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Synthetic Approaches toward Glidobamine, the Core Structure of the Glidobactin Antibiotics

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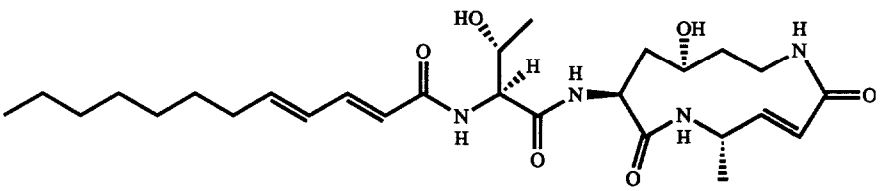
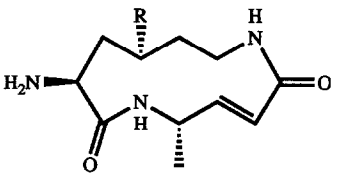
Abstract: *Peptide synthesis method was first employed to synthesize glidobamine, the core structure of the glidobactin antibiotics (2), but in a model study all attempts failed to cyclize the linear precursor 10. Then a N-N bond cleavage method was developed to construct the ring skeleton of glidobamine (2). A new synthetic plan was designed according to this strategy and the two requisite building blocks 19 and 32 were synthesized. Therefore a route to 2 has been laid. In the synthesis of the right-hand side building block (Scheme 6) a trouble of competitive lactonization was encountered This problem was finally solved by using a strong eletron-withdrawing group (31).*

INTRODUCTION

The glidobactin antibiotics as exemplified by glidobactin A (**1**) have been, since 1987, isolated from the bacteria *Polyangium brachysporum* sp. nov. K481-B101 collected in Greece[1] and *Pseudomonas* sp. CB-3 collected in Japan[2]. They are unique acylated cyclic tripeptides with a 12-membered core ring, structurally unrelated to any previously known antibiotics. These antibiotics exhibit broad inhibitory activity against fungi and yeasts, and prolong the life span of mice inoculated with p388 leukemia cells. Glidobactin A (**1**) can be selectively hydrolyzed by enzymes. Upon treatment with papain or ficin, glidobactin A gives the core cyclic amine, glidobamine (**2**) and the acyl-L-threonine residue[1]. The structural novelty of glidobactins exists in glidobamine (**2**), which is a key intermediate for the synthesis of glidobactins and analogs. In continuation of the interest in synthetic methodology of macrocyclic compounds in our laboratory[3], we have chosen glidobamine (**2**) as a synthetic target. In this paper, synthetic approaches toward glidobamine are described.



1 Glidobactin A



2 Glidobamine (R = OH)

3 R = H

RESULTS AND DISCUSSION

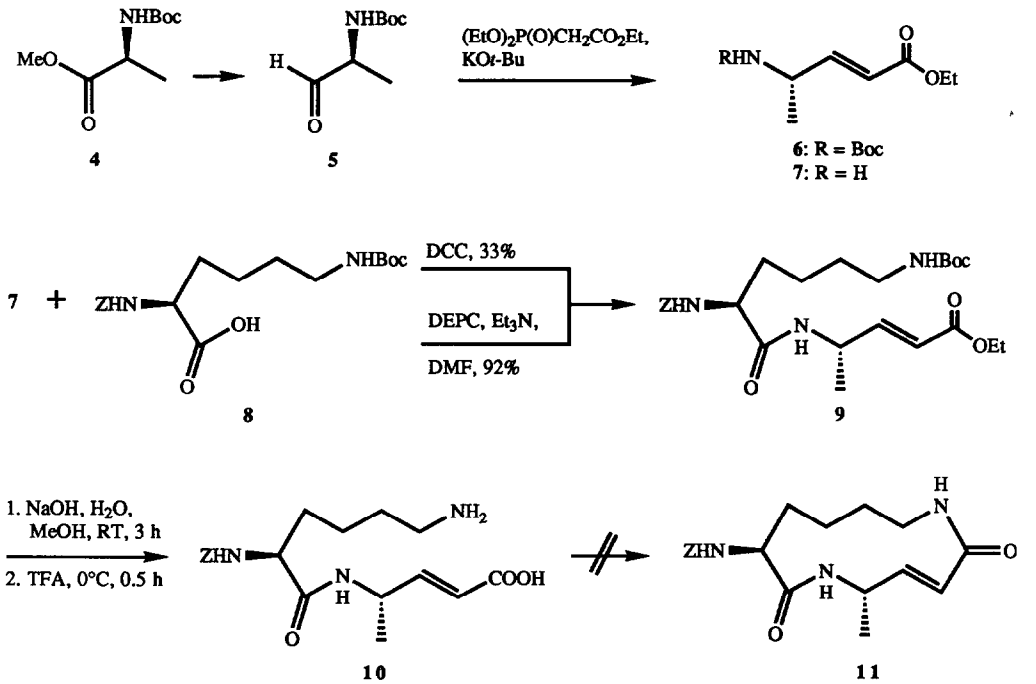
The Peptide Synthesis Approach

Glidobamine (**2**), 8(*S*)-amino-10(*S*)-hydroxy-5(*S*)-methyl-1,6-diaza-3(*E*)-cyclododecene-2,7-dione, is in fact a cyclic dipeptide consisting of *erythro*-γ-hydroxy-L-lysine and 4(*S*)-amino-2(*E*)-pentenoic acid. The most reasonable approach to the synthesis of glidobamine (**2**) would be the peptide synthesis method. Before applied to the target molecule, this strategy was examined for the synthesis of a model molecule, 8(*S*)-amino-5(*S*)-methyl-1,6-diaza-3(*E*)-cyclododecene-2,7-dione (**3**), which lacks only the 10(*S*)-hydroxyl group of glidobamine (**2**).

As shown in Scheme 1, the synthesis started from methyl Boc-L-alaninate (**4**), which was converted to Boc-L-alaninal (**5**) by conventional procedures[4]. *N*-Protected α-amino aldehydes are relatively unstable, particularly in solution[5]. For this reason their elemental analysis and optical rotation measurements should be considered as only approximate. For example, the $[\alpha]_D$ value of Boc-L-alaninal (**5**) was documented from + 1°[6] to + 36°[7]. We subjected aldehyde **5** immediately to the next step of synthesis. Treatment of **5** with the potassium salt of triethyl phosphonoacetate at -78°C afforded the *trans*-α,β-unsaturated ester **6** in 71% overall yield from **4**. No *cis*-isomer was detected from this Wittig-Horner reaction. The unsaturated ester **6** was then deprotected to the free amine **7** by treatment with trifluoroacetic acid (TFA). Then compound **7** was coupled with the free acid *Nε*-Boc-*Nα*-Z-L-lysine (**8**) which was liberated from its dicyclohexylamine salt by washing a suspension of the solid in ethyl acetate with aqueous sodium bisulfate solution[8]. The coupling reaction was first promoted by the most common peptide coupling reagent, *N, N'*-dicyclohexylcarbodiimide (DCC)[9], but the yield of the product **9** was not higher than 33% using several different solvent systems. However, this reaction was achieved in very high yield (92%) using diethylphosphoryl cyanide (DEPC) as coupling reagent[10].

