 mmol) in dry dichloromethane (250 mL) degassed by $N_2$ gas was added Grubbs catalyst (56 mg, 0.068 mmol, 3 mmol %), and the mixture was stirred at room temperature for 6 h under $N_2$ atmosphere. The solvent was evaporated in a rotary evaporator to a black gummy residue. It was purified by column chromatography on silica gel using an EtOAc−petroleum ether (1:24) mixture as the eluent to furnish **16** (380 mg, 87%) as a crystalline solid.

**16.** mp 68−70 °C. $[\alpha]^{27}_D$ +72.2 (*c* 0.72, $CHCl_3$). IR (KBr): $\nu_{max}$ 3523, 1664, 1614, 1379, 1233, 1075, 990, 947, 876 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.41 (s, 3H), 1.62 (s, 3H), 2.54 (d, 1H, $J$ = 18.0 Hz), 2.66 (td, 1H, $J$ = 2.0, 2.0, 18.0 Hz), 3.05 (s, 1H), 4.40 (d, 1H, $J$ = 3.6 Hz), 4.79 (s, 1H), 5.83 (m, 1H), 5.87 (d, 1H, $J$ = 3.6 Hz), 6.00 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 27.5 ($CH_3$), 27.9 ($CH_3$), 43.5 ($CH_2$), 83.5 (CH), 85.9 (C), 92.4 (CH), 106.7 (CH), 113.6 (C), 129.7 (CH), 136.0 (CH). ESIMS, *m*/*z*: 221 $(MNa)^+$. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.49; H, 7.10.

**(3a*R*,4a*R*,7a*R*,7b*R*)-2,2-Dimethyl Hexahydrocyclopenta[4,5]-furo[2,3-*d*][1,3]dioxol-7a-ol (17).** A solution of **16** (1.20 g, 6.06 mmol) in dry ethanol (20 mL) was hydrogenated in the presence of Pd/C (10%, 150 mg). Usual workup and purification by column chromatography on silica gel and elution using EtOAc−petroleum ether (3:47) afforded **17** (1.09 g, 90%) as a semisolid mass.

**17.** $[\alpha]^{29}_D$ +28.4 (*c* 0.82, $CHCl_3$). IR (KBr): $\nu_{max}$ 3439, 1378, 1218, 1106, 1035, 1063, 1003, 755 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.37 (s, 3H), 1.58 (s, 3H), 1.73−1.88 (m, 7H), 4.22 (s, 1H), 4.36 (d, 1H, $J$ = 3.6 Hz), 5.82 (d, 1H, $J$ = 3.6 Hz). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 23.7 ($CH_2$), 27.2 ($CH_3$), 27.4 ($CH_3$), 30.5 ($CH_2$), 35.4 ($CH_2$), 83.4 (CH), 87.9 (C), 88.0 (CH), 105.8 (CH), 112.7 (C). ESIMS, *m*/*z*: 223 $(MNa)^+$. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.73; H, 8.00.

**(3a*R*,4a*R*,7a*R*,7b*R*)-7a-Allyloxy-2,2-dimethyl Hexahydrocyclopenta[4,5]furo[2,3-*d*][1,3]dioxole (18).** To a solution of **17** (1.0 g, 5.0 mmol) in dry THF (30 mL) at 10 °C was added oil-free sodium hydride (200 mg, 8.34 mmol) portionwise under $N_2$. The mixture was stirred at room temperature for 30 min. Allyl bromide (0.7 mL) was added, and the mixture was heated at reflux for 5 h under $N_2$. After the mixture was cooled to ∼10 °C, $NH_4Cl$ solution (saturated) was added to destroy excess NaH. The solvent was evaporated in vacuo, and the residue was extracted with $CHCl_3$ (2 × 30 mL). The $CHCl_3$ solution was washed with water (2 × 20 mL), dried ($Na_2SO_4$), and evaporated to obtain the crude product, which was purified by column chromatography on silica gel using EtOAc−petroleum ether (1:49) as the eluent to furnish **18** (1.04 g, 87%) as a thick syrup.

**18.** $[\alpha]^{28}_D$ +67.8 (*c* 2.00, $CHCl_3$). IR (neat): $\nu_{max}$ 1644, 1377, 1218, 1166, 1117, 1071, 927, 877 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.35 (s, 3H), 1.50 (m, 1H), 1.58 (s, 3H), 1.83 (m, 4H), 1.96 (m, 1H), 4.01 (dd, 1H, $J$ = 5.7, 12.0 Hz), 4.15 (dd, 1H, $J$ = 5.0, 12.0 Hz, with further fine splitting), 4.47 (d, 2H, $J$ = 3.6 Hz), 5.15 (dd, 1H, $J$ = 1.5, 10.4 Hz), 5.29 (dd, 1H, $J$ = 3.3, 17.1 Hz, with further fine splitting), 5.78 (d, 1H, $J$ = 3.6 Hz), 5.89−6.02 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 22.9 ($CH_2$), 26.9 ($CH_3$), 27.0 ($CH_3$), 30.1 ($CH_2$), 31.7 ($CH_2$), 66.1 ($CH_2$), 81.9 (CH), 86.7 (CH), 92.9 (C), 105.8 (CH), 112.6 (C), 116.2 ($CH_2$), 135.0 (CH). ESIMS, *m*/*z*: 263 $(MNa)^+$. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.73; H, 8.40.

**(1*R*,2*R*,3′a*S*,7′*S*,7′a*R*)-1′-Benzyl-spiro[cyclopenta-1.6′-tetrahydropyran[3,4-*d*]-isoxazole]-2,7′-diol (19) and (1*R*,2*R*,3′a*R*,7′*S*,7′a*S*)-1-Benzyl-spiro[cyclopenta-1.6′-tetrahydropyran[3,4-*d*]-isoxazole]-2,7′-diol (20).** Compound **18** (0.5 g, 2.08 mmol) was treated with 25 mL of 4% $H_2SO_4$ in $CH_3CN-H_2O$ (3:1) using the procedure identical to that adopted for the generation of **11** to furnish an anomeric mixture of 1,2-dihydroxy derivative (316 mg), which after drying ($P_2O_5$) was used directly in the next step. A solution of the above mixture (150 mg, 0.75 mmol) in dry ethanol (30 mL) was treated with *N*-benzyl hydroxylamine (132 mg, 1.07 mmol), and the solution was heated at reflux for 6 h. Usual workup and purification by column chromatography on silica gel using EtOAc−petroleum ether (2:23) as the eluting solvent furnished **19** (102 mg, 45%) and **20** (75 mg, 33%), respectively, as light yellow crystalline solids.

