Applications of Sugar Nitrones in Synthesis: The Total Synthesis of (+)-Polyoxin J[1]

Alessandro Dondoni,*,† Santiago Franco,‡ Federico Junquera,‡ Francisco L. Merchán,‡ Pedro Merino,*,‡,§ and Tomás Tejero‡

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, I- 44100 Ferrara, Italy, and Departamento de Quimica Orgánica, ICMA, Universidad de Zaragoza, E-50009 Zaragoza, Aragon, Spain

Received February 14, 1997[⊗]

A convergent synthesis of the peptidyl nucleoside antibiotic (inhibitor of chitin biosynthesis) polyoxin J (**2**) by coupling of 5-*O*-carbamoyl polyoxamic acid (**3**) and thymine polyoxin C (**4**) is described. These compounds were prepared by chain elongation and amination of sugar-derived aldehydes employing their nitrones as iminium derivatives and the furan ring as a masked carboxyl. Thus, the stereoselective addition of 2-lithiofuran to the L-threose derived *N*-benzyl nitrone **5** followed by reduction of the resulting hydroxylamine to amine, carbamoylation of the free hydroxy group, and oxidative cleavage of the furan ring to the carboxylate group gave a protected derivative of **3** (30%). The same method was followed for the synthesis of the ribofuranosyl α-amino acid nucleoside **4** (12.6%) starting from the D-ribose derived nitrone **6**. The final coupling was performed by the *N*-hydroxysuccinimide active ester method in DMSO with the Hünig base (i-Pr_2EtNH) using a derivative of **3** and unprotected **4**.

The polyoxins are a group of peptidyl nucleoside antibiotics produced in the fermentation broth of *Streptomyces cacaoi* var *asoensis* and have been isolated and characterized by Isono and co-workers about 30 years ago.[2] In total, about 15 compounds having closely related structures have been identified and designated with alphabetical letters. Their structure showed the presence of a unique ribofuranosyl α-amino acid nucleoside that constitutes the common skeleton to all of the members of the family. The nucleoside portion that eventually bears different pyrimidine bases is connected through amide bonds to an open chain polyalkoxy α-amino acid and to an azetidine-2-carboxylic acid. This tripeptide structure is illustrated by the first member of the family, polyoxin A (**1**).[3] Some polyoxins, however, are simply dipeptides incorporating in their structure only two of the above amino acids. This is the case of polyoxin J (**2**) where hydrolytic degradation leads to the polyalkoxy α-amino acid 5-*O*-carbamoylpolyoxamic acid (**3**) and the amino acid nucleoside thymine polyoxin C (**4**) (Chart 1).

The original interest for polyoxins and the closely related natural products nikkomycins[4] and neopolyoxins[5] as well as their synthetic analogs[6] stemmed from their marked activity against phytopathogenic fungi while being nontoxic to bacteria, plants, or animals. These biological effects apparently are due to the ability of polyoxins to inhibit the enzyme chitin synthase and therefore to prevent the biosynthesis of chitin, an essential component of the fungal cell wall structure. Hence, the polyoxin complex obtained by fermentative processes proved to be an excellent agricultural fungicide of wide use, particularly for the sheath blight disease of rice plant.[2] More recently, considerable attention to all the above families of peptidyl nucleosides antibiotics, especially nikkomycins and neopolyoxins, has been given as inhibitors of opportunistic fungal infections by *Candida albicans* in immunocompromised hosts, such as AIDS victims and organ transplant patients.[6,7]

The usual procedure for the synthesis of polyoxins involves the condensation of the amino acid portions, which is the reversal of their hydrolytic cleavage. This approach has been followed in the two total syntheses of polyoxin J (**2**) that have been hitherto carried out and reported in the form of short communications with a 20-year gap betwen them.[8,9] Both methods involved, as a final step, the coupling between suitably protected derivatives of **3** and **4** which in turn were obtained by elaboration of two different monosaccharides in one case (α-L-sorbopyranose and α-D-allofuranose)[8] and by elaboration of the antipode *myo*-inositol derivatives obtained

† Università di Ferrara. Prof. A. Dondoni. Internet: adn@dns.unife.it.
‡ Universidad de Zaragoza. Dr. P. Merino. Internet: pmerino@posta.unizar.es.
§ To whom correspondence relative to X-ray analysis should be addressed.

⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) A preliminary account of this work has been published: Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2127.

(2) (a) Isolation: Suzuki, S.; Isono, K.; Nagatsu, J.; Mizutani, T.; Kawashima, Y.; Mizuno, T. *J. Antibiot., Ser. A.* **1965**, *18*, 131. Isono, K.; Kobinata, K.; Suzuki, S. *Agr. Biol. Chem.* **1968**, *32*, 792. (b) Structure elucidation: Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (c) Reviews: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333. Isono, K. *J. Antibiot.* **1988**, *41*, 1711.

(3) A stereochemical revision (*cis* instead of *trans*) of the 3-ethylidene-L-azetine-2-carboxilic acid (polyoximic acid) that is present in this compound has been recently reported. See: Hanessian, S.; Fu, J.-M.; Tu, Y.; Isono, K. *Tetrahedron Lett.* **1993**, *34*, 4153.

(4) (a) König, W. A.; Hass, W.; Dehler, W.; Fiedler, H. P.; Zähner, H. *Liebigs Ann. Chem.* **1980**, 622. (b) König, W. A.; Hahn, H.; Rathmann, R.; Hass, W.; Keckeisen, A.; Hagenmaier, H.; Borrman, C.; Dehelr, W.; Kurth, R.; Zähner, H. *Liebigs Ann. Chem.* **1986**, 407. (c) Barrett, A. G.; Lebold, S. *J. Org. Chem.* **1991**, *56*, 4875. (d) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Guzik, H.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 3267.

(5) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron. Lett.* **1980**, *21*, 3395. Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron* **1982**, *38*, 1599.

(6) Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A. S.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518. Emmer, G.; Ryder, N. S.; Grassberger, M. A. *J. Med. Chem.* **1985**, *28*, 278. Boehm, J. C.; Kingsbury, W. D. *J. Org. Chem.* **1986**, *51*, 2307. Fiandor, J.; Garcia-López, M.-T.; De las Heras, F. G.; Méndez-Castrillón, P. P. *Synthesis* **1987**, 978. Krainer, E.; Becker, J. M.; Naider, F. *J. Med. Chem.* **1991**, *34*, 174. Cooper, A. B.; Desai, J. Lovey, R. G.; Saksena, A. K.; Girijavallabhan, V. M.; Ganguly, A. K.; Loebenberg, D.; Parmegiani, R.; Cacciapuoti, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1079.

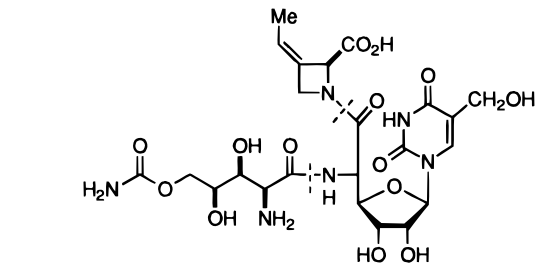
(7) For a review on this topic, see: Saksena, A. K.; Girijavallabhan, V. M.; Cooper, B.; Loebenberg, D. *Annu. Rep. Med. Chem.* **1989**, *24*, 111.

(8) Kuzuhara, H.; Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1973**, 5055.

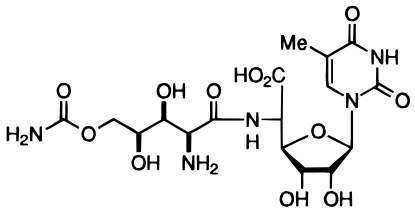
(9) Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 111.

S0022-3263(97)00291-0 CCC: $14.00

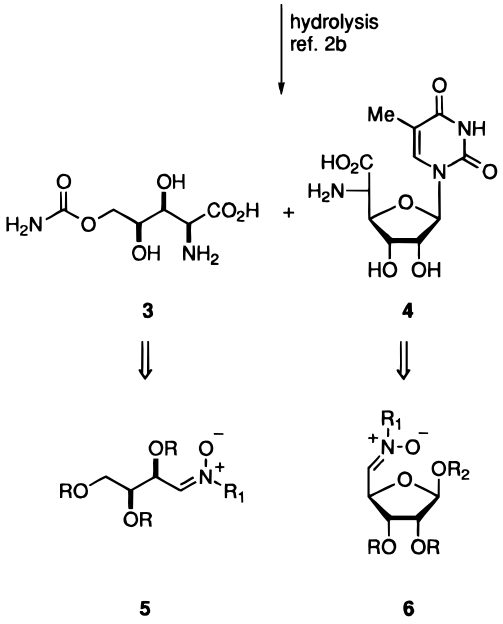
Chart 1



Polyoxin A, **1**

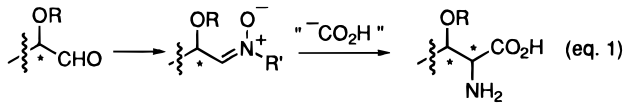


Polyoxin J, **2**



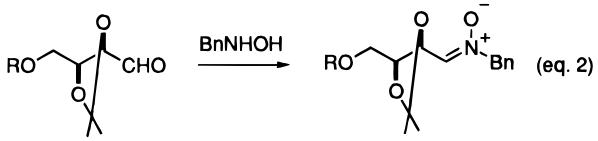
from racemic *myo*-inositol in the other case.[9] Other syntheses of **3** or **4** or their ultimate precursors have been reported over the years starting from the most disparate building blocks, mainly carbohydrates.[10−12] In most of the cases the fundamental problem associated with the stereocontrolled introduction of the amino group was solved through nucleophilic substitution of the activated hydroxy group using azide as the nitrogen nucleophile. Other methods, particularly the Strecker reaction, appeared less satisfactory. A conceptually new method was described by Garner and Park some years ago by the use of D-serinal as starting material.[12c] In this case the nitrogen functionality was already in place and its *R*-configuration was employed for the construction of the other stereocenters. The first *de novo* asymmetric synthesis of (+)-polyoxamic acid has been recently reported by Trost and his co-workers via Pd-based opening of a vinyl epoxide by phthalimide in the presence of a chiral ligand.[13]

We considered that both the constituent fragments **3** and **4** of polyoxin J (**2**) could be obtained by our own method of introducing the nitrogen functionality consisting of the homologative amination of sugar-derived aldehydes using their nitrones as iminium derivatives and the furan as a masked carboxylic acid d_1-synthon[14,15] (eq 1). Thus, a synthetic plan was developed based on the use of the readily available[16] L-threose- and D-ribose-derived nitrones **5** and **6** (see Chart 1). Following earlier and concise reports[17,18] that culminated in the total synthesis[1] of **2**, we would like to describe here *in extenso* the results of this work.



Results and Discussion

Synthesis of 5-*O*-Carbamoyl Polyoxamic Acid (3). In seeking a practical route to **3**, and more usefully still, to a derivative with suitable protection for peptide coupling, we began with the protected L-threose *N*-benzyl nitrones **5a** and **5b**. These compounds were prepared[16] in gram quantities by condensation of *N*-benzylhydroxylamine with the corresponding aldehydes **7a**[19] and **7b**[20] (eq 2), themselves obtained from acetonide (*S*,*S*)-dimethyl tartrate in three steps.



7a, R = Bn
7b, R = TBDMS

5a, R = Bn (85%)
5b, R = TBDMS (80%)

(10) For early syntheses of polyoxamic acid derivatives and the nucleoside portions of polyoxins, see: Garner, P. *Studies in Natural Products Chemistry. Vol. 1. Stereoselective Synthesis. Part A*; Atta-Ur Rahman, Ed., Elsevier: Amsterdam, 1988; p 397.

(11) Recent syntheses of polyoxamic acid derivatives: (a) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024. (b) Duréault, A.; Carreaux, F.; Depezay, J. C. *Tetrahedron Lett.* **1989**, *30*, 4527. (c) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265. (d) Banik, B. K. Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307. (e) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990. (f) Matsumura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733.(g) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139 (h) Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431.

(12) Recent syntheses of ribofuranosyl α-amino acid nucleosides (polyoxins C): (a) ref 11b; (b) ref 11h. (c) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772. (d) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853. (e) Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019. (f) Chen, A.; Savagen, I.; Thomas, E. J.; Wilson, P. D. *Tetrahedron Lett.* **1993**, *34*, 6769. (g) Evina, C. M.; Guillerm, G. *Tetrahedron Lett.* **1996**, *37*, 163. (h) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1971**, 4267.

(13) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.

(14) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synthesis* **1994**, 1450.

(15) Dondoni, A.; Junquera, F.; Merchán F. L.; Merino, P.; Schermann, M.-C.; Tejero, T., accompanying paper.

(16) Dondoni, A.; Franco S.; Junquera, F.; Merchán F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537.

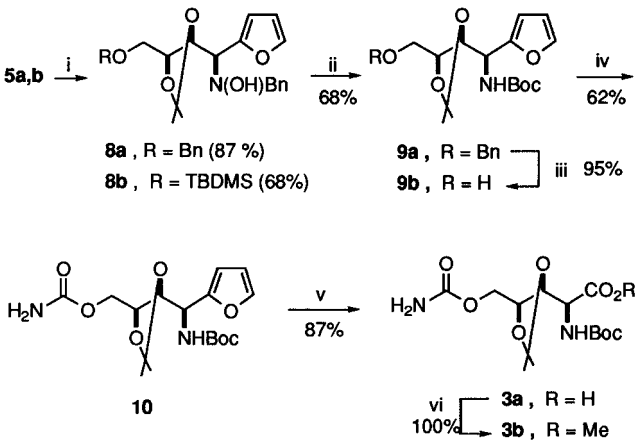
(17) Synthesis of 5-*O*-carbamoylpolyoxamic acid: Dondoni, A.; Franco S.; Merchán F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479.

