IR ($CDCl_3$) 3480 (br), 2970, 2945, 2910, 1738, 1725 cm^{-1}; mass spectrum (70 eV), *m/e* (relative abundance) 515 (6.6) [M - 15], 452 (23.9) [M - CH_3COOH - H_2O], 437 (22.8), 310 (30.6), 173 (75.3), 160 (100).

Alkylation of 7 with Dimethyl Malonate. To a suspension of 12 mg (0.5 mmol) of sodium hydride in 2 mL of tetrahydrofuran was added 0.06 mL (0.5 mmol) of dimethyl malonate in 2 mL of tetrahydrofuran. After this mixture was stirred for 1 h under an argon atmosphere, a solution of 81 mg (0.2 mmol) of **7** in 1 mL of THF was added. Following a 10-h reaction period, the reaction was quenched by addition of ice water and extracted with ether. Evaporation of the washed and dried extracts gave a white solid, which was chromatographed (silica gel, ethyl acetate/hexane) to yield 70.5 mg (75% yield) of **11** and 6 mg (6%) of a compound tentatively identified as **10b**, based on its similarity to **10a**. Compound **11** exhibited the following properties: mp 185-187 °C; ^1H NMR ($CDCl_3$) δ 5.35 (2 H, two overlapping doublets), 4.6 (1 H, m), 4.29 (1 H, dd, J = 6.3 and 13 Hz), 3.76 (3 H, s), 2.75 (1 H, dd, J = 13 and 18 Hz), 2.49 (1 H, dd, J = 6.3 and 18 Hz), 1.99 (3 H, s), 1.74 (3 H, s), 0.99 (3 H, s), 0.86 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 170.62, 170.41, 169.04, 143.19, 139.64, 128.96, 122.1, 78.53, 73.71, 52.62, 51.59, 49.4, 46.71, 45.95, 37.98, 37.42, 36.75, 34.69, 32.57, 31.24, 30.79, 27.63, 21.36, 21.07, 19.65, 19.19, 16.88; IR ($CDCl_3$) 2950, 1752, 1737, 1726, 1440 cm^{-1}; mass spectrum (70 eV), *m/e* (relative abundance) 410 (75) [M - CH_3COOH], 395 (21), 370 (8.7), 355 (10.4), 295 (46), 157 (67.4), 135 (100). Calculated for $C_{26}H_{34}O_4$: 410.24570. Found: 410.2456.

Rearrangement of 11 to 12. To a solution of 50 mg (0.1 mmol) of **11** in 3 mL of diethyl ether was added 9 mg of zinc-copper couple, and this mixture was stirred under an argon atmosphere while a solution of 0.013 mL of trichloroacetyl chloride in 3 mL of ether was added dropwise. Following 4 h at reflux, the reaction mixture was filtered through a Celite pad with additional ether and washed successively with saturated aqueous bicarbonate and brine solutions. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield 43.5 mg (87%) of **12**. The ^1H NMR of this product indicated it was a mixture of epimers (4:1), the major isomer showing the following signals: δ 5.68 (1 H, dd, J = 1.5 and 3.0 Hz), 5.34 (1 H, d, J = 4.0 Hz), 4.6 (1 H, m), 3.75 (3 H, s), 3.6 (1 H, dd, J = 6 and 18 Hz), 2.025 (3 H, s), 1.67 (3 H, s), 1.03 (3 H, s), 0.97 (3 H, s); IR ($CDCl_3$) 2950, 1775, 1735, 1720 cm^{-1}.

Hydrolysis and Decarboxylation of 12 to 6a. To a solution of **12** (47 mg, 0.1 mmol) in 2 mL of methanol was added 3 mL of 0.1 M methanolic potassium hydroxide, and this mixture was refluxed for 3 h. The cooled reaction mixture was acidified to pH 5 by addition of 0.1 N HCl and then evaporated to dryness. The residue was mixed with 5 mL of benzene, refluxed for 1 h, cooled, and then partitioned in a water-ether mixture. The ether extracts were washed and dried and on evaporation gave 32 mg (>86%) of **6a**, identical in all respects with the sample prepared by hydrolysis of **6b**.

Acknowledgment. We thank Mr. Ernest Oliver for assistance in obtaining mass spectra.

Supplementary Material Available: X-ray data for **5**, experimental procedures, positional and thermal parameters, bond distances, bond angles, torsion angles, a drawing of a single molecule showing 50% probability ellipsoids, and a stereoview of the unit cell showing 20% probability ellipsoids (23 pages). Ordering information is given on any current masthead page.

Efficient Synthesis of 5-(β-D-Ribofuranosyl)nicotinamide and Its α-Isomer[1]

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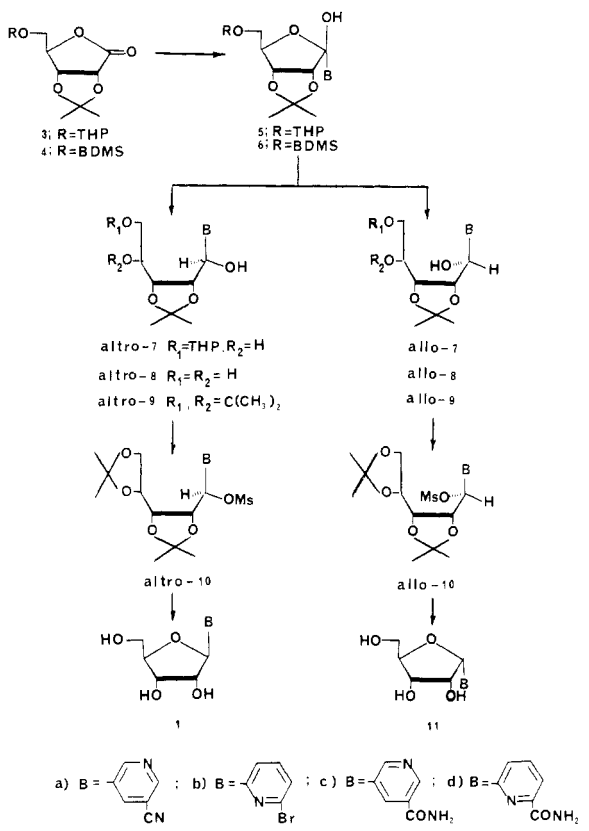
Condensation of 2,3-*O*-isopropylidene-5-*O*-(tetrahydropyranyl)-D-ribonolactone (**3**) with 3-cyano-5-lithiopyridine afforded 1-(3-cyanopyridin-5-yl)-2,3-*O*-isopropylidene-5-*O*-(tetrahydropyranyl)-β-D-ribofuran-1-ulose (**5a**), which was reduced with $NaBH_4$ to a 1:1 *allo/altro* mixture of 5-[2,3-*O*-isopropylidene-5-*O*-(tetrahydropyranyl)-D-pentitol-1-yl]-3-cyanopyridine (**7a**). The isomers were chromatographically separated. Treatment of *allo*-**7a** with TsOH/MeOH gave 5-(2,3-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-**8a**), which was acetonated to give 5-(2,3:4,5-di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-**9a**). Mesylation of *allo*-**9a** to *allo*-**10** followed by acid hydrolysis with $CF_3CO_2H/CHCl_3$ afforded 5-(α-D-ribofuranosyl)-3-cyanopyridine (**11a**). The β-isomer **1a** was synthesized in a similar manner from *altro*-**7a**. Inversion of the configuration at the C-1 position of 6-(2,3:4,5-di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-2-bromopyridine (*allo*-**9b**) into the corresponding *altro* isomer *altro*-**9b** was achieved albeit in modest yield (24%) by mesylation of *allo*-**9b** to *allo*-**10b** followed by treatment with potassium superoxide. Interconversion of *altro*-**9a** or **-9b** into the corresponding *allo* derivatives was readily achieved in excellent yield by oxidation with CrO_3/pyridine/Ac_2O to the corresponding keto intermediates **19** followed by borohydride reduction. Treatment of the 1-*O*-mesylate *allo*-**10b** with NaN_3 in DMF afforded the corresponding 1-azido-1-deoxy *altro* derivative (**17**). Similar treatment of the 1-*O*-triflyl derivatives *allo*-**15a,b** with NaN_3 or NaOAc in DMF surprisingly afforded *allo*-**9a,b** in good yield.

