Stereocontrolled Synthesis of Heterocyclic C-Nucleosides. Protecting Group Effect and Molecular Modeling Studies

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We report herein a short stereocontrolled synthesis of heterocyclic C-nucleosides (indole, imidazole, benzimidazole, and 6-iodobenzimidazole). First, condensation of 2-lithiated heterocycles **2**−**5** with 5-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-γ-ribonolactone (**1**) afforded the hemiacetals **6**−**9** in good yields. Then, borohydride reduction ($NaBH_4$) of the protected hemiacetals proceeded stereoselectively to give predominantly the *S* diols **10**−**13**, which upon Mitsunobu cyclization afforded the α-C-nucleosides **14**−**17**. In contrast, the same PPh_3/DEAD treatment of the 1:1 diastereomeric mixture of the free heterocyclic diols **10d** and **11d** gave exclusively the β-anomers **14d*β*** and **15d*β***, respectively, by a stereocontrolled process. The mechanisms of these stereocontrolled steps are discussed with the support of molecular modeling studies.

Introduction

For many years, natural C-nucleosides and their synthetic analogues have attracted wide interest in view of the importance of their biological activities.[1] Recently, a renewed interest in these compounds arose as a consequence of their potential applications in nucleic acid chemistry.[2] In view of our current research which proposes to incorporate extended heterocyclic C-nucleosides in triple-helix forming oligonucleotides, we needed to design an efficient diastereoselective general procedure toward the synthesis of highly functionalized imidazole, benzimidazole and indole C-nucleosides. A large number of synthetic approaches to a variety of C-nucleosides have been reported,[1] with several C-nucleosides being synthesized by addition of an organometallic reagent to a ribonolactone derivative followed by Lewis acid induced hemiacetal deoxygenation.[3] In many cases the deoxygenation step was met with difficulties, leading to poor yield and/or diastereoselectivity.[4] Although most biologically active C-nucleosides possess the β configuration, there is growing interest in those of the α configuration, which show promising biological activity.[5] Therefore, a stereoselective synthetic methodology providing one or the other anomer would be of a great interest.

We describe herein a short stereoselective synthesis of either α or β heterocyclic C-nucleosides, by (i) condensation of 2-lithiated heterocycles **2**−**5** (indole, benzimidazole, imidazole, and 6-iodobenzimidazole) with protected ribonolactone **1**, followed by (ii) borohydride reduction and (iii) Mitsunobu cyclization of the resulting diols. The diastereoselective access to the α-anomers was controlled in the borohydride reduction step by just keeping an appropriate protecting group on the heterocycle. In contrast, the removal of the protecting group resulted in total stereocontrol of the Mitsunobu ring-closing step, even from a mixture of diastereomeric diols affording exclusively the β anomers (Scheme 1). On the basis of molecular modeling studies, we can propose a rational explanation for the stereoselectivity of the reduction and for the stereocontrol observed in the Mitsunobu ring-closing step.

Results and Discussion

Condensation of 2-Lithiated Heterocycles with 5-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-γ-ribonolactone. In our synthetic methodology we used

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(1) For reviews on the chemistry, biochemistry, and synthesis of C-nucleoside analogues, see: (a) Buchanan, J. G. *Prog. Chem. Org. Nat. Prod*. **1983**, *44*, 243−299. (b) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem*. **1985**, *22*, 1−65. (c) Postema, M. H. D. *Tetrahedron* **1992**, *40*, 8545−8599. (d) Watanabe, K. A. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994; Vol. 3, pp 421−535. (e) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20. (f) Yokoyama, M.; Toyoshima, H.; Shimizu, M.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 29−33. (g) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−716.

(2) (a) Von Krosigk, U.; Benner, S. A. *J. Am. Chem. Soc.* **1995**, *117*, 5361−5362. (b) Matulic-Adamic, J.; Beigelman, L.; Portman, S.; Egli, M.; Usman, N. *J. Org. Chem*. **1996**, *61*, 3909−3911. (c) Hildbrand, S.; Leuman, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1968−1970. (d) Chaudhuri, N. C.; Ren, R. X. F.; Kool, E. T. *Synlett* **1997**, 341−347.

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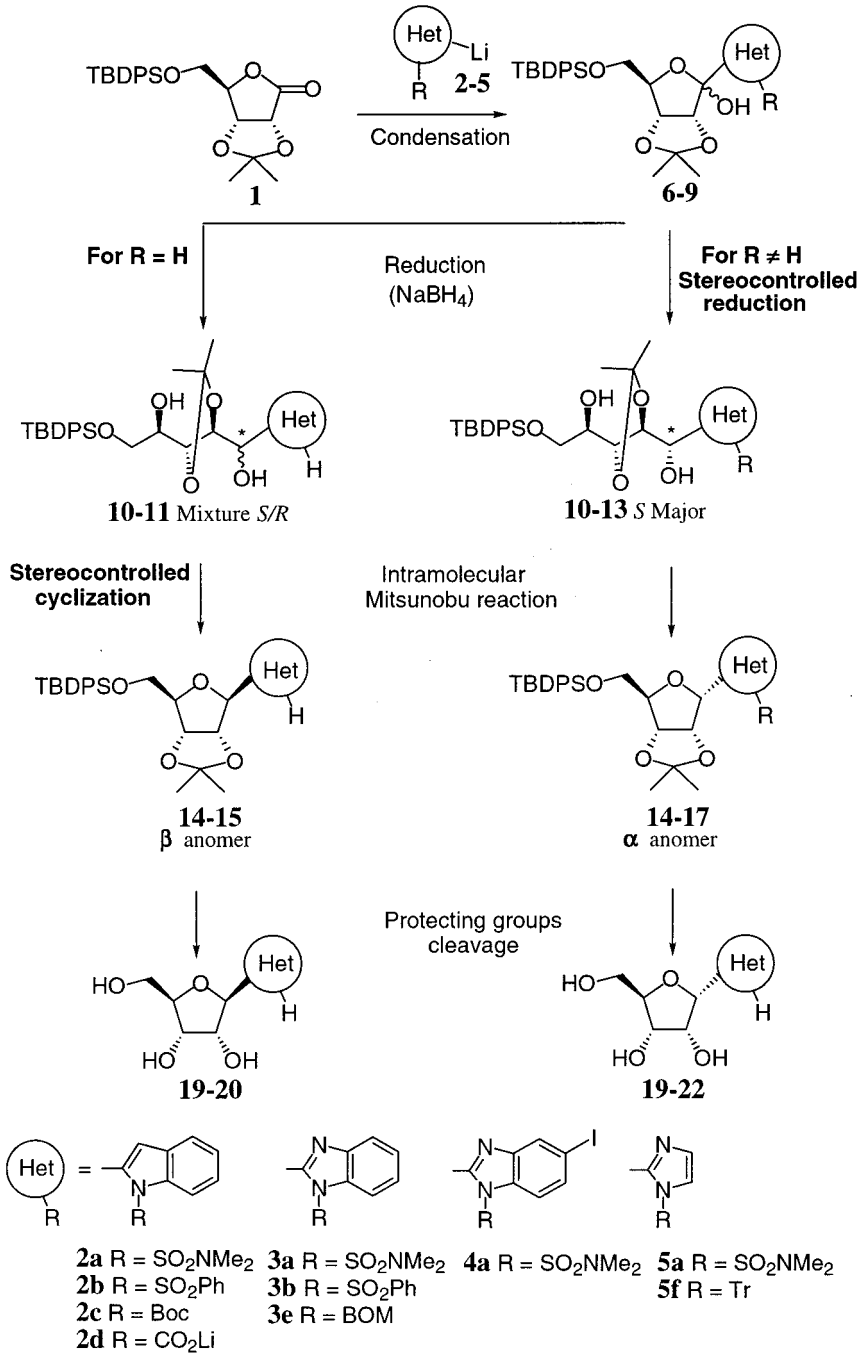
Scheme 1. Synthetic Strategy



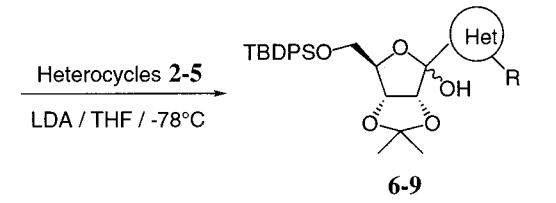
the ribonolactone **1**[3a] and the protected heterocycles **2**−**5**[6] as starting materials. First, the conditions for the quantitative formation of 2-lithiated heterocycles **2**−**5** were determined using hexachloroethane as a trapping agent, indicating that, in all cases, the heterocycles (except **2d**) could be quantitatively metalated by 1.1 equiv of LDA in THF at −78 °C in 45 min. Then, hemiacetals **6**−**9** were obtained by slow addition of ribonolactone **1** to freshly prepared lithiated heterocycles **2**−**5** in good yields (75−91%, Table 1).