(18) Synthesis of thymine polyoxin C: Dondoni, A.; Junquera, F.; Merchán F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1994**, *35*, 9439.

(19) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.

(20) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

Scheme 1[a]



[a] i, 2-lithiofuran, THF. ii, $TiCl_3$, MeOH-H_2O, then SiO_2, CH_2Cl_2-H_2O, then Boc_2O, dioxane. iii, Na, NH_3 (l). iv, p-nitrophenylchloroformate, pyridine, then NH_3, MeOH. v, $RuCl_3$ - $NaIO_4$, CH_3CN-H_2O-CCl_4. vi, CH_2N_2, Et_2O.

Since the structure of **3** features an all *syn* arrangement of the substituents at the three stereocenters (*xylo* configuration), the initial problem was the stereoselective addition of the furan ring to **5a** in a *syn*-selective manner. To this aim, the initial part of the synthetic plan was easily carried out taking advantage of earlier observations.[14] Addition of 2-lithiofuran to the 4-OBn L-threose nitrone **5a** in THF at −80 °C proceeded with good *syn* diastereoselectivity (ds 92%) to give the α-alkoxyhydroxylamine **8a** as the major product in 87% yield after chromatography[21] (Scheme 1). The same reaction with the 4-OTBDMS nitrone **5b** was slightly more stereoselective (ds 94%) but gave the corresponding hydroxylamine **8b** in lower yield (68%). Then, hydroxylamines **8a** and **8b** were subjected to the titanium(III) chloride promoted dehydration and hydrolysis of the benzaldimine intermediates by treatment with wet silica gel.[14] Under these conditions also the removal of the TBDMS group of **8b** occurred almost completely. Crude amines were treated with di-*tert*-butyl dicarbonate (Boc_2O) to give the corresponding *N*-Boc derivatives **9a** and **9b**, suitable for isolation and characterization. The continuation of our synthetic plan from these compounds involved unexplored steps. The choice was between the unmasking of the latent carboxylic acid functionality embodied in the furan ring and carbamoylation of the primary alcohol. Since previous work demonstrated[14] that the oxidative cleavage of the furan ring of **9a** by ruthenium dioxide−sodium periodate complex was accompanied by the formation of side products arising from the oxidation of the benzyl group to benzoyl, the carbamoylation process was given the precedence. While the required alcohol **9b** formed directly from **8b**, this compound was obtained in markedly higher yield via debenzylation of **9a** using sodium in liquid ammonia. The carbamoylation of **9b** was carried out in one pot under standard conditions, i.e. treatment with *p*-nitrophenyl chloroformate followed by ammonolysis of the resulting carbonate to give the urethane **10** in 62% isolated yield.

Next we considered the release of the carboxylate function from the furan ring, a crucial operation for the completion of the synthetic plan. The main limitation of the furan−carboxylic acid equivalence[22] stems from the harsh oxidizing conditions (ozone and ruthenium(IV)) under which the cleavage of the heterocyclic ring takes place. These conditions are not tolerated by common functionalities and protecting groups.[23,24] In our preliminary report[17] we described the conversion of **10** into **3a** by Ru-based oxidation of the furan ring using 1.2 equiv of RuO_2 hydrate in the presence of excess $NaIO_4$ as a carrier oxidant. This reaction showed the formation of decomposition products that made the isolation of pure **3a** quite troublesome. A reexamination of this oxidation in the light of the original conditions described by Sharpless and co-workers[25] showed that the use of catalytic $RuCl_3$ hydrate and excess $NaIO_4$ as a reoxidant gives rise to the clean formation of the polyoxamic acid derivative **3a** in 87% yield after purification by a standard chemical procedure (30.3% from the nitrone **5a**). X-ray crystallographic analysis of this compound confirmed the assigned configuration at C-2.[26] Treatment of **3a** with CH_2N_2 provided the corresponding methyl ester **3b** which showed physical and spectral properties ($[\alpha]_D$, ^1H and ^{13}C NMR) identical to those of authentic material.[27] The conversion of **3b** into unprotected 5-*O*-carbamoyl L-polyoxamic acid **3** was reported earlier by Saksena and Lovey and their co-workers.[11a]

Synthesis of Thymine Polyoxin C (4). Despite the simple structure of this compound, its efficient synthesis is far for being a trivial problem.[12] Methods have been described for the synthesis of the glycosidic moiety of polyoxins employing various starting materials,[10,12] mainly carbohydrate and α-amino acid derivatives. Quite judiciously, Barrett and Lebold employed the D-*ribo*-pentodialdofuranoside **11** (see eq 3) that in turn was easily prepared in two steps from D-ribose in 35% overall yield.[12d] This sugar aldehyde was condensed with (phenylthio)nitromethane[28] and the resultant nitro olefin was elaborated into a furanosyl α-azido ester that served as precursor to polyoxin C and uracyl polyoxin C. A similar approach has been recently followed by Jackson and coworkers[11h] who, however, obtained the C-5 epimer of the sugar moiety of **4**. Since the dialdose **11** was also the

(21) The same reaction carried out with Et_2AlCl precomplexed nitrone **5a** leads to the *anti* isomer of **9a** (*lyxo* configuration) with 90% diastereoselectivity.

(22) For earlier examples of the use of furan as precursor to carboxylic acid, see: (a) Mukaiyama, T.; Tsuzuki, R.; Kato, J. *Chem. Lett.* **1985**, 837. (b) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929. (c) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 4346. (d) Dondoni, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7323. (e) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1993**, *58*, 6229.

(23) It is worth mentioning that this problem does not exist in the exploitation of the thiazole−formyl group equivalence since the cleavage of the thiazole ring involves almost neutral and nonoxidizing reaction conditions. Aldehydes obtained by the thiazole-based method can be converted into carboxylic acids under mild oxidizing conditions. Both the unmasking of the aldehyde and the oxidation to carboxylic acid are tolerant to a wide range of functional and protecting groups. See for instance: (a) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162. (b) Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324. (c) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181. (d) Dondoni, A.; Marra, A.; Sansone, F. *J. Org. Chem.* **1996**, *61*, 5155.

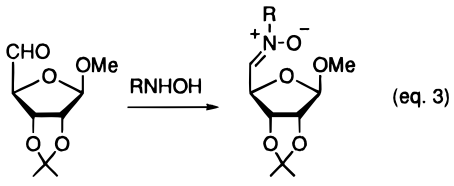
(24) Although we have reported the stereoselective thiazole-based homologation of aldehydes through their nitrones (Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P. Tejero, T.; Bertolasi, V. *Chem. Eur. J.* **1995**, *1*, 505), this synthetic approach to **3** was excluded by the moderate *syn*-selectivity (ds 70%) and low yield of isolated adducts (76%) in the reaction of 2-lithiothiazole with the nitrone **5a**.

(25) Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(26) The authors have deposited atomic coordinates and bond lengths and angles for structure **3a** with the Cambridge Crystallographic Data Centre. The data can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(27) This was kindly provided by Dr. A. K. Saksena and Dr. R. G. Lovey (Schering-Plough Research Institute, Kenilworth, NJ).

starting material in our methodology, the challenge laid in comparing the synthetic value of the nitrone-based approach with the nitro olefin method.

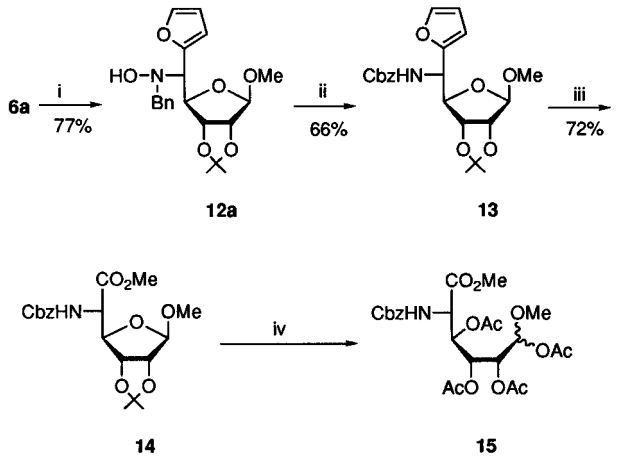


11

6a, R = Bn (76%)
6b, R = PMB (78%)

The *N*-benzyl nitrone **6a**, a crystalline and stable compound, was prepared from the aldehyde **11**[29] by the hydroxylamine method as described[16] (eq 3). The stereocontrolled addition of 2-lithiofuran to **6a** was the key step in this approach. Recent work showed[15] that the use of the nitrone **6a** precomplexed with diethylaluminum chloride afforded the *N*-benzyl hydroxylamine **12a** as major product (ds 85%) (Scheme 2). Conditions were also described[15] for converting **12a** into the carbon-linked furanosyl glycinate **14**, through the protected furylamine **13**, by a $TiCl_3$-based dehydroxylation and oxidative cleavage of the furan ring.[30] The acetolysis of **14** was then considered as the necessary glycosyl activation for

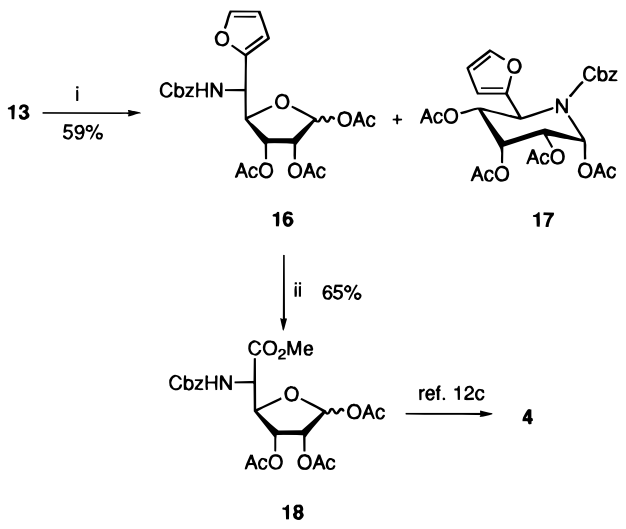
Scheme 2[a]



[a] i,Et_2AlCl, Et_2O, then 2-lithiofuran in THF. ii, $TiCl_3$, MeOH-H_2O, then SiO_2, CH_2Cl_2-H_2O, then CbzCl, dioxane. iii, $RuCl_3$, $NaIO_4$, CH_3CN-H_2O-CCl_4, then CH_2N_2. iv, AcOH-Ac_2O-HCl

the installation of the thymine moiety by the Vorbrüggen pyrimidine nucleoside synthesis.[31] The exposure of **14** to the Hudson acetolysis conditions[32] gave numerous products in low yields. Earlier observations by Garner and Park[12c] suggested that endocyclic glycosyl cleavage and deacetonization might have occurred to give among

Scheme 3[a]



[a] i, AcOH-Ac_2O-H_2O. ii, $RuCl_3$, $NaIO_4$, CH_3CN-H_2O-CCl_4, then CH_2N_2.

other compounds the open chain α-amino ester **15**. However, no efforts were made to isolate this compound because of the unsuccessful elaboration of a similar product toward the target nucleoside.[12c] Hence, attention was focussed on the anomeric activation of the glycosyl amine **13**.

The acetolysis of the *O*-methyl glycoside **13** occurred with concomitant exocylic and endocyclic mode of glycosyl cleavage to give a mixture of the *O*-acetyl glycoside **16** and the aza sugar **17** in 1:3 ratio (Scheme 3). Although compound **16** was isolated in low yield (16%), its elaboration to the sugar-linked α-amino ester **18** was completed by oxidative cleavage of the furan ring as described above ($RuCl_3$−$NaIO_4$) and esterification. The conversion of **18** into thymine polyoxin C (**4**) (46%) was previously reported by Garner and Park by sequential thymine installation and a standard deprotection sequence (saponification and hydrogenolysis).[12c]

Although a formal synthesis of **4** had been achieved, the unefficient anomeric activation of **13** via acetolysis precluded a convenient application of this approach. Hence we examined an alternative route[33] to the α-amino ester **18** starting from the hydroxylamine **12a.** This compound was converted into the *O*-acetyl, *O*-benzyl, and *O*-benzyloxycarbonyl derivatives **19**, **20**, and **21** in quite different yields (Scheme 4). The acetolysis of the almost quantitatively formed compound **19** afforded the tetraacetate **22** in a 60% overall yield. The direct transformation of **12a** into **22** by treatment with a mixture of Ac_2O−AcOH in aqueous HCl gave a much lower overall yield. We next proceeded with the oxidative unmasking of the carboxylate group from the furan ring by treatment of **22** with $RuCl_3$−$NaIO_4$ and esterification. The *N*,*N*-diprotected α-amino ester **23** obtained in this way was converted into the *N*-Cbz derivative **18** by hydrogenolysis over Pd and treatment with benzyl chloroformate under standard conditions. Having prepared a sufficient amount

(28) It has been pointed pointed out (ref 12d) that in the nucleophilic additions to aldehydes of dialdose derivatives, modest to good diastereoselectivity has been achieved only in the case where Lewis acid catalysts or chelation control have been employed. Hence it is worth recalling here that an exception to this behavior is the addition of the organometal 2-(trimethylsilyl)thiazole to dialdoses wherein high levels of nonchelation-controlled diastereoselectivity (ds ≥ 95%) were registered. See: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. One of us (A.D.) thanks Professor A. G. M. Barrett for the correspondence on this matter.