**19.** mp 128−129 °C. $[\alpha]^{30}_D$ +7.9 (*c* 1.16, $CHCl_3$). IR (KBr): $\nu_{max}$ 3430, 3311, 1453, 1430, 1221, 1074, 700 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + $D_2O$, 300 MHz): 1.46−2.00 (m, 6H), 2.91 (m, 1H), 3.18 (t, 1H, $J$ = 7.5 Hz), 3.71−3.91 (m, 5H), 4.01−4.05 (m, 2H), 4.22 (t, 1H, $J$ = 8.0 Hz), 7.34 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 21.2 ($CH_2$), 25.4 ($CH_2$), 33.3 ($CH_2$), 39.3 (CH), 58.5 ($CH_2$), 61.0 ($CH_2$), 66.7 (CH), 67.6 (CH), 68.7 ($CH_2$), 80.6 (CH), 85.3 (C), 127.5 (CH), 128.3 (2 × CH), 129.3 (2 × CH), 136.2 (C). ESIMS, *m*/*z*: 306 $(MH)^+$, 328 $(MNa)^+$. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.81; H, 7.57; N, 4.38.

**20.** mp 150−152 °C. $[\alpha]^{29}_D$ −101.0 (*c* 1.62, $CHCl_3$). IR (KBr): $\nu_{max}$ 3434, 1449, 1382, 1320, 1098, 1035 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + $D_2O$, 300 MHz): $\delta$ 1.49 (m, 1H), 1.75 (m, 2H), 2.08−2.17 (m, 3H), 2.88 (m, 1H), 3.40 (dd, 1H, $J$ = 4.0, 6.7 Hz), 3.54 (dd, 1H, $J$ = 3.4, 8.0 Hz), 3.68 (dd, 1H, $J$ = 6.6, 11.7 Hz), 3.76 (dd, 1H, $J$ = 9.8, 11.4 Hz), 3.93 (d, 1H, $J$ = 14.0 Hz), 3.97−4.02 (m, 2H), 4.18 (d, 1H, $J$ = 4.0 Hz), 4.31 (d, 1H, $J$ = 14.0 Hz), 7.23−7.42 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 20.8 ($CH_2$), 27.4 ($CH_2$), 33.2 ($CH_2$), 42.5 (CH), 60.1 ($CH_2$), 62.8 ($CH_2$), 64.5 (CH), 67.3 ($CH_2$), 68.7 (CH), 81.0 (CH), 85.0 (C), 126.9 (CH), 128.1 (2 × CH), 128.5 (2 × CH), 137.9 (C). ESIMS, *m*/*z*: 328 $(MNa)^+$. Anal.

Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.58; H, 7.48; N, 4.30.

**(3a*R*,4a*R*,7a*R*,7b*R*)-7a-Allyloxy-2,2-dimethyl-4a,7,7a,7b-tetrahydrocyclopenta[4,5]furo[2,3-*d*][1,3]dioxole (21).** Compound **16** (0.5 g, 2.52 mmol) was allylated using allyl bromide (0.30 mL, 417 mg, 3.45 mmol), oil-free sodium hydride (100 mg, 4.17 mmol), and dry THF (20 mL) to furnish **21** (470 mg, 78%) as a thick syrup following the procedure described in the preparation of **18**.

**21.** $[\alpha]^{27}_D$ +44.8 (*c* 0.63, $CHCl_3$). IR (neat): $\nu_{max}$ 1641, 1377, 1220, 1186, 874 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.40 (s, 3H), 1.61 (s, 3H), 2.35 (brd, 1H, $J$ = 17.7 Hz), 2.78 (td, 1H, $J$ = 2.0, 2.0, 17.7 Hz), 4.00 (m, 1H), 4.21 (m, 1H), 4.49 (d, 1H, $J$ = 3.6 Hz), 5.01 (brs, 1H), 5.14 (ddd, 1H, $J$ = 1.6, 3.3, 10.3 Hz), 5.29 (ddd, 1H, $J$ = 1.6, 3.3, 17.1 Hz), 5.81 (d, 1H, $J$ = 3.3 Hz), 5.87−5.95 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 27.8 ($CH_3$), 28.1 ($CH_3$), 40.5 ($CH_2$), 67.5 ($CH_2$), 84.1 (CH), 91.0 (CH), 91.6 (C), 107.1 (CH), 114.2 (C), 116.8 ($CH_2$), 131.0 (CH), 134.7 (CH), 135.5 (CH). ESIMS, *m*/*z*: 261 $(MNa)^+$. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.28; H, 7.53.

**[1*S*,2*R*,3′a*R*,6′a*S*]-1′-Benzyl-spiro[cyclopent-1.6′-tetrahydrofuro(3,4-*d*)isoxazole]-3,4-en-2-ol (23) and [1*S*,2*R*,3′a*R*,6′a*S*]-1-Benzyl-2-formyloxyspiro[cyclopent-1.6′-tetrahydrofuro(3,4-*d*)-isoxazole]-3,4-ene (24).** Compound **21** (330 mg, 1.39 mmol) was dissolved in 25 mL of 4% $H_2SO_4$ in $CH_3CN-H_2O$ (3:1) and stirred at room temperature for 24 h. Usual workup as described earlier for **11** afforded the crude anomeric mixture of 1,2-dihydroxy derivative, which was used directly in the next step. To a solution of this mixture (200 mg, 1.01 mmol) in MeOH (25 mL) at ~10 °C was added an aqueous solution (5 mL) of $NaIO_4$ (260 mg, 1.21 mmol) dropwise with vigorous stirring. After being stirred at the same temperature for 45 min, the mixture was filtered and the solvent was evaporated. The residue was dissolved in $CHCl_3$ (30 mL), and the $CHCl_3$ solution was washed with water (2 × 20 mL) and dried ($Na_2SO_4$). Evaporation of the solvent afforded the crude aldehyde **22** (150 mg) as a thick liquid, which was dried ($P_2O_5$) and used for further reaction in the next step. This compound (150 mg, 0.89 mmol) dissolved in dry ethanol (30 mL) was treated with *N*-benzyl hydroxylamine (164 mg, 1.33 mmol), and the solution was stirred at room temperature for 20 h. The solvent was evaporated to a gummy residue, which was purified by column chromatography on silica gel. Elution with EtOAc−petroleum ether (2:23) furnished **23** (114 mg, 47%) as a solid material. On the other hand, EtOAc−petroleum ether (1:9) eluted **24** (70 mg, 29%) as a thick liquid.

