DOI: 10.1002/ejoc.200900971

Synthesis of Highly Functionalized Amino Acids: An Expedient Access to L- and D-β-Hydroxyenduracididine Derivatives

Clemens J. Schwörer[a] and Markus Oberthür*[a]

Keywords: Amino acids / Antibiotics / Chiral pool / Total synthesis / Nucleophilic substitution

The nonproteinogenic amino acids (3*S*,4*S*)-L- and (3*S*,4*S*)-D-β-hydroxyenduracididine (βhEnd), each containing a cyclic guanidine group and three contiguous stereocenters, have been synthesized for the first time, starting from commercially available diacetone D-glucose. The key inversion reactions for the introduction of the two nitrogen groups at C-2 and C-4 afford products that are diastereomerically pure and easy to purify, thereby allowing the gram-scale preparation of βhEnd derivatives that are suitably protected for peptide coupling reactions.
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

Nonribosomally synthesized peptides often contain unusual amino acids that are functionalized by hydroxylation, amination, methylation, halogenation, etc.[1] In many cases, these structural modifications exert a distinct influence on the biological activities of these compounds.[2] Detailed structure–activity relationship studies or investigations into mechanisms of action often rely on the de novo chemical synthesis of the parent natural products as well as their analogues. Straightforward and reliable access to such amino acids and, more importantly, suitably protected derivatives is therefore a basic prerequisite for such endeavors.

The availabilities of such amino acids from natural sources, however, are often limited. Although the biosyntheses of a number of nonproteinogenic amino acids have been elucidated,[3] enzymatic methods usually do not provide sufficient amounts for total synthesis efforts. Accordingly, the chemical synthesis of nonproteinogenic amino acids remains an important task.[4] As part of our ongoing research program directed towards the synthesis of bioactive cyclic peptides, we became interested in efficient routes to protected derivatives of two highly functionalized amino acids: the β-hydroxyenduracididines (βhEnds, Figure 1). Both amino acids are constituents of the mannopeptimycins (e.g., mannopeptimycin ε, Figure 1), a group of glycopeptides produced by *Streptomyces hygroscopicus* NRRL 30439 with promising antibiotic activity against resistant bacterial strains.[5]

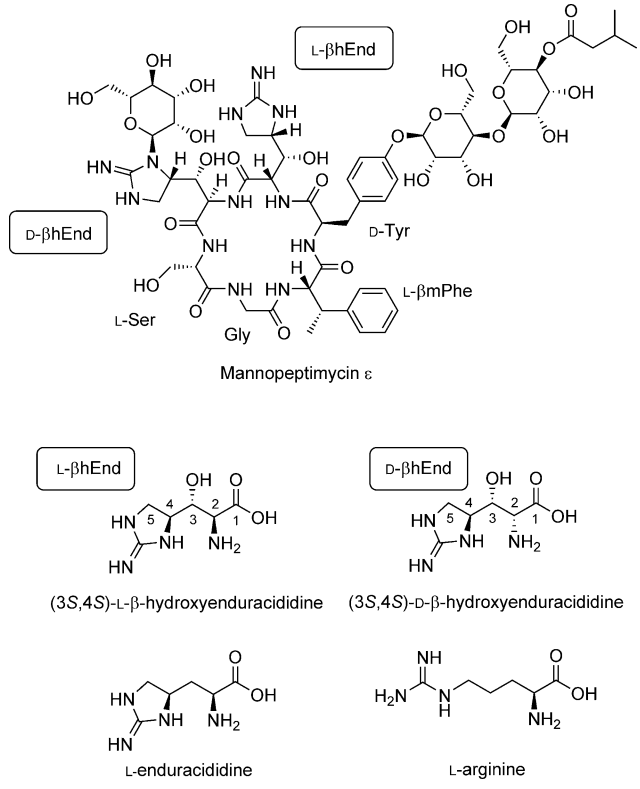


Figure 1. Structures of mannopeptimycin ε and the two β-hydroxyenduracididine diastereomers and structural comparisons with enduracididine and arginine.

The cyclic hexapeptide portion of the mannopeptimycins contains two different βhEnd diastereomers: (3*S*,4*S*)-L-βhEnd (L-βhEnd) and (3*S*,4*S*)-D-βhEnd (D-βhEnd). These linear α-amino acids, which differ only in the stereochemistry at C-2, are each hydroxylated at C-3 and possess an unusual, five-membered cyclic guanidine at C-4 and C-5.

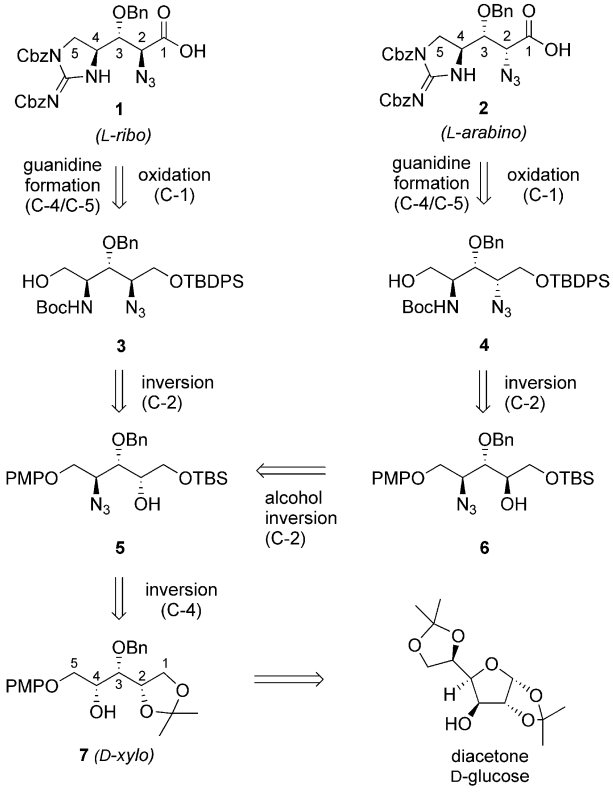
[a] Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35032 Marburg, Germany
Fax: +49-6421-2822021
E-mail: oberthuer@chemie.uni-marburg.de
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900971.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

They can thus be regarded as conformationally restricted and hydroxylated analogues of L- and D-arginine, respectively.

Biosynthetically, L-βhEnd is derived from L-enduracididine by C-3 hydroxylation through the action of the enzyme MppO,[6] whereas D-βhEnd is presumably generated from L-βhEnd by an epimerization domain of the NRPS assembly line at the stage of the tethered linear hexapeptide.[7]

Recently, it was shown that the simultaneous replacement of both βhEnds with L- and D-arginine renders the resulting mannopeptimycin derivative antibiotically inactive.[8] In addition, the hydroxylation of βhEnd was also reported to be beneficial for optimal activity,[5b] thereby highlighting the importance of these structural elements. Currently, the two isomers can only be obtained as a mixture after hydrolysis of the mannopeptimycins,[5a] which makes a chemical synthesis desirable. Accordingly, here we describe an efficient and reliable route to protected derivatives of both diastereomers of βhEnd (**1** and **2**, see Scheme 1) on a synthetically useful scale by a chiral pool approach.



Scheme 1. Retrosynthetic scheme for the preparation of β-hydroxyenduracididine derivatives **1** and **2**.

Results and Discussion

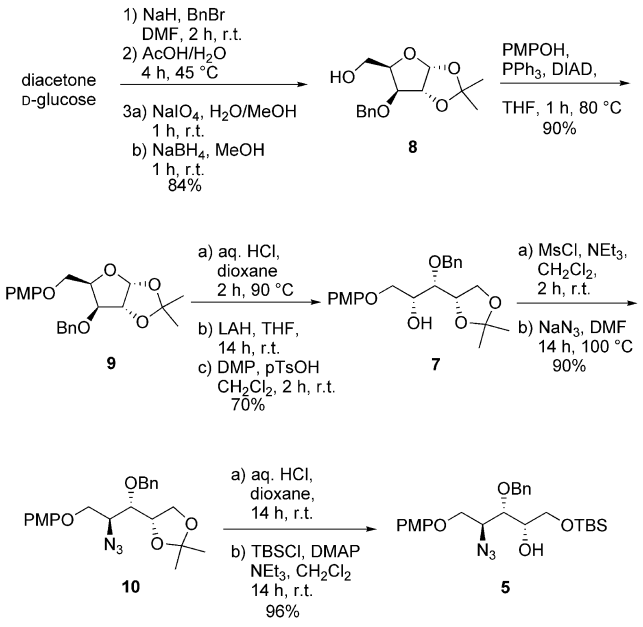
The synthesis of the βhEnd derivatives **1** and **2** not only requires the implementation of three contiguous stereocenters of the L-*ribo*- (L-βhEnd, **1**) and the L-*arabino* configuration (D-βhEnd, **2**), but also needs to establish the correct order of the individual reaction steps required for the introduction of the various functional groups (generation of the cyclic guanidine at C-4/C-5, adjustment of the oxidation state at C-1, introduction of the nitrogen functionalities at C-2, C-4, and C-5). In a number of exploratory studies we have observed that the close proximity of functional groups present in this system can lead to a variety of unexpected side reactions in normally straightforward transformations. From these results we have devised a synthesis for both diastereomers of βhEnd, a retrosynthetic overview of which is given in Scheme 1. The synthesis is based on a chiral pool approach, in which the configuration of the three stereocenters is traced back to diacetone D-glucose as a cheap and readily available starting material.

According to this plan, the protected βhEnd derivatives **1** and **2** would be obtained from the same azido alcohol **5**, which, in the forward direction, was envisaged initially to deliver azide **3** by means of an inversion reaction at C-2. This would then be followed by introduction of the cyclic C-4/C-5 guanidino group and oxidation at C-1 to yield the L-βhEnd derivative **1**. It was also envisioned that alcohol **5** would supply the corresponding C-2 epimeric D-βhEnd precursor **6** by inversion of the C-2 hydroxy group. The azido alcohol **6** would then be subjected to the same reaction sequence as described above, thereby providing the D-βhEnd derivative **2** via the azide **4**. The common precursor **5** was traced back to the differentially protected D-xylitol **7**, which would allow the introduction of the C-4 azido group with inversion. Finally, the D-xylitol **7** would be derived from commercially available diacetone D-glucose by standard procedures.

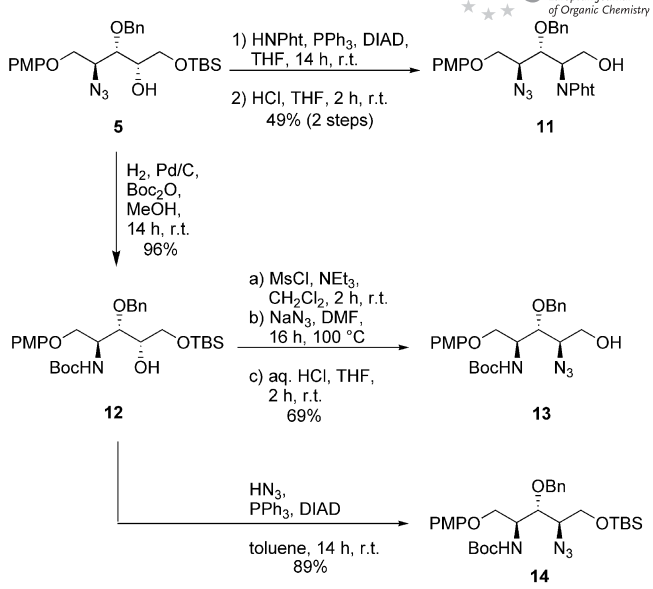
The synthesis of the common precursor for both βhEnd diastereomers, the azido alcohol **5**, started with the known 3-*O*-benzyl-1,2-*O*-isopropylidene-D-xylose (**8**, Scheme 2),[9] which is easily obtainable on a multigram scale from diacetone D-glucose in three steps and in 84% yield (1. NaH, BnBr; 2. $AcOH/H_2O$; 3. $NaIO_4$, then $NaBH_4$). Protection of the primary 5-OH group as a *p*-methoxyphenyl (PMP) ether[10] was achieved under Mitsunobu conditions (PMPOH, DIAD, PPh_3)[11] and afforded the xylose derivative **9** in 90% yield. After acidic cleavage of the isopropylidene group, the subsequent reduction of the crude lactol either with $NaBH_4$ or with $LiAlH_4$ proceeded slowly, with some starting material remaining even after prolonged reaction times. The best results were obtained with $LiAlH_4$ in THF for 14 h, which afforded a xylitol/lactol mixture (ca. 6:1) that was difficult to separate, so the mixture was therefore treated directly after workup with 2,2-dimethoxypropane and *p*TsOH. At this stage, the desired xylitol 1,2-acetonide **7**, which was obtained as the major product (70%, three steps), could be easily separated from xylofuranose **9** (15%) by flash chromatography.

