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Hetaryleneaminopolyols and Hetarylenecarbopeptoids: a New Type of Glyco- and Peptidomimetics. Syntheses and Studies on Solution Conformation and Dynamics

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Ready access to a new class of oligomers has been demonstrated by the synthesis of hetaryleneaminopolyols and hetarylenecarbopeptoids using 3-hydroxymethyl-5-(4-amino-4-deoxy-D-*arabino*tetritol-1-yl)-2-methylfuran and 5-(4-amino-4-deoxy-D-*arabino*tetritol-1-yl)-2-methyl-3-furoic acid as novel scaffolds. The conformational behavior of peptidomimetics **22**, **23**, **25**, **26**, and **36** have been analyzed by NMR spectroscopy and extensive molecular dynamics simulations. MD simulations using the GB/SA continuum solvent model for water and the MM3* force field provide a population distribution of conformers which satisfactorily agrees with the experimental NMR data for the torsional degrees of freedom of the molecule.

Introduction

In recent years, the mimickry of the structure and biological function of biopolymers have attracted much attention, and a large variety of biomimetics with oligomeric structures have been prepared.[1] A number of scaffolds that mimick the fundamental building blocks used in nature are threaded together in specific sequences using iterative synthetic procedures giving access to natural-like or unnatural oligomeric structures with multifunctional groups anchored on a lineal, two-dimensional, or three-dimensional backbone.[2] Peptides and proteins have been extensively targeted in biomimetics design[1−3] due to their fundamental role in biological processes and because of the limitations of natural bioactive peptides. Potentially useful peptidomimetics should resist *in vivo* hydrolysis and present some conformational bias[3] having been already developed a number of peptide-based drugs.[4] For the synthesis of oligopeptides, a variety of structurally constrained molecular scaffolds have been used.[5] For instance, Gellman and coworkers[6] have prepared peptides from rigidified cyclic amino acids. Glycosamino acids, which are hybrid structures of carbohydrates and amino acids, are good scaffolds to generate glyco- and peptidomimetics because of the rigidity of the furan or pyran moiety.[7] These compounds may be inserted in appropriate sites of small peptides originating the specific three-dimensional structures required for binding to their receptors[2,8] or can be connected furnishing peptide-bond linked carbohydrates[9]

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(1) (a) Kirshenbaum, K.; Zuckermann, R. N.; Dill, H. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530−535. (b) Barron, A. E.; Zuckermann, R. N. *Curr. Opin. Chem. Biol.* **1999**, *3*, 681−687.

(2) (a) Recent Advances in Peptidomimetics. Aubé, J. *Tetrahedron* **2000**, *56* (50), ix. (b) Robinson, J. A. *Synlett* **2000**, 429−441. (c) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1223−1226. (d) Rohui, A. M. *Chem. Eng. News* **1999**, *77*, 39−47. (e) Nielsen, P. E. *Acc. Chem. Res.* **1999**, *32*, 624−630. (f) Uhlman, E.; Peyman, A.; Breipohl, G.; Will, D. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 2796−2823. (g) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145−148. (g) Mowick, J. S. Chung, D. M.; Maitra, K.; Maitra, S.; Stigers, K. D.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7654−7661

(3) (a) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541−558. (b) Eguchi, M.; Kahn, M. *Mini-Rev. Med. Chem.* **2002**, *2*, 447−462. (c) *Peptides and peptidomimetics that Adopt Folded structures*; Symposia in print No.15; Kelly, J. W., Guest Ed.; Pergamon Press: Oxford, 1999; *Bioorg. Med. Chem.* **1999**, *7* (1). Gante, I. *Angew. Chem., Int. Ed. Engl.* **1994**, *33* 1699−1720. (d) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1−19. (e) Schiller, P. W.; Nguyen, T. M.-D.; Weltrowska, G.; Wilkes, B. C.; Marsden, B. J.; Lemieux, C.; Chung, N. N. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11871−11879.

(4) (a) Brodin, B.; Nielsen, C. U.; Steffansen, B.; Frokjaer, S. *Pharmacol. Toxicol.* **2002**, 90, 285−296. (b) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Brown, E. L.; Maldonado, F. C.; Furhman, S. A.; Zalman, L. S.; Tuntland, T.; Lee, C. A.; Patik, A. K.; Mattews. D. A.; Hendrickson, T. F.; Kosa, M. B.; Liu. B.; Batugo, M. R.; Gleeson, J. P. R.; Sakata, S. K. Chen, L.; Guzman, M. C.; Meador, J. W., III; Ferre, R. A.; Worlan, S. T. *J. Med. Chem.* **2002**, *45*, 1607−1623. (c) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **200**, *43*, 305−341. (d) Hoekstra, W. J.; Hulshizer, B. L.; McComsey, D. F.; Andrade-Gordon, P.; Kauffman, J. A.; Addo, M. F.; Oksenberg, D.;.Scarborough, R. M.; Maryanoff. B. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1649−1654. (e) Keinam, S.; Avnir, D. *J. Am. Chem. Soc.* **2000**, *122*, 4378−4384. (f) Marcaurelle, L. A.; Rodriguez, E. C. Bertozzi, C. R. *Tetrahedron Lett.* **1998**, *39*, 8417−8410.

(5) Ro, S.; Shin, D.-K.; Han, H.-J.; Jeon, Y. H.; Jeong, E.-J.; Hwang, K. Y.; Kim, H.-Y.; Heo, Y.-S.; Lee, T. G.; Kim, J. H. *Peptide Sci.* **2002**, 19−20.

(6) Apella, D. H.; Christianson, L. A.;. Klein, D.A; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381−384.

(7) (a) Schewizer, F. *Angew. Chem., Int. Ed.* **2001**, *41*, 230−253. (b) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stöckle, M.; Kessler, H. *Chem. Eur. J.* **2002**, *8*, 4366−4371.

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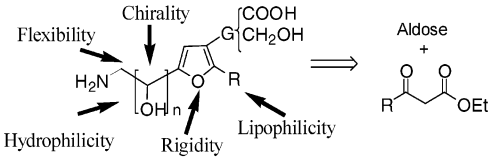
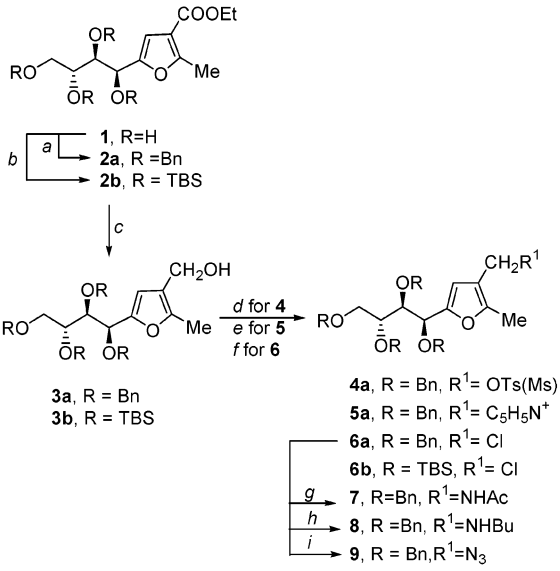


FIGURE 1.

(carbopeptoids). Some of them exhibit interesting biological properties, such as HIV replication inhibition.[10] Aminoglycoside antibiotic mimetics, made from *N*-acetylneuraminic acid, have been reported.[11] In addition, Fleet and co-workers[12] have made extensive use of carbohydrate-derived tetrahydrofuran systems for the synthesis of peptidomimetics that adopt interesting secondary structures. On their side, Kunwar and co-workers[13] have prepared peptidomimetics containing furanoid sugar amino acids and sugar dicarboxylic acids. In a similar way, scaffolds based on pyrrolidine systems[14] have been used as a means to introduce some rigidity in peptidomimetics.

Searching for new molecules that can be assembled with themselves and/or other amino acids using well-established combinatorial techniques, we propose a new scaffold, Aij (Figure 1), which contains a polyol fragment (i) the length and chirality of which are given by the aldose used to make it, and a 5-alkylfuran moiety, the alkyl group (j) of which can be varied on changing the acyl acetate employed in the condensation together with the starting aldose.[15] We now describe the synthesis of one member of the sub-library Aij (i, $n = 3$, configuration: D-arabino) and demonstrate that it can be combined to generate oligomers by applying either solution- or solid-phase procedures. The polyhydroxy and alkylfuran moieties make these compounds attractive, as complex biochemical processes involve molecular recognition based on polar (e.g., hydrogen bonds) and hydrophobic interactions.[16] We have also studied the solution conformation and dynamics of these oligomers (compounds **22**, **23**, **25**, **26**, and **36**) using NMR techniques and molecular dynamics calculations.[17,18] The combination of both techniques give us a first picture of the conformation[19] of these new systems in water, methanol, and DMSO.

SCHEME 1. Synthesis of Buildings Blocks, Electrophiles[a]



[a] Reagents and conditions: (a) NaH/BnBr, DMF, 77%; (b) TBDMSCl/imidazole, DMF, 70°, 90%; (c) $LiAlH_4$, THF, 87%; (d) Ts(Ms)Cl (2 equiv)/py (2 equiv), Cl_2CH_2, 80% conversion; (e) Ts(Ms)Cl (2 equiv)/py (exc) 47% conversion; (f) CCl_4, Ph_3P, reflux, MS 4A, 100% conversion; (g) (1) NH_3, DMF, rt, (2) Ac_2O/py (i + ii), 43%; (h) $BuNH_2$, DMF, rt, 84%; (i) NaN_3, DMF, rt, 90%.

Results and Discussions

Syntheses of Hetaryleneaminopolyols. These compounds, formed by enantiomerically pure polyols with heterocyclic spacers joined by amine-type linkages, have been designed as an attempt to have them acting as amino-oligosaccharide mimetics.

They are prepared by nucleophilic displacement between electrophile and nucleophile buildings blocks. Scheme 1 discloses the preparation of several electrophilic reactants. Starting from compound **1**, which is readily available from D-glucose and ethyl acetoacetate,[15] *O*-protection with benzyl and TBS groups followed by reduction with $LiAlH_4$ gave **3a**[20] and **3b**, respectively.

(8) (a) Moitessier, N.; Dufour, S.; Chrétien, F.; Thiery, J. P.; Maigret, B.; Chapleur, Y. *Bioorg. Med. Chem.* **2001**, *9*, 511−523. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubel, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267. (d) Hirschamann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascier, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550−12568.

(9) Nicolaou, K. C.; Flörke, H.; Egan, M. G.; Barth, T.; Estevez, V. A. *Tetrahedron Lett.* **1995**, *36* 1775−1779.

(10) Yoshimoto, S.; Ichikawa, M.; Hildreth, J. E. K.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 2549−2552.

(11) (a) Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 10150−10155. (b) Ramamoorthy, P. S.; Gervay, J. *J. Org. Chem.* **1997**, *62*, 7801−7805.

(12) (a) Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans 1* **2000**, 3666−3679. (b) Hungerford, N. L.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3680−3685. (c) Smith, M. D.; Fleet, G. W. J. *J. Peptide Sci.* **1999**, *5*, 425−441 and references therein.

(13) (a) Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Madhavendra, S. S.; Ravi Sankar, A.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 2853−2859. (b) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S.; Sharma, J. A. R. P.; Ravikanth, V.; Diwan, P. V.; Nagaraj, R.; Kunwar, A. C. *J. Org. Chem.* **2000**, *65*, 6441−6457.

(14) (a) Chakraborty, T. K.; Srinivasu, P.; Kiran Kumar, S.; Kunwar, A. C. *J. Org. Chem.* **2002**, *67*, 2093-2100. (b) Crespo, L.; Sanclimens, G.; Royo, M.; Giralt, E.; Albericio, F. *Eur. J. Org. Chem.* **2002**, 1756−1762.

(15) García González, F.; Gómez Sánchez, A. *Adv. Carbohydr. Chem.* **1965**, *20*, 303−355.

(16) (a) Silverman, D. N.; Lindskog, S. *Acc. Chem. Res.* **1988**, *21*, 30−36; Greener, B.; Rose, J. *Chem. Commun.* **1999**, 2361−2362. (b) Lehn, J. M. *Supramolecular Chemistry−Concepts and Perspectives*; VCH: Weinheim 1995.

(17) Rutherford, T. J.; Spackman, D. G.; Simpson, P. J.; Homans, S. W. *Glycobiology* **1994**, *4*, 49−57. (b) Poveda, A.; Asensio, J. L.;. Martin-Pastor, M.; Jiménez-Barbero, J. *J. Chem. Soc., Chem. Commun.* **1996**, 421−422. (c) Harris, R. Kiddle, G. R., Field, R. A., Milton, M. A., Ernst, B.; Magnani, J. L.; Homans, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 2546−2551.

(18) (a) Meyer, B. *Top. Curr. Chem.* **1990**, *154*, 141−208. (b) Imberty, A. *Curr. Opin. Struct. Biol.* **1997**, *7*, 617−623. (c) Peters, T.; Pinto, B. M. *Curr. Opin. Struct. Biol.* **1996**, *6*, 710−720.

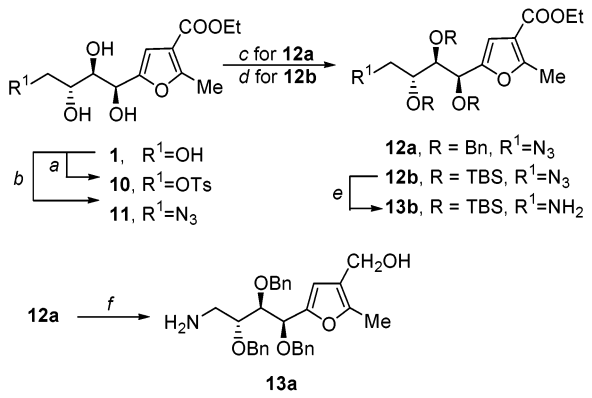
(19) (a) Imberty, A.; Hardman, K. D.; Carver, J. P.; Perez, S. *Glycobiology* **1991**, *1*, 631−642. (b) Espinosa, J. F.; Cañada, F. J.; Asensio, J. L.; Martín-Pastor, M.; Dietrich, H.; Martín-Lomas, M.;. Schmidt, R. R.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1996**, *118*, 10862−10871. (c) Dowd, M. K., Reilly, O. J.; French, A. D. *Biopolymers* **1994**, *34*, 625−638.

