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Conformationally Restricted Nucleocyclitols: a Study into their Conformational Preferences and Supramolecular Architecture in the Solid State

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With the intent of probing the feasibility of employing annulation as a tactic to engender axial rich conformations in nucleoside analogues, two adenine-derived, "conformationally restricted" nucleocylitols, **9** and **10**, have been conceptualized as representatives of a hitherto unexplored class of nucleic acid base-cyclitol hybrids. A general synthetic strategy, with an inherent scope for diversification, allowed rapid functionalization of indane and tetralin to furnish **9** and **10** respectively in fair yield. Single-crystal X-ray diffraction analysis revealed that the two nucleocyclitols under study, though homologous, present completely dissimilar modes of molecular packing, marked, in particular, by the nature of involvement of the adenynyl NH_2 group in the supramolecular assembly. In addition, the crystal structures of **9** and **10** also exhibit two different conformations of the functionalized cyclohexane ring. Thus, while the six-membered carbocycle in cyclopenta-annulated **9** exists in the expected chair (C) conformation that in cyclohexaannulated **10**, which crystallizes as a dihydrate, shows an unusual twist-boat (TB) conformation. From a close analysis of the ^{1}HNMR spectroscopic data recorded for **9** and **10** in CD_3OD, it was possible to put forth a putative explanation for the uncanny conformational preferences of crystalline **9** and **10**.

Introduction

In 2003, a flexible de novo synthetic strategy was delineated to transform stereoselectively the aromatic nucleus of hydrocarbons, such as tetralin and indane, into inositol moieties, transcribed onto a *trans*-decalin/*trans*-hydrindane framework.[1a] In these conformationally locked inositols, as they were named, annulation was used as a tool not only to freeze the cyclitols into a high-energy *axial-rich* conformation, but also to fine-tune the hydrophilic-hydrophobic balance in the otherwise polar inositols (see Figure 1 for a comparison between natural **1** and annulated *myo*-inositol **2**).[1a,2] The versatility of this manoeuvre was further demonstrated by us towards the synthesis of a new class of cyclohexane-annulated, conformationally locked hexoses from tetralin.[1b] Like their inositol siblings, these annulated sugars also retained the hydroxy configuration of their natural counterparts but were pre-destined to have an unnatural conformation with preponderance of axial OH groups (see Figure 2 for a comparison between natural **3** and annulated β-glucopyranose **4**).

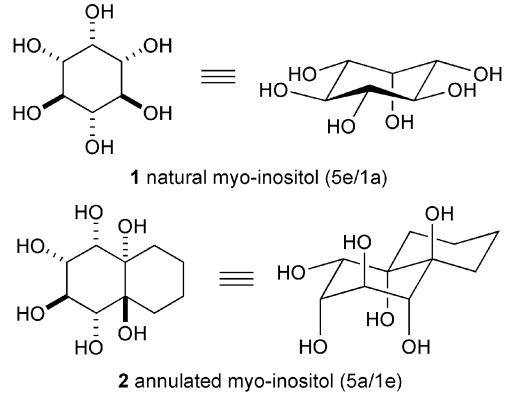

Figure 1. Conformationally locked, *axial-rich* annulated *myo*-inositol **2**.

The idea of employing the tactic of annulation as a novel method of engendering conformational restriction in nucleosides and their analogues[3] appealed to us as a natural extension to the foregoing studies. A major impetus for such an endeavor also came from the observation that among the various structurally modified nucleosides which have been developed in recent years, those involving conformationally constrained analogues have offered promising therapeutic leads. These include the bridged nucleic acids **5** (LNA/BNA),[4] hexitol nucleic acids (HNA) **6**,[5] tricyclo-DNA (tc-DNA) **7**[6] and very recently, [4.3.0]bicyclo-DNA

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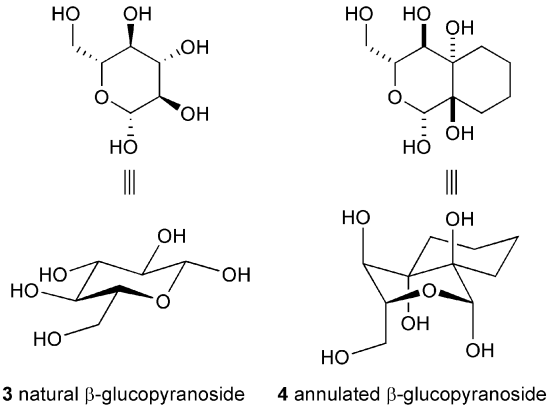


Figure 2. Conformationally locked, *axial-rich* annulated β-glucopyranose **4**.

(bc^{4,3}-DNA) **8**,[7] which incorporates interestingly a six-membered ring, fused in a *cis*-fashion to the furanose unit (Figure 3).