(29) The reference for the preparation of the dialdose **11** has been misreported in our paper quoted in ref 16. The procedure adopted is that given in ref 12d.

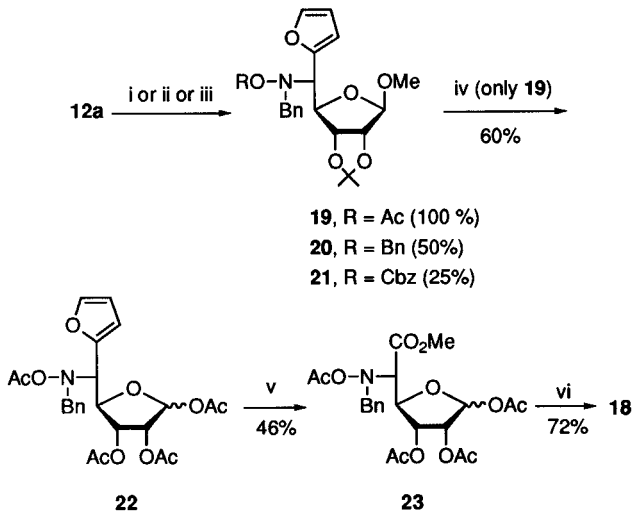
(30) Details of this reaction sequence as well as the characteristics of compounds **12a**, **13**, and **14** are reported in the Experimental Section for convenience.

(31) (a) Niedbala, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654. (b) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(32) Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1934**, *56*, 2465.

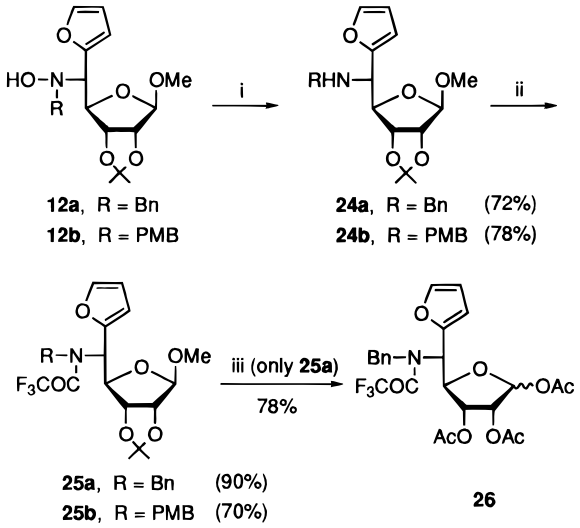
(33) For an earlier report of this precedure, see ref 18.

Scheme 4[a]



[a] i, Ac_2O, Py, DMAP. ii, NaH, DMF, then BrBn. iii, CbzCl, $NaHCO_3$. iv, AcOH-Ac_2O, HCl-H_2O. v, $RuCl_3$, $NaIO_4$, CH_3CN-H_2O-CCl_4, then CH_2N_2, Et_2O. vi, H_2, 7atm., AcOH, 10% Pd-C, then CbzCl, $NaHCO_3$.

Scheme 5[a]

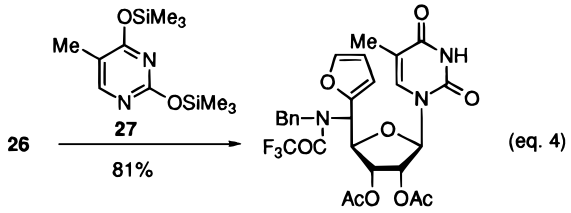


[a] i, Zn, $(AcO)_2Cu$, AcOH. ii, $(CF_3CO_2)_2O$, CH_2Cl_2, pyridine . iii, AcOH-Ac_2O, HCl, H_2O.

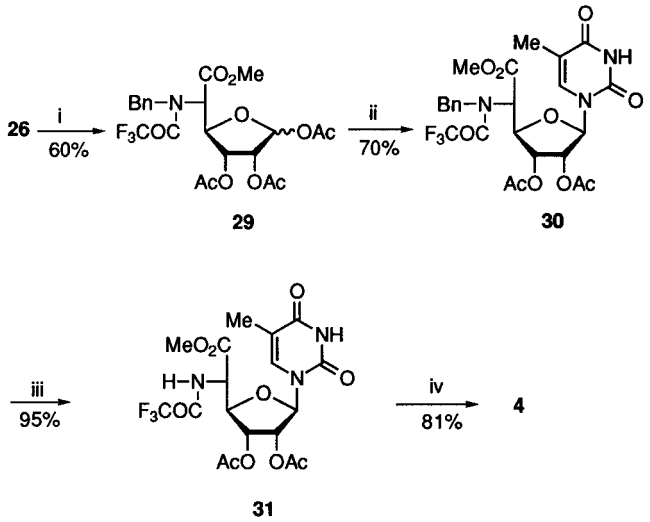
of this key intermediate (15.3% from the nitrone **6a**), we proceeded with its conversion into thymine polyoxin C (**4**) following the same procedure of Garner and Park.[12c] The nucleoside **4** was isolated in a rewarding comparable yield (52%) and with identical characteristics (mp, $[\alpha]_D$, ^1H and ^{13}C NMR, see below). The overall yield of **4** from the nitrone **6a** was 7.6%.

Pursuing a higher yield synthesis of **4**, we examined a different protecting group scheme (Scheme 5). Deoxygenation of the *N*-Bn hydroxylamine **12a** using the Zn–Cu couple[34] afforded the *N*-Bn amine **24a** which upon treatment with trifluoroacetic anhydride was converted into the *N,N*-diprotected compound **25a** in good yield (90%). The use of the trifluoroacetyl as a protecting group was suggested by the possibility of its easy removal under mild basic conditions. Attempted double protection of **24a** with bulkier nitrogen-protecting groups such as Boc, Cbz, or fluorenyl resulted in lower yields presumably because of the considerable steric congestion around the nitrogen atom. The necessary anomeric activation was achieved by submitting **25a** to the Hudson acetolysis conditions[32] which afforded **26** as a mixture of α- and β-anomers in 1:3 ratio and 78% combined yield. We also considered the use of the *N*-*p*-methoxybenzyl (PMB) hydroxylamine **12b** in this route since we thought that the removal of the PMB group under oxidative conditions[35] would provide another oportunity for an improved synthesis of **4**. Both the deoxygenation of **12b** to the amine **24b** and the acylation of the latter to **25b** gave comparable yields to the previous reactions starting from **12a**. Unfortunately the modest diastereoselectivity (ds = 70%) of the addition of 2-lithiofuran to the nitrone **6b** led to the isolation of the *N*-PMB hydroxylamine **12b** in low yield. Consequently, the synthetic route with PMB derivatives became unfavorable and was abandoned.

Instead, the synthesis was continued with the *N,N*-diprotected furylamine **26** which was first subjected to the introduction of the thymine moiety by the Vorbrüggen method.[31] Trimethylsilyl triflate (TMSOTf) catalyzed coupling of **26** and bis-silylated thymine **27** resulted in the formation of the nucleoside **28** in 81% isolated yield (eq 4). This route could not be followed since attempted liberation of the carboxylate function from the furan ring by exposure of **28** to the $RuCl_3$–$NaIO_4$ mixture produced several oxidation products. Evidently the thymine moiety did not tolerate the oxidative conditions employed.[36] Hence the ruthenium(IV)-based oxidative cleavage of the furan ring of **26** was carried out first (Scheme 6). This reaction and the esterification (diazomethane) of the



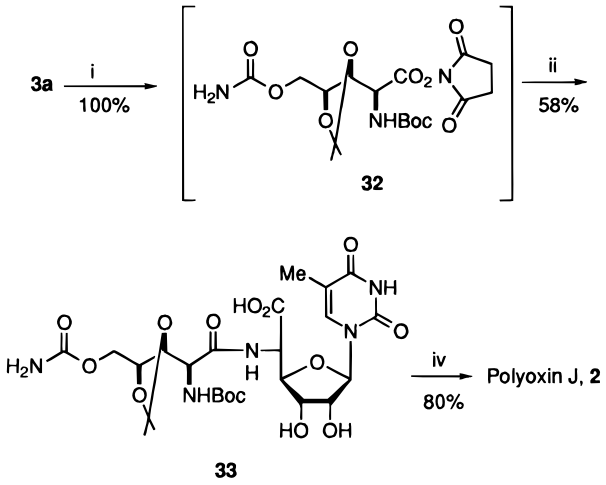
Scheme 6[a]



[a] i, $RuCl_3$, $NaIO_4$, CH_3CN-H_2O-CCl_4, then CH_2N_2, Et_2O. ii, **27**,TMSOTf, CH_2Cl_2. iii, H_2, MeOH, 10% $Pd(OH)_2$-C, 1 atm. iv, LiOH, THF, 0 °C.

(34) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289.

Scheme 7[a]



[a] i, *N*-hydroxysuccinimide, DCC, EtOAc. ii, **4**, *i*-Pr_2EtN, DMSO. iii, TFA, MeOH, H_2O.

resulting α-amino acid proceeded without problems in one pot to give the C-4 furanoside linked methyl glycinate **29** (mixture of α and β anomers). This material reacted with the bis-silylated thymine **27** to give the β-linked N^1-nucleoside **30**. Finally, compound **30** was completely deprotected by the standard hydrogenolysis−saponification sequence to give the free amino-uronic acid nucleoside **4**, which was identical in all respects with the sample which we had prepared from the α-amino ester **18** (see Scheme 4). Quite gratifyingly the overall yield of isolated **4** (12.6%) by this route was almost twice that of Scheme 4. This yield compares with that of polyoxin C (16%) obtained from the sugar aldehyde **11** by the nitro olefin route.[12d]

Synthesis of Polyoxin J (2). Having obtained the α-amino acids **3** and **4**, we saw that what remained to complete the synthesis of **2** was their coupling via an amide bond. The condensation of these amino acids was earlier performed by the *N*,*N*-dicyclohexylcarbodiimide-*N*-hydroxysuccinimide (DCC-HOSu) active ester method[8] and more recently by the diethylphosphoryl cyanide method.[9] However, the lack of experimental details in both reports and the poor yields that have been registered[4d] in the coupling of similar amino acids by the DCC-HOSu active ester protocol led us to perform our own synthesis (Scheme 7). Thus, the polyoxamic acid derivative **3a** by treatment with DCC-HOSu was converted into the active ester **32** which was then condensed with unprotected thymine polyoxin C (**4**) to give the dipeptide **33** in satisfactory yield (58%) after purification. The key element of the coupling procedure was the use of DMSO as solvent and *N*,*N*-diisopropylethylamine as base, a simple yet efficacious expedient that has been recently reported for the synthesis of small peptides of the polyoxin family.[37] Complete deprotection of **33** by treatment with aqueous trifluoroacetic acid afforded the target product **2** which after purification by column chromatography was identical in all respects (mp, $[\alpha]_D$, ^1H and ^{13}C NMR) with authentic material kindly provided by Professor Isono. The overall yield of pure isolated **2** was 46.4%.

Conclusion

The main feature of the above synthesis of the natural product **2** is the nitrone−furan-based stereoselective approach to the building block α-amino acids, i.e. the polyoxamic acid derivative **3** and the amino-uronic nucleoside **4**. The successful synthesis of these compounds with higher or comparable yields of earlier methods demonstrates the utility of this aminohomologation methodology. Other members of the polyoxin family and analogues should be accessible by the application of these techniques.

Experimental Section

General Comments. The reaction flasks and other equipment were stored in an oven at 130 °C overnight and assembled in a stream of argon. Syringes were assembled and fitted with needles while hot and cooled in a stream of argon. Special techniques were used in handling moisture- and air-sensitive materials,[38] and solvents were purified and dried by standard methods.[39] Preparative chromatography was performed on columns of silica gel (60−240 mesh) with freshly distilled solvents. Reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were detected with 254 nm UV light and by charring with 50% methanolic sulfuric acid as staining system.

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter at 20 °C in the stated solvent. Elemental analyses were performed on a Perkin Elmer 240B microanalyzer. ^1H and ^{13}C NMR spectra were recorded either on a Varian 300 Unity or a Bruker 300 spectrometer operating at 300 MHz for ^1H and 75.5 MHz for ^{13}C at 20 °C in $CDCl_3$ unless otherwise specified. Chemical shifts are expressed in parts per million positive values downfield from internal TMS. Mass spectra were recorded on a VG Autospec mass spectrometer. Nitrones **5a**, **5b**, **6a**, and **6b** were prepared as described.[16] 2,4-Bis((trimethyl)silyloxy)-5-methylpyrimidine (**27**) was prepared by a literature method.[40]

2-Lithiofuran. To a well-stirred solution of freshly distilled furan (2.04 g, 2.18 mL, 30 mmol) in THF (100 mL), cooled to −80 °C, was added butyllithium (20 mL of a 1.6 M solution in hexanes, 32 mmol), and the mixture was stirred at 0 °C for 2 h. The solution of 2-lithiofuran in THF (ca. 0.2 M) was stored at 0 °C and used within a few hours after preparation.