TABLE 1. Reactivity of the Nucleophilic Substitution with 4a, 5a, 6a

	compounds[a]		
reagents and conditions	**4a**	**5a**	**6a**
b	N.R.	N. R.	N.R. **7**
c	N.R.	N.R. **8**	43% **8**
d	N.R. **9**	<10% **9**	84% **9**
e	65%	70%	90%

[a] Obtained compound, %,yield; N.R. = no reaction. [b] BuOH,NaH, DMF, 100 °C. [c] (1) NH_3, DMF, rt, (2) Ac_2O/py. [d] $BuNH_2$, DMF, 75 °C. [e] NaN_3, DMF, 90 °C.

SCHEME 2. Synthesis of Buildings Blocks, Nucleophiles[a]



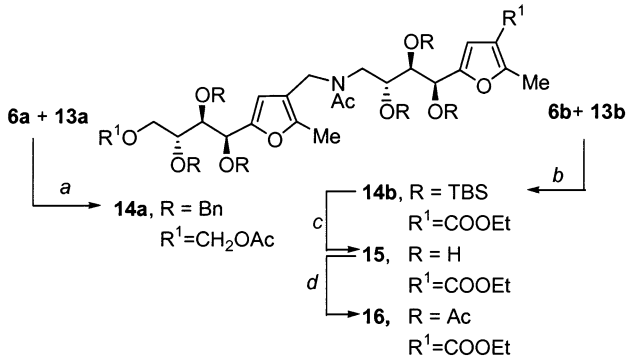
[a] Reagents and conditions: (a) TsCl/py, −15 °C, 57%; (b) N_3Na/DMF 100°, 65%; (c) BnBr, NaH, DMF, 85%; (d) TBDMSCl/imidazole, DMF, 70 °C, 86%; (e) H_2/Pd−C (10%), EtOH (85%); (f) $LiAlH_4$/THF, 87%.

Reaction of **3a** with an equimolar amount of TsCl or MsCl and pyridine gave compounds **4a** that were unstable and were used without purification in the next steps. When the reaction took place with py as solvent, the pyridinium salt **5a** was obtained. Reaction of **3a** and **3b** with an excess of MsCl/DMF or with CCl_4/Ph_3P at reflux gave **6a** and **6b** with 100% of conversion, respectively. To evaluate the electrophile efficiency of compounds **4a**, **5a**, and **6a**, they were made to react with several nucleophilic reagents. The results are summarized in Table 1. They indicate that the higher reactivity is observed with the chloro derivative **6**.

The preparation of the nucleophile building blocks is depicted in Scheme 2. Azido ester **11** is obtained by S_N2 displacement of tosylate **10**.[21] Subsequent *O*-protection (OBn, OTBS) gave compounds **12a** and **12b** in 85% and 86% yield, respectively. Reduction of **12a** with $LiAlH_4$ gave amino alcohol **13a** in 87% yield. Reduction of **12b** with H_2/Pd/C gave **13b** in 85% yield.

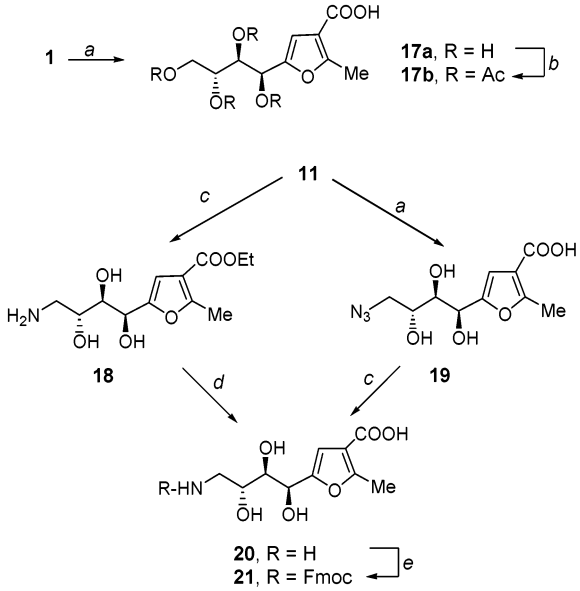
The coupling reaction (Scheme 3) between **6a** (crude product) and **13a** in the presence of Na_2CO_3 was completed in 1 h, and the dimeric compound **14a** was isolated after conventional acetylation in an overall yield (based on **3a**) of 45%. The ^{13}C NMR and HRFABMS data

SCHEME 3. Hetarylene Aminopolyol Coupling Reactions[a]



[a] Reagents and conditions: (a) (i) Na_2CO_3, DMF, 80 °C, 1.5 h, (ii) Ac_2O/py; (b) (i) Na_2CO_3, DMF, 80 °C, 18 h, (ii) Ac_2O/py; (c) TBAF (1 M)/THF; (d) Ac_2O/py.

SCHEME 4. Hetarylene Carbopeptoid Buildings Blocks[a]



[a] Reagents and conditions: (a) NaOH 1 M, EtOH, 60 °C, 3 h, (ii) IR-120 (H^+), MeOH, (i + ii) 80−90%); (b) Ac_2O/py, 100%; (c) H_2, Pd/C, EtOH, 98%; (d) (i) NaOH 1 M, EtOH, 60 °C, 3 h, (ii) HCl 1 M, (i + ii), 80%; (e) (i) TMSCl/py, 1 h, (ii) FmocCl, 1 h, (iii) H_2O, 2h, (i + ii + iii) 95%.

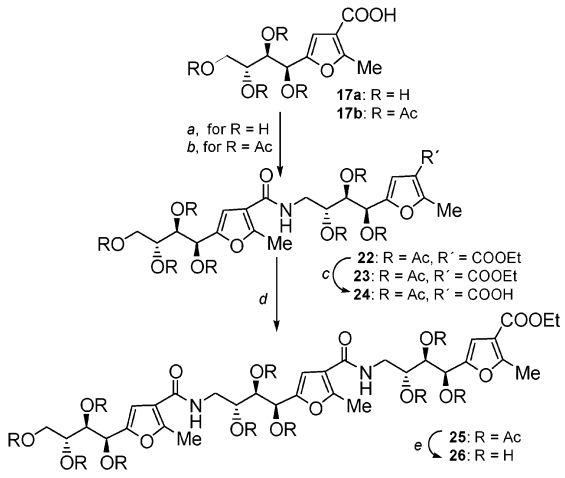
supported the proposed structure of **14a**. Furthermore, its ^1H NMR spectrum indicates the existence of equilibria between various conformers. Hydrogenolysis of **14a** led to a complex mixture of compounds resulting from hydrogenolysis of benzyl ethers and from the furan moiety and the partial debenzylation of benzyl ethers. Other debenzylation procedures led to the formation of undesired products.[20] Hetarylene aminopolyol **15** was then successfully obtained applying a coupling reaction (18 h) between **6b** and **13b** with subsequent deprotetion with TBAF in THF. The dimeric product **15** was characterized as its peracetate, the latter being isolated in an overall yield of 32% (based on **3b**).

Syntheses of Hetarylene Carbopeptoids. Scheme 4 outlines the synthesis of the corresponding building blocks that starts from ester **1** and azidoester **11**. Hydrolysis of esters **1** and **11** provided carboxylic acids **17a**[15]

(20) Moreno-Vargas, A. J.; Fernández-Bolaños, J. G.; Fuentes, J.; Robina, I. *Tetrahedron*: *Asymmetry*, **2001**, *12*, 3257−3266.

(21) Moreno-Vargas, A. J.; Robina, I.; Demange, R.; Vogel, P. *Helv. Chim. Acta*, in press.

SCHEME 5. Head Elongation[a]



[a] Reagents and conditions: (a) (1) 2 equiv of Ph_3P, 2 equiv of PyS−SPy, DMF, 2 equiv of of **18**, 12 h, (2) Ac_2O, py, 12 h (54% for two steps); (b) (1) 2 equiv of Ph_3P, 2 equiv of PyS−SPy, DCM/DMF (3:1), 1 equiv of **19**, 6 h, (2) (74% for two steps); (c) (1) NaOH 1 M, EtOH, 10 h, 60 °C, (2) IR-120 (H^+), MeOH, (3) Ac_2O, py (89% for three steps); (d) step b (60% for two steps); (e) NaOMe, MeOH (quant).

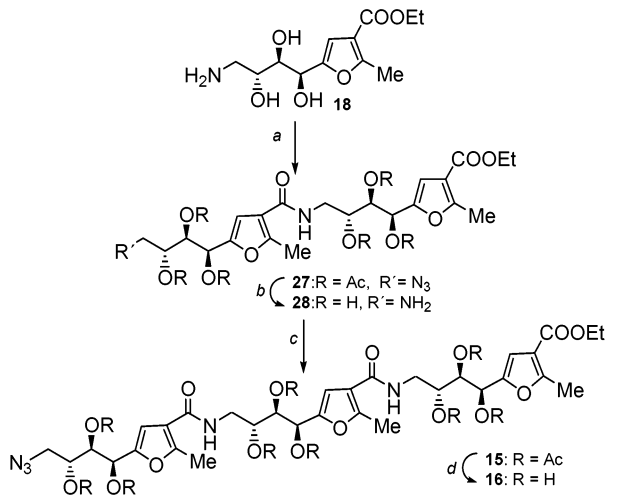
and **19**, respectively. The analogue **17b** was obtained from **17a** after acetylation. Hydrogenation of **11** rendered aminoester **18**. Reduction of the azide **19** delivered amino acid **20** which was *N*-protected as the Fmoc derivative **21**.

The polyol moiety had to be protected as a polysilyl ether in order to avoid formation of carbonates (a regioselective direct reaction gives complex mixtures and a low yield for **21**). Koole's procedure[22] (TMSCl/py, then FmocCl, then, H_2O) led to **21** in 95% overall yield.

Considering the nature of our scaffold, we define the alkylfuran moiety as the *head* and the polyolic chain as the *tail* of the systems. The strategy of *head elongation* (Scheme 5) is based on the condensation of acid **17a** with the aminoester **18** under Mukaiyama conditions.[23] After acetylation, this gave the dimeric derivative **22**. The latter was treated with methanolic NaOMe to give ester **23**. Compound **22** was hydrolyzed into acid **24** and coupled again with the aminoester **18** to give the trimer **25**. When using a mixture of Cl_2CH_2/DMF, the protected peracetate **17b**, and **18**, the yield was increased.

For the *tail elongation* (Scheme 6), the coupling of unprotected **18** and **19** was carried out in DMF with PyBOP (benzotriazolyloxytrispyrrolidinophosphonium hexafluorophosphate) and DIPEA[24] (*N*,*N*-diisopropylethylamine) as activating reagents. After 45 min of reaction and subsequent acetylation, the dimeric product **27** was isolated in 70% yield. Methanolysis and reduction of the azido group gave **28**. Subsequent coupling reaction with azidocarboxylic acid **19** gave the corresponding trimeric product that was purified as the peracetated **29** isolated in 60% yield.

SCHEME 6. Tail Elongation[a]



[a] Reagents and conditions: (a) PyBOP, DIPEA, DMF, 1 equiv of **19**, 45 min (62%); (b) H_2, Pd/C, EtOH, 30 min (95%); (c) (1) step a, (2) Ac_2O, pyridine, 12 h (60% for two steps); (d) NaOMe, MeOH (quant).

As we wanted to test whether the solid-phase techniques could be used in the preparation of oligomeric systems incorporating our scaffold Aij, we envisaged the synthesis of the pseudotetrapeptide **38** according to the following method (Scheme 7). We chose to use the Fmoc strategy and the HMBA-AM resin in which the linker is the 4-hydroxymethylbenzoic acid.[25] The coupling reactions were accomplished without protection of the polyol moiety of the Fmoc-amino acid **21**. The commercially available Fmoc-glycine was attached to the OH resin using 2,6-dichlorobenzoyl chloride and pyridine.[26] This offers a double advantage: to favor the anchoring to the HO-resin by avoiding competitive reactions with the free OH groups of **21** on one hand and to facilitate the final cleavage of the oligomer from the resin on the other hand. Subsequent treatment with piperidine gave the solid-supported amine **31**. The Fmoc-amino acid **21** was then coupled by treatment with PyBOP and DIPEA in DMF, affording the immobilized dimer **32** after further treatment with piperidine. The process was repeated two, three, and four times to obtain the polymer-bound compounds **33**, **34**, and **35** that were removed from the solid support on treatment with 1 M NaOH and THF as cosolvent to assist swelling of the resin.

Finally, it is worth noting that to increase the efficiency of the coupling reactions the Fmoc-amino acid **21** as well as PyBOP and DIPEA have to be used in excess. Fortunately, the excess of activated Fmoc-amino acid **39** (see Scheme 7) can be recovered by extraction from the resin by washing with DMF. Compound **39** is a stable compound that can be purified by chromatography (see the Experimental Section).

The amino acids **36**−**38** showed high water solubility and can be obtained in good overall yields This method open ways to libraries of oligomers that can expected to have high bioavailability.

(22) Koole, L. H.; Moody, H. M.; Broeders, N. L. H. L.; Quaedflieg, P. J. L. M.; Kuijpers, W. H. A.; van Genderen, M. H. P.; Coenen, A. J. J. M.; van der Wal, S.; Buck, H. M. *J. Org. Chem*. **1989**, *54*, 1657−1664.