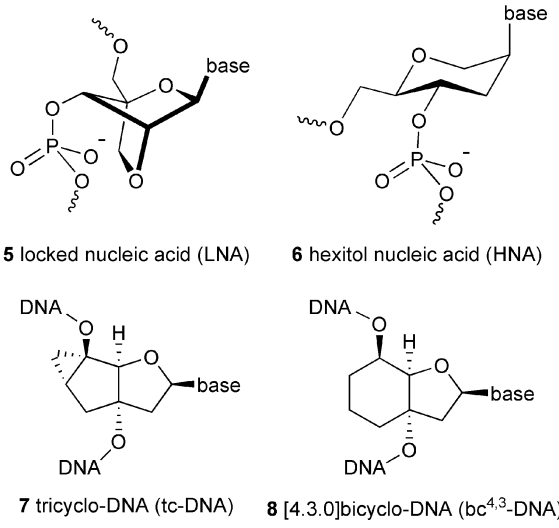


Figure 3. Examples of conformationally restricted analogues of nucleic acids.

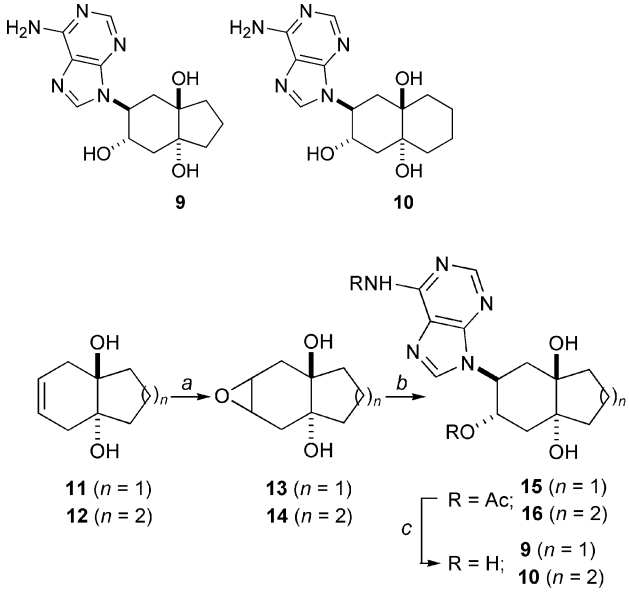
In effect, the present study was conceptualized as a prelude to the actual construction of an "annulated nucleoside" architecture and focused on examining the feasibility of engaging annulation as a tool to generate "axial rich" conformations in a simpler, yet interesting class of nucleoside analogues termed nucleocyclitols.[8]

Interest in the synthesis of nucleocyclitols, a term coined by Cadenas for hydrid molecules obtained by condensing cyclitols with purine or pyrimidine bases, largely stemmed as an offshoot from the efforts towards the development of novel nucleoside analogues as potential antitumor, antiviral or antibiotic agents. Devoid of an endocyclic oxygen and thus the "oside" structure, nucleocyclitols present a base-cyclitol C–N bond which, unlike that present in nucleosides, is stable towards both chemical and enzymatic hydrolysis, a property perceived as a definite vantage point for in vivo testing.[8a] However, literature reports on the bioactivity profile of nucleocyclitols are rather sparse, barring a study by Carceller and Cadenas, which revealed that 3-(adenin-9-yl)-3-deoxy-1,5,6-tri-*O*-(methylsulfonyl)-*muco*-inositol exhibited cytokinin-like activity in promoting cell proliferation in soybean cotyledon callus tissue, cell expansion in excised radish cotyledons, and delay of senescence in detached leaves.[8b] Though dwarfed in comparison to other nucleoside analogues in respect to the body of literature dealing with their chemistry and interaction with biological systems, nucleocyclitols presented themselves to us as ideal starter systems for studying the effect of annulation on the conformation and self-assembling process of nucleic acid base-cyclitol hybrids. Tweaking with our earlier synthetic strategies towards polycyclitols and amino alcohols,[9] we therefore sought a general scheme that would allow rapid functionalization of the aromatic nucleus of indane and tetralin to lend acess to the first two chosen examples of conformationally restricted nucleocyclitols, **9** and **10**.

Results and Discussion

Synthesis of the Nucleocyclitols 9 and 10

Synthesis of the nucleocyclitols **9** and **10** was accomplished from the annulated *trans*-4-cyclohexene-1,2-diols, **11** and **12**, which were readily obtained from indane and tetralin respectively.[1a] *m*CPBA mediated epoxidation in **11** and **12**, followed by $LiClO_4$ catalyzed ring opening in the epoxy diols **13** and **14**[9a] with sodium adeninide, furnished the desired nucleocyclitols **9** and **10** in fair yield, which were conveniently purified via their corresponding acetates **15** and **16** (Scheme 1). The nucleocyclitols **9** and **10** as well as all their precursors were duly characterized spectroscopically prior to detailed single-crystal X-ray diffraction analysis.



Scheme 1. Reagents and conditions. (a) *m*CPBA, CH_2Cl_2, 0 °C to room temp.; (b) i) adenine, NaH, $LiClO_4$, dry DMF, 100 °C; (ii) Ac_2O, DMAP, room temp.; (c) 10% NH_3 (aq.), room temp.