With the linear precursor **9** available, the synthetic stage was set up to ring closure. Compound **9** was hydrolyzed to the corresponding carboxylic acid with 1 N NaOH aqueous solution in MeOH. After workup, the resultant glass was stirred at 0°C with TFA to cleave the Boc group, yielding the free amino

acid **10**. Trace amounts of acid and water were removed azeotropically with methanol and toluene. The resultant glass was dried over P_2O_5 under vacuum prior to use. However, all attempts to effect direct ring closure of **10** to **11** with DCC, DEPC, or diphenylphosphoryl azide (DPPA) proved fruitless under several different conditions at high dilutions. Either the starting material remained intact or a complex mixture was obtained depending on conditions. Some more methods[4] including the use of pentafluorophenyl ester[11] were also tried without success.

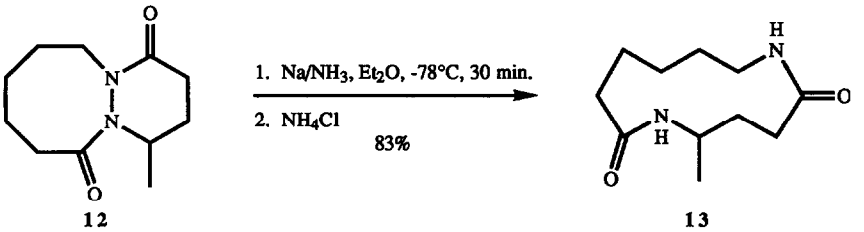


Scheme 1

While we were trying to find other efficient methods to solve this ring closure problem, Oka *et al.*[1c] reported a relay synthesis of glidobactin A (**1**). They opted to close the other lactam bond of the 12-membered core ring. However, the yield for the single step of ring closure was only 2.3%. It has been noted[12] that the presence of bulky substituents on the linear precursor accelerate the macrocyclization. This is akin to the "gem-dimethyl effect"[13], which inspires higher population of reactive rotamers aiding the ring closure. On the other hand, intramolecular hydrogen bonds, when available, can bring the two reacting ends together so that they have more opportunity to interact with each other[14]. In the case of linear precursor **10** the above effects are not available.

The N-N Bond Cleavage Approach

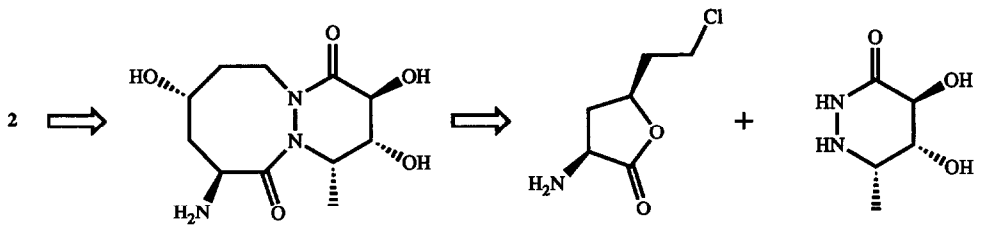
Then we abandoned further efforts on ring closure and successfully developed a N-N bond cleavage approach to the skeleton (**13**) of glidobamine (**2**) (Scheme 2)[15].



12 13

Scheme 2

According to this strategy a retrosynthesis of glidobamine (**2**) could be designed as shown in Scheme 3. Thus, **2** could be obtained by reductive cleavage of the N-N bond of the bicyclic hydrazide **14**. The configuration at the hydroxyl group of **14** is opposite to that of **2**. It could be inverted in a later step of synthesis. Presumably, **14** could be disconnected into **15** (the left-hand side) and **16** (the right-hand side).

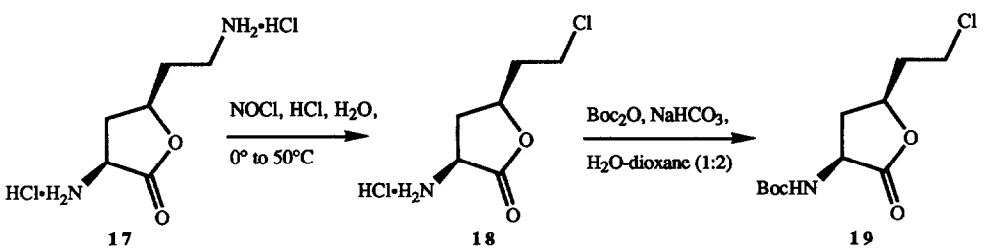


14 15 16

Scheme 3

Synthesis of the Left-Hand Side

As shown in Scheme 4, lactone **17** was prepared according to a known procedure[16]. Selective chlorination of the terminal primary amine of **17** was undertaken by treating it with 1.2 equiv of nitrosyl chloride in hydrochloric acid at 0°, 20°, and 50°C consecutively, each 1 h. Then to protect the amino group, crude **18** was dissolved in a 1:2 mixture of water and dioxane and treated with 1.2 equiv of di-*t*-butyl dicarbonate and 1 equiv of sodium hydrogen carbonate. The product **19** was obtained in 65% yield from **17**.

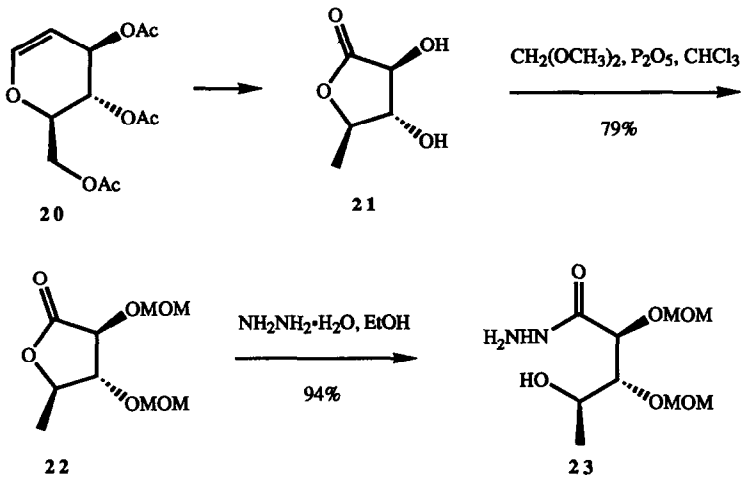


17 18 19

Scheme 4

Synthesis of the Right-Hand Side

The D-Glucal Approach. Presumably, the right-hand side block **16** could be synthesized from 5-deoxy-D-arabinono-1,4-lactone (**21**). Torii *et al.*[17] reported a synthesis of **21** from D-glucal triacetate (**20**). However, the yield of **21** dropped down when the scale was enlarged[4]. As shown in Scheme 5, the hydroxyl groups of **21** were protected as methoxymethyl (MOM) ethers by treatment with an excess of dimethoxymethane in the presence of phosphorus pentoxide in chloroform. Treatment of **22** with hydrazine hydrate afforded the linear hydrazide **23** in high yield. However, we then found that **23** was not easy to cyclize to the corresponding 6-membered hydrazide and we would need a good amount of **21** or an alternative.