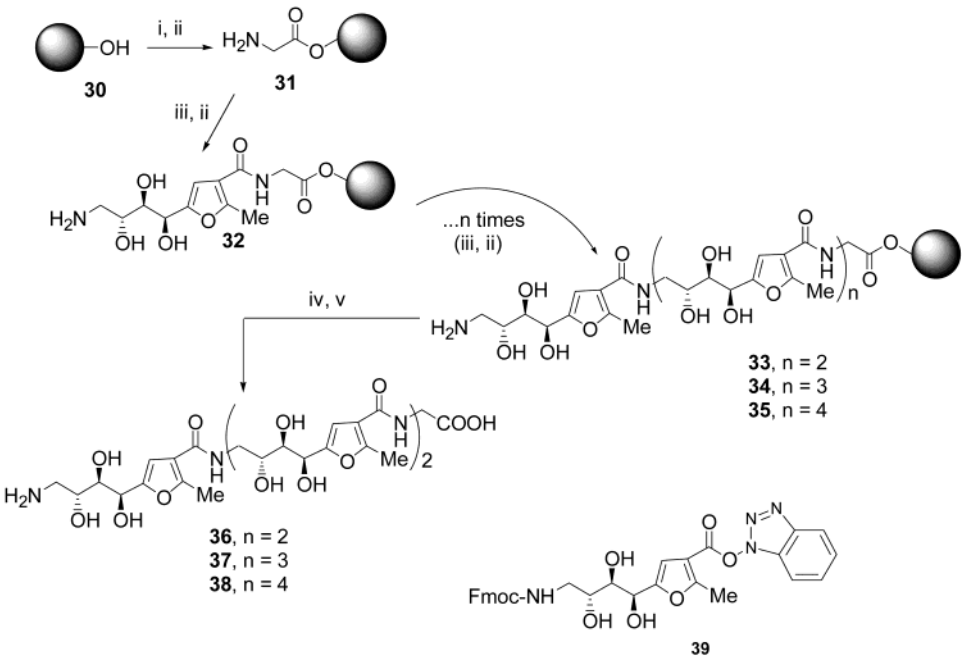
(23) Mukaiyama. T. In *Challenges in Synthetic Organic Chemistry*; Rowlinson, J. S., Ed.; Clarendon Press: Oxford, 1994.

(24) J. Coste, D. Le-Nguyen and B. Castro *Tetrahedron Lett*. **1990**, *31*, 205−208.

(25) Atherton, E.; Sheppard, R. C. In *Solid Phase Peptide Synthesis. A Practical Approach*; Rickwood, D. R., Jones, B. D., Eds.; IRL Press: Oxford, 1989.

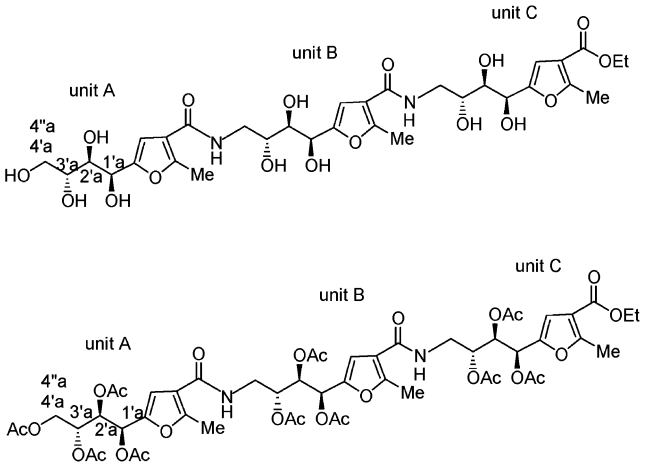
(26) Sieber, P. *Tetrahedron Lett*. **1987**, *28*, 6147−6150.

SCHEME 7. Solid-Phase Synthesis: Fmoc Strategy[a]



[a] Reagents and conditions: (i) 2,6-dichlorobenzoyl chloride, py, DMF, Fmoc-Gly-OH; (ii) 20% PIP/DMF; (iii) PyBOP, DIPEA, DMF, 1 equiv of **21**; (iv) 1 M, NaOH, THF; (v) 1 M AcOH (60% overall).

SCHEME 8. Schematic View of the Acetylated and Deacylated Trimers Showing the Atomic and Monomer Numbering



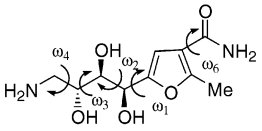
Conformational Analysis. NMR Studies. Since NMR parameters are averaged on time and on many molecules, the information that is possible to deduce from these experiments corresponds to the time-averaged conformation of the oligomers in solution. ^{1}H NMR spectra of the oligomers **22**, **23**, **25**, **26**, and **36** were completely assigned by a combination of homonuclear COSY and TOCSY techniques. A schematic view of the acetylated and deacetylated trimers showing the atomic and monomer numbering is outlined in Scheme 8. The corresponding ^{1}H NMR chemical shifts are listed in Table 2, and a comparison of the 1D of **22**, **23**, **25**, and **26** is given in the figures found in the Supporting Information.

The couplings for the C1′−C4′ lateral chains are defined by ω_2, ω_3, and ω_4 torsion angles (Figure 2). The corresponding values (Table 3) were constant in all molecules, independent of the position of the monomer in the chain and of the solvent. The couplings were in the range $J_{1',2'}$ 1.5−3.0 Hz and $J_{2',3'}$ 8.0−8.5 Hz, $J_{3',4'}$ 3.0−4.0 Hz, and $J_{3,4''}$ 5.0−6.0 Hz. Clearly, there is a very predominant gauche-like relationship between H-1′ and H-2′ and an anti-type orientation between H-2′ and H-3′. The ω_4 torsion is flexible, as deduced for the two averaged $J_{3',4'}$ coupling constant values between 3 and 6 Hz. In fact, according to the well-known relationship between couplings and torsion angles,[27] these values indicate the existence of one or two major conformations around the

TABLE 2. ^{1}H Chemical Shifts (δ, ppm) of 22, 23, 25, 26, and 36

proton/unit	**22**[a]	**23**[b]	**25**[a]	**26**[b]	**36**[c]
4, 4′/a	4.11, 4.24	3.96, 4.11	4.11, 4.24	3.97, 4.11	2.77, 2.95
b	3.16, 4.00	3.81, 4.01	3.16, 4.00	3.76,4.02	3.41, 3.41
c	3.14, 3.99			3.78, 4.01	3.31, 3.45
d					3.54, 3.54
3/a	5.15	4.05	5.15	4.05	3.66
b	5.03	4.18	5.03	4.18	3.64
c	5.02			4.19	3.60
2/a	5.58	4.08	5.59	4.10	3.54
b	5.46	4.15	5.46	4.18	3.52
c	5.45			4.18	3.53
1/a	6.01	5.23	6.01	5.23	4.75
b	6.06	5.22	6.06	5.22	4.71
c	6.05			5.22	4.65
furan H-5/a	6.41	6.92	6.41	6.96	6.62
b	6.60	6.97	6.61	6.96	6.65
c	6.61			6.98	6.58
CH_3-6/a	2.55	2.82	2.56	2.85	2.52
b	2.54	2.81	2.56	2.82	2.52
c	2.54			2.81	2.52
NH/a					
b	6.14		6.14		7.67
c	6.09				7.62
d					7.25

[a] $CDCl_3$. [b] D_2O. [c] DMSO-d_6.



ω_1 as O-C5 –C1'-C2'

ω_2 as C5-C1'-C2'-C3'

($J_{1',2'}$ 1.5-3.0) (a,g-)

ω_3 as C1'-C2'-C3'-C4' ($J_{2',3'}$ 8.0-8.5) (a)

ω_4 as C2'-C-3'-C4'-N,

($J_{3',4'}$ 3.0-4.0, $J_{3',4''}$ 5.0-6.0) (a,g-)

ω_5 as C3'-C4'– N-CO.

ω_6 as N-CO-C3-C2.

FIGURE 2. Schematic view of the monomer showing the relevant torsion angles

TABLE 3. Vicinal Proton/Proton Coupling Constants for 22, 23, 25, 26, and 36 (Hz)[a]

H-pair/unit	22	23	25	26	36
1−2/a	4.5	3.5	4.5	3.5	3.0
1−2/b	3.5	3.5	4.0	3.5	2.5
1−2/c	4.0			3.5	1.5
1−2/d					
2−3/a	8.0	9.2	9.2	9.2	8.5
2−3/b	8.5	9.2	9.2	9.2	8.5
2−3/c	8.5			9.2	8.5
3−4	3.0	3.3	3.3	3.3	3.0
3−4′/a	5.5	6.0	6.0	6.0	5.5
3−4	3.5	3.5	3.5	3.5	3.0
3−4′/b	5.5	6.6	6.6	6.6	5.0
3−4	3.5			3.5	3.5
3−4′/c	5.5			6.6	5.5

[a] Couplings involving amide protons were in all cases between 5.5 and 6.0 Hz.

ω_2 (anti and/or g−) and ω_3 (anti) linkages, and the existence of a conformational equilibrium for ω_4 (anti, g− > g+).

Then, the NOESY/ROESY experiments performed with different mixing times were used to qualitatively estimate proton/proton interresidue distances.[28] For all the molecules, all NOESY cross-peaks were positive at 500 MHz as expected for a fast tumbling molecule. NOEs were assigned as strong (s), medium (m), and weak (w) and then quantitated. The NOEs can be grouped into different groups: The first group defines the presence of conformational equilibria around the carbonyl−furan linkages. Indeed, NOEs between the NH protons (**25**, **26**, and **36**) and both the methyl groups and H-4 attached to their adjacent furane rings may be appreciated in $CDCl_3$ and DMSO-d_6 solvents. Additionally, in all solvents, the H-4 at the furan rings give NOEs to their attached H-3, H-2, and H-5. Taking into account the simultaneous existence of all these NOEs, the existence of conformational equilibrium around ω_1 and ω_6 is granted, as also deduced from the coupling information. No remote NOEs between different subunits were observable. Thus, the

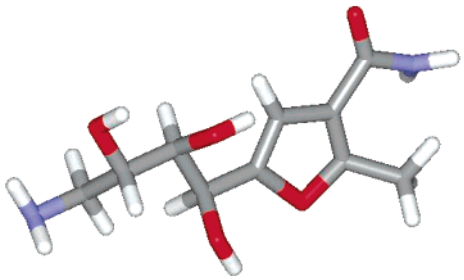


FIGURE 3. Perspective of the global minimum of the monomer as deduced by MM3* calculations.

data from the NOESY and ROESY experiments were in also in agreement with the *J* data, and the complete set of observed data indicated the existence of conformational equilibria in all cases.

Conformational Analysis. Molecular Dynamics Studies. (a) The Monomer: Starting Conformations and Conformational Distributions. As a first step to determine the overall three-dimensional structure of the molecules, molecular mechanics and dynamics calculations were performed on the monomer building block (Figure 3). After MM2* minimization of the starting geometries, information on the conformational space accessible was obtained through molecular dynamics simulations.[29] In particular, the MD simulations were performed using several output geometries of the molecular mechanics calculations as starting structures (see above). Thus, different ω_i torsions were considered. A summary of the MM2* results is given in Table S1 (Supporting Information).

Two clusters of values are observed for ω_2: In the first cluster, this torsion angle adopts a value around −60°. In the second cluster, the angle changes to 180°, providing a smaller relative steric energy value. Regarding ω_3, the computed dihedral angle values are close to 180°. Major equilibria are predicted around ω_5 and ω_6, independent of the starting structure. Therefore, although the presence of other conformers cannot be discarded and it is, indeed, fairly possible that several geometries are simultaneously taking place, a representative view of the global minimum is shown in the Figure 3.

(b) Toward a Model of Oligomeric Fragments. Once the repeating units had been analyzed, three units were built from the global minima, extensively minimized, and then combined to generate models of **22**, **23**, **25**, **26**, and **36**. These geometries were minimized, and the two lowest energy minima obtained in this manner were then submitted to MD simulations. The initial conformations of the lateral chains were selected to agree with the experimental data (see above).

From the MD (Figure 4 and 5), it can be observed that a major syn relationship between the five-membered ring and the lateral chain is adopted, with values around −120°. In all cases, the torsional oscillations were more pronounced around ω_1, ω_5, and ω_6. With respect to the

(27) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2793.

(28) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.

(29) (a) Homans, S. W. *Biochemistry* **1990**, *29*, 9110−9118. (b) Mukhopadhyay, C.; Miller, K. E.; Bush, C. A. *Biopolymers* **1994**, *34*, 21. (c) Rutherford, T. J.; Partridge, J.; Weller, C. T.; Homans, S. W. *Biochemistry* **1993**, *32*, 12715−12724. (d) Siebert, H. C.; Reuter, G.; Schauer, R.; von der Lieth, C. W.; Dabrowski, J. *Biochemistry* **1992**, *31*, 6962−6971. (e) Engelsen, S. B.; Herve du Penhoat, C.; Perez, S. *J. Phys. Chem.* **1995**, *99*, 13334−13351.

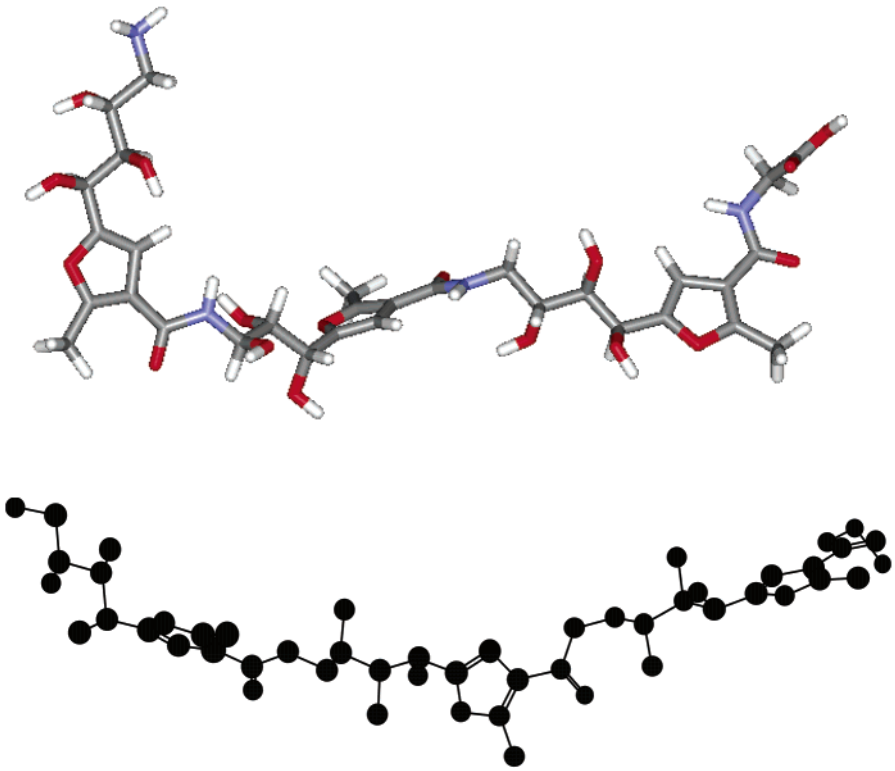


FIGURE 4. Different perspectives of the global minimum of compound **36** as deduced by MM3* calculations.