Recently an interest in the preparation of analogues of nicotinamide riboside has grown increasingly.[2-5] Biochemical behavior of the nicotinamide adenine dinucleotide (NAD) analogues containing the α-anomer of nicotinamide nucleosides has become of current interest.[3,5] We have reported the synthesis of 5-(β-D-ribofuranosyl)-nicotinamide[6] (**1c**, Scheme I), the C-nucleoside isostere of nicotinamide riboside, by condensation of 2,4:3,5-di-*O*-benzylidene-D-*aldehydo*-ribose[7] with 3-bromo-5-lithiopyridine to an *altro/allo* mixture followed by conversion of the bromopyridine aglycon into the nicotinamide moiety. This procedure, however, was inefficient and not amenable to large-scale preparations due to (i) involvement of a ribose dithioacetal during the preparation of the key starting material, (ii) the formation of an *altro/allo* isom-

(1) Nucleosides. 151.
(2) Dixon, M.; Webb, E. C. *Enzymes*, 3rd ed.; Academic: New York, 1979; p 478.
(3) Kam, B. L.; Malver, O.; Marschner, T. M.; Oppenheimer, N. J. *Biochemistry* **1987**, *26*, 3453.
(4) Robins, R. K.; Revankar, G. R. *Med. Res. Rev.* **1985**, *5*, 273.
(5) Oppenheimer, N. J. *J. Biol. Chem.* **1986**, *261*, 12209.
(6) Kabat, M. M.; Pankiewicz, K. W.; Watanabe, K. A. *J. Med. Chem.* **1987**, *30*, 924.
(7) Potgierter, J. J.; MacDonald, D. L. *J. Org. Chem.* **1961**, *26*, 3934.

0022-3263/88/1953-3473$01.50/0

Scheme I



eric mixture during the condensation of the aldehyde and lithiopyridine, (iii) the difficulty of separation of these isomers, and (iv) consequently, the low yield of the desired C-nucleoside **1c**. In order to circumvent some of the above problems, we recently developed an alternative procedure[8] for the synthesis of pyridine C-nucleosides by using 5-*O*-(tetrahydropyran-2-yl)-2,3-*O*-isopropylidene-D-ribonolactone[9] (**3**) as the starting material, which was condensed with 2-bromo-6-lithiopyridine to give 6-(β-D-ribofuranosyl)picolinamide (**1d**). Although only one condensation product, 1-(2-bromopyridin-6-yl) 2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-β-D-ribofuran-1-ulose (**5**), was obtained, the subsequent reduction of **5** afforded the *allo* isomer as the major product from which the α-C-nucleoside was obtained. The β-C-nucleoside **1d** was prepared only from the minor *altro* isomer.

In this paper we describe a condensation reaction of **3** with 3-cyano-5-lithiopyridine, which, after $NaBH_4$ reduction, afforded almost a 1:1 ratio for the *altro*/*allo* formation. We also present the results of our studies on the interconversion of the *allo* derivatives of 3-cyanopyridine **9a** and 2-bromopyridine **9b** into their corresponding *altro* counterparts, which gave rise eventually to the desired β-C-nucleosides. We also demonstrate the conversion of the *altro*-**9** derivatives into their corresponding *allo*-**9** isomers.

Addition of **3** with 3-cyano-5-lithiopyridine[10] afforded the diastereomeric 1-(3-cyanopyridin-5-yl)-2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-β-D-ribofuran-1-ulose (**5a**) in 43% yield. One of the diastereomers was obtained in crystalline form, which was assigned the β configuration on the basis of Imbach's rule.[11] A similar condensation of **3** with benzothiazole and 1-benzylbenzimidazole had been reported by Ogura and Takahashi,[12] and the β configuration was assigned to their products on the basis of Cotton effects.

All our attempts at removal of the anomeric hydroxyl group from **5a**, which would lead directly to the desired pyridine C-nucleoside, including chlorination, sulfonylation, and direct reduction with Et_3SiH, failed. We found, however, that the hemiketal ring in **5a** could be hydrogenolyzed by treatment with $NaBH_4$, giving rise to an *allo*/*altro* mixture of 1-substituted pentitols **7a**. Both crystalline and diastereomeric **5a** gave **7a** with the same *allo*/*altro* ratio. These isomers were separated on a silica gel column. The *allo* isomer (*allo*-**7a**) was obtained in 35% yield as crystals while the *altro* isomer (*altro*-**7a**) was obtained in 38% yield as an oil. After selective removal of the 5′-*O*-tetrahydropyranyl (THP) group of *altro*-**7a**, the product *altro*-**8a** was treated with acetone and *p*-TsOH to give 5-(2,3:4,5-di-*O*-isopropyliden-D-*altro*-pentitol-1-yl)-3-cyanopyridine (*altro*-**9a**) in which only one hydroxyl at C-1 is free. Compound *altro*-**9a** was mestylated to *altro*-**10a**, which, upon treatment with trifluoroacetic acid (TFA), was converted into 5-(β-D-ribofuranosyl)-3-cyanopyridine (**1a**). In a similar manner, 5-(α-D-ribofuranosyl)-3-cyanopyridine (**11a**) was prepared from *allo*-**7a**.

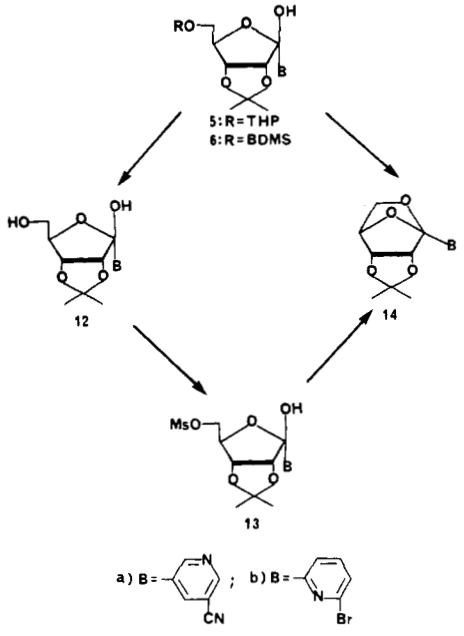
The cyano group of both *allo*-**9a** and *altro*-**9a** was converted in the presence of Amberlite IRA 400 (OH^-) into the corresponding nicotinamide analogues **9c**. Mesylation of *allo*-**9c** followed by TFA treatment of the mesylate *allo*-**10c** afforded 5-(α-D-ribofuranosyl)nicotinamide (**11c**). Similarly, 5-(β-D-ribofuranosyl)nicotinamide (**1c**) was obtained from *altro*-**9c**.

Reaction of 2-bromo-6-lithiopyridine with **3** gave a diastereomeric mixture (due to chirality at C-2 of THP), which, upon treatment with $NaBH_4$ followed by removal of the THP group, afforded a mixture of *allo*/*altro* isomers in a 4:1 ratio.[8] In order to examine the effects of the 5′ protecting group on the stereochemical course of borohydride reduction, we first attempted to remove the THP group from the addition reaction product. All our attempts at selective removal of the THP group from the condensation product, however, failed: THP removal with *p*-TsOH in MeOH was always accompanied by deacetonation to a considerable extent. We then synthesized 1-(2-bromopyridin-6-yl)-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuran-1-ulose (**6b**), which was obtained as a single anomeric product when 2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-D-ribonolactone[13] was allowed to react with 2-bromo-6-lithiopyridine. The assignment of the anomeric configuration of **6b** according to Imbach's method by ^1H NMR spectroscopy, however, was not possible, since the difference in chemical shifts of two methyl signals of the isopropylidene group ($\Delta\delta$ value) was large (0.15 ppm) in $CDCl_3$ and very small (0.03 ppm) in Me_2SO-d_6. A chemical means was, therefore, sought to establish the anomeric structure of **6b**.