(1*S*)-*N*-Benzyl-4-*O*-benzyl-1-deoxy-1-(2-furyl)-1-(hydroxyamino)-2,3-*O*-isopropylidene-L-threitol (8a). A cooled (−90 °C) solution of 2-lithiofuran in THF (prepared from 30 mmol of furan) was treated with a solution of the nitrone **5a** (3.55 g, 10 mmol) in THF (60 mL) added drop by drop. The rate of the addition was adjusted so as to keep the internal temperature below −80 °C and took approximately 30 min to complete. After stirring for 2 h at −80 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL). Stirring was continued for 10 min at ambient temperature and then diethyl ether (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl

(35) It is worth mentioning that while the benzyl group is removed by hydrogenolysis, the *p*-methoxy derivative is removed under oxidative conditions using cerium ammonium nitrate. See: Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.

(36) Pyrimidine nucleosides have been reported to be unstable under oxidative conditions by ruthenium(IV). See: Singh, A. K.; Varma, R. S. *Tetrahedron Lett.* **1992**, *33*, 2307.

(37) Krainer, E.; Becker, J. M.; Naider, F. *J. Med. Chem.* **1991**, *34*, 174.

(38) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd ed.; Wiley-Interscience: New York, 1986.

(39) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.

(40) Nishimura, T.; Iwai, I. *Chem. Pharm. Bull.* **1964**, *12*, 352.

ether (3 × 50 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure (ds = 92% by ^{1}H NMR analysis). Column chromatography (hexane−diethyl ether, 90:10) afforded pure **8a** (3.68 g, 87%) as an oil; $[\alpha]_D$ = −42.7 (*c* 1.03, $CHCl_3$); ^{1}H NMR δ 1.29 (s, 3 H), 1.43 (s, 3 H), 3.11 (dd, 1 H, *J* = 10.8, 4.0 Hz), 3.24 (dd, 1 H, *J* = 10.8, 6.0 Hz), 3.67 (d, 1 H, *J* = 13.8 Hz), 3.93 (d, 1 H, *J* = 13.8 Hz), 3.98 (d, 1 H, *J* = 7.6 Hz), 4.11 (ddd, 1 H, *J* = 7.2, 6.0, 4.0 Hz), 4.42 (d, 1 H, *J* = 12.5 Hz), 4.45 (d, 1 H, *J* = 12.5 Hz), 4.50 (t, 1 H, *J* = 7.4 Hz), 6.25 (bs, 1 H, ex D_2O), 6.32 (dd, 1 H, *J* = 3.2, 1.7 Hz), 6.36 (d, 1 H, *J* = 3.2 Hz), 7.19−7.38 (m, 11 H); ^{13}C NMR δ 26.9, 27.3, 61.4, 65.3, 70.6, 73.3, 77.6, 78.0, 109.7, 110.3, 110.9, 127.2, 127.5, 127.6, 128.2, 128.2, 129.3, 137.2, 137.7, 142.2, 149.4. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.91; H, 6.90; N, 3.31. Found: C, 70.64; H, 6.96; N, 3.49.

(1*S*)-*N*-Benzyl-4-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-(2-furyl)-1-(hydroxyamino)-2,3-*O*-isopropylidene-L-threitol (8b). From **5b** (3.79 g, 10 mmol) as described for the preparation of **8a**. ^{1}H NMR analysis of the crude showed ds = 94%. Column chromatography (hexane−diethyl ether, 90:10) afforded pure **8b** (3.03 g, 68%) as an oil; $[\alpha]_D$ = −33.5 (*c* 1.40, $CHCl_3$); ^{1}H NMR δ −0.04 (s, 3 H), −0.01 (s, 3 H), 0.82 (s, 9 H), 1.23 (s, 3 H), 1.38 (s, 3 H), 3.65 (d, 1 H, *J* = 12.9 Hz), 3.90 (d, 1 H, *J* = 12.9 Hz), 4.02−4.10 (m, 2 H), 4.50 (dd, 1 H, *J* = 10.7, 4.5 Hz), 4.55 (t, 1 H, *J* = 4.5 Hz), 5.20 (dd, 1 H, *J* = 10.7, 5.2 Hz), 6.39 (dd, 1 H, *J* = 3.3, 1.7 Hz), 6.41 (dd, 1 H, *J* = 3.3, 0.8 Hz), 6.80 (bs, 1 H, int D_2O), 7.20−7.35 (m, 5 H), 7.46 (dd, 1 H, *J* = 1.7, 0.8 Hz); ^{13}C NMR δ −5.6, −5.5, 18.3, 25.8, 27.1, 27.4, 61.4, 64.1, 65.4, 78.2, 79.1, 109.4, 110.4, 110.7, 127.2, 128.2, 129.4, 137.5, 142.2, 150.1. Anal. Calcd for $C_{24}H_{37}NO_5Si$: C, 64.39; H, 8.33; N, 3.13. Found: C, 64.22; H, 7.96; N, 3.33.

(1*S*)-4-*O*-Benzyl-1-((*tert*-butoxycarbonyl)amino)-1-deoxy-1-(2-furyl)-2,3-*O*-isopropylidene-L-threitol (9a). A solution of the hydroxylamine **8a** (1.69 g, 4 mmol) in MeOH (50 mL) was treated with a 20% aqueous solution of $TiCl_3$ (1.55 g, 10 mmol of $TiCl_3$ in 6.2 mL of water) at ambient temperature for 15 min. Then 5 M aqueous NaOH (10 mL) was added, and stirring was continued for additional 10 min. After extraction with EtOAc (4 × 25 mL), the organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and treated with SiO_2 (9.0 g) and H_2O (3 mL). The mixture was stirred vigorously at ambient temperature for 12 h and then filtered. The filter was washed with EtOAc containing 0.5% Et_3N (3 × 120 mL), and the combined filtrates were dried over magnesium sulfate and evaporated. The residue was taken up in dioxane (30 mL) and treated with Boc_2O (1.53 g, 8.8 mmol). The resulting solution was stirred at ambient temperature for 12 h. The mixture was partitioned between saturated aqueous $NaHCO_3$ (80 mL) and CH_2Cl_2 (50 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane−diethyl ether, 80:20) to give pure **9a** (1.14 g, 68%) as an oil: $[\alpha]_D$ = −41.9 (*c* 0.47, $CHCl_3$); ^{1}H NMR δ 1.39 (s, 6 H), 1.49 (s, 9 H), 3.51 (dd, 1 H, *J* = 10.4, 4.6 Hz), 3.56 (dd, 1 H, *J* = 10.4, 4.9 Hz), 4.06 (dt, 1 H, *J* = 8.0, 4.8 Hz), 4.23 (dd, 1 H, *J* = 8.1, 3.0 Hz), 4.56 (s, 2 H), 4.91 (dd, 1 H, *J* = 9.0, 3.0 Hz), 5.21 (d, 1 H, *J* = 9.0 Hz), 6.22 (dd, 1 H, *J* = 3.2, 0.8 Hz), 6.28 (dd, 1 H, *J* = 3.2, 1.8 Hz), 7.25−7.33 (m, 6 H); ^{13}C NMR δ 26.9, 27.1, 28.4, 49.5, 70.2, 73.7, 76.8, 79.2, 79.9, 106.9, 109.9, 110.3, 127.7, 127.7, 128.4, 138.1, 141.9, 153.2, 155.4. Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.35. Found: C, 66.43; H, 7.32; N, 3.60.

(1*S*)-1-((*tert*-Butoxycarbonyl)amino)-1-deoxy-1-(2-furyl)-2,3-*O*-isopropylidene-L-threitol (9b). To a solution of sodium (150 mg, 6 mmol) in liquid NH_3 (20 mL), cooled at −50 °C, was added α-((*tert*-butoxycarbonyl)amino)-2-alkylfuran **9a** (0.621 g, 1.5 mmol) in diethyl ether (5 mL). The mixture was stirred for 15 min and then treated with solid NH_4Cl until the solution become colorless. The NH_3 was allowed to evaporate at ambient temperature and water (10 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL) and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Column chromatography (hexane−diethyl ether, 60:40) afforded pure **9b** (0.466 g, 95%) as an oil: $[\alpha]_D$ = −24.4 (*c* 1.72, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 3 H), 1.42 (s, 9 H), 1.45 (s, 3 H), 2.21 (bs, 1 H, ex D_2O), 3.57 (dd, 1 H, *J* = 12.0, 4.2 Hz), 3.71 (dd, 1 H, *J* = 12.0, 4.2 Hz), 3.90 (dt, 1 H, *J* = 8.1, 4.2 Hz), 4.28 (dd, 1 H, *J* = 8.1, 2.4 Hz), 4.90 (bd, 1 H, *J* = 7.4 Hz), 5.22 (bd, 1 H, *J* = 7.6 Hz), 6.24 (d, 1 H, *J* = 3.2 Hz), 6.29 (t, 1 H, *J* = 3.3 Hz), 7.34 (pseudo t, 1 H, *J* = 0.9 Hz); ^{13}C NMR δ 27.1, 27.9, 28.3, 61.6, 76.9, 77.8, 77.9, 80.2, 107.0, 109.6, 110.3, 142.1, 142.5, 155.6. Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.42; H, 7.83; N, 4.59.

(1*S*)-4-*O*-(Aminocarbonyl)-1-((*tert*-butoxycarbonyl)amino)-1-deoxy-1-(2-furyl)-2,3-*O*-isopropylidene-L-threitol (10). To a solution of the alcohol **9b** (0.440 g, 1.35 mmol) in pyridine (7.2 mL) at 0 °C, was added *p*-nitrophenyl chloroformate (0.426 g, 2.1 mmol) was added. The mixture was stirred for 18 h at 0 °C, diluted with EtOAc (15 mL), and washed successively with cold water (3 × 10 mL), saturated aqueous $CuSO_4$ (3 × 10 mL), and brine. The resulting organic extract was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The gummy residue was dissolved in MeOH (10 mL) and the solution cooled to 0 °C. This solution was treated with 25 mL of 8% NH_3−MeOH and stirred for 1 h at 0 °C. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexane−diethyl ether, 40:60) to give pure **10** (0.309 g, 62%) as an oil: $[\alpha]_D$ = −24.0 (*c* 1.50, $CHCl_3$); ^{1}H NMR δ 1.36 (s, 3 H), 1.37 (s, 3 H), 1.40 (s, 9 H), 4.03 (dt, 1 H, *J* = 7.8, 5.0 Hz), 4.11−4.13 (m, 2 H), 4.18 (dd, 1 H, *J* = 7.8, 3.2 Hz), 4.82 (bs, 2 H), 4.92 (dd, 1 H, *J* = 9.0, 3.2 Hz), 5.14 (d, 1 H, *J* = 9.0 Hz), 6.23 (dd, 1 H, *J* = 3.2, 0.7 Hz), 6.29 (dd, 1 H, *J* = 3.2, 1.7 Hz), 7.32 (dd, 1 H, *J* = 1.7, 0.7 Hz); ^{13}C NMR δ 26.9, 27.0, 28.3, 49.4, 64.6, 75.8, 79.1, 80.1, 107.0, 110.1, 110.3, 142.1, 152.7, 155.4, 156.3. Anal. Calcd for $C_{17}H_{26}N_2O_7$: C, 55.13; H, 7.08; N, 7.56. Found: C, 54.96; H, 7.34; N, 7.65.

5-*O*-(Aminocarbonyl)-2-((*tert*-butoxycarbonyla)mino)-2-deoxy-3,4-*O*-isopropylidene-L-xylonic Acid (3a) and Methyl Ester (3b). To a well-stirred solution of $NaIO_4$ (0.351 g, 1.65 mmol) in H_2O−CCl_4−CH_3CN 3:2:3 (7.4 mL) was added $RuCl_3$ (2.8 mg, 0.013 mmol). After 15 min stirring, the 2-furyl derivative **10** (0.1 g, 0.27 mmol) in CH_3CN (0.5 mL) was added. The color of the solution turned instantaneously from yellowish to black. Then enough $NaIO_4$ was added to restore the yellowish color. After 5 min, the mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The organic combined extracts were washed successively with 20% aqueous $NaHSO_3$ until colorless and brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. This residue was taken up with saturated aqueous K_2CO_3 (10 mL), the solution stirred for 10 min and then washed with EtOAc (2 × 15 mL). Acidification (pH = 2) of the aqueous layer by addition of 2 N HCl, extraction with CH_2Cl_2 (3 × 20 mL), drying of the combined organic extracts over magnesium sulfate, and evaporation of the solvent under reduced pressure gave pure **3a** (0.082 g, 87%) as a white solid: mp 50−52 °C; $[\alpha]_D$ = +0.4 (*c* 1.2, acetone) [Lit.[11a] mp 50 °C; $[\alpha]_D$ = +0.3 (*c* 1.0, acetone)]; ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.38 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 9 H), 3.94−4.02 (m, 1 H), 4.22−4.34 (m, 3 H), 4.48 (dd, 1 H, *J* = 9.3 Hz), 5.36 (bs, 2 H), 5.42 (d, 1 H, *J* = 9.3 Hz); ^{13}C NMR ($CDCl_3$ + D_2O) δ 26.7, 26.8, 28.3, 53.4, 63.8, 75.4, 77.9, 80.5, 110.0, 156.2, 157.3, 173.8. Anal. Calcd for $C_{14}H_{24}N_2O_8$: C, 48.27; H, 6.94; N, 8.04. Found: C, 48.40; H, 7.14; N, 8.32.