X-ray Crystallographic Studies on the Nucleocyclitols 9 and 10

On account of their polar nature and tendency to form at times tenaciously gummy materials upon evaporation of their solution, a judicious choice of the solvent proved crucial for obtaining crystals of **9** and **10**, suitable for single-crystal X-ray crystallography. Accordingly, crystallization of the nucleocyclitols **9** and **10** were carried out under ambient conditions from their dilute solutions in 1:1 MeOH/EtOAc and 2:1 MeOH/H_2O respectively, employing the slow solvent evaporation method. Unlike **9**, the nucleocyclitol **10** crystallized, under these conditions, as a hydrate (vide infra) and displayed a profound tendency to undergo dehydration, upon exposure to air, even at low temperatures. This necessitated an expeditious data collection strategy for **10** in order to obtain a decent X-ray diffraction data, amenable to structure solution and providing the desired convergence upon refinement. Details of the molecular conformations and packing patterns of the nucleocyclitols **9** and **10**, as gleaned from analysis of their respective crystal data (see Table 3), are discussed below.

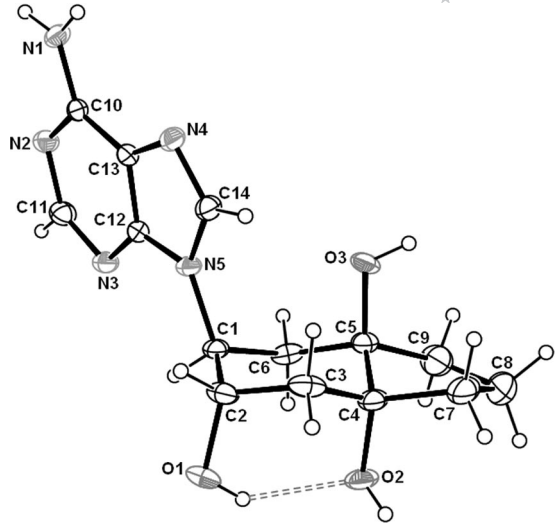


Figure 4. ORTEP diagram of the nucleocyclitol **9**, with the atom numbering scheme for the asymmetric unit. Displacement ellipsoids have been drawn at 30% probability level and H atoms are shown as small spheres of arbitary radii. The grey dotted lines indicate the intramolecular O–H···O hydrogen bonds.

Crystal Structure of (3aR,5S*,6S*,7aR*)-6-(6-Amino-9H-9-purinyl)perhydro-3a,5,7a-indenetriol (9)*

Though the synthetic route, adopted in the study, yields **9** in the racemic form, spontaneous resolution during crystallization causes the nucleocyclitol to pack in the chiral orthorhombic space group $P2_12_12_1$ ($Z = 4$).[10,11] Since it is well known that 90% of the compounds, that are capable of crystallizing in racemic or chiral space groups, prefer the former,[12] the preference of **9** to crystallize as a conglomerate of its two enantiomeric forms is interesting and probably the consequence of a kinetically favoured pathway. Embedded in the rigid *trans*-hydrindane scaffold, the nucleocyclitol moiety in **9** exhibits the expected high energy, all-axial conformation of the adenynyl and three hydroxy groups (Figure 4). Owing to the resulting non-bonding 1,3-diaxial interactions, particularly between the purine nucleus at C1 and the OH group at C5, the cyclohexane ring in **9** distorts significantly from an ideal chair conformation. This distortion is evident not only from an analysis of the puckering parameters[13] of the cyclohexane ring [q_2 = 0.1315(28) Å, q_3 = 0.5019(29) Å, ϕ_2 = –160.4(14)°, Q_T = 0.5188(29) Å, θ_2 = 14.68(32)°], but also from the apparent flattening of the C1–C6–C5 bond angle (ca. 113°) from the ideal tetrahedral value. On the other hand, puckering parameters of the cyclopentane annulus in **9** are q_2 = 0.4417(31) Å, ϕ_2 = 32.88(50)° and therefore describe a slightly distorted C_s-symmetric envelope (E) conformation.[13]

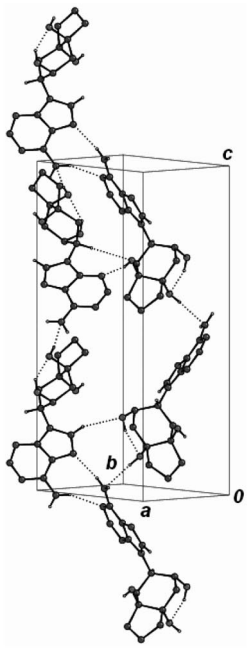
Besides tipping the cyclohexane ring from an ideal chair to a near twist-boat conformation, the all-axial disposition of the functional groups in **9** also favorably positions the 1,3-syndiaxial hydroxy groups at C2 and C4 to participate in intramolecular O–H···O hydrogen bonding (Figure 4, Table 1). Following the 2_1 symmetry parallel to the *c* axis, intermolecular O–H···N H-bonding, involving O2···N1, link the molecules to form zigzag strands along [001] direction. These molecular strands are interconnected, following the 2_1 symmetry parallel to the *a* and *b* axes, by N–H···N hydrogen bonds, involving N1···N4 and N1···N2, and O–H···N H-bonds, involving O3···N3, respectively. The intricate three-dimensional supramolecular assembly of **9**, thus generated, is further supported by C–H···O hydrogen bonding, involving C1···O3 and C14···O1 (Figure 5, Table 1).