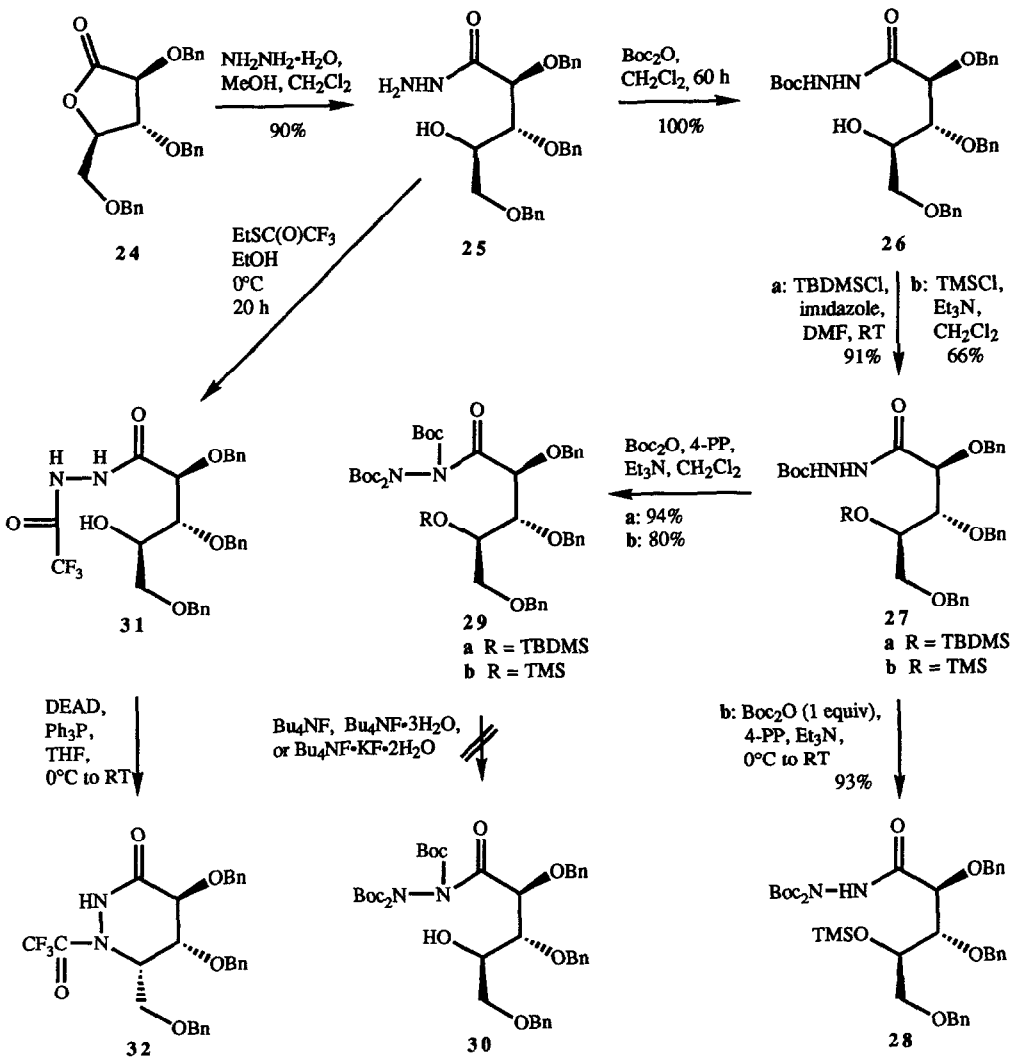


Scheme 5

The D-Arabinose Approach. Lactone **24** (Scheme 6) is easily available from 2,3,5-tri-O-benzyl-D-arabinofuranose[18]. The C-(5) in **24**, corresponding to the methyl group in **2**, could be deoxygenated in a later stage. Treatment of **24** with hydrazine hydrate in a mixture of methanol and dichloromethane at RT afforded hydroxyl hydrazide **25** in 90% yield. Treatment of **25** with di-*t*-butyl dicarbonate at RT for 60 h afforded the monoprotected product **26** quantitatively. Here no base was needed. It is interesting to note that an analogous reaction using benzyl chloroformate or dimethyl dicarbonate, instead of Boc_2O, did not occur. At this stage many methods[4] were tried to bring about the ring closure of **25** and **26** to the corresponding 6-membered cyclic hydrazides. However, lactone **24** was always the major product.

Then, compound **26** was treated with *t*-butyldimethylsilyl (TBDMS) chloride and imidazole in DMF at RT and the protected product **27a** was obtained in 91% yield. Alternatively, **24** was protected as trimethylsilyl ether **27b** in 66% yield by treating with trimethylsilyl chloride and triethylamine. The NH groups of the silyl ethers **27** were fully protected to yield **29** when they were treated with Boc_2O, 4-pyrrolidinopyridine (4-PP), and Et_3N. Again, when Boc_2O was replaced by Ac_2O or *p*-nitrobenzoic chloride the corresponding products could not be accessed. More interestingly, the two NH groups of **27** could be selectively protected. For example, when **27b** was treated with 1 equiv of Boc_2O in the presence of Et_3N and the *N'*, *N'*-di-Boc hydrazide **28**, instead of the *N*, *N'*-di-Boc hydrazide, was obtained in 93% yield. The next step was to deprotect the hydroxyl group of compounds **29**. In fact, we first worked with

29a in which the TBDMS group was rather difficult to remove using different methods[4]. Therefore, we turned our attention to the easy-cleaved TMS ether **29b**. Subjection of **29b** to $Bu_4NF{\cdot}3H_2O$ in THF brought about complete conversion within 15 min. However, the products were complicated. All attempts to purify them failed because they changed spontaneously to lactone **24**. Finally, we tried to use a neutral condition to cleave the TMS group. When **29b** was stirred in MeOH under reflux for 6 h it was completely converted to lactone **24**. Now we realized that the problem was more than the difficulty to remove the TBDMS group. Virtually the problem was still the lactonization.



Scheme 6

In order to get a successful ring closure of hydrazide **25** to the 6-membered cyclic hydrazide an efficient reaction has to be designed to compete with the lactonization. Although we failed the Mitsunobu reaction[19] several times, we still thought that it is a logical means to realize this ring closure. However, for a Mitsunobu reaction to be able to compete with the lactonization, the NH(2) group of **25** has to be made more acidic by introducing an electron-withdrawing substituent on it. Trifluoroacetyl group is a suitable one. *S*-Ethyl trifluorothioacetate has been reported[20] as an efficient and mild acetylating agent and employed in the synthesis of a 5-membered cyclic hydrazide[21]. As shown in Scheme 6, **25** was treated with an excess of *S*-ethyl trifluorothioacetate in ethanol at 0°C. After the solution was stirred for 20 h, TLC indicated that the starting material was almost converted. A competitive reaction was the lactonization. When less *S*-ethyl trifluorothioacetate or higher temperature (RT) was used the yield of the final product was worse. The intermediate **31**, without purification, had to be evaporated and dried at RT using an oil pump. The residue was subjected as soon as possible to a Mitsunobu reaction by treatment with diethyl azodicarboxylate (DEAD) and triphenylphosphine. The long-sought-after 6-membered cyclic hydrazide, 2,3,5-O-tribenzyl-*N'*-trifluoroacetyl-4-deoxy-L-xylono-1,4-hexacyclohydrazide (**32**), was obtained in 34% yield from **25** together with lactone **24** in 48% yield. The lactonization occured mainly in the step of **25** to **31**. Compound **32** was stable and could be left at RT for weeks without any decomposition.

In conclusion, a route toward to glidobamine (**2**) has been laid. The synthesis of **2** is currently under investigation in this laboratory.