**23.** mp 57−58 °C. $[\alpha]^{29}_D$ −67.8 (*c* 1.06, $CHCl_3$). IR (KBr): $\nu_{max}$ 3492, 1611, 1385, 1038, 856 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 2.38 (d, 1H, $J$ = 17.5 Hz), 3.05 (dd, 1H, $J$ = 1.2, 17.5 Hz), 3.40 (m, 1H), 3.69 (dd, 1H, $J$ = 4.0, 9.5 Hz), 3.74 (dd, 1H, $J$ = 3.0, 8.7 Hz), 3.83 (d, 1H, $J$ = 12.9 Hz), 3.98 (dd, 1H, $J$ = 6.8, 9.3 Hz), 4.05 (d, 1H, $J$ = 12.9 Hz), 4.19−4.24 (m, 2H), 4.29 (brs, 1H), 5.72 (m, 1H), 6.00 (m, 1H), 7.24−7.38 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 38.5 ($CH_2$), 48.5 (CH), 60.8 ($CH_2$), 70.6 ($CH_2$), 70.7 (CH), 70.8 ($CH_2$), 81.1 (CH), 93.2 (C), 127.4 (CH), 128.3 (2 × CH), 129.0 (2 × CH), 130.0 (CH), 134.9 (CH), 137.2 (C). FABMS, *m*/*z*: 274 $(MH)^+$. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.11; H, 7.00; N, 5.06.

**24.** $[\alpha]^{29}_D$ −75.9 (*c* 1.54, $CHCl_3$). IR (KBr): $\nu_{max}$ 1716, 1614, 1455, 1322, 1180, 1024, 712 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 2.47 (d, 1H, $J$ = 18.0 Hz), 3.11 (d, 1H, $J$ = 18.0 Hz), 3.38 (m, 1H), 3.72−3.81 (m, 2H), 3.88 (d, 1H, $J$ = 8.3 Hz), 4.00 (dd, 1H, $J$ = 6.5, 9.5 Hz), 4.08 (d, 1H, $J$ = 12.6 Hz), 4.25 (t-like, 1H, $J$ = 8.0 Hz), 5.43 (s, 1H), 5.69 (m, 1H), 6.14 (m, 1H), 7.29−7.39 (m, 5H), 7.61 (s, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 39.0 ($CH_2$), 48.3 (CH), 60.9 ($CH_2$), 70.8 ($CH_2$), 70.9 (CH), 71.1 ($CH_2$), 82.2 (CH), 92.1 (C), 126.6 (CH), 127.4 (CH), 128.3 (2 × CH), 129.2 (2 × CH), 136.8 (C), 137.6 (CH), 160.2 (CH). EIMS, *m*/*z*: 301 $(M^+)$, 272, 256. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.49; H, 6.31; N, 4.48.

**(1*S*,2*R*,3*R*,4*R*,5*R*)-2-(5-Amino-6-chloropyrimidin-4-ylamino)-3-hydroxymethyl-6-oxa-spiro[4.5]decane-1,4-diol (25).** Compound **14** (0.40 g, 1.30 mmol) (dried over $P_2O_5$) was dissolved in dry ethanol (20 mL), Pd/C (10%, 0.130 g) and cyclohexene (2 mL) were added, and the solution was heated at reflux under $N_2$ atmosphere for 5 h. The catalyst was filtered off, and the solvent was evaporated in vacuo to obtain a crude trihydroxy amine derivative[31] (0.270 g), which was dried (over $P_2O_5$). To the above amine (0.270 g, 1.24 mmol) dissolved in dry *n*-BuOH (25 mL) were added 5-amino-4,6-dichloropyrimidine (297 mg, 1.81 mmol, 1.5 equiv) and $Et_3N$ (2 mL), and the mixture was heated at reflux for 30 h under $N_2$. The solvent was evaporated in vacuo to give a semisolid residue, the aqueous solution of which was washed with $CH_2Cl_2$ (2 × 20 mL). The aqueous part was evaporated to a thick oil, which was purified by reverse phase flash chromatography using water as the eluent to furnish **25** (206 mg, 50%).

**25.** mp 110−112 °C (shrinks). $[\alpha]^{26}_D$ −46.2 (*c* 0.48, $CH_3OH$). IR (KBr): $\nu_{max}$ 3343, 3256, 1582, 1423, 1075, 978, 932, 850, 764 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.51 (m, 2H), 1.65−1.74 (m, 4H), 2.34 (m, 1H), 3.41 (dd, 1H, $J$ = 4.0, 11.7 Hz), 3.56 (dd, 1H, $J$ = 5.2, 11.7 Hz), 3.72 (d, 1H, $J$ = 8.6 Hz), 3.74 (d, 1H, $J$ = 9.6 Hz), 4.00 (m, 2H), 4.56 (t, 1H, $J$ = 10.2 Hz), 7.83 (s, 1H). $^{13}C$ NMR ($D_2O$, 75 MHz): $\delta$ 19.2 ($CH_2$), 25.1 ($CH_2$), 30.3 ($CH_2$), 45.6 (CH), 56.0 (CH), 59.6 ($CH_2$), 65.6 ($CH_2$), 77.1 (CH), 77.5 (C), 81.1 (CH), 123.1 (C), 140.3 (C), 148.4 (CH), 154.9 (C). ESIMS, *m*/*z*: 345 ($MH^+$, for $Cl^{35}$), 347 ($MH^+$, for $Cl^{37}$), 367 ($MNa^+$, for $Cl^{35}$), 369 ($MNa^+$, for $Cl^{37}$). Anal. Calcd for $C_{14}H_{21}ClN_4O_4$: C, 48.77; H, 6.14; N, 16.25. Found: C, 48.62; H, 6.00; N, 16.03.

**(1*S*,2*R*,3*R*,4*R*,5*R*)-2-(6-Chloropurin-9-yl)-3-hydroxymethyl-6-oxa-spiro[4.5]decane-1,4-diol (26) and (1*S*,2*R*,3*R*,4*R*,5*R*)-2-(6-Dimethylaminopurin-9-yl)-3-hydroxymethyl-6-oxa-spiro[4.5]-decane-1,4-diol (27).** To a solution of the aminopyrimidine derivative **25** (42 mg, 0.122 mmol) dissolved in dry DMF (4 mL) were added *p*-TSA (35 mg, 0.183 mmol) and $HC(OEt)_3$ (2 mL), and the reaction mixture was stirred at 10 °C for 16 h under $N_2$. The solvent was removed under vacuum, the residue was dissolved in MeOH (5 mL), and the solution was treated with Dowex-$OH^-$ resin for 5 h to neutralize the acid. It was then filtered, and the filtrate was evaporated to give a crude residue, which was subjected to flash column chromatography using reverse phase material. Elution with water furnished the chloronucleoside **26** (32 mg, 74%) and **27** (3.0 mg, 6.8%) as foamy solids.