For the introduction of the nitrogen functionality at C-4, the *O*-4 mesylate derived from the alcohol **7** was inverted with NaN_3 in DMF to give the azide **10** (90%). Acid-catalyzed removal of the isopropylidene acetal and selective protection of the primary hydroxy group with TBSCl then afforded the azido alcohol **5** (96%, two steps), which was obtained in multigram quantities.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Synthesis of the azido alcohol **5**.



Scheme 3. Introduction of nitrogen at C-2 to establish the required configuration of the L-series.

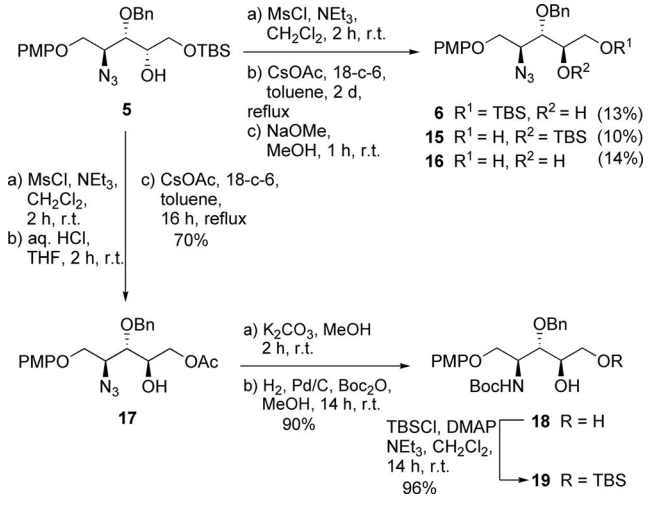
Inversion of Sterically Hindered Secondary Alcohols

The inversion of secondary alcohols can be a challenging task because alternative reaction pathways (elimination, intramolecular attack of nucleophilic groups within the molecule, etc.) can become prominent if backside attack of external nucleophiles is hindered. Whereas the displacement of the *O*-4 mesylate derived from alcohol **7** with sodium azide had proceeded smoothly (see above), for the inversion of the C-2 hydroxy group we had to explore various methods and nitrogen nucleophiles. Our initial efforts in the L-series concentrated on the direct inversion of the hydroxy group in the azido alcohol **5** under Mitsunobu conditions (DIAD, PPh_3, THF, room temp.), with phthalimide as the acidic component (Scheme 3). In these attempts, however, the isolated yields of the corresponding phthalimido derivative **11**, obtained after deprotection of the primary TBS group to facilitate chromatographic purification, never exceeded 50%.

To overcome these problems, we next converted the C-4 azide into the Boc-protected amine (H_2, Pd/C, Boc_2O, MeOH; 96%).[12] With alcohol **12** now to hand, it was possible to introduce the C-2 nitrogen by means of an azide nucleophile. Mesylation of O-2 and subsequent inversion with NaN_3, for example, proceeded smoothly, but gave rise to a mixture of two products due to partial removal of the primary TBS group under the reaction conditions. The crude mixture was therefore treated with aqueous HCl in THF to remove the TBS group completely, which afforded the azido alcohol **13** in 69% yield over three steps.

Even better yields were obtained when alcohol **12** was subjected to Mitsunobu reaction conditions with hydrazoic acid in toluene. Under these conditions, the primary TBS group was completely stable, and the inverted C-2 azide **14**, which contains the required configuration of the L-βhEnd system, was obtained in an excellent yield (89%).

According to our synthetic plan for the corresponding D-βhEnd derivative **2**, it was necessary to invert the C-2 hydroxy group of the azide **5**. To achieve this goal, we first converted the alcohol into the corresponding mesylate (Scheme 4). Subsequent inversion with cesium acetate and saponification of the obtained ester led to a product mixture that contained the expected C-2 alcohol **6**, but also two additional products resulting from cleavage (diol **16**) and 1,2-migration of the TBS group (2-*O*-TBS ether **15**) in an unsatisfying combined yield of 37%.



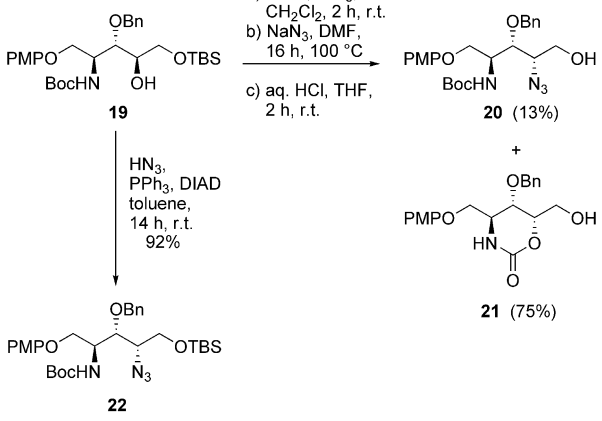
Scheme 4. Inversion of the C-2 hydroxy group.

We therefore opted to cleave the silyl group of the intermediate mesylate prior to treatment with CsOAc. This strategy not only improved the yield of the inversion, but now also led to a single product that was easily purifiable on a short silica gel column and was identified as the *O*-1 acetate **17**, resulting from a 2,1-migration of the ester (70% from **5**). Because of potential problems associated with

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

O,*N*-migration in the later steps of the synthesis, we next removed the acetyl group (K_2CO_3, MeOH) prior to formation of the Boc-protected C-4 amine **18** (H_2, Pd/C, Boc_2O, MeOH; 90% for both steps). Reprotection of the primary hydroxy group as the TBS ether (TBSCl, DMAP, 96%) gave the secondary alcohol **19**.

With alcohol **19** to hand, we tested the same transformations as had been used for the epimeric alcohol **12** for the introduction of nitrogen at C-2 (Scheme 5). Interestingly, for this stereoisomer, the azide displacement reaction of the intermediate mesylate led to the inverted azido alcohol **20** (obtained after cleavage of the primary TBS ether) only as the minor product (13%), because in this case the intramolecular displacement of the mesylate by the carbonyl oxygen of the adjacent C-4 carbamate became predominant, thus leading to the cyclic carbamate **21** in 75% yield.[13] This difference in behavior emphasizes the often hard to predict influence of the relative configuration on the reaction outcome in a highly functionalized system such as the present one.

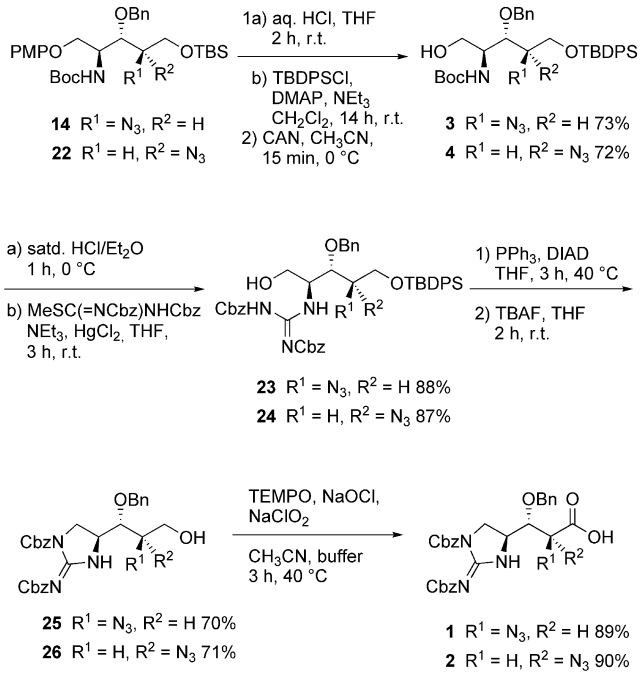


Scheme 5. Introduction of the C-2 azido group to establish the required configuration of the D-series.

Successful inversion at C-2, however, was again accomplished under Mitsunobu conditions (DIAD, PPh_3, HN_3, 0 °C, 92%), which afforded the azide **22** in excellent yields with no formation of the cyclic carbamate, thus highlighting the efficiency of the Mitsunobu reaction with hydrazoic acid for the inversion of a sterically hindered secondary hydroxy group.

Introduction of the Cyclic Guanidine and Oxidation at C-1

After the successful elaboration of the L-*ribo*-configured **14** and the L-*arabino*-configured **22**, we focused on the installment of the cyclic C-4/C-5 guanidine system and oxidation at C-1 in both series. For the remaining transformations, the primary TBS group proved to be too labile and was therefore exchanged for the TBDPS group in a two-step sequence (i. aq. HCl, THF; ii. TBDPSCl, DMAP).[14] On starting from the TBS ether **14** in the L-series, the corresponding TBDPS derivative was obtained nearly quantitatively. Next, the PMP group was cleaved with CAN[10] to afford the primary alcohol **3** (77%, three steps, Scheme 6), which served as the precursor for the introduction of the cyclic guanidine.



Scheme 6. Completion of the syntheses of βhEnd derivatives **1** and **2**.

Towards this end, the Boc-protected amine at C-4 was first liberated (satd. HCl/Et_2O) and converted to afford the linear guanidine **23** by treatment with *S*-methyl *N*,*N*′-bis(benzyloxycarbonyl)isothiourea (88%, two steps).[15] Cyclization of the guanidine by means of an intramolecular Mitsunobu reaction, followed by removal of the TBDPS group (Bu_4NF, THF; 70%, two steps), then smoothly produced the cyclic guanidine **25** (Scheme 6). Finally, direct oxidation of the primary alcohol, by use of a combination of TEMPO, $NaOCl_2$, and bleach,[16] afforded carboxylic acid **1** (89%). In an analogous manner, the TBS ether **22** was then converted into the D-βhEnd derivative **2** in 40% yield by the six-step sequence described for the preparation of the corresponding L-configured **1**.

In summary, the L-βhEnd derivative **1** has been synthesized in 21 steps (13 straightforward chromatographic purifications), starting from diacetone glucose, in 15.6% overall yield, whereas the D-βhEnd carboxylic acid **2** was obtained in 24 steps and in an overall yield of 10.3%. Our synthetic approach utilizes easily scalable transformations and provides both βhEnd isomers in gram quantities.