The 2-lithiated derivative of 1-carboxyindole **2d**, used in the synthesis of the free indole hemiacetal **6d**, was prepared by following the Katritzky method, which utilized carbon dioxide for similtaneous protection of the indole NH and subsequent 2-lithiation.[7] This procedure, when applied to the lithiated derivative of carboxybenzimidazole **3d** (R = CO_2Li), was however unsuccessful for the synthesis of the benzimidazole analogue **7d**. Alternatively, this free hemiacetal (**7d**) could be quantitatively obtained from the protected hemiacetal **7e** by selective removal of the (benzyloxy)methyl group using catalytic hydrogenation (see Table 2, entry 6). Therefore, we observed that the condensation step was very sensitive to steric factors between the 2-lithiated heterocycles **2**−**5** and the bulky ribonolactone **1**. This is further supported by the fact that no significant reaction occurred

(6) Heterocycles **2**−**5** were protected using standard literature protocols (Greene, T. W. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999); see the Supporting Information.

(7) Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935−5938.

Table 1. Synthesis of Hemiacetals 6−9

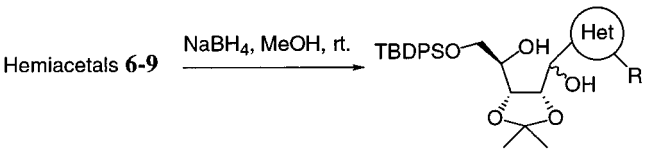


6-9

entry	heterocycle	product	yield (%)
	N1-R-Indole		
1	**2a**, R = SO_2NMe_2	**6a**	91
2	**2b**, R = SO_2Ph	**6b**	89
3	**2c**, R = Boc	**6c**	*a*
4	**2d**, R = CO_2Li	**6d** (R = H)	75
	N1-R-Benzimidazole		
5	**3a**, R = SO_2NMe_2	**7a**	90
6	**3b**, R = SO_2Ph	**7b**	81
7	**3e**, R = BOM	**7e**	75
	N1-R-5-Iodobenzimidazole		
8	**4a**, R = SO_2NMe_2	**8a**	85
	N1-R-Imidazole		
9	**5a**, R = SO_2NMe_2	**9a**	80
10	**5f**, R = Tr	**9f**	*a*

[a] Only small amounts of these products were detected by GC/MS analyses of the crude extracted mixtures.

Table 2. Borohydride Reduction of Hemiacetals 6−9



10-13

entry	hemiacetal	product (%)	*S*/*R* ratio[a,b]
	N1-R-Indole		
1	**6a**, R = SO_2NMe_2	**10a** (97)	75/25
2	**6b**, R = SO_2Ph	**10b** (94)	65/35
3	**6d**, R = H	**10d** (96)	50/50
	N1-R-Benzimidazole		
4	**7a**, R = SO_2NMe_2	**11a** (98)	90/10
5	**7b**, R = SO_2Ph	**11b** (97)	70/30
6	**7d**, R = H[c]	**11d** (95)	55/45
7	**7e**, R = BOM	**11e** (95)	95/5
	N1-R-5-Iodobenzimidazole		
8	**8a**, R = SO_2NMe_2	**12a** (92)	90/10
	N1-R-Imidazole		
9	**9a**, R = SO_2NMe_2	**13a** (97)	90/10

[a] The diastereomeric ratio was determined by reverse phase HPLC analysis of the crude products. [b] The stereochemistry of each diol was determined on the basis of their cyclized products, in which the anomeric configuration was assigned by ^{1}H NMR and 2D COSY-NOESY experiments. [c] Compound **7d** was obtained from **7e** after removal of the (benzyloxy)methyl group: H_2 (50 psi), Pd/C, THF.

in the case of *N*-Boc- or *N*-trityl-protected indole or imidazole (Table 1, entries 3 and 10), while their 2-lithiated derivatives reacted with other classically used electrophiles such as Bu_3SnCl, C_2Cl_6, and cyclohexanone, giving the expected 2-substituted derivatives. The NMR spectra of each coupled products **6**−**9** revealed the presence of three interconvertible species: i.e., the hemiacetal diastereoisomers (major products) and their open carbonyl form. For example, the ^{1}H NMR spectrum (300 MHz) of compound **9a** shows the signals at 4.80 and 5.55 ppm (singlets) for the *1′-OH* of the hemiacetals and at 5.95 ppm (doublet) for the proton $H_{2'}$ of the carbonyl opened form. The diastereomeric chemical ratio of all hemiacetals **6**−**9** was further found to be concentration and solvent dependent.[8] At this step, we have first examined the 1′-deoxygenation of the hemiacetals **6**−**9** under different reaction conditions. Unfortunately, treatment of hemiacetals **6**−**9** with triethylsilane (Et_3SiH) in the presence of Lewis acid reagents ($BF_3.Et_2O$, $ZnCl_2$, TMSOTf) at −78 °C resulted in unchanged starting materials. The increase of the concentration of the reducing agent only induced product decomposition, as shown by TLC and GC/MS analyses. Moreover, we failed to acetylate or to mesylate the tertiary *$C_{1'}$-OH* in order to make the deoxygenation step more efficient. Such a problem has been already encountered, and the stereochemistry of the deoxygenation step remains unclear in view of the heterogeneous results.[3a,4] In our case, this failure indicates that the *$C_{1'}$-OH* group of the hemiacetals is sterically constrained by both α and *β* faces.

Borohydride Reduction of Hemiacetals 6−9. However, borohydride reduction of the ketone form of hemiacetals **6**−**9**, using $NaBH_4$ in methanol, proceeded in a quantitative yield to afford a mixture of diastereomeric diols **10**−**13** (*S* and *R*) in variable ratio, depending on the nature of the heterocycle and its protecting group (Table 2).

In most cases, except for **6d** and **7d**, the borohydride reduction provided predominantly the *S* diol. For the same protecting group, the diastereoselectivity is better for imidazole and benzimidazoles than for the indole series. For example, the reduction of indole hemiacetal **6a** (Table 2, entry 1) led to a diastereoisomeric mixture of diols **10a** with a 75:25 *S*/*R* ratio, while reduction of benzimidazole hemiacetal having the same sulfamoyl protecting group **7a** (Table 2, entry 4) gave a mixture of diastereoisomeric diols **11a** with a 90:10 *S*/*R* molecular ratio. The diastereoselectivity is strongly dependent on the protecting group of the heterocycles. Indeed, we noticed an increased diastereoselectivity, especially with more sterically hindered groups such as sulfamoyl (Table 2, entries 4, 8, and 9) or (benzyloxy)methyl, which gave high diastereomeric excesses (Table 2, entry 7). In contrast, the reduction of the hemiacetals **6d** and **7d**, having an unprotected heterocyclic moiety, gave a mixture of diastereomeric diols **10d** and **11d**, respectively, in nearly a 1:1 ratio (Table 2, entries 3 and 6). The observed diastereoselective borohydride reduction for the heterocycle-protected hemiacetals is in agreement with the Felkin−Ahn model.[9,10] All these results are further supported by our molecular modeling study (see below), which suggested that the presence of a hindered protecting group on the heterocycle generates torsional constraints, resulting in a weakly twisted ketone−heterocycle conformation (ketone out of the heterocycle plane), thus inducing a diastereofacial hydride differentiation in favor of the *S* diol. Our molecular modeling study also indicated that the absence of diastereofacial differentiation in the case of **6d** and **7d** may result from a ketone−heterocycle planar conformation, allowing hydride approach by both faces.

(8) Similar observations, concerning equilibrium in solution of such hemiacetals, were reported: Dondoni, A.; Schermann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404−6412.