**26.** $[\alpha]^{27}_D$ −22.0° (*c* 0.44, $CH_3OH$). IR (KBr): $\nu_{max}$ 3410, 1639, 1596, 1570, 1385, 1343, 1081, 1044, 957 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.50 (brs, 2H), 1.76 (brs, 4H), 2.55 (m, 1H), 3.27 (d, 2H, $J$ = 5.7 Hz), 3.81 (d, 1H, $J$ = 8.7 Hz), 4.05 (m, 2H), 4.62 (d, 1H, $J$ = 10.2 Hz), 5.18 (t, 1H, $J$ = 10.5 Hz), 8.55 (s, 1H), 8.63 (s, 1H). $^{13}C$ NMR ($D_2O$, 75 MHz): $\delta$ 19.1 ($CH_2$), 25.1 ($CH_2$), 29.8 ($CH_2$), 45.6 (CH), 59.5 ($CH_2$), 60.2 (CH), 65.7 ($CH_2$), 76.7 (CH), 77.6 (C), 78.0 (CH), 131.3 (C), 147.6 (CH), 150.5 (C), 152.0 (CH), 153.0 (C). ESIMS, *m*/*z*: 377 ($MNa^+$, for $Cl^{35}$), 379 ($MNa^+$, for $Cl^{37}$). Anal. Calcd for $C_{15}H_{19}ClN_4O_4$: C, 50.78; H, 5.40; N, 15.79. Found: C, 50.72; H, 5.32; N, 15.50.

**27.** $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.52 (brs, 2H), 1.77 (brs, 4H), 2.50 (m, 1H), 3.18−3.33 (s, 6H at $\delta$ 3.29, merged with a m, 2H), 3.78 (d, 1H, $J$ = 8.5 Hz), 4.05 (m, 2H), 4.49 (d, 1H, $J$ = 10.5 Hz), 5.04 (t, 1H, $J$ = 10.8 Hz), 8.04 (s, 2H). ESIMS, *m*/*z*: 364 $(MH)^+$, 386 $(MNa)^+$.

**(1*S*,2*R*,3*R*,4*R*,5*R*)-2-(6-Aminopurin-9-yl)-3-hydroxymethyl-6-oxa-spiro[4.5]decane-1,4-diol (28).** Compound **26** (28 mg, 0.08 mmol) was dissolved in a saturated solution of ammonia in MeOH (5 mL) and heated at 100 °C in a sealed tube for 40 h. The sealed tube was cooled, broken, and $NH_3$ gas was removed by heating at 40 °C. The solvent was evaporated to obtain a crude mass, which

(31) $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.47 (m, 2H), 1.62 (m, 2H), 1.69 (m, 2H), 2.13 (m, 1H), 3.25−3.38 (m, 2H), 3.56 (d, 1H, $J$ = 9.0 Hz), 3.68 (d, 2H, $J$ = 5.5 Hz), 3.93 (t, 2H, $J$ = 5.5 Hz). ESIMS, *m*/*z*: 218 $(MH)^+$.

was purified by flash chromatography using reverse phase material and water as eluent to furnish **28** (22 mg, 83%) as a foamy solid.

**28.** mp 124−125 °C (shrinks), 175−177 °C (melts). $[\alpha]^{29}_D$ −37.9 (*c* 0.35, $CH_3OH$). IR (KBr): $\nu_{max}$ 3343, 3219, 1647, 1603, 1079, 1040 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.51 (brs, 2H), 1.77 (brs, 4H), 2.51 (m, 1H), 3.22−3.34 (m, 2H), 3.79 (d, 1H, $J$ = 8.6 Hz), 4.05 (m, 2H), 4.51 (d, 1H, $J$ = 10.5 Hz), 5.05 (t, 1H, $J$ = 10.5 Hz), 8.10 (s, 1H), 8.12 (s, 1H). $^{13}C$ NMR ($D_2O$, 300 MHz): $\delta$ 19.1 ($CH_2$), 25.1 ($CH_2$), 29.9 ($CH_2$), 45.7 (CH), 59.3 (CH), 59.6 ($CH_2$), 65.7 ($CH_2$), 76.9 (CH), 77.6 (C), 78.2 (CH), 118.9 (C), 142.1 (CH), 150.5 (C), 152.9 (CH), 155.9 (C). ESIMS, *m*/*z*: 336 $(MH)^+$, 358 $(MNa)^+$. Anal. Calcd for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88. Found: C, 53.48; H, 6.25; N, 20.60.

**(1*R*,5*R*,8*S*,9*S*,10*R*)-9-(5-Amino-6-chloropyrimidin-4-ylamino)-8-hydroxymethyl-6-oxa-spiro[4.5]decane-1,10-diol (29).** A solution of **19** (130 mg, 0.426 mmol) in dry ethanol (20 mL) was hydrogenolyzed with Pd/C (10%, 40 mg) and cyclohexene (2 mL) as described earlier. Usual workup followed by drying ($P_2O_5$) of the residue yielded a trihydroxy aminospirocycle (88 mg) as a thick oil. This oil was dissolved in dry *n*-BuOH and treated with 5-amino-4,6-dichloro pyrimidine (91 mg, 0.56 mmol) and $Et_3N$ (2 mL) (using procedure as adopted for the preparation of **25**). Usual workup and purification by flash chromatography using $H_2O$−MeOH (9:1) furnished **29** (102 mg, 80%) as a foamy solid.

**29.** mp 170−171 °C. $[\alpha]^{26}_D$ −62.4 (*c* 7.8, MeOH). IR (KBr): $\nu_{max}$ 3362, 1585, 1465, 1424, 1103, 1030, 853 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.50−1.71 (m, 3H), 1.88−1.96 (m, 3H), 2.26 (m, 1H), 3.69−3.77 (m, 4H), 3.99 (t-like, 1H, $J$ = 5.5 Hz), 4.03 (d, 1H, $J$ = 10.4 Hz), 4.27 (dd, 1H, $J$ = 4.5, 10.4 Hz), 7.80 (s, 1H). $^{13}C$ NMR ($D_2O$, 75 MHz): $\delta$ 20.2 ($CH_2$), 26.3 ($CH_2$), 33.0 ($CH_2$), 40.1 (CH), 53.2 (CH), 58.5 ($CH_2$), 61.3 ($CH_2$), 67.1 (CH), 80.8 (CH), 88.2 (C), 123.4 (C), 140.1 (C), 148.1 (CH), 154.1 (C). ESIMS, *m*/*z*: 345 $(MH^+$, for $Cl^{35})$, 347 $(MH^+$, for $Cl^{37})$, 367 $(MNa^+$, for $Cl^{35})$, 369 $(MNa^+$, for $Cl^{37})$. Anal. Calcd for $C_{14}H_{21}ClN_4O_4$: C, 48.77; H, 6.14; N, 16.25. Found: C, 48.58; H, 6.02; N, 16.05.

**(1*R*,5*R*,8*S*,9*S*,10*R*)-9-(6-Chloropurin-9-yl)-8-hydroxymethyl-6-oxa-spiro[4.5]decane-1,10-diol (30).** Compound **29** (48 mg, 0.139 mmol) dissolved in dry DMF (4 mL) was converted into the foamy material **30** (40 mg, 80%) using $HC(OEt)_3$ (2 mL) and *p*-TSA (40 mg, 0.209 mmol) through the procedure described in the preparation of **26**.