Conclusions

In conclusion, we have developed a reliable and straightforward route to β-hydroxyenduracididine building blocks in synthetically useful amounts. The presented route is the result of an extensive optimization with regard to the reaction sequence and features consistently high-yielding trans-

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

formations, such as the introduction of azido groups at sterically hindered secondary carbon atoms by use of the Mitsunobu reaction. Both carboxylic acids **1** and **2** are suitably protected for peptide coupling reactions and open access to the corresponding amines by esterification (e.g., AllBr, $KHCO_3$, DMF, room temperature) and reduction of the azide (H_2S, NEt_3, CH_2Cl_2; see Supporting Information). In addition, the carbobenzyloxy and benzyl groups can be easily removed by hydrogenolysis (H_2, Pd-C, MeOH and Pd-C, $HCOONH_4$, MeOH, reflux, respectively). The use of these building blocks in the total synthesis of the mannopeptimycins is currently being explored and will be reported in due course. In addition, the two diastereomers can serve as surrogates for L- or D-arginine, featuring conformationally restricted guanidino groups, and could be used to study the influence of arginine side-chains on the interactions of biologically active peptides with their targets.

Experimental Section

General Methods: TLC chromatography was performed with silica gel (60 F_{254}. Detection was carried out by fluorescence quenching under UV light (λ = 254 nm) or by staining with 20% H_2SO_4 or ninhydrin solution followed by heating to ca. 300 °C. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck KGaA). NMR spectra were recorded with Bruker AV 300, Bruker DRX 500, and Bruker DRX 600 spectrometers. Mass spectra were recorded with a Finnigan MAT 95 spectrometer. Specific rotations were measured with a Perkin–Elmer 241 polarimeter. Elemental analysis was performed with a Heraeus CHN-Rapid instrument.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-(4-methoxyphenyl)-α-D-xylofuranose (9): DIAD (7.9 mL, 39.3 mmol) was added dropwise at 0 °C under Ar to a solution of xylofuranose **8** (8.47 g, 30.2 mmol), PPh_3 (10.3 g, 39.3 mmol), and *p*-methoxyphenol (11.2 g, 90.6 mmol) in dry THF (250 mL). After the mixture had been heated at 80 °C for 1 h, the solvent was removed and the residue was dissolved in CH_2Cl_2. The organic layer was washed with aq. NaOH (10%, 2×) and brine (1×). The aqueous layers were reextracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in diethyl ether (20 mL), and petroleum ether (100 mL) was then added to precipitate the phosphane oxide formed during the reaction. After standing overnight at room temperature, the resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded the PMP ether **9** (10.25 g, 88%) as a colorless oil. R_f = 0.50 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{21}$ = –36.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, isopropyl-CH_3), 1.51 (s, 3 H, isopropyl-CH_3), 3.77 (s, 3 H, PMP-OCH_3), 4.07 (d, $^3J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 4.18 (d, $^3J_{4,5}$ = 6.1 Hz, 2 H, 5-H_2), 4.51 (d, ^2J = 12.0 Hz, 1 H, Ph-C*H*^{a}H^b), 4.55 (dt, $^3J_{4,5}$ = 6.1, $^3J_{3,4}$ = 3.2 Hz, 1 H, 4-H), 4.65 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, 2-H), 4.68 (d, ^2J = 12.0 Hz, 1 H, Ph-CH^a*H*^{b}), 5.98 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 6.81–6.87 (m, 4 H, PMP-H_{Ar}), 7.24–7.32 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.4, 27.0 (isopropyl-CH_3), 55.8 (PMP-OCH_3), 65.8 (C-5), 72.2 (Ph-CH_2), 78.8 (C-4), 81.5 (C-3), 82.6 (C-2), 105.3 (C-1), 112.0 (isopropyl-C_q), 114.8 (PMP-C_{Ar}), 115.7 (PMP-C_{Ar}), 127.9 (Bn-C_{Ar}), 128.0 (Bn-C_{Ar}), 128.6 (Bn-C_{Ar}), 137.5 (Bn-C_{Ar}), 152.9 (PMP-C_{Ar}), 154.1 (PMP-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{22}H_{26}O_6Na]^+$: 409.1622; found 409.1628. $C_{22}H_{26}O_6$ (386.44): calcd. C 68.38, H 6.78; found C 67.89, H 7.13.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-(4-methoxyphenyl)-D-xylitol (7): Xylofuranose **9** (9.63 g, 24.9 mmol) was dissolved in 1,4-dioxane (160 mL) and HCl (1 M, 98.0 mL) and the mixture was heated at 80 °C for 2 h. After cooling, the mixture was neutralized with satd. aq. $NaHCO_3$ and then extracted with EtOAc, (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. After the solvent had been removed under reduced pressure, the obtained lactol (R_f = 0.25, petroleum ether/EtOAc, 1:1) was dissolved in dry THF (125 mL), and $LiAlH_4$ (1.89 g, 49.8 mmol) was added at 0 °C. After stirring for 14 h at room temperature, the solution was acidified by careful addition of HCl (2 M) and subsequently stirred for 1 h at room temperature. The suspension was filtered off through a pad of Celite, and the precipitate was thoroughly washed with EtOAc. The filtrate was extracted with EtOAc (3×), and the combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the residual xylitol/lactol mixture was dissolved in CH_2Cl_2 (150 mL). After addition of 2,2-dimethoxypropane (12.5 mL, 99.6 mmol) and a catalytic amount of *p*TsOH, the solution was stirred at room temperature for 2 h and was then neutralized with NEt_3 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 4:1→2:1→1:1) gave the xylitol **7** (6.64 g, 69%) as a colorless oil; in addition, xylofuranose **8** (1.44 g, 15%) was recovered. R_f = 0.25 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{20}$ = –34.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, isopropyl-CH_3), 1.47 (s, 3 H, isopropyl-CH_3), 2.63 (br. s, 1 H, 4-OH), 3.69 (dd, ^3J = 6.6, ^3J = 1.8 Hz, 1 H, 3-H), 3.78 (s, 3 H, PMP-OCH_3), 3.80–3.88 (m, 2 H, 1-H^a, 5-H^a), 3.90–3.96 (m, 2 H, 4-H, 5-H^b), 4.01 (dd, ^2J = 8.3, $^3J_{1,2}$ = 6.6 Hz, 1 H, 1-H^b), 4.45 (q, $^3J_{1.2/2,3}$ = 6.8 Hz, 1 H, 2-H), 4.67 (d, ^2J = 11.6 Hz, 1 H, Ph-C*H*^{a}H^b), 4.87 (d, ^2J = 11.6 Hz, 1 H, Ph-CH^a*H*^{b}), 6.77–6.85 (m, 4 H, PMP-H_{Ar}), 7.27–7.35 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.7 (isopropyl-CH_3), 26.7 (isopropyl-CH_3), 55.9 (PMP-OCH_3), 66.2 (C-1), 69.4 (C-5), 70.3 (C-4), 74.4 (Ph-CH_2), 77.3 (C-2), 78.3 (C-3), 109.6 (isopropyl-C_q), 114.8 (PMP-C_{Ar}), 115.6 (PMP-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.5 (Bn-C_{Ar}), 128.6 (Bn-C_{Ar}), 138.1 (Bn-C_{Ar}), 152.7 (PMP-C_{Ar}), 154.3 (PMP-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{22}H_{28}O_6Na]^+$: 411.1778; found 411.1781.

4-Azido-3-*O*-benzyl-4-deoxy-1,2-*O*-isopropylidene-5-*O*-(4-methoxyphenyl)-L-arabinitol (10): Xylitol **7** (9.58 g, 24.7 mmol) was dissolved in dry CH_2Cl_2 (230 mL) under Ar, and NEt_3 (5.86 mL, 41.9 mmol) and MsCl (2.70 mL, 34.5 mmol) were added at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with satd. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude mesylate (R_f = 0.25, petroleum ether/EtOAc, 4:1) as an oil. The residue was dissolved in dry DMF (170 mL), and NaN_3 (9.74 g, 148.0 mmol) was added. After stirring for 17 h at 100 °C, the solvent was removed in vacuo and the residue was coevaporated with toluene (2×). The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 4:1) gave the azide **10** (9.14 g, 90%) as a colorless oil. R_f = 0.85 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{19}$ = +8.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, isopropyl-CH_3), 1.47 (s, 3 H, isopropyl-CH_3), 3.67 (dd, ^3J = 6.6, ^3J = 5.3 Hz, 1 H, 3-H), 3.79 (s, 3 H, PMP-OCH_3), 3.76–3.85 (m, 2 H, 4-H, 1-H^a), 4.09 (dd, *J* = 8.2, *J* = 6.6 Hz, 1 H, 1-H^b), 4.14 (dd, ^2J = 10.1, $^3J_{4,5}$ = 6.3 Hz, 1 H, 5-H^a), 4.30 (dd, ^2J

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

= 10.1, $^3J_{4,5}$ = 3.2 Hz, 1 H, 5-H^b), 4.33–4.38 (m, 1 H, 2-H), 4.66 (d, ^2J = 11.3 Hz, 1 H, Ph-CH^{a}H^b), 4.78 (d, ^2J = 11.3 Hz, 1 H, Ph-CH^{a}H^b), 6.83–6.88 (m, 4 H, PMP-H$_{Ar}$), 7.28–7.36 (m, 5 H, Bn-H$_{Ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.8 (isopropyl-CH_3), 26.5 (isopropyl-CH_3), 55.9 (PMP-OCH_3), 61.8 (C-4), 66.1 (C-1), 68.2 (C-5), 74.9 (Ph-CH_2), 77.1 (C-2), 78.4 (C-3), 109.6 (isopropyl-C$_q$), 114.9 (PMP-C$_{Ar}$), 115.7 (PMP-C$_{Ar}$), 128.1 (Bn-C$_{Ar}$), 128.3 (Bn-C$_{Ar}$), 128.6 (Bn-C$_{Ar}$), 137.8 (Bn-C$_{Ar}$), 152.4 (PMP-C$_{Ar}$), 154.5 (PMP-C$_{Ar}$) ppm. HRMS (ESI): calcd. for [$C_{22}H_{27}N_3O_5$-Na]$^+$: 436.1843; found 436.1839. $C_{22}H_{27}N_3O_5$ (413.47): calcd. C 63.91, H 6.58, N 10.16; found C 63.67, H 6.73, N 9.94.

4-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-5-*O*-(4-methoxyphenyl)-L-arabinitol (5): Arabinitol **10** (9.14 g, 22.1 mmol) was dissolved in 1,4-dioxane (150 mL) and HCl (1 M, 75 mL), and the mixture was stirred at room temperature for 14 h. The reaction mixture was neutralized with satd. aq. $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to afford the crude diol (R_f = 0.15, petroleum ether/EtOAc, 2:1) as an oil. The residue was redissolved in dry CH_2Cl_2 (220 mL), and NEt_3 (6.20 mL, 44.2 mmol), TBSCl (4.3 g, 28.7 mmol), and a catalytic amount of DMAP were added at 0 °C. After stirring for 14 h at room temperature, the reaction was quenched by addition of MeOH (10 mL) and stirred for another 15 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with satd. aq. $NaHCO_3$. The aqueous layer was reextracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 4:1→2:1) afforded the primary TBS ether **5** (10.3 g, 96%) as a colorless oil. R_f = 0.70 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{20}$ = +23.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, TBS-CH_3), 0.10 (s, 3 H, TBS-CH_3), 0.93 (s, 9 H, TBS-*t*Bu-CH_3), 2.37 (br. s, 1 H, 2-OH), 3.55 (dd, ^2J = 10.0, $^3J_{1,2}$ = 7.1 Hz, 1 H, 1-H^a), 3.74 (dd, ^2J = 10.0, $^3J_{1,2}$ = 6.0 Hz, 1 H, 1-H^b), 3.79 (s, 3 H, PMP-OCH_3), 3.85–3.91 (m, 2 H, 2-H, 3-H), 3.97 (dt, $^3J_{4,5}$ = 6.5, $^3J_{4,5}$ = 2.7 Hz, 1 H, 4-H), 4.12 (dd, ^2J = 9.9, $^3J_{4,5}$ = 6.5 Hz, 1 H, 5-H^a), 4.30 (dd, ^2J = 9.9, $^3J_{4,5}$ = 2.7 Hz, 1 H, 5-H^b), 4.66 (m, 2 H, Ph-CH_2), 6.83–6.89 (m, 4 H, PMP-H$_{Ar}$), 7.28-7.38 (m, 5 H, Bn-H$_{Ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.3 (TBS-CH_3), –5.2 (TBS-CH_3), 18.4 (TBS-*t*Bu-C$_q$), 26.0 (TBS-*t*Bu-CH_3), 55.6 (PMP-OCH_3), 61.2 (C-4), 63.8 (C-1), 68.6 (C-5), 71.4 (C-2), 75.0 (Bn-CH_2), 76.7 (C-3), 114.9 (PMP-C$_{Ar}$), 115.7 (PMP-C$_{Ar}$), 128.3 (Bn-C$_{Ar}$), 128.4 (Bn-C$_{Ar}$), 128.7 (Bn-C$_{Ar}$), 137.6 (Bn-C$_{Ar}$), 152.5 (PMP-C$_{Ar}$), 154.4 (PMP-C$_{Ar}$) ppm. HRMS (ESI): calcd. for [$C_{35}H_{37}N_3O_5SiNa$]$^+$: 510.2395; found 510.2395.