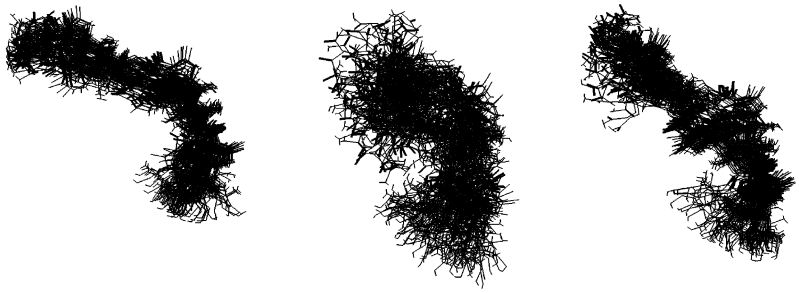


FIGURE 5. Superimposition of 3 × 100 structures obtained by MD simulations of **36** with the MM3* force field. Structures from three different time periods are superimposed.

rest of ω_i torsions, although, according to the simulations, a variety of possibilities could occur, the most stable one by far corresponds to ω_2 g−, ω_3 anti, ω_4 anti (Table S2, Supporting Information).

Conclusion

We have prepared a new class of peptidomimetics that can be obtained in combinatorial fashion potentially. The subunits are readily available with high structural diversity with respect to functionality and stereochemistry. The water solubility and stability of the new oligomers may lead to new bioactive compounds. Some of the new oligomers have been submitted to conformational studies. From the experimental and computational results, it seems that there is an important amount of conformational freedom for the torsion angles of these molecules, which do not depend on the solvent and on the size. Unrestrained MM and MD simulations provide a picture that agrees satisfactorily with the NMR experimental data when a homogeneous distribution of lateral chains are considered.

Experimental Section

General Methods. Dried solvents and reagents were freshly distilled under N_2 prior to use: THF from sodium and benzophenone, CH_2Cl_2, DMF from BaO, and *i*-Pr_2NEt from CaH_2. TLC was performed on silica gel HF_{254} (Merck), with detection by UV light and charring with H_2SO_4. Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography. Optical rotations were measured in a 0.1 dm tube at 25 °C in a spectropolarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on solutions in $CDCl_3$, DMSO-d_6, CD_3OD and D_2O, *J* values are given in Hz and δ in ppm. Assignments were confirmed by homonuclear 2D COSY and heteronuclear 2D correlated (HETCOR) experiments. The HRFABMS spectra were obtained with 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt.

3-Ethoxycarbonyl-2-methyl-5-(1′,2′,3′,4′-tetra-*O*-*tert*-butyldimethylsilyl-D-*arabino*-tetritol-1-yl)furan (2b). To a solution of **1**[15] (200 mg, 0.73 mmol) in dry DMF (2.5 mL) were added *tert*-butyldimethylsilyl chloride (1.31 g, 8.76 mmol) and

imidazole (1.2 g, 17.5 mmol), and the mixture was heated at 60 °C for 10 h. Then, the solution was concentrated, and the residue was diluted with dichloromethane and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (ether/petroleum ether, 1:10 → 1:5) to give **2b** as a colorless oil (460 mg, 0.63 mmol, 87%): $[\alpha]_D$ +3 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, H-4), 4.66 (d, $J_{1',2'}$ = 6.6, H-1′), 4.26 (q, $^3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.91 (d, H-2′), 3.72 (dd, $J_{3',4'a}$ = 6.8, $J_{3',4'b}$ = 4.5, H-3′), 3.21 (dd, $J_{4'a,4'b}$ = 10.3, H-4′a), 3.12 (dd, H-4′b), 2.53 (s, CH_3), 1.33 (t, CH_2CH_3), 0.91−0.84 (m, CH_3 de *tert*-butyl), 0.11−0.05 (m, CH_3 of TBS); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.1 (*C*OOEt), 157.8, 152.7 (C-2, C-5), 113.9 (C-3), 108.3 (C-4), 79.6 (C-2′), 74.7 (C-3′), 70.3 (C-1′), 64.7 (C-4′), 59.9 (*C*H$_2$CH$_3$), 26.0−25.9 (12 C, (*C*H$_3$)$_3$C), 18.3−18.0 (4 C, (CH$_3$)$_3$*C*), 14.2 (CH$_2$*C*H$_3$), 13.6 (CH$_3$), from −4.4 to −5.7 (8 C, *t*-Bu(*C*H$_3$)$_2$Si). Anal. Calcd for $C_{36}H_{74}O_7Si_4$: C, 59.12; H, 10.20. Found: C, 59.05; H, 10.02.

3-Hydroxymethyl-2-methyl-5-(1′,2′,3′,4′-tetra-*O*-*tert*-butyldimethylsilyl-D-*arabino*-tetritol-1′-yl)furan (3b). To a suspension of $LiAlH_4$ (41 mg, 1.08 mmol) in dry THF (1 mL) was added a solution of **2b** (393 mg, 0.54 mmol) in dry THF (2 mL) under N_2. The reaction mixture was stirred for 15 min and then diluted with ether (10 mL). A saturated aqueous solution of Na_2SO_4 (10 mL) was added, and the resulting precipitate was filtered off and washed with ethanol. The filtrate was concentrated to give **3b** as a colorless oil (320 mg, 0.47 mmol, 87%): $[\alpha]_D$ −10 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (s, H-4), 4.65 (d, $J_{1',2'}$ = 6.7, H-1′), 4.41 (d, $J_{CH,OH}$ = 5.6, CH_2OH), 3.91 (d, H-2′), 3.71 (dd, $J_{3',4'a}$ = $J_{3',4'b}$ = 5.4, H-3′), 3.21 (d, H-4′a, H-4′b), 2.24 (s, CH_3), 1.16 (t, CH$_2$O*H*), 0.91−0.85 (m, CH_3 of *tert*-butyl), 0.11−0.06 (m, CH_3 of TBS); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.7, 147.8 (C-2, C-5), 119.5 (C-3), 108.8 (C-4), 79.8 (C-2′), 74.7 (C-3′), 70.5 (C-1′), 64.7 (C-4′), 56.7 (CH$_2$OH), 26.0−25.9 (12 C, (*C*H$_3$)$_3$C), 18.4−18.1 (4 C, (CH$_3$)$_3$*C*), 11.5 (*C*H$_3$), −4.4 to −5.6 (8 C, *t*-Bu(*C*H$_3$)$_2$Si). Anal. Calcd for $C_{34}H_{72}O_6Si_4$: C, 59.24; H, 10.53. Found: C, 59.29; H, 10.78.

5-(4′-Azido-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-ethoxycarbonyl-2-methylfuran (11). To a stirred solution of **10**[21] (254 mg, 0.59 mmol) in DMF (2.5 mL) was added sodium azide (82 mg, 1.18 mmol). The mixture was heated at 110 °C for 3 h. Then, the solvent was evaporated and the residue partitioned between AcOEt and water. The organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (ether/petroleum ether, 1:3 → 1:1) to give **11** as a white solid (115 mg, 0.38 mmol, 65%) that crystallized from ether/petroleum ether: mp = 85−87 °C; $[\alpha]_D$ +7 (*c* 0.9, CH_3OH); IR ν_{max} 3357, 2928, 2109, 1720, 1672, 1394, 1236, 1093 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 6.57 (s, H-4), 4.86 (under MeOH, H-1′), 4.26 (q, $3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.82 (m, H-3′), 3.69 (dd, $J_{1',2'}$ = 2.3 $J_{2',3'}$ = 8.4, H-2′), 3.51 (dd, $J_{3',4'a}$ = 2.8, $J_{4'a,4'b}$ = 12.8, H-4′a), 3.38 (dd, $J_{3',4'b}$ = 6.4, H-4′b), 2.53 (s, CH_3), 1.32 (t, CH$_2$C*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.7 (*C*OOEt), 159.6, 155.5 (C-2, C-5), 115.1 (C-3), 108.5 (C-4), 74.3 (C-2′), 71.6 (C-3′), 67.6 (C-1′), 61.3 (*C*H$_2$CH$_3$), 55.5 (C-4′), 14.7 (CH$_2$*C*H$_3$), 13.8 (CH$_3$); FABMS *m*/*z* 322 [100, (M + Na)$^+$]. Anal. Calcd. for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.15; H, 5.43; N, 14.25.

5-(4′-Azido-1′,2′,3′-tri-*O*-benzyl-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-ethoxycarbonyl-2-methylfuran (12a). To a solution of **11** (1 g, 3.34 mmol) and sodium hydride (721 mg, 30.1 mmol) in dry DMF (5 mL) cooled at 0 °C was added benzyl bromide (3.6 mL, 30.1 mmol). The reaction mixture was stirred at rt for 2 h and then quenched with triethylamine and methanol. The mixture was concentrated and the residue dissolved in dichloromethane and washed with water and brine. The organic layer was dried over Na_2SO_4 and the solvent evaporated. The resulting residue was purified by column chromatography (ether/petroleum ether, 1:3 → 1:1) to give **12a** as a colorless oil (1.61 g, 2.84 mmol, 85%): $[\alpha]_D$ −21 (*c* 2.8, CH_2Cl_2); IR ν_{max} 2928, 2109, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.21 (m, Ph), 6.63 (s, H-4), 4.62, 4.33 (2d, $^2J_{H,H}$ = 11.8, CH_2Ph), 4.60, 4.55 (2d, $^2J_{H,H}$ = 11.1, CH_2Ph), 4.56 (d, $J_{1',2'}$ = 5.1, H-1′), 4.49, 4.34 (2d, $^2J_{H,H}$ = 11.3, CH_2Ph), 4.31 (q, $^3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.97 (t, $J_{2',3'}$ = 5.3, H-2′), 3.65 (m, H-3′), 3.42 (d, $J_{3,4}$ = 4.4, H-4a, H-4b), 2.54 (s, CH_3), 1.37 (t, CH$_2$C*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 163.8 (*C*OOEt), 159.2, 149.3 (C-2, C-5), 137.9, 137.9, 137.5 (3 C-1 of Ph), 128.3−127.6 (15 C of Ph), 114.2 (C-3), 110.1 (C-4), 80.1 (C-2′), 78.2 (C-3′), 74.9, 74.3 (C-1′, *C*H$_2$Ph), 72.0, 71.1 (2 *C*H$_2$Ph), 60.1 (*C*H$_2$CH$_3$), 50.6 (C-4′), 14.3 (CH$_2$*C*H$_3$), 13.8 (CH$_3$); FABMS *m*/*z* 592 [100, (M + Na)$^+$]. Anal. Calcd for $C_{33}H_{35}O_6N_3$: C, 69.57; H, 6.19; N, 7.34. Found: C, 69.71; H, 6.14; N, 7.64.

5-(4′-Azido-1′,2′,3′-tri-*O*-*tert*-butyldimethylsilyl-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-ethoxycarbonyl-2-methylfuran (12b). To a solution of **11** (155 mg, 0.52 mmol) in dry DMF (2.5 mL) were added *tert*-butyldimethylsilyl chloride (0.71 g, 4.7 mmol) and imidazole (0.64 g, 9.36 mmol). The mixture was stirred at 70 °C for 10 h, and then the solvent was evaporated. The residue was diluted with dichloromethane and washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (petroleum ether → ether/petroleum ether 1:10) to give **12b** as a colorless oil (287 mg, 0.45 mmol, 86%): $[\alpha]_D$ −9 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, H-4), 4.53 (d, $J_{1',2'}$ = 5.2, H-1′), 4.28 (q, $^3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.99 (dd, $J_{3',4'a}$ = 8.4, $J_{3',4'b}$ = 2.3, H-3′), 3.91 (d, H-2′), 2.96 (dd, $J_{4'a,4'b}$ = 13.0, H-4′a), 3.12 (dd, H-4′b), 2.56 (s, 3 H, CH_3), 1.35 (t, CH$_2$C*H*$_3$), 0.91−0.88 (m, (CH$_3$)$_3$), 0.12 to −0.05 (m, CH_3Si); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 163.9 (*C*OOEt), 158.1, 151.1 (C-2, C-5), 114.0 (C-3), 108.7 (C-4), 79.7 (C-2′), 72.0 (C-3′), 70.6 (C-1′), 60.0 (*C*H$_2$CH$_3$), 54.4 (C-4′), 25.7−25.6 (9 C, (*C*H$_3$)$_3$C), 18.1−17.8 (3 C, (CH$_3$)$_3$*C*), 14.1 (CH$_2$*C*H$_3$), 13.6 (CH$_3$), −4.5 to −5.2 (6 C, *t*-Bu(*C*H$_3$)$_2$Si). Anal. Calcd. for $C_{30}H_{59}O_6Si_3N_3$: C, 56.12; H, 9.26; N, 6.54. Found: C, 56.62; H, 9.02; N, 6.71.