**30.** $[\alpha]^{26}_D$ −105.8 (*c* 1.26, MeOH). IR (KBr): $\nu_{max}$ 3393, 1593, 1565, 1340, 1219, 1088 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.53−1.74 (m, 3H), 2.00 (m, 3H), 2.39 (m, 1H), 3.48 (dd, 1H, $J$ = 5.2, 11.0 Hz), 3.77−3.93 (m, 3H), 4.03 (t, 1H, $J$ = 6.5 Hz), 4.92 (d, 1H, $J$ = 11.8 Hz), 4.99 (dd, 1H, $J$ = 4.7, 11.8 Hz), 8.64 (s, 1H), 8.69 (s, 1H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): $\delta$ 20.4 ($CH_2$), 23.5 ($CH_2$), 32.9 ($CH_2$), 42.5 (CH), 57.1 ($CH_2$), 58.2 (CH), 60.4 ($CH_2$), 63.9 (CH), 81.1 (CH), 86.9 (C), 130.9 (C), 146.9 (CH), 148.9 (C), 151.4 (CH), 152.4 (C). ESIMS, *m*/*z*: 377 $(MNa^+$, for $Cl^{35})$, 379 $(MNa^+$, for $Cl^{37})$. Anal. Calcd for $C_{15}H_{19}ClN_4O_4$: C, 50.78; H, 5.40; N, 15.79. Found: C, 50.53; H, 5.25; N, 15.61.

**(1*R*,5*R*,8*S*,9*S*,10*R*)-9-(6-Aminopurin-9-yl)-8-hydroxymethyl-6-oxa-spiro[4.5]decane-1,10-diol (31).** Chloropurine **30** (35 mg, 0.099 mmol) was converted into aminopurine **31** (28 mg, 85%) as a foamy solid using the same procedure as described previously for **28**.

**31.** mp: 99−100 °C (shrinks), 184−185 °C (melts). $[\alpha]^{26}_D$ −99.4 (*c* 0.65, MeOH). IR (KBr): $\nu_{max}$ 3342, 1649, 1604, 1479, 1381, 1084, 1044, 953, 648 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.46−1.75 (m, 3H), 1.92−2.07 (m, 3H), 2.30 (m, 1H), 3.37 (dd, 1H, $J$ = 4.5, 11.0 Hz), 3.73−3.88 (m, 3H), 4.00 (t, 1H, $J$ = 6.4 Hz), 4.79−4.94 (2H, merged with HOD signal), 8.13 (s, 1H), 8.19 (s, 1H). $^{13}C$ NMR ($D_2O$, 75 MHz): $\delta$ 20.3 ($CH_2$), 24.9 ($CH_2$), 32.8 ($CH_2$), 42.0 (CH), 57.4 (CH), 58.4 ($CH_2$), 61.8 ($CH_2$), 64.9 (CH), 81.7 (CH), 88.5 (C), 119.0 (C), 141.5 (CH), 149.9 (C), 153.0 (CH), 156.0 (C). ESIMS, *m*/*z*: 358 $(MNa)^+$. Anal. Calcd for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88. Found: C, 53.70; H, 6.28; N, 20.80.

**(1*R*,5*R*,8*R*,9*R*,10*R*)-9-(5-Amino-6-chloropyrimidin-4-ylamino)-8-hydroxymethyl-6-oxa-spiro[4.5]decane-1,10-diol (32).** Compound **20** (130 mg, 0.43 mmol) was hydrogenolyzed, and the aminospirocycle thus obtained was converted to the chloropyrimidine derivative **32** (65 mg, 44%) as gum as described earlier (in the preparation of **29**).

**32.** $[\alpha]^{25}_D$ −8.3 (*c* 1.17, MeOH). IR (KBr): $\nu_{max}$ 3392, 1642, 1579, 1501, 1424, 1110, 1032, 855, 758 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 1.56−1.72 (m, 4H), 1.82 (m, 1H), 2.03 (m, 1H), 2.14 (m, 1H), 3.66 (dd, 1H, $J$ = 4.0, 11.0 Hz), 3.71−3.80 (m, 2H), 3.87 (dd, 1H, $J$ = 3.0, 12.5 Hz), 3.94 (d, 1H, $J$ = 3.0 Hz), 4.40 (d, 1H, $J$ = 3.3 Hz), 4.57 (dd, 1H, $J$ = 3.0, 5.4 Hz), 7.80 (s, 1H). $^{13}C$ NMR ($D_2O$, 75 MHz): $\delta$ 19.6 ($CH_2$), 33.1 ($CH_2$), 33.7 ($CH_2$), 38.4 (CH), 50.2 (CH), 59.9 ($CH_2$), 61.8 ($CH_2$), 68.5 (CH), 73.8 (CH), 89.8 (C), 123.2 (C), 140.2 (C), 148.0 (CH), 153.3 (C). ESIMS, *m*/*z*: 345 $(MH^+$, for $Cl^{35})$, 347 $(MH^+$, for $Cl^{37})$. Anal. Calcd for $C_{14}H_{21}ClN_4O_4$: C, 48.77; H, 6.14; N, 16.25. Found: C, 48.52; H, 6.12; N, 16.13.

**(1*R*,5*R*,8*R*,9*R*,10*R*)-9-(6-Dimethylaminopurin-9-yl)-8-hydroxymethyl-6-oxa-spiro[4.5]decane-1,10-diol (33).** To a solution of **32** (50 mg, 0.145 mmol) in freshly distilled dry DMF (4 mL) were added *p*-TSA (42 mg, 0.218 mmol) and $HC(OEt)_3$ (2 mL); the mixture was stirred under $N_2$ at 10 °C for 16 h and then at room temperature for 8 h. The solvent was removed in vacuo to a gummy residue. This residue was dissolved in MeOH (5 mL), and Dowex-$OH^-$ resin was added portionwise to neutralize the acid. The crude nucleoside was purified by reverse phase column chromatography using water−MeOH as eluent to furnish **33** (8 mg, 15%) as an amorphous solid.