Table 1. Hydrogen bond geometry in the nucleocyclitol **9**.

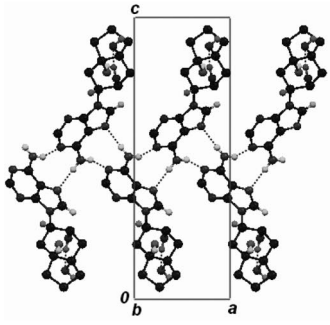
D–H···A	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O1–H1O···O2 [i]	0.82	2.06	2.731(3)	140
O2–H2O···N1 [ii]	0.82	2.25	2.953(3)	144
O3–H3O···N3 [iii]	0.82	2.10	2.897(3)	165
N1–H1N···N4 [iv]	0.86	2.10	2.922(3)	158
N1–H2N···N2 [v]	0.86	2.20	2.992(4)	153
C1–H1···O3 [vi]	0.98	2.60	3.561(4)	168
C14–H14···O1 [vii]	0.93	2.56	3.436(4)	158

Symmetry codes: (i) *x*, *y*, *z*; (ii) –*x* + 1/2, –*y* + 1, *z* – 1/2; (iii) –*x*, *y* – 1/2, –*z* + 1/2; (iv) *x* – 1/2, –*y* + 1/2, –*z* + 1; (v) *x* + 1/2, –*y* + 1/2, –*z* + 1; (vi) –*x*, *y* + 1/2, –*z* + 1/2; (vii) –*x* + 1, *y* – 1/2, –*z* + 1/2

A novel feature of the self-assembly in crystalline **9** is that the amino group of the adenynyl moiety engages not only its H-atoms in intermolecular N–H···N hydrogen bonding with an $R^2_2(9)$ motif, but also its lone pair in an O–H···N H-bond (Figure 5). Indeed, the crystal structure of the nucleocyclitol **9** presents the first instance of molecular packing in an adenine derivative in which such a H-bonding pattern, involving the amino group, has been observed.[14]



(a)



(b)

Figure 5. (a) Molecular packing in the nucleocyclitol **9**, showing details of the intra- and inter-strand hydrogen bond connectivity. (b) Molecular packing in the nucleocycltol **9** along the *a* axis, showing details of the N–H···N hydrogen bonding with an $R^2_2(9)$ motif. Non-interacting H-atoms have been omitted for clarity.

Crystal Structure of (2S,3S*,4aR*,8aR*)-3-(6-Amino-9H-9-purinyl)perhydro-2,4a,8a-naphthalenetriol (10)*

The adenine-derived nucleocyclitol **10** crystallized as a dihydrate in the centrosymmetric triclinic space group $P\bar{1}$ ($Z = 2$). Unlike that observed for its sibling **9**, the functionalized cyclohexane ring in **10** was found to adopt a twist-boat conformation [$q_2 = 0.7281(41)$ Å, $q_3 = 0.0063(45)$ Å, $\phi_2 = 35.51(34)°$, $Q_T = 0.7282(41)$ Å, $\theta_2 = 89.51(35)°$][13] with the effect that the adenynyl and secondary OH groups now occupied the sterically less encumbered equatorial positions on the six-membered carbocycle (Figure 6). Barring a slight distortion, the cyclohexane annulus, on the other hand, retained the expected chair conformation ($q_2 = 0.0502(56)$ Å, $q_3 = 0.5292(50)$ Å, $\phi_2 = 147(6)°$, $Q_T = 0.5316(51)$ Å, $\theta_2 = 5.42(59)°$].[13]