The acid **3a** was dissolved in diethyl ether and treated with an ethereal solution of diazomethane to give the ester **3b** (0.09 g, 100%) as an oil: $[\alpha]_D$ = −3.6 (*c* 0.49, CH_2Cl_2); ^{1}H NMR δ 1.36 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 9 H), 3.76 (s, 3 H), 3.99 (dt, 1 H, *J* = 8.3, 5.0 Hz), 4.20−4.24 (m, 2 H), 4.26 (dd, 1 H, *J* = 8.3, 1.8 Hz), 4.48 (dd, 1 H, *J* = 9.8, 1.8 Hz), 4.49 (bs, 2 H), 5.27 (d, 1 H, *J* = 9.8 Hz); ^{13}C NMR δ 27.7, 26.8, 28.2, 52.8, 53.0, 64.1, 74.8, 78.2, 80.4, 110.1, 155.9, 156.2, 170.6. Anal. Calcd for $C_{15}H_{26}N_2O_8$: C, 49.73; H, 7.23; N, 7.73. Found: C, 49.80; H, 7.35; N, 7.97.

Methyl *N*-Benzyl-5-deoxy-5-(2-furyl)-5-(hydroxyamino)-2,3-*O*-isopropylidene-*β*-D-*allo*-1,4-pentofuranoside (12a). A 1.0 M solution of Et_2AlCl in hexane (5 mL, 5 mmol) was added via syringe under stirring to a solution of the nitrone **6a** (3.08 g, 10 mmol) in diethyl ether (100 mL) at ambient temperature. The mixture was stirred for 5 min, transferred under argon atmosphere into a dropping funnel, and added slowly to a cooled (−90 °C) solution of 2-lithiofuran in THF (prepared from 30 mmol of furan). The rate of the addition was adjusted so as to keep the internal temperature below −80 °C and took approximately 1 h to complete. The reaction mixture was stirred for 2 h at −80 °C and then treated with 1.0 M aqueous NaOH (50 mL). After 15 min stirring at ambient temperature, the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. ^{1}H NMR analysis of the residue showed a ds = 85%. Column chromatography on silica gel (80:20 hexane−diethyl ether) gave **12a** (2.88 g, 77%) as an oil: $[\alpha]_D = -12.2$ (*c* 2.30, $CHCl_3$); ^{1}H NMR δ 1.34 (s, 3 H), 1.46 (s, 3 H), 3.04 (s, 3 H), 3.64 (d, 1 H, J = 13.0 Hz), 3.72 (d, 1 H, J = 13.0 Hz), 3.93 (d, 1 H, J = 11.0 Hz), 4.58 (d, 1 H, J = 6.1 Hz), 4.75 (dd, 1 H, J = 11.0, 1.0 Hz), 4.88 (s, 1 H), 4.97 (s, 1 H, ex D_2O), 5.16 (dd, 1 H, J = 6.1, 1.0 Hz), 6.39 (dd, 1 H, J = 3.3, 0.7 Hz), 6.43 (dd, 1 H, J = 3.3, 1.8 Hz), 7.22−7.34 (m, 5 H), 7.47 (dd, 1 H, J = 1.8, 0.7 Hz); ^{13}C NMR δ 25.2, 26.5, 55.1, 62.0, 65.4, 82.5, 85.1, 86.0, 109.5, 110.4, 110.4, 112.4, 127.4, 128.9, 129.3, 137.5, 142.2, 150.4. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.84; H, 6.80; N, 3.79.

Methyl 5-((Benzyloxycarbonyl)amino)-5-deoxy-2,3-*O*-isopropylidene-5-(2-furyl)-*β*-D-*allo*-1,4-pentofuranoside (13). The *N*-benzylhydroxylamine **12a** (1.5 g, 4 mmol) was subjected to the reductive process with 20% aqueous $TiCl_3$ and SiO_2-H_2O as described for compound **9a.** The crude amine was dissolved in dioxane (40 mL) and the solution treated with 7% aqueous $NaHCO_3$ (20 mL). After stirring for 10 min at 0 °C, the reaction mixture was treated with benzyl chloroformate (0.64 mL, 1.1 mmol) and stirred for 12 h at ambient temperature. Then water (80 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic combined extracts were dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by column chromatography (hexane−diethyl ether, 80:20) to give pure **13** (1.06 g, 66%) as a white solid: mp 86 °C; $[\alpha]_D = -88.1$ (*c* 0.35, $CHCl_3$); ^{1}H NMR δ 1.28 (s, 3 H), 1.46 (s, 3 H), 3.18 (s, 3 H), 4.36 (d, 1 H, J = 10.2 Hz), 4.61 (d, 1 H, J = 5.8 Hz), 4.84−4.96 (m, 3 H), 5.06 (d, 1 H, J = 12.5 Hz), 5.12 (d, 1 H, J = 12.5 Hz), 5.20 (bd, 1 H, J = 8.3 Hz), 6.27 (dd, 1 H, J = 2.7, 0.9 Hz), 6.30 (dd, 1 H, J = 2.7, 1.9 Hz), 7.30−7.35 (m, 5 H), 7.37 (dd, 1 H, J = 1.9, 0.9 Hz); ^{13}C NMR δ 25.2, 26.6, 51.5, 55.5, 67.2, 81.9, 85.3, 87.7, 108.1, 110.1, 110.3, 112.6, 128.2, 128.2, 128.5, 135.6, 142.2, 152.4, 155.9. Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.40; H, 6.48; N, 3.26.

Methyl 5-((Benzyloxycarbonyl)amino)-5-deoxy-2,3-*O*-isopropylidene-1-*O*-methyl-*β*-D-*allo*-hexofuranuronate (14). The oxidation of **13** (0.201 g, 0.5 mmol) with $RuCl_3$ in the presence of $NaIO_4$ was carried out as described for the preparation of compound **3a**. The treatment of the crude acid with diazomethane and purification by column chromatography (hexane−diethyl ether, 80:20) afforded **14** (0.14 g, 72%) as a white solid: mp 68−70 °C; $[\alpha]_D = -12.8$ (*c* 2.86, $CHCl_3$); ^{1}H NMR δ 1.27 (s, 3 H), 1.43 (s, 3 H), 3.30 (s, 3 H), 3.72 (s, 3 H), 4.31 (dd, 1 H, J = 7.6, 1.1 Hz), 4.45 (pst, 1 H, J = 7.9 Hz), 4.52 (d, 1 H, J = 6.0 Hz), 4.89 (dd, 1 H, J = 6.0, 1.1 Hz), 4.93 (s, 1 H), 5.10 (s, 2 H), 5.50 (bd, 1 H, J = 7.9 Hz), 7.25−7.35 (m, 5 H); ^{13}C NMR δ 25.1, 26.6, 52.3, 55.7, 56.8, 67.3, 81.4, 85.3, 87.9, 110.4, 112.7, 128.1, 128.2, 128.5, 136.2, 155.7, 170.3. Anal. Calcd for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.64; H, 6.53; N, 3.79.

5-((Benzyloxycarbonyl)amino)-5-deoxy-5-(2-furyl)-1,2,3-tri-*O*-acetyl-D-*allo*-1,4-pentofuranoside (16) and *N*-(Benzyloxycarbonyl)-5-deoxy-5-(2-furyl)-1,5-imino-1,2,3,4-tetra-*O*-acetytl-D-α-ribitol (17). A solution of compound **13** (0.403 g, 1 mmol) in a 1:1 mixture of AcOH−Ac_2O was treated with aqueous HCl 0.5 N (7.5 mL) and stirred for 4 h at 70 °C. The solvent was removed under reduced pressure.The ^{1}H NMR of the crude material showed a 1:3 ratio of products **16** and **17** which were separated by column chromatography (hexane−diethyl ether, 40:60). Compound **17** was eluted first (0.222 g, 43%) as an oil; $[\alpha]_D = -32.5$ (*c* 0.40, $CHCl_3$); ^{1}H NMR (55 °C) δ 1.98 (s, 3 H), 2.00 (s, 3 H), 2.02 (s, 3 H), 2.13 (s, 3 H), 5.17 (pseudo t, 1 H, J = 2.8 Hz), 5.20 (d, 1 H, J = 12.4 Hz), 5.30 (dd, 1 H, J = 12.4 Hz), 5.65 (pseudo t, 1 H, J = 3.5 Hz), 5.68 (bs, 1 H), 5.78 (pst, 1 H, J = 2.4 Hz), 6.32 (dd, 1 H, J = 3.1, 1.7 Hz), 6.35 (dd, 1 H, J = 3.1, 0.7 Hz), 6.85 (d, 1 H, J = 1.9 Hz), 7.28−7.34 (m, 5 H), 7.36 (dd, 1 H, J = 1.9, 0.7 Hz); ^{13}C NMR (55 °C) δ 20.3, 20.6, 20.6, 20.7, 52.8, 64.6, 66.3, 66.9, 68.3, 76.8, 107.1, 110.8, 127.9, 128.2, 128.5, 135.9, 142.2, 150.2, 155.2, 168.1, 169.5, 169.9, 169.9. Anal. Calcd for $C_{25}H_{27}NO_{11}$: C, 58.03; H, 5.26; N, 2.71. Found: C, 58.36; H, 5.11; N, 2.64.

Eluted second was **16** (0.076 g, 16%) as an oil. ^{1}H NMR of this product showed a 2:7 ratio of α and *β* anomers. *β*-Anomer (selected) ^{1}H NMR δ 1.91 (s, 3 H), 1.97 (s, 3 H), 1.98 (s, 3 H), 4.47 (dd, 1 H, J = 7.8, 4.9 Hz), 5.25−5.31 (m, 3 H), 5.20 (d, 1 H, J = 4.9 Hz), 5.37 (dd, 1 H, J = 7.8, 4.9 Hz), 5.56 (bd, 1 H, J = 8.1 Hz), 6.04 (s, 1 H), 6.25−6.30 (m, 2 H), 7.25−7.40 (m, 6 H); ^{13}C NMR δ 20.3, 20.5, 20.8, 50.7, 67.2, 70.3, 74.0, 81.9, 97.7, 108.3, 110.5, 128.1, 128.3, 128.5, 136.0, 142.5, 149.9, 155.6, 168.3, 168.8, 169.4. Anal. Calcd for $C_{23}H_{25}NO_{10}$: C, 58.10; H, 5.30; N, 2.95. Found: C, 58.23; H, 5.56; N, 3.14.

Methyl 5-((Benzyloxycarbonyl)amino)-5-deoxy-1,2,3-tri-*O*-acetyl-D-*allo*-hexofuranuronate (18). The oxidation of the mixture of α- and *β*-anomers **16** (0.237 g, 0.5 mmol) with $RuCl_3$ in the presence of $NaIO_4$ was carried out as described for the preparation of compound **3a**. Treatment of the reaction mixture with diazomethane and purification by column chromatography (hexane−diethyl ether, 20:80) afforded **18** (0.137 g, 65%) as an oil; ^{1}H NMR showed that this product was a mixture of α and *β* anomers in 2:7 ratio. ^{1}H NMR δ 2.00 (s, 3 H), 2.02 (s, 3 H), 2.09 (s, 3 H), 3.75 (s, 3 H), 4.45 (dd, 1 H, J = 7.5, 4.4 Hz), 4.67 (dd, 1 H, 8.5, 4.4 Hz), 5.08 (s, 2H), 5.28 (d, 1 H, J = 4.6 Hz), 5.52 (dd, 1 H, J = 7.5, 4.6 Hz), 5.61 (bd, 1 H, J = 8.5 Hz), 6.08 (s, 0.77 H, H_β), 6.35 (d, 0.23 H, J = 4.3 Hz, H_α), 7.38 (s, 5 H); ^{13}C NMR δ 20.8, 20.5, 20.4, 52.6, 55.2, 67.0, 70.2, 73.9, 81.5, 97.9, 128.1, 128.5, 128.4, 135.9, 153.7, 168.4, 169.3, 169.4 (2C). Anal. Calcd for $C_{21}H_{25}NO_{11}$: C, 53.96; H, 5.39; N, 3.00. Found: C, 53,68; H, 5.60; N, 3.37.

Methyl 5-(Acetoxyamino)-*N*-benzyl-5-deoxy-2,3-*O*-isopropylidene-5-(2-furyl)-*β*-D-*allo*-1,4-pentofuranoside (19). A solution of **12a** (0.375 g, 1 mmol) in pyridine (1.5 mL) was treated with Ac_2O (1.5 mL) and DMAP (2 mg) at ambient temperature. After stirring for 2 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL). The aqueous layer was reextracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed sequentially with saturated aqueous $CuSO_4$ (3 × 20 mL) and brine and dried over magnesium sulfate.The solvent was evaporated under reduced pressure. The column chromatography of the residue (hexane−diethyl ether, 60:40) afforded **19** (0.417 g, 100%) as an oil; $[\alpha]_D = -94.4$ (*c* 0.24, $CHCl_3$); ^{1}H NMR δ 1.34 (s, 3 H), 1.44 (s, 3 H), 1.87 (s, 3 H), 2.97 (s, 3 H), 3.69 (d, 1 H, J = 13.3 Hz), 3.97 (d, 1 H, J = 13.3 Hz), 4.15 (d, 1 H, J = 11.1 Hz), 4.50−4.55 (m, 2 H), 4.83 (s, 1 H), 5.40 (d, 1 H, J = 5.6 Hz), 6.36 (dd, 1 H, J = 3.2, 0.9 Hz), 6.44 (dd, 1 H, J = 3.2, 1.9 Hz), 7.20−7.38 (m, 5 H), 7.50 (dd, 1 H, J = 1.9, 0.9 Hz); ^{13}C NMR δ 19.2, 25.3, 26.6, 55.2, 59.4, 64.1, 82.6, 85.0, 85.3, 110.2, 110.3, 110.9, 112.3, 127.7, 128.3, 129.3, 135.9, 142.5, 150.0, 169.2. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.49; H, 6.79; N, 3.27

Methyl *N*-Benzyl-5-((benzyloxy)amino)-5-deoxy-2,3-*O*-isopropylidene-5-(2-furyl)-*β*-D-*allo*-1,4-pentofuranoside (20). To a cooled (0 °C) solution of *N*-benzylhydroxylamine **12a** (0.375 g, 1 mmol) in DMF (10 mL), was added NaH (43 mg of a 60% dispersion in mineral oil, 1.07 mmol). After stirring for 30 min at 0 °C, benzyl bromide (0.187 g, 1 mmol) was added and stirring was continued for 10 h. The reaction mixture was treated with water (20 mL) and extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The

column chromatography (hexane−diethyl ether, 80:20) of the residue gave **20** (0.232 g, 50%) as an oil containing a 5% of an impurity which could not be separated. ^{1}H NMR δ 1.35 (s, 3 H), 1.47 (s, 3 H), 2.99 (s, 3 H), 3.60 (d, 1 H, J = 12.0 Hz), 3.77 (d, 1 H, J = 12.0 Hz), 3.92 (d, 1 H, J = 11.7 Hz), 4.28 (d, 1 H, J = 10.5 Hz), 4.47 (d, 1 H, J = 6.0 Hz), 4.66 (d, 1 H, J = 10.5 Hz), 4.73 (d, 1 H, J = 11.7 Hz), 4.84 (s, 1 H), 5.08 (d, 1 H, J = 6.0 Hz), 6.33 (dd, 1 H, J = 3.1, 0.9 Hz), 6.40 (dd, 1 H, J = 3.1, 1.2 Hz), 7.20−7.38 (m, 10 H), 7.44 (dd, 1 H, J = 1.2, 0.9 Hz); ^{13}C NMR δ 25.5, 26.6, 55.0, 60.1, 65.1, 76.3, 82.8, 85.0, 86.0, 109.5, 110.3, 110.3, 112.3, 127.41, 127.8, 128.1, 128.2, 128.8, 129.9, 137.1, 137.3, 141.8, 151.0.

Methyl *N*-Benzyl-5-(((benzyloxycarbonyl)oxy)amino)-5-deoxy-2,3-*O*-isopropylidene-5-(2-furyl)-β-D-*allo*-1,4-pentofuranoside (21). To a cooled (0 °C) solution of **12a** (0.375 g, 1 mmol) in DMF (10 mL), was added NaH (43 mg of a 60% dispersion in mineral oil, 1.07 mmol). After stirring for 30 min at 0 °C, the reaction mixture was treated with benzyl chloroformate (0.16 mL, 1.07 mmol) and stirred for additional 20 h. Water (20 mL) was added carefully, and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography (hexane−diethyl ether, 95:5) afforded **21** (0.127 g, 25%) as an oil: $[\alpha]_D$ = −14.4 (*c* 1.07, $CHCl_3$); ^{1}H NMR δ 1.31 (s, 3 H), 1.44 (s, 3 H), 2.99 (s, 3 H), 3.72 (d, 1 H, J = 13.1 Hz), 3.98 (d, 1 H, J = 13.1 Hz), 4.21 (d, 1 H, J = 11.0 Hz), 4.52 (d, 1 H, J = 5.9 Hz), 4.59 (d, 1 H, J = 11.0 Hz), 4.85 (s, 1 H), 5.00−5.10 (m, 2 H), 5.38 (d, 1 H, J = 5.9 Hz), 6.41 (dd, 1 H, J = 3.2, 0.8 Hz), 6.38 (dd, 1 H, J = 3.2, 1.7 Hz), 7.20−7.40 (m, 10 H), 7.49 (dd, 1 H, J = 1.7, 0.8 Hz); ^{13}C NMR δ 25.3, 26.6, 55.2, 59.9, 64.7, 69.8, 82.5, 85.0, 85.2, 110.1, 110.4, 111.1, 112.2, 127.7, 128.1, 128.2,128.3, 128.4, 129.5, 135.0, 135.4, 142.5, 149.6, 154.7. Anal. Calcd for $C_{28}H_{31}NO_8$: C, 66.00; H, 6.13; N, 2.75. Found: C, 66.16; H, 6.27; N, 2.90.

5-(Acetoxyamino)-*N*-benzyl-5-deoxy-5-(2-furyl)-1,2,3-tri-*O*-acetyl-D-*allo*-1,4-pentofuranoside (22). A solution of **19** (0.417 g, 1 mmol) in a 80:19:1 AcOH−H_2O−HCl mixture (37.1 mL) was stirred for 4 h at 70 °C. The solvent was evaporated under reduced pressure, and the residue was treated with pyridine (1.5 mL), Ac_2O (1.5 mL), and DMAP (2 mg). After stirring for 2 h at ambient temperature, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL). The aqueous layer was reextracted with EtOAc (2 × 20 mL), the combined organic extracts were washed sequentially with saturated aqueous $CuSO_4$ and brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. ^{1}H NMR of the crude material showed a 2:3 ratio of α- and β-anomers that were separated by column chromatography (hexane−diethyl ether, 60:40).

α-**22**: 0.117 g, 24%; oil; $[\alpha]_D$ = +73.5 (*c* 0.23, $CHCl_3$); ^{1}H NMR δ 1.85 (s, 3 H), 2.00 (s, 3 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 3.80 (d, 1 H, J = 12.9 Hz), 3.88 (d, 1 H, J = 12.9 Hz), 4.29 (d, 1 H, J = 4.8 Hz), 4.75 (t, 1 H, J = 4.6 Hz), 4.81 (dd, 1 H, J = 7.3, 4.6 Hz), 5.18 (dd, 1 H, J = 7.3, 4.2 Hz), 6.29 (d, 1 H, J = 4.8 Hz), 6.44 (dd, 1 H, J = 3.3, 1.2 Hz), 6.49 (dd, 1 H, J = 3.3, 0.9 Hz), 7.25−7.40 (m, 5 H), 7.48 (dd, 1 H, J = 1.2, 0.9 Hz); ^{13}C NMR δ 19.2, 20.2, 20,6, 21.0, 60.3, 63.7, 69.1, 70.5, 83.2, 93.9, 110.8, 111.9, 127.8, 128.4, 129.4, 135.5, 142.9, 147.4, 169.0, 169.2, 169.6, 170.0. Anal. Calcd for $C_{24}H_{27}NO_{10}$: C, 58.59; H, 5.56; N, 2.86. Found: C, 58.72; H, 5.38; N, 2.94.

β-**22**: 0.176 g, 36%; oil; $[\alpha]_D$ = −25.0 (*c* 0.18, $CHCl_3$); ^{1}H NMR δ 1.95 (s, 3 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.15 (s, 3 H), 3.72 (d, 1 H, J = 12.5 Hz), 3.99 (d, 1 H, J = 7.2 Hz), 4.04 (d, 1 H, J = 12.5 Hz), 4.67 (t, 1 H, J = 7.0 Hz), 5.19 (d, 1 H, J = 4.9 Hz), 5.32 (dd, 1 H, J = 6.8, 4.9 Hz), 5.98 (s, 1 H), 6.40 (dd, 1 H, J = 3.4, 0.9 Hz), 6.43 (dd, 1 H, J = 3.4, 1.9 Hz), 7.24−7.40 (m, 5 H), 7.47 (dd, 1 H, J = 1.9, 0.9 Hz); ^{13}C NMR δ 19.5, 20.5, 20.5, 20.8, 59.6, 63.7, 72.5, 73.7, 81.0, 98.4, 110.5, 111.3, 127.9, 128.5, 129.6, 135.4, 142.7, 148.3, 168.6, 169.1, 169.4, 169.7. Anal. Calcd for $C_{24}H_{27}NO_{10}$: C, 58.59; H, 5.56; N, 2.86. Found: C, 58.67; H, 5.78; N, 2.94.

Methyl 5-(Acetoxyamino)-*N*-benzyl-5-deoxy-1,2,3-tri-*O*-acetyl-D-*allo*-hexofuranuronate (23). The oxidation of the mixture of α- and β-**22** (0.244 g, 0.5 mmol) with $RuCl_3$ in the presence of $NaIO_4$ as described for the preparation of **3a** and subsequent esterification with diazomethane gave crude **23** as a 2:3 mixture of α- and β-anomers. Purification by column chromatography (hexane−diethyl ether, 60:40) gave first α-**23** (0.043 g, 18%) as an oil: $[\alpha]_D$ = +68.3 (*c* 0.32, $CHCl_3$); ^{1}H NMR δ 1.87 (s, 3 H), 2.02 (s, 3 H), 2.08 (s, 3 H), 2.15 (s, 3 H), 3.48 (d, 1 H, J = 6.8 Hz), 3.83 (s, 3 H), 4.17 (d, 1 H, J = 12.7 Hz), 4.30 (d, 1 H, J = 12.7 Hz), 4.63 (dd, 1 H, J = 6.8, 3.2 Hz), 5.07 (dd, 1 H, J = 6.8, 4.4 Hz), 5.54 (dd, 1 H, J = 6.8, 3.2 Hz), 6.29 (d, 1 H, J = 4.4 Hz), 7.25−7.50 (m, 5 H); ^{13}C NMR δ 19.1, 20.3, 20.6, 21.0, 52.2, 60.3, 65.8, 69.3, 70.4, 82.1, 93.1, 128.1, 128.6, 129.4, 135.2, 167.5, 168.1, 168.8, 169.2, 169.9. Anal. Calcd for $C_{22}H_{27}NO_{11}$: C, 54.88; H, 5.65; N, 2.91. Found: C, 54.79; H, 5.54; N, 2.83.

Eluted second was β-**23** (0.067 g, 28%): oil; $[\alpha]_D$ = −43.1 (*c* 0.17, $CHCl_3$); ^{1}H NMR δ 1.73 (s, 3 H), 1.95 (s, 3 H), 2.00 (s, 3 H), 2.06 (s, 3 H), 3.43 (d, 1 H, J = 9.3 Hz), 3.85 (s, 3 H), 4.14 (d, 1 H, J = 11.7 Hz), 4.32 (d, 1 H, J = 11.7 Hz), 4.60 (dd, 1 H, J = 9.3, 6.4 Hz), 5.18 (d, 1 H, J = 4.9 Hz), 5.40 (t, 1 H, J = 5.1 Hz), 6.03 (s, 1 H), 7.25−7.45 (m, 5 H); ^{13}C NMR δ 19.3, 20.4, 20.5, 20.7, 52.2, 59.5, 67.3, 72.3, 73.8, 78.9, 98.5, 128.2, 128.6, 129.9, 134.8, 167.9, 168.1, 168.4, 169.4, 169.5. Anal. Calcd for $C_{22}H_{27}NO_{11}$: C, 54.88; H, 5.65; N, 2.91. Found: C, 54.76; H, 5.71; N, 2.97.

Methyl 5-((Benzyloxycarbonyl)amino)-5-deoxy-1,2,3-tri-*O*-acetyl-D-*allo*-hexofuranuronate (18) from 23. To a solution of α-**23** and β-**23** (0.240, 0.5 mmol) in acetic acid (10 mL) was added 10% palladium on activated charcoal (140 mg), and the resulting mixture was hydrogenated at 7 atm for seven days in a Parr hydrogenation apparatus. The crude mixture was filtered through Celite previously washed with methanol (30 mL). The filtrate was evaporated under reduced pressure, and the residue was taken up in dioxane (5 mL). Aqueous $NaHCO_3$ (2.5 mL) was added, and the resulting solution was cooled to 0 °C and then treated with benzyl chloroformate (0.08 mL, 0.55 mmol). After stirring for 30 min at 0 °C, water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (hexane-ethyl acetate, 60:40) to give **18** (0.168 g, 72%) as a mixture of α- and β-anomers. The characteristics of this material were identical to those of the product obtained from **16** as described above.

Methyl 5-Deoxy-5-(2-furyl)-5-(hydroxyamino)-2,3-*O*-isopropylidene-*N*-(*p*-methoxybenzyl)-β-D-*allo*-1,4-pentofuranoside (12b). 2-Lithiofuran was added to the nitrone **6b** (3.37 g, 1 mmol) in the presence of 1.0 equiv of Et_2AlCl as described above for the addition to **6a.** The reaction mixture was also worked up as above. The ^{1}H NMR analysis of the crude product showed ds = 72%. Column chromatography (hexane−diethyl ether, 80:20) afforded pure **12b** (2.02 g, 50%) as an oil: $[\alpha]_D$ = −21.6 (*c* 1.92, $CHCl_3$); ^{1}H NMR δ 1.35 (s, 3 H), 1.48 (s, 3 H), 3.06 (s, 3 H), 3.61 (d, 1 H, J = 13.2 Hz), 3.66 (d, 1 H, J = 13.2 Hz), 3.79 (s, 3 H), 3.95 (d, 1 H, J = 11.2 Hz), 4.58 (d, 1 H, J = 6.1 Hz), 4.77 (d, 1 H, J = 11.2 Hz), 4.82 (bs, 1 H, ex D_2O), 4.90 (s, 1 H), 5.15 (d, 1 H, J = 6.1 Hz), 6.41 (dd, 1 H, J = 3.2, 0.7 Hz), 6.45 (dd, 1 H, J = 3.2, 1.7 Hz), 6.86 (d, 2 H, J = 8.5 Hz), 7.24 (d, 2 H, J = 8.5 Hz), 7.49 (dd, 1 H, J = 1.7, 0.7 Hz); ^{13}C NMR δ 25.3, 26.5, 55.1, 55.2, 61.4, 65.2, 82.6, 85.1, 86.0, 109.5, 110.4, 110.5, 112.4, 113.7, 129.5, 130.5, 142.2, 150.4, 158.9. Anal. Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.45; H, 6.70; N, 3.08.

Methyl 5-(Benzylamino)-5-deoxy-5-(2-furyl)-2,3-*O*-isopropylidene-β-D-*allo*-1,4-pentofuranoside (24a). To a solution of copper(II) acetate (18 mg, 0.1 mmol) in acetic acid (1.4 mL) was added Zn dust (0.33 g, 5.1 mmol), and the mixture was stirred at ambient temperature for 15 min. A solution of **12a** (0.375 g, 1 mmol) in 3:1 acetic acid−water (2 mL) was added, and the mixture was heated at 70 °C for 1 h. After cooling to 20 °C, the sodium salt of EDTA (1.0 g) was added, and the solution was basified with 3 M aqueous NaOH to pH = 10. The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous EDTA (20 mL) and brine (20 mL). The

organic layer was dried over magnesium sulfate and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (hexane−diethyl ether, 80:20) afforded **24a** (0.258 g, 72%) as an oil: $[\alpha]_D = -95.9$ (*c* 0.83, $CHCl_3$); ^{1}H NMR δ 1.32 (s, 3 H), 1.44 (s, 3 H), 1.71 (bs, 1 H), 3.17 (s, 3 H), 3.51 (d, 1 H, $J = 14.2$ Hz), 3.67 (d, 1 H, $J = 8.2$ Hz), 3.73 (d, 1 H, $J = 14.2$ Hz), 4.34 (d, 1 H, $J = 8.2$ Hz), 4.52 (d, 1 H, $J = 5.6$ Hz), 4.88 (s, 1 H), 5.05 (d, 1 H, $J = 5.6$ Hz), 6.23 (d, 1 H, $J = 3.3$ Hz), 6.34 (dd, 1 H, $J = 3.3$, 1.8 Hz), 7.20−7.32 (m, 5 H), 7.41 (d, 1 H, $J = 1.8$ Hz); ^{13}C NMR δ 25.2, 26.5, 51.0, 55.5, 57.9, 82.4, 85.3, 88.7, 108.4, 109.9, 110.0, 112.2, 127.0, 128.2, 128.3, 135.5, 142.0, 153.9. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.99; H, 6.85; N, 4.11.

Methyl 5-((*p*-Methoxybenzyl)amino)-5-deoxy-5-(2-furyl)-2,3-*O*-isopropylidene-*β*-D-*allo*-1,4-pentofuranoside (24b). The reduction of **12b** (0.405 g, 1 mmol) was carried out with Zn^0/Cu^{II} as described above for the preparation of **24a**. Column chromatography (hexane−diethyl ether, 80:20) afforded pure **24b** (0.303 g, 78%) as an oil: $[\alpha]_D = -95.5$ (*c* 0.32, $CHCl_3$); ^{1}H NMR δ 1.31 (s, 3 H), 1.45 (s, 3 H), 1.65 (bs, 1 H), 3.16 (s, 3 H), 3.44 (d, 1 H, $J = 12.9$ Hz), 3.65 (d, 1 H, $J = 9.0$ Hz), 3.66 (d, 1 H, $J = 12.9$ Hz), 3.77 (s, 3 H), 4.34 (d, 1 H, $J = 9.0$ Hz), 4.52 (d, 1 H, $J = 6.1$ Hz), 4.87 (s, 1 H), 5.02 (d, 1 H, $J = 6.1$ Hz), 6.22 (dd, 1 H, $J = 3.2$, 0.9 Hz), 6.34 (dd, 1 H, $J = 3.2$, 1.9 Hz), 6.82 (d, 2 H, $J = 8.5$ Hz), 7.17 (d, 2 H, $J = 8.5$ Hz), 7.41 (dd, 1 H, $J = 1.9$, 0.9 Hz); ^{13}C NMR δ 25.2, 26.è, 50.4, 55.3, 55.5, 57.8, 8.44, 85.3, 88.7, 108.3, 109.9, 110.0, 112.2, 113.7, 129.4, 132.1, 142.0, 154.0, 158.6. Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.98; H, 6.75; N, 3.57.

Methyl *N*-Benzyl-5-deoxy-5-(2-furyl)-2,3-*O*-isopropylidene-5-(trifluoroacetamido)-*β*-D-*allo*-1,4-pentofuranoside (25a). To a solution of **24a** (0.359 g, 1 mmol) in CH_2Cl_2 (15 mL) were added pyridine (6.05 mL, 3 mmol) and trifluoroacetic anhydride (0.471 g, 2.2 mmol). After stirring for 3 h, the solvent was removed under reduced pressure, and the residue was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and diethyl ether (20 mL). The aqueous layer was reextracted with diethyl ether (2 × 20 mL), the organic combined extracts were washed with saturated aqueous $CuSO_4$ (3 × 30 mL) and brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (hexane−diethyl ether, 90:10) to give pure **25a** (0.410 g, 90%) as an oil; $[\alpha]_D = -71.1$ (*c* 0.97, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 140 °C) δ 1.26 (s, 3 H), 1.38 (s, 3 H), 3.06 (s, 3 H), 4.43 (d, 1 H, $J = 6.1$ Hz), 4.59 (d, 1 H, $J = 16.3$ Hz), 4.63 (d, 1 H, $J = 6.1$ Hz), 4.67 (d, 1 H, $J = 16.3$ Hz), 4.78 (d, 1 H, $J = 10.2$ Hz), 4.87 (s, 1 H), 5.33 (d, 1 H, $J = 10.2$ Hz), 6.35 (dd, 1 H, $J = 3.4$, 1.9 Hz), 6.49 (dd, 1 H, $J = 3.4$, 0.6 Hz), 7.03−7.09 (m, 2 H), 7.20−7.28 (m, 3 H), 7.47 (dd, 1 H, $J = 1.9$, 0.6 Hz);^{13}C NMR (DMSO-d_6, 95 °C) δ 24.5, 26.0, 54.3, 56.0, 80.5, 83.4, 84.2, 84.2, 109.1, 110.9, 110.3, 111.8, 116.1 (q, $J = 288.0$ Hz), 126.8, 127.8, 135.2, 142.5, 142.6, 148.8, 156.7 (q, $J = 34.7$ Hz); ^{19}F NMR (DMSO-d_6, 140 °C) δ −66.4; EI-MS *m*/*s* (%): 455 (M^+, 9), 440 (27), 423 (51), 173 (59), 91 (100). Anal. Calcd for $C_{22}H_{24}F_3NO_6$: C, 58.02; H, 5.31; N, 3.08. Found: C, 58.20; H, 5.27; N, 3.21.

Methyl 5-Deoxy-5-(2-furyl)-2,3-*O*-isopropylidene-5-(trifluoroacetamido)-*N*-(*p*-methoxybenzyl)-*β*-D-*allo*-1,4-pentofuranoside (25b). The trifluoroacetylation of **24b** (0.389 g, 1 mmol) was carried out as described for the preparation of **25a**. Purification of the crude product by column chromatography (hexane−diethyl ether, 80:20) afforded **25b** (0.339 g, 70%) as an oil: $[\alpha]_D = -62.3$ (*c* 0.81, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.27 (s, 3 H), 1.39 (s, 3 H), 3.07 (s, 3 H), 3.75 (s, 3 H), 4.46 (d, 1 H, $J = 5.7$ Hz), 4.50 (d, 1 H, $J = 16.2$ Hz), 4.60 (d, 1 H, $J = 5.7$ Hz), 4.62 (d, 1 H, $J = 16.2$ Hz), 4.80 (d, 1 H, $J = 10.5$ Hz), 4.88 (s, 1 H), 5.28 (d, 1 H, $J = 10.5$ Hz), 6.40 (dd, 1 H, $J = 3.0$, 1.5 Hz), 6.51 (d, 1 H, $J = 3.0$ Hz), 6.84 (d, 2 H, $J = 8.6$ Hz), 7.03 (d, 2 H, $J = 8.6$ Hz), 7.52 (d, 1 H, $J = 1.5$ Hz); ^{13}C NMR (DMSO-d_6, 120 °C) δ 24.4, 26.0, 54.2, 54.9, 55.0, 56.0, 80.4, 83.5, 84.2, 109.1, 110.2 (2C), 111.7, 113.7, 115.9 (q, $J = 287.8$ Hz), 127.1, 128.5, 142.5, 149.0, 156.4 (q, $J = 36.1$ Hz), 158.6; ^{19}F NMR (DMSO-d_6, 120 °C) δ −66.3; EI-MS *m*/*s* (%): 485 (M^+, 7), 453 (37), 364 (29), 332 (32), 173 (25), 121 (100). Anal. Calcd for $C_{23}H_{26}F_3NO_7$: C, 56.91; H, 5.40; N, 2.89. Found: C, 56.74; H, 5.35; N, 3.04.

***N*-Benzyl-5-deoxy-5-(2-furyl)-5-(trifluoroacetamido)-1,2,3-tri-*O*-acetyl-*β*-D-*allo*-1,4-pentofuranose (26).** Treatment of **25a** (0.228 g, 0.5 mmol) with a 80:19:1 AcOH−H_2O−HCl mixture and subsequent acetylation under the conditions described above for the preparation of **22** gave **26** as a mixture of α- and *β*-anomers in 24:76 ratio by ^{1}H NMR analysis. Column chromatography (hexane−diethyl ether, 60:40) afforded α-**26** (0.05 g, 19%) as an oil: $[\alpha]_D = +13.5$ (*c* 0.33, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 140 °C) δ 2.01 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 4.75 (bs, 2 H), 4.82 (dd, 1 H, $J = 6.9$, 4.0 Hz), 5.15−5.22 (m, 3 H), 5.47 (d, 1 H, $J = 6.9$ Hz), 6.35 (dd, 1 H, $J = 3.2$, 1.9 Hz), 6.52 (bd, 1 H, $J = 3.2$ Hz), 7.00 (bs, 2 H), 7.16−7.28 (m, 3 H), 7.48 (dd, 1 H, $J = 1.9$, 0.8 Hz); ^{13}C NMR (DMSO-d_6, 95 °C) δ 19.4, 19.5, 20.2, 48.9, 56.4, 71.0, 73.8, 81.0, 93.6, 110.3, 111.7, 115.1 (q, $J = 285.0$ Hz), 126.2, 126.7, 127.8, 135.4, 142.6, 146.9, 157.0 (q, $J = 32.0$ Hz), 168.3, 168.4, 168.8; ^{19}F NMR (DMSO-d_6, 140 °C) δ −66.6. Anal. Calcd for $C_{24}H_{24}F_3NO_9$: C, 54.65; H, 4.59; N, 2.66. Found: C, 54.73; H, 4.70; N, 2.56.

Eluted second was *β*-**26** (0.155 g, 59%); oil; $[\alpha]_D = -33.9$ (*c* 1.07, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 140 °C) δ 1.99 (s, 3 H), 2.04 (s, 3 H), 2.09 (s, 3 H), 4.72 (ABq, 2 H, $J = 18.3$ Hz, $\Delta\delta = 0.01$), 4.92 (dd, 1 H, $J = 8.3$, 6.3 Hz), 5.24 (dd, 1 H, $J = 5.2$, 1.0 Hz), 5.30 (dd, 1 H, $J = 6.3$, 5.2 Hz), 5.35 (d, 1 H, $J = 8.3$ Hz), 6.05 (d, 1 H, $J = 1.0$ Hz), 6.32 (dd, 1 H, $J = 3.2$, 1.9 Hz), 6.50 (bd, 1 H, $J = 3.2$ Hz), 7.02 (bd, 2 H, $J = 6.3$ Hz), 7.15−7.30 (m, 3 H), 7.45 (dd, 1 H, $J = 1.9$, 0.9 Hz); ^{13}C NMR (DMSO-d_6, 95 °C) δ 19.6, 19.8, 20.0, 49.0, 56.7, 71.0, 73.5, 79.4, 98.0, 110.2, 110.8, 116.3 (q, $J = 290.0$ Hz), 126.3, 126.9, 127.8, 135.2, 142.9, 147.3, 157.2 (q, $J = 32.0$ Hz), 167.9, 168.6 (2C); ^{19}F NMR (DMSO-d_6, 140 °C) δ −66.7. Anal. Calcd for $C_{24}H_{24}F_3NO_9$: C, 54.65; H, 4.59; N, 2.66. Found: C, 54.48; H, 4.81; N, 2.72.

***N*-Benzyl-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-5-(2-furyl)-5-(trifluoroacetamido)-2,3-di-*O*-acetyl-*β*-D-*allo*-1,4-pentofuranose (28).** To a solution of **26** (0.263 g, 0.5 mmol) in CH_2Cl_2 (20 mL) were added sequentially 2,4-bis(trimethylsiloxy)-5-methylpyrimidine (**27**)-(0.448 g, 1.7 mmol) and TMSOTf (0.55 mL, 3 mmol) under an argon atmosphere. The reaction mixture was refluxed for 2 h, cooled to 20 °C, diluted with CH_2Cl_2 (100 mL), and then washed with saturated aqueous $NaHCO_3$ (100 mL) and brine. The organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. Column chromatography of the residue (hexane−diethyl ether, 20:80) gave pure **28** (0.240 g, 81%) as a white solid: mp 64−66 °C; $[\alpha]_D = -17.7$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (at 55 °C) δ 1.86 (d, 3 H, $J = 1.2$ Hz), 2.02 (s, 3 H), 2.06 (bs, 3 H), 4.65 (d, 1 H, $J = 15.9$ Hz), 4.70−4.85 (m, 2 H), 5.18−5.32 (m, 2H), 5.49 (d, 1 H, $J = 7.1$ Hz), 5.73 (bs, 1 H), 6.27 (bs, 1 H), 6.37 (bs, 1 H), 6.72 (s, 1 H), 7.00−7.15 (m, 2 H), 7.17−7.38 (m, 4 H), 7.08 (bs, 1 H); ^{13}C NMR δ (at 55 °C) δ 12.5, 20.3 (2C), 50.6, 55.7, 70.8, 72.0, 80.0, 88.7, 110.8, 111.9, 111.9, 116.3 (q, $J = 277.0$ Hz), 127.3, 128.0, 128.6, 135.0, 135.6, 142.8, 147.3, 149.9, 158.0 (q, $J = 45.0$ Hz), 163.0, 169.3, 169.4; ^{19}F NMR (55 °C) δ −72.7. Anal. Calcd for $C_{27}H_{26}F_3N_3O_9$: C, 54.64; H, 4.42; N, 7.08. Found: C, 54.72; H, 4.70; N, 6.91.

Methyl *N*-Benzyl-5-deoxy-1,2,3-tri-*O*-acetyl-5-(trifluoroacetamido)-D-*allo*-hexofuranuronate (29). The oxidation of the mixture of α- and *β*-**26** (0.264 g, 0.5 mmol) with $RuCl_3$−$NaIO_4$ was carried out as described for the preparation of **3a**. The esterification with diazomethane and purification by column chromatography (hexane−diethyl ether, 60:40) gave **29** (0.156 g, 60%) as a mixture of α- and *β*-anomers in 24:76 ratio by ^{1}H NMR analysis.

β-**29**: oil; $[\alpha]_D = -35.4$ (*c* 1.06, $CHCl_3$); ^{1}H NMR δ 1.93 (s, 3 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 3.67 (s, 3 H), 4.01 (d, 1 H, $J = 6.8$ Hz), 4.75 (ABq, 2H, $J = 15.0$ Hz, $\Delta\delta = 0.01$), 5.09 (dd, 1 H, $J = 8.2$, 4.6 Hz), 4.94 (dd, 1 H, $J = 8.2$, 6.8 Hz), 5.15 (d, 1 H, $J = 4.6$ Hz) 6.05 (s, 1 H), 7.24−7.50 (m, 5 H); ^{13}C NMR δ 20.0, 20.2, 20.8, 52.6, 52.7, 61.1, 70.8, 73.3, 77.0, 97.7, 116.0 (q, $J = 287.3$ Hz), 128.8, 128.9, 128.9, 133.2, 158.0 (q, $J = 42.9$ Hz), 167.3, 168.3, 169.2, 169.2; ^{19}F NMR δ −72.9. Anal. Calcd for $C_{22}H_{24}F_3NO_{10}$: C, 50.87; H, 4.66; N, 2.70. Found: C, 50.72; H, 4.73; N, 2.98.

Methyl *N*-Benzyl-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-2,3-di-*O*-acetyl-5-(trifluoroacetamido)-*β*-D-*allo*-hexofuranuronate (30). The reaction of **29** (0.259 g, 0.5 mmol) with **27** as described above for the preparation of **28** afforded, after column chromatography (hexane−diethyl ether, 15:85), pure **30** (0.205 g, 70%) as a white solid: mp 65−67 °C; $[\alpha]_D = -12.9$ (*c* 0.78, $CHCl_3$); ^{1}H NMR δ 1.90 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 3.60 (s, 3 H), 4.45 (d, 1 H, $J = 5.1$ Hz), 4.51 (t, 1 H, $J = 5.0$ Hz), 4.70 (d, 1 H, $J = 15.8$ Hz), 4.84 (d, 1 H, $J = 15.8$ Hz), 5.29 (dd, 1 H, $J =$ 6.2, 5.4 Hz), 5.38 (t, 1 H, $J = 5.6$ Hz), 5.69 (d, 1 H, $J = 4.4$ Hz), 6.97 (s, 1 H), 7.24−7.50 (m, 5 H), 8.63 (bs, 1 H, ex D_2O); ^{13}C NMR δ 12.4, 20.1, 20.4, 52.7, 52.7, 60.3, 70.9, 72.5, 80.1, 89.7, 111.7, 116.2 (q, $J = 286.0$ Hz), 128.6, 128.8, 129.0, 133.5, 136.9, 150.0, 157.6 (q, $J = 45.0$ Hz), 163.4, 167.6, 169.7, 169.7; ^{19}F NMR (at 55 °C) δ −72.5; FAB-MS *m*/*e* (%) 586 (MH^+, 35), 460 (48). Anal. Calcd for $C_{25}H_{26}F_3N_3O_{10}$: C, 51.29; H, 4.48; N, 7.18. Found: C, 51.11; H, 4.53; N, 7.01.

Methyl 1,5-Dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-1,2,3-tri-*O*-acetyl-5-(trifluoroacetamido)-*β*-D-*allo*-hexofuranuronate (31). To a solution of **30** (0.293 g, 0.5 mmol) in MeOH (10 mL), was added 20% $Pd(OH)_2$/C (70 mg). After stirring for 6 h under hydrogen and ambient temperature, the reaction mixture was filtered through Celite previously washed with methanol (40 mL). The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (diethyl ether 100%) to give pure **31** (0.235 g, 95%) as a white solid: mp 70 °C; $[\alpha]_D =$ +24.2 (*c* 1.25, $CHCl_3$); ^{1}H NMR δ 1.90 (d, 3 H, $J = 1.0$ Hz), 2.07 (s, 3 H), 2.09 (s, 3 H), 3.80 (s, 3 H), 4.48 (dd, 1 H, $J = 6.9$, 3.9 Hz), 5.00 (dd, 1 H, $J = 7.2$, 3.9 Hz), 5.47 (dd, 1 H, $J = 6.5$, 3.8 Hz), 5.51 (d, 1 H, $J = 3.8$ Hz), 5.64 (t, 1 H, $J = 6.7$ Hz), 6.93 (d, 1 H, $J = 1.0$ Hz), 8.00 (bd, 1 H, $J = 7.2$ Hz), 9.21 (bs, 1 H, ex D_2O); ^{13}C NMR δ 12.3, 20.2, 20.4, 53.2, 53.5, 69.4, 73.1, 80.3, 92.2, 112.1, 115.5 (q, $J = 286.0$ Hz), 137.3, 150.3, 157.5 (q, $J = 38.0$ Hz), 163.2, 167.4, 169.5, 170.1; ^{19}F NMR δ −76.1; FAB-MS *m*/*e* (%) 496 (MH^+, 46), 370 (36), 185 (100). Anal. Calcd for $C_{18}H_{20}F_3N_3O_{10}$: C, 43.64; H, 4.07; N, 8.48. Found: C, 43.52; H, 4.18; N, 8.20.

5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-*β*-D-*allo*-hexofuranuronic Acid (thymine polyoxin C) (4). To a cooled (0 °C) solution of **31** (0.247 g, 0.5 mmol) in a 5:1 THF−H_2O mixture (12 mL) was added lithium hydroxide monohydrate (72 mg, 1.71 mmol). The reaction mixture was stirred for 1 h at 0 °C and then treated with water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were acidified with 1 N HCl to pH 2 and then extracted with EtOAc (6 × 20 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (chloroform−methanol−water, 5:4:1) to give pure **4** (0.121 g, 81%) as a white solid: mp 192 °C (170 °C, soft); $[\alpha]_D = +8.8$ (*c* 0.09, H_2O) [lit. mp 180−183 °C;[12e] 182−185;[12c] 242−244;[12h] 240−244;[2b] $[\alpha]_D = +8.7$ (*c* 0.23, H_2O);[2b,12e] +8.0 (*c* 0.37, H_2O);[12c] +8.2 (*c* 0.70, H_2O);[12h] ^{1}H NMR (D_2O) δ 1.74 (s, 3 H), 4.00 (d, 1 H, $J = 2.7$ Hz), 4.15−4.22 (m, 2 H), 4.45 (t, 1 H, $J = 5.8$ Hz), 5.70 (d, 1 H, $J = 5.1$ Hz), 7.33 (s, 1 H); ^{13}C NMR (D_2O) δ 10.1, 53.8, 68.0, 71.2, 80.6, 88.3, 110.3, 136.6, 150.5, 156.1, 168.7; FAB-HRMS *m*/*e* 302.0987, M + 1, calcd ($C_{11}H_{16}N_3O_7$: 302.0988). Anal. Calcd for $C_{11}H_{15}N_3O_7$: C, 43.86; H, 5.02; N, 13.95. Found: C, 43.90; H, 5.14; N, 14.06.

Coupling between Polyoxamic Acid (3) and Thymine Polyoxin C (4). To a cooled (0 °C) solution of the polyoxamic acid derivative **3a** (20.7 mg, 0.059 mmol) in EtOAc (7 mL) were added DCC (11.7 mg, 0.059 mmol) and *N*-hydroxysuccinimide (6.85 mg, 0.059 mmol). The mixture was stirred at 0 °C for 8 h and then the solvent was evaporated under reduced pressure. The ^{1}H NMR analysis showed the formation of the activated amide **32**. This crude product was dissolved in DMSO (3 mL), and the solution was treated with **4** (18 mg, 0.06 mmol) and diisopropylethylamine (10.4 μl, 0.06 mmol). The reaction mixture was stirred at ambient temperature for 24 h. The solvent was evaporated under reduced pressure at a temperature below 40 °C. Purification of the residue by column chromatography ($CHCl_3$−MeOH−H_2O, 5:2:0.5) gave the product **33** (21 mg, 58%) as a slightly yellow solid: mp 164−165 °C (soft 110 °C); $[\alpha]_D = -17.7$ (*c* 0.34, MeOH); ^{1}H NMR (D_2O) δ 1.21 (s, 3 H), 1.27 (s, 9 H), 1.28 (s, 3 H), 3.90−4.10 (m, 3 H), 4.11−4.38 (m, 6 H), 4.45 (bd, 1 H, $J = 1.5$ Hz), 5.72 (bd, 1 H, $J = 6.1$ Hz), 7.31 (bs, 1 H); ^{13}C NMR (D_2O) δ 11.6, 25.5, 25.8, 27.4, 54.3, 62.4, 63.1, 69.6, 73.2, 75.4, 76.3, 82.0, 85.1, 87.2, 110.6, 111.5, 137.2, 151.8, 157.2, 158.7, 163.2, 166.2, 170.8; FAB-MS *m*/*e* (%) 632 (MH^+, 62), 532 (100). Anal. Calcd for $C_{25}H_{37}N_5O_{14}$: C, 47.54; H, 5.91; N, 11.09. Found: C, 47.89; H, 5.87; N, 11.10.

Polyoxin J (2). A solution of **33** (13 mg, 0.022 mmol) in 2:1 trifluoroacetic acid−water (3 mL) was stirred at 0 °C for 2 h. The solvent was evaporated under reduced pressure and below 40 °C. The brownish solid residue was purified by column chromatography ($CHCl_3$−MeOH−H_2O, 5:4:1) to give pure polyoxin J (**2**) (8 mg, 80%) as a white solid: mp 198−205 °C dec; $[\alpha]_D = +30.0$ (*c* 0.10, H_2O) [lit. mp 198−208 °C,[2b] 200−210 °C;[9] $[\alpha]_D = +32$ (*c* 1.00, H_2O),[2b] +33 (*c* 0.75, H_2O),[8] +35 (*c* 0.80, H_2O)[9]]; ^{1}H NMR (D_2O) δ 1.76 (s, 3 H), 3.85−4.05 (m, 4 H), 4.08 (dd, 1 H, $J = 5.0$, 1.3 Hz), 4.12−4.15 (m, 2 H), 4.20 (t, 1 H, $J = 5.7$ Hz), 4.35 (t, 1 H, $J = 5.7$ Hz), 4.44 (d, 1 H, $J = 4.0$ Hz), 5.70 (d, 1 H, $J = 5.6$ Hz), 7.40 (s, 1 H); ^{13}C NMR (D_2O) δ 10.1, 54.9, 55.2, 63.9, 67.1, 68.2, 68.7, 71.3, 82.6, 87.6, 110.3, 136.4, 150.5, 157.7, 165.1, 165.9, 172.2; MS (FAB-MS) *m*/*e* (%) 492 (MH^+, 26), 219 (55), 176 (55), 149 (100); MS (FAB^-) *m*/*e* (%) 490 [$(M - H)^-$, 100]. Anal. Calcd for $C_{17}H_{25}N_5O_{12}$: C, 41.56; H, 5.13; N, 14.25. Found: C, 41.63; H, 4.95; N, 14.32.

Acknowledgment. We are grateful to the Ministerio of Educacion y Ciencia (DGICYT, Madrid, Project PB94-0598) and the CNR (Rome) for financial support. Special thanks by one of us (A.D.) are addressed to Professor K. Isono (Tokai University, Shimizu, Japan) for the correspondence and for providing a sample of polyoxin J (**2**) and to Dr. A. K. Saksena and Dr. R. G. Lovey (Schering-Plough Research Institute, New Jersey) for a generous gift of the polyoxamic acid derivative **3a**. A fellowship from the DGA (Aragón, Spain) to S.F. is gratefully acknowledged.

JO9702913