**33.** $^1H$ NMR (DMSO-$d_6$, 300 MHz): $\delta$ 1.58−1.67 (m, 4H), 1.85 (m, 1H), 2.00−2.09 (m, 2H), 3.07 (d, 1H, $J$ = 10.5 Hz), 3.85 (brs, 3H), 4.14 (brs, 1H), 4.31 (brs, 1H), 4.55 (brs, 1H), 4.90 (brs, 1H), 5.10 (brs, 1H), 5.75 (brs, 1H), 8.22 (s, 1H), 8.32 (s, 1H), the signal for $NMe_2$ merged under solvent peak. $^1H$ NMR (DMSO-$d_6$, 300 MHz at 60 °C): $\delta$ 1.57−1.71 (m, 4H), 1.90 (m, 1H), 2.05 (m, 1H), 2.21 (m, 1H), 3.18 (d, 1H, $J$ = 10.5 Hz), 3.49 (s, 6H, $NMe_2$), 3.77 (t-like, 1H, $J$ = 8.5 Hz), 3.90 (brs, 1H), 4.20 (brs, 1H), 4.31 (brs, 1H), 4.59 (brs, 1H), 5.19 (brd, 1H, $J$ = 3.0 Hz), 5.55 (brs, 1H), 8.21 (s, 1H), 8.22 (s, 1H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): $\delta$ 20.7 ($CH_2$), 35.0 ($CH_2$), 35.5 ($CH_2$), 38.8 (CH), 54.8 (CH), 58.9 ($CH_2$), 61.9 ($CH_2$), 67.9 (CH), 72.5 (CH), 90.2 (C), 119.5 (C), 140.0 (CH), 151.2 (C), 152.4 (CH), 155.2 (C), C-signal due to $NMe_2$ merged under solvent peak. ESIMS, *m*/*z*: 364 $(MH)^+$, 386 $(MNa)^+$. Anal. Calcd for $C_{17}H_{25}N_5O_4$: C, 56.18; H, 6.93; N, 19.27. Found: C, 56.10; H, 6.72; N, 19.02.

**(1*R*,3*R*,6*R*,7*S*,8*R*,9*S*)-1-Allyloxy-5-benzyl-4-oxa-5-aza-tricyclo-[4.2.1.0$^{3,7}$]nonane-8,9-diol (35).** Compound **21** (75 mg, 0.31 mmol) was converted to the anomeric mixture of 1,2-dihydroxy derivative (45 mg, 73%) using 4% $H_2SO_4$ in $CH_3CN$−$H_2O$ (3:1) (25 mL). To a solution of the above material (0.23 mmol) in dry EtOH (25 mL) was added *N*-benzyl hydroxylamine (34 mg, 0.28 mmol), and the solution was heated at reflux for 4 h. The solvent was evaporated in vacuo to afford a gummy residue, which was purified by column chromatography on silica gel using EtOAc−petroleum ether (3:22) as the eluent to furnish **35** (52 mg, 75%) as a crystalline solid.

**35.** mp 159−160 °C. $[\alpha]^{29}_D$ +82.9 (*c* 0.96, $CHCl_3$). IR (KBr): $\nu_{max}$ 3509, 3354, 1645, 1308, 1176, 1072, 1050, 753, 732 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 1.52 (d, 1H, $J$ = 13.5 Hz), 1.75 (dd, 1H, $J$ = 7.5, 13.5 Hz), 3.08 (dt, 1H, $J$ = 2.0, 5.3 Hz), 3.16 (brd, 1H, $J$ = 4.3 Hz, exchangeable), 3.48 (brs, 1H, exchangeable), 3.78 (d, 1H, $J$ = 12.9 Hz), 3.84 (d, 1H, $J$ = 5.0 Hz), 3.91 (d, 1H, $J$ = 12.9 Hz), 3.95 (brs, 1H), 4.01 (dd, 1H, $J$ = 5.5, 12.0 Hz with fine splitting), 4.09 (dd, 1H, $J$ = 6.0, 12.0 Hz with fine splitting), 4.14 (brs, 1H), 4.50 (dd, 1H, $J$ = 5.7, 7.2 Hz), 5.18 (dd, 1H, $J$ = 1.2, 10.2 Hz), 5.30 (dd, 1H, $J$ = 1.5, 17. 0 Hz), 5.89−6.02 (m, 1H), 7.27−7.37 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 33.8 ($CH_2$), 48.6 (CH), 63.3 ($CH_2$), 66.6 ($CH_2$), 73.2 (CH), 73.4 (CH), 78.5 (CH), 82.4 (C), 117.3 ($CH_2$), 127.4 (CH), 128.3 (2 × CH), 129.1 (2 × CH), 134.6 (CH), 136.6 (C), one CH not discernible.

ESIMS, *m*/*z*: 326 $(MNa)^+$, 304 $(MH)^+$. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.09; H, 6.91; N, 4.38.

**(1*R*,3*R*,6*R*,7*S*,8*R*,9*S*)-5-Benzyl-4-oxa-5-aza-tricyclo[4.2.1.0$^{3,7}$]-nonane-1,8,9-triol (36).** A solution of **16** (500 mg, 2.52 mmol) in 4% $H_2SO_4$ in $CH_3CN-H_2O$ (3:1) 25 mL) was stirred at room temperature for 24 h. Usual workup afforded the crude anomeric mixture of 1,2-dihydroxy derivative (287 mg), which was used in the next step without further purification. *N*-Benzyl hydroxylamine (258 mg, 2.1 mmol) was added to a solution of the above anomeric mixture (280 mg, 1.77 mmol) in dry ethanol (30 mL), and the solution was heated at reflux for 4 h. The solvent was evaporated in vacuo to a gummy residue, which was purified by column chromatography on silica gel using with an EtOAc−petroleum ether (7:13) mixture as eluent, affording **36** (326 mg, 70%) as an amorphous solid.

**36.** mp 107−108 °C. $[\alpha]^{27}_D$ +52.4 (*c* 0.99, MeOH). IR (KBr): $\nu_{max}$ 3423, 3253, 1160, 1118, 752, 717, 694 cm$^{-1}$. $^1$H NMR ($C_5D_5N$, 300 MHz): $\delta$ 1.72 (d, 1H, $J$ = 13.0 Hz), 2.01 (dd, 1H, $J$ = 7.3, 13.0 Hz), 3.33 (m, 1H), 3.88 (d, 1H, $J$ = 13.0 Hz), 4.06 (d, 1H, $J$ = 13.0 Hz), 4.27 (m, 2H), 4.37 (brs, 1H), 4.56 (t-like, 1H, $J$ = 6.5 Hz), 6.15 (d, 1H, $J$ = 3.9 Hz, exchangeable), 6.95 (brs, 1H, exchangeable), 7.12 (d, 1H, $J$ = 4.7 Hz, exchangeable), 7.22−7.31 (m, 3H), 7.49 (d, 2H, $J$ = 7.0 Hz). $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 39.1 ($CH_2$), 49.1 (CH), 63.1 ($CH_2$), 73.7 (CH), 74.3 (CH), 78.0 (C), 79.0 (CH), 79.5 (CH), 128.5 (CH), 129.1 (2 × CH), 130.3 (2 × CH), 136.3 (C). FABMS, *m*/*z*: 264 $(MH)^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.59; H, 6.52; N, 5.16.