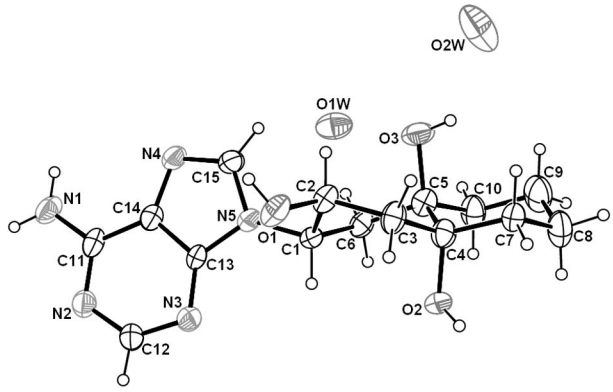
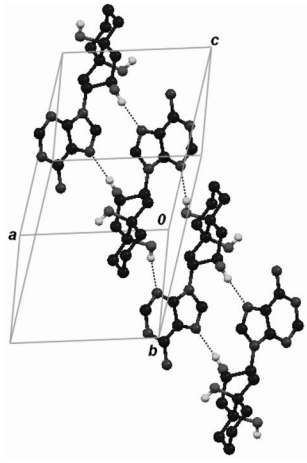
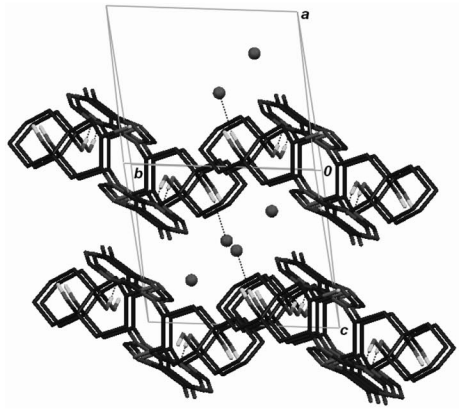


Figure 6. ORTEP diagram of the nucleocyclitol **10**, with the atom numbering scheme for the asymmetric unit. Displacement ellipsoids have been drawn at 30% probability level and H atoms are shown as small spheres of arbitary radii.

A pair of intermolecular O–H···N hydrogen bonds, involving O1 and N4, connect two enantiomerically related molecules of **10** to form a centrosymmetric dimer [graph set: $R^2_2(14)$] around the inversion center at (1/2, 0, 1/2). Weak offset π-π stacking interactions between the two pu-



(a)



(b)

Figure 7. Details of the O–H···N hydrogen bonds (a), generating the columnar self-assembly (b) in the nucleocyclitol **10**. Non-interacting H-atoms have been omitted for clarity.

rine rings of the molecular dimer, thus formed, impart further stability to the self-assembly. Intermolecular O–H···N hydrogen bonds, involving O2 and N3, connect the translationally related dimers around the inversion centers at (0, 0, 0) to form a columnar self-assembly, growing essentially parallel to the (1 –1 –1) plane (see part a of Figure 7, Table 2). Characterized by a polar interior, defined by the purine and OH groups, and a non-polar exterior, formed by the cyclohexane annuli disposed parallel to each other, these columnar architectures interact among themselves with weak van der Waals forces along the b axis and via the agency of H-bonding with the sandwiched water molecules along the [1 0 –1] direction (see part b of Figure 7, Table 2).

Table 2. Hydrogen bond geometry in the nucleocyclitol **10**.

D–H···A	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O1–H1O···N4 [i]	0.82	2.06	2.829(7)	155
O2–H2O···N3 [ii]	0.82	2.18	2.950(7)	157
O3–H3O···O2W [iii]	0.82	2.29	2.923(10)	134

Symmetry codes: (i) x, $y-1$, z; (ii) $-x$, $-y$, $-z$; (iii) x, y, z

It is well known that in crystal structures of adenine, its hydrates and salts, the hydrogen atoms of the amino group of adenine participate actively in H-bonding in the supramolecular assembly.[14] However, in distinct contrast to this literature precedence, the H-atoms of the amino group in the adenynyl moiety in **10** remain largely as bystanders and engage themselves in, at best, extremely weak hydrogen bonding. This unusual abstinence of the amino hydrogens in **10** to hydrogen bonding should also be compared to the maximization of hydrogen bonding observed for the amino group in the crystal structure of its lower homologue **9** (vide supra). This maverick behaviour of the amino hydrogen atoms in **10** might be caused by the inability of the NH_2 group, buried within the polar interior of the columnar architecture, to find a suitable H-bonding partner.[9b]

Can Solvation Influence the Preferred Conformation of the Conformationally Restricted Nucleocyclitols 9 and 10?

Our previous studies with polycyclitols and the dogma of a conformationally "locked" *trans*-hydrindane/decalin framework made it reasonable to anticipate that a chair form, *albeit* distorted, would be the most stable conformation of the functionalized cyclohexane ring in the nucleocyclitols **9** and **10**. DFT-based geometry optimization at B3LYP/6-31+G(d) level, carried out on both chair (C) and twist-boat (TB) conformations of the nucleocyclitol moieties in **9** and **10**, revealed that the C form was evidently more stable than the TB form by around 3.2 kcal mol^{-1} in case of **9** and 1.6 kcal mol^{-1} in case of **10**.[15] Hence, the observed TB conformation of the cyclohexane ring in the crystal structure of hydrated **10**, as opposed to the *C* form noted for its lower homologue **9**, was intriguing and goaded speculation on plausible causes for its stability. Though putative, it would appear that solvation might play a determinant role in tilting the balance towards an otherwise energetically less favourable TB conformation of the functionalized cyclohexane ring in **9** and **10**. This conjecture derives support not only from earlier reports on the effect of the solvation on the conformation preferences of cyclohexanes,[16] but also from a close analysis of the coupling pattern observed for the ^{1}H NMR signals (spectrum taken in CD_3OD) of the protons attached to the carbon atoms, bonded to the adenynyl and 2° hydroxy groups in **9** and **10**. These protons were found to exhibit a near identity in their coupling patterns, and that connected to the carbon atom bonded to the purine nucleus showed a dd splitting with the larger coupling equating to 10 Hz, typical for that observed between two axial protons on a TB conformation of cyclohexane.[16]