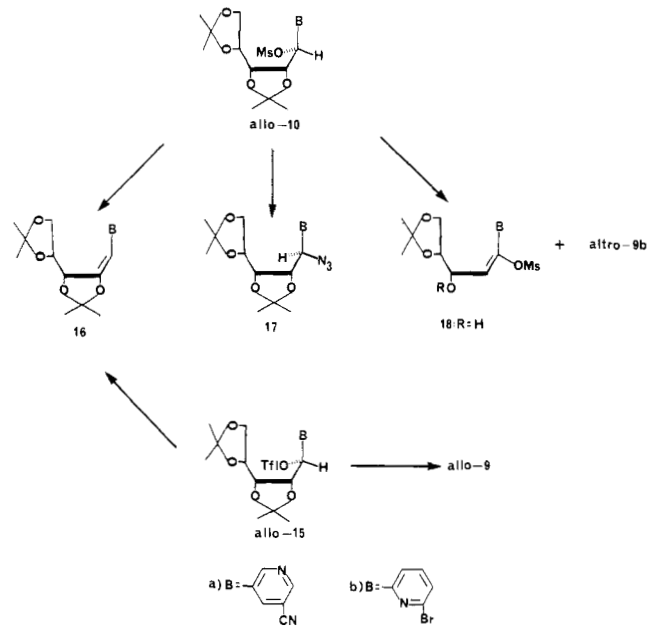
Desilylation of **6b** with Et_3NHF to **12b** (Scheme II), followed by mesylation of **12b**, gave the mesylate **13b** in

(8) Kabat, M. M.; Pankiewicz, K. W.; Sochacka, E.; Watanabe, K. A. *Chem. Pharm. Bull.* **1988**, *36*, 634.
(9) Ogura, H.; Takahashi, H.; Itoh, T. *J. Org. Chem.* **1972**, *37*, 72.
(10) 3-Bromo-5-cyanopyridine has been reported by Zwart and Wibaut (Zwart, C.; Wibaut, J. P. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1062), who synthesized this compound from 3,5-dibromopyridine via an elaborated, multistep procedure. We prepared this pyridine from commercially available 3-bromonicotinic acid, which was converted into 3-bromonicotinamide and then dehydrated with $POCl_3$. This procedure is much superior to the original method in terms of simplicity and yield.
(11) Imbach, J.-L. *Ann. N.Y. Acad. Sci.* **1975**, *255*, 177. Chu, C. K.; El-Kabbani, F. M.; Thompson, B. B. *Nucleosides Nucleotides* **1984**, *3*, 1.
(12) Ogura, H.; Takahashi, H. *J. Org. Chem.* **1974**, *39*, 1374.
(13) Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395. In carbohydrate nomenclature, designation of anomeric configuration is determined by the orientation of the C-1′ hydroxyl group.

Scheme II



Scheme III



high yield. Treatment of **13b** with DBU in CH_2Cl_2 afforded the 1,5-anhydro derivative **14b** in quantitative yield. The 3-cyanopyridine derivative **6a**, upon desilylation with Et_3NHF, afforded **12a**, which was then mesylated to **13a**. Although the mesylate **13a** was detected on TLC, a large portion of **13a** was converted into the 1,5-anhydro derivative **14a** in our attempts at purification on a silica gel column. Apparently, the formation of **14a** with the 2,7-dioxabicyclo[2.2.1]heptane system occurred readily on the silica gel column. The results unambiguously established the β configuration[13] of the condensation products **6a** and **6b**, providing evidence that $NaBH_4$ reduction was not stereospecific and excess *allo*-**7b** was produced during the reduction of **5b**.

Cyclization of the mesylates **10** to the corresponding C-nucleosides was regio- and stereospecific. No formation of pyranosyl isomers or α,β-isomerization was observed. Thus, treatment of *allo*-**10** or *altro*-**10** with trifluoroacetic acid (TFA) afforded exclusively the α-C-nucleoside **11** and the β-C-nucleoside **1**, respectively. The conversion of the *allo* isomer, *allo*-**9** or -**10**, into the corresponding *altro* counterpart, *altro*-**9** or -**10**, became of particular importance for the efficient synthesis of the β-C-nucleoside **1**. Treatment of *allo*-**10b** with NaOAc in DMF or HMPA at 100–120 °C afforded a less polar product, which was assigned as 6-[2,3:4,5-di-*O*-isopropylidene-2,3(*S*),4(*S*),5-tetrahydroxy-(*E*)-pent-1-en-1-yl]-2-bromopyridine (**16b**) (Scheme III). The ^1H NMR spectrum of **16b** showed the presence of two isopropylidene groups, the absence of a mesyl group in the molecule, a doublet at δ 5.89 readily assignable to H-1′, which coupled to H-3′ with a typical allylic coupling constant[14] ($J_{1',3'}$ = 1.9 Hz), and a double doublet for H-3′ at δ 5.57 ($J_{1',3'}$ = 1.9 Hz, $J_{3',4'}$ = 2.7 Hz). This spectrum was fully consistent with the olefinic structure of **16b**. The elemental analyses were also consistent with structure **16b**. Elimination rather than nucleophilic displacement occurred.

When *allo*-**10** was treated with a better nucleophile N_3^-, however, displacement reaction proceeded smoothly, and the corresponding 1′-azido product **17b** was obtained in 72% yield. These results indicate that a stronger oxygen nucleophile might displace the mesyloxy group in *allo*-**10a** to give the desired *altro*-**9b**. Indeed, treatment of *allo*-**10b** with potassium superoxide and 18-crown-6, according to the procedure of Corey et al.,[15] afforded *altro*-**9b** (albeit in low yield, 24%). From the reaction mixture was isolated a more polar, second product. The ^1H NMR spectrum of the second product (25%) showed three methyl and one dissociable proton signals at δ 1.36, 1.42, 3.42, and 2.66, respectively, indicating the presence of only one isopropylidene and the intact mesyl group in the molecule. Also, a doublet at δ 6.55 ($J_{2',3'}$ = 9.0 Hz) and a double doublet at δ 4.70 ($J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 5.3 Hz) are consistent with the 1′,2′-ene structure of **18b**. Compound **18b**, apparently, was produced by abstraction of the proton from C-1′, followed by trans elimination forming the 1′,2′-olefin with concomitant release of an acetone molecule from *allo*-**10b** giving rise to **18b**. Indeed, when *allo*-**10b** was treated with NaOH in DMF, the olefin **18b** was obtained in high yield.

We also triflylated *allo*-**9a** and *allo*-**9b** to the corresponding 1′-*O*-triflyl derivatives, *allo*-**15a** and *allo*-**15b** (Scheme III), in the hope that these latter triflates may increase the rate of nucleophilic reaction compared to the rate of elimination in the above reactions. Surprisingly, however, treatment of these triflyl derivatives with NaOAc or NaN_3 afforded the corresponding products with retention of the C-1′ configuration, namely, *allo*-**9a** and *allo*-**9b**. The latter product was contaminated with a significant amount of the elimination product **16b**. Apparently, the rate of intermolecular solvolysis of the triflyl ester was greater than that of nucleophilic displacement of the triflate group. Recently, we reported[16] a *triflyl migration* in which the sulfur atom in the triflyl group was attacked by the vicinal cis hydroxyl group, leading to cleavage of the S–O bond in triflates (*intramolecular* solvolysis). Intermolecular solvolysis of triflyl esters, to our knowledge, is quite rare.

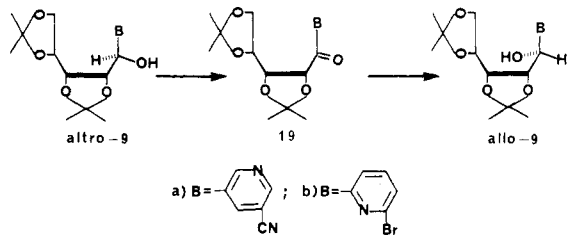
Conversion of *altro*-**9** to *allo*-**9** via an oxidation–reduction approach was simple and straightforward. Actually, both *allo*-**9** and *altro*-**9** gave the same keto derivative **19**

(14) Watanabe, K. A.; Goody, R. S.; Fox, J. J. *Tetrahedron* **1970**, *26*, 3883.

(15) Corey, E. J.; Nicolaon, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183.

(16) Pankiewicz, K. W.; Nawrot, B. C.; Watanabe, K. A. *J. Org. Chem.* **1986**, *51*, 1525.

Scheme IV



in high yield upon oxidation with CrO_3/pyridine/Ac_2O. Studies with a molecular model predicted that the oxidation intermediate **19** (Scheme IV), upon reduction, would give the *allo* isomer as the major product according to Cram's rule.[17] Indeed, reduction of **19** with $NaBH_4$ proceeded in highly stereoselective manner, and the *allo*-**9** was obtained in high yield as the only product of the reaction.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70–230 mesh, ASTM, Merck). TLC was performed on Analtech Uniplates with short-wavelength UV light for visualization. Elementary analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^1H NMR spectra were recorded on a JEOL FX90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), and dd (double doublet). Values given for coupling constants are first order.