**(1*R*,2*S*,3*R*,4*S*,5*R*,7*R*)-3-(5-Amino-6-chloro-pyrimidin-4-ylamino)-bicyclo[2.2.1]heptane-1,2,5,7-tetraol (37).** Compound **36** (200 mg, 0.76 mmol) dissolved in ethanol (20 mL) was hydrogenolyzed in the presence of Pd/C (50 mg) and cyclohexene (2 mL) at the refluxing temperature under $N_2$ for 5 h. The catalyst was filtered off, and the solvent was evaporated in vacuo to obtain the crude amine (120 mg), which was dried (over $P_2O_5$) and used in the next step. The crude amine (120 mg, 0.69 mmol) dissolved in dry *n*-BuOH was reacted with 5-amino-4,6-dichloropyrimidine (135 mg, 0.82 mmol) in the presence of $Et_3N$ (2 mL) as described earlier for **29**. Usual workup and purification by flash chromatography on reverse phase material eluting with water furnished **37** (104 mg, 50%) as a foamy solid.

**37.** $[\alpha]^{27}_D$ +35.8 (*c* 0.85, MeOH). IR (KBr): $\nu_{max}$ 3504, 3415, 3301, 1585, 1510, 1432, 1340, 1060, 1003, 850, 637 cm$^{-1}$. $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 1.32 (dd, 1H, $J$ = 4.0, 13.4 Hz), 2.17 (dd, 1H, $J$ = 10.7, 13.4 Hz), 2.44 (dd, 1H, $J$ = 2.4, 4.0 Hz), 3.58 (t, 1H, 2.4 Hz), 3.83 (s, 1H), 4.35 (m, 1H), 4.77 (s, 1H), 7.80 (s, 1H). $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 39.7 ($CH_2$), 45.1 (CH), 62.0 (CH), 67.9 (CH), 78.3 (CH), 79.9 (C), 81.0 (CH), 123.0 (C), 140.4 (C), 148.8 (CH), 154.5 (C). FABMS, *m*/*z*: 303 ($MH^+$, for $Cl^{35}$), 305 ($MH^+$, for $Cl^{37}$), 325 ($MNa^+$, for $Cl^{35}$), 327 ($MNa^+$, for $Cl^{37}$). Anal. Calcd for $C_{11}H_{15}ClN_4O_4$: C, 43.64; H, 4.99; N, 18.51. Found: C, 43.48; H, 4.88; N, 18.35.

**(1*R*,2*S*,3*R*,4*S*,5*R*,7*R*)-3-(6-Chloropurin-9-yl)-bicyclo[2.2.1]heptane-1,2,5,7-tetraol (38).** Compound **37** (165 mg, 0.546 mmol) in dry DMF (4 mL) was treated with $HC(OEt)_3$ (2 mL) in the presence of *p*-TSA (156 mg, 0.819 mmol) as described earlier for the preparation of **30**. Usual workup as well as purification afforded **38** (119 mg, 70%) as a foamy solid.

**38.** $[\alpha]^{26}_D$ −56.5 (*c* 0.75, MeOH). IR (KBr): $\nu_{max}$ 3393, 1593, 1402, 1222, 1095, 1014, 638 cm$^{-1}$. $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 1.45 (dd, 1H, $J$ = 3.6, 13.5 Hz), 2.22 (dd, 1H, $J$ = 10.7, 13.5 Hz), 2.83 (brs, 1H), 3.94 (s, 1H), 4.22 (m, 1H), 4.67 (1H, merged with HOD), 5.30 (t-like, 1H, $J$ = 3.9 Hz), 8.64 (s, 1H), 8.73 (s, 1H). $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 39.8 ($CH_2$), 46.1 (CH), 65.4 (CH), 66.6 (CH), 75.3 (CH), 77.9 (CH), 80.1 (C), 131.1 (C), 148.1 (CH), 149.9 (C), 151.8 (CH), 152.4 (C). ESIMS, *m*/*z*: 313 ($MH^+$, for $Cl^{35}$), 315 ($MH^+$, for $Cl^{37}$), 335 ($MNa^+$, for $Cl^{35}$), 337 ($MNa^+$, for $Cl^{37}$). Anal. Calcd for $C_{12}H_{13}ClN_4O_4$: C, 46.09; H, 4.19; N, 17.92. Found: C, 45.88; H, 4.18; N, 17.75.

**(1*R*,2*S*,3*R*,4*S*,5*R*,7*R*)-3-(6-Aminopurin-9-yl)-bicyclo[2.2.1]heptane-1,2,5,7-tetraol (39).** Chloropurine **38** (40 mg, 0.128 mmol) was converted to **39** (31 mg, 83%) as foam (hygroscopic) through amination as described earlier for the preparation of **31**.

**39.** $[\alpha]^{26}_D$ −11.2 (*c* 0.56, MeOH). IR (KBr): $\nu_{max}$ 3386 (br), 3159 (br), 1660, 1402 cm$^{-1}$. $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 1.44 (dd, 1H, $J$ = 3.8, 13.5 Hz), 2.22 (dd, 1H, $J$ = 10.8, 13.5 Hz), 2.79 (m, 1H), 3.93 (s, 1H), 4.22 (m, 1H), 4.61 (1H, merged with HOD), 5.21 (t, 1H, $J$ = 3.9 Hz), 8.22 (s, 1H), 8.40 (s, 1H). $^{13}$C NMR ($D_2O$, 75 MHz): 39.9 ($CH_2$), 46.4 (CH), 65.1 (CH), 66.7 (CH), 75.5 (CH), 78.0 (CH), 80.1 (C), 118.7 (C), 144.0 (CH), 148.8 (CH), 149.8 (C), 153.1 (C). ESIMS, *m*/*z*: 294 $(MH)^+$. Anal. Calcd for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 49.02; H, 5.08; N, 23.60.

**(1*S*,4*S*,7*R*,8*S*,9*R*,10*S*)-6-Benzyl-2,5-dioxa-6-aza-tricyclo[5.2.1.0$^{4,8}$]-decane-9,10-diol (42).** Compound **40**[29] (500 mg, 2.53 mmol) was treated with 4% $H_2SO_4$ in $CH_3CN-H_2O$ (3:1) (25 mL) following the method described earlier for **35**. Usual workup followed by reaction of the generated hemi-acetal with *N*-benzyl hydroxylamine (340 mg, 2.76 mmol) in dry EtOH (30 mL) furnished **42** (405 mg, 61%) as a white crystalline solid material after purification by column chromatography using EtOAc−petroleum ether (3:22) as the eluent.

**42.** mp 166−167 °C. $[\alpha]^{28}_D$ +39.5 (*c* 2.3, $CHCl_3$). IR (neat): $\nu_{max}$ 3351 (br), 1343, 1119, 1082, 1056, 728 cm$^{-1}$. $^1$H NMR ($CDCl_3$ + $D_2O$, 300 MHz): $\delta$ 3.47 (m, 1H), 3.55 (s, 2H), 3.78 (d, 1H, $J$ = 13.0 Hz), 3.83 (d, 1H, $J$ = 6.0 Hz), 3.94 (t-like, 2H, $J$ = 6.3 Hz), 4.06 (s, 1H), 4.56 (partially merged d, 1H, $J$ = 10.0 Hz), 4.59 (s, 1H), 7.34 (m, 5H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 51.0 (CH), 62.4 ($CH_2$), 62.7 ($CH_2$), 71.5 (CH), 77.8 (CH), 77.9 (CH), 82.2 (CH), 84.2 (CH), 127.9 (CH), 128.9 (2 × CH), 130.0 (2 × CH), 138.7 (C). ESIMS, *m*/*z*: 264 ($MH^+$). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.63; H, 6.47; N, 5.08.