EXPERIMENTAL

General Remarks. Melting points (m.p.) were taken on a *Mettler FP5/FP52* melting point apparatus. Optical rotations were measured on a *Perkin-Elmer 241* polarimeter. Infrared (IR) spectra were recorded by using a *Perkin-Elmer 297* infrared spectrometer. Absorption frequencies are reported in wave numbers (cm^{-1}) and calibrated with use of the 1601.4 cm^{-1} absorbance of polystyrene. If not otherwise mentioned chloroform was used as solvent. Proton nuclear magnetic resonace (^{1}H-NMR) spectra were obtained on a *Varian XL-200* (200 MHz), *Bruker AC-300* (300 MHz), or *Bruker AM-400* (400 MHz) spectrometer. If not otherwise mentioned 300 MHz and $CDCl_3$ were used. The spectral data are reported as follows: chemical shifts (δ) in parts per million (ppm) downfield from tetramethylsilane (TMS), multiplicity, coupling constants (*J*) in Hertz (Hz), relative number of protons by integration, and, if appropriate, assignments. Carbon-13 nuclear magnetic resonace (^{13}C-NMR) spectra were obtained on a *Varian XL-200* (50 MHz) spectrometer. If not otherwise mentioned $CDCl_3$ was used as solvent. Multiplicities were determined by the DEPT sequence. The spectral data are reported in a similar way to the ^{1}H-NMR. Mass spectra (MS) were recorded on a *Varian MAT-112S* or *Finnigan MAT-90* mass spectrometer. Ionization was initiated by electron impact (EI) with 70 eV of energy or chemical ionization (CI) utilizing isobutane as carrier gas (if not otherwise mentioned), ionized with 100-150 eV of energy. Data are reported as the mass to charge ratio (m/z) of the observed ion, where $M^{+\cdot}$ refers to the molecular ion, followed by the intensity of the ion relative to the largest (base) peak assigned as 100%. Some peaks are explained if appropriate. Thin-layer chromatography (TLC) was performed on precoated 0.25-mm *silica gel 60 F_{254}* aluminium plates (*Merck*). Column chromatographies were performed with *silica gel 60* (230-400 mesh, *Merck*). Solvents for chromatography were distilled prior to use. All air- and water-sensitive reactions were carried

out under argon. Reagents were purchased from *Fluka*, unless stated otherwise. Solvents for chemical reactions were generally distilled from proper drying agents prior to use: CH_2Cl_2 from CaH_2, THF and toluene from benzophenone ketyl, DMF from P_2O_5, and Et_3N from KOH. In the work-up stage organic solutions were dried over anhydrous $MgSO_4$ and evaporated under a water pump.

*Ethyl 4(*S*)-t-Butyloxycarbonylamino-2(*E*)-pentenoate* (**6**). The crude product **5** obtained[4] from **4** (1.004 g, 4.95 mmol) was directly used in this step. To a solution of triethyl phosphonoacetate (1.32 ml, 6.60 mmol) in THF (25 ml) was added potassium *t*-butoxide (739.3 mg, 6.60 mmol). The resultant solution was stirred at RT for 5 min. and then cooled to - 78°C. The crude oil of **5** in THF (10 ml) was added slowly and the resultant solution was stirred overnight while warming to RT. The mixture was poured into 20% NaCl aqueous solution (40 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The organic phase was dried and evaporated to a yellow oil. Chromatography (CH_2Cl_2/hexane 1:1): **6** (852.5 mg, 71% from **4**, colorless oil). $[\alpha]_D^{22}$ = - 31.4° (*c* = 1.463, MeOH). IR: 3440, 3005, 2980, 2930, 1710, 1660, 1500, 1370, 1275, 1165, 1045. ^{1}H-NMR (200 MHz): 1.27 (*d*, *J* = 7, 3 H, Me), 1.29 (*t*, *J* = 7, 3 H, Me), 1.45 (*s*, 9 H, Boc), 4.20 (*q*, *J* = 7, 2 H, OCH_2), 4.40 (br, *s*, 1 H, H-C(4)), 4.54 (br. *s*, 1 H, NH), 5.90 (*dd*, *J* = 2, 16, 1 H, H-C(2)), 6.58 (*dd*, *J* = 5, 16, 1 H, H-C(3)). ^{13}C-NMR: 14.2 (*q*), 20.3 (*q*), 28.3 (3 *q*), 47.0 (*d*), 60.4 (*t*), 79.7 (*s*), 120.1 (*d*), 149.3 (*d*), 154.8 (*s*), 166.3 (*s*). CI-MS: 244 (8, $[M + 1]^+$), 188 (100), 145 (17), 144 (48), 57 (94), 43 (24). Anal. calc. for $C_{21}H_{21}NO_4$ (243.317): C 59.24, H 8.71, N 5.76; found: C 58.06, H 8.65, N 6.03.

Ethyl N_α*-Benzyloxycarbonyl-*N_ε*-(t-butyloxycarbonyl)-*L*-lysyl-4(*S*)-amino-2(*E*)-penten-oate* (**9**). N_α-Benzyloxycarbonyl-N_ε-(*t*-butyloxycarbonyl)-L-lysine dicyclohexylamine salt (131.8 mg, 0.235 mmol) was distributed between EtOAc (20 ml) and 2 M aqueous $NaHSO_4$ solution (10 ml). The aqueous layer was discarded and the EtOAc solution was once again extracted with 2 M $NaHSO_4$ solution (10 ml), washed with 20% NaCl aqueous solution (3 x 10 ml), dried, and concentrated to a colorless oil, which was dried over P_2O_5 under vacuum for 2 h prior to use. Compound **6** (57.0 mg, 0.235 mmol) was dissolved in TFA (1 ml) and stirred at 0°C for 0.5 h. The solution was concentrated. Trace amounts of acid and water were removed azeotropically with EtOH and toluene. The resultant colorless oil, **7**, was dried over P_2O_5 under vacuum for 2 h prior to use. To a 0°C solution of the two oils obtained above in DMF (2 ml) was added DEPC (95%, 37.5 ml, 0.282 mmol) in DMF (0.5 ml), followed by Et_3N (65.4 ml). The resultant solution was stirred for 24 h, during which time the ice/water bath was allowed to warm to RT. The reaction mixture was diluted with CH_2Cl_2 (100 ml) and washed with H_2O, 2 M $NaHSO_4$ solution, and 20% NaCl solution (each 50 ml). Then it was dried and concentrated to a colorless oil. Chromatography (CH_2Cl_2/EtOAc 5:1): **9** (109.4 mg, 92%, colorless oil). Alternatively, when the above reaction was run with DCC, instead of DEPC, as coupling reagent, **9** was obtained in low yield (33%). M.p. 86.5-88.5°C. $[\alpha]_D^{22}$ = - 15.4° (*c* = 0.32, MeOH). IR: 3450 (sh), 3430, 3005, 2980, 2930, 1710 (br.), 1510, 1505 (sh), 1370, 1240, 1165. ^{1}H-NMR (200 MHz): 1.26 (*d*, *J* = 7, 3 H, Me), 1.28 (*t*, *J* = 7, 3 H, Me), 1.42 (*s*, 9 H, Boc), 1.48 (*m*, 2 H), 1.72 (*m*, 2 H), 1.85 (*m*, 2 H), 3.05-3.15 (*m*, 2 H), 4.07-4.20 (*m*, 1 H), 4.19 (*q*, *J* = 7, 2 H), 4.60-4.75 (*m*, 2 H), 5.11 (*d*, *J* = 3, 2 H), 5.44-5.50 (*m*, 1 H, NH), 5.88 (*dd*, *J* = 2, 16, 1 H), 6.37-6.40 (*m*, 1 H, NH), 6.85 (*dd*, *J* = 5, 16, 1 H), 7.35 (br. *s*, 5 arom. H). ^{13}C-NMR: 14.2 (*q*), 19.8 (*q*), 22.5 (*t*), 28.4 (3 *q*), 29.5 (*t*), 32.1 (*t*), 39.8 (*t*), 45.6 (*d*), 54.8 (*d*), 60.5 (*t*), 67.0 (*t*), 79.1 (*s*), 120.5 (*d*), 128.0 (2 *d*), 128.1 (*d*), 128.5 (2 *d*), 136.1 (*s*), 148.5 (*d*), 156.2 (*s*), 156.4 (*s*), 166.2 (*s*), 171.3 (*s*).