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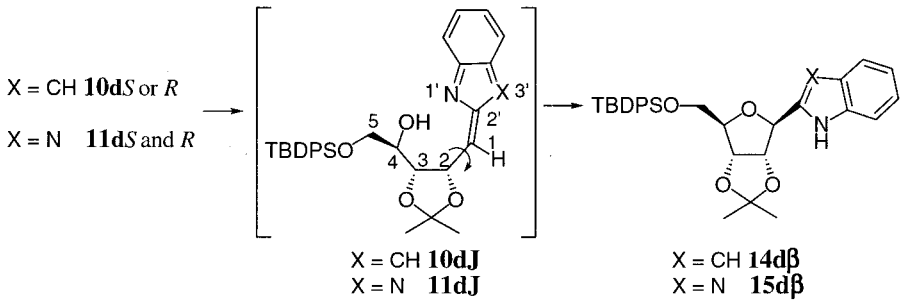
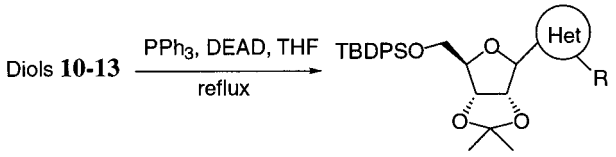


Figure 1. Proposed intermediate for the stereocontrolled cyclization.

Table 3. Mitsunobu Ring-Closing Step Leading to C-Nucleosides 14−17



14-17

entry	diol		*S*/*R* ratio[a]	product (yield, %)
		N1-R-Indole		
1	R = SO_2NMe_2	**10a**	100:0	**14aα** (85)
2	R = SO_2Ph	**10b**	100:0	**14bα** (82)
3	R = H	**10d**	50:50	**14dβ** (92)
4	R = H	**10d**	100:0	**14dβ** (92)
5	R = H	**10d**	0:100	**14dβ** (90)
		N1-R-Benzimidazole		
6	R = SO_2NMe_2	**11a**	90:10	**15aα** (75)
7	R = SO_2Ph	**11b**	90:10	**15bα** (70)
8	R = H	**11d**	55:45	**15dβ** (90)
9	R = BOM	**11e**	95:5	**15eα** (75)
		N1-R-5-Iodobenzimidazole		
10	R = SO_2NMe_2	**12a**	90:10	**16aα** (80)
		N1-R-Imidazole		
11	R = SO_2NMe_2	**13a**	90:10	**17aα** (75)

[a] The *S*/*R* ratio was determined by ^{1}H NMR and HPLC analyses of the pure diols.

The diastereoselectivity of the borohydride reduction seems also to depend on the chemical nature of the heterocycle. Among the heterocycle sulfamoyl protected derivatives, the diastereoselectivity is higher for the (benz)imidazole series (Table 2, entries 4, 8, and 9) than for the indole analogues **6a** (Table 2, entry 1).

Mitsunobu Ring-Closing Step. The treatment of diols **10**−**13** under standard Mitsunobu conditions (DEAD/PPh_3/THF reflux) led to the cyclized products **14**−**17** in good yields (70−92%). The anomeric configuration of the cyclized products was found to depend on the nature of the starting heterocyclic diol (Table 3).

Thus, the diols whose heterocyclic moiety is protected gave, upon cyclization, the corresponding α-protected C-nucleosides (Table 3, entries 1, 2, 6, 7, and 9−11) through an intramolecular S_N2 process and the *R* epimer (minor product) remained unchanged.[11] In contrast, treatment of a 1:1 mixture of diastereomeric free diols **10d** (Table 3, entry 3) and **11d** (Table 3, entry 8) under the same conditions afforded exclusively the β-C-nucleosides **14dβ** and **15dβ** in good yields, respectively. This observation is in disagreement with the findings of Yokoyama et al.,[12] in which the cyclization of a mixture (*S*/*R* = 1/8) of an NH free indole diol similar to **10d** (5′-trityl instead of 5′-TBDPS) provided the α- and β-C-nucleoside anomers in an unchanged ratio (α/β = 1/8), through an intramolecular S_N2 process. In our case, we have verified that the PPh_3/DEAD treatment of separated pure diols **10d***S* and **10d***R* gave only the same cyclized β-anomer **14dβ**, in high yields (Table 3, entries 4 and 5). In addition, we did not observe any α vs β epimerization under the present reaction conditions. In our preliminary communication,[10] we suggested that the stereocontrol may result from benzylic elimination ($Ph_3P{=}O$) from **10d** (or **11d** in the benzimidazole series) and spontaneous cyclization via the more favorable rotamer intermediate **10dJ** (or **11dJ**) to give the β-anomer (Figure 1).[13] In accordance with our experimental results, molecular modeling studies for this ring-closing step (**10d** to **14dβ** and **11d** to **15dβ**) show clearly that the cyclization leading to the β-anomers **14dβ** and **15dβ** is a highly favorable process, while the formation of the α-anomer is strongly constrained in view of the calculated energies and geometrical parameters of their respective transition states TSβ and TSα.

α/β Configuration Assignment. After the cyclization of diols **10**−**13** under Mitsunobu conditions, the anomeric configuration for each series was established by NOESY experiments realized for compounds **14bα** and **18dα** and for **14dβ** and **18dβ**. **18dα** was obtained from **15eα** by successive 1-(benzyloxy)methyl and 5′-TBDPS protecting group cleavage (Figure 2). **18dβ** was obtained from **15dβ** after 5′-deprotection. The most significant correlations are represented in Figure 2. Indeed, the β configuration of compounds **14dβ** and **18dβ** was clearly evidenced by the observed NOE correlation between H-1′ and H-4′. In the same way, we observed for the other anomers (**14bα** and **18dα**) an NOE correlation between H-1′ and H-2′ (cis relationship), in accordance with an α configuration.

The final protecting group cleavage of C-nucleosides **14**−**17** was achieved in one step, under acidic conditions. Thus, treatment of the cyclized products **14aα**, **14dβ**, **15aα**, **15dβ**, **16aα**, and **17aα** with 2 N HCl in dioxane or by using TFA/EtOH solution (see Experimental Section) afforded the free C-nucleosides **19α**, **19β**, **20α**, **20β**, **21α**, and **22α**, respectively, in high yields (Figure 3).

(11) When the reaction time was prolonged, we observed the formation of a complex mixture from which we could not isolate the β-protected C-nucleosides.

(12) (a) Yokoyama, M.; Tanabe, T.; Toyoshima, A.; Togo, H. *Synthesis* **1993**, 517−520. (b) Yokoyama, M.; Toyoshima, A.; Akiba, T.; Togo, H. *Chem. Lett.* **1994**, 265−268.

(13) Similar observations were reported in the imidazole series but, with the formation of a small amount of the α-anomer (α/β = 1/26). See: (a) Harusawa, S.; Murai, Y.; Moriyama, H.; Ohishi, H.; Yoneda, R.; Kurihara, T. *Tetrahedron Lett.* **1995**, *36*, 3165−3168. (b) Harusawa, S.; Murai, Y.; Moriyama, H.; Imazu, T.; Ohishi, H.; Yoneda, R.; Kurihara, T. *J. Org. Chem.* **1996**, *61*, 4405−4411.

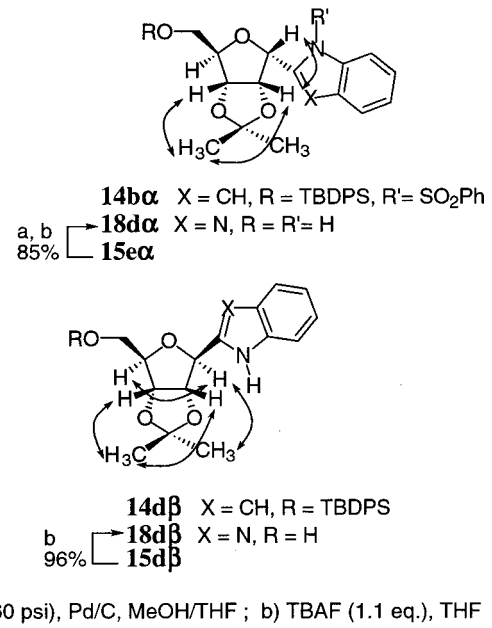


Figure 2. α/β configuration assignment by NOESY experiments.

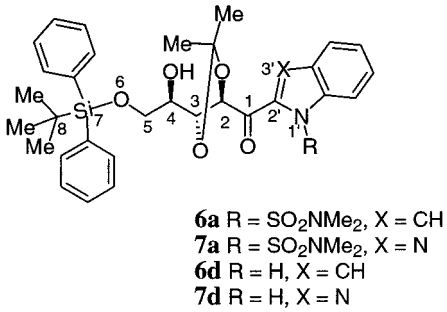


Figure 4. Structure and atom numbering of the hemiacetals (ketone form) studied by molecular modeling.

Molecular Modeling Studies. (a) Molecular Modeling Studies of the Reduction Step (6−9 → 10−13). The molecular modeling studies were performed on ketones **6a**,**d** (indole series) and on **7a**,**d** (benzimidazole series) (Figure 4) and gave similar results for both series (the calculated energies and geometrical parameters are summarized in Tables 4 and 7 in the Supporting Information). For clarity, only the discussions concerning the indole series are given in this section.