**(1*S*,4*S*,5*S*,6*R*,7*S*,8*R*)-6-(5-Amino-6-chloro-pyrimidin-4-ylamino)-2-oxa-bicyclo[3.2.1]octane-4,7,8-triol (43).** Compound **42** (200 mg, 0.76 mmol) in dry ethanol (20 mL) was hydrogenolyzed using Pd/C (10%, 40 mg) and cyclohexene (2 mL) by refluxing under $N_2$ for 5 h. Usual workup furnished the corresponding trihydroxy amine, which was dried ($P_2O_5$) for further reaction. This amine (114 mg, 0.65 mmol) in dry *n*-BuOH was coupled with 5-amino-4,6-dichloropyrimidine (160 mg, 0.975 mmol) in the presence of $Et_3N$ (2 mL) following the procedure described earlier for **37** to afford **43** (80 mg, 41%) as a foam.

**43.** mp 225−226 °C (dec). $[\alpha]^{28}_D$ −3.3 (*c* 1.35, $D_2O$). IR (KBr): $\nu_{max}$ 3443, 3388, 3312, 1640, 1585, 1503, 1423, 1325, 1037, 781 cm$^{-1}$. $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 2.89 (m, 1H), 3.27 (t, 1H, $J$ = 11.0 Hz), 3.81−3.88 (m, 2H), 3.93 (s, 1H), 4.02−4.11 (m, 2H), 4.43 (t, 1H, $J$ = 4.6 Hz), 7.89 (s, 1H). $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 48.8 (CH), 63.4 (CH), 64.6 ($CH_2$), 67.8 (CH), 74.9 (CH), 79.6 (CH), 81.2 (CH), 123.1 (C), 140.6 (C), 149.0 (CH), 155.2 (C). ESIMS, *m*/*z*: 325 ($MNa^+$, for $Cl^{35}$), 327 ($MNa^+$, for $Cl^{37}$). Anal. Calcd for $C_{11}H_{15}ClN_4O_4$: C, 43.64; H, 4.99; N, 18.51. Found: C, 43.60; H, 4.89; N, 18.26.

**(1*S*,4*S*,5*S*,6*R*,7*S*,8*R*)-6-(6-Chloropurin-9-yl)-2-oxa-bicyclo-[3.2.1]octane-4,7,8-triol (44).** Compound **43** (165 mg, 0.55 mmol) was dissolved in dry DMF (4 mL) and treated with $HC(OEt)_3$ (2 mL) and *p*-TSA·$H_2O$ (156 mg, 0.82 mmol) using the previously described procedure. Usual workup as well as purification of the crude residue furnished **44** (125 mg, 73%) as a foamy material.

**44.** mp 216−218 °C (dec). $[\alpha]^{26}_D$ −15.5 (*c* 0.86, MeOH). IR (KBr): $\nu_{max}$ 3333, 1592, 1342, 1224, 1041, 946, 820 cm$^{-1}$. $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 3.36−3.43 (m, 2H), 3.81 (dd, 1H, $J$ = 7.0, 12.0 Hz), 3.94−3.99 (m, 2H), 4.08 (s, 1H), 5.28 (t, 1H, $J$ = 5.3 Hz), 5.53 (dd, 1H, $J$ = 1.4, 5.0 Hz), 8.70 (s, 1H), 8.87 (s, 1H). $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 50.1 (CH), 64.1 ($CH_2$), 65.6 (CH), 66.8 (CH), 73.2 (CH), 74.4 (CH), 81.5 (CH), 131.4 (C), 146.9 (CH), 150.2 (C), 151.9 (CH), 153.1 (C). ESIMS, *m*/*z*: 336 ($MNa^+$, for

$Cl^{35}$), 338 ($MNa^+$, for $Cl^{37}$). Anal. Calcd for $C_{12}H_{13}ClN_4O_4$: C, 46.09; H, 4.19; N, 17.92. Found: C, 46.00; H, 4.02; N, 17.76.

**(1*S*,4*S*,5*S*,6*R*,7*S*,8*R*)-6-(6-Aminopurin-9-yl)-2-oxa-bicyclo[3.2.1]-octane-4,7,8-triol (45).** Compound **44** (20 mg, 0.064 mmol) was transformed into the foamy solid **45** (16 mg, 85%) by heating with a saturated solution of methanolic ammonia, adopting a procedure similar to that described earlier for the preparation of **28**.

**45.** mp 219−220 °C (dec). $[\alpha]^{26}_D$ −14.9 (*c* 0.33, MeOH). IR (KBr): $\nu_{max}$ 3393, 3336, 1656, 1609, 1483, 1415, 1316, 1259, 1032, 729, 643 $cm^{-1}$. $^1H$ NMR ($D_2O$, 300 MHz): $\delta$ 3.26 (brs, 1H), 3.36 (t, 1H, $J = 11.0$ Hz), 3.79 (dd, 1H, $J = 7.0$, 12.0 Hz), 3.90 (s, 1H), 3.92 (partially merged signal, 1H), 4.04 (s, 1H), 5.03 (t, 1H, $J =$ 5.4 Hz), 5.36 (d, 1H, $J = 3.9$ Hz, with fine splitting), 8.13 (s, 1H), 8.43 (s, 1H). $^{13}C$ NMR ($D_2O$, 75 MHz): $\delta$ 50.0 (CH), 64.2 ($CH_2$), 64.8 (CH), 66.9 (CH), 73.5 (CH), 74.6 (CH), 81.4 (CH), 119.2 (C), 141.3 (CH), 150.5 (C), 152.5 (CH), 155.6 (C). ESIMS, *m*/*z*: 316 $(MNa)^+$, 294 $(MH)^+$. Anal. Calcd for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 48.90; H, 5.02; N, 23.58.

**Acknowledgment.** A grant from the Department of Science and Technology (Govt. of India) supported this work. We gratefully acknowledge the Council of Scientific and Industrial Research for providing Senior Research Fellowships (to A.R. and B.G.R.) and an Emeritus Scientist scheme (to B.A.). We also thank EPSRC and the University of Reading for funds for the ImagePlate System.

**Supporting Information Available:** Crystallographic data (Table 1), cif files and ORTEP diagrams for **14**, **19**, **20**, and **42**, experimental details for X-ray crystallography, general experimental details, copies of $^1H$ and $^{13}C$ NMR spectra of **9**−**21**, **23**−**26**, **28**−**39**, **42**−**45**, and the $^1H$ NMR spectrum of **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0606554