CI-MS: 506 (68, $[M + 1]^+$), 451 (11), 450 (51), 407 (23), 406 (100), 298 (28), 57 (75), 43 (24). Anal. calc. for $C_{26}H_{39}N_3O_7$ (505.638): C 61.76, H 7.78, N 8.31; found: C 61.49, H 7.90, N 8.31.

2(S)-t-Butyloxycarbonylamino-6-chloro-4(R)-hydroxyhexanolide (**19**). Compound **17**[4,16] (112.2 mg, 0.622 mmol) was dissolved in 32% HCl solution (5 ml) and cooled to 0°C. A solution of NOCl, prepared by addition of $AgNO_2$ (114.9 mg, 1.2 equiv) to 1 N HCl (3 ml) at 0°C and filtration from AgCl, was added slowly. The resultant solution was stirred consecutively at 0°, 20°, and 50°C, each for 1 h, respectively. Then it was evaporated to an oil, which contained mainly *2(S)-amino-6-chloro-4(R)-hydroxyhexan-4-olide hydrochloride* (**18**). IR (film): 3380 (br.), 3120, 2990 (br.), 1770 (γ-lactone), 1600, 1500, 1200, 1000, 940. This oil was dissolved in a mixture of H_2O (5 ml) and dioxane (10 ml). $(Boc)_2O$ (162.7 mg, 1.2 equiv) and $NaHCO_3$ (53.0 mg, 1.0 equiv) were added. The resultant solution was stirred at RT overnight, poured into 20% NaCl solution, and extracted several times with ether. The combined ether phase was dried and evaporated to an oil. Chromatography (hexane/EtOAc 3:1): **19** (107.0 mg, 65% from **17**, colorless oil). $[\alpha]_D^{22} = +28.1°$ (c = 0.370, $CHCl_3$). IR: 3455, 3005, 2990, 2965, 1785 (γ-lactone), 1710 (Boc), 1505 (NH), 1270 (sh), 1250, 1165, 1045. ^{1}H-NMR: 1.44 (*s*, 9 H, Boc), 1.81-1.91 (*m*, 1 H), 1.92-1.99 (*m*, 1 H), 2.35 (*ddd*, J = 7, 9, 15, 1 H,), 2.57 (*ddd*, J = 2, 6, 15, 1 H), 3.26-3.33 (*m*, 2 H, H-C(6)), 4.42 (*dd*, J = 2, 7, 1 H, H-C(2)), 4.77-4.85 (*m*, 2 H, H-C(4), NH). ^{13}C-NMR: 29.0 (*q*), 36.2, 38.0, 39.9 (3*t*), 53.1, 79.4 (2 *d*), 80.4, 158.6, 174.3 (3 *s*). CI-MS: 264 (3, $[M + 1]^+$), 210, 208 (33, 100, $[M - C_4H_8 + 1]^+$), 172 (18), 148 (40), 103 (21), 99 (20). Anal. calc. for $C_{11}H_{18}ClNO_4$ (263.721): C 50.10, H 6.88, N 5.31, Cl 13.44; found: C 50.09, H 7.03, N 5.03, Cl 13.48.

*5-Deoxy-2,3-bis-*O*-methoxymethyl-*D*-arabinono-1,4-lactone* (**22**). To a solution of **21**[4,17] (35.6 mg, 0.270 mmol) in chloroform (dried over P_2O_5, 2 ml) were added dimethoxymethane (distilled prior to use, 2 ml) and P_2O_5 (*ca.* 1 g). After stirred at RT for 1 h, the mixture was poured into ice-cooled dilute $NaHCO_3$ solution and extracted several times with ether. The ether phase was washed with H_2O, dried, and evaporated to a colorless oil which solidified upon standing (48.8 mg, 79%). M.p. 44-45°C. IR: 2985, 2960, 2935, 2900, 1790 (γ-lactone), 1445, 1385, 1320, 1240, 1185, 1150, 1125, 1070 1050, 1030, 980, 950, 920. ^{1}H-NMR (CD_3OD): 1.50 (*d*, J = 6, 3 H, H-C(5)), 3.40 (*s*, 3 H, OMe), 3.45 (*s*, 3 H, OMe), 4.00 (*dd*, J = 7, 7.5, 1 H, H-C(3)), 4.32 (*dq*, J = 6, 7, 1 H, H-C(4)), 4.49 (*d*, J = 7.5, 1 H, H-C(2)), 4.70, 4.76, 4.82, 5.06 (each *d*, J =7, 1 H, OCH_2O). CI-MS: 221 (13, $[M + 1]^+$), 189 (100, $[M - MeOH + 1]^+$).

*5-Deoxy-2,3-bis-*O*-methoxymethyl-*D*-arabinonohydrazide* (**23**). To a solution of **22** (11.2 mg, 0.051 mmol) in EtOH (5 ml) was added hydrazine hydrate (24.4 mg, 1 equiv) and the resultant solution was stirred under reflux for 2 h. It was evaporated to an oil which was dissolved in CH_2Cl_2, dried, and evaporated to dryness. Chromatography (CH_2Cl_2/EtOAc 20:1): **23** (12.1 mg, 94%, colorless slush). $[\alpha]_D^{22} = -36.7°$ (c = 0.813, $CHCl_3$). IR: 3440 (OH), 3005, 1680 (C=O), 1625, 1235, 1200, 1150, 1100, 1025, 925. ^{1}H-NMR (CD_3OD): 1.32 (*d*, J = 6, 3 H, H-C(5)), 2.86 (br. *s*, OH), 3.39 (*s*, 3 H, OMe), 3.46 (*s*, 3 H, OMe), 3.79 (*dd*, J = 3, 7, 1 H, H-C(3)), 3.91 (br. *m*, 3 H, H-C(4), NH_2), 4.47 (*d*, J = 3, 1 H, H-C(2)), 4.65 (*s*, 2 H, OCH_2O), 4.75, 4.76 (each *d*, J = 7, 1 H, OCH_2O), 7.76 (br. *s*, 1 H, NH). ^{13}C-NMR: 19.5 (*q*), 56.0 (*q*), 56.5 (*q*), 66.5 (*d*), 77.4 (*d*), 83.3 (*d*), 97.4, 97.9 (2 *t*), 171.2 (*s*). CI-MS: 253 (100, $[M + 1]^+$), 235 (11, $[M - H_2O + 1]^+$), 221 (13, $[M - N_2H_4 + 1]^+$). Anal. calc. for $C_9H_{20}N_2O_6$ (252.268): C 42.58, H 7.99, N 11.10; found: C 42.97, H 7.94, N 10.99.