1-(3-Cyanopyridin-5-yl)-2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-β-D-ribofuran-1-ulose (5a). To a solution of 3-bromo-5-cyanopyridine[10] (2.15 g, 11.7 mmol) in dry Et_2O (150 mL) was slowly added *n*-BuLi (4.65 mL of 2.5 M solution in *n*-hexane, 11.7 mmol) at −78 °C under an argon atmosphere with stirring. After the addition was completed, a solution of **3** (2.45 g, 9 mmol) in THF (20 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature, and stirring continued overnight. The reaction was quenched by addition of H_2O (30 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layer and extracts were washed (H_2O, 30 mL), dried (Na_2SO_4), and concentrated in vacuo, and the residue was chromatographed on a silica gel column ($CHCl_3$) to give **5a** (2.0 g, 43%): ^1H NMR ($CDCl_3$) δ 1.25 (3 H, s, *i*-Pr), 1.39 (3 H, s, *i*-Pr), 1.62–1.71 (6 H, m, THP), 3.61–4.17 (4 H, m, H-5′,5″ and THP), 4.58–4.70 (3 H, m, H-2′,3′,4′), 4.98–5.06 (1 H, m, THP), 5.60 (0.5 H, s, O*H*), 5.70 (0.5 H, s, O*H*), 8.17 (0.5 H, t, H-4), 8.18 (0.5 H, t, H-4), 8.81 (1 H, d, H-6), 8.98 (1 H, d, H-2).

One of the diastereomers was crystallized from $CHCl_3$/*n*-hexane: mp 135–137 °C; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, s, *i*-Pr), 1.39 (3 H, s, *i*-Pr), 1.62–1.71 (6 H, m, THP), 3.61–4.17 (4 H, m, H-5′,5″ and THP), 4.60–4.70 (3 H, m, H-2′,3′,4′), 5.00 (1 H, dd, THP-2″, $J_{2'',Hax}$ = 5.8 Hz, $J_{2'',Heq}$ = 1.4 Hz), 5.60 (1 H, s, O*H*), 8.17 (1 H, dd, H-4, $J_{4,6}$ = 1.9 Hz, $J_{2,4}$ = 2.1 Hz), 8.82 (1 H, d, H-6), 8.98 (1 H, d, H-2); ^1H NMR (Me_2SO-d_6) δ 1.19 (3 H, s, *i*-Pr), 1.28 (3 H, s, *i*-Pr). Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.74; H, 6.37; N, 7.44.

1-(3-Cyanopyridin-5-yl)-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuran-1-ulose (6a). In a similar manner as above, 2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-D-ribonolactone[13] (**4**) was treated with 3-cyano-5-lithiopyridine. The crude product was chromatographed on a silica gel column (*n*-hexane/EtOAc, 9:1) to give **6a** (1.08 g, 21%) as crystals: mp 114–116 °C; ^1H NMR ($CDCl_3$) δ 0.19 (3 H, s, MeSi), 0.21 (3 H, s, MeSi), 0.97 (9 H, s, *t*-BuSi), 1.25 (3 H, s, *i*-Pr), 1.40 (3 H, s, *i*-Pr), 3.89 (2 H, d, H-5′,5″), 4.54–4.60 (2 H, m, H-2′,4′), 4.92 (1 H, dd, H-3′, $J_{2',3'}$ = 5.5 Hz, $J_{3',4'}$ = 0.5 Hz), 5.92 (1 H, s, O*H*), 8.19 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.81 (1 H, d, H-6), 8.99 (1 H, d, H-2). Anal. Calcd for $C_{20}H_{30}N_2O_5Si$: C, 59.09; H, 7.44; N, 6.89. Found: C, 58.96; H, 7.36; N, 6.95.

(17) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

1-(2-Bromopyridin-6-yl)-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuran-1-ulose (6b). To a solution of 2-bromo-6-lithiopyridine (prepared from 200 mg, 0.53 mmol, of 2,6-dibromopyridine with *n*-butyllithium) was added slowly a solution of 2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-D-ribonolactone[13] (**4**, 200 mg, 0.69 mmol) in Et_2O (10 mL), and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of H_2O, the aqueous layer was extracted with Et_2O, the combined organic solutions were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (*n*-hexane/EtOAc, 9:1) to give **6b** (240 mg, 79%) as a foam: ^1H NMR ($CDCl_3$) δ 0.14 (6 H, s, Me_2Si), 0.94 (9 H, s, *t*-Bu), 1.27 (3 H, s, *i*-Pr), 1.42 (3 H, s, *i*-Pr), 3.73–3.90 (2 H, m, H-5′,5″), 4.43–4.45 (1 H, m, H-4′), 4.73 (1 H, d, H-2′, $J_{2',3'}$ = 5.5 Hz), 4.90–5.04 (1 H, m, H-3′), 7.41–7.49 (3 H, m, H-3,4,5). This product is contaminated with 10% of starting material as evidenced by ^1H NMR, MS, and elemental analyses but was used directly in the synthesis of **12**. MS: *m/z* 460 (MH^+, 100).

5-[2,3-*O*-Isopropylidene-5-*O*-(tetrahydropyran-2-yl)-D-*allo*-pentitol-1-yl]-3-cyanopyridine (*allo*-7a) and 5-[2,3-*O*-Isopropylidene-5-*O*-(tetrahydropyran-2-yl)-D-*altro*-pentitol-1-yl]-3-cyanopyridine (*altro*-7a). A mixture of crystalline **5a** (5.4 g, 14.36 mmol) and $NaBH_4$ (1.63 g, 43 mmol) in MeOH (100 mL) was stirred at room temperature for 24 h. The mixture was concentrated in vacuo, and the residue was partitioned between Et_2O (100 mL) and H_2O (50 mL). The organic layer was separated, and the aqueous layer was extracted first with Et_2O (2 × 150 mL) and then with $CHCl_3$ (3 × 150 mL). The combined organic layer and ethereal extracts were washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo, and the residue was chromatographed on a silica gel column using $CHCl_3$ containing 2% EtOH as the eluent.

The isomer *allo*-**7a** (1.55 g, mp 70–75 °C) was eluted first, followed by *altro*-**7a** (0.15 g, liquid). From the $CHCl_3$ extracts, in a similar chromatographic separation, were obtained 0.35 g of *allo*-**7a** and 1.9 g of *altro*-**7a**.

Compound *allo*-**7a**: ^1H NMR ($CDCl_3$) δ 1.24 (3 H, s, *i*-Pr), 1.41 (3 H, s, *i*-Pr), 1.41–1.56 (6 H, m, THP), 3.63–4.51 (8 H, m, H-2′,3′,4′,5′,5″ and THP), 4.85–5.09 (2 H, m, H-1′ and OH, collapsed to a doublet at δ 4.90 upon addition of D_2O, $J_{1',2'}$ = 9.0 Hz), 5.37 (1 H, d, OH), 8.10 (1 H, dd, H-4, $J_{4,6}$ = 1.9, $J_{2,4}$ = 2.2 Hz), 8.79 (1 H, d, H-6), 8.88 (1 H, d, H-2). Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.21; H, 6.93; N, 7.40. Found: C, 59.91; H, 7.05; N, 7.42.

Compound *altro*-**7a**: ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s, *i*-Pr), 1.54 (3 H, s, *i*-Pr), 1.55–1.85 (6 H, m, THP), 3.49–4.32 (9 H, m, H-2′,3′,4′,5′,5″, OH, THP), 5.28 (2 H, m, H-1′ and OH, became a singlet upon addition of D_2O), 8.11 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 hz), 8.77 (1 H, d, H-6), 8.83 (1 H, d, H-2). Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.21; H, 6.93; N, 7.40. Found: C, 59.89; H, 6.97; N, 7.34.

5-(2,3-*O*-Isopropylidene-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-8a). A mixture of *allo*-**7a** (1.9 g, 5.0 mmol) and a catalytic amount of *p*-TsOH (ca. 10 mg) in MeOH (100 mL) was stirred at room temperature overnight. The reaction was quenched by addition of Et_3N (1 mL), and the mixture was concentrated in vacuo. The residue was chromatographed on a silica gel column ($CHCl_3$/EtOH, 9:1 v/v) to give *allo*-**8a** (1.25 g, 85%): mp 124–126 °C; ^1H NMR (Me_2SO-d_6) δ 1.17 (3 H, s, *i*-Pr), 1.31 (3 H, s, *i*-Pr), 3.45–4.34 (5 H, m, H-2′,3′,4′,5′,5″), 4.62 (1 H, t OH), 4.84 (1 H, d, H-1′, $J_{1',2'}$ = 8.2 Hz), 5.41 (1 H, d, OH), 6.25 (1 H, d, OH), 8.30 (1 H, dd, H-4, $J_{4,6}$ = 1.9 Hz, $J_{2,4}$ = 2.2 Hz), 8.84 (1 H, d, H-6), 8.93 (1 H, d, H-2). Anal. Calcd for $C_{14}H_{18}N_2O_5 \cdot {}^1/_4H_2O$: C, 56.27; H, 6.20; N, 9.37. Found: C, 56.42; H, 6.20; N, 9.12. A small amount of H_2O in the analytical sample was detected by ^1H NMR.