The geometry analysis of all the possible conformations of the reactive ketone form of **6d** (Figure 4) within 3 kcal/mol from the global minimum reveals that, in all cases, the double bond of the carbonyl group is practically in the plane of the indole ring: the O=C(1)−C(2′)−N(1′) dihedral angles are about −30, +30° or −150, +170°. The approach of the hydride ion is not hampered by the indole ring. Moreover, it is noteworthy that the C(2′)−C(1)−C(2)−C(3) dihedral angles vary, on one hand, from about −60 to −140° and, on the other hand, from +80 to +180°. In the first case, the side chain bearing the TBDPS group is localized in one face of the indole ring and, in the second case, it is localized in the other face. As nucleophilic attack on the positive face is favored at first because of Coulombic attraction, the face occupied by the 5-CH_2OTBDPS side chain is disfavored.

Figure 5 displays the two lowest energy conformers of **6d** (E_S = −139.89 kJ/mol and E_R = −139.05 kJ/mol). In these conformations, the O=C(1)−C(2′)−N(1′) dihedral angles are −160.4 and +176.0°, respectively, and the C(2′)−C(1)−C(2)−C(3) dihedral angles are +165.5 and −66.4°. These two geometries suggest that borohydride reduction of the most stable conformer leads to diol **10d***S* (Figure 5a) and that borohydride reduction of the second lowest energy conformer leads to diol **10d***R* (Figure 5b). As their calculated steric energy difference is only 0.84 kJ/mol ($\Delta(E_S - E_R)$), the observed mixture of diastereomeric diols **10d** (*S*/*R* 1:1) is explained.

For the ketone form of compound **6a**, the geometry analysis of all the possible conformations within 3 kcal/mol from the global minimum reveals that, in contrast to **6d**, because of the steric effect due to the protecting group, there are only a few conformers having the double bond of the carbonyl group approximately in the plane of the bicycle and, for these conformers, the C(2′)−C(1)−C(2)−C(3) dihedral angles vary from 150 to 180°. This means that only one face of the bicycle is hindered by the TBDPS group. Figure 6 displays the most stable energy conformer having the double bond of the carbonyl group nearly in the plane of the bicycle of **6a**. In this conformation, the O=C(1)−C(2′)−N(1′) dihedral angle is −153.7° and the C(2′)−C(1)−C(2)−C(3) dihedral angle is

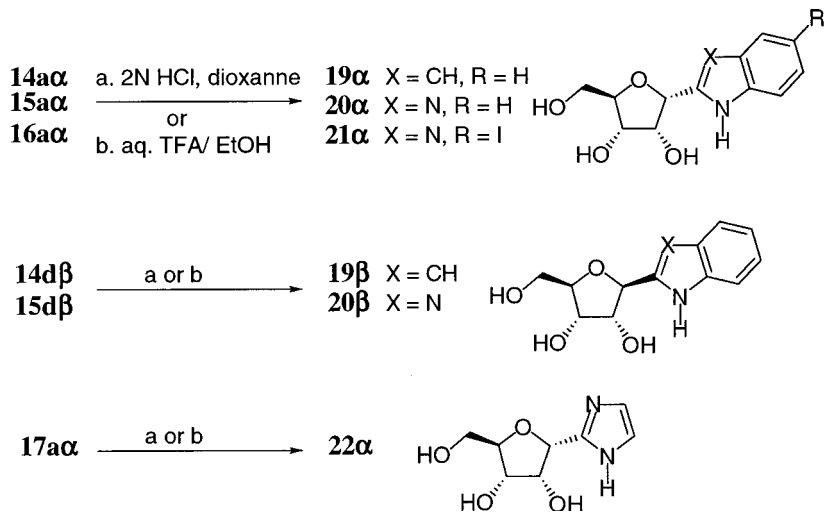


Figure 3. Structures of the obtained free C-nucleosides.

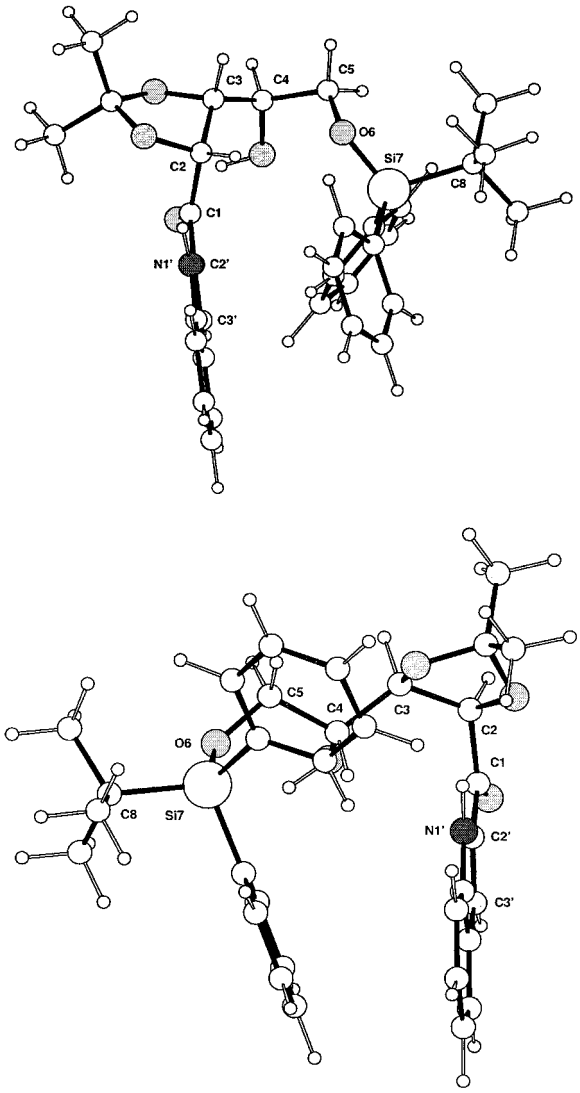


Figure 5. Ball and stick drawings of (a, top) the most stable conformer of **6d** (Conf*S* precursor of diol **10d***S*) and (b, bottom) the second lowest energy conformer of **6d** (Conf*R* precursor of diol **10d***R*).

+156.2°. Borohydride reduction of this conformer led to the diol **10a***S*. The difficulty in forming the diol **10a***R* is due to the nonexistence of the conformer having the double bond of the carbonyl group in the plane of the indole ring with the C(2′)−C(1)−C(2)−C(3) dihedral angle varying from about −60 to −140°.

(b) Molecular Modeling Studies of the Cyclization Step. Similar results were obtained for both indole and benzimidazole series. Therefore, only the discussions for the indole series are given in this section.

The calculated steric energies (MM2) and the geometrical parameters of the most relevant conformations of the intermediate precursor **10dJ** (Figure 1) and of the α- and *β*-anomers **14d** are summarized in Table 5 (see the Supporting Information). The formation enthalpies (AM1) and the most relevant geometrical parameters of the intermediate **10dJ** and of the corresponding constrained transition structures (TSα and TS*β*) of the α- and *β*-anomers **14d** in the ground state are summarized in Table 6 (see the Supporting Information). Both methods (molecular mechanics and orbital molecular methods) lead to similar results. The calculation results reveal that

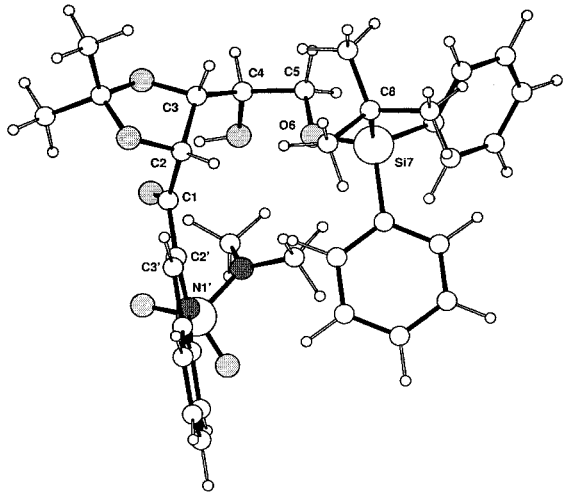


Figure 6. Ball and stick drawing of the most stable conformer of **6a** (Conf*S* precursor of diol **10a***S*).

the *β*-anomer **14d*β*** is more stable than the α-anomer **14d**α; i.e., the energy difference is 7.15 kJ/mol with the molecular mechanics method (Table 5) and 6.31 kJ/mol with the molecular orbital method at the RHF/AM1 level (Table 6).