2,3,5-Tri-O-benzyl-D-arabinonohydrazide (**25**). To a solution of *2,3,5-Tri-O-benzyl-D-arabinono-1,4-lactone*[18] (2.634 g, 6.294 mmol) in MeOH (50 ml) and CH_2Cl_2 (20 ml) was added hydrazine hydrate (0.34 ml, 1.1 equiv). The resultant solution was stirred at RT for 2 h. It was concentrated to an oil, dissolved in EtOAc, dried, and evaporated again to an oil. Crystallization (hexane/EtOAc): **25** (2.552 g, 90%, colorless solid). M.p. 85.5-86.5°C. $[\alpha]_D^{22} = +2.5°$ (*c* = 1.197, $CHCl_3$). IR: 3440, 3330, 3005, 2920, 2870, 1675 (C=O), 1625, 1495, 1445, 1395, 1340, 1240, 1090 (sh), 1070, 785, 725. ^{1}H-NMR: 2.46 (*d, J* =7, 1 H, disappeared on addition of D_2O, OH), 3.59 (*dd, J* = 4, 9, 1 H, H-C(5)), 3.65 (*dd, J* = 3, 9, 1 H, H-C(5)), 3.70 (br, *d, J* = 4, 2 H, NH_2), 3.89-3.96 (*m*, 1 H, H-C(4)), 3.99 (*dd, J* = 2, 9, 1 H, H-C(3)), 4.39 (*d, J* = 2, 1 H, H-C(2)), 4.42 (*s*, 2 H, OC*H*$_2$Ph), 4.48 (*d, J* = 12, 1 H, OC*H*$_2$Ph), 4.53 (*d, J* = 12, 1 H, OC*H*$_2$Ph), 4.59 (*d, J* = 11, 1H, OC*H*$_2$Ph), 4.64 (*d, J* = 11, 1 H, OC*H*$_2$Ph), 7.16-7.19 (*m*, 3 arom. H), 7.27-7.36 (*m*, 12 arom. H), 7.76 (br. *s*, 1 H, disappeared upon addition of D_2O, NH). ^{13}C-NMR: 69.1 (*d*), 70.4, 73.4, 74.5, 74.6 (4 *t*), 79.2, 79.9 (2 *d*), 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6 (15 *d*), 136.7, 137.6, 137.7, 171.7 (4 *s*). CI-MS: 451 (38, $[M + 1]^+$), 327 (23), 271 (26), 239 (34), 181 (100), 91 (41). Anal. calc. for $C_{26}H_{30}N_2O_5$ (450.533): C 69.31, H 6.71, N 6.22; found: C 69.14, H 6.86, N 6.07.

2,3,5-Tri-O-benzyl-N′-t-butyloxycarbonyl-D-arabinonohydrazide (**26**). To a solution of **25** (15.74 g, 34.94 mmol) in CH_2Cl_2 (400 ml) was added Boc_2O (15.3 g, 2 equiv). The resultant solution was stirred at RT for 60 h. It was concentrated to a syrup. Chromatography (hexane/EtOAc 5:2): **26** (19.23 g, 100%, colorless syrup). $[\alpha]_D^{22} = -11.5°$ (*c* = 0.810, $CHCl_3$). IR: 3420, 3005, 2990, 2940, 2875, 1740, 1700, 1500, 1480, 1455, 1395, 1375, 1240, 1160, 1100, 1075, 1030. ^{1}H-NMR: 1.49 (*s*, 9 H, Boc), 3.59 (*dd, J* = 4, 10, 1 H, H-C(5)), 3.64 (*dd, J* = 3, 10, 1 H, H-C(5)), 3.91-4.10 (*m*, 2 H), 4.428 (*d, J* = 2, 1 H, H-C(2)), 4.43 (*d, J* = 11, 1 H, OC*H*$_2$Ph), 4.50 (*d, J* = 4, 2 H, OC*H*$_2$Ph), 4.59 (*d, J* = 11, 1, OC*H*$_2$Ph), 4.63 (*d, J* = 11, 1 H, OC*H*$_2$Ph), 4.77 (*d, J* = 11, 1 H, OC*H*$_2$Ph), 6.23 (br. *s*, 1 H, NH), 7.20-7.25 (*m*, 3 arom. H), 7.29-7.38 (*m*, 12 arom. H), 8.27 (*d, J* = 1, 1 H, NH). ^{13}C-NMR: 28.1 (3 *q*), 69.1 (*d*), 70.4, 73.3, 74.2, 74.4 (4 *t*), 79.1, 79.7 (2*d*), 81.7 (*s*), 127.7, 127.8, 127.9, 128.2, 128.24, 128.4, 128.5, 128.53, (15 *d*), 136.7, 137.6, 137.7, 154.8, 170.5 (5 *s*). CI-MS: 551 (93, $[M + 1]^+$), 451 (16), 419 (20), 369 (19), 344 (20), 343 (70), 317 (77), 291 (52), 265 (20), 239 (19), 191 (17), 185 (63), 159 (69), 133 (100), 129 (47), 103 (52), 76 (62). Anal. calc. for $C_{31}H_{38}N_2O_7$ (550.650): C 67.62, H 6.96, N 5.09; found: C 67.62, H 7.20, N 4.86.

2,3,5-Tri-O-benzyl-4-O-t-butyldimethylsilyl-N′-t-butyloxycarbonyl-D-arabinonohydrazide (**27a**). To a solution of **26** (4.51 g, 8.19 mmol) and imidazole (1.40 g, 2.5 equiv) in DMF (30 ml) was added *t*-butyldimethylsilyl chloride (1.48 g, 1.2 equiv). The resultant solution was stirred at RT for 24 h. Then ether (300 ml) was added and the solution was washed twice with H_2O, dried, and evaporated to a syrup. Chromatography (hexane/EtOAc 5:1): **27a** (4.97 g, 91%, colorless syrup). $[\alpha]_D^{22} = -19.1°$ (*c* = 1.000, $CHCl_3$). IR: 3420, 3005, 2985, 2960, 2930, 2860, 1730, 1705, 1495, 1470, 1455, 1370, 1250, 1160, 1110, 1095, 1070, 1045, 835. ^{1}H-NMR: 0.06 (*s*, 3 H, SiMe), 0.89 (*s*, 3 H, SiMe), 0.89 (*s*, 9 H, *t*-BuSi), 1.47 (*s*, 9 H, Boc), 3.63 (*dd, J* = 4, 10, 1 H, H-C(5)), 3.78 (*dd, J* = 3, 10, 1 H, H-C(5)), 3.99 (*dd, J* = 3, 7, 1 H, H-C(3)), 4.14-4.20 (*m*, 1 H, H-C(4)), 4.32 (*d, J* = 3, 1 H, H-C(2)), 4.49 (*s*, 2 H, OC*H*$_2$Ph), 4.55 (*d, J* = 11, 2 H, OC*H*$_2$Ph), 4.63 (*d, J* = 11, 1 H, OC*H*$_2$Ph), 4.75 (*d, J* = 11, 1 H, OC*H*$_2$Ph), 6.10 (br. *s*, 2 H, NH_2), 7.21-7.24 (*m*, 3 arom. H), 7.27-7.39 (*m*, 12 arom. H), 8.08 (br. *s*, 1 H, NH). ^{13}C-NMR: -4.8 (*q*), -4.1 (*q*), 18.1 (*s*), 25.9 (3 *q*), 28.1 (3 *q*), 71.3 (*t*), 71.5 (*d*), 73.2 (*t*), 73.5

(*t*), 75.2 (*t*), 79.7 (*d*), 81.6 (*s*), 81.8 (*d*), 127.5, 127.56, 127.7, 127.75, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4 (15 *d*), 136.9, 137.0, 138.3, 154.8, 170.5 (5 *s*). CI-MS: 665 (100, $[M + 1]^+$), 609 (31), 551 (10), 436 (22), 327 (13), 271 (14), 239 (18), 181 (63), 91 (52). Anal. calc. for $C_{37}H_{52}N_2O_7Si$ (664.913): C 66.84, H 7.88, N 4.21; found: C 66.53, H 7.76, N 4.37.