In a similar manner, *altro*-**7a** (2.5 g, 6.6 mmol) was converted into **5-(2,3-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-3-cyanopyridine (*altro*-8a)** (1.48 g, 76%, oil): ^1H NMR (Me_2SO-d_6) δ 1.22 (3 H, s, *i*-Pr), 1.47 (3 H, s, *i*-Pr), 3.58–4.19 (5 H, m, H-2′,3′,4′,5′,5″), 4.55 (1 H, br s, OH), 5.08 (2 H, br s, H-1′ and OH, became a sharp singlet for 1 H upon addition of D_2O), 5.44 (1 H, d, OH), 8.17 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.81 (1 H, d, H-6), 8.89 (1 H, d, H-2). Anal. Calcd for $C_{14}H_{18}N_2O_5 \cdot {}^1/_6H_2O$: C, 56.55; H, 6.21; N, 9.40. Found: C, 56.83; H, 6.43; N, 9.19. A small amount of H_2O in the analytical sample was detected by ^1H NMR.

5-(2,3:4,5-Di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-9a). A mixture of *allo*-**8a** (1.25 g, 4.25 mmol) and *p*-TsOH (ca. 10 mg) in Me_2CO (30 mL) was stirred overnight at room temperature. After addition of Et_3N (1 mL), the mixture was concentrated in vacuo and the residue chromatographed on a silica gel column (2% EtOH in $CHCl_3$) to give *allo*-**9a** (1.2 g, 84%): mp 139–140 °C (after crystallization from $CHCl_3/Et_2O$); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, s, *i*-Pr), 1.41–1.53 (9 H, br s, *i*-Pr), 3.96–4.32 (5 H, m, H-2′,3′,4′,5′,5″), 4.94 (2 H, dd, H-1′ and 1-OH, became a doublet upon addition of D_2O, $J_{1',2'}$ = 9.0 Hz), 8.10 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.80 (1 H, d, H-6), 8.90 (1 H, d, H-2). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 61.06; H, 6.66; N, 8.31.

In a similar manner, *altro*-**8a** (1.25 g, 4.25 mmol) was isopropylidenated to give **5-(2,3:4,5-di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-3-cyanopyridine (*altro*-9a)** (1.02 g, 72%): mp 101–102 °C (after crystallization from $CHCl_3$/*n*-hexane); ^1H NMR ($CDCl_3$) δ 1.25–1.44 (9 H, br s, *i*-Pr), 1.53 (3 H, s, *i*-Pr), 3.86–4.59 (5 H, m, H-2′,3′,4′,5′,5″), 5.21 (2 H, m, H-1′ and OH, became a doublet upon addition of D_2O, $J_{1',2'}$ = 2.5 Hz), 8.10 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.79 (1 H, d, H-6), 8.84 (1 H, d, H-2). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.86; H, 6.62; N, 8.31.

5-(2,3:4,5-Di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-nicotinamide (*allo*-9c). A mixture of *allo*-**9a** (1.5 g, 4.5 mmol), Amberlite IRA-400 (OH^- form) (7 g), MeOH (25 mL), and H_2O (25 mL) was heated at reflux for 4 h. The resin was filtered and washed with MeOH (2 × 15 mL). The combined filtrate and washings were concentrated in vacuo, and the residue was crystallized from $CHCl_3$/*n*-hexane to give *allo*-**9c** (1.44 g, 93%): mp 165–167 °C; ^1H NMR ($CDCl_3$) δ 1.22 (3 H, s, *i*-Pr), 1.38 (3 H, s, *i*-Pr), 1.44 (3 H, s, *i*-Pr), 1.50 (3 H, s, *i*-Pr), 4.03–4.29 (5 H, m, H-2′,3′,4′,5′,5″), 4.39 (1 H, d, H-1′, $J_{1',2'}$ = 8.8 Hz), 6.12 (2 H, br s, NH_2), 8.25 (1 H, dd, H-4, $J_{2,4}$ = 1.6 Hz, $J_{4,6}$ = 1.9 Hz), 8.83 (1 H, d, H-6), 8.97 (1 H, d, H-2). Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.87; N, 7.95. Found: C, 57.73; H, 7.08; N, 7.77.

By following the same procedure but using *altro*-**9a** (1.5 g, 4.5 mmol) as the starting material, we prepared **5-(2,3:4,5-di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)nicotinamide (*altro*-9c)** (1.4 g, 92%): mp 150–152 °C; ^1H NMR (Me_2SO-d_6) δ 1.22–1.27 (9 H, br s, *i*-Pr), 1.45 (3 H, s, *i*-Pr), 3.70–4.56 (5 H, m, H-2′,3′,4′,5′,5″), 4.90 (1 H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 5.47 (1 H, d, OH), 7.55 (1 H, br s, NH), 8.17 (2 H, m, H-4, NH), 8.67 (1 H, d, H-6, $J_{4,6}$ = 1.9 Hz), 8.89 (1 H, d, H-2, $J_{2,4}$ = 1.9 Hz). Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.87; N, 7.95. Found: C, 57.76; H, 6.81; N, 7.94.

5-(2,3:4,5-Di-*O*-isopropylidene-1-*O*-mesyl-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-10a). To a mixture of *allo*-**9a** (669 mg, 2 mmol), DMAP (5 mg), and Et_3N (870 μL, 6.2 mmol) in CH_2Cl_2 (10 mL) was added MsCl (390 μL, 5 mmol), and the mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of H_2O (2 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on a silica gel column ($CHCl_3$) to give *allo*-**10a** (700 mg, 85%) as a foam: ^1H NMR ($CDCl_3$) δ 1.33 (6 H, s, *i*-Pr), 1.36 (3 H, s, *i*-Pr), 1.45 (3 H, s, *i*-Pr), 2.97 (3 H, s, Ms), 3.79–4.23 (4 H, m, H-3′,4′,5′,5″), 4.62 (1 H, t, H-2′, $J_{1',2'}$ = $J_{2',3'}$ = 5.8 Hz), 5.92 (1 H, d, H-1′), 8.20 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.88 (1 H, d, H-6), 8.95 (1 H, d, H-2); MS, *m*/*z* 413 (MH^+, 100).

By using the same procedure, *altro*-**9a**, *allo*-**9c**, and *altro*-**9c**, the following compounds were prepared. **5-(2,3:4,5-Di-*O*-isopropylidene-1-*O*-mesyl-D-*altro*-pentitol-1-yl)-3-cyanopyridine (*altro*-10a)**: foam (82%); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, s, *i*-Pr), 1.33 (3 H, s, *i*-Pr), 1.37 (3 H, s, *i*-Pr), 1.56 (3 H, s, *i*-Pr), 3.02 (3 H, s, Ms), 3.82–4.49 (5 H, H-2′,3′,4′,5′,5″), 5.92 (1 H, d, H-1′, $J_{1',2'}$ = 4.9 Hz),8.13 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.87 (1 H, d, H-6), 8.91 (1 H, d, H-2). Anal. Calcd for $C_{18}H_{24}N_2O_7S$: C, 52.42; H, 5.87; N, 6.79. Found: C, 52.40; H, 5.90; N, 6.71.

5-(2,3:4,5-Di-*O*-isopropylidene-1-*O*-mesyl-D-*allo*-pentitol-1-yl)nicotinamide (*allo*-10c): foam (77%); ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s, *i*-Pr), 1.33 (3 H, s, *i*-Pr), 1.38 (3 H, s, *i*-Pr), 1.45 (3 H, s, *i*-Pr), 2.89 (3 H, s, Ms), 3.87–4.16 (4 H, m, H-3′,4′,5′,5″), 4.67 (1 H, dd, H-2′, $J_{1',2'}$ = 6.3 Hz, $J_{2',3'}$ = 4.7 Hz), 5.92 (1 H, d, H-1′), 6.50 (2 H, br s, NH_2), 8.40 (1 H, dd, H-4, $J_{2,4}$ = 1.9 Hz, $J_{4,6}$ = 2.2 Hz), 8.87 (1 H, d, H-6), 9.03 (1 H, d, H-2). Anal. Calcd for $C_{18}H_{26}N_2O_8S$: C, 49.76; H, 6.32; N, 6.27. Found: C, 49.46; H, 6.71; N, 6.58.