Moreover, since the activation energies for conformational changes in large molecules may be considerable, a process which can lower the rotations may be expected to lead to a substantial acceleration of the overall rate of the reaction. Therefore, only the possible conformations of the intermediate **10dJ** that have similar torsional angles related to the α- and *β*-anomers **14d** were considered. The geometry analysis of these selected conformations of the intermediate **10dJ** and the two lowest energy conformations of the α- and *β*-anomers **14d** suggests that the reaction leading to α-anomer **14d**α is strongly hampered. In addition, the geometry analysis reveals that the second lowest energy conformation of the intermediate **10dJ** is comparable to the most stable conformation of the *β*-anomer **14d*β***. The energy difference between the second lowest energy conformation and the most stable conformation of the intermediate **10dJ** is only 0.84 kJ/mol. The geometry analysis also indicates that no conformation of the intermediate **10dJ** within 3 kcal/mol from the global minimum is comparable to the most stable conformation of the α-anomer **14d**α (E = −82.59 kJ/mol) and that the most stable conformation of the intermediate **10dJ** (E = −134.19 kJ/mol) is comparable to the conformation of the α-anomer **14d**α with steric energy equal to −80.83 kJ/mol (Table 5). The energy difference between the α- and *β*-anomers **14d** that can be obtained is 8.91 kJ/mol. Moreover, the energy difference between the constrained transition structures TSα and TS*β* (Table 5) corresponding to the cyclization leading respectively to the α- and *β*-anomers **14d** is significantly important (ΔE = 11.73 kJ/mol). AM1 calculations lead to similar results. The energy differences between the α- and *β*-anomers **14d** that can be obtained and between the constrained transition structures TSα and TS*β* are 13.04 and 24.79 kJ/mol, respectively (Table 6). Similar results were obtained in the benzimidazole series for the studied compounds **11dJ**, **15d**α, and **15d*β*** (Figure 1) (Tables 8 and 9, see the Supporting Information).

All together, these considerations correlate nicely with the experimental findings.

Conclusion

A short stereocontrolled approach for the synthesis of heterocyclic C-nucleosides has been developed for both α- and β-anomers. Our synthesis started by condensation of a range of 2-lithiated heterocycles with ribonolactone **1** to give the hemiacetals **6**−**9** in good yields. We observed that the choice of an appropriate protecting group on the heterocycle allowed a high stereoselective borohydride reduction of the hydroxy ketone to the corresponding diol in quantitative yield which, upon Mitsunobu cyclization, gave the α-anomer. In contrast, removal of the protecting group allowed the total stereocontrol of the ring closure of diol, leading to the β-anomer exclusively. In view of the given examples, the strategy should hold great promise for stereoselective synthesis of a wide range of C-nucleosides and in particularly the purine C-nucleosides.

Experimental Section

Reactions were monitored by TLC on silica gel 60 F-254, and compounds were visualized with UV light, iodine, or 10% sulfuric acid in ethanol followed by heating. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with $CDCl_3$ or CD_3OD as solvent and are so indicated: chemical shifts are reported in ppm (δ) from tetramethylsilane; coupling constants are reported in Hz. Flash chromatography was carried out on silica gel 60 (230−400 mesh) using heptane/ethyl acetate and methylene chloride/methanol mixtures as eluents. The diastereomeric ratios were determined by reverse phase analytical HPLC analysis using Waters Symmetry 4.6 × 250 mm column and acetonitrile/water (75/25 v/v) as eluent. All moisture-sensitive reactions were carried out under a nitrogen atmosphere. All solvents were dried over standard drying agents and freshly distilled prior to use.

Computational Procedure. Molecular Mechanics Method. Five thousand conformations of each studied compound, i.e. the reactive ketone forms of the hemiacetals **6a**,**d**, the intermediate **10d*J***, and the α- and β-anomers **of 14d**, were generated by a random search Monte Carlo method[14] and optimized by the TNCG truncated Newton molecular mechanics minimization method[15] using the Macromodel (version 5.5) program[16] with an MM2 force field.[17] The search was carried out on blocks of 500 Monte Carlo steps until no additional conformation was found to be of lower energy than the current minimun. Duplicated conformations as well as those that had chirality changes were discarded. From these conformational searches, all the possible conformations within 3 kcal/mol from the global minimum were analyzed. Therefore, for each cyclization leading to α- and β-anomers **14d**, the constrained transition structures with the forming O- - -C bond equal to about 2.1 Å were performed.

Orbital Molecular Semiempirical Method. The geometries for all the selected structures of the intermediate **10d*J*** and of the α- and β-anomers **14d** summarized in Tables 4 and 5 were studied using the orbital molecular method and were optimized by means of gradient techniques at the RHF/AM1 level[18] using the MOPAC program (version 5.0).[19] Therefore, for each cyclization, the constrained transition structures were performed by freezing the forming O- - -C bond at 2.1 Å.

Preparation of Hemiacetals 6−9. These compounds were obtained in pure form as an unseparable diastereomeric mixture (in equilibrium; see text). However, the signals of the two diastereoisomeric hemiacetals were clearly shown by ^{1}H, ^{13}C, and 2D COSY NMR and are given in this section as **M** and **m**, for the major and the minor diastereoisomers, respectively.

2-[5′-*O*-(*tert*-Butyldiphenylsilyl)-1′-hydroxy-2′,3′-*O*-isopropylidene-D-ribofuranosyl-1′]-1-(*N*,*N*-dimethylsulfamoyl)indole (6a). To a stirred solution of *N*-(*N*′,*N*′-dimethylsulfamoyl)indole (**2a**; 1.5 g, 4.4 mmol) in dry tetrahydrofuran (50 mL) cooled to −78 °C was added LDA (2 M solution in hexane, 2.42 mL, 1.1 equiv) dropwise. After 45 min a solution of 5-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**; 1.5 g, 0.8 equiv) in dry THF (25 mL) was slowly added. The mixture, which was allowed to react at room temperature over 3 h, was quenched with a solution of ammonium chloride (10 mL) and extracted with methylene chloride (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil. Silica gel column chromatography purification using 10% of ethyl acetate in heptane afforded **6a** as a white foam (2 g, 91%). R_f = 0.50 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H$_m$), 1.11 (s, 9H$_M$), 1.26 (s, 6H$_M$), 1.41 (s, 3H$_m$), 1.65 (s, 3H$_m$), 2.80 (s, 6H$_m$), 2.88 (s, 6H$_M$), 3.84 (m, 4H$_{m+M}$), 4.42 (m, 2H$_{m+M}$), 4.72 (dd, 1H$_m$, J = 6.9 and 4.1 Hz), 4.82 (dd, 1H$_M$, J = 5.7 and 1.1 Hz), 5.07 (d, 1H$_M$, J = 5.7 Hz), 5.07 (s, 1H$_M$), 5.14 (d, 1H$_m$, J = 6.9 Hz), 5.42 (s, 1H$_m$), 7.02 (br s, 2H$_{m+M}$), 7.19−7.70 (m, 26H$_{m+M}$), 7.89 (m, 1H$_M$), 8.00 (m, 1H$_m$). ^{13}C NMR ($CDCl_3$): δ 19.32, 25.54, 26.58, 26.89, 27.01, 38.49, 38.78, 63.56, 65.52, 81.41, 82.81, 82.97, 84.44, 85.50, 88.00, 100.76, 106.24, 112.01, 112.56, 114.74, 115.26, 121.37, 121.52, 122.94, 123.25, 124.43, 124.81, 127.32, 127.84, 127.97, 128.12, 129.87, 130.06, 130.15, 132.68, 133.29, 135.70, 135.74, 135.82, 137.66, 140.12, 151.00. MS (ES): *m*/*z* 673 $[M + Na]^+$, 633 $[M - H_2O + H]^+$. Anal. Calcd for $C_{34}H_{42}N_2O_7SiS$: C, 62.74; H, 6.50; N, 4.30. Found: C, 62.37; H, 6.83; N, 4.74.