2,3,5-Tri-O-*benzyl*-N′-t-*butyloxycarbonyl-4*-O-*trimethylsilyl*-D-*arabinonohydrazide* (**27b**). To a solution of **26** (1.16 g, 2.11 mmol) and Et_3N (1.5 ml) in CH_2Cl_2 (15 ml) was added Me_3SiCl (0.60 ml, 2.2 equiv) and the resultant solution was stirred at RT for 24 h. It was poured into CH_2Cl_2 (150 ml), washed with saturated $NaHCO_3$ solution and H_2O, dried, and evaporated to a syrup. Chromatography (hexane/EtOAc 8:1): **27b** (867.3 mg, 66%, colorless syrup). $[\alpha]_D^{22} = -13.8°$ (*c* = 1.040, $CHCl_3$). IR: 3420, 3005, 2990, 2960, 2930, 2870, 1745, 1700, 1480, 1470, 1455, 1390, 1370, 1335, 1250, 1160, 1115, 1090, 1070, 1030, 845. ^{1}H-NMR: 0.10 (*s*, 9 H, OTMS), 1.47 (*s*, 9 H, Boc), 3.56 (*dd*, *J* = 5, 10, 1 H, H-C(5)), 3.69 (*dd*, *J* = 3, 10, 1 H, H-C(5)), 3.97 (*dd*, *J* = 2.5, 8, 1 H, H-C(3)), 4.12-4.15 (*m*, 1 H, H-C(4)), 4.38 (*d*, *J* = 2.5, 1 H, H-C(2)), 4.50 (*s*, 4 H, OC*H*$_2$Ph), 4.56 (*d*, *J* = 11, 1 H, OC*H*$_2$Ph), 4.75 (*d*, *J* = 11, 1 H, OCH$_2$Ph), 6.12 (br. *s*, 2 H, NH_2), 7.17-7.21 (*m*, 3 arom. H), 7.27-7.40 (*m*, 12 arom. H), 8.14 (br. *d*, *J* = 3, 1 H, NH). ^{13}C-NMR: 0.6 (3 *q*), 28.1 (3 *q*), 71.2 (*d*), 71.4 (*t*), 73.3 (*t*), 74.0 (*t*), 74.9 (*t*), 79.5 (*d*), 80.8 (*d*), 81.7 (*s*), 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.23, 128.3, 128.4, 128.5 (15*d*), 136.9, 137.9, 138.0, 154.8, 170.8 (5 *s*). CI-MS: 623 (93, $[M + 1]^+$), 91 (100), 77 (21). Anal. calc. for $C_{34}H_{46}N_2O_7Si$ (622.832): C 65.57, H 7.44, N 4.50; found: C 65.71, H 7.47, N 4.60.

2,3,5-Tri-O-*benzyl*-N′,N′-*bis*-t-*butyloxycarbonyl-4*-O-*trimethylsilyl*-D-*arabinonohydrazide* (**28**). To a solution of **27b** (265.5 mg, 0.427 mmol) in CH_2Cl_2 (20 ml) cooled to 0°C were added Boc_2O (91.2 mg, 1 equiv), Et_3N (43.1 mg, 1 equiv), and 4-PP (6.3 mg, 0.1 equiv) consecutively. The resultant solution was stirred for 48 h while the cooling bath was allowed to warm up to RT. CH_2Cl_2 (20 ml) was added and the solution was washed with saturated $NaHCO_3$ solution and H_2O, dried, and evaporated to a syrup. Chromatography (hexane/EtOAc 10:1): **28** (285.3 mg, 93%, colorless syrup). IR: 3410, 3070 (sh), 3030 (sh), 3005, 2990, 2960 (sh), 2940, 2910, 2870, 1760, 1730, 1500, 1480, 1455, 1390, 1370, 1340, 1270 (sh), 1255, 1150, 1125, 1075, 1050, 1030, 850, 790, 730. ^{1}H-NMR: 0.00 (*s*, 9 H, OTMS), 1.41 (*s*, 18 H, 2 Boc), 3.40 (*dd*, *J* = 5, 10, 1 H, H-C(5)), 3.62 (*dd*, *J* = 3, 10, 1 H, H-C(5)), 3.88 (*dd*, *J* = 3, 7, 1 H, H-C(3)), 4.07-4.12 (*m*, 1 H, H-C(4)), 4.33 (*d*, *J* = 3, 1 H, H-C(2)), 4.36 (*s*, 2 H, OCH$_2$Ph), 4.42, 4.45, 4.74, 4.78 (4 *d*, each *J* = 14, 1 H, OC*H*$_2$Ph), 7.12-7.31 (*m*, 15 arom. H), 8.36 (*s*, 1 H, NH). ^{13}C-NMR: 0.3 (3 *q*), 27.7 (6 *q*), 70.9 (*d*), 71.3, 72.9, 73.4, 74.3 (4 *t*), 79.3 (*d*), 80.4 (*d*), 83.6 (2 *s*), 127.1, 127.3, 127.4, 127.5, 127.7, 127.8, 128.00, 128.04, 128.2 (15 *d*), 137.0, 137.7, 138.3 (3 *s*), 150.3 (2 *s*), 169.9 (*s*). CI-MS: 723 (8, $[M + 1]^+$), 695 (14), 623 (75), 613 (10), 567 (100), 523 (77), 477 (16), 433 (10), 181 (21).

2,3,5-Tri-O-*benzyl-4*-O-t-*butyldimethylsilyl*-N, N′, N′-*tris*-t-*butyloxycarbonyl*-D-*arabinono-hydrazide* (**29a**). To a solution of **27a** (4.69 g, 7.063 mmol) in CH_2Cl_2 (50 ml) were added Boc_2O (3.08 g, 2 equiv), 4-PP (1.05 g, 1.2 equiv), and Et_3N (1 ml) at RT. The resultant solution was stirred for 24 h. Then ether (100 ml) was added and the solution was washed with 5 % citric acid, saturated $NaHCO_3$, and H_2O, dried, and evaporated to a syrup. Chromatography (hexane/EtOAc 5:1): **29a** (5.03 g, 94%, colorless syrup). $[\alpha]_D^{22} = +6.4°$ (*c* = 1.020, $CHCl_3$). IR: 3005, 2985, 2960, 2930, 2890, 2860, 1755, 1740, 1455, 1395, 1370, 1280, 1255, 1150, 1120, 1085, 1030, 840. ^{1}H-NMR: 0.04 (*s*, 3 H, SiMe), 0.06 (*s*, 3 H, SiMe), 0.90 (*s*, 9 H, *t*-BuSi), 1.43 (*s*, 9 H, Boc), 1.49 (*s*, 9 H, Boc), 1.50 (*s*, 9 H, Boc), 3.61 (*dd*, *J*