5-(4′-Amino-1′,2′,3′-tri-*O*-benzyl-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-hydroxymethyl-2-methylfuran (13a). To a stirred suspension of $LiAlH_4$ (43 mg, 1.06 mmol) in dry THF (1.5 mL) was added a solution of **12a** (156 mg, 0.27 mmol) in dry THF (3 mL) under N_2. The mixture was stirred at rt for 15 min and diluted with ether (25 mL). Saturated aqueous solution of Na_2SO_4 (25 mL) in water was added. The precipitate was filtered off and washed with ether. The filtered solution was concentrated and the residue diluted with dichloromethane and washed with water, dried (Na_2SO_4) and concentrated to give **13a** as a colorless oil. (118 mg, 0.23 mmol, 87%). $[\alpha]_D$ −36 (*c* 1, CH_2Cl_2); IR ν_{max} 3370, 2920, 2864, 1578, 1454, 1101, 1063, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, Ph), 6.31 (s, H-4), 4.76, 4.70 (2d, $^2J_{H,H}$ = 11.4, CH_2Ph), 4.61, 4.40 (2d, $^2J_{H,H}$ = 11.8, CH_2Ph), 4.51 (d, $J_{1',2'}$ = 6.5, H-1′), 4.45, 4.36 (2d, $^2J_{H,H}$ = 11.6, CH_2Ph), 4.41 (s, CH_2OH), 4.12 (dd, $J_{2',3'}$ = 4.1, H-2′), 3.28 (m, H-3′), 2.87 (dd, 1 H, $J_{4a,4b}$ = 13.5, $J_{3,4a}$ = 6.7, H-4a), 2.70 (dd, 1 H, $J_{3,4b}$ = 3.4, H-4b), 2.28 (s, 3 H, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 149.2, 149.1 (C-2, C-5), 138.5, 138.2, 137.9 (3 C-1 of Ph), 128.2−126.8 (15 C of Ph), 119.7 (C-3), 110.8 (C-4), 80.4 (C-3′), 80.1 (C-2′), 75.6 (C-1′), 74.7, 71.3, 70.9 (3 *C*H$_2$Ph), 56.2 (CH$_2$OH), 41.4 (C-4′), 11.6 (CH$_3$); CIMS *m*/*z* 502 [100, (M + H)$^+$]; HRCIMS *m*/*z* found 502.2589, calcd for $C_{31}H_{35}NO_5$ + H 502.2593. Anal. Calcd for $C_{31}H_{35}NO_5$: C, 74.28; H, 7.00; N, 2.79. Found: C, 74.86; H, 6.47; N, 2.40.

5-(4′-Amino-1′,2′,3′-tri-*O*-*tert*-butyldimethylsilyl-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-ethoxycarbonyl-2-methylfuran (13b). A solution of **12b** (89 mg, 0.14 mmol) in methanol (8 mL) was hydrogenated with Pd−C (10%)(10 mg) at 1 atm for 12 h. The catalyst was filtered off and the solvent concentrated to give pure **13b** as a colorless oil (80 mg, 0.13 mmol, 93%): $[\alpha]_D$ −6 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, H-4), 4.56 (d, $J_{1',2'}$ = 5.7, H-1′), 4.25 (q, $^3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.93 (d, H-2′), 3.75 (dd, $J_{3',4'a}$ = 6.7, $J_{3',4'b}$ = 3.5, H-3′), 2.53 (s, CH_3), 2.38 (dd, $J_{4'a,4'b}$ = 13.9, H-4′a), 2.11 (dd, H-4′b), 1.34 (t, CH$_2$C*H*$_3$), 0.91−0.84 (m, (CH$_3$)$_3$), 0.11- −0.05 (m, CH$_3$-Si); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 163.9 (*C*OOEt), 157.9, 151.9 (C-2, C-5), 114.0 (C-3), 108.3 (C-4), 80.1 (C-2′), 74.5 (C-3′), 70.6

(C-1′), 59.9 (CH_2CH_3), 43.9 (C-4′), 25.8−25.7 (9 C, $(CH_3)_3C$), 18.1−17.9 (3 C, $(CH_3)_3C$), 14.1 (CH_2CH_3), 13.6 (CH_3), −4.1 to −5.1 (6 C, *t*-Bu$(CH_3)_2$Si). Anal. Calcd for $C_{30}H_{61}NO_6Si_3$: C, 58.48; H, 9.98; N, 2.27. Found: C, 58.21; H, 9.80; N, 2.23.

5-[4′-[*N*-Acetyl-*N*-[2-methyl-5-(1′,2′,3′,4′-tetra-*O*-benzyl-D-*arabino*-tetritol-1′-yl)furan-3-ylmethyl]amino]-1′,2′,3′-tri-*O*-benzyl-4′-deoxy-D-*arabino*-tetritol-1′-yl]-3-acetoxymethyl-2-methylfuran (14a). To a solution of **3a** (300.9 mg, 0.51 mmol) in dry CCl_4 (6.4 mL) containing molecular sieves (4 Å) was added triphenylphosphine (273 mg, 1.02 mmol) in CCl_4 (5 mL) under N_2 atmosphere. The mixture was heated at reflux for 8 h. The solution was concentrated to give 3-chloromethyl-2-methyl-5-(1′,2′,3′,4′-tetra-*O*-benzyl-D-*arabino*-tetritol-1′-yl)furan (**6a**) which was used without further purification in the next step. To a solution of **13a** (286 mg, 0.57 mmol) and Na_2CO_3 (60 mg, 0.57 mmol) in dry DMF (2 mL) with molecular sieves (4 Å) was added a solution of **6a** in dry DMF (3 mL) under N_2 atmosphere. The reaction mixture was stirred at 70 °C for 1.5 h and then filtered. The filtrate was evaporated and the residue acetylated conventionally. Column chromatography (dichloromethane/acetone → dichloromethane,-10:1) gave **14a** as a colorless oil (248 mg, 0.21 mmol, 42%, three steps): $[\alpha]_D$ −19 (*c* 1.7, CH_2Cl_2); ^{13}C NMR (125.7 MHz, $CDCl_3$, mixture of two conformers) δ 170.9, 170.9, 170.7, 169.9 ($CONR_1R_2$, CH_3COOR), 151.2, 150.8, 150.3, 149.6, 149.3, 149.1, 149.1 148.5 (2 C-2, 2 C-5), 138.9−137.4 (7 C-1 of Ph), 128.3−127.2 (35 C of Ph), 116.3, 115.8, 115.5, 115.3 (2 C-3), 112.4, 111.6, 111.0, 109.5 (2 C-4), 81.2, 80.9, 80.9 (C-2′a, C-2′b), 78.3, 78.2, 78.1, 76.5 (C-3′a, C-3′b), 75.7, 75.7, 75.5, 75.2, 74.9, 74.8, 74.7, 74.6 (C-1′a, C-1′b, 2 CH_2Ph), 73.2, 73.1, 71.9, 71.8, 71.6, 71.2, 71.0, 70.9 (5 CH_2Ph), 69.5, 69.4 (C-4′a), 57.9, 57.5 (CH_2-OAc), 47.1, 45.5 (C-4′b), 45.1, 39.6 (CH_2RNAc), 21.5, 21.4, 20.9, 20.8 (CH_3COOR, $CH_3CONR_1R_2$), 11.6, 11.6, 11.4, 11.4 (2 CH_3); FABMS *m*/*z* 1182 [100, $(M + Na)^+$]; HRFABMS *m*/*z* calcd for $C_{73}H_{77}NO_{12}$ + Na 1182.5376, found 1182.5376.

5-[4′-[*N*-Acetyl-*N*-[2-methyl-5-(1′,2′,3′,4′-tetra-*O*-*tert*-butyldimethylsilyl-D-*arabino*-tetritol-1′-yl)furan-3-ylmethyl]-amino]-1′,2′,3′-tri-*O*-*tert*-butyldimethylsilyl-4′-deoxy-D-*arabino*-tetritol-1′-yl]-3-ethoxycarbonyl-2-methylfuran (14b). To a solution of **3b** (422 mg, 0.58 mmol) in dry CCl_4 (5 mL) containing molecular sieves (4 Å) was added triphenylphosphine (321 mg, 1.2 mmol) in CCl_4 (2 mL) under N_2 atmosphere. The mixture was heated at reflux for 8 h, and then the solution was concentrated to give 3-chloromethyl-2-methyl-5-(1′,2′,3′,4′-tetra-*O*-*tert*-butyldimethylsilyl-D-*arabino*-tetritol-1′-yl)furan (**6b**) which was used without further purification in the next step. A solution of compound **6b** in dry DMF (4 mL) was added under N_2 atmosphere to a solution of **13b** (535 mg, 0.87 mmol) and Na_2CO_3 (97 mg, 0.87 mmol) in dry DMF (4 mL) containing molecular sieves 4 Å. The reaction mixture was stirred at 90 °C for 8 h and then filtered. The filtrate was evaporated and the residue acetylated conventionally. Column chromatography (ether/petroleum ether, 1:30 → 1:8) gave **14b** as a colorless oil (290 mg, 0.22 mmol, 38%, three steps): $[\alpha]_D$ −9 (*c* 1.6, CH_2Cl_2); ^{13}C NMR (125.7 MHz, $CDCl_3$, mixture of two conformers) δ 170.7, 170.9 ($CONR_1R_2$), 164.1, 163.5 (*C*OOEt), 158.2 (C-2b), 153.1, 152.6 (C-2a), 152.2, 152.1 (C-5b), 147.4, 146.3 (C-5a), 116.4, 116.0 (C-3a), 114.3, 114.0 (C-3b), 109.6 (C-4a), 109.2, 108.0 (C-4b), 80.1, 79.9, 79.8, 79.5 (C-2′a, C-2′b), 74.9, 74.8 (C-3′b), 71.5−70.0 (C-1′a, C-1′b, C-3′a), 64.6 (C-4′a), 60.2, 59.9 (CH_2CH_3), 48.9, 48.4 (C-4′b), 46.6 (CH_2-NR_1R_2), 26.2−25.2 ($(CH_3)_3C$), 22.1, 21.5 ($CH_3CONR_1R_2$), 18.5−17.9 ($(CH_3)_3C$), 14.2 (CH_2CH_3), 13.6 (CH_3b), 11.7, 11.6 (CH_3a); Anal. Calcd for $C_{66}H_{133}NO_{12}Si_7$: C, 59.63; H, 10.08; N, 1.05. Found: C, 59.88; H, 10.09; N, 1.06.

5-[4′-[*N*-Acetyl-*N*-[(5-D-*arabino*-tetritol-1′-yl)-2-methyl]-furan-3-ylmethyl]amino]-4′-deoxy-D-*arabino*-tetritol-1′-yl]-3-ethoxycarbonyl-2-methylfuran (15) and 5-[4′-[*N*-Acetyl-*N*-[1′,2′,3′,4′-tetra-*O*-acetyl(5-D-*arabino*-tetritol-1′-yl)-2-methyl]furan-3-ylmethyl]amino]-1′,2′,3′-tri-*O*-acetyl-4′-deoxy-D-*arabino*-tetritol-1′-yl]-3-ethoxycarbonyl-2-methylfuran (16). To a solution of **14b** (147 mg, 0.11 mmol) in THF (5 mL) at 0 °C was added a solution of TBAF in THF (1 M, 1.54 mL, 1.54 mmol). The mixture was stirred for 2.5 h and then the solvent evaporated. Column chromatography (dichloromethane/methanol, 20:1 → 10:1) gave the unprotected compound as a white solid. **15** (49 mg, 0.093 mmol, 85%): $[\alpha]_D$ −11 (*c* 1, CH_3OH); FABMS *m*/*z* 552 [100, $(M + Na)^+$]; HRFABMS *m*/*z* found 552.2065, calcd for $C_{24}H_{35}NO_{12}$ + Na 552.2057.

Conventional acetylation of **15** with acetic anhydride and pyridine gave **16** (mixture of two conformers) as an oil in 100% yield. Major conformer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, H-4b), 6.20 (s, H-4a), 5.99−5.97 (m, H-1′a), 5.95 (d, $J_{1'b,2'b}$ = 5.7, H-1′b), 5.54−5.51 (m, H-2′a), 5.48 (t, $J_{2'b,3'b}$ = 5.6, H-2′b), 5.26−5.20 (m, H-3′b), 5.16−5.12 (m, H-3′a), 4.56, 3.86 (2d, $^2J_{H,H}$ = 15.0, CH_2NAcR), 4.28−4.14 (m, RCOOCH_2CH$_3$, H-4′a), 4.09−4.03 (m, H-4″a), 3.45−3.40 (m, H-4′b), 3.15 (dd, $J_{4''b,3'b}$ = 2.9, $J_{4''b,4'b}$ = 15.4, H-4″b), 2.55 (s, CH_3b), 2.26 (s, 3 H, CH_3a), 2.08−2.01 (m, 7 CH_3CO), 1.33−1.30 (m, 6 H, COOCH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.7−169.2 (7 CO of Ac, *C*ONRR′), 163.2 (*C*OOEt), 159.8, 150.5 (C-2b, C-5b), 146.7, 146.2 (C-2a, C-5a), 115.8 (C-3a), 114.5 (C-3b), 111.7 (C-4a), 111.0 (C-4b), 71.3 (C-2′b), 70.2 (C-2′a), 68.6 (C-3′a), 67.1 (C-3′b), 65.8 (C-1′a), 65.4 (C-1′b), 61.5 (C-4′a), 60.3 (COOCH_2CH_3), 46.4 (C-4′b), 38.4 (CH_2NAcR), 21.4 (CH_3CONRR′), 20.7−20.4 (7 CH_3CO), 14.2 (COOCH_2CH_3), 13.7 (CH_3b), 11.4 (CH_3a). Minor conformer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, H-4b), 6.11 (s, H-4a), 6.04 (d, $J_{1'b,2'b}$ = 5.1, H-1′b), 5.99−5.97 (m, 2 H, H-1′a), 5.54−5.51 (m, H-2′a), 5.48 (t, $J_{2'b,3'b}$ = 5.6, H-2′b), 5.26−5.20 (m, H-3′b), 5.16−5.12 (m, H-3′a), 4.28−4.14 (m, RCOOCH_2-CH$_3$, H-4′a, CH_2NAcR), 4.09−4.03 (m, H-4″a), 3.53 (dd, $J_{4''b,3'b}$ = 8.6, $J_{4''b,4'b}$ = 14.5, H-4′b), 3.45−3.40 (m, H-4″b), 2.53 (s, CH_3b), 2.22 (s, 3 H, CH_3a), 2.08−2.01 (m, 7 CH_3CO), 1.33−1.30 (m, COOCH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.7−169.2 (7 CO of Ac, *C*ONRR′), 163.4 (*C*OOEt), 159.6, 149.2 (C-2b, C-5b), 147.4, 146.5 (C-2a, C-5a), 115.6 (C-3a), 114.3 (C-3b), 110.6 (C-4a), 109.7 (C-4b), 71.3 (C-2′b), 70.0 (C-2′a), 69.3 (C-3′b), 68.5 (C-3′a), 65.8 (C-1′a, C-1′b), 61.5 (C-4′a), 60.1 (COOCH_2CH_3), 44.4 (C-4′b), 43.8 (CH_2NAcR), 21.5 (CH_3-CONRR′), 20.7−20.4 (7 CH_3CO), 14.2 (COOCH_2CH_3), 13.7 (CH_3b), 11.5 (CH_3a).