4-Azido-3-*O*-benzyl-2,4-deoxy-2-(1,3-dioxoisoindolinyl)-5-*O*-(4-methoxyphenyl)-L-ribitol (11): DIAD (2.55 mL, 12.7 mmol) and phthalimide (2.18 g, 14.8 mmol) were added at 0 °C to a solution of PPh_3 (3.32 g, 12.7 mmol) in dry THF (65 mL). A solution of alcohol **5** (2.06 g, 4.23 mmol) in dry THF (24 mL) was then added and the mixture was stirred at room temperature for 14 h. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with NaOH (1 M), and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was dissolved in diethyl ether (20 mL), and petroleum ether (100 mL) was then added to precipitate the phosphane oxide formed during the reaction. After standing overnight at room temperature, the resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 8:1→4:1) afforded the phthalimide derivative (R_f = 0.70, petroleum ether/EtOAc, 4:1), that still contained some unidentified impurities according to the ^{1}H NMR spectrum. It was dissolved in THF (25 mL), and HCl (8 M, 1.9 mL) was added. After stirring for 2 h at room temperature, the reaction mixture was diluted with EtOAc (150 mL), washed with satd. aq. $NaHCO_3$ (2×), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 2:1→1:1) afforded the ribitol **11** (1.04 g, 49%) as a colorless oil. R_f = 0.25 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{22}$ = –10.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.79 (br. s, 1 H, 1-OH), 3.74 (s, 3 H, PMP-OCH_3), 3.83–3.87 (m, 1 H, 4-H), 4.07–4.19 (m, 3 H, 1-H$_2$, 5-H^a), 4.21 (dd, J = 10.0, J = 4.0 Hz, 1 H, 5-H^b), 4.51 (dd, ^3J = 9.1, ^3J = 4.4 Hz, 1 H, 3-H), 4.55–4.59 (m, 1 H, 2-H), 4.79 (d, ^2J = 10.7 Hz, 1 H, Ph-CH^{a}H^b), 4.83 (d, ^2J = 10.7 Hz, 1 H, Ph-CH^{a}H^b), 6.73–6.79 (m, 4 H, PMP-H$_{Ar}$), 7.27–7.37 (m, 5 H, Bn-H$_{Ar}$), 7.70–7.75 (m, 2 H, Pht-H$_{Ar}$), 7.80–7.84 (m, 2 H, Pht-H$_{Ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1 (C-2), 55.8 (OCH_3), 61.8 (C-1), 62.3 (C-4), 68.0 (C-5), 75.3 (Ph-CH_2), 76.4 (C-3), 114.8 (PMP-C$_{Ar}$), 115.8 (PMP-C$_{Ar}$), 123.8 (Pht-C$_{Ar}$), 128.3 (Bn-C$_{Ar}$), 128.5 (Bn-C$_{Ar}$), 128.7 (Bn-C$_{Ar}$), 131.7 (Pht-C$_{Ar}$), 134.5 (Pht-C$_{q,Ar}$), 137.4 (Bn-C$_{Ar}$), 152.2 (PMP-C$_{Ar}$), 154.4 (PMP-C$_{Ar}$), 168.9 (Pht-C=O) ppm. HRMS (ESI): calcd. for [$C_{27}H_{26}N_4O_6Na$]$^+$: 525.1745; found 525.1746.

3-*O*-Benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-[(*tert*-butyloxycarbonyl)-amino]-4-deoxy-5-*O*-(4-methoxyphenyl)-L-arabinitol (12): Boc_2O (3.43 g, 15.7 mmol) and Pd/C (1.18 g, 10%) were added to a solution of arabinitol **5** (5.89 g, 12.1 mmol) in MeOH (60 mL). After stirring for 16 h under H_2 (1 bar) at room temperature, the reaction mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (petroleum ether/EtOAc, 6:1→4:1) to yield the *N*-Boc derivative **12** (6.53 g, 96%) as a colorless oil. R_f = 0.55 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{21}$ = +12.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, TBS-CH_3), 0.09 (s, 3 H, TBS-CH_3), 0.93 (s, 9 H, TBS-*t*Bu-CH_3), 1.47 (s, 3 H, Boc-*t*Bu-CH_3), 3.37 (bd, $^3J_{OH,2}$ = 5.1 Hz, 1 H, 2-OH), 3.63–3.69 (m, 1 H, 1-H^a), 3.75–3.79 (m, 1 H, 1-H^b), 3.79 (s, 3 H, OCH_3), 3.81–3.87 (m, 2 H, 2-H, 3-H), 3.99 (dd, J = 9.2, J = 4.8 Hz, 1 H, 5-H^a), 4.19–4.29 (m, 2 H, 4-H, 5-H^b), 4.56 (d, ^2J = 11.2 Hz, 1 H, Ph-CH^{a}H^b), 4.63 (d, ^2J = 11.2 Hz, 1 H, Ph-CH^{a}H^b), 5.43 (d, $^3J_{NH,4}$ = 9.0 Hz, 1 H, 4-NH), 6.82–6.88 (m, 4 H, PMP-H$_{Ar}$), 7.22–7.31 (m, 5 H, Bn-H$_{Ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.3 (TBS-CH_3), –5.2 (TBS-CH_3), 18.2 (TBS-*t*Bu-C$_q$), 25.9 (TBS-*t*Bu-CH_3), 28.4 (Boc-*t*Bu-CH_3), 50.0 (C-4), 55.8 (PMP-OCH_3), 63.5 (C-1), 67.4 (C-5), 71.0 (C-2), 73.9 (Ph-CH_2), 76.0 (C-3), 80.1 (Boc-*t*Bu-C$_q$), 114.8 (PMP-C$_{Ar}$), 115.4 (PMP-C$_{Ar}$), 127.8 (Bn-C$_{Ar}$), 128.2 (Bn-C$_{Ar}$), 128.4 (Bn-C$_{Ar}$), 138.0 (Bn-C$_{Ar}$), 152.4 (PMP-C$_{Ar}$), 154.2 (PMP-C$_{Ar}$), 156.4 (Boc-C=O) ppm. HRMS (ESI): calcd. for [$C_{30}H_{47}N_1O_7SiNa$]$^+$: 584.3014; found 584.3022.

2-Azido-3-*O*-benzyl-4-[(*tert*-butyloxycarbonyl)amino]-2,4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (13): NEt_3 (1.47 mL, 10.5 mmol) and MsCl (0.63 mL, 8.02 mmol) were added at 0 °C to a solution of alcohol **12** (3.46 g, 6.17 mmol) in dry CH_2Cl_2 (60 mL). After stirring for 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with satd. aq. $NaHCO_3$ and brine, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude mesylate (R_f = 0.55, petroleum ether/EtOAc, 4:1) was dissolved in dry DMF (55 mL), and NaN_3 (2.44 g, 37.0 mmol) was added. After the mixture had been heated at 100 °C for 17 h, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc, and water, the layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was dissolved in THF (55 mL), and aq. HCl (8 M, 2.17 mL) was added. After stirring for 2 h at

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

room temperature, the reaction mixture was neutralized with satd. aq. $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 2:1→1:1) afforded the ribitol **13** (2.00 g, 69%) as a colorless amorphous solid. R_f = 0.20 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{26}$ = +1.4 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, Boc-*t*Bu-CH_3), 2.85 (br. s, 1 H, 1-OH), 3.75–3.81 (m, 1 H, 2-H), 3.79 (s, 3 H, PMP-OCH_3), 3.90 (dd, ^3J = 8.2, ^3J = 2.9 Hz, 1 H, 3-H), 3.93–4.08 (m, 3 H, 1-H_2, 5-H^a), 4.08–4.15 (m, 1 H, 4-H), 4.18–4.23 (m, 1 H, 5-H^b), 4.50 (d, ^2J = 11.0 Hz, 1 H, Ph-CH^aH^b), 4.78 (d, ^2J = 11.0 Hz, 1 H, Ph-CH^aH^b), 5.15 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, 4-NH), 6.81–6.88 (m, 4 H, PMP-H_{Ar}), 7.20–7.39 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3 (Boc-*t*Bu-CH_3), 50.9 (C-4), 55.8 (PMP-OCH_3), 61.8 (C-1), 64.1 (C-2), 67.1 (C-5), 74.7 (Ph-CH_2), 79.4 (C-3), 80.5 (Boc-*t*Bu-C_q), 114.8 (PMP-C_{Ar}), 115.4 (PMP-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.5 (Bn-C_{Ar}), 137.4 (Bn-C_{Ar}), 152.3 (PMP-C_{Ar}), 154.3 (PMP-C_{Ar}), 155.8 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{24}H_{42}N_4O_6Na]^+$: 495.2214; found 495.2219.

2-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-[(*tert*-butyloxycarbonyl)amino]-2,4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (14): PPh_3 (4.84 g, 18.5 mmol) and DIAD (3.73 mL, 18.5 mmol) were added at 0 °C to a solution of the arabinitol **12** (5.76 g, 10.3 mmol) in dry toluene (150 mL). A solution of HN_3 in toluene[17] (2 M, 9.20 mL) was then added. The mixture was stirred for 30 min at 0 °C and then for another 16 h at room temperature. The reaction mixture was diluted with EtOAc, and washed with satd. aq. $NaHCO_3$. The aqueous layer was reextracted with EtOAc (2×), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:1→6:1) to yield the ribitol **14** (5.26 g, 88%) as a colorless oil. R_f = 0.65 (petroleum ether/EtOAc, 8:1). $[\alpha]_D^{15}$ = +8.1 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 6 H, TBS-CH_3), 0.89 (s, 9 H, TBS-*t*Bu-CH_3), 1.43 (s, 9 H, Boc-*t*Bu-CH_3), 3.73–4.15 (m, 10 H, 5-H_2, 4-H, 3-H, 2-H, 1-H_2, PMP-OCH_3), 4.46 (d, ^2J = 11.0 Hz, 1 H, Ph-CH^aH^b), 4.71 (d, ^2J = 11.0 Hz, 1 H, Ph-CH^aH^b), 5.01 (d, $^3J_{NH,4}$ = 9.2 Hz, 1 H, 4-NH), 6.78–6.82 (m, 4 H, PMP-H_{Ar}), 7.16–7.27 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5 (2 × TBS-CH_3), 18.2 (TBS-*t*Bu-C_q), 25.8 (TBS-*t*Bu-CH_3), 28.3 (Boc-*t*Bu-CH_3), 50.8 (C-4), 55.8 (PMP-OCH_3), 62.9 (C-1), 64.5 (C-2), 67.3 (C-5), 74.5 (Ph-CH_2), 78.1 (C-3), 79.9 (Boc-*t*Bu-C_q), 114.8 (PMP-C_{Ar}), 115.4 (PMP-C_{Ar}), 127.9 (Bn-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.4 (Bn-C_{Ar}), 137.6 (Bn-C_{Ar}), 152.5 (PMP-C_{Ar}), 154.2 (PMP-C_{Ar}), 155.2 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{30}H_{46}N_4O_6SiNa]^+$: 609.3079; found 609.3085. $C_{30}H_{46}N_4O_6Si$ (586.79): calcd. C 61.40, H 7.90, N 9.55; found C 61.27, H 7.98, N 9.32.