Conclusions

In conclusion, the present study ushers two "conformationally restricted" adenine-derived nucleocyclitols, **9** and **10**, as representatives of a hitherto unexplored class of nucleoside analogues through a synthetic strategy which is amenable to diversification and may enable access to other members of this novel family of nucleocyclitols.

Experimental Section

General: Melting points were recorded with a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded with a JASCO FT-IR 410 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER 400 and JEOL JNM-LA 300 spectrometers; chemical shifts δ in ppm are reported relative to Me_4Si (δ = 0 ppm) by using solvent signals as internal reference [$CDCl_3$: δ = 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR). CD_3OD: δ = 3.31 ppm (^{1}H NMR) and 49.2 ppm (^{13}C NMR); D_2O: δ = 4.81 ppm (^{1}H NMR)].

The standard abbreviations s, d, t, q, dd and m refer to singlet, doublet, triplet, quartet, doublet of doublet and multiplet, respectively. Coupling constant (*J*), wherever discernible, are reported in Hz. Both low-resolution (LRMS) and high-resolution mass spectra (HRMS) were recorded with a Q-TOF Micromass mass spectrometer. Reactions were monitored by thin-layer chromatography (TLC) performed either on (10 × 5 cm) glass plates, coated with silica gel GF_{254}, containing 15% calcium sulfate as a binder. Visualization of the spots on the TLC plates was achieved by exposure to iodine vapor or UV radiation, or by spraying with either ethanolic vanillin or 30% sulfuric acid-methanol solution and heating the plates at 120 °C. Commercial silica gel (100–200 mesh particle size) was used for column chromatography. All moisture-sensitive reactions were performed under nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions using standard syringe-septum technique. Dimethylformamide was distilled from calcium hydride and stored over molecular sieves (4 Å). All solvent extracts were concentrated under reduced pressure on a rotary evaporator unless specified otherwise. Yields reported are isolated yields of materials judged homogeneous by TLC and NMR spectroscopy.

(1a*S,2a*R**,5a*R**,6a*R**)-Octahydro-1a*H*-indeno[5,6-*b*]oxirene-2a,5a-diol (13):** A solution of *m*CPBA (384 mg, 1.56 mmol, 70% purity) in dichloromethane (10 mL) was added dropwise to a solution of the diol **11** (200 mg, 1.30 mmol) in dichloromethane (20 mL) at 0 °C. The reaction was stirred at ambient temperature

for 1 h and then quenched with saturated sodium hydrogen carbonate solution (10 mL). The product was extracted with dichloromethane (2 × 10 mL) and the combined extracts dried with anhydrous sodium sulfate. Removal of the solvent and subsequent purification by column chromatography with 40% ethyl acetate/petroleum ether afforded the epoxy diol **13** (260 mg, 72%) as a colorless solid; m.p. 112–114 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3406, 3376, 2969, 2943, 1647, 1416 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.46 (br. s, 2 H), 3.34 (t, J = 4.0 Hz, 1 H), 1.55–2.38 (m, 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 80.3, 79.6, 55.9, 51.9, 36.1, 34.6, 33.5, 30.0, 19.2 ppm. LRMS (ES, 70 eV): m/z = 193 [M + Na]$^+$. HRMS (ES): calcd. for $C_9H_{14}O_3Na$ [M + Na]$^+$ 193.0841; found 193.0840.