5-(2,3:4,5-Di-*O*-isopropylidene-1-*O*-mesyl-D-*altro*-pentitol-1-yl)nicotinamide (*altro*-10c): foam (86%); ^1H NMR ($CDCl_3$) δ 1.17 (3 H, s, *i*-Pr), 1.33 (3 H, s, *i*-Pr), 1.39 (3 H, s, *i*-Pr), 1.55 (3 H, s, *i*-Pr), 2.97 (3 H, s, Ms), 3.80–4.43 (4 H, m, H-3′,4′,5′,5″), 4.53 (1 H, dd, H-2′, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 5.7 Hz), 5.96 (1 H, d, H-1′), 6.10 (2 H, br s, NH_2), 8.33 (1 H, dd, H-4, $J_{2,4}$ = 1.9 Hz, $J_{4,6}$ = 2.2 Hz), 8.89 (1 H, d, H-6), 9.09 (1 H, d, H-2); MS, *m*/*z* 429 (MH^+, 25). This compound decomposed in a few days at room temperature.

5-(α-D-Ribofuranosyl)-3-cyanopyridine (11a). A solution of *allo*-**10a** (412 mg, 1 mmol) in TFA and $CHCl_3$ (4:1 v/v, 3 mL) was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was chromatographed on a silica gel column (15% EtOH in $CHCl_3$) to give 140 mg of **11a** (59%): mp 182–184 °C (after crystallization from EtOH); ^1H NMR (Me_2SO-d_6) δ 3.36–3.61 (2 H, m, H-5′,5″), 3.65–4.21 (3 H, m, H-2′,3′,4′), 4.65–5.10 (3 H, m, H-1′ and 2 × OH, became a doublet upon addition of D_2O, $J_{1',2'}$ = 3.0 Hz), 8.12 (1 H, t, H-4, $J_{2,4}$ = $J_{4,6}$ = 2.2 Hz), 8.75 (1 H, d, H-6), 8.83 (1 H, d, H-2). Anal. Calcd for $C_{11}H_{12}N_2O_4.{}^1/_2H_2O$: C, 53.87; H, 5.34; N, 11.43. Found: C, 53.73; H, 4.95; N, 11.13. Contamination of $^1/_2$ mol of H_2O in this sample was detected in the ^1H NMR spectrum at δ 3.35.

In a similar manner, *altro*-**10a** was converted into **5-(β-D-ribofuranosyl)-3-cyanopyridine (1a)** in 63% yield as colorless crystals: mp 129–131 °C (from EtOH); ^1H NMR (Me_2SO-d_6) δ 3.58–3.68 (2 H, m, H-5′,5″), 3.74–4.00 (3 H, m, H-2′,3′,4′), 4.72 (1 H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 4.92 (1 H, t, OH), 5.05 (1 H, d, OH), 5.17 (1 H, d, OH), 8.31 (1 H, t, H-4, $J_{2,4}$ = $J_{4,6}$ = 1.9 Hz), 8.85 (1 H, d, H-6), 8.92 (1 H, d, H-2). Anal. Calcd for $C_{11}H_{12}N_2O_4.{}^1/_2H_2O$: C, 53.87; H, 5.34; N, 11.43. Found: C, 54.19; H, 5.16; N, 11.19.

5-(α-D-Ribofuranosyl)nicotinamide (11c). Compound *allo*-**10c** (2.0 g, 4.64 mmol) was dissolved in a mixture of TFA and $CHCl_3$ (4:1 v/v, 3 mL), and the solution was stirred for 1.5 h at room temperature. The mixture was concentrated in vacuo, and the residue, after coevaporation with toluene (3 × 80 mL), was dissolved in a mixture of MeOH and H_2O (1:1), neutralized with Amberlite IRA 400 (OH^-). The resin was removed by filtration, the filtrate concentrated in vacuo, and the residue crystallized from EtOH to give **11c** (673 mg), mp 210–212 °C. The mother liquor of crystallization was concentrated and the residue chromatographed on a silica gel column ($CHCl_3$/EtOH, 9:1 v/v) to give an additional amount (70 mg) of **11c**, mp 210–212 °C (total yield 72%) (lit.[6] mp 210–212 °C). The ^1H NMR spectrum of this sample was identical with that of an authentic sample.[6]

By following the same procedure but using *altro*-**10c**, we obtained **5-(β-D-ribofuranosyl)nicotinamide (1c)** in 70% yield as colorless crystals, mp 178–180 °C (lit.[5] mp 176–178 °C). The ^1H NMR spectrum of this compound was identical with that of an authentic sample.[5]

1-(3-Cyanopyridin-5-yl)-2,3-*O*-isopropylidene-β-D-ribofuran-1-ulose (12a). Compound **6a** (414 mg, 1.02 mmol) was treated with a 1 M solution of Et_3NHF in THF (3.5 mL) at room temperature for 72 h. Excess Et_3NHF was decomposed by addition of $NaHCO_3$. The mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ (40 mL) and H_2O (10 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 5 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated in vacuo to give **12a** as a foam (291 mg, 98%): ^1H NMR ($CDCl_3$) δ 1.24 (3 H, s, *i*-Pr), 1.35 (3 H, s, *i*-Pr), 3.87 (2 H, d, H-5,5″), 4.54–4.68 (2 H, m, H-2′,4′), 5.00 (1 H, dd, H-3′, $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 1.4 Hz), 8.16 (1 H, dd, H-4, $J_{2,4}$ = 2.2 Hz, $J_{4,6}$ = 1.9 Hz), 8.77 (1 H, d, H-6), 8.92 (1 H, d, H-2). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.55; H, 5.52; N, 9.58. Found: C, 57.59; H, 5.60; N, 9.42.

In a similar manner, **6b** (525 mg, 1.14 mmol) was converted into **1-(2-bromopyridin-6-yl)-2,3-*O*-isopropylidene-β-D-ribofuran-1-ulose (12b)** (392 mg, 83%): mp 135–138 °C (after crystallization from Et_2O); ^1H NMR ($CDCl_3$) δ 1.27 (3 H, s, *i*-Pr), 1.48 (3 H, s, *i*-Pr), 3.14–3.83 (3 H, m, H-5′,5″, OH, collapsed to a doublet upon D_2O exchange), 4.48–4.52 (1 H, m, H-4′), 4.65 (1 H, d, H-2′, $J_{2',3'}$ = 5.7 Hz), 5.00 (1 H, dd, H-3′, $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 1.4 Hz), 6.21 (1 H, br s, OH), 7.45–7.68 (3 H, m, H-3,4,5); ^1H NMR (Me_2SO-d_6) δ 1.18 (3 H, s, *i*-Pr), 1.20 (3 H, s, *i*-Pr). Anal.

Calcd for $C_{13}H_{16}BrNO_5$: C, 45.10; H, 4.66; N, 4.05. Found: C, 44.87; H, 4.81; N, 3.91.

Compound **12b** was also prepared from **5b** in the following manner. A 1:1 diastereomeric mixture of **5b** (540 mg, 1.25 mmol) was dissolved in MeOH (15 mL) containing *p*-TsOH (ca. 15 mg), and the mixture was stirred at room temperature for 2 h. The solution was neutralized with NH_4OH and concentrated in vacuo and the residue chromatographed on a silica gel column (2% EtOH in $CHCl_3$). Unreacted **5b** (80 mg) was eluted first, followed by **12b**, which was crystallized from Et_2O (120 mg), mp 135–137 °C, undepressed upon admixture of **12b** sample prepared from **6b**.

1-(2-Bromopyridin-6-yl)-2,3-*O*-isopropylidene-5-*O*-mesyl-β-D-ribofuran-1-ulose (13b). To a solution of **12b** (100 mg, 0.29 mmol) in pyridine (5 mL) was added MsCl (25 μL, 0.3 mmol), and the mixture was stirred at room temperature for 3 h. Ethanol (5 mL) was added, the mixture was concentrated in vacuo, and the residue was chromatographed on a silica gel column (*n*-hexane/EtOAc, 3:2) to give 112 mg (91%) of **13b** as a foam: ^1H NMR (Me_2SO-d_6) δ 1.20 (3 H, s, *i*-Pr), 1.24 (3 H, s, *i*-Pr), 3.23 (3 H, s, Ms), 4.28–4.47 (3 H, m, H-4′,5′,5″), 4.72 (1 H, d, H-2′, $J_{2',3'}$ = 5.7 Hz), 4.90 (1 H, d, H-3′, $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 0 Hz), 7.16 (1 H, s, OH), 7.52–7.85 (3 H, m, H-3,4,5). Anal. Calcd for $C_{14}H_{18}BrNO_7S$: C, 39.63; H, 4.27; N, 3.30. Found: C, 39.80; H, 4.24; N, 3.29.