4-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (6), 4-Azido-3-*O*-benzyl-2-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (15), and 4-Azido-3-*O*-benzyl-4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (16): NEt_3 (2.70 mL, 19.5 mmol) and MsCl (1.25 mL, 16.1 mmol) were added at 0 °C to a solution of the arabinitol **5** (5.58 g, 11.4 mmol) in dry CH_2Cl_2 (110 mL). After stirring for 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with satd. aq. $NaHCO_3$ and brine, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude mesylate (R_f = 0.45, petroleum ether/EtOAc, 4:1) was dissolved in dry toluene (110 mL), and 18-crown-6 (1.51 g, 5.7 mmol) and CsOAc (12.0 g, 57.2 mmol) were added. After having been heated at reflux for 48 h, the reaction mixture was diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was dissolved in petroleum ether/EtOAc, (4:1) and filtered through a pad of silica, and the solvent was removed in vacuo. The crude acetate (R_f = 0.65, petroleum ether/EtOAc, 4:1) was dissolved in MeOH (50 mL), and NaOMe (5.4 M solution in MeOH, 0.22 mL, 1.20 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was neutralized by addition of Lewatit S acidic ion-exchange resin and filtered, and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 6:1→4:1→1:1) afforded the 1-*O*-TBS ether **6** (0.75 g, 13%), the 2-*O*-TBS ether **15** (0.55 g, 10%), and the diol **16** (0.60 g, 14%) as colorless oils.

Compound 6: R_f = 0.65 (petroleum ether/EtOAc, 6:1). $[\alpha]_D^{26}$ = +17.6 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, TBS-CH_3), 0.10 (s, 3 H, TBS-CH_3), 0.93 (s, 9 H, TBS-*t*Bu-CH_3), 2.57 (d, $^3J_{OH,2}$ = 5.0 Hz, 1 H, 2-OH), 3.64–3.71 (m, 2 H, 1-H^a, 3-H), 3.77–3.83 (m, 2 H, 1-H^b, 2-H), 3.78 (s, 3 H, PMP-OCH_3), 4.17–4.26 (m, 2 H, 5-H^a, 4-H), 4.30 (dd, ^2J = 9.3, $^3J_{4,5}$ = 2.6 Hz, 1 H, 5-H^b), 4.60 (d, ^2J = 11.3 Hz, 1 H, Ph-CH^aH^b), 4.79 (d, ^2J = 11.3 Hz, 1 H, Ph-CH^aH^b), 6.82–6.92 (m, 4 H, PMP-H_{Ar}), 7.30–7.39 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.4 (TBS-CH_3), 18.3 (TBS-*t*Bu-C_q), 25.9 (TBS-*t*Bu-CH_3), 55.7 (PMP-OCH_3), 62.0 (C-4), 63.7 (C-1), 68.4 (C-5), 71.0 (C-2), 74.1 (Ph-CH_2), 79.1 (C-3), 114.7 (PMP-C_{Ar}), 115.7 (PMP-C_{Ar}), 128.0 (Bn-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.5 (Bn-C_{Ar}), 137.7 (Bn-C_{Ar}), 152.5 (PMP-C_{Ar}), 154.2 (PMP-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{35}H_{37}N_3O_5SiNa]^+$: 510.2395; found 510.2398.

Compound 15: R_f = 0.40 (petroleum ether/EtOAc, 6:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 3 H, TBS-CH_3), 0.14 (s, 3 H, TBS-CH_3), 0.94 (s, 9 H, TBS-*t*Bu-CH_3), 1.97 (br. s, 1 H, 1-OH), 3.68–3.83 (m, 3 H, 1-H_2, 3-H), 3.78 (s, 3 H, PMP-OCH_3), 3.93–3.99 (m, 1 H, 2-H), 4.00–4.15 (m, 2 H, 4-H, 5-H^a), 4.24 (dd, ^2J = 9.4, $^3J_{4,5}$ = 2.5 Hz, 1 H, 5-H^b), 4.69 (d, ^2J = 11.0 Hz, 1 H, Ph-CH^aH^b), 4.76 (d, ^2J = 11.0 Hz, 1 H, Ph-CH^aH^b), 6.80–6.89 (m, 4 H, PMP-H_{Ar}), 7.27–7.38 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6 (TBS-CH_3), –4.5 (TBS-CH_3), 18.1 (TBS-*t*Bu-C_q), 25.8 (TBS-*t*Bu-CH_3), 55.7 (PMP-OCH_3), 61.7 (C-4), 63.7 (C-1), 68.7 (C-5), 72.7 (C-2), 74.5 (Ph-CH_2), 80.1 (C-3), 114.7 (PMP-C_{Ar}), 115.7 (PMP-C_{Ar}), 128.0 (Bn-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.5 (Bn-C_{Ar}), 137.6 (Bn-C_{Ar}), 152.5 (PMP-C_{Ar}), 154.3 (PMP-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{35}H_{37}N_3O_5SiNa]^+$: 510.2395; found 510.2392.

Compound 16: R_f = 0.15 (petroleum ether/EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (br. s, 1 H, 1-OH), 2.87 (br. s, 1 H, 2-OH), 3.63–3.83 (m, 4 H, 1-H_2, 3-H), 3.77 (s, 3 H, PMP-OCH_3), 3.83–3.93 (m, 1 H, 2-H), 4.07–4.20 (m, 2 H, 5-H^a, 4-H), 4.20–4.31 (m, 1 H, 5-H^b), 4.63 (d, ^2J = 11.1 Hz, 1 H, Ph-CH^aH^b), 4.73 (d, ^2J = 11.1 Hz, 1 H, Ph-CH^aH^b), 6.77–6.94 (m, 4 H, PMP-H_{Ar}), 7.27–7.42 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7 (PMP-OCH_3), 61.7 (C-4), 63.4 (C-1), 68.5 (C-5), 71.4 (C-2), 74.1 (Ph-CH_2), 79.0 (C-3), 114.7 (PMP-C_{Ar}), 115.7 (PMP-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.6 (Bn-C_{Ar}), 137.3 (Bn-C_{Ar}), 152.3 (PMP-C_{Ar}), 154.4 (PMP-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{19}H_{23}N_3O_5Na]^+$: 396.1530; found 396.1532.

1-*O*-Acetyl-4-azido-3-*O*-benzyl-4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (17): NEt_3 (3.64 mL, 26 mmol) and MsCl (1.85 mL, 23.7 mmol) were added to a solution of the arabinitol **5** (8.11 g, 13.2 mmol) in dry CH_2Cl_2 (100 mL). After stirring for 2 h at room temperature, the solution was diluted with CH_2Cl_2 and washed with satd. aq. $NaHCO_3$ (2×), and the aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was re-

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

moved under reduced pressure. The crude mesylate (R_f = 0.45, petroleum ether/EtOAc, 4:1) was dissolved in THF (150 mL), and HCl (6 M, 10.0 mL) was added. After stirring for 3 h at room temperature, the reaction mixture was neutralized with satd. aq. $NaHCO_3$ and then extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude primary alcohol (R_f = 0.20, petroleum ether/EtOAc, 4:1) was dissolved in dry toluene (130 mL), and 18-crown-6 (1.71 g, 6.47 mmol) and cesium acetate (13.6 g, 70.6 mmol) were added. After heating for 24 h to reflux, the cooled reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc (2×), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded the ribitol **17** (3.84 g, 70%) as a colorless oil. R_f = 0.15 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{17}$ = +37.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, OAc-CH_3), 2.66 (s, 1 H, 2-OH), 3.70 (m,1 H, 3-H), 3.77 (s, 3 H, PMP-OCH_3), 4.05 (m, 1 H, 2-H), 4.11–4.28 (m, 4 H, 4-H, 1-H^a, 5-H_2), 4.36 (dd, J = 11.8, J = 2.9 Hz, 1 H, 1-H^b), 4.62 (d, ^2J = 11.2 Hz, 1 H, Ph-CH^aH^b), 4.74 (d, ^2J = 11.2 Hz, 1 H, Ph-CH^aH^b), 6.85 (m, 4 H, PMP-H_{Ar}), 7.33 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (OAc-CH_3), 55.3 (PMP-OCH_3), 61.0 (C-4), 65.5 (C-1), 68.1 (C-5), 69.7 (C-2), 73.6 (Bn-CH_2), 78.3 (C-3), 114.4 (PMP-C_{Ar}), 115.3 (PMP-C_{Ar}), 127.8 (Bn-C_{Ar}), 127.9 (Bn-C_{Ar}), 128.2 (Bn-C_{Ar}), 136.8 (Bn-C_{Ar}), 151.9 (PMP-C_{Ar}), 154.0 (PMP-C_{Ar}), 171.1 (OAc-C=O) ppm. HRMS (ESI): calcd. for $[C_{21}H_{25}N_3O_6Na]^+$: 438.1636; found 438.1642. $C_{21}H_{25}N_3O_6$ (415.44): calcd. C 60.71, H 6.07, N 10.11; found C 60.19, H 6.35, N 9.76.

3-*O*-Benzyl-4-[(*tert*-butyloxycarbonyl)amino]-4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (18): K_2CO_3 (0.62 g, 4.44 mmol) was added to a solution of the ribitol **17** (3.72 g, 8.94 mmol) in MeOH/CH_2Cl_2 (1:1, 90 mL). After stirring for 4 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude diol (R_f = 0.20, petroleum ether/EtOAc, 2:1) was dissolved in MeOH (50 mL), Boc_2O (2.54 g, 11.6 mmol) and Pd/C (10%, 0.30 g) were added, and the mixture was stirred under H_2 (1 bar) for 16 h at room temperature. The reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. After flash chromatography (petroleum ether/EtOAc, 2:1→1:1), the *N*-Boc derivative **18** (3.60 g, 90%) was obtained as a colorless oil. R_f = 0.30 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{19}$ = +6.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, Boc-tBu-CH_3), 2.67 (m, 2 H, 1-OH, 2-OH), 3.78 (s, 3 H, PMP-OCH_3), 3.84–3.90 (m, 4 H, 2-H, 3-H, 5-H_2), 3.98–4.07 (m, 1 H, 1-H^a), 4.09–4.21 (m, 2 H, 4-H, 1-H^b), 4.56 (d, ^2J = 11.1 Hz, 1 H, Ph-CH^aH^b), 4.68 (d, ^2J = 11.1 Hz, 1 H, Ph-CH^aH^b), 5.11 (d, ^3J = 8.3 Hz, 1 H, 4-NH), 6.80–6.87 (m, 4 H, PMP-H_{Ar}), 7.20–7.34 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (Boc-tBu-CH_3), 50.8 (C-4), 55.8 (OCH_3), 63.4 (C-5), 67.6 (C-1), 72.0 (C-2), 74.5 (Bn-CH_2), 80.1 (C-3), 80.2 (Boc-tBu-C_q), 114.8 (PMP-C_{Ar}), 115.4 (PMP-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.6 (Bn-C_{Ar}), 137.7 (Bn-C_{Ar}), 152.3 (PMP-C_{Ar}), 154.3 (PMP-C_{Ar}), 155.8 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{24}H_{33}N_1O_7]^+$: 470.2149; found 470.2160.