2-Methyl-5-(1′,2′,3′,4′-tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-furoic Acid (17b). A solution of **1** (3 g, 10.9 mmol) in EtOH−NaOH 1M (2:1, 60 mL) was heated at 60 °C for 8 h and then neutralized with Amberlite IR-120 (H^+). The solution was filtered and evaporated, and the residue was acetylated conventionally. Column chromatography (dichloromethane/methanol, 80:1 → 30:1) afforded **17b** as a colorless oil (4.06 g, 9.8 mmol, 90%): $[\alpha]_D$ −33 (*c* 1.6, CH_2Cl_2); IR ν_{max} 3500−2800 (CO*OH*), 1760 (CO), 1696 (CO), 1379, 1228, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 1 H, H-4), 6.03 (d, $J_{1',2'}$ = 4.4, H-1′), 5.58 (dd, $J_{2',3'}$ = 7.6, H-2′), 5.17 (m, H-3′), 4.24 (dd, $J_{3',4'a}$ = 3.1, $J_{4'a,4'b}$ = 12.4, H-4′a), 4.12 (dd, $J_{3',4'b}$ = 5.3, H-4′b), 2.57 (s, CH_3), 2.09, 2.08, 2.06 y 2.05 (4s, 4 CH_3CO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.4, 169.6, 169.5, 169.2 (4 CH_3*C*O), 168.5 (*C*OOH), 161.2, 147.0 (C-2, C-5), 113.6 (C-3), 110.5 (C-4), 69.6 (C-2′), 68.4 (C-3′), 65.7 (C-1′), 61.5 (C-4′), 20.6, 20.5 (2 *C*H_3CO), 13.8 (*C*H_3); FABMS *m*/*z* 437 [100, $(M + Na)^+$]. Anal. Calcd for $C_{18}H_{22}O_{11}$: C, 52.17; H, 5.35; O, 42.47. Found: C, 52.07; H, 5.36.

5-(4′-Amino-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-ethoxycarbonyl-2-methylfuran (18). A solution of benzyl derivative **11** (500 mg, 1.67 mmol) in anhydrous ethanol (15 mL) was hydrogenated with Pd−C (10%) (50 mg) at 1 atm for 20 min. The catalyst was removed by filtration, and the solvent was concentrated giving as a white solid **18** (445 mg, 1.63 mmol, 98% yield): $[\alpha]_D$ −17 (*c* 1, CH_3OH); mp 118−120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 6.57 (s, H-4), 4.8 (bs, 1 H, H-1′), 4.26 (c, $^3J_{H,H}$ = 7.1, CH_2CH_3), 3.68−3.58 (m, H-2′,H-3′), 2.93 (dd, $J_{3',4'a}$ = 3.3, $J_{4'a,4'b}$ = 13.2, H-4′a), 2.71 (dd, $J_{3',4'b}$ = 6.8, H-4′b), 2.53 (s, CH_3), 1.32 (t, CH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.7 (*C*OOEt), 159.6, 155.4 (C-2, C-5), 115.2 (C-3), 108.5 (C-4), 75.4, 72.5 (C-2′, C-3′), 67.9 (C-1′), 61.3 (CH_2CH_3), 45.3 (C-4′), 14.7

(CH_2CH_3), 13.8 (CH_3); FABMS *m/z* 274 [100, $(M + H)^+$]. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.41; H, 6.75; N, 5.03.

5-(4′-Azido-4′-deoxy-D-*arabino*-tetritol-1′-yl)-2-methyl-3-furoic Acid (19). To a solution of **11** (0.41 g, 1.36 mmol) in EtOH (10 mL) was added NaOH (1 M) (5 mL). The reaction mixture was heated at 60 °C during 2 h, cooled to rt, and neutralized with Amberlite IR-120 (H^+). After filtration and evaporation, column chromatography of the residue (dichloromethane/methanol 20:1 → 10:1) gave **19** as a pale yellow solid (332 mg, 1.22 mmol, 90%): $[\alpha]_D$ +8 (*c* 0.6, CH_3OH); IR ν_{max} 3500−2260 (OH, CO*OH*), 2106 (N_3), 1686 (CO), 1588, 1408, 1103 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.57 (s, H-4), 4.87 (m, H-1′), 3.83 (ddd, $J_{2',3'} = 8.4$, $J_{3',4'b} = 6.4$, $J_{3',4'a} = 2.8$, H-3′), 3.70 (dd, $J_{1',2'} = 2.4$, H-2′), 3.51 (dd, $J_{4'a,4'b} = 12.8$, H-4′a), 3.38 (dd, H-4′b), 2.53 (s, CH_3); ^{13}C NMR (75.4 MHz, CD_3OD) δ 167.6 (*C*OOH), 159.6, 155.3 (C-2, C-5), 115.5 (C-3), 108.8 (C-4), 74.3 (C-2′), 71.6 (C-3′), 67.6 (C-1′), 55.5 (C-4′), 13.7 (CH_3); FABMS *m/z* 294 [33, $(M + Na)^+$], *m/z* 316 [28, $(M - H + 2Na)^+$]. Anal. Calcd for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 43.80; H, 5.09; N, 15.37.

5-(4′-Amino-4′-deoxy-D-*arabino*-tetritol-1′-yl)-2-methyl-3-furoic Acid (H-Thabf-OH)[30] (20). A solution of **19** (272 mg, 1 mmol) in abs EtOH (12 mL), was hydrogenated at 1 atm and rt over Pd−C (10%) (55 mg) for 1 h. The reaction mixture was filtered and evaporated giving pure **20** as an amorphous white solid (222 mg, 0.9 mmol, 90%): $[\alpha]_D$ −6 (*c* 0.5, H_2O); IR ν_{max} 3397, 2917 (NH, OH, CO*OH*), 1636 (CO), 1522, 1435, 1098, 812 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 6.50 (s, H-4), 4.87 (under H_2O, H-1′), 3.92 (dd, $J_{1',2'} = 4.8$, $J_{2',3'} = 6.3$, H-2′), 3.85 (m, H-3′), 3.26 (dd, $J_{3',4'a} = 3.2$, $J_{4'a,4'b} = 13.2$, H-4′a), 3.00 (dd, $J_{3',4'b} = 9.2$, H-4′b), 2.45 (s, CH_3); ^{13}C NMR (75.4 MHz, D_2O) δ 172.9 (*C*OOH), 156.7, 150.2 (C-2, C-5), 118.9 (C-3), 109.4 (C-4), 74.3 (C-2′), 67.4 (C-3′), 66.6 (C-1′), 41.6 (C-4′), 12.8 (CH_3). Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 48.72; H, 6.24; N, 5.98.

5-[4′-Deoxy-4-(fluorenylmethoxycarbonyl)amino-D-*arabino*-tetritol-1′-yl]-2-methyl-3-furoic Acid Fmoc-Thabf-OH (21). To a stirred mixture of **20** (803 mg, 3.26 mmol) in dry pyridine (25 mL) at 0 °C was dropped trimethylsilyl chloride (4.2 mL, 32.6 mmol), and the reaction mixture was stirred for 45 min at rt. Then the reaction mixture was cooled to 0 °C, 9-fluorenylmethoxycarbonyl chloride (1.09 g, 4.23 mmol) was added, and the mixture was stirred for 1.5 h at rt. Water (2.5 mL) was added, and the reaction mixture stirred for 1 h at rt and then evaporated. Column chromatography (dichloromethane/methanol, 15:1 → 8:1) afforded pure **21** as an amorphous white solid (1.39 g, 3 mmol, 92%): $[\alpha]_D$ 0 (*c* 1, CH_3OH), $[\alpha]_{405}$ −8 (*c* 1, CH_3OH), $[\alpha]_{435}$ −4 (*c* 1, CH_3OH), $[\alpha]_{546}$ −2 (*c* 1, CH_3OH), $[\alpha]_{577}$ 0 (*c* 1, CH_3OH); IR ν_{max} 3600−2200 (OH, CO*OH*), 1705 (CO), 1663 (CO) 1537, 1262, 735 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 45 °C) δ 7.77−7.61 (m, H-aromat. Fmoc), 7.39−7.25 (m, H-aromat. Fmoc), 6.57 (s, H-4), 4.84 (broad d, $J_{1',2'} = 2.5$, H-1′), 4.36 (d, $3J_{H,H} = 6.8$, CH_2 of Fmoc), 4.20 (t, C*H* of Fmoc), 3.78−3.65 (m, H-2′, H-3′), 3.49 (dd, $J_{3',4'a} = 3.1$, $J_{4'a,4'b} = 13.9$, H-4′a), 3.23 (dd, $J_{3',4'b} = 6.5$, H-4′b), 2.50 (s, CH_3); ^{13}C NMR (75.4 MHz, CD_3OD, 45 °C, δ ppm) δ 167.8 (*C*OOH), 159.5, 155.0 (C-2, C-5), 145.4, 142.6 (4 C, C-aromat. of Fmoc), 128.7, 128.1, 126.1, 120.9 (8 C, C-aromat. of Fmoc), 115.8 (C-3), 109.1 (C-4), 75.1, 71.7 (C-2, C-3), 68.0 (C-1′, CH_2 of Fmoc), 48.7 (CH de Fmoc), 45.1 (C-4′), 13.7 (CH_3); FABMS *m/z* 490 [100, $(M + Na)^+$], *m/z* 512 [55, $(M + 2Na - H)^+$]; HRFABMS *m/z* obsd 490.1485, calcd for $C_{25}H_{25}NO_8 + Na$ 490.1478. Anal. Calcd for $C_{25}H_{25}NO_8$: C, 62.23; H, 5.39; N, 3.00. Found: C, 61.84; H, 5.77; N, 2.83.

3-Ethoxycarbonyl-2-methyl-5-[1′,2′,3′-tri-*O*-acetyl-4′-deoxy-4′-[2-methyl-5-(1′,2′,3′,4′-tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-furamide]-D-*arabino*tetritol-1′-yl]furan (22). To a stirred solution of **18** (180 mg, 0.66 mmol) and Ph_3P (346 mg, 1.32 mmol) in dry DMF (1.5 mL) was added a solution of **17b** (272 mg, 0.65 mmol) and 2,2′-dithiodipyridine (292 mg, 1.32 mmol) in dichloromethane (2.5 mL) under N_2. After 6 h at rt, the solution was concentrated and the resulting residue was acetylated conventionally. Column chromatography (ether/petroleum ether, 1:1 → 4:1 gave **22** as a white solid (393 mg, 0.49 mmol, 74%): $[\alpha]_D$ −15 (*c* 2.8, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) Tables 1 and 2, and δ 4.24 (q, $^3J_{H,H} = 7.1$, CH_2CH_3), 2.13−2.02 (m, 7 Ac), 1.30 (t, CH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.5−169.3 (7 *C*OCH$_3$), 163.4, 163.2 (*C*ONHR, *C*OOEt), 159.4, 157.6 (2 C-2), 146.7, 146.4 (2 C-5), 116.1, 114.3 (2 C-3), 110.5, 108.4 (2 C-4), 70.5 (C-2′b), 69.8 (C-2′a), 69.2 (C-3′b), 68.5 (C-3′a), 65.7 (C-1′a), 65.6 (C-1′b), 61.4 (C-4′a), 60.2 (CH_2CH_3), 38.1 (C-4′b), 20.7−20.5 (7 CO*C*H$_3$), 14.2 (CH_2CH_3), 13.7, 13.4 (2 CH_3); FABMS *m/z* 818 [100, $(M + Na)^+$]. Anal. Calcd for $C_{36}H_{45}NO_{19}$: C, 54.34; H, 5.70; N, 1.76. Found: C, 54.61; H, 5.89; N, 1.94.

3-Ethoxycarbonyl-2-methyl-5-[4′-deoxy-4′-[2-methyl-5-(D-*arabino*-tetritol-1′-yl)-3-furamide]-D-*arabino*-tetritol-1′-yl]furan (23). To a solution of **22** (100 mg, 0.12 mmol) in dry methanol (4 mL) was added NaOMe/MeOH (1 M) until pH = 12. The reaction mixture was allowed to stand a rt for 2 h and then neutralized with Amberlite IR-120 (H^+). Filtration and evaporation gave pure **23** as a white solid (53 mg, 0.116 mmol, 98%): ^1H NMR Table 1; FABMS *m/z* 524 [70, $(M + Na)^+$]; ^{13}C NMR (75.4 MHz, CD_3OD) δ 167.4 (*C*ONHR, *C*OOEt), 159.6, 157.1 (2 C-2), 155.4, 155.2 (2 C-5), 117.0, 115.0 (2 C-3), 108.6, 107.0 (2 C-4), 75.1, 74.3 (2 C-2′), 72.7 (C-3′a), 71.4 (C-3′b), 68.0, 67.8 (2 C-1′), 64.8 (C-4′a), 61.3 (CH_2CH_3), 43.9 (C-4′b), 14.6 (CH_2CH_3), 13.8, 13.6 (2 CH_3); HRFABMS *m/z* found 524.1744, calcd for $C_{22}H_{31}NO_{12} + Na$ 524.1741.

2-Methyl-5-[1′,2′,3′-tri-*O*-acetyl-4′-deoxy-4′-[2-methyl-5-(1′,2′,3′,4′-tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-furamide]-D-*arabino*-tetritol-1′-yl]-3-furoic Acid (24). To a solution of **22** (244 mg, 0.36 mmol) in EtOH (6 mL) was added NaOH (1 M) (3 mL). The reaction mixture was heated at 60 °C for 10 h, cooled to rt, and neutralized with Amberlite IR-120 (H^+). The solvent was evaporated and the residue acetylated conventionally. Column chromatography (dichloromethane/methanol (50:1 → 20:1) afforded **24** as a white solid (230 mg, 0.33 mmol, 89%): $[\alpha]_D$ −17 (*c* 1.8, CH_2Cl_2); IR ν_{max} 3600−2875 (CO*OH*), 1760 (CO), 1379, 1228, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61, 6.45 (s each, 2 H-4), 6.24 (t a, NH), 6.06 (d, $J_{1'b,2'b} = 3.5$, H-1′b), 5.99 (d, $J_{1'a,2'a} = 4.8$, H-1′a), 5.58 (dd, $J_{2'a,3'a} = 7.3$, H-2′a), 5.44 (dd, $J_{2'b,3'b} = 8.5$, H-2′b), 5.17−5.12 (m, H-3′a), 5.05−4.99 (m, H-3′b), 4.23 (dd, $J_{3'a,4'a} = 3.0$, $J_{4'a,4''a} = 12.4$, H-4′a), 4.09 (dd, $J_{3'a,4''a} = 4.1$, H-4″a), 3.98 (ddd, $J_{3'b,4'b}$, $J_{NH,4'b} = 2.7$, 7.0, $J_{4'b,4''b} = 14.9$, H-4′b), 3.15 (dt, $J_{3'b,4''b} = J_{NH,4''b} = 4.9$, H-4″b), 2.56, 2.53 (s, 2 CH_3), 2.14−2.03 (m, 7 Ac); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.5−169.3 (7 *C*OCH$_3$), 167.9 (*C*OOH), 163.2 (*C*ONHR), 160.9, 157.6 (2 C-2), 147.1, 146.4 (2 C-5), 116.0, 113.7 (2 C-3), 110.4, 108.5 (2 C-4), 70.4 (C-2′b), 69.8 (C-2′a), 69.2 (C-3′b), 68.5 (C-3′a), 65.7 (C-1′a), 65.6 (C-1′b), 61.4 (C-4′a), 38.1 (C-4′b), 20.7−20.5 (7 C, 7 CO*C*H$_3$), 13.8, 13.4 (2 CH_3); FABMS *m/z* 790 [100, $(M + Na)^+$]. Anal. Calcd for $C_{34}H_{41}NO_{19}$: C, 53.19; H, 5.38; N, 1.83. Found: C, 52.69; H, 5.59; N, 1.94.

2-Methyl-5-(1′,2′,3′,4′-tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-furamide-(*N*→4′)-2-methyl-5-(1′,2′,3′-tri-*O*-acetyl-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-furamide-(*N*→4′)-3-ethoxycarbonyl-2-methyl-5-(1′,2′,3′-tri-*O*-acetyl-4-deoxy-D-*arabino*-tetritol-1′-yl)furan (25). To a stirred solution of **18** (180 mg, 0.66 mmol) and Ph_3P (91 mg, 0.35 mmol) in dry DMF (0.75 mL) was added a solution of **24** (134 mg, 0.17 mmol) and 2,2′-dithiodipyridine (77 mg, 0.35 mmol) in dichloromethane (2.5 mL) under N_2. After 7 h at rt, the solution was concentrated and the resulting residue was acetylated conventionally. Column chromatography (ether/acetone, 100:1 → 25:1) gave **25** as a white solid (120 mg, 0.10 mmol, 60%): $[\alpha]_D$ −10 (*c* 2.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) Table 1 and δ 4.23 (q, $^3J_{H,H} = 7.1$, CH_2CH_3), 2.13−2.01 (m, 10 Ac), 1.30 (t,

(30) To simplify the nomenclature of this compound and further derivatives, we introduce an alternative nomenclature based on petides where Thabf stands for trihydroxyaminobutylfuran.

CH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.3−169.2 (10 $COCH_3$), 163.3, 163.2, 163.1 (2 CONHR, COOEt), 159.4, 157.4, 157.3 (3 C-2), 146.7, 146.6, 146.5 (3 C-5), 116.2, 116.1, 114.3 (3 C-3), 110.4, 108.5, 108.4 (3 C-4), 70.6, 70.5, 69.9 (3 C-2′), 69.5, 69.4, 68.6 (3 C-3′), 65.8−65.7 (3 C-1′), 61.4 (C-4′a), 60.1 (CH_2CH_3), 38.2, 38.1 (C-4′b, C-4′c), 20.6−20.4 (10 $COCH_3$), 14.1 (CH_2CH_3), 13.6, 13.3 (3 CH_3); FABMS *m/z* 1171 [100, $(M + Na)^+$]. Anal. Calcd for $C_{52}H_{64}N_2O_{27}$: C, 54.35; H, 5.61; N, 2.44. Found: C, 53.89; H, 5.65; N, 2.84.

2-Methyl-5-(D-*arabino*-tetritol-1′-yl)-3-furamide-(*N*→4′)-2-methyl-5-(4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-furamide-(*N*→4′)-3-ethoxycarbonyl-2-methyl-5-(4-deoxy-D-*arabino*-tetritol-1′-yl)furan (26). Conventional methanolysis of **25** (60 mg, 0.05 mmol) as described above for the preparation of **101** afforded **26** as a white solid (35 mg, 0.049 mmol, 97%): $[\alpha]_D$ −2 (*c* 0.7, CH_3OH); ^1H NMR Table 1; ^{13}C NMR (125.7 MHz, CDCl) δ 167.4 (2 CONHR), 165.8 (COOEt), 159.6, 157.1, 157.0, 155.4, 155.2, 155.1 (3 C-2, 3 C-5), 117.3 (C-3a, C-3b), 115.2 (C-3c), 108.6 (C-4c), 107.1, 106.9 (C-4a, C-4b), 75.3, 75.2 (C-2′b, C-2′c), 74.4 (C-2′a) 72.8 (C-3′a), 71.5 (C-3′b, C-3′c), 68.1, 68.0, 67.8 (3 C-1′), 64.8 (C-4′a), 61.3 (CH_2CH_3), 44.0, 43.9 (C-4′b, C-4′c), 14.6 (CH_2CH_3), 13.8, 13.6 (3 CH_3); FABMS *m/z* 751 [35, $(M + Na)^+$]; HRFABMS *m/z* found 751.2530, calcd for $C_{32}H_{44}N_2O_{17}$ + Na 751.2538.

3-Ethoxycarbonyl-2-methyl-5-[1′,2′,3′-tri-*O*-acetyl-4′-deoxy-4′-[2-methyl-5-(1′,2′,3′,3′-tri-*O*-acetyl-4′-azido-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-furamide]-D-*arabino*-tetritol-1′-yl]furan (27). To a stirred solution of **18** (36 mg, 0.13 mmol) and **19** (36 mg, 0.13 mmol) in dry DMF (2 mL) were added PyBOP (69 mg, 0.132 mmol) and diisopropilethylamine (46 μL, 0.26 mmol). The reaction mixture was stirred for 1 h, evaporated to dryness, and acetylated conventionally. Column chromatography (ether/petroleum ether 1:3 → 3:1) gave **27** as a white solid (64 mg, 0.08 mmol, 62%): $[\alpha]_D$ −7 (*c* 0.6, CH_2Cl_2); IR ν_{max} 2943, 2104 (N_3), 1751 (CO), 1373, 1217, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61, 6.45 (s each, 2 H-4), 6.17 (dd a, $J_{NH,4'b}$ = 6.9, $J_{NH,4''b}$ = 5.1, NH), 6.06 (d, $J_{1'b,2'b}$ = 3.6, H-1′b), 5.98 (d, $J_{1'a,2'a}$ = 5.2, H-1′a), 5.59 (dd, $J_{2'a,3'a}$ = 6.8, H-2′a), 5.44 (dd, $J_{2'b,3'b}$ = 8.6, H-2′b), 5.12 (m, H-3′a), 5.01 (m, H-3′b), 4.26 (q, 2 H, $3J_{H,H}$ = 7.1, CH_2CH_3), 4.02 (ddd, $J_{4'b,4''b}$ = 15.1, $J_{4'b,3'b}$ = 3.1, H-4′b), 3.44 (dd, $J_{3'a,4'a}$ = 3.6, $J_{4'a,4''a}$ = 13.4, H-4′a), 3.32 (dd, $J_{3'a,4''a}$ = 6.2, H-4″a), 3.14 (dt, $J_{4''b,3'b}$ = 5.0, H-4″b), 2.56, 2.55 (s each, 2 CH_3), 2.17−2.05 (m, 6 Ac), 1.32 (t, CH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.1−169.2 (6 $COCH_3$), 163.3, 163.0 (CONHR, COOEt), 159.5, 157.6 (2 C-2), 146.7, 146.2 (2 C-5), 116.4, 114.3 (2 C-3), 110.4, 108.5 (2 C-4), 70.4, 70.3 (2 C-2′), 69.4, 69.1 (2 C-3′), 65.6, 65.5 (2 C-1′), 60.1 (CH_2CH_3), 50.1 (C-4′a), 38.0 (C-4′b), 20.7−20.5 (6 C, 6 $COCH_3$), 14.1 (CH_2CH_3), 13.6, 13.4 (2 CH_3); FABMS *m/z* 801 [100, $(M + Na)^+$]. Anal. Calcd for $C_{34}H_{42}N_4O_{17}$: C, 52.44; H, 5.44; N, 7.20. Found: C, 52.40; H, 5.62; N, 7.15.

5-[4′-[5-(4′-Amino-4′-deoxy-D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide]-4′-deoxy-D-*arabino*-tetritol-1′-yl]-3-ethoxycarbonyl-2-methylfuran (28). Conventional methanolysis of **27** (75 mg, 0.096 mmol), as described above for the preparation of **23**, afforded after evaporation a residue that was dissolved in absolute EtOH (5 mL) and hydrogenated at 1 atm over Pd−C (10%) (10 mg). After 30 min, the reaction mixture was filtered and evaporated giving pure **28** as a colorless oil (40 mg, 0.08 mmol, 84%): $[\alpha]_D$ −6 (*c* 0.8, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 6.68, 6.58 (s each, 2 H-4), 4.9 (m, H-1′a, H-1′b), 4.26 (q, $3J_{H,H}$ = 7.1, CH_2CH_3), 3.83−3.78 (m, H-3′b), 3.68−3.62 (m, H-2′a, H-2′b, H-3′a, H-4′b), 3.47 (dd, $J_{3'b,4''b}$ = 6.5, $J_{4'b,4''b}$ = 14.0, H-4″b), 2.96 (dd, $J_{3'a,4'a}$ = 3.1, $J_{4'a,4''a}$ = 12.9, H-4′a), 2.74 (dd, $J_{3'a,4''a}$ = 6.2, H-4″a), 2.53, 2.52 (s, 6 H, 2 CH_3), 1.32 (t, CH_2CH_3); ^{13}C NMR (75.4 MHz, CD_3OD) δ 167.4 (CONHR), 165.7 (COOEt), 159.6, 157.1 (2 C-2), 155.4, 155.1 (2 C-5), 117.3, 115.1 (2 C-3), 108.5, 107.0 (2 C-4), 75.6, 75.1 (2 C-2′), 72.0 (C-3′a), 71.4 (C-3′b), 68.8, 67.7 (2 C-1′), 61.3 (CH_2CH_3), 45.0 (C-4′a), 43.9 (C-4′b), 14.6 (CH_2CH_3), 13.8, 13.6 (2 CH_3); FABMS *m/z* 523 [95, $(M + Na)^+$]; HRFABMS *m/z* obsd 523.1912, calcd for $C_{22}H_{32}N_2O_{11}$ + Na 523.1903.

2-Methyl-5-(1′,2′,3′-tri-*O*-acetyl-4′-azido-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-furamide-(*N*→4′)-2-methyl-5-(1′,2′,3′-tri-*O*-acetyl-4′-deoxy-D-*arabino*-tetritol-1′-yl)-3-furamide-(*N*→4′)-3-ethoxycarbonyl-2-methyl-5-(1′,2′,3′-tri-*O*-acetyl-4-deoxy-D-*arabino*-tetritol-1′-yl)furan (29). To a stirred solution of **28** (28 mg, 0.056 mmol) and **19** (15 mg, 0.056 mmol) in dry DMF (1.5 mL) were added PyBOP (29 mg, 0.056 mmol) and diisopropiletilamine (20 μL, 0.112 mmol). The reaction mixture was stirred for 1 h, concentrated, and conventionally acetylated. Column chromatography (ether → ether/acetone 10:1) gave **29** (38 mg, 0.034 mmol, 61%) as a white solid: $[\alpha]_D$ −9 (*c* 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, H-4), 6.45 (s, 2 H-4), 6.27, 6.20 (t a each, 2 NH), 6.06, 6.04 (d each, 2 H, $J_{1'b,2'b}$, $J_{1'c,2'c}$ = 3.8, 4.1, H-1′b, H-1′c), 5.97 (d, 1 H, $J_{1'a,2'a}$ = 5.3, H-1′a), 5.59 (dd, $J_{2'a,3'a}$ = 6.8, H-2′a), 5.48−5.42 (m, H-2′b, H-2′c), 5.13−5.01 (m, H-3′a), 5.05−4.97 (m, H-3′b, H-3′c), 4.26 (q, $3J_{H,H}$ = 7.1, CH_2CH_3), 4.02−3.98 (m, H-4′b, H-4′c), 3.44 (dd, $J_{3'a,4'a}$ = 3.6, $J_{4'a,4''a}$ = 13.4, H-4′a), 3.32 (dd, $J_{3'a,4''a}$ = 6.2, H-4″a), 3.17−3.11 (m, H-4″b, H-4″c), 2.55, 2.54 (s each, 3 CH_3), 2.18−2.05 (m, 9 Ac), 1.30 (, CH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.5−169.2 (9 $COCH_3$), 163.3, 163.2, 163.1 (2 CONHR, COOEt), 159.4, 157.6, 157.4 (3 C-2), 146.7, 146.5, 146.3 (3 C-5), 116.1, 114.3 (3 C-3), 110.4, 108.5 (3 C-4), 70.5, 70.4, 70.3 (3 C-2′) 69.4, 69.3, 69.2 (3 C-3′), 65.6−65.5 (3 C-1′), 60.1 (CH_2CH_3), 50.1 (C-4′a), 38.1, 38.0 (C-4′b, C-4′c), 20.7−20.5 (9 $COCH_3$), 14.1 (CH_2CH_3), 13.6, 13.3 (3 CH_3); FABMS *m/z* 1154 [100, $(M + Na)^+$]. Anal. Calcd for $C_{50}H_{61}N_5O_{25}$: C, 53.05; H, 5.43; N, 6.19. Found: C, 52.95; H, 5.38; N, 6.50.