(3a*R,5*S**,6*S**,7a*R**)-6-(6-Acetamido-9*H*-purin-9-yl)-3a,7a-dihydroxy-octahydro-1*H*-inden-5-yl Acetate (15):** A mixture of the epoxy diol **13** (40 mg, 0.24 mmol) and lithium perchlorate (80 mg, 1.25 mmol) in dry dimethylformamide (1 mL) was heated at 80 °C under nitrogen for 2 h. The solution was then allowed to attain room temperature and subsequently added to a suspension of sodium adeninide in dimethylformamide [generated by heating a mixture of adenine (96 mg, 0.72 mmol) and sodium hydride (17 mg, 0.69 mmol, 95% in hexane) in dimethylformamide (2 mL) at 80 °C under nitrogen for 2 h]. The reaction mixture, thus obtained, was stirred vigorously at 100 °C under nitrogen for 15 h. The solvent was then evaporated under vacuum; 4-(dimethylamino)pyridine (80 mg, 0.65 mmol) and acetic anhydride (3.5 mL) were added to the crude reaction mixture and the suspension stirred at room temperature under nitrogen for 4 d. After completion of the reaction, the reaction mixture was evaporated to dryness and the residue purified by column chromatography with 10% methanol/dichloromethane to give 43 mg (48%) of the pure diacetate **15** as colorless solid. IR (KBr): $\tilde{\nu}_{max}$ = 3472, 2926, 2855, 1722, 1616 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 8.62 (s, 1 H), 8.41 (s, 1 H), 6.03–5.94 (m, 1 H), 5.52–5.42 (m, 1 H), 2.69 (dd, J = 14.4, 9.6 Hz, 1 H), 2.64 (dd, J = 14.4, 9.0 Hz, 1 H), 2.36 (s, 3 H), 2.29 (t, J = 7.0 Hz, 2 H), 1.97–1.71 (m, 6 H), 1.64 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 172.0, 171.7, 153.5, 152.8, 150.4, 145.0, 123.8, 83.0, 82.6, 73.0, 54.9, 39.4, 38.5, 37.9, 37.6, 24.6, 21.7, 20.5 ppm. LRMS (ES, 70 eV): m/z = 426 [M + H + Na – Ac]$^+$. HRMS (ES): calcd. for $C_{16}H_{21}N_5NaO_4$ [M + H + Na – Ac]$^+$ 370.1491; found 370.1509.

(2*S,3*S**,4a*R**,8a*R**)-3-(6-Acetamido-9*H*-purin-9-yl)-4a,8a-dihydroxy-decahydronaphthalen-2-yl Acetate (16):** $LiClO_4$-catalyzed ring opening in the epoxy diol **14** with sodium adeninide was carried out under essentially the same conditions as described for **13**. Thus, a solution of **14** (50 mg, 0.27 mmol) and lithium perchlorate (84 mg, 1.35 mmol) in dry dimethylformamide (1 mL), previously heated at 80 °C under nitrogen for 2 h, was to a supension of sodium adeninide in dry dimethylformamide [generated by heating a mixture of adenine (110 mg, 0.81 mmol) and sodium hydride (18 mg, 0.87 mmol, 95% in hexane) in dimethylformamide (2 mL) at 80 °C under nitrogen for 2 h]. After stirring the reaction mixture for 15 h at 100 °C under nitrogen, the solvent was removed under vacuum and the residue allowed react with acetic anhydride (3.5 mL) in presence of 4-(dimethylamino)pyridine (80 mg, 0.65 mmol) for four days at ambient temperature. After completion of the reaction, the reaction mixture was evaporated to dryness and the residue purified by column chromatography with 10% methanol/dichloromethane to give 63 mg (58%) of the pure diacetate **16**. IR (KBr): $\tilde{\nu}_{max}$ = 3438, 2929, 2858, 1736, 1610, 1238 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 8.60 (s, 1 H), 8.41 (s, 1 H), 5.91–5.83 (m, 1 H), 5.39–5.29 (m, 1 H), 2.54–2.39 (m, 2 H), 2.35 (s, 3 H), 2.08 (dd, J = 14.7, 7.8 Hz, 1 H), 1.67 (s, 3 H) 1.60–1.43 (m, 9 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 172.0, 171.6, 153.5, 152.8, 150.4, 145.0, 123.8, 73.4, 73.1, 72.1, 54.5, 42.4, 41.5, 36.0, 35.7, 24.6, 21.6 (2 C), 20.6 ppm. LRMS (ES, 70 eV): m/z = 426 [M + Na]$^+$. HRMS (ES): calcd. for $C_{19}H_{25}N_5NaO_5$ [M + Na]$^+$ 426.1753; found 426.1746.

(3a*R,5*S**,6*S**,7a*R**)-6-(6-Amino-9*H*-9-purinyl)perhydro-3a,5,7a-indenetriol (9):** The diacetate **15** (13 mg, 0.03 mmol) was stirred at ambient temperature with aqueous ammonia solution (2 mL, 10% v/v in H_2O) for 2 h. After completion of the reaction, the volatiles were removed under vacuum and the crude product, thus obtained, was purified by column chromatography with 20% methanol/dichloromethane to furnish the nucleocyclitol **9** (11 mg, quantitative) as a colorless solid. IR (KBr): $\tilde{\nu}_{max}$ = 3423, 2930, 1647, 1607 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 8.23 (s, 1 H), 8.20 (s, 1 H), 5.03–4.97 (m, 1 H), 4.62 (dd, J = 10.0, 5.6 Hz, 1 H), 2.62 (dd, J = 14.8, 7.7 Hz, 1 H), 2.55 (dd, J = 14.4, 5.9 Hz, 1 H), 2.16 (dd, J = 14.9, 4.3 Hz, 1 H), 2.01–1.56 (m, 7 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 157.3, 153.4, 151.0, 142.7, 119.9, 83.0, 81.7, 70.5, 57.5, 38.4, 37.2, 37.1, 35.6, 20.7 ppm. LRMS (ES, 70 eV): m/z = 306 [M + H]$^+$. HRMS (ES): calcd. for $C_{14}H_{20}N_5O_3$ [M + H]$^+$ 306.1566; found 306.1566.