3-*O*-Benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-[(*tert*-butyloxycarbonyl)-amino]-4-deoxy-5-*O*-(4-methoxyphenyl)-L-ribitol (19): TBSCl (1.74 g, 11.5 mmol), NEt_3 (2.16 mL, 15.4 mmol), and a catalytic amount of DMAP were added to a solution of the diol **18** (3.44 g, 7.69 mmol) in dry CH_2Cl_2 (50 mL). After stirring for 16 h at room temperature, the reaction mixture was quenched by addition of MeOH (20 mL) and then stirred for another 15 min. The solution was diluted with CH_2Cl_2 and washed with satd. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2×), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (petroleum ether/EtOAc, 6:1→4:1) to yield the TBS ether **19** (4.15 g, 96%) as a colorless oil. R_f = 0.65 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{24}$ = +11.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, TBS-CH_3), 0.10 (s, 3 H, TBS-CH_3), 0.93 (s, 9 H, TBS-tBu-CH_3), 1.46 (s, 9 H, Boc-tBu-CH_3), 2.86 (br. s, 1 H, 2-OH), 3.72 (dd, ^2J = 9.9, $^3J_{1,2}$ = 6.6 Hz, 1 H, 1-H^a), 3.78 (s, 3 H, PMP-OCH_3), 3.82 (dd, ^2J = 9.9, $^3J_{1,2}$ = 4.6 Hz, 1 H, 1-H^b), 3.84–3.89 (m, 2 H, 2-H, 3-H), 4.82 (dd, ^2J = 9.2, $^3J_{4,5}$ = 4.7 Hz, 1 H, 5-H^a), 4.11–4.17 (m, 1 H, 5-H^b), 4.21–4.28 (m, 1 H, 4-H), 4.58 (d, ^2J = 11.3 Hz, 1 H, Ph-CH^aH^b), 4.68 (d, ^2J = 11.3 Hz, 1 H, Ph-CH^aH^b), 5.14 (d, $^3J_{4,NH}$ = 8.9 Hz, 1 H, 4-NH), 6.83–6.85 (m, 4 H, PMP-H_{Ar}), 7.23–7.32 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.4 (TBS-CH_3), 18.2 (TBS-tBu-C_q), 25.9 (TBS-tBu-CH_3), 29.3 (Boc-CH_3), 50.4 (C-4), 55.7 (PMP-OCH_3), 63.6 (C-1), 67.7 (C-5), 72.2 (C-2), 73.6 (Ph-CH_2), 78.0 (C-3), 79.6 (Boc-tBu-C_q), 114.6 (PMP-C_{Ar}), 115.4 (PMP-C_{Ar}), 127.7 (Bn-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.3 (Bn-C_{Ar}), 138.0 (Bn-C_{Ar}), 152.6 (PMP-C_{Ar}), 154.0 (PMP-C_{Ar}), 155.6 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{30}H_{47}N_1O_7SiNa]^+$: 584.3014; found 584.3022.

2-Azido-3-*O*-benzyl-4-[(*tert*-butyloxycarbonyl)amino]-2,4-deoxy-5-*O*-(4-methoxyphenyl)-L-arabiniol (20) and Cyclic Carbamate 21: The alcohol **19** (0.88 g, 1.57 mmol) was converted into the corresponding mesylate and treated with sodium azide as in the procedure described for the synthesis of **13**. Flash chromatography (petroleum ether/EtOAc, 4:1→CH_2Cl_2/MeOH, 10:1) afforded the arabinitol **20** (0.11 g, 13%) as a colorless oil and the cyclic carbamate **21** (0.44 g, 75%) as a colorless solid.

Compound 20: R_f = 0.20 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{22}$ = +22.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, Boc-tBu-CH_3), 2.22 (br. s, 1 H, 1-OH), 3.64–3.70 (m, 1 H, 2-H), 3.73–3.80 (m, 1 H, 1-H^a), 3.78 (s, 3 H, PMP-OCH_3), 3.83 (dd, ^3J = 7.2, ^3J = 3.2 Hz, 1 H, 3-H), 3.87 (dd, ^2J = 11.1, $^3J_{1,2}$ = 6.8 Hz, 1 H, 1-H^b), 4.01 (dd, ^2J = 9.4, $^3J_{4,5}$ = 4.3 Hz, 1 H, 5-H^a), 4.17 (dd, ^2J = 9.4, $^3J_{4,5}$ = 3.4 Hz, 1 H, 5-H^b), 4.31 (br. s, 1 H, 4-H), 4.46–4.64 (m, 2 H, Ph-CH_2), 5.13 (d, $^3J_{4,NH}$ = 8.9 Hz, 1 H, 4-NH), 6.82–6.89 (m, 4 H, PMP-H_{Ar}), 7.23–7.36 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3 (Boc-tBu-CH_3), 50.4 (C-4), 55.7 (PMP-OCH_3), 62.5 (C-1), 63.6 (C-2), 67.1 (C-5), 74.2 (Ph-CH_2), 77.0 (C-3), 80.0 (Boc-tBu-C_q), 114.8 (PMP-C_{Ar}), 115.3 (PMP-C_{Ar}), 128.1 (Bn-C_{Ar}), 128.3 (Bn-C_{Ar}), 128.5 (Bn-C_{Ar}), 137.3 (Bn-C_{Ar}), 152.2 (PMP-C_{Ar}), 154.2 (PMP-C_{Ar}), 155.4 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{24}H_{32}N_4O_6Na]^+$: 495.2214; found 495.2223.

Compound 21: R_f = 0.60 (CH_2Cl_2/MeOH, 10:1). $[\alpha]_D^{22}$ = –22.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.85 (br. s, 1 H, 1-OH), 3.69–3.78 (m, 1 H, 1-H^a), 3.76 (s, 3 H, PMP-OCH_3), 3.81 (dd, ^2J = 9.5, $^3J_{4,5}$ = 7.2 Hz, 1 H, 5-H^a), 3.85–3.92 (m, 2 H, 2-H, 5-H^b), 3.94–4.02 (m, 2 H, 1-H^b, 4-H), 4.39–4.44 (m, 1 H, 3-H), 4.50 (d, ^2J = 12.1 Hz, 1 H, Ph-CH^aH^b), 4.67 (d, ^2J = 12.1 Hz, 1 H, Ph-CH^aH^b), 6.50 (d, $^3J_{4,NH}$ = 2.6 Hz, 1 H, 4-NH), 6.77–6.86 (m, 4 H, PMP-H_{Ar}), 7.28–7.38 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.5 (C-4), 55.7 (PMP-OCH_3), 61.3 (C-1), 68.3 (C-2), 69.0 (C-5), 71.5 (Ph-CH_2), 76.7 (C-3), 114.8 (PMP-C_{Ar}), 115.5 (PMP-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.3 (Bn-C_{Ar}), 128.6 (Bn-C_{Ar}), 136.8 (Bn-C_{Ar}), 151.9 (PMP-C_{Ar}), 153.8 (PMP-C_{Ar}), 155.4 [NH-(C=O)-O] ppm. HRMS (ESI): calcd. for $[C_{20}H_{23}N_1O_6Na]^+$: 396.1418; found 396.1425.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

2-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-[(*tert*-butyloxycarbonyl)amino]-2,4-deoxy-5-*O*-(4-methoxyphenyl)-L-arabinitol (22): The ribitol **19** (4.32 g, 7.69 mmol) was converted into the azide **22** by the procedure described for the synthesis of the azide **14**. Flash chromatography (petroleum ether/EtOAc, 8:1→6:1) afforded the arabinitol **22** (4.15 g, 92%) as a colorless oil. R_f = 0.45 (petroleum ether/EtOAc, 8:1). $[\alpha]_D^{19}$ = +22.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, TBS-CH_3), 0.08 (s, 3 H, TBS-CH_3), 0.91 (s, 9 H, TBS-tBu-CH_3), 1.45 (s, 9 H, Boc-tBu-CH_3), 3.62–3.78 (m, 2 H, 3-H, 5-H^a), 3.72–3.86 (m, 5 H, PMP-OCH_3, 2-H, 5-H^b), 3.95–4.03 (m, 1 H, 1-H^a), 4.18 (dd, ^2J = 9.4, $^3J_{1,2}$ = 3.0 Hz, 1 H, 1-H^b), 4.25–4.37 (m, 1 H, 4-H), 4.51 (d, ^2J = 11.2 Hz, 1 H, Ph-CH^aH^b), 4.57 (d, ^2J = 11.2 Hz, 1 H, Ph-CH$^a H^b$), 5.16 (d, $^3J_{NH,4}$ = 9.7 Hz, 1 H, 4-NH), 6.77–6.89 (m, 4 H, PMP-H_{Ar}), 7.15–7.33 (m, 5 H, Bn-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5 (TBS-CH_3), –5.4 (TBS-CH_3), 14.2 (TBS-tBu-C_q), 18.2 (TBS-tBu-C_q), 25.8 (TBS-tBu-CH_3), 28.3 (Boc-tBu-CH_3), 50.4 (C-4), 55.8 (OCH_3), 63.5 (C-5/C-2), 63.7 (C-5/C-2), 67.5 (C-1), 74.1 (Bn-CH_2), 76.3 (Boc-tBu-C_q), 79.8 (C-3), 114.8 (PMP-C_{Ar}), 115.3 (PMP-C_{Ar}), 127.9 (Bn-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.4 (Bn-C_{Ar}), 137.5 (Bn-C_{Ar}), 152.3 (PMP-C_{Ar}), 154.2 (PMP-C_{Ar}), 155.3 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{30}H_{46}N_4O_6SiNa]^+$: 609.3079; found 609.3088. $C_{30}H_{46}N_4O_6Si$ (586.79): calcd. C 61.40, H 7.90, N 9.55; found C 61.35, H 7.76, N 9.72.