2-[5′-*O*-(*tert*-Butyldiphenylsilyl)-1′-hydroxy-2′,3′-*O*-isopropylidene-D-ribofuranosyl-1′]indole (6d). The lithium salt of indole-1-carboxylic acid (**2d**) was prepared from indole (0.5 g, 4.27 mmol), following the procedure described by Katritzky.[7] To a solution of **2d** in dry THF (20 mL) cooled to −78 °C was added dropwise *t*-BuLi (1.5 M solution in *n*-pentane, 1.2 equiv). The reaction mixture was stirred at the same temperature for 1.5 h, and a solution of ribonolactone **1** (1 g, 0.8 equiv) in dry THF (10 mL) was slowly added. The mixture was stirred and warmed slowly to room temperature over 3 h and then quenched with ammonium chloride solution (10 mL) and extracted with methylene chloride (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude oil. Silica gel column chromatography purification using 10% of ethyl acetate in heptane afforded **6d** as a white foam (955 mg, 75%). R_f = 0.44 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 9H$_M$), 1.10 (s, 9H$_m$), 1.39 and 1.48 (2s, 6H$_m$), 1.43 and 1.64 (2s, 6H$_M$), 3.68 (m, 2H$_{m+M}$), 3.97 (m, 3H$_{m+M}$), 4.43 (m, 1H$_m$), 4.56 (dd, 1H$_M$, J = 6.4 and 8.7 Hz), 4.73 (d, 1H$_m$, J = 5.6 Hz), 4.92 (dd, 1H$_m$, J = 5.6 and 1.6 Hz), 5.48 (d, 1H$_M$, J = 6.4 Hz), 6.65 (m, 1H$_m$), 6.66 (m, 1H$_M$), 7.04−7.74 (m, 28H$_{m+M}$), 8.58 (br s, 1H$_m$), 9.35 (br s, 1H$_M$). ^{13}C NMR ($CDCl_3$): δ 19.35, 25.00, 25.64, 26.62, 26.77, 26.91, 27.01, 27.35, 63.73, 64.97, 65.53, 69.88, 78.72, 80.93, 81.98, 82.65, 85.38, 86.44, 88.06, 100.09, 100.46, 101.52, 110.37, 110.73, 111.22, 112.34, 113.01, 115.77, 119.68, 119.88, 121.14, 122.14, 123.45, 126.77, 127.66, 127.84, 128.10, 129.90, 130.12, 130.24, 130.39, 133.01, 134.21, 134.99, 135.59, 135.58, 135.68, 135.89, 137.46, 139.18. MS (ES): *m*/*z* 566 $[M + Na]^+$. Anal. Calcd for $C_{32}H_{37}NO_5Si$: C, 70.69; H, 6.86; N, 2.58. Found: C, 70.82; H, 6.81; N, 2.37.

2-[5′-*O*-(*tert*-Butyldiphenylsilyl)-1′-hydroxy-2′,3′-*O*-isopropylidene-D-ribofuranosyl-1′]benzimidazole (7d). A so-

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(19) Stewart, J. J. P. MOPAC 5.0, QCPE Program No. 455 and *J. Comput. Chem.* **1989**, *101*, 221.

lution of **7e** (400 mg, 0.6 mmol) in EtOH/THF (1/1 v/v, 8 mL) was hydrogenated over 10% palladium on carbon (40 mg) for 15 h at 50 psi. The catalyst was removed by filtration through Celite and washed several times with ethanol. The filtrate was evaporated to give a crude residue, which was purified by silica gel column chromatography, using 20% of ethyl acetate in heptane, to afford **7d** as a white foam (293 mg, 90%). R_f = 0.25 (4:1 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.03 (s, $9H_m$), 1.12 (s, $9H_M$), 1.25 (s, $3H_M$), 1.36 (s, $3H_M$), 1.37 (s, $3H_m$), 1.66 (s, $3H_m$), 3.74 (dd, $1H_m$, J = 5.1 and 11.6 Hz), 3.82 (dd, $1H_m$, J = 3.8 and 11.6 Hz), 3.92 (dd, $1H_M$, J = 5.3 and 10.6 Hz), 4.07 (dd, $1H_M$, J = 7.8 and 10.6 Hz), 4.44 (m, $2H_{m+M}$), 4.85 (d, $1H_m$, J = 6.8 Hz), 4.87 (d, $1H_M$, J = 5.6 Hz), 4.92 (d, $1H_M$, J = 5.6 Hz), 5.24 (d, $1H_m$, J = 6.8 Hz), 7.12−7.93 (m, $28H_{m+M}$), 9.30 (s, $1H_M$), 9.63 (s, $1H_m$). ^{13}C NMR ($CDCl_3$): δ 19.43, 24.73, 25.10, 26.65, 26.98, 27.13, 63.63, 65.62, 81.60, 83.08, 83.80, 86.95, 87.58, 100.03, 104.11, 112.77, 128.01, 130.05, 133.25, 135.77, 151.89. MS (ES): m/z 567 $[M + Na]^+$, 545 $[M + H]^+$, 527 $[M - H_2O + H]^+$. Anal. Calcd for $C_{31}H_{36}N_2O_5Si$: C, 68.35; H, 6.66; N, 5.14. Found: C, 68.69; H, 6.45; N, 4.86.

Preparation of Diols 10−13. Diol 10a. Compound **6a** (700 mg, 1.07 mmol) was dissolved in dry methanol (10 mL), and sodium borohydride (100 mg, 2.5 equiv) was added slowly. The mixture was stirred at room temperature for 1 h, quenched with ice−water, and neutralized with HCl solution (0.1 N). The aqueous phase was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude solid. Silica gel column chromatography purification using 5% of ethyl acetate in heptane afforded **10a***S* (513 mg) and **10a***R* (169 mg) as a white foam (*S*/*R*: 75/25; 97%). **10a***S*: R_f = 0.50 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.17 (s, 3H), 1.32 (s, 3H), 2.85 (s, 6H), 3.61 (br s, 1H), 3.83 (dd, 1H, J = 10.3 and 6.8 Hz), 3.98 (dd, 1H, J = 2.9 and 10.3 Hz), 4.03 (m, 1H), 4.29 (dd, 1H, J = 9.4 and 5.1 Hz), 4.50 (br s, 1H), 4.65 (dd, 1H, J = 9.6 and 5.1 Hz), 5.64 (d, 1H, J = 9.6 Hz), 6.80 (s, 1H), 7.25 (m, 3H), 7.39 (m, 5H), 7.54 (m, 1H), 7.65 (m, 4H), 8.01 (d, 1H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 19.43, 25.64, 27.01, 27.92, 38.50, 64.01, 65.49, 69.88, 77.65, 79.40, 108.67, 109.18, 114.96, 121.31, 123.13, 124.53, 127.93, 128.71, 130.00, 133.03, 135.69, 141.18. MS (ES): m/z 698 $[M + 2Na]^+$, 675 $[M + Na]^+$, 635 $[M - H_2O + H]^+$. **10a***R*: R_f = 0.45 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9H), 1.34 (s, 3H), 1.46 (s, 3H), 2.81 (s, 6H), 3.28 (br s, 1H), 3.89 (m, 2H), 4.27 (m, 2H), 4.70 (d, 1H, J = 6.5 Hz), 5.89 (br s 1H), 6.85 (s, 1H), 7.25 (m, 3H), 7.40 (m, 5H), 7.53 (m, 1H), 7.68 (m, 4H), 8.01 (d, 1H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 19.45, 24.71, 26.98, 38.54, 64.82, 65.45, 70.01, 76.54, 78.56, 108.72, 108.82, 115.02, 121.07, 123.26, 124.24, 127.85, 127.90, 128.94, 129.94, 133.04, 135.66, 135.72, 142.82. MS (ES): m/z 698 $[M + 2Na]^+$, 675 $[M + Na]^+$. Anal. Calcd for **10a***S*, $C_{34}H_{44}N_2O_7SSi$: C, 62.55; H, 6.79; N, 4.29. Found: C, 62.45; H, 6.74; N, 4.25.