(2*S,3*S**,4a*R**,8a*R**)-3-(6-Amino-9*H*-9-purinyl)perhydro-2,4a,8a-naphthalenetriol (10):** Treating **16** (63 mg, 0.16 mmol) with aqueous ammonia solution (5 mL, 10% v/v in H_2O) under the same conditions as **15** gave a residue upon evaporation of the volatiles, which was purified by column chromatography with 20% methanol/dichloromethane to furnish the nucleocyclitol **10** (50 mg, quantitative) as a colorless solid. IR (KBr): $\tilde{\nu}_{max}$ = 3493, 3452, 3364, 3219, 2924, 2854, 1641, 1384 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 8.31 (s, 1 H), 8.20 (s, 1 H), 4.97–4.91 (m, 1 H), 4.52 (dd, J = 9.7, 4.9 Hz, 1 H), 2.51 (dd, J = 15.1, 7.4 Hz, 1 H), 2.42 (dd, J = 14.7, 5.3 Hz, 1 H), 1.91–1.61 (m, 6 H), 1.51–1.27 (m, 4 H) ppm. ^{13}C NMR (75 MHz, D_2O, 25 °C): δ = 156.0, 152.8, 149.7, 142.0, 118.9, 73.9, 73.2, 68.6, 56.1, 41.0, 38.1, 34.5, 34.4, 20.4 (2 C) ppm. LRMS (ES, 70 eV): m/z = 320 [M + H]$^+$. HRMS (ES): calcd. for $C_{15}H_{22}N_5O_3$ [M + H]$^+$ 320.1722; found 320.1720.

Crystal Structure Analysis: Single-crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K. The X-ray generator was operated at 50 kV and 35 mA using Mo-K_α radiation. The data was collected with a ω scan width of 0.3°. A total of 606 frames per set were collected using SMART[17] in four different settings of ϕ (0°, 90°, 180° and 270°) keeping the sample to detector distance of 6.062 cm and the 2θ value fixed at –28°. The data were reduced by SAINTPLUS;[17] an empirical absorption correction was applied using the package SADABS[18] and XPREP[17] was used to determine the space group. The crystal structures were solved by direct methods using SIR92[19] and refined by full-matrix least-squares methods using SHELXL97.[20] Molecular and packing diagrams were generated using ORTEP32,[21] CAMERON[22] and MERCURY[23] respectively. The geometric calculations were done by PARST[24] and PLATON.[25] The methine (CH) and methylene (CH_2) H atoms of the polycyclitol moiety were placed in geometrically idealized positions and allowed to ride on their parent atoms with C–H distances in the range 0.97–0.98 Å and U_{iso}(H) = 1.2U_{eq}(C). The OH hydrogen atoms were constrained to an ideal geometry with O–H distances fixed at 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O). During refinement, each hydroxy group was however allowed to rotate freely about its C–O bond. For the adenynyl group, the CH and NH_2 hydrogen atoms were constrained to an ideal geometry with C–H bond lengths fixed at 0.93 Å and U_{iso}(H) = 1.2U_{eq}(C), and N–H bond lengths fixed at 0.86 Å and U_{iso}(H) = 1.2U_{eq}(N) (Table 3).

Table 3. Summary of crystal data, data collection, structure solution and refinement details.

	9	**10**
Formula	$C_{14}H_{19}N_5O_3$	$C_{15}H_{21}N_5O_5$
M_r	305.34	351.37
Crystal size [mm]	0.43, 0.29, 0.10	0.30, 0.28, 0.26
Crystal system	orthorhombic	triclinic
Space group	$P2_12_12_1$	$P\bar{1}$
a [Å]	6.8969(15)	8.6370(13)
b [Å]	10.135(2)	10.2022(15)
c [Å]	20.311(4)	11.0208(17)
α [°]	90	113.999(7)
β [°]	90	106.939(7)
γ [°]	90	92.863(7)
V [Å^3]	1419.7(5)	832.8(2)
Z	4	2
F (000)	648	372
$\rho_{calcd.}$ [g cm^{-3}]	1.429	1.401
μ [mm^{-1}]	0.104	0.107
Reflections collected	10420	10462
l.s. parameters	201	229
Unique reflections	1528	3035
Observed reflections	1354	1376
Index range	$-8 \le h \le 8$	$-10 \le h \le 10$
	$-12 \le k \le 12$	$-12 \le k \le 12$
	$-24 \le l \le 22$	$-13 \le l \le 13$
R_1 [$I > 2\sigma(I)$]	0.0430	0.0723
wR_2 [$I > 2\sigma(I)$]	0.0981	0.1658
Goodness of fit	1.119	0.883
$\Delta\rho_{max./min.}$ [e Å^{-3}]	0.199/–0.183	0.334/–0.253

CCDC-734567 (for **9**) and -734568 (for **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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