Similar treatment of **12a** (247 mg, 0.85 mmol), however, resulted in the formation of **13a** (R_f 0.4, major spot) and **14a** (R_f 0.8 minor) as evidenced by TLC (hexane/EtOAc, 3:2). Flash chromatography of this mixture in the above solvent system afforded **14a** (165 mg, 75%) as the only isolated product (mp 196–198 °C, from MeOH): ^1H NMR (Me_2SO-d_6) δ 1.22 (3 H, s, *i*-Pr), 1.37 (3 H, s, *i*-Pr), 3.48–3.69 (2 H, m, H-5′,5″), 4.47 (1 H, d, H-2′, $J_{2',3'}$ = 5.5 Hz), 4.70 (1 H, d, H-3′, $J_{2',3'}$ = 5.5 Hz, $J_{3',4'}$ = 0 Hz), 4.99 (1 H, m, H-4′), 8.37 (1 H, t, H-4, $J_{2,4}$ = $J_{4,6}$ = 2.2 Hz), 8.95 (1 H, s, H-6), 9.09 (1 H, d, H-2); ^{13}C NMR (Me_2SO-d_6) δ 152.9 (d, C-2, $J_{C2,H2}$ = 166.7 Hz), 151.0 (d, C-4, $J_{C4,H4}$ = 163.5 Hz), 137.9 (d, C-6, $J_{C6,H6}$ = 173.3 Hz), 129.4 (s, C-3), 116.4 (s, C-5), 111.3 (s, *i*-Pr), 108.2 (s, CN), 105.0 (s, C-1′), 82.3 (d, C-2′, $J_{C2',H2'}$ = 168.2 Hz), 79.9 (d, C-3′, $J_{C3',H3'}$ = 162.2 Hz), 78.2 (d, C-2′, $J_{C2',H2'}$ = 175.0 Hz), 64.2 (t, C-5′, $J_{C5',H5'}$ = $J_{C5',H5''}$ = 155.0 Hz), 25.7 (q, *i*-Pr, $J_{C,H}$ = 125.9 Hz), 24.9 (q, *i*-Pr, $J_{C,H}$ = 125.7 Hz). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.15; H, 5.12; N, 10.12.

1,5-Anhydro-1-(2-bromopyridin-6-yl)-2,3-*O*-isopropylidene-β-D-ribofuran-1-ulose (14b). Method A. A 1:1 diastereomeric mixture of **5b** (500 mg, 1.16 mmol) was dissolved in MeOH (15 mL) containing *p*-TsOH (ca. 15 mg), and the solution was stirred overnight at room temperature. Compound **14b** (124 mg, 32%), mp 180–182 °C, was eluted from the column first: ^1H NMR (Me_2SO-d_6) δ 1.21 (3 H, s, *i*-Pr), 1.26 (3 H, s, *i*-Pr), 3.51 (2 H, d, H-5′,5″, $J_{4',5'}$ = $J_{4',5''}$ = 3.3 Hz), 4.56–4.62 (2 H, m, H-2′,3′), 4.94 (1 H, dd, H-4′, $J_{3',4'}$ = 1.1 Hz), 7.58–7.93 (3 H, m, H-3,4,5); ^{13}C NMR (Me_2SO-d_6) δ 153.6 (s, C-2), 140.5 (s, C-6), 140 (d, C-3, $J_{C3,H3}$ = 184.7 Hz), 128.5 (d, C-4, $J_{C4,H4}$ = 166.0 Hz), 121.3 (d, C-5, $J_{C5,H5}$ = 163.6 Hz), 111.0 (s, *i*-Pr), 106.3 (s, C-1′), 81.9 (d, C-2′, $J_{C2',H2'}$ = 159.8 Hz), 79.8 (d, C-3′, $J_{C3',H3'}$ = 161.2 Hz), 78.1 (d, C-4′, $J_{C4',H4'}$ = 167.2 Hz), 64.0 (t, C-5′, $J_{C5',H5'}$ = $J_{C5',H5''}$ = 155.0 Hz), 25.7 (q, *i*-Pr, $J_{C,H}$ = 126.9 Hz), 25.0 (q, *i*-Pr, $J_{C,H}$ = 127.1 Hz). Anal. Calcd for $C_{13}H_{14}BrNO_4$: C, 47.58; H, 4.30; N, 4.27. Found: C, 47.79; H, 4.59; N, 4.24.

Compound **12b** (71 mg) was then eluted from the column. The melting point and ^1H NMR spectrum of this sample were identical with those of **12b** reported above.

Method B. Compound **13b** (100 mg, 0.23 mmol) was dissolved in DMF (2 mL) containing DBU (34 μL, 0.23 mmol), and the solution was stirred at room temperature for 10 min. After removal of the solvent in vacuo, the residue was triturated with Et_2O (5 mL) to give crystalline **14b**, which was filtered and washed with Et_2O, quantitative yield, mp 180–182 °C, undepressed upon admixture of **14b** prepared above.

5-(2,3:4,5-Di-*O*-isopropylidene-1-*O*-triflyl-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-15a). To a mixture of *allo*-**9a** (198 mg, 0.6 mmol), DMAP (63 mg, 0.5 mmol), and Et_3N (101 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added CF_3SO_2Cl (105 μL, 1 mmol). The mixture was stirred at room temperature for 1 h and then was washed with H_2O (2 × 2 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column (*n*-hexane/EtOAc, 4:1 and 2:1) to give *allo*-**15a** (143 mg, 52%) as a syrup: ^1H NMR (Me_2SO-d_6) δ 1.27–1.31 (12 H, br s, *i*-Pr), 3.69–4.14 (4 H, m, H-3′,4′,5′,5″), 4.65–4.90 (1 H, m, H-2′), 6.10 (1 H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 8.53 (1 H, t, H-4, $J_{2,4}$ = $J_{4,6}$ = 2.2 Hz), 9.02–9.05 (2 H, m, H-2,6). This compound decomposed in a few days at room temperature.

In a similar manner, *allo*-**9b**[8] (388 mg, 1 mmol) was converted into **6-(2,3:4,5-di-*O*-isopropylidene-1-*O*-triflyl-D-*allo*-pentitol-1-yl)-2-bromopyridine (*allo*-15b)** (390 mg, 75%) as a syrup: ^1H NMR (Me_2SO-d_6) δ 1.05–1.30 (12 H, br s, *i*-Pr), 3.76–4.88 (4 H, m, H-3′,4′,5′,5″), 4.80–4.88 (1 H, m, H-2′), 5.88 (1 H, d, H-1′, $J_{1',2'}$ = 7.7 Hz), 7.60–7.95 (3 H, m, H-3,4,5). This compound was too unstable for combustion analyses.

6-[2,3:4,5-Di-*O*-isopropylidene-2,3(*S*),4(*S*),5-tetrahydroxy-(*E*)-pent-1-en-1-yl]-2-bromopyridine (16b). Method A. A mixture of *allo*-**10b** (70 mg, 0.15 mmol) and NaOAc (123 mg, 1.5 mmol) in HMPA (3 mL) was stirred at 120 °C for 12 h and then partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated and the residue chromatographed on a silica gel column (*n*-hexane/EtOAc, 19:1) to give **16b** (45 mg, 81%) as a syrup, which solidified upon standing at room temperature: mp 84–87 °C; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, s, *i*-Pr), 1.43 (3 H, s, *i*-Pr), 1.47 (3 H, s, *i*-Pr), 1.63 (3 H, s, *i*-Pr), 3.83 (2 H, d, H-5′,5″, spacing 7.4 Hz), 5.04 (1 H, dt, H-4′, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'}$ = $J_{4',5''}$ = 7.4 Hz), 5.74 (1 H, dd, H-3′, $J_{1',3'}$ = 1.9 Hz, $J_{3',4'}$ = 2.7 Hz), 5.89 (1 H, d, H-1′), 6.88–7.65 (3 H, m, H-3,4,5). Anal. Calcd for $C_{16}H_{20}BrNO_4$: C, 51.90; H, 5.44; N, 3.78. Found: C, 51.82; H, 5.60; N, 3.69.

Method B. A mixture of *allo*-**15b** (135 mg, 0.29 mmol) and NaOAc (246 mg, 3 mmol) in HMPA (6 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc (100 mL) and H_2O (50 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo and the residue chromatographed on a silica gel column (*n*-hexane/EtOAc, 19:1 and 3:2). Compound **16b** (20 mg, 21%) was eluted from the column first, mp 84–87 °C, undepressed upon admixture of an authentic sample, followed by *allo*-**9b** (60 mg, 60%), mp 104–106 °C (lit.[8] mp 104–106 °C). The ^1H NMR spectra of these samples are identical with those of **16b** and *allo*-**9b**,[8] respectively.

6-(1-Azido-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (17b). A mixture of *allo*-**10b** (150 mg, 0.32 mmol) and NaN_3 (300 mg, 4.6 mmol) in HMPA (3 mL) was stirred at room temperature for 10 days. The mixture was partitioned between EtOAc (50 mL) and H_2O (25 mL). The organic layer was separated, washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo and the residue chromatographed on a silica gel column (2% EtOAc in *n*-hexane) to give **17b** (93 mg, 72%) as a syrup: ^1H NMR ($CDCl_3$) δ 1.17 (3 H, s, *i*-Pr), 1.26 (3 H, s, *i*-Pr), 1.37 (3 H, s, *i*-Pr), 1.51 (3 H, s, *i*-Pr), 3.81–4.40 (4 H, m, H-3′,4′,5′,5″), 4.71–4.92 (2 H, m, H-1′,2′), 7.31–7.69 (3 H, m, H-3,4,5); MS, *m/z* 413 (MH^+, 100), 370 ($M^+ - N_3$, 20); IR 2120 cm^{-1} (N_3).

Similar treatment of **15a**, however, afforded a single product in 87% yield, which was identical with *allo*-**9a** prepared earlier.

6-[4,5-*O*-Isopropylidene-1-*O*-mesyl-1,3(*S*),4(*S*),5-tetrahydroxy-(*E*)-pent-1-en-1-yl]-2-bromopyridine (18b). A mixture of *allo*-**10b** (100 mg, 0.21 mmol) and 1 N NaOH (100 μL) in DMF (3 mL) was stirred at room temperature for 1 h. The mixture was neutralized with 1 N HCl and concentrated in vacuo and the residue chromatographed on a silica gel column (*n*-hexane/EtOAc, 3:2) to give **18b** (74 mg, 85%) as a foam: ^1H NMR ($CDCl_3$) δ 1.36 (3 H, s, *i*-Pr), 1.44 (3 H, s, *i*-Pr), 2.66 (1 H, d, OH), 3.42 (3 H, s, Ms), 3.89–4.33 (3 H, m, H-4′,5′,5″), 4.75 (1 H, m, H-3′, collapsed to a double doublet upon D_2O exchange, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 5.2 Hz), 6.57 (1 H, d, H-2′), 7.26–7.61 (3 H, m, H-3,4,5). Anal. Calcd for $C_{14}H_{18}BrNO_6S$: C, 41.18; H, 4.44; N, 3.43. Found: C, 41.10; H, 4.51; N, 3.48.

6-(2,3:4,5-Di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (*altro*-9b) from *allo*-10b. *allo*–*altro* Conversion. A mixture of *allo*-**10b** (300 mg, 0.65 mmol), 18-crown-6 (663 mg, 252 mmol), and KO_2 (180 mg, 252 mmol) in DMSO (10 mL) was stirred at room temperature for 20 min. To the mixture were added EtOAc (150 mL), H_2O (30 mL), and Dowex 50 (H^+) (10 mL), and the mixture was shaken for 1 min. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo and the residue chromatographed on a silica gel column (*n*-hexane-

/EtOAc, 3:2). Compound *altro*-**9b** (60 mg, 24%) (the ^{1}H NMR spectrum was identical with that of an authentic sample) was eluted first from the column, followed by **18b** (66 mg, 25%) (the ^{1}H NMR spectrum of this sample was identical with that for **18b** prepared above).

1-(3-Cyanopyridin-5-yl)-2,3:4,5-di-*O*-isopropylidene-1-keto-D-*ribo*-pent-1-ulose (19a). To a mixture of CrO_3 (300 mg), pyridine 0.5 mL), and Ac_2O (0.3 mL) in CH_2Cl_2 (7 mL) was added *altro*-**9a** (334 mg, 1 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (50 mL) and filtered through a silica gel pad from an insoluble solid. The solid was washed with EtOAc (50 mL). The combined organic solutions were concentrated in vacuo, and the residue was crystallized from EtOH to give **19a** (293 mg, 88%): mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (6 H, s, *i*-Pr), 1.45 (3 H, s, *i*-Pr), 1.60 (3 H, s, *i*-Pr), 3.87-4.07 (3 H, m, H-4',5',5''), 4.40 (1 H, dd, H-3', $J_{3',4'}$ = 2.7 Hz, $J_{2',3'}$ = 6.3 Hz), 5.49 (1 H, d, H-2'), 8.50 (1 H, t, H-4, $J_{2,4} = J_{4,6}$ = 2.2 Hz), 9.01 (1 H, d, H-6), 9.30 (1 H, d, H-2). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.42. Found: C, 61.31; H, 6.06; N, 8.35.

In a similar manner, *altro*-**9b** (388 mg, 1.0 mmol) was oxidized to **1-(2-bromopyridin-6-yl)-2,3:4,5-di-*O*-isopropylidene-1-keto-D-*ribo*-pent-1-ulose (19b)** as a foam: ^{1}H NMR ($CDCl_3$) δ 0.77 (3 H, s, *i*-Pr), 1.00 (3 H, s, *i*-Pr), 1.46 (3 H, s, *i*-Pr), 1.57 (3 H, s, *i*-Pr), 3.91-4.10 (3 H, m, H-4',5',5''), 4.51-4.80 (1 H, m, H-3'), 6.00 (1 H, d, H-2', $J_{2',3'}$ = 5.7 Hz), 7.26-7.91 (2 H, m, H-3,5), 8.00 (1 H, dd, H-4, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 6.0 Hz). Anal. Calcd for $C_{16}H_{20}BrNO_5$: C, 49.75; H, 5.22; N, 3.63. Found: C, 49.69; H, 5.43; N, 3.60.

Reduction of 19a. Synthesis of *allo*-9a. To a solution of **19a** (100 mg, 0.3 mmol) in EtOH (10 mL) was added $NaBH_4$ (445 mg, 116 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was diluted with MeOH (4 mL) and concentrated in vacuo, and the residue was flash chromatographed on a silica gel column (1% EtOH in $CHCl_3$, v/v) to give *allo*-**9a** (80 mg, 79%). The ^{1}H NMR spectrum of this sample was identical with that of *allo*-**9a** prepared before.

In a similar manner, **9b** (110 mg, 0.29 mmol) was reduced with $NaBH_4$ (43 mg, 1.13 mmol) to give *allo*-**9b** (79 mg, 72%).

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On the Origin of Cavity-Filling Conformations of Macrocycles: A ^{1}H NMR Spectroscopic and Force-Field Computational Study

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Recently reported ^{1}H NMR studies indicated that the phenanthrene macrocycle **2** preferred a conformation with the phenanthrene unit turned inside the intramolecular cavity formed by the diphenylmethane unit and the two alkyl side chains. The preference of this cavity-filling conformation was supported by molecular mechanics force-field calculations of a few arbitrary conformations of the macrocycle **2**. Force-field calculations were also performed on the closely related biphenyl macrocycle **3** and suggested different conformation characteristics of the biphenyl unit. These computational predictions initiated the synthesis of **3** and the analysis of macrocycles **2** and **3** by 1D NOE and 2D NOESY and COSY ^{1}H NMR spectroscopic methods. These experimental studies support a conformation in which the phenanthrene unit is embedded deeply inside the cavity of macrocycle **2**. The studies also indicate that the conformational behavior of the biphenyl macrocycle **3** consists of conformations that have one phenyl ring folded into the cavity in dynamic equilibrium with conformations consisting of the biphenyl unit outside the cavity. In addition, a more rigorous conformational analysis using the ELLIPSE algorithm to generate initial conformations, AMBER and MM2 force-field calculations to minimize conformations, and molecular dynamics simulations was performed to understand better the origin of cavity-filling conformations and the differences in conformational behavior between **2** and **3**. These computational studies indicate that the cavity-filling conformation of macrocycle **2** is favored by 4-6 kcal/mol, while the conformations of macrocycle **3** with the biphenyl inside the cavity or with one phenyl ring inside the cavity are the favored conformations.

Introduction

In a series of systematic studies, Cram et al. have demonstrated elegantly the importance of host preorganization for the strength of host-guest interactions.[1] For complexes exhibiting similar stereoelectronic complementarity between the molecular binding site and the guest, the degree of preorganization largely determines the amount of free energy gained by complexation in a specific solvent. If a section of the host can block or close off the binding cavity, some of the energy gained in the complexation process will be needed for the reorganization of the binding site, thus reducing the complexation capabilities of the host. The extraordinarily strong binding of cations by spherands[2] and the strong binding of neutral arenes in aqueous and organic solvents by a macrobicyclic cyclophane host[3] illustrates the significance of enforced, preorganized binding sites for efficient host-guest interactions.[4]

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