Diol 10d. By the same procedure as described for the preparation of **10a**, **6d** (410 mg, 0.75 mmol) was reduced with sodium borohydride to give **10d** (195 mg, F_1, *R* or *S*) and **10d** (201 mg, F_2, *S* or *R*) as a white foam (*S*/*R*: 1/1; 96%). **10d** (F_1): R_f 0.52 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.28 (s, 3H), 1.36 (s, 3H), 3.02 (br s, 1H), 3.17 (br s, 1H), 3.81 (dd, 1H, J = 10.5 and 5.3 Hz), 3.92 (dd, 1H, J = 3.0 and 10.5 Hz), 4.10−4.23 (m, 2H), 4.52 (dd, 1H, J = 2.6 and 6.0 Hz), 5.36 (m, 1H), 6.47 (s, 1H), 7.12 (m, 2H), 7.35 (m, 5H), 7.65 (m, 7H), 8.84 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.42, 24.92, 26.98, 27.07, 65.37, 65.76, 69.74, 76.45, 79.78, 99.97, 108.93, 111.12, 119.75, 120.72, 121.93, 127.91, 127.96, 128.11, 130.04, 132.93, 135.65, 136.055, 139.25. MS (ES): m/z 568 $[M + Na]^+$, 546 $[M + H]^+$. **10d** (F_2): R_f = 0.50 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.27 (s, 6H), 3.78 (dd, 1H, J = 10.5 and 7.4 Hz), 3.98 (m, 2H), 4.17 (dd, 1H, J = 5.2 and 9.7 Hz), 4.34 (dd, 1H, J = 9.2 and 5.2 Hz), 5.13 (d, 1H, J = 9.2 Hz), 6.56 (s, 1H), 7.14 (m, 2H), 7.33 (m, 5H), 7.65 (m, 7H), 8.61 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.41, 25.71, 27.03, 28.13, 65.39, 66.43, 69.67, 77.58, 80.61, 100.17, 109.41, 111.03, 119.66, 120.68, 121.66, 128.04, 128.50, 130.23, 135.70, 135.93, 138.84. MS (ES): m/z 568 $[M + Na]^+$, 546 $[M + H]^+$. Anal. Calcd for $C_{32}H_{39}NO_5Si$: C, 70.43; H, 7.20; N, 2.57. Found: C, 70.71; H, 6.95; N, 2.41.

Diol 11d. By the same procedure as described above for the preparation of **10a**, **7d** (400 mg, 0.73 mmol) was reduced with sodium borohydride to give an inseparable mixture of diastereoisomers **11d** (*S*/*R* 55/45; 380 mg, 95%) as a white foam. R_f = 0.50 (1:1 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.09 (s, 9H), 1.32 (s, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 3.87 (dd, 1H, J = 10.6 and 5.7 Hz), 3.95 (m, 2H), 3.98 (dd, 1H, J = 10.6 and 2.5 Hz), 4.07 (m, 2H), 4.45 (m, 2H), 4.50 (dd, 1H, J = 8.5 and 5.3 Hz), 4.56 (dd, 1H, J = 5.3 and 5.5 Hz), 5.17 (d, 1H, J = 8.5 Hz), 5.30 (d, 1H, J = 5.3 Hz), 7.26 (m, 4H), 7.40 (m, 10H), 7.60 (m, 4H), 7.72 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 19.46, 25.33, 25.62, 26.99, 27.55, 28.12, 65.51, 65.66, 66.09, 66.67, 69.94, 69.70, 76.88, 77.37, 78.73, 79.25, 109.18, 122.98, 127.83, 127.89, 129.86, 133.38, 135.78, 154.21. MS (ES): m/z 547 $[M + H]^+$. Anal. Calcd for $C_{31}H_{38}N_2O_5Si$: C, 68.10; H, 7.01; N, 5.12. Found: C, 67.93; H, 6.86; N, 4.82.

Preparation of Cyclized Products 14−22. 2-[5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-*O*-isopropylidene-α-D-ribofuranosyl-1′]-1-(*N*,*N*-dimethylsulfamoyl)indole (14aα). By the typical procedure of the Mitsunobu reaction, **10a***S* (155 mg, 0.23 mmol) and PPh_3 (1.5 equiv, 93 mg) were dissolved in THF and the mixture was refluxed. Diethylazodicarboxylate (1.5 equiv, 50 mL) was then added dropwise to the refluxing mixture, and heating was continued for 1 h. The solvent was evaporated to give a residual oil, which was chromatographed on a silica gel column using 5% of ethyl acetate in heptane to give **14a**α (123 mg, 85%) as a white foam. R_f = 0.46 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 9H), 1.24 (s, 3H), 1.26 (s, 3H), 2.73 (s, 6H), 3.75 (dd, 1H, J = 3.2 and 11.2 Hz), 3.92 (dd, 1H, J = 3.4 and 11.2 Hz), 4.35 (m, 1H), 4.94 (d, 1H, J = 6.0 Hz), 5.25 (t, 1H, J = 3.2 Hz), 5.84 (d, 1H, J = 4.2 Hz), 6.87 (s, 1H), 7.30 (m, 2H), 7.40 (m, 7H), 7.53 (m, 1H), 7.67 (m, 3H), 7.90 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 19.30, 25.13, 26.12, 27.01, 38.38, 66.05, 80.57, 82.90, 83.48, 83.85, 108.93, 112.47, 114.41, 120.78, 122.95, 123.63, 127.95, 129.22, 129.93, 130.05, 133.02, 135.60, 135.73, 137.07, 138.83. MS (ES): m/z 657 $[M + Na]^+$.

2-[5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl-1]indole (14dβ). 10d*S* (150 mg, 0.27 mmol) and **10d***R* (150 mg, 0.27 mmol) were independently cyclized, by the same procedure as described for the preparation of **14a**α, to give the same compound **14d**β (92% from **10d***S* and, 90% from **10d***R*) as a white foam. R_f = 0.50 (7:3 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 9H), 1.37 (s, 3H), 1.62 (s, 3H), 3.73 (dd, 1H, J = 11.4 and 4.8 Hz), 3.85 (dd, 1H, J = 3.5 and 11.4 Hz), 4.30 (m, 1H), 4.77 (dd, 1H, J = 2.8 and 6.3 Hz), 4.83 (dd, 1H, J = 3.6 and 6.3 Hz), 5.24 (d, 1H, J = 3.6 Hz), 6.44 (m, 1H), 6.97 (m, 1H), 7.08 (m, 2H), 7.30−7.47 (m, 6H), 7.55 (m, 1H), 7.75 (m, 4H), 8.50 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.48, 25.54, 27.07, 27.49, 64.30, 81.38, 81.93, 85.21, 86.94, 111.10, 114.03, 119.83, 120.53, 121.93, 128.04, 130.09, 132.91, 133.14, 135.57, 135.69, 135.98, 137.36. MS (FAB): m/z 528 $[M + H]^+$. Anal. Calcd for $C_{32}H_{37}NO_4Si$: C, 72.83; H, 7.07; N, 2.65. Found: C, 72.74; H, 7.05; N, 2.61.

2-[5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl-1′]benzimidazole (15dβ). 11d (*S*/*R* mixture 55/45; 460 mg, 0.84 mmol) was cyclized by the same procedure as described for the preparation of **14a**α, to give **15d**β (401 mg, 90%) as a white foam. R_f = 0.40 (1:1 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.35 (s, 3H), 1.60 (s, 3H), 3.62 (dd, 1H, J = 5.9 and 11.6 Hz), 3.84 (dd, 1H, J = 3.6 and 11.6 Hz), 4.38 (m, 1H), 4.67 (dd, 1H, J = 6.1 and 2.8 Hz), 5.17 (dd, 1H, J = 2.8 and 2.8 Hz), 5.40 (d, 1H, J = 2.8 Hz), 7.00 (m, 1H), 7.13−7.48 (m, 8H), 7.74 (m, 1H), 7.62 (m, 4H), 9.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.22, 25.26, 26.91, 27.14, 64.34, 80.08, 82.25, 85.02, 86.49, 114.34, 114.86, 125.00, 128.00, 130.11, 132.71, 133.58, 139.70, 151.60. MS (ES): m/z 529 $[M + H]^+$. Anal. Calcd for $C_{31}H_{36}N_2O_4Si$: C, 70.42; H, 6.86; N, 5.30. Found: C, 70.51; H, 6.78; N, 5.11.

2-(5′-Hydroxy-2′,3′-*O*-isopropylidene-α-D-ribofuranosyl-1′)benzimidazole (18dα). A solution of **15e**α (220 mg, 0.34 mmol) in 1:1 EtOH/THF (v/v; 5 mL) was hydrogenated over 10% palladium on carbon (22 mg) for 15 h at 50 psi. The

catalyst was removed by filtration through Celite and washed several times with ethanol. The filtrate was evaporated to give a crude residue which was dissolved in THF (5 mL). After addition of 1 M TBAF in THF (0.5 mL, 1.5 equiv), the reaction mixture was stirred at room temperature for 1 h and then evaporated. The residue was purified by column chromatography, using 50% of ethyl acetate in heptane, to afford **18dα** as a white foam (84 mg, 85%). R_f = 0.20 (1:4 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.55 (s, 3H), 3.89 (m, 1H), 3.97 (dd, 1H, J = 3.7 and 12.0 Hz), 4.06 (dd, 1H, J = 6.3 and 12.0 Hz), 4.83 (dd, 1H, J = 3.8 and 6.0 Hz), 5.41 (s, 1H), 5.69 (d, 1H, J = 3.8 Hz), 7.24 (m, 4H), 7.58 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.52, 26.09, 61.30, 79.98, 81.35, 81.65, 84.50, 113.10, 123.01, 151.19. MS (IC, isobut): m/z =291 $[M + H]^+$.

2-(5′-Hydroxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl-1′)benzimidazole (18dβ). 15dβ (210 mg; 0.39 mmol) was dissolved in THF (5 mL), and a 1 M TBAF solution in THF (0.6 mL, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 1 h and then evaporated. The residue was purified by column chromatography, using 50% of ethyl acetate in heptane, to afford **18dβ** as a white foam (112 mg, 96%). R_f = 0.25 (1:4 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 3H), 1.58 (s, 3H), 3.77 (dd, 1H, J = 12.3 and 3.3 Hz), 4.03 (dd, 1H, J = 2.1 and 12.3 Hz), 4.48 (m, 1H), 4.95 (dd, 1H, J = 2.3 and 6.1 Hz), 5.02 (dd, 1H, J = 3.1 and 6.0 Hz), 5.30 (d, 1H, J = 3.1 Hz), 7.27 (m, 4H), 7.58 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 25.38, 27.38, 63.25, 82.09, 82.44, 86.25, 87.20, 113.90, 123.13, 143.58, 153.90. MS (ES): m/z 313 $[M + Na]^+$, 291 $[M + H]^+$.

2-α-D-Ribofuranosylindole (19α). 14aα (150 mg, 0.23 mmol) was dissolved in EtOH (3 mL), and a solution of TFA/H_2O (4/1, 3 mL) was added. The reaction mixture was stirred for 2 h at 60 °C, cooled to 0 °C, and neutralized with $NaHCO_3$ solution. The mixture was evaporated, and the crude residue was purified by silica gel column chromatography using 5% of methanol in methylene chloride, to afford **19α** (48 mg, 82%). R_f = 0.40 (9:1 methylene chloride/methanol). ^{1}H NMR (CD_3OD): δ 3.64 (dd, 1H, J = 12.0 and 4.5 Hz), 3.68 (dd, 1H, J = 2.3 and 12.0 Hz), 4.01 (m, 1H), 4.29 (dd, 1H, J = 8.6 and 4.5 Hz), 4.56 (dd, 1H, J = 3.4 and 4.5 Hz), 5.70 (dd, 1H, J = 1.3 and 3.4 Hz), 6.83 (s, 1H), 7.38 (t, 1H, J = 7.2 Hz), 7.50 (t, 1H, J = 7.3 Hz), 7.74 (d, 1H, J = 7.2 Hz), 7.96 (d, 1H, J = 7.9 Hz). ^{13}C NMR (CD_3OD): δ 62.99, 73.57, 74.63, 79.89, 83.13, 112.88, 115.56, 121.80, 124.83, 125.15, 131.45, 138.55, 139.59. MS (IC, isobut): m/z 250 $[M + H]^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.89; H, 6.32; N, 5.86.

2-β-D-Ribofuranosylindole (19β). 14dβ (64 mg, 0.26 mmol) was dissolved in dioxane (3 mL), and 2 N HCl (0.5 mL) was added. The reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C, and neutralized by a saturated solution of $NaHCO_3$. The mixture was evaporated, and the crude residue was purified by silica gel column chromatography using 5% of methanol in methylene chloride, to afford **19β** as an oil (59 mg, 91%). R_f = 0.50 (9:1 methylene chloride/methanol). ^{1}H NMR (CD_3OD): δ 3.68 (dd, 1H, J = 12.0 and 4.1 Hz), 3.85 (dd, 1H, J = 3.1 and 12.0 Hz), 3.96 (m, 1H), 4.10 (m, 2H), 4.90 (d, 1H, J = 5.3 Hz), 6.38 (s, 1H), 6.93 (t, 1H, J = 7.3 Hz), 7.02 (t, 1H, J = 7.4 Hz), 7.30 (d, 1H, J = 7.9 Hz), 7.43 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD): δ 63.18, 72.49, 77.41, 80.71, 86.02, 100.79, 111.92, 120.08, 120.99, 123.32, 129.42, 137.88, 138.39. MS (IC, isobut): m/z 250 $[M + H]^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.75; H, 6.29; N, 5.38.

2-α-D-Ribofuranosylbenzimidazole (20α). Treatment of **15aα** (200 mg, 0.31 mmol) under the same conditions as described for **19β** gave **20α** (71 mg, 90%). R_f = 0.25 (9:1 methylene chloride/methanol). ^{1}H NMR (CD_3OD): δ 3.90 (td, 2H, J = 11.5, 6.4, and 4.8 Hz), 4.31 (m, 1H), 4.35 (m, 1H), 4.40 (m, 1H), 5.21 (d, 1H, J = 8.0 Hz), 7.45 (m, 2H), 7.68 (m, 2H). ^{13}C NMR (CD_3OD): δ 62.24, 73.52, 77.83, 79.39, 84.68, 115.49, 126.95. MS (IC, isobut): m/z 251 $[M + H]^+$.

2-β-D-Ribofuranosylbenzimidazole (20β). By the same procedure as described above for the preparation of **19β**, **15dβ** (250 mg, 0.47 mmol) was converted to **20β** (108 mg, 92%). R_f = 0.31 (9:1 methylene chloride/methanol). ^{1}H NMR (CD_3OD): δ 3.77 (dd, 1H, J = 3.6 and 12.2 Hz), 3.95 (dd, 1H, J = 2.9 and 12.2 Hz), 4.08 (m, 1H), 4.19 (m, 1H), 4.24 (m, 1H), 5.06 (d, 1H, J = 5.0 Hz), 7.26 (m, 2H), 7.56 (m, 2H). ^{13}C NMR (CD_3OD): δ 62.61, 72.09, 77.66, 80.78, 86.27, 115.85, 123.76. MS (IC, isobut): m/z 251 $[M + H]^+$.

2-α-D-Ribofuranosyl-5-iodobenzimidazole (21α). By the same procedure as described above for the preparation of **19β**, **16aα** (300 mg, 0.4 mmol) was converted to **21α** (127 mg, 86%). R_f = 0.30 (9:1 methylene chloride/methanol). ^{1}H NMR (CD_3OD): δ 3.86 (2dd, 2H, J = 11.6, 6.1, and 4.8 Hz), 4.31 (m, 1H), 4.38 (m, 1H), 4.44 (dd, 1H, J = 4.4 and 7.2 Hz), 5.02 (d, 1H, J = 7.2 Hz), 7.35 (d, 1H, J = 8.5 Hz), 7.52 (dd, 2H, J = 1.8 and 8.5 Hz), 7.91 (br s, 1H). ^{13}C NMR (CD_3OD): δ 62.03, 73.27, 78.64, 79.19, 83.20, 117.02, 132.39, 156.68. MS (ES): m/z 377 $[M + H]^+$. Anal. Calcd for $C_{12}H_{13}IN_2O_4$: C, 38.32; H, 3.48; N, 7.45. Found: C, 38.59; H, 3.70; N, 7.72.

2-α-D-Ribofuranosylimidazole (22α). By the same procedure as described above, **17aα** (585 mg, 1 mmol) was converted to **22α** (165 mg, 83%). R_f = 0.15 (9:1 methylene chloride/methanol). ^{1}H NMR (CD_3OD): δ 3.85 (2dd, 2H, J = 11.8, 6.5, and 4.7 Hz), 4.32 (m, 2H), 4.43 (m, 1H), 5.02 (d, 1H, J = 7.5 Hz), 7.50 (s, 2H). ^{13}C NMR (CD_3OD): δ 61.72, 72.75, 75.99, 78.56, 83.93, 120.41, 148.31. MS (ES): m/z 201 $[M + H]^+$. Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 47.76; H, 6.31; N, 13.82.

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Supporting Information Available: Molecular modeling results (Tables 4−9), copies of MS and NMR spectra (^{1}H, ^{13}C, 2D COSY ^{1}H−^{1}H and ^{1}H−^{13}C) of compounds **3e**, **4a**, **7a**, **7b**, **9a**, **10a**, **11a**, **14aα**, **15aα**, **18dα**, **18dβ**, **20α**, and **20β**, and text giving experimental procedures and characterization data for **2**−**5**, **6b**, **7a**,**b**,**e**, **8a**, **9a**, **10b**, **11a**,**b**,**e**, **12a**, **13a**, **14bα**, **15aα**, **15bα**, **15eα**, **16aα**, and **17aα**. This material is available free of charge via the Internet at http://pubs.acs.org.

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