2-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldiphenylsilyl)-4-[(*tert*-butyloxycarbonyl)amino]-2,4-deoxy-L-ribitol (3): The ribitol **14** (5.00 g, 8.52 mmol) was dissolved in THF (85 mL) and HCl (6 M, 5.00 mL). After stirring for 3 h at room temperature, the reaction mixture was neutralized with satd. aq. $NaHCO_3$ and then extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude alcohol (R_f = 0.20, petroleum ether/EtOAc, 4:1) was dissolved in dry CH_2Cl_2 (80 mL), and NEt_3 (2.98 mL, 21.3 mmol), TBDPSCl (3.35 mL, 12.8 mmol), and a catalytic amount of DMAP were added at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched by addition of MeOH (10 mL) and stirred for another 15 min. The reaction mixture was diluted with CH_2Cl_2, washed with satd. aq. $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 6:1) afforded the TBDPS ether (5.81 g, 95%, R_f = 0.50, petroleum ether/EtOAc, 6:1) as a colorless oil. The *O*1-TBDPS ether (5.81 g, 8.17 mmol) was dissolved in acetonitrile/water (4:1, 60 mL) and CAN (13.2 g, 19.5 mmol) was added at 0 °C. After stirring for 15 min at 0 °C, the reaction mixture was poured into EtOAc (300 mL). The organic layer was extracted with satd. aq. $NaHCO_3$ (2×) and the aqueous layer was reextracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. After flash chromatography (petroleum ether/EtOAc, 4:1→3:1→2:1), the alcohol **3** (3.84 g, 73%) was obtained as a yellow oil. R_f = 0.25 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{14}$ = –48.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 9 H, TBDPS-tBu-CH_3), 1.44 (s, 9 H, Boc-tBu-CH_3), 2.40 (br. s, 1 H, 5-OH), 3.58–4.05 (m, 7 H, 1-H_2, 2-H, 3-H, 4-H, 5-H_2), 4.42–4.45 (m, 2 H, Ph-CH_2), 5.15 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, 4-NH), 7.08–7.20 (m, 2 H, TBDPS-H_{Ar}), 7.23–7.33 (m, 3 H, TBDPS-H_{Ar}), 7.34–7.51 (m, 6 H, Bn-H_{Ar}, TBDPS-H_{Ar}), 7.66–7.76 (m, 4 H, TBDPS-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (TBDPS-tBu-C_q), 26.8 (TBDPS-tBu-CH_3), 28.4 (Boc-tBu-CH_3), 52.1 (C-4), 62.1 (C-1), 64.3 (C-2), 64.4 (C-5), 74.6 (Ph-CH_2), 79.4 (C-3), 79.8 (Boc-tBu-C_q), 127.8 (TBDPS-C_{Ar}), 128.1 (TBDPS-C_{Ar}), 128.2 (Bn-C_{Ar}), 128.6 (Bn-C_{Ar}), 129.9 (Bn-C_{Ar}), 132.8 (TBDPS-C_{Ar}), 135.6 (TBDPS-C_{Ar}), 135.7 (TBDPS-C_{Ar}), 137.1 (Bn-C_{Ar}), 155.6 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{33}H_{45}N_4O_5Si]^+$: 605.3154; found 605.3153.

2-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldiphenylsilyl)-4-[(*tert*-butyloxycarbonyl)amino]-2,4-deoxy-L-arabinitol (4): The arabinitol **22** (4.02 g, 6.86 mmol) was converted into the alcohol **4** by the procedure described for the synthesis of the alcohol **3**. Flash chromatography (petroleum ether/EtOAc, 4:1→3:1→2:1) afforded the arabinitol **4** (2.98 g, 72%) as a colorless oil. R_f = 0.15 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{19}$ = –21.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 9 H, TBDPS-tBu-CH_3), 1.44 (s, 9 H, Boc-tBu-CH_3), 3.53–3.92 (m, 7 H, 1-H_2, 2-H, 3-H, 4-H, 5-H_2), 4.55 (d, ^2J = 11.4 Hz, 1 H, Ph-CH^aH^b), 4.60 (d, ^2J = 11.4 Hz, 1 H, Ph-CH$^a H^b$), 5.24 (d, $^3J_{NH,4}$ = 7.0 Hz, 1 H, 4-NH), 7.18–7.31 (m, 5 H, TBDPS-H_{Ar}), 7.33–7.50 (m, 6 H, Bn-H_{Ar}, TBDPS-H_{Ar}), 7.60–7.71 (m, 4 H, TBDPS-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (TBDPS-tBu-C_q), 26.8 (TBDPS-tBu-CH_3), 28.3 (Boc-tBu-CH_3), 52.6 (C-4), 62.5 (C-2), 63.9 (C-1/C-5), 64.2 (C-1/C-5), 74.3 (Bn-CH_2), 77.1 (C-3), 79.9 (Boc-tBu-C_q), 127.9 (Bn-C_{Ar}), 128.1 (2 signals, TBDPS-C_{Ar}, Bn-C_{Ar}), 128.4 (Bn-C_{Ar}), 129.9 (2 signals, TBDPS-C_{Ar}), 132.7 (TBDPS-C_{Ar}), 132.9 (TBDPS-C_{Ar}), 135.6 (2 signals, TBDPS-C_{Ar}), 137.3 (Bn-C_{Ar}), 156.0 (Boc-C=O) ppm. HRMS (ESI): calcd. for $[C_{33}H_{45}N_4O_5Si]^+$: 605.3154; found 605.3153.

2-Azido-3-*O*-benzyl-4-[*N*,*N*′-bis(benzyloxycarbonyl)guanidino]-1-*O*-(*tert*-butyldiphenylsilyl)-2,4-deoxy-L-ribitol (23): Satd. HCl/Et_2O (80 mL) was added at 0 °C to a solution of the ribitol **3** (2.56 g, 4.23 mmol) in ethyl ether (10 mL). After the mixture had been stirred for 1 h at 0 °C, the solvent was removed under reduced pressure. The crude amine was dissolved in THF (35 mL), and NEt_3 (1.78 mL, 12.7 mmol), 1,3-bis(benzyloxycarbonyl)-2-methyl-2-thiopseudourea (1.97 g, 5.50 mmol), and $HgCl_2$ (2.30 g, 8.46 mmol) were added. After stirring for 3 h at room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was diluted with EtOAc, and washed with satd. aq. NH_4Cl (2×). The aqueous layer was reextracted with EtOAc, the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 4:1→2:1) furnished the guanidine **23** (3.03 g, 88%) as a colorless oil. R_f = 0.30 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{14}$ = –22.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 9 H, TBDPS-tBu-CH_3), 3.54–3.67 (m, 2 H, 5-H_2), 3.72–3.88 (m, 3 H, 1-H^a, 2-H, 3-H), 3.93 (dd, J = 10.8, J = 3.2 Hz, 1 H, 1-H^b), 4.22–4.33 (m, 1 H, 4-H), 4.33 (d, ^2J = 10.9 Hz, 1 H, Ph-CH^aH^b), 4.43 (d, ^2J = 10.9 Hz, 1 H, Ph-CH$^a H^b$), 4.96–5.03 (m, 2 H, Cbz-CH_2), 5.05–5.15 (m, 2 H, Cbz-CH_2), 6.98–7.06 (m, 2 H, TBDPS-H_{Ar}), 7.07–7.40 (m, 19 H, Bn-H_{Ar}, TBDPS-H_{Ar}, Cbz-H_{Ar}), 7.55–7.65 (m, 4 H, TBDPS-H_{Ar}), 8.88 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, 4-NH), 11.59 (s, 1 H, guanidine-NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (TBDPS-tBu-C_q), 26.8 (TBDPS-tBu-CH_3), 53.0 (C-4), 61.9 (C-1), 64.0 (C-2), 64.2 (C-5), 67.2 (Cbz-CH_2), 68.3 (Cbz-CH_2), 74.5 (Ph-CH_2), 78.5 (C-3), 127.9–128.9 (9 signals, TBDPS-C_{Ar}, Bn-C_{Ar}, Cbz-C_{Ar}), 129.9 (Bn-C_{Ar}), 132.8 (TBDPS-C_{Ar}, Cbz-C_{Ar}), 134.6 (Cbz-C_{Ar}), 134.7 (TBDPS-C_{Ar}), 135.7 (TBDPS-C_{Ar}), 136.8 (Bn-C_{Ar}, Cbz-C_{Ar}), 153.6 (Cbz-C=O), 155.9 (Cbz-C=O), 163.4 (guanidine-C) ppm. HRMS (ESI): calcd. for $[C_{45}H_{51}N_6O_7Si]^+$: 815.3583; found 815.3598.

2-Azido-3-*O*-benzyl-4-[*N*,*N*′-bis(benzyloxycarbonyl)guanidino]-1-*O*-(*tert*-butyldiphenylsilyl)-2,4-deoxy-L-arabinitol (24): The arabinitol **4** (2.44 g, 4.03 mmol) was converted into the guanidine **24** by the procedure described for the synthesis of compound **23**. Flash chromatography (petroleum ether/EtOAc, 4:1→2:1) afforded **24** (2.86 g, 87%) as a colorless oil. R_f = 0.25 (petroleum ether/EtOAc,

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

4:1). $[\alpha]_D^{19}$ = –2.7 (*c* = 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, TBDPS-*t*Bu-CH_3), 3.39–3.48 (m, 1 H, 2-H), 3.65 (dd, ^2J = 11.6, $^3J_{4,5}$ = 3.3 Hz, 1 H, 5-H^a), 3.75–3.94 (m, 4 H, 1-H_2, 3-H, 5-H^b), 4.28–4.38 (m, 1 H, 4-H), 4.52 (d, ^2J = 11.5 Hz, 1 H, Ph-C*H*^{a}H^b), 4.65 (d, ^2J = 11.5 Hz, 1 H, Ph-CH^a*H*^{b}), 5.04–5.14 (m, 2 H, Cbz-CH_2), 5.21 (s, 2 H, Cbz-CH_2), 7.19–7.14 (m, 5 H, TBDPS-H_{Ar}), 7.27–7.45 (m, 16 H, TBDPS-H_{Ar}, Cbz-H_{Ar}, Bn-H_{Ar}), 7.59–7.67 (m, 5 H, TBDPS-H_{Ar}), 9.13 (d, $^3J_{4,NH}$ = 7.4 Hz, 1 H, 4-NH), 11.65 (s, 1 H, guanidine-NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (TBDPS-*t*Bu-C_q), 26.7 (TBDPS-*t*Bu-CH_3), 53.8 (C-4), 62.5 (C-5), 63.3 (C-2), 63.6 (C-1), 67.1 (Cbz-CH_2), 68.3 (Cbz-CH_2), 73.6 (Bn-CH_2), 76.1 (C-3), 127.8–128.1 (5 signals, Cbz-C_{Ar}, Bn-C_{Ar}), 128.4 (Bn-C_{Ar}), 128.7 (Bn-C_{Ar}), 128.8 (TBDPS-C_{Ar}), 129.9 (2 signals, TBDPS-C_{Ar}), 132.8 (TBDPS-C_{Ar}, Cbz-C_{Ar}), 134.6 (Cbz-C_{Ar}), 135.6 (TBDPS-C_{Ar}/Bn-C_{Ar}), 136.7 (Bn-C_{Ar}, Cbz-C_{Ar}), 153.4 (Cbz-C=O), 156.2 (Cbz-C=O), 163.2 (guanidine-C_q) ppm. HRMS (ESI): calcd. for $[C_{45}H_{51}N_6O_7Si]^+$: 815.3583; found 815.3584.

4-Amino-2-azido-3-*O*-benzyl-5-[(benzyloxycarbonyl)amino]-4,5-*N*,*N*′-[(benzyloxycarbonyl)carbimino]-2,4,5-deoxy-L-ribitol (25): A solution of the ribitol **23** (2.13 g, 2.61 mmol) in dry THF (25 mL) was added dropwise to a solution of PPh_3 (1.71 g, 6.53 mmol) and DIAD (1.31 mL, 6.53 mmol) in dry THF (25 mL). After the mixture had been stirred for 3 h at 40 °C, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography (petroleum ether/EtOAc, 4:1→2:1) to give the cyclic guanidine, which coeluted with the DIAD-derived hydrazine (R_f = 0.55, petroleum ether/EtOAc, 2:1). The mixture was dissolved in THF (25 mL), and TBAF (1 M in THF, 5.22 mL, 5.22 mmol) was added. After the mixture had been stirred for 2.5 h at room temperature, the solvent was removed in vacuo. Flash chromatography (petroleum ether/EtOAc, 1:1→1:2) of the residue afforded the ribitol **25** (1.02 g, 70%) as a colorless oil. R_f = 0.55 (petroleum ether/EtOAc, 1:2). $[\alpha]_D^{22}$ = –24.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 6.6, *J* = 3.6 Hz, 1 H, 1-H^a), 3.67–3.97 (m, 5 H, 1-H^b, 2-H, 3-H, 4-H, 5-H_2), 4.22–4.37 (m, 1 H, 1-OH), 4.52 (d, ^2J = 11.5 Hz, 1 H, Ph-C*H*^{a}H^b), 4.72 (d, ^2J = 11.5 Hz, 1 H, Ph-CH^a*H*^{b}), 5.05–5.26 (m, 4 H, 2 × Cbz-CH_2), 7.11–7.49 (m, 15 H, Bn-H_{Ar}, Cbz-H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.3 (C-5), 60.4 (C-4), 61.4 (C-1), 62.9 (C-2), 67.8 (Cbz-CH_2), 68.4 (Cbz-CH_2), 73.2 (Ph-CH_2), 81.7 (C-3), 128.2–128.7 (6 signals, Bn-C_{Ar}, Cbz-C_{Ar}), 134.9 (Cbz-C_{Ar}), 135.5 (Cbz-C_{Ar}), 137.2 (Bn-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{29}H_{31}N_6O_6]^+$: 559.2300; found 559.2307.