= 4, 10, 1 H, H-C(5)), 3.79 (br. *d*, *J* = 10, 1 H, H-C(5)), 4.18-4.19 (*m*, 2 H, H-C(3), H-C(4)), 4.41 (*d*, *J* = 11, 1 H, OC*H*$_2$Ph), 4.47 (*d*, *J* = 3, 2 H, OC*H*$_2$Ph), 4.63 (*s*, 2 H, OC*H*$_2$Ph), 4.70 (*d*, *J* = 11, 1 H, OC*H*$_2$Ph), 5.43 (br. *s*, 1 H, H-C(2)), 7.19-7.39 (*m*, 15 arom. H). ^{13}C-NMR: - 5.0 (*q*), - 4.1 (*q*), 18.1 (*s*), 25.9 (3 *q*), 27.76 (3 *q*), 27.8 (3 *q*), 27.9 (3 *q*), 72.2 (*t*), 72.4 (*d*), 72.5 (*t*), 73.1 (*t*), 74.4 (*t*), 78.9 (*d*), 81.2 (*d*), 84.0 (*s*), 84.2 (*s*), 84.5 (*s*), 127.1, 127.15, 127.4, 127.6, 127.7, 127.9, 128.0, 128.1 (15 *d*), 138.0 (*s*), 138.8 (2*s*), 149.2, 149.5, 150.5 (3*s*), 170.2 (*s*). CI-MS: 865.7 (0.24, [*M* + 1]$^+$), 665 (72), 609 (37), 565 (63), 507 (13), 181 (13), 91 (100). Anal. calc. for $C_{68}H_{52}N_2O_{11}Si$ (865.147): C 65.25, H 7.92, N 3.24; found: C 64.26, H 7.72, N 3.15.

2,3,5-Tri-O-*benzyl*-N, N′, N′-*tris*-t-*butyloxycarbonyl*-*4*-O-*trimethylsilyl*-D-*arabinono-hydrazide* (**29b**). To a solution of **27b** (552.6 mg, 0.835 mmol) and Et_3N (2 ml) in CH_2Cl_2 (15 ml) were added Boc_2O (727.9 mg, 4 equiv) and 4-PP (247.1 mg, 1.2 equiv). The resultant solution was stirred at RT for 20 h. Then it was washed with 20 % NaCl solution (2 x 20 ml) and H_2O (2 x 20 ml), dried, and evaporated to a syrup. Chromatography (hexane/EtOAc 15:1): **29b** (578.0 mg, 80%, colorless syrup). $[\alpha]_D^{22}$ = + 5.3° (*c* = 0.750, $CHCl_3$). IR: 2985, 2930, 2860, 1755, 1730 (sh), 1455, 1395, 1370, 1290, 1255, 1145, 845. ^{1}H-NMR: 0.08 (*s*, 9 H, OTMS), 1.47 (*s*, 9 H, Boc), 1.50 (*s*, 9 H, Boc), 1.51 (*s*, 9 H, Boc), 3.53 (*dd*, *J* = 6, 10, 1 H, H-C(5)), 3.71 (*dd*, *J* = 3, 10, 1 H, H-C(5)), 4.11 (*dd*, *J* = 2.5, 7, 1 H, H-C(3)), 4.19 (*dt*, *J* = 3, 6, 1 H, H-C(4)), 4.39 (*d*, *J* = 11, 1 H, OC*H*$_2$Ph), 4.47 (*s*, 2 H, OC*H*$_2$Ph), 4.55, 4.61, 4.70 (3 *d*, each *J* = 11, 1 H, OC*H*$_2$Ph), 5.38 (*d*, *J* = 2.5, 1 H, H-C(2)), 7.19-7.32 (*m*, 13 arom. H), 7.34-7.42 (*m*, 2 arom. H). ^{13}C-NMR: 0.2 (3 *q*), 27.4 (3 *q*), 27.49 (3 *q*), 27.52 (3 *q*), 71.4 (*d*), 71.8 (*t*), 72.2 (*t*), 72.8 (*t*), 73.7 (*t*), 78.2 (*d*), 80.0 (*d*), 83.7 (*s*), 83.8 (*s*), 84.3 (*s*), 126.8-128.1 (15 *d*), 137.5 (*s*), 138.1 (2 *s*), 149.0 (*s*), 149.4 (*s*), 150.1 (*s*), 170.1 (*s*). CI-MS: 823 (6, [*M* + 1]$^+$), 723 (13), 623 (100, [*M* - 2 Boc + 1]$^+$), 567 (80), 523 (67), 508 (12), 239 (13), 181 (32). Anal. calc. for $C_{44}H_{62}N_2O_{11}Si$ (823.069): C 62.21, H 7.58, N 3.40; found: C 61.47, H 7.14, N 3.21.

2,3,5-O-*Tribenzyl*-N'-*trifluoroacetyl*-*4*-*deoxy*-L-*xylono*-*1,4*-*hexacyclohydrazide* (**32**). To a solution of **25** (817.9 mg, 1.816 mmol) in EtOH (20 ml) cooled to 0°C was added $CF_3C(O)SEt$ (2.65 ml, 20.9 mmol) and the resultant solution was stirred at 0°C for 20 h. TLC indicated that the starting material was almost completely converted. The mixture was evaporated and dried over oil pump at RT. Then the residue was dissolved in anhydrous THF (20 ml) and cooled to 0°C. Ph_3P (475.8 mg, 1 equiv) and DEAD (0.287 ml, 1 equiv) were added. The resultant solution was stirred for 24 h while warming to RT. Ph_3P and DEAD (each 1 equiv) were added again and the solution was stirred at RT for another 24 h and evaporated to a slightly yellow oil. Chromatography (hexane/EtOAc 12:1, then 10:1): **24** (393.5 mg, 48%) and **32** (213.6 mg, 34%, colorless syrup). $[\alpha]_D^{22}$ = - 6.3° (*c* = 0.887, $CHCl_3$). IR: 3380 (NH), 2960, 2930, 2870, 2855, 1735 ($CF_3C(O)N$), 1685 (C(O)N), 1530, 1495, 1465, 1455, 1375, 1250, 1160, 1095, 1075 (sh), 1060, 1030, 895. ^{1}H-NMR: 3.70 (*dd*, *J* = 4, 11, 1 H, H-C(5)), 3.78 (*dd*, *J* = 4.5, 11, 1 H, H-C(5)), 4.06 (*dd*, *J* = 2, 4, 1 H, H-C(3)), 4.33 (*d*, *J* = 12, 1 H, OC*H*$_2$Ph), 4.41 (*d*, *J* = 1, 1 H, H-C(2)), 4.46-4.56 (*m*, 4 H), 4.77 (*d*, *J* = 12, 1 H, OC*H*$_2$Ph), 4.89 (*dt*, *J* =4, 7, 1H, H-C(4)), 7.12-7.31 (*m*, 15 arom. H), 9.10 (br. *s*, 1H, NH). NOE (400 MHz): When δ9.10 was irradiated no NOE was observed. ^{13}C-NMR: 67.0, 71.4, 72.1, 73.3 (4 *t*), 77.6, 79.6, 85.0 (3 *d*), (107.0, 112.7, 118.5, 124.2) (*q*, $^1J_{C,F}$ = 288, *C*F_3), 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, (15 *d*, 15 arom. CH), 136.3, 136.6, 137.2 (3 *s*), (152.3, 153.0) (*d*, $^2J_{C,F}$ = 37, *C*(O)CF_3), 157.6 (*s*). CI-MS: 529 (100, [*M* + 1]$^+$), 447 (11), 391 (24), 374 (25), 313 (19).

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