2-[5-(4′-Amino-4′-deoxy-D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide]acetic Acid (36).

2-[5-(4′-Amino-4′-deoxy-D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide]acetic Acid (37).

2′-[5-(4′-Amino-4′-deoxy-D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide-(*N*→4′)-5-(D-*arabino*-tetritol-1′-yl)-2-methyl-3-furamide]acetic Acid (38).

Esterification of HMBA-AM Resin. A mixture of HMBA-AM resin (100 mg, substitution = 1.16 mmol/g) and Fmoc-glycine (103 mg, 0.35 mmol) in dry DMF (1.5 mL) was agitated for 15 min, and then a mixture of pyridine (44μL, 0.55 mmol) and 2,6-dichlorobenzoyl chloride (50 μL, 0.35 mmol) was added and agitated for 12 h. The reaction mixture was filtered and the resin washed with DMF (5 × 3 mL) and DCM (3 × 3 mL). The resin was dried under vacuum giving 132 mg of a solid residue (100% sustitution). The residue was treated with piperidine in DMF (20%) (1 mL) and stirred for 10 min. The resin was collected by filtration, washed with DMF (3 × 2 mL) and DCM (4 × 2 mL), and dried under vacuum to afford the Fmoc-glycine bound resin **32** (106.6 mg).

Successive Coupling of 5-[4-Deoxy-4-(Fluorenylmethoxycarbonyl)amino-D-*arabino*-tetritol-1-yl]-2-methyl-3-furoic Acid Units (21) to H-Gly-OResin (31). To **31** (106.6 mg, 0.116 mmol) in a filtrating reaction tube was added a solution of **21**(108 mg, 0.23 mmol), PyBOP (120 mg, 0.23 mmol), and DIPEA (40 μL, 0.23 mmol) in dry DMF (2.5 mL). The reaction mixture was agitated for 1 h. The resin was collected by filtration, washed with DMF (4 × 3 mL) and DCM (4 × 3 mL), and dried. The same treatment was repited twice until constant weight of the amino acid bound resin (158.6 mg, 94% sustitution). Treatment with piperidine as described above, washing of the resin and drying under vacuum gave **32** (132.4 mg, 100%).

Subsequent treatment as described above gave the resin bound amino acids **32**−**34** (92−100% sustitution).

Cleavage from the Resin. To the resin-bound products **32**−**34** was added a solution of NaOH (1 M)−THF (1:1) (2 mL /100 mg) at 0 °C, and the mixture was stirred for 15 min and filtered. The resin was washed with water (3 × 3 mL) and the filtrate neutralized to pH 6−7 with aqueous acetic acid (10%) (2 mL) and evaporated to dryness. Column chromatography (biogel P-2) eluting with MeOH−water (1:1) gave **36**, **37**, or **38** (98−100%), respectively.

***Tetramer* 36:** $[\alpha]_D$ +13 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, DMSO-d_6) Table 1 and δ 3.80−3.95 (m, CH_2COOH); ^{13}C NMR (125.7 MHz, D_2O) δ 178.0 (COOH), 168.0, 168.0, 167.4 (3 *C*ONHR), 157.9−157.8 (3 C-2), 152.9 (3 C-5), 116.8 (3 C-3), 108.0, 108.0, 107.8 (3 C-4), 75.2 (3 C-2), 70.8, 70.7 (C-3′b,c), 68.7 (C-3′a), 67.8, 67.8, 67.6 (3 C-1′), 44.4 (C-2′d), 43.2−42.8 (C-4′a,b,c), 14.0 (3 CH_3); MALDI-TOF MS *m*/*z* 756 [100, $(M + H)^+$], 778 [70, $(M + Na)^+$], 800 [40, $(M - H + 2Na)^+$].

***Pentamer* 37:** $[\alpha]_D$ +13 (*c* 0.5, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 6.60, 6.59, 6.58, 6.58 (s each, 4 H-4), 4.86−4.83 (m, 4 H-1′), 3.92−3.80 (m, 4 H-2′, 4 H-3′, H-2′e, H-2″e), 3.80−3.95 (m, CH_2COOH),0.67−3.62 (m, H-4′b,c,d), 3.43−3.36 (m, H-4″b,c,d), 3.32 (dd, $J_{3a,4a} = 3.1$, H-4′a), 3.04 (dd, $J_{3'a,4''a} = 8.6$, $J_{4'a,4''a} = 13.0$, H-4″a), 2.45, 2.43, 2.43, 2.42 (s each, 4 CH_3); ^{13}C NMR (75.5 MHz, D_2O) δ 178.6 (COOH), 169.2 (3 *C*ONHR), 168.3 (*C*ONHR), 159.1−159.0 (4 C-2), 154.1 (4 C-5), 118.0−117.9 (4 C-3), 109.1−109.0 (4 C-4), 76.3 (4 C-2′), 71.8 (C-3′b,c,d), 69.5 (C-3′a), 68.9−68.7 (4 C-1′), 45.5 (C-2′e), 44.3−43.9 (C-4′a,b,c,d), 15.1 (4 CH_3); ESIMS *m*/*z* 984.2 [90, $(M + H)^+$].

***Hexamer* 38:** $[\alpha]_D$ +12 (*c* 0.4, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 6.59, 6.58, 6.57, 6.57, 6.56 (s each, 5 H-4), 4.85 (m, $J_{1'a,2'a} = 3.5$, H-1′a), 4.85−4.82 (m, 4 H-1′b,c,d,e), 3.80−3.95 (m, CH_2-COOH), 3.90−3.77 (m, 5 H-2′, 5 H-3′, H-2′f, H-2″f), 3.65−3.59 (m, H-4′b,c,d,e), 3.39−3.34 (m, H-4″b,c,d,e), 3.31 (dd, $J_{3'a,4'a} = 3.2$, $J_{4'a,4''a} = 13.6$, H-4′a), 3.03 (dd, $J_{3'a,4''a} = 8.7$, H-4″a), 2.44, 2.43, 2.42, 2.41, 2.40 (s each, 5 CH_3); ^{13}C NMR (125.7 MHz, D_2O) δ 175.1 (COOH), 165.1 (*C*ONHR), 165.0 (3 *C*ONHR), 164.4 (*C*ONHR), 155.0−154.8 (5 C-2), 150.0−149.9 (5 C-5), 113.9−113.8 (5 C-3), 105.0−104.8 (5 C-4), 72.2−72.1 (5 C-2′), 67.8 (C-3′b,c,d,e), 65.6 (C-3′a), 64.8−64.6 (5 C-1′), 41.5 (C-2′f), 44.3−43.9 (C-4′a,b,c,d,e), 11.0 (5 CH_3); ESIMS *m*/*z* 1211.5 [100, $(M + H)^+$].

3-Benzotriazoloxicarbonyl-5-[4-deoxy-4-*N*-(9-fluorenylmethoxycarbonyl)amino-D-*arabino*-tetritol-1-yl]-2-methylfuran ó Fmoc-Thabf-OBt (39). The excess of activated amino acid, PyBOP and DIPEA, were extracted from the resin after each coupling by washing with DMF. After concentration to dryness, the residue was diluted with Cl_2CH_2, washed with HCl (1 M) and water, dried (Na_2SO_4), and evaporated. Column chromatography of the residue (ether/petroleum ether,1:2 → 3:1) gave **39** as a white amorphous solid: $[\alpha]_D$ −7 (*c* 1, CH_3OH); IR ν_{max} 3579−2230 (OH), 1788 (*CO*BOHt), 1692 (CO), 1576, 1101, 963 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD, 45 °C) δ 8.05−7.27 (m, 12 H, H-arom of Fmoc and BOHt), 6.87 (s, 1 H, H-4), 4.97 (d, $J_{1',2'} = 2.2$, H-1′), 4.36 (d, $3J_{H,H} = 7.2$, CH_2 of Fmoc), 4.21 (t, C*H* of Fmoc), 3.77−3.72 (m, H-2′, H-3′), 3.54 (dd, $J_{3',4'a} = 3.2$, $J_{4'a,4'b} = 14.1$, H-4′a), 3.30 (dd, $J_{3',4'b} = 6.6$, H-4′b), 2.63 (s, CH_3); ^{13}C NMR (75.4 MHz, CD_3OD, 45 °C) δ 164.4 (*C*OOBOHt), 161.1 (CO of Fmoc), 159.5, 157.3 (C-2, C-5), 145.3, 142.6 (4 C, C-arom of Fmoc), 128.8, 128.1, 126.2, 120.9 (8 C, C-arom of Fmoc), 144.5, 130.3, 126.5, 120.7, 109.9 (6 C, C arom of Fmoc), 109.5 (C-3), 107.7 (C-4), 74.9 (C-2′), 71.3 (C-3′), 68.0, 67.8 (C-1′, CH_2 of Fmoc), 49.9−48.2 (CH of Fmoc), 45.1 (C-4′), 14.1 (CH_3); FABMS *m*/*z* 607 [70, $(M + Na)^+$]; HRFABMS *m*/*z* obsd 607.1808, calcd for $C_{31}H_{28}N_4O_8 + Na$ 607.1805.

Molecular Mechanics and Dynamics Calculations. Starting Structures. Molecular mechanics and dynamics calculations were performed using the MM2* force field[31] as implemented in MACROMODEL 4.5.[32] A schematic view is given in Figure 2. Starting geometries were selected according to the NMR data (*J* couplings, see below) as follows: ω_2 was set as 180° and −60° (anti), ω_3 was set as 180° (anti), (see below), although both angles were let free during the minimizations and the molecular dynamics simulations. The three possible staggered orientations of ω_1, ω_4, ω_5, and ω_6 torsions were then combined to give the 81 initial conformations of the monosaccharide. The torsion angles for all angles ω_i are dubbed as g+, g−, or anti, denoting angles in the proximity of +60, −60, or 180°.

Molecular Mechanics Calculations. Oligomers **22**, **23**, **25**, **26**, and **36** were built from the minimized structures of the monomers. The amide linkages were built in their usual trans conformations. Calculations for a dielectric constant $\epsilon = 80$ and for the continuum GB/SA solvent model[33] (MM2*) were performed in order to search different ways to satisfactorily reproduce the conformational behavior of these derivatives in solution.[34] First, the 81 starting structures were minimized with 5000 conjugate gradient iterations or until the rms derivative was smaller than 0.05 kcal mol^{-1} Å^{-1}. These calculations were carried out with all the initial geometries. From the individual minimizations, the probability distributions for the chain orientations were calculated.

Molecular Dynamics Simulations. The two lowest energy minima of the minimizations of the starting geometries of **1**−**5** were used as input for molecular dynamics (MD) simulations at 300 K, and their results were analyzed. Average torsions and proton−proton distances were calculated for the 10 MD simulations.

Separate calculations were performed with the GB/SA (Generalized Born solvent-accessible surface area) solvent model for water and for a bulk dielectric constant of 80. For all molecules, the simulations were carried out with a time step of 1 fs. The equilibration period was 100 ps. Structures were saved every 1 ps. The total simulation time was 1.0 ns for every run.[35]

NMR Spectroscopy. NMR experiments were recorded on a 500 spectrometer, using approximate 5 mM solutions at different temperatures (between 299 and 320 K). The spectra were recorded in $CDCl_3$ (**22**, **25**), D_2O (**23**, **26**), and DMSO-d_6 (**36**). Chemical shifts are reported in ppm, using external DSS or TMS (0 ppm) as reference. The double quantum filtered COSY35 spectrum was performed using 256 increments of 1K real points to digitize a spectral width of 2000 Hz. Sixteen scans were used with a relaxation delay of 1 s. The 2D TOCSY experiment was performed using a data matrix of 256 increments of 1K real points to digitize a spectral width of 2000 Hz. Four scans were used per increment with a relaxation delay of 2 s. MLEV 17 was used for the 100 ms isotropic mixing time. 2D−T-ROESY[36] experiments were performed using four different mixing times, namely 150, 300, 450, and 600 ms, with 256 increments of 2K real points. Good linearity was observed in the cross-peak built up. Estimated errors in the NOE intensities are smaller than 20%. 1D-NOESY experiments

(31) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551−8556. The MM3* force field implemented in MACROMODEL differs of the regular MM3 force field in the treatment of the electrostatic term since it uses charge−charge instead of dipole−dipole interactions.

(32) Mohamadi, F.; Richards, N. G. I.; Guida, W. C.; Liskamp, R.;. Canfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(33) Still, W. C.; Tempczyk, A.; Hawley R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6128.

(34) (a) Martín-Pastor, M.; Espinosa, J. F.; Asensio, J. L.; Jiménez-Barbero, J. *Carbohydr. Res.* **1997**, *298*, 15−47. (b) J. M. Coteron, K. Singh, J. L. Asensio, M. D. Dalda, A. Fernández-Mayoralas, J. Jiménez-Barbero, M. Martín-Lomas, *J. Org. Chem.* **1995**, *60*, 1502−1513. (c) Espinosa, J. F.; Asensio, J. L.; Bruix, M.; Jiménez-Barbero, J. *An. Quim. Int. Ed.* **1996**, *96*, 320−324. (d) Asensio, J. L.; Martin-Pastor, M.; Jiménez-Barbero, J. *J. Mol. Struct.* **1997**, *395*−*396*, 245−270.

(35) For a relevant survey of the application of molecular mechanics and dynamics simulations to carbohydrate molecules, see: French, A. D., Brady, J. D., Eds. *Computer Modelling of Carbohydrate Molecules*; ACS Symposium Series 430; American Chemical Society: Washington, D.C., 1990.

(36) Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 3157−3159.

using the double pulse field gradient spin−echo technique[37] were also acquired with the same mixing times.

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(37) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199−4203.

Supporting Information Available: Experimental procedures for **6**−**9**. ^{1}H and ^{13}C of **14a**, **15**, **16**, **21**, **23**, **26**, **28**, and **37**−**39**. Comparison of ^{1}H NMR of **22**, **23**, **25**, **26**, and **36**. TOCSY spectrum of **36** and T-RO. ESY spectra **25** and **22**. Summary of the MM2* results of the monomer (Table S1) and average torsion angles for the MD-based structures of **22**, **23**, **25**, **26** and **36** (Table S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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