4-Amino-2-azido-3-*O*-benzyl-5-[(benzyloxycarbonyl)amino]-4,5-*N*,*N*′-[(benzyloxycarbonyl)carbimino]-2,4,5-deoxy-L-arabinitol (26): The guanidine **24** (1.98 g, 2.43 mmol) was cyclized and deprotected to afford **26** by the procedure described for the synthesis of compound **25**. Flash chromatography (petroleum ether/EtOAc, 1:1→1:2) afforded the arabinitol **26** (0.96 g, 71%) as a colorless oil. R_f = 0.30 (petroleum ether/EtOAc, 1:2). $[\alpha]_D^{18}$ = –24.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.47–3.56 (m, 1 H, 2-H), 3.61–4.01 (m, 5 H, 1-H_2, 3-H, 5-H_2), 4.07–4.19 (m, 1 H, 4-H), 4.61 (d, ^2J = 11.0 Hz, 1 H, Ph-C*H*^{a}H^b), 4.81–4.94 (m, 1 H, Ph-CH^a*H*^{b}), 5.11–5.27 (m, 4 H, Cbz-CH_2), 7.21–7.45 (m, 15 H, Cbz-H_{Ar}, Bn-H_{Ar}), 9.71 (br. s, 1 H, 4-NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.4 (C-5), 62.2 (C-1), 64.3 (C-4), 67.8 (C-2), 68.4 (Cbz-CH_2), 75.2, (Bn-CH_2), 82.3 (C-3), 128.1–128.7 (Cbz-C_{Ar}, Bn-C_{Ar}) ppm. HRMS (ESI): calcd. for $[C_{29}H_{31}N_6O_6]^+$: 559.2300; found 559.2299.

4-Amino-2-azido-3-*O*-benzyl-5-[(benzyloxycarbonyl)amino]-4,5-*N*,*N*′-[(benzyloxycarbonyl)carbimino]-2,4,5-deoxy-L-ribonic Acid (1): NaH_2PO_4 buffer (0.67 M, 3.0 mL) and Na_2HPO_4 buffer (0.67 M, 3.0 mL) were added to a solution of the alcohol **25** (980 mg, 1.75 mmol) in acetonitrile (10 mL). TEMPO (14 mg, 0.09 mmol), $NaClO_2$ (317 mg, 3.50 mmol), and aq. NaOCl solution (ca. 10%, 0.20 mL) were then added. After the mixture had been stirred for 1 h at 40 °C, additional amounts of TEMPO (14 mg, 0.09 mmol), $NaClO_2$ (317 mg, 3.50 mmol), and aq. NaOCl (ca. 10%, 0.20 mL) were added, and the reaction mixture was stirred for another 1 h at 40 °C. This procedure was repeated until no more starting material could be detected by TLC (petroleum ether/EtOAc, 1:2). The solution was then diluted with CH_2Cl_2 and washed with aq. $NaHSO_3$ (10%, 2×) and brine. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1→4:1) to give the protected L-β-hydroxyenduracididine **1** (892 mg, 89%) as a colorless amorphous solid. R_f = 0.35 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{21}$ = –41.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 3.83–3.94 (m, 1 H, 5-H^a), 3.97–4.04 (m, 1 H, 5-H^b), 4.04–4.16 (m, 3 H, 2-H, 3-H, 4-H), 4.48 (d, ^2J = 11.7 Hz, 1 H, Ph-C*H*^{a}H^b), 4.72 (d, ^2J = 11.7 Hz, 1 H, Ph-CH^a*H*^{b}), 5.04 (s, 2 H, Cbz-CH_2), 5.19 (s, 2 H, Cbz-CH_2), 7.17–7.49 (m, 15 H, Bn-H_{Ar}, Cbz-H_{Ar}), 8.81 (s, 1 H, 4-NH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 45.1 (C-5), 52.9 (C-4), 64.2 (C-2), 66.2 (Cbz-CH_2), 67.0 (Cbz-CH_2), 71.9 (Ph-CH_2), 79.8 (C-3), 127.3–128.3 (9 signals, Bn-C_{Ar}, Cbz-C_{Ar}), 136.0 (Cbz-C_{Ar}), 137.2 (Cbz-C_{Ar}), 138.2 (Bn-C_{Ar}), 150.4 (Cbz-C=O), 158.2 (Cbz-C=O), 162.9 (guanidine-C), 169.9 (C-1) ppm. HRMS (ESI): calcd. for $[C_{29}H_{29}N_6O_7]^+$: 573.2092; found 573.2097.

4-Amino-2-azido-3-*O*-benzyl-5-[(benzyloxycarbonyl)amino]-4,5-*N*,*N*′-[(benzyloxycarbonyl)carbimino]-2,4,5-deoxy-L-arabinonic Acid (2): The arabinitol **26** (1.98 g, 2.43 mmol) was oxidized by the procedure described for the synthesis of the acid **1**. Flash chromatography (CH_2Cl_2/MeOH, 9:1→4:1) afforded the protected D-β-hydroxyenduracididine derivative **2** (886 mg, 90%) as a colorless amorphous solid. R_f = 0.15 (CH_2Cl_2/MeOH, 10:1). $[\alpha]_D^{20}$ = –42.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.54–3.62 (m, 1 H, 2-H), 3.87–4.09 (m, 3 H, 4-H, 5-H_2), 4.31–4.40 (m, 1 H, 3-H), 4.52 (d, ^2J = 11.4 Hz, 1 H, Ph-C*H*^{a}H^b), 4.73 (d, ^2J = 11.4 Hz, 1 H, Ph-CH^a*H*^{b}), 5.05 (s, 2 H, Cbz-CH_2), 5.19 (s, 2 H, Cbz-CH_2), 7.17–7.25 (m, 5 H, Cbz-H_{Ar}/Bn-H_{Ar}), 7.26–7.39 (m, 8 H, Cbz-H_{Ar}/Bn-H_{Ar}), 7.40–7.48 (m, 2 H, Cbz-H_{Ar}/Bn-H_{Ar}), 9.07 (br. s, 1 H, 4-NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 45.1 (C-5), 54.5 (C-4), 64.0 (C-2), 66.1 (Cbz-CH_2), 67.0 (Cbz-CH_2), 73.4 (Bn-CH_2), 80.2 (C-3), 127.3–128.3 (8 signals, Cbz-C_{Ar}/Bn-C_{Ar}), 135.9 (Cbz-C_{Ar}/Bn-C_{Ar}), 137.2 (Cbz-C_{Ar}/Bn-C_{Ar}), 138.4 (Cbz-C_{Ar}/Bn-C_{Ar}), 150.5 (Cbz-C=O), 163.5 (guanidine-C), 171.0 (C-1) ppm. HRMS (ESI): calcd. for $[C_{29}H_{27}N_6O_7]^-$: 571.1947; found 571.1928.

Supporting Information (see also the footnote on the first page of this article): Detailed procedures for the synthesis of 3-*O*-benzyl-1,2-*O*-isopropylidene-D-xylose (**8**), and the esterification and reduction of the azido function of compound **2**, ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) (Ob 332/1-1 and Ob 332/1-2).

[1] a) E. A. Felnagle, E. E. Jackson, Y. A. M. Podevels, A. D. Berti, M. D. MacMahon, M. G. Thomas, *Mol. Pharmaceutics* **2008**, *5*, 191–211; b) A. Chan, S. A. Sieber, M. A. Marahiel, *Chem. Rev.* **2005**, *105*, 715–738.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[2] For recent examples, see: a) F. von Nussbaum, S. Anlauf, C. Freiberg, J. Benet-Buchholz, J. Schamberger, T. Henkel, G. Schiffer, D. Häbich, *ChemMedChem* **2008**, *3*, 619–626; b) J. Grünewald, S. A. Sieber, C. Mahlert, U. Linne, M. A. Marahiel, *J. Am. Chem. Soc.* **2004**, *126*, 17025–17031.
[3] E. S. Sattely, M. A. Fischbach, C. T. Walsh, *Nat. Prod. Rep.* **2008**, *25*, 757–793.
[4] a) C. Najera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584–4671; b) V. J. Hruby, V. A. Soloshonok, *Tetrahedron* **2001**, *57*, 6329–6650.
[5] a) H. He, R. T. Williamson, B. Shen, E. I. Graziani, H. Y. Yang, S. M. Sakya, P. J. Petersen, G. T. Carter, *J. Am. Chem. Soc.* **2002**, *124*, 9729–9736; b) F. E. Koehn, *J. Med. Chem.* **2008**, *51*, 2613–2617.
[6] B. Haltli, Y. Tan, N. A. Magarvey, M. Wagenaar, X. Yin, M. Greenstein, J. A. Hucul, T. M. Zabriskie, *Chem. Biol.* **2005**, *12*, 1163–1168.
[7] N. A. Magarvey, B. Haltli, M. He, M. Greenstein, J. A. Hucul, *Antimicrob. Agents Chemoth.* **2006**, *50*, 2167–2177.
[8] T.-Z. Wang, K. L. Wheless, A. G. Sutherland, R. G. Dushin, *Heterocycles* **2004**, *62*, 131–135.
[9] Y. Yoshimura, K. Kitano, K. Yamada, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki, A. Matsuda, *J. Org. Chem.* **1997**, *62*, 3140–3152.
[10] T. Fukuyama, A. A. Laird, L. M. Hotchkiss, *Tetrahedron Lett.* **1985**, *26*, 6291–6292.
[11] O. Mitsunobu, *Synthesis* **1981**, *1*, 1–28.
[12] S. Saito, H. Nakajima, M. Inaba, T. Moriwake, *Tetrahedron Lett.* **1989**, *30*, 837–838. It should be noted that the 3-*O*-benzyl ether is stable under these conditions.
[13] For a similar observation, see: P. D. Croucher, R. H. Furneaux, G. P. Lynch, *Tetrahedron* **1994**, *50*, 13200–13312.
[14] When the TBDPS analogue of **12** was subjected to the Mitsunobu reaction conditions (HN_3, DIAD, PPh_3, THF, room temp.), the inversion proceeded in diminished yields.
[15] L. Sanière, L. Leman, J.-J. Bourguignon, P. Dauban, R. H. Dodd, *Tetrahedron* **2004**, *60*, 5889–5897.
[16] M. M. Zhao, J. Li, E. Mano, Z. J. Song, D. M. Tschaen, *Org. Synth.* **2005**, *81*, 195–199.
[17] L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis* (Ed.: M. Fieser), John Wiley & Sons, Inc., New York, **1967**, vol. 1, p. 446.

Received: August 25, 2009
Published Online: October 27, 2009

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim