Liposidomycins − Synthetic Studies Towards the Ribosyldiazepanone Moiety

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A synthesis of the enantiopure 2-ribosyl-1,4-diazepan-3-one core of liposidomycins, a class of complex lipid nucleoside antibiotics, according to a flexible asymmetric synthesis strategy is described. It involves two building blocks, an enantiopure α-azido-β,γ-epoxybutanol readily available from L-ascorbic acid, and an α-ribosylamino acid obtained from D-ribose. Subsequent cyclization by regiospecific nucleophilic opening of the epoxide by the amino acid followed by peptidic coupling affords the target ribosyl diazepanone.

Introduction

Liposidomycins are nucleoside antibiotics isolated from *Streptomyces griseosporeus*[1] that are involved in the inhibition of bacterian peptidoglycan synthesis.[2] Based on chemical degradations,[3] it has been shown that these molecules are characterized by a 5′-substituted uridine, a 5-amino-5-deoxyribose, and a disubstituted 1,4-diazepan-3-one moiety (Figure 1). Several members of this family are known, which differ mainly in the nature of their lipid side chain and in the presence or absence of a sulfate on the sugar. Because of the great structural complexity of these antibiotics, only a few approaches have been developed for their synthesis[4] and the absolute configuration at the chiral centers (C-5, C-2′, C-5′, C-6′) remains hypothetical. However, recent work[5] related to the synthesis of a simplified molecule, which may represent the minimum structure responsible for the activity of tunicamycins, liposidomycins, and mureidomycins towards translocase (MraY), has demonstrated improved activity of the (5*S*) compared to the (5*R*) derivative. This observation is in agreement with the (5*S*,2′*S*) absolute configuration suggested by Ubukata et al.[4a] on the basis of NMR-spectroscopic data.

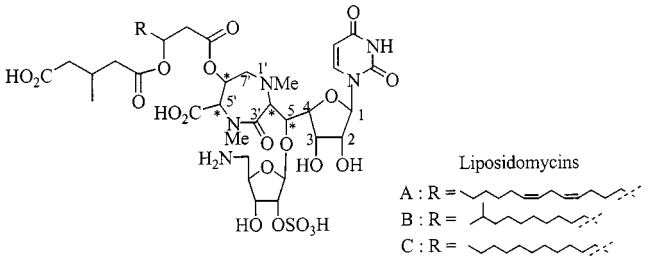

Figure 1. Structure of liposidomycins

Due to their potent inhibition of bacterian peptidoglycan synthesis, which makes liposidomycins good candidates for the elaboration of potential new antibacterial entities, and in view of their chemical complexity, we have embarked on the synthesis of these challenging molecules. Our goal has been first to determine the absolute configuration of the natural product, and then to establish structure-activity relationships of modified subunits. To this end, our aim has been to develop a flexible strategy that would allow facile access to various configurations at the chiral centers.

Several factors were taken into account in proposing a definite absolute configuration for the target molecule. First, assuming that the biosynthetic route to liposidomycins involves naturally occurring amino acids, we postulated an (*S*) absolute configuration at C-2′ and C-5′. Secondly, by comparing coupling constants for the uridinyldiazepanone part of liposidomycins, which suggest a *trans* relative configuration for C-5′−C-6′, with those of *cis*- and *trans*-5,6-disubstituted 1,4-diazepan-3-ones obtained by Knapp et al.,[4b] we have tentatively assigned the (*S*) configuration at the four chiral centers (C-5, C-2′, C-5′, C-6′) of the ribosyldiazepanone core of liposidomycins. In accordance with these hypotheses, our retrosynthetic analysis is indicated in Figure 2. Disconnections at N-1′−C-7′ on one hand, and at C-3′−N-4′ on the other, lead to two enantiopure building blocks: an α-azido-β,γ-epoxybutanol and an α-ribosylamino acid. Part of this work has already been reported in a preliminary form;[4h] an additional route to the α-ribosylamino acid, allowing access to different relative configurations at C-2′−C-5, has since been devised and we now wish to report our results concerning both approaches.

Results and Discussion

Access to (2*R*,3*R*)-3-azido-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane (**2**) in enantiomerically pure form was accomplished from ethyl 3,4-*O*-methylethylidene-L-threonate (**4**), which is readily available from L-ascorbic acid[6] (Scheme 1). The carboxylic acid moiety of **4** was reduced to a primary alcohol for stability reasons, which was then

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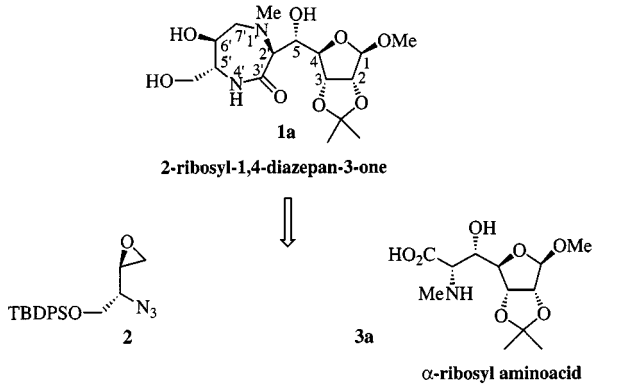
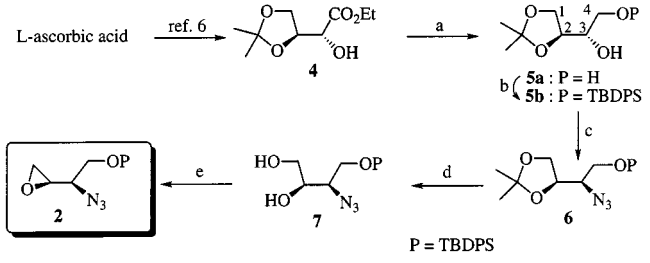


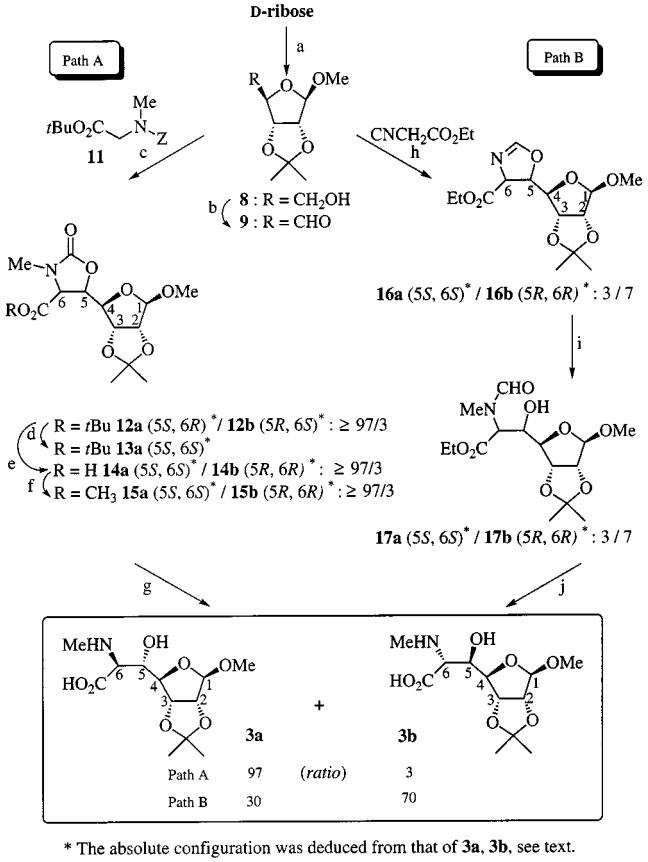
Figure 2. Retrosynthetic analysis towards the 2-ribosyl-1,4-diazepan-3-one core of the postulated natural liposidomycins

protected as its *tert*-butyldiphenylsilyl derivative **5b**. Introduction of the azido group with inversion of the configuration required a two-step, one-pot protocol involving initial activation of the secondary alcohol function as a triflate followed by nucleophilic substitution with tetramethylguanidinium azide,[7] which furnished the azido compound **6** in 81% yield. Acetal hydrolysis in a 3:3:1 trifluoroacetic acid/H_2O/THF mixture afforded the corresponding diol **7**. Epoxidation was then efficiently achieved under Mitsunobu conditions[8] to give the target building block **2**.



Scheme 1. (a) $LiAlH_4$, THF, 95%; (b) TBDPSCl, ImH, DMF, 97%; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, then excess TMGA, −78 °C to 20 °C, 81%; (d) TFA, H_2O, THF, 0 °C, 65%; (e) PPh_3, DIAD, 130 °C, 0.01 Torr, 79%

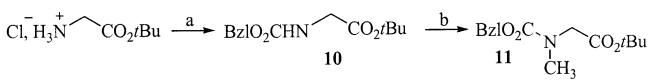
The α-ribosylamino acid synthon **3a** was obtained according to two different pathways (Scheme 2), both of which started from enantiomerically pure aldehyde **9**. The latter was derived from D-ribose in two steps involving concomitant protection of the anomeric hydroxy group and secondary alcohols[9] followed by oxidation of the primary alcohol.[10] Both synthetic pathways involve the formation of a heterocyclic compound, an oxazolidinone or an oxazoline, which can be isomerized to give the thermodynamically more stable *trans* isomer so as to ensure predominant formation of the *threo* isomer.[11] In the first route, aldehyde **9** was condensed with the anion of *tert*-butyl *N*-benzyloxysarcosinate (**11**), generated at −78 °C using lithium diisopropylamide in THF,[12] as outlined in path A.[13] Compound **11** was readily prepared in two steps (Scheme 3) from commercially available *tert*-butyl glycinate hydrochloride by *N*-protection of the amino acid with benzyl chloroformate in the presence of pyridine (90% yield of **10**), followed by *N*-methylation with methyl iodide in the presence of silver oxide. This gave Z−Sar−O*t*Bu (**11**) in 70% yield. The diastereoselectivity of this condensation reaction of the aldehyde **9** favored exclusive formation of the *cis*-oxazolidinones **12a** and **12b** ($^3J_{5,6}$ = 7.8 Hz)[14] with a large predominance of **12a**. Thus, the **12a/12b** ratio in our experiments ranged from 100:0 to 97:3. The *cis*-oxazolidinone **12a** could either be isolated and quantitatively isomerized to the *trans*-oxazolidinone **13a** ($^3J_{5,6}$ = 2 Hz) in the presence of DBU in acetonitrile at 80 °C[15] (overall yield of **13a**: 26% based on **9**) or isomerized by refluxing with ethanolic potassium hydroxide in a one-pot reaction. Under the latter conditions, concomitant saponification of the *tert*-butyl ester moiety occurred to intermediately afford a mixture of acids **14a/14b** (in the corresponding proportion of 100:0 to 97:3), which was then esterified with diazomethane to give the *trans*-oxazolidinone esters **15a/15b** (in the same proportion as **14a/14b**) so as to facilitate purification. Flash-chromatographic separation furnished the enantiomerically pure *trans*-oxazolidinones **15a** and **15b** ($^3J_{5,6}$ = 2.5 and 5 Hz, respectively) in an overall yield of 47% based on aldehyde **9**.[16] Basic hydrolysis of the oxazolidinone moiety



* The absolute configuration was deduced from that of **3a**, **3b**, see text.

Scheme 2. (a) $Me_2C(OMe)_2$, Me_2CO, MeOH, HCl (g), 75%; (b) *i.* DMSO, DCC, pyridine, H_3PO_4, *ii.* $(CO_2H)_2$, 60%; (c) LDA, −78 °C, 30 min at −78 °C and 10 min at 20 °C prior to addition of **9** at −78 °C; (d) DBU, CH_3CN, 48 h, 80 °C, 26% based on **9** for **9** → **12a/12b** → **13a**; (e) KOH, EtOH, 80 °C; (f) CH_2N_2, CH_2Cl_2, 47% based on **9** for **9** → **12a/12b** → **14a/14b** → **15a/15b**; (g) KOH, H_2O, 100 °C, 72%; (h) $CNCH_2CO_2Et$, Et_3N, THF; (i) *i.* Me_3OBF_4, CH_2Cl_2, *ii.* $NaHCO_3$ (aq.), 76% based on **9**; (j) 2 N KOH, 80 °C, 4 h, 50%

of **15a** and **15b** using aqueous potassium hydroxide at 100 °C cleanly afforded the expected α-ribosylamino acid **3a** and its isomer **3b** (up to 3%) in 72% yield.



Scheme 3. (a) $BzlO_2CCl$, CH_2Cl_2, pyridine, 90%; (b) CH_3I, Ag_2O, DMF, 70%

The absolute configuration at the newly created chiral center C-6 of the diastereomeric amino acids **3a** and **3b** was determined by the Cotton effect,[17] and that at C-5 could then be deduced from the *trans* relationship observed in oxazolidinones **15a** and **15b**. The absolute configurations deduced for each compound are as indicated in Scheme 2.

In the second route, the α-ribosylamino acid building block was synthesized by diastereoselective condensation of ethyl isocyanoacetate[18] with the aldehyde **9** (path B).[4h] This reaction was carried out at 10 °C in THF in the presence of triethylamine and led to a 3:7 mixture of *trans*-oxazolines **16a** and **16b** ($^3J_{5,6}$ = 5.2 and 7.2 Hz, respectively).[19] The corresponding *N*-methylformamides **17a** and **17b** (ratio 3:7) were then obtained in 76% overall yield by subsequent treatment with a solution of trimethyloxonium tetrafluoroborate in dichloromethane and hydrolysis with aqueous sodium hydrogen carbonate.[20] Basic hydrolysis of the **17a/17b** mixture with 2 N aqueous KOH at 80 °C afforded the α-ribosylamino acids **3a/3b** in 50% yield (ratio 3:7) after purification by flash chromatography. Again, absolute configurations at the chiral centers of each compound were deduced from both the Cotton effect measured for **3a** and **3b**[17] and from the *trans* relationship observed in oxazolines **16a** and **16b**.

Thus, by following path A or path B, both possible *threo* diastereomers of the ribosylamino acid may be predominantly obtained by selecting appropriate experimental conditions. Furthermore, if the relative configuration of the target ribosyldiazepanone moiety happened to differ from the natural one, path A should facilitate efficient access to the (5*S*,6*R*) isomer of the ribosylamino acid since this absolute configuration corresponds to that of the major product (**12a**) obtained prior to isomerization. Finally, although access to the (5*R*,6*S*) isomer of the ribosylamino acid would not be possible according to our method, it does not seem to be relevant in view of the biological evaluation reported by Dini et al.[5]

The different behavior seen in the condensation of the anion of Z−Sar−O*t*Bu and of ethyl isocyanoacetate may be explained in terms of a Felkin model (Figure 3) leading preferentially to the (5*R*) configuration (path B). However, in path A, the reaction involves addition of the nucleophile to the carbonyl group on the opposite side of the furanoside moiety in a stabilized conformation involving chelation between the lithium cation and the furanoside ring, thus leading to the predominantly observed (5*S*) absolute configuration.

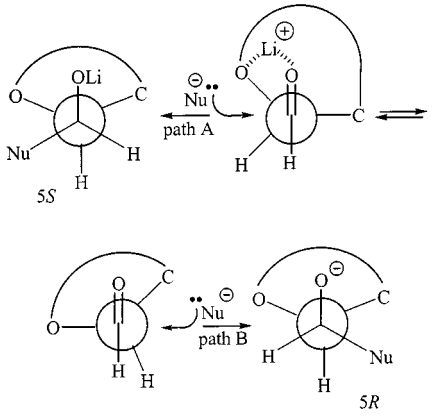
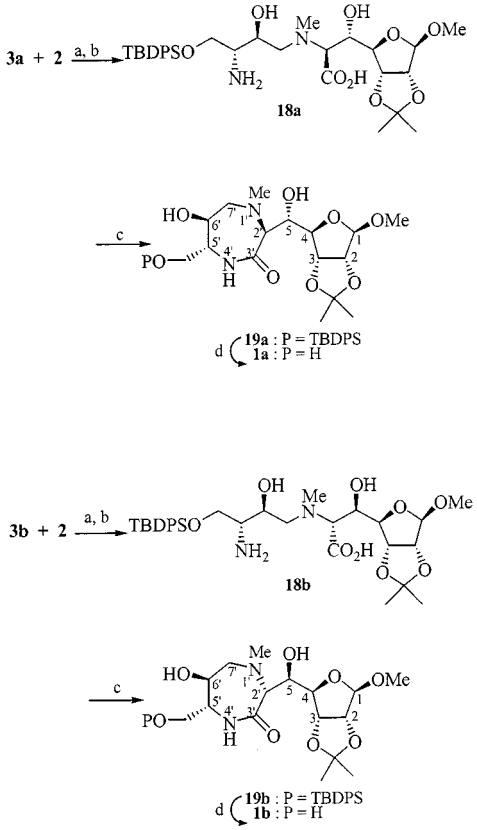


Figure 3. Interpretation of the observed diastereoselectivity for oxazolidinone (path A) or oxazoline (path B) formation

With both *threo* diastereomers **3a** and **3b** of the ribosylamino acid in hand, we next turned to the synthesis of the ribosyldiazepanone (Scheme 4). Regiospecific opening of the azido epoxide **2** by the amine of the amino acid **3a** (or **3b**, respectively) was efficiently achieved in the presence of sodium *tert*-butoxide at 100 °C in 48 h. This was followed by reduction of the azide in the presence of palladium on charcoal in methanol to afford the amine **18a** (or **18b**, respectively) in 65% overall yield. Intramolecular peptidic



Scheme 4

coupling with an excess of dicyclohexyl carbodiimide in CH_2Cl_2 at 0 °C smoothly led to the expected lactam **19a** (or **19b**, respectively), which was then desilylated to give the target ribosyldiazepanone **1a** (or **1b**, respectively).

Conclusion

By means of two distinct approaches that rely on the formation of a heterocyclic compound, an oxazolidinone or an oxazoline, which can be isomerized to the thermodynamically more stable *trans* isomer, we describe a straightforward route to two *threo* diastereomers of the ribosyldiazepanone encountered in liposidomycins. Our strategy also allows access to an *erythro* stereomer of this moiety. Furthermore, by selecting L-ascorbic or D-isoascorbic acid as the starting material for the synthesis of the α-azido epoxide, different absolute configurations at C-5′ and C-6′ can be achieved. Although coupling constants observed for the obtained molecules do not allow a definitive assignment of the absolute configuration of the natural product, notably because available NMR-spectroscopic data concern the uridinyldiazepanone core of the liposidomycins, the results reported herein can be expected to facilitate efficient access to the uridinyldiazepanone part of liposidomycins based on similar strategies. Work towards this goal is currently in progress.

Experimental Section

General Remarks: ^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded with samples in $CDCl_3$ (unless otherwise indicated). − High-resolution mass spectra (HRMS) were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure. Specific rotations were measured with a Perkin−Elmer 241C polarimeter using light from sodium (589 nm) or mercury (365 nm) lamps. − All reactions were carried out under nitrogen using dried solvents and were monitored by thin-layer chromatography on Merck glass-backed 60F-254 precoated silica plates (thickness 0.2 mm). − Flash chromatography was performed on Merck Kieselgel 60H (5−40 μm). Spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples. In many cases, chemical shifts and coupling constants were assigned with the aid of 2D NMR experiments (COSY 45 and HMQC). To simplify interpretation of NMR-spectroscopic data, the signal assignments are in accordance with the atom numberings indicated in the schemes which do not always correspond with nomenclature.

4-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-L-threitol (5b): To a solution of the diol **5a**, obtained by $LiAlH_4$ reduction of the ester **4** (6.08 g, 37.5 mmol) in DMF (170 mL) in the presence of imidazole (5.62 g, 2.2 equiv.), a solution of *tert*-butyldiphenylsilyl chloride (10.74 mL, 1.1 equiv.) in DMF (30 mL) was added dropwise at −10 °C. After stirring overnight at −10 °C, the mixture was concentrated in vacuo. The residue was taken up in water (20 mL) and extracted with dichloromethane (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc/Et_3N, 8:2:0.01; R_f = 0.32) afforded 14.6 g (97%) of the silyl ether **5b** as an oil; $[\alpha]_D$ = +5.6 (c = 1.07, CH_2Cl_2). − ^{1}H NMR: δ = 7.65−7.37 (m, 10 H, Ph), 4.19 (ddd, $J_{2,1a}$ = 6.8 Hz, $J_{2,1b}$ = 6.5 Hz, $J_{2,3}$ = 4 Hz, 1 H, 2-H), 3.97 (dd, $J_{1a,1b}$ = 8 Hz, $J_{1a,2}$ = 6.8 Hz, 1 H, 1a-H), 3.79 (dd, $J_{1b,1a}$ = 8 Hz, $J_{1b,2}$ = 6.5 Hz, 1 H, 1b-H), 3.73−3.55 (m, 3 H, 3-H, 4a-H, 4b-H), 1.39, 1.35 (2 s, 6 H, CMe_2), 1.05 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 135.5, 133.0, 129.8, 127.7 (Ph), 109.1 (CMe_2), 76.4, 71.9 (C-2, C-3), 66.0, 65.0 (C-1, C-4), 26.8, 19.2 (*t*Bu), 26.4, 25.3 (CMe_2). − $C_{23}H_{32}O_4Si$ (400.59): calcd. C 68.96, H 8.05; found C 68.93, H 7.92.

(2*R*,3*R*)-3-Azido-4-*tert*-butyldiphenylsilyloxy-1,2-*O*-isopropylidenebutane-1,2-diol (6): To a solution of the alcohol **5b** (14.5 g, 36.25 mmol) in CH_2Cl_2 (110 mL), 2,6-lutidine (5.90 mL, 1.4 equiv.) and trifluoromethanesulfonic anhydride (7.92 mL, 1.3 equiv.) were successively added dropwise at −78 °C. TLC monitoring (cyclohexane/EtOAc, 8:2) revealed complete transformation of the alcohol into its corresponding triflate (R_f = 0.60) within 30 min. Tetramethylguanidinium azide (28.64 g, 5 equiv.) was then added at −78 °C. The temperature was raised to 20 °C over a period of 1 h and stirring was maintained overnight to complete the reaction. After concentration in vacuo, the residue was dissolved in ethyl acetate and filtered through a silica pad to remove the precipitated lutidinium salts. Flash chromatography of the concentrated mixture (cyclohexane/EtOAc, 95:5; R_f = 0.45) gave 12.48 g (81%) of the azido derivative **6** as a yellow oil; $[\alpha]_D$ = −11 (c = 1.11, CH_2Cl_2). − ^{1}H NMR: δ = 7.69−7.38 (2 m, 10 H, Ph), 4.10−3.95 (m, 2 H, 1a-H, 2-H), 3.91−3.87 (m, 1 H, 1b-H), 3.86 (dd, $J_{4a,4b}$ = 11 Hz, $J_{4a,3}$ = 3.5 Hz, 1 H, 4a-H), 3.74 (dd, $J_{4b,4a}$ = 11 Hz, $J_{4b,3}$ = 6 Hz, 1 H, 4b-H), 3.55 (ddd, $J_{3,2}$ = $J_{3,4b}$ = 6 Hz, $J_{3,4a}$ = 3.5 Hz, 1 H, 3-H), 1.35, 1.30 (2 s, 6 H, CMe_2), 1.06 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 135.6, 132.8, 129.8, 127.7 (Ph), 109.6 (CMe_2), 74.6, 64.9 (C-2, C-3), 66.7, 64.4 (C-1, C-4), 26.7, 19.1 (*t*Bu), 26.5, 25.2 (CMe_2). − $C_{23}H_{31}O_3N_3Si$ (425.61): calcd. C 64.91, H 7.34, N 9.87; found C 64.96, H 7.42, N 9.91.

(2*R*,3*R*)-3-Azido-4-(*tert*-butyldiphenylsilyloxy)butane-1,2-diol (7): To a solution of acetonide **6** (3.4 g, 8 mmol) in THF (20 mL) and H_2O (57 mL), trifluoroacetic acid (57 mL) was added at 0 °C. After stirring for 2 h, the resulting mixture was neutralized at 0 °C with 25% aqueous NH_4OH solution until pH = 8, and then extracted with diethyl ether (5 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc, 6:4; R_f = 0.28) afforded 2.0 g (65%) of the diol **7** as an oil; $[\alpha]_D$ = −30 (c = 1.00, CH_2Cl_2). − ^{1}H NMR: δ = 7.68−7.39 (m, 10 H, Ph), 3.92, 3.86 (AB from ABX, $J_{4a,4b}$ = 11 Hz, $J_{4b,3}$ = 5.6 Hz, $J_{4a,3}$ = 4.8 Hz, 2 H, 4a-H, 4b-H), 3.74−3.66 (m, 3 H, 1a-H, 1b-H, 2-H), 3.53 (X of ABX, $J_{3,2}$ = 6 Hz, $J_{3,4b}$ = 5.6 Hz, $J_{3,4a}$ = 4.8 Hz, 1 H, 3-H). − ^{13}C NMR: δ = 135.4, 132.6, 129.8, 127.7 (Ph), 70.9, 64.1 (C-2, C-3), 64.2, 63.4 (C-1, C-4), 26.6, 19.0 (*t*Bu). − $C_{20}H_{27}O_3N_3Si$ (385.54): calcd. C 62.31, H 7.06, N 10.90; found C 62.32, H 7.09, N 11.04.

(2*R*,3*R*)-3-Azido-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane (2): Prior to the reaction, both triphenylphosphane (1.58 g, 1.17 equiv.) and the diol **7** (1.985 g, 5.16 mmol) were taken up in toluene (20 mL) and the respective solutions were concentrated in vacuo to remove any traces of water. This procedure was repeated twice more. To a solution of the dried triphenylphosphane in toluene (10 mL), diisopropyl azodicarboxylate (1.2 mL, 1.19 equiv.) was added at 0 °C. The mixture was stirred for 10 min and then a solution of the diol **7** in toluene (10 mL) was added and stirring was continued for 30 min at 0 °C. After concentration under reduced pressure, the residue was gradually heated to 130 °C in vacuo (0.01 Torr) for 2.5 h. Flash chromatography of the crude product (cyclohexane/EtOAc, 97:3; R_f = 0.38) gave 1.26 g (79%) of the expected epoxide **2** as a pale-yellow oil; $[\alpha]_D$ = −19 (c = 1.04,

CH_2Cl_2). – ^{1}H NMR: δ = 7.69–7.41 (2 m, 10 H, Ph), 3.86, 3.79 (AB of ABX, $J_{4a,4b}$ = 10.5 Hz, $J_{4b,3}$ = 5.5 Hz, $J_{4a,3}$ = 4 Hz, 2 H, 4a-H, 4b-H), 3.39 (X of ABX, $J_{3,2}$ = $J_{3,4b}$ = 5.5 Hz, $J_{3,4a}$ = 4 Hz, 1 H, 3-H), 3.08 (X′ of A′B′X′, $J_{2,3}$ = 5.5 Hz, $J_{2,1a}$ = 4 Hz, $J_{2,1b}$ = 2.8 Hz, 1 H, 2-H), 2.78, 2.72 (A′B′ of A′B′X′, $J_{1a,1b}$ = 5.5 Hz, $J_{1a,2}$ = 4 Hz, $J_{1b,2}$ = 2.8 Hz, 2 H, 1a-H, 1b-H), 1.06 (s, 9 H, *t*Bu). – ^{13}C NMR: δ = 135.6, 132.6, 129.9, 127.9 (Ph), 64.3 (C-4), 63.4 (C-2), 50.3 (C-3), 44.9 (C-1), 26.6, 19.0 (*t*Bu). – $C_{20}H_{25}O_2N_3Si$ (367.53): calcd. C 65.36, H 6.86, N 11.43; found C 65.37, H 6.87, N 11.41.

Methyl 2,3-*O*-Isopropylidene-β-D-ribofuranoside (8): Prepared according to ref.[9]; $[\alpha]_D$ = –82 (*c* = 1.00, CH_2Cl_2), $[\alpha]_D$ [9] = –82.3 (*c* = 1.00, CH_2Cl_2). – ^{1}H NMR: δ = 4.94 (s, 1 H, 1-H), 4.80 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.55 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.39 (dd, 1 H, $J_{4,5a}$ = $J_{4,5b}$ = 2.8 Hz, 4-H), 3.65–3.57 (m, 2 H, 5-H), 3.40 (s, 3 H, OMe), 1.45, 1.28 (2 s, 6 H, CMe_2). – ^{13}C NMR: δ = 111.8 (CMe_2), 109.5 (C-1), 87.9, 86.0, 85.4 (C-2, C-3, C-4), 63.5 (C-5), 54.9 (OMe), 26.1, 24.4 (CMe_2). – $C_9H_{16}O_5$ (204.22): calcd. C 52.93, H 7.90; found C 52.74, H 7.98.

Methyl 2,3-*O*-Isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (9): Prepared according to ref.[10]; $[\alpha]_D$ = –204 (*c* = 1.00, CH_2Cl_2), $[\alpha]_D$ [10] = –214 (*c* = 0.10, $CHCl_3$). – ^{1}H NMR: δ = 9.53 (s, 1 H, 5-H), 5.03 (s, 1 H, 1-H), 4.99 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.45 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.42 (s, 1 H, 4-H), 3.41 (s, 3 H, OMe), 1.44, 1.28 (2 s, 6 H, CMe_2). – ^{13}C NMR: δ = 200.7 (C-5), 112.6 (CMe_2), 109.2 (C-1), 89.5, 83.9, 80.5 (C-2, C-3, C-4), 55.7 (OMe), 26.2, 24.8 (CMe_2).

***tert*-Butyl *N*-(Benzyloxycarbonyl)glycinate (10):** To a solution of *tert*-butyl glycinate hydrochloride (0.86 g, 5.15 mmol) in CH_2Cl_2 (15 mL) and pyridine (1.8 mL), benzyl chloroformate (1.25 mL, 1.7 equiv.) was added at 0 °C and the mixture was stirred at 20 °C for 15 h. Saturated aqueous $NaHCO_3$ solution was then added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the crude product (cyclohexane/EtOAc, 8:2; R_f = 0.36) afforded 1.3 g (90%) of compound **10** as a colorless oil. – ^{1}H NMR: δ = 7.34–7.29 (m, 5 H, Ph), 5.10 (s, 2 H, Bzl), 3.85 (d, $J_{2,NH}$ = 5.4 Hz, 2 H, 2-H), 1.44 (s, 9 H, *t*Bu). – ^{13}C NMR: δ = 168.9 (C-1), 156.1 (CO_2Bzl), 136.2, 128.2, 127.8, 126.6 (Ph), 81.8 (CMe_3), 66.6 (Bzl), 43.2 (C-2), 27.8 (CMe_3). – $C_{14}H_{19}NO_4$ (265.31): calcd. C 63.38, H 7.22, N 5.28; found C 63.24, H 7.19, N 5.21.

***tert*-Butyl *N*-(Benzyloxycarbonyl)sarcosinate (11):** To a solution of compound **10** (0.5 g, 1.88 mmol) in DMF (5 mL), methyl iodide (0.94 mL, 8 equiv.) followed, in darkness, by silver oxide (1.75 g, 4 equiv.) were added at 20 °C. The resulting mixture was stirred for 16 h at 20 °C in the dark. After hydrolysis and CH_2Cl_2 extraction (3 × 20 mL), the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 0.37 g (70%) of pure Z–Sar–O*t*Bu (**11**) (single spot by TLC, cyclohexane/EtOAc, 2:8; R_f = 0.7). The presence of rotamers was evident from both the ^{1}H and ^{13}C NMR spectra through increased multiplicities. – ^{1}H NMR: δ = 7.33–7.30 (m, 5 H, Ph), 5.14, 5.11 (2 s, 2 H, Bzl), 3.92, 3.85 (2 s, 2 H, 2-H), 2.98, 2.96 (2 s, 3 H, NMe), 1.44, 1.39 (2 s, 9 H, CMe_3). – ^{13}C NMR: δ = 168.5 (C-1), 156.5, 156.0 (CO_2Bzl), 136.5, 128.3, 127.8, 127.6 (Ph), 81.6 (CMe_3), 67.1 (Bzl), 51.2 (C-2), 35.9, 35.1 (NMe), 27.9 (CMe_3). – $C_{15}H_{21}O_4N$ (279.34): calcd. C 64.50, H 7.58, N 5.01; found C 64.33, H 7.51, N 5.04.

***tert*-Butyl (4′*R*,5′*S*)-3′-Methyl-5′-[(methyl (4*R*)-2,3-*O*-isopropylidene-β-D-erythrofuranosid-4-yl]-2′-oxooxazolidine-4′-carboxylate (12a):** To a solution of diisopropylamine (0.52 mL, 1.5 equiv.) in THF (5 mL), *n*-butyllithium (1.6 M in hexanes, 2.16 mL, 1.4 equiv.) was added dropwise at –78 °C. After stirring for 30 min at this temperature, then for 10 min at –40 °C, and finally for a further 10 min at –78 °C, a solution of the *tert*-butyl *N*-benzyloxysarcosinate (**11**) (0.76 g, 1.1 equiv.) in THF (2 mL) was added. The resulting mixture was stirred at –78 °C for 30 min, in the course of which a yellow coloration appeared. It was then allowed to warm to 20 °C and stirring was continued for 30 min. After cooling to –78 °C once more, a solution of the aldehyde **9** (0.5 g, 2.47 mmol) in THF (2 mL) was added dropwise and the mixture was slowly allowed to warm to 20 °C over a period of 16 h. After concentration in vacuo, the residue was taken up in water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the crude product (EtOAc/cyclohexane/Et_3N, 8:2:0.01; R_f = 0.5) afforded 0.24 g (26%) of **12a**. – ^{1}H NMR: δ = 4.90 (s, 1 H, 1-H), 4.84 (d, $J_{3,2}$ = 6 Hz, 1 H, 3-H), 4.58 (d, $J_{2,3}$ = 6 Hz, 1 H, 2-H), 4.49 (dd, $J_{5,4}$ = 10.8 Hz, $J_{5,6}$ = 7.8 Hz, 1 H, 5-H), 4.38 (d, $J_{4,5}$ = 10.8 Hz, 1 H, 4-H), 4.11 (d, $J_{6,5}$ = 7.8 Hz, 1 H, 6-H), 3.36 (s, 3 H, OMe), 2.82 (s, 3 H, NMe), 1.50 (s, 9 H, *t*Bu), 1.43, 1.28 (2 s, 6 H, CMe_2). – ^{13}C NMR: δ = 166.7 (CO_2tBu), 156.9 (NCO), 112.6 (CMe_2), 110.1 (C-1), 84.9, 83.8, 82.4 (C-2, C-3, C-4), 83.5 (*t*Bu), 73.5 (C-5), 63.1 (C-6), 55.6 (OMe), 29.6 (NMe), 27.8 (*t*Bu), 26.3, 24.9 (CMe_2). – MS (70 eV, CI, NH_3): *m*/*z* = 374 $[M + 1]^+$, 391 $[M + 18]^+$.

***tert*-Butyl (4′*S*,5′*S*)-3′-Methyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-D-erythrofuranosid-4-yl]-2′-oxooxazolidine-4′-carboxylate (13a):** To a solution of *cis*-oxazolidinone **12a** (30 mg, 0.08 mmol) in acetonitrile (3 mL), DBU (13.2 μL, 1.1 equiv.) was added dropwise. The resulting colorless mixture was then refluxed for 48 h. After concentration in vacuo, the residue was treated with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 30 mg of the oxazolidinone **13a** (quantitative yield) as an oil (EtOAc; R_f = 0.65). – ^{1}H NMR: δ = 4.96 (s, 1 H, 1-H), 4.82 (d, $J_{3,2}$ = 6 Hz, 1 H, 3-H), 4.59 (d, $J_{2,3}$ = 6 Hz, 1 H, 2-H), 4.36 (dd, $J_{5,4}$ = 10 Hz, $J_{5,6}$ = 2 Hz, 1 H, 5-H), 4.08 (d, $J_{6,5}$ = 2 Hz, 1 H, 6-H), 4.06 (d, $J_{4,5}$ = 10 Hz, 1 H, 4-H), 3.32 (s, 3 H, OMe), 2.90 (s, 3 H, NMe), 1.48 (s, 9 H, *t*Bu), 1.44, 1.28 (2 s, 6 H, CMe_2).

Methyl (4′*S*,5′*S*)-3′-Methyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-D-erythrofuranosid-4-yl]-2′-oxooxazolidine-4′-carboxylate (15a) and Its (4′*R*,5′*R*) Isomer 15b: To a solution of diisopropylamine (1.04 mL, 1.5 equiv.) in THF (5 mL), *n*-butyllithium (1.6 M in hexanes, 4.33 mL, 1.4 equiv.) was added dropwise at –78 °C. After stirring for 30 min at this temperature, the mixture was allowed to warm to –40 °C for a few minutes and then cooled to –78 °C once more, whereupon Z–Sar–O*t*Bu (**11**) (1.52 g, 1.1 equiv.) was added. After stirring for 30 min at –78 °C, the mixture was allowed to warm to 20 °C for 10 min and then cooled to –78 °C once more, whereupon a solution of the aldehyde **9** (1.0 g, 4.95 mmol) in THF (5 mL) was added dropwise. The resulting mixture was allowed to warm to 20 °C over a period of 40 min and then a 0.49 M ethanolic solution of potassium hydroxide (20 mL, 2 equiv.) was added. After stirring for 25 min at 80 °C, the mixture was cooled to 0 °C and concentrated in vacuo. The residue was partitioned between water and Et_2O (1:1; 40 mL) and the aqueous layer was extracted with further Et_2O (2 × 20 mL). The aqueous phase was then acidified to pH = 2 with 0.1 N HCl and extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and the residue was taken up in CH_2Cl_2. The resulting solution was treated with an excess of diazomethane in Et_2O

until a yellow color persisted. After stirring for 30 min, concentration in vacuo and flash chromatography (toluene/EtOAc/Et_3N, 5:5:0.01) afforded a mixture of oxazolidinones **15a/15b** in a proportion ranging from 100:0 to 97:3 in an overall yield of 47% based on the aldehyde **9**.[16] − **Compound 15a:** R_f = 0.3 (cyclohexane/EtOAc, 2:8); m.p. 137 °C. − $[\alpha]_D$ = −62 (c = 0.24, $CDCl_3$). − ^{1}H NMR: δ = 4.97 (s, 1 H, 1-H), 4.81 (d, $J_{3,2}$ = 6 Hz, 1 H, 3-H), 4.58 (d, $J_{2,3}$ = 6 Hz, 1 H, 2-H), 4.38 (dd, $J_{5,4}$ = 10 Hz, $J_{5,6}$ = 2.5 Hz, 1 H, 5-H), 4.24 (d, $J_{6,5}$ = 2.5 Hz, 1 H, 6-H), 4.07 (d, $J_{4,5}$ = 10 Hz, 1 H, 4-H), 3.79 (s, 3 H, CO_2Me), 3.32 (s, 3 H, OMe), 2.91 (s, 3 H, NMe), 1.44, 1.28 (2 s, 6 H, CMe_2). − ^{13}C NMR: δ = 169.7 (CO_2Me), 156.1 (NCO), 112.7 (CMe_2), 110.3 (C-1), 85.6, 84.9, 81.3 (C-2, C-3, C-4), 74.9 (C-5), 61.5 (C-6), 55.8 (OMe), 52.8 (CO_2Me), 30.2 (NMe), 26.3, 24.7 (CMe_2). − MS (70 eV, CI, NH_3): m/z = 332 $[M + 1]^+$, 349 $[M + 18]^+$. − **Compound 15b:** R_f = 0.15 (cyclohexane/EtOAc, 2:8). − ^{1}H NMR: δ = 4.99 (s, 1 H, 1-H), 4.81 (dd, $J_{3,2}$ = 6 Hz, $J_{3,4}$ = 1.3 Hz, 1 H, 3-H), 4.64 (d, $J_{2,3}$ = 6 Hz, 1 H, 2-H), 4.50 (dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 4.6 Hz, 1 H, 5-H), 4.30 (dd, $J_{4,5}$ = 4.6 Hz, $J_{4,3}$ = 1.3 Hz, 1 H, 4-H), 4.21 (d, $J_{6,5}$ = 5 Hz, 1 H, 6-H), 3.82 (s, 3 H, CO_2Me), 3.30 (s, 3 H, OMe), 2.95 (s, 3 H, NMe), 1.44, 1.28 (2 s, 6 H, CMe_2). − ^{13}C NMR: δ = 169.7 (CO_2Me), 156.7 (NCO), 112.8 (CMe_2), 110.5 (C-1), 86.8, 85.5, 80.5 (C-2, C-3, C-4), 75.6 (C-5), 60.1 (C-6), 55.7 (OMe), 52.9 (CO_2Me), 30.4 (NMe), 26.5, 24.9 (CMe_2).

Ethyl (4′*S*,5′*S*)-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-D-erythrofuranosid-4-yl]-2′-oxazoline-4′-carboxylate (16a) and Its (4′*R*,5′*R*) Isomer 16b: To a solution of Et_3N (2.0 mL, 14.9 mmol) in THF (10 mL), first ethyl isocyanoacetate (1.3 mL, 11.9 mmol) and then a solution of the aldehyde **9** (2.0 g, 9.9 mmol) in THF (10 mL) were added at −10 °C. The resulting mixture was stirred at 20 °C for 24 h. Concentration in vacuo afforded the crude oxazolines **16a/16b** as a 3:7 mixture. Due to partial hydrolysis of the oxazoline moiety during purification by flash chromatography, only a sample of the mixture was purified (toluene/EtOAc/Et_3N, 8:2:0.01; **16a:** R_f = 0.37, **16b:** R_f = 0.52). − **Compound 16a:** ^{1}H NMR: δ = 6.85 (d, $J_{NCH,6}$ = 2 Hz, 1 H, NCH), 4.96 (s, 1 H, 1-H), 4.78 (d, $J_{3,2}$ = 6 Hz, 1 H, 3-H), 4.74 (dd, $J_{5,4}$ = 7.2 Hz, $J_{5,6}$ = 5.2 Hz, 1 H, 5-H), 4.61 (dd, $J_{6,5}$ = 7.2 Hz, $J_{6,NCH}$ = 2 Hz, 1 H, 6-H), 4.56 (d, $J_{2,3}$ = 6 Hz, 1 H, 2-H), 4.28−4.19 (m, 3 H, 4-H, OEt), 3.29 (s, 3 H, OMe), 1.46, 1.30 (2 s, 6 H, CMe_2), 1.28 (t, 3 H, J_{Et} = 7 Hz, OEt). − **Compound 16b:** ^{1}H NMR: δ = 6.89 (d, $J_{NCH,6}$ = 2 Hz, 1 H, NCH), 4.94 (s, 1 H, 1-H), 4.79 (d, $J_{3,2}$ = 6 Hz, 1 H, 3-H), 4.70 (dd, $J_{5,4}$ = 9.2 Hz, $J_{5,6}$ = 5.2 Hz, 1 H, 5-H), 4.64 (dd, $J_{6,5}$ = 5.2 Hz, $J_{6,NCH}$ = 2 Hz, 1 H, 6-H), 4.60 (d, $J_{2,3}$ = 6 Hz, 1 H, 2-H), 4.19 (q, J_{Et} = 7 Hz, 2 H, OEt), 3.93 (d, $J_{4,5}$ = 9.2 Hz, 1 H, 4-H), 3.25 (s, 3 H, OMe), 1.43, 1.28 (2 s, 6 H, CMe_2), 1.26 (t, J_{Et} = 7 Hz, 3 H, OEt).

Ethyl (Methyl 6-deoxy-6-[formyl(methyl)amino]-2,3-*O*-isopropylidene-β-L-*glycero*-L-*talo*-heptafuranosid)uronate (17a) and Its D-*glycero*-D-*allo* Isomer 17b: To a solution of the crude mixture of oxazolines **16a/16b** (3.472 g, 9.9 mmol) in CH_2Cl_2 (42 mL), trimethyloxonium tetrafluoroborate (1.919 g, 12.9 mmol) was added at 20 °C and stirring was maintained at this temperature for 12 h. After the addition of water (15.8 mL), aqueous $NaHCO_3$ solution was added until pH = 7. After decantation and extraction with CH_2Cl_2 (2 × 30 mL), the combined organic layers were washed with H_2O (50 mL) and brine (50 mL). After drying (Na_2SO_4) and concentrating in vacuo, flash chromatography (CH_2Cl_2/Et_2O, 7:3) of the residue afforded a 3:7 mixture of the diastereomeric formamides **17a/17b** (R_f = 0.30 and 0.36, respectively) in 76% overall yield based on aldehyde **9**. However, the products could not be efficiently separated under these conditions and hence the reported NMR spectroscopic data correspond to those of the mixture **17a/17b**. − ^{1}H NMR: δ = 8.14 (s, 0.7 H, NCH_bO), 8.12 (s, 0.3 H, NCH_aO), 4.98 (s, 0.3 H, 1a-H), 4.97 (s, 0.7 H, 1b-H), 4.96−4.92 (m, 0.7 H, 3b-H), 4.90−4.82 (m, 0.3 H, 3a-H), 4.62−4.54 (m, 1 H, 2-H), 4.40 (m, 0.7 H, 4b-H), 4.28−4.16 (m, 3.3 H, 4a-H, 5-H, OEt), 4.15−3.99 (m, 1 H, 6-H), 3.39 (s, 2.1 H, OMe_b), 3.37, (s, 0.9 H, OMe_a), 3.11 (s, 2.1 H, NMe_b), 2.96 (s, 0.9 H, NMe_a), 1.58, 1.45 (2 s, 6 H, CMe_2), 1.29, 1.26 (2 m, 3 H, OEt). − MS (70 eV, CI, NH_3): m/z = 348 $[M + 1]^+$.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-6-(methylamino)-L-*glycero*-L-*talo*-heptafuranosiduronic Acid (3a) and Its β-D-*glycero*-D-*allo* Isomer 3b. − From Oxazolidinone 15a: The oxazolidinone **15a** (20 mg, 0.06 mmol) was added to 2 N aqueous KOH solution (270 μL, 9 equiv.) and the resulting mixture was refluxed for 5 h. After cooling to 0 °C, the mixture was acidified to pH = 2 by the addition of Dowex® H^+ (50X8-100) resin. The resulting suspension was then loaded onto a H_2O-packed column of Dowex® 50X8-100 resin. Elution with 5% aqueous ammonia solution followed by lyophilization of the appropriate fraction furnished the expected amino acid **3a** (12.6 mg, 72%) in its zwitterionic form (beige powder; m.p. 216 °C). − **From Formamides 17a/17b:** A mixture of formamides **17a/17b** (204 mg, 0.58 mmol) in 2 N aqueous KOH solution (1.37 mL, 9 equiv.) was heated at 80 °C for 4 h. The resulting mixture was then cooled to 0 °C and acidified to pH = 5 by the addition of a 2 N aq. HCl. After lyophilization and flash chromatography (CH_2Cl_2/MeOH/H_2O/AcOEt, 7:3:0.6:1.5) of the residue, the expected amino acids **3a** and **3b** (R_f = 0.28 and 0.38, respectively) were isolated in 50% yield. − **Compound 3a:** $[\alpha]_D$ = −14 (c = 1.0, 0.1 N NaOH). − ^{1}H NMR (D_2O): δ = 5.17 (s, 1 H, 1-H), 5.03 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.84 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.25 (d, $J_{4,5}$ = 10.1 Hz, 4-H), 4.17 (dd, $J_{5,4}$ = 10.1 Hz, $J_{5,6}$ = 2.3 Hz, 1 H, 5-H), 3.76 (d, $J_{6,5}$ = 2.3 Hz, 1 H, 6-H), 3.49 (s, 3 H, OMe), 2.85 (s, 3 H, NMe), 1.58, 1.44 (2 s, 6 H, CMe_2). − ^{13}C NMR: δ = 172.5 (CO_2 H), 116.1 (CMe_2), 112.2 (C-1), 88.7, 87.1, 84.6 (C-2, C-3, C-4), 71.5 (C-5), 67.4 (C-6), 58.8 (OMe), 34.5 (NMe), 28.2, 26.7 (CMe_2). − C.D. (c = 3 × 10^{-3} M, 20 °C, H_2O): λ (Δε) = 235 nm (0), 215 (+0.37), 210 +(0.90), 196 (+2.17), 190 (+1.50). − HRMS (FAB^+): calcd. for $C_{12}H_{18}O_7N$: 292.1396; found 292.1394. − **Compound 3b:** $[\alpha]_D$ = −38 (c = 1.0, 0.1 N NaOH). − ^{1}H NMR (D_2O): δ = 5.18 (s, 1 H, 1-H), 5.04 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.85 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.50 (d, $J_{4,5}$ = 10.1 Hz, 4-H), 4.03 (dd, $J_{5,4}$ = 10.1 Hz, $J_{5,6}$ = 2.2 Hz, 1 H, 5-H), 3.84 (d, $J_{6,5}$ = 2.2 Hz, 1 H, 6-H), 3.50 (s, 3 H, OMe), 2.81 (s, 3 H, NMe), 1.56, 1.43 (2 s, 6 H, CMe_2). − ^{13}C NMR: δ = 174.2 (CO_2 H), 116.1 (CMe_2), 112.4 (C-1), 88.3, 87.3, 84.8 (C-2, C-3, C-4), 72.6 (C-5), 67.6 (C-6), 58.9 (OMe), 36.3 (NMe), 28.3, 26.7 (CMe_2). − C.D. (c = 3 × 10^{-3} M, 20 °C, H_2O): λ (Δε) = 235 nm (0), 215 (−1.16), 210 (−1.64), 196 (−2.65), 190 (−2.47). − HRMS (FAB^+): calcd. for $C_{12}H_{18}O_7N$: 292.1396; found 292.1402.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-6-{methyl[(2′*S*,3′*R*)-3-amino-4′-(*tert*-butyldiphenylsilyloxy)-2′-hydroxybutyl]amino}-β-L-*glycero*-L-*talo*-heptafuranosiduronic Acid (18a) and Its D-*glycero*-D-*allo* Isomer 18b: To a solution of sodium *tert*-butoxide, prepared from sodium hydride (9.6 mg, 0.4 mmol) and *tert*-butyl alcohol (2 mL), was added the enantiomerically pure amino acid **3a** or **3b** (60 mg, 0.2 mmol), followed, after 30 min, by a solution of the epoxide **2** (75.7 mg, 0.2 mmol) in *tert*-butyl alcohol (2 mL). The mixture was then stirred at 100 °C for 48 h. After concentration in vacuo, the residue was taken up in chloroform. This solution was filtered through a Celite pad and concentrated in vacuo once more. The crude product was dissolved in methanol (3 mL) and reduced with dihydrogen in the presence of palladium on charcoal (10%, 40 mg). The catalyst was removed by filtration through a Celite pad and

the filtrate was concentrated in vacuo prior to purification by flash chromatography (CH_2Cl_2/cyclohexane/H_2O/EtOAc, 14:4:0.5:2) to afford 85 mg of **18a** or **18b** (65% overall yield based on the amino acid **3a** or **3b**). − **Compound 18a:** TLC (same conditions as for purification by flash chromatography): R_f = 0.36. − $[\alpha]_D$ = −105 (c = 1.0, MeOH). − ^{1}H NMR (CD_3OD): δ = 4.89 (s, 1 H, 1-H), 4.94 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.59 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.26 (d, $J_{4,5}$ = 10.1 Hz, 4-H), 3.92−3.78 (m, 5 H, 5-H, 6-H, 8-H, 10-H), 3.40−3.20 (m, 4 H, 9-H, OMe), 2.88 (dd, $J_{7a,7b}$ = 13 Hz, $J_{7a,8}$ = 7.5 Hz, 1 H, 7a-H), 2.74 (dd, $J_{7b,7a}$ = 13 Hz, $J_{7b,8}$ = 4.8 Hz, 1 H, 7b-H), 2.44 (s, 3 H, NMe), 1.41, 1.26 (2 s, 6 H, CMe_2), 1.09 (s, 9 H, tBu). − ^{13}C NMR: δ = 138.5, 135.6, 133.0, 130.8 (Ph), 115.1 (CMe_2), 113.6 (C-1), 91.3, 88.2, 85.4 (C-2, C-3, C-4), 71.6 (C-5), 67.5 (C-8), 65.3 (C-6, C-10), 62.0 (C-7), 60.6 (C-9), 58.3 (OMe), 42.8 (NMe), 29.2, 28.6 (CMe_2), 27.0, 21.9 (tBu). − MS (FAB$^+$, thioglycerol): m/z = 633 (100), 589 (17), 587 (12), 469 (13), 272 (13), 214 (10), 199 (16), 197 (17), 137 (12), 133 (13). − HRMS (FAB$^+$) calcd. for $C_{32}H_{46}O_9N_4Si$: 633.3207; found 633.3212. − **Compound 18b:** TLC (same conditions as for purification by flash chromatography): R_f = 0.47. − $[\alpha]_D$ = 22 (c = 1.0, MeOH). − ^{1}H NMR (CD_3OD): δ = 4.92 (s, 1 H, 1-H), 4.87 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.55 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.39 (d, $J_{4,5}$ = 5.3 Hz, 4-H), 4.10−3.80 (m, 5 H, 5-H, 6-H, 8-H, 10-H), 3.42−3.20 (m, 4 H, 9-H, OMe), 3.05−2.70 (m, 2 H, 7a-H, 7b-H), 2.51 (s, 3 H, NMe), 1.42, 1.29 (2 s, 6 H, CMe_2), 1.10 (s, 9 H, tBu). − ^{13}C NMR: δ = 136.7, 133.7, 133.1, 131.1, 129.9, 128.9 (Ph), 113.2 (CMe_2), 111.3 (C-1), 89.5, 86.8, 82.3 (C-2, C-3, C-4), 72.8 (C-5), 65.8 (C-8), 63.0 (C-6, C-10), 61.3 (C-7), 58.7 (C-9), 56.1 (OMe), 43.2 (NMe), 27.3, 26.8 (CMe_2), 25.0, 22.2 (tBu). − MS (FAB$^+$, thioglycerol): m/z = 633 (100), 589 (16), 587 (13), 272 (11), 234 (10), 199 (13), 197 (14), 135 (28), 133 (13), 109 (13). − HRMS (FAB$^+$): calcd. for $C_{32}H_{46}O_9N_4Si$: 633.3207; found 633.3232.

Methyl (5*S*)-5-*C*-[(2′*R*,5′*S*,6′*R*)-5′-(*tert*-Butyldiphenylsilyloxymethyl)-6′-hydroxy-1′-methyl-3′-oxo-1′,4′-diazepan-2′-yl]-5-hydroxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (19a) and Its (5*R*,2′*S*) Isomer 19b: To a solution of **18a** or **18b** (35 mg, 55 μmol) in CH_2Cl_2 (1 mL) was added dicyclohexyl carbodiimide (16 mg, 77 μmol) and the mixture was stirred at 0 °C for 15 h. H_2O (300 μL) was then added to convert the excess DCC into dicyclohexylurea and stirring was continued at 0 °C for 30 min. After concentration in vacuo, cold EtOAc (2 mL) was added and the precipitated dicyclohexylurea was removed by filtration through a Celite pad. Concentration of the filtrate in vacuo was followed by purification by flash chromatography (CH_2Cl_2/MeOH/EtOAc, 7:1:3) to afford 11.4 mg (34%) of the expected lactam **19a** or **19b**. − **Compound 19a:** TLC (CH_2Cl_2/MeOH/EtOAc, 7:0.25:3): R_f = 0.33. − $[\alpha]_D$ = +7 (c = 1.0, CH_2Cl_2). − ^{1}H NMR (500 MHz): δ = 7.75−7.40 (m, 10 H, Ph), 6.00 (d, $J_{NH,5'}$ = 2.5 Hz, 1 H, NH), 4.96 (s, 1 H, 1-H), 4.95 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.54 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.49 (d, $J_{4,5}$ = 2.8 Hz, 1 H, 4-H), 4.10−4.00 (m, 1 H, 5-H), 3.92 (dd, J_{CH_2OSi} = 11 Hz, $J_{CH_aOSi,5'}$ = 4.0 Hz, 1 H, CH_aOSi), 3.87−3.78 (m, 3 H, 5′-H, CH_bOSi, 6′-H), 3.40 (s, 3 H, OMe), 3.38 (br. d, $J_{2',5}$ = 5.6 Hz, 1 H, 2′-H), 3.10 (dd, $J_{7'b,7'a}$ = 14.5 Hz, $J_{7'b,6'}$ = 2.5 Hz, 1 H, 7′b-H), 2.87 (dd, $J_{7'a,7'b}$ = 14.5 Hz, $J_{7'a,6'}$ = 4 Hz, 1 H, 7′a-H), 2.52 (s, 3 H, NMe), 1.46, 1.30 (2 s, 6 H, CMe_2), 1.06 (s, 9 H, tBu). − ^{13}C NMR (126 MHz): δ = 172.7 (C-3′), 135.6, 132.6, 130.1, 128.0 (Ph), 112.1 (CMe_2), 110.2 (C-1), 89.2 (C-4), 85.5 (C-2), 80.3 (C-3), 74.1 (C-2′), 71.5 (C-5), 67.7, 56.1 (C-5′, C-6′), 62.4 (CH_2OSi), 59.2 (C-7′), 55.8 (OMe), 44.5 (NMe), 26.9, 19.3 (tBu), 26.4, 24.8 (CMe_2). − MS (FAB$^+$, thioglycerol): m/z = 615 (100), 583 (35), 412 (26), 411 (32), 307 (24), 289 (17). − HRMS (FAB$^+$): calcd. for $C_{32}H_{47}O_8N_2Si$: 615.3102; found 615.3101. − **Compound 19b:** TLC (same conditions as for purification by flash chromatography): R_f = 0.35. − $[\alpha]_D$ = +43 (c = 0.9, CH_2Cl_2). − ^{1}H NMR (500 MHz): δ = 7.67−7.40 (m, 10 H, Ph), 5.99 (d, $J_{NH,5'}$ = 4.0 Hz, 1 H, NH), 4.92 (s, 1 H, 1-H), 4.91 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.54 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.37 (d, $J_{4,5}$ = 8 Hz, 1 H, 4-H), 4.00 (dd, J_{CH_2OSi} = 11 Hz, $J_{CH_aOSi,5'}$ = 3.0 Hz, 1 H, CH_aOSi), 3.95 (dd, $J_{5,4}$ = 8 Hz, $J_{5,2'}$ = 4.5 Hz, 1 H, 5-H), 3.86 (dd, J_{CH_2OSi} = 11 Hz, $J_{CH_bOSi,5'}$ = 3.0 Hz, 2 H, CH_bOSi, 6′-H), 3.56 (d, $J_{2',5}$ = 4.5 Hz, 1 H, 2′-H), 3.30 (s, 3 H, OMe), 3.26 (m, 1 H, 5′-H), 3.26 (dd, $J_{7'b,7'a}$ = 14 Hz, $J_{7'b,6'}$ = 4.0 Hz, 1 H, 7′b-H), 2.84 ($J_{7'a,7'b}$ = 14 Hz, $J_{7'a,6'}$ = 10.5 Hz, 1 H, 7′a-H), 2.56 (s, 3 H, NMe), 1.46, 1.29 (2 s, 6 H, CMe_2), 1.07 (s, 9 H, tBu). − ^{13}C NMR (126 MHz): δ = 175.1 (C-3′), 135.5, 132.4, 130.3, 128.0 (Ph), 112.1 (CMe_2), 110.1 (C-1), 85.6 (C-4), 85.2 (C-2), 81.4 (C-3), 70.9 (C-5), 65.0 (C-7′), 62.6 (C-6′), 62.1 (C-2′, CH_2OSi), 58.2 (C-5′), 55.5 (OMe), 38.0 (NMe), 26.9, 19.2 (tBu), 26.4, 24.8 (CMe_2). − MS (FAB$^+$, thioglycerol): m/z = 615 (37), 583 (12), 412 (24), 411 (17). − HRMS (FAB$^+$) calcd. for $C_{32}H_{47}O_8N_2Si$: 615.3102; found 615.3120.

Methyl (5*S*)-5-Hydroxy-5-*C*-[(2′*R*,5′*S*,6′*R*)-6′-hydroxy-5′-(hydroxymethyl)-1′-methyl-3′-oxo-1′,4′-diazepan-2′-yl]-2,3-*O*-isopropylidene-β-D-ribofuranoside (1a) and Its (5*R*,2′*S*) Isomer 1b: To the silylated lactam **19a** or **19b** (10 mg, 16.2 μmol) in THF (375 μL) at 20 °C was added tetrabutylammonium fluoride (1 M in THF, 17.9 μL, 1.1 equiv.) and the mixture was stirred for 15 h. Concentration in vacuo was followed by chromatographic purification on a Merck 60F-254 precoated silica plate (thickness 0.2 mm; eluent CH_2Cl_2/EtOAc/MeOH, 7:3:1.2) to give 4.5 mg (74%) of the expected ribosyldiazepanone **1a** or **1b**. − **Compound 1a:** TLC (same conditions as for purification by flash chromatography): R_f = 0.17. − $[\alpha]_D$ = −3 (c = 1.0, CH_2Cl_2). − ^{1}H NMR (CD_3OD, 500 MHz): δ = 4.92 (s, 1 H, 1-H), 4.90 (d, $J_{3,2}$ = 6.2 Hz, 1 H, 3-H), 4.59 (d, $J_{2,3}$ = 6.2 Hz, 1 H, 2-H), 4.23 (d, $J_{4,5}$ = 9.2 Hz, 1 H, 4-H), 4.10 (ddd, $J_{5',6'}$ = 9 Hz, J_{5',CH_aOH} = 5 Hz, J_{5',CH_bOH} = 3.3 Hz, 1 H, 5′-H), 3.93 (dd, $J_{5,4}$ = 9.2 Hz, $J_{5,2'}$ = 2.2 Hz, 1 H, 5-H), 3.81−3.70 (m, J_{CH_2OH} = 11 Hz, $J_{CH_aOH,5'}$ = 5 Hz, $J_{CH_bOH,5'}$ = 3.3 Hz, 3 H, CH_2OH, 6′-H), 3.44 (d, 1 H, $J_{2',5}$ = 2.2 Hz, 2′-H), 3.37 (s, 3 H, OMe), 3.01 (dd, $J_{7'b,7'a}$ = 15 Hz, $J_{7'b,6'}$ = 3.3 Hz, 1 H, 7′b-H), 2.90 (dd, $J_{7'a,7'b}$ = 15 Hz, $J_{7'a,6'}$ = 3.5 Hz, 1 H, 7′a-H), 2.46 (s, 3 H, NMe), 1.43, 1.30 (2 s, 6 H, CMe_2). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.08 (s, 1 H, NH), 4.97 (s, 1 H, 1-H), 4.93 (d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.56 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.46 (d, $J_{4,5}$ = 4.3 Hz, 1 H, 4-H), 4.15−4.05 (m, 1 H, 5-H), 3.95−3.75 (m, 4 H, CH_2OH, 5′-H, 6′-H), 3.41 (s, 3 H, OMe), 3.39 (d, $J_{2',5}$ = 5.8 Hz, 1 H, 2′-H), 3.10 (br. d, $J_{7'b,7'a}$ = 14 Hz, 1 H, 7′b-H), 2.95 (br. d, $J_{7'a,7'b}$ = 14 Hz, 1 H, 7′a-H), 2.52 (s, 3 H, NMe), 1.46, 1.31 (2 s, 6 H, CMe_2). − ^{13}C NMR (126 MHz, CD_3OD): δ = 175.7 (C-3′), 113.3 (CMe_2), 111.6 (C_1), 88.5 (C-4), 86.6 (C-2), 83.3 (C-3), 75.9 (C-2′), 72.7 (C-5), 69.7(C-6′), 61.4 (CH_2OH), 61.3 (C-7′), 56.9 (C-5′), 56.5 (OMe), 44.6 (NMe), 26.8, 25.2 (CMe_2). − MS (FAB$^+$, thioglycerol): m/z = 377 (100), 345 (52), 309 (21), 282 (22), 259 (12). − HRMS (FAB$^+$) calcd. for $C_{16}H_{29}O_8N_2$:377.1924; found 377.1933. − **Compound 1b:** TLC (same conditions as for purification by flash chromatography): R_f = 0.30. − $[\alpha]_D$ = +73 (c = 0.81, CH_2Cl_2). − ^{1}H NMR (500 MHz): δ = 5.79 (d, $J_{NH,5'}$ = 3.4 Hz, 1 H, NH), 4.58 (s, 1 H, 1-H), 4.57 (d, $J_{3,2}$ ≈ 5.5 Hz, 1 H, 3-H), 4.23 (d, $J_{2,3}$ ≈ 5.3 Hz, 1 H, 2-H), 4.06 (d, $J_{4,5}$ = 6.8 Hz, 1 H, 4-H), 3.78 (dd, J_{CH_2OH} = 10 Hz, $J_{CH_aOH,5'}$ = 4.0 Hz, 1 H, CH_aOH), 3.92 (dd, $J_{5,4}$ = 6.8 Hz, $J_{5,2'}$ = 4.3 Hz, 1 H, 5-H), 3.67 (ddd, $J_{6',7'a}$ = 9 Hz, $J_{6',5'}$ ≈ 8.5 Hz, $J_{6',7'b}$ = 3.4 Hz, 1 H, 6′-H), 3.60 (dd, J_{CH_2OH} = 10 Hz, $J_{CH_bOH,5'}$ = 3.0 Hz, 1 H, CH_bOH), 3.38 (d, $J_{2',5}$ = 4.3 Hz, 1 H, 2′-H), 3.21 (dddd, $J_{5',6'}$ = 8.5 Hz, J_{5',CH_aOH} = 4.0 Hz, J_{5',CH_bOH} = 3.0 Hz, $J_{5',NH}$ = 3.4 Hz, 1 H, 5′-H), 3.11 (dd, $J_{7'b,7'a}$ = 12.6 Hz, $J_{7'b,6'}$ = 3.4 Hz, 1 H, 7′b-H), 3.14 (s, 3 H, OMe), 2.81 (dd, $J_{7'a,7'b}$ =

12.6 Hz, $J_{7'a,6'}$ = 9.0 Hz, 1 H, 7′a-H), 2.44 (s, 3 H, NMe), 1.46, 1.29 (2 s, 6 H, CMe_2). − ^{13}C NMR (126 MHz): δ = 175.6 (C-3′), 112.2 (CMe_2), 110.2 (C-1), 86.7 (C-4), 85.2 (C-2), 81.3 (C-3), 70.9 (C-5), 65.5 (C-7′), 63.3, 62.1, 61.6 (C-2′, C-6′, CH_2OH), 58.1 (C-5′), 55.6 (OMe), 37.9 (NMe), 26.4, 24.8 (CMe_2). − MS (FAB^+, thioglycerol): *m*/*z* = 377 (100), 345 (95), 309 (22), 282 (28), 257 (12). − HRMS (FAB^+): calcd. for $C_{16}H_{29}O_8N_2$: 377.1924; found 377.1952.

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