DOI: 10.1002/ejoc.200700333

Synthetic Routes to Three Novel Scaffolds for Potential Glycosidase Inhibitors

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Keywords: Synthesis / Ketalisation / Hydroxypyridine / Cyclopentane / Glycosidase inhibitor

Efficient syntheses of three novel scaffolds for potential β-glycosidase inhibitors were developed: The first consists of a 2,7-dioxabicyclo[2.2.1]heptane derivative, which was prepared by an intramolecular ketalisation. The second scaffold consists of a hydroxylated cyclopentylamine, which could be synthesised stereoselectively from 2-azabicyclo[2.2.1]hept-5-en-3-one. The third scaffold, a 4,5-dihydroxynicotinic acid, was accessible through a sequence of substituent directed *ortho*-lithiations. Selected compounds were tested as inhibitors for a number of glycosidases. Three nicotinic acid derivatives were found to be selective β-glucosidase inhibitors.

Introduction

The oligosaccharides of the glycocalix are involved in many disease-relevant cellular molecular-recognition events. Glycosidases, which interfere and control the cellular oligosaccharide processing are therefore an important class of targets for pharmaceutical research. For that reason, glycosidase inhibitors present an important substance class for drug development.[1] Currently, glycosidase inhibitors are established for the treatment of diabetes[2] and influenza.[3] Furthermore, their function as antiviral agents is also useful for the development of potential applications against hepatitis,[4] HIV[5] and cancer.[6] Representative examples for β-glycosidase inhibitors of natural-product and non-natural-product origin are shown in Figure 1. Isofagomine (**1**) is an isomer of the natural product fagomine,[7] while siastatin B (**2**), a natural product from *Clostridium perfringens*, inhibits sialidase.[8] The isoquinuclidine **3**, a mimic of the β-D-mannopyranoside $^{1,4}B$ conformer,[9] as well as the iminosugar **4**,[10] are the results of inhibitor design and synthetic efforts.

The search for efficient and selective glycosidase inhibitors challenges transition-state-analogue design[11] and organic synthesis. Based on the mechanism for a retaining β-glycosidase, we had proposed a 2,7-dioxabicyclo[2.2.1]heptane derivative as potential inhibitor.[12] Here, we report in full detail the synthetic route to this novel scaffold, as well as another two inhibitor frameworks: 4,5-dihydroxynicotinic acid derivatives and hydroxylated cyclopentylamines. In addition, selected compounds were tested as inhibitors for a number of glycosidases and the results are reported.

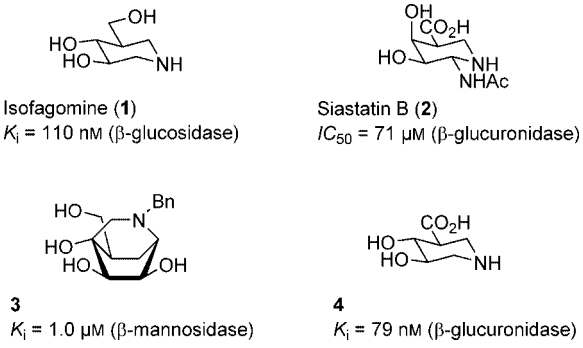

Figure 1. Naturally occurring and synthetic β-glycosidase inhibitors.

Results and Discussion

Design of the Scaffolds

For retaining β-glycosidases the cleavage of the glycosidic bond proceeds through a boat-like conformer in which the scissile C–O bond is oriented antiperiplanar to the doubly occupied non-bonding orbital of the endocyclic oxygen atom.[13,14] The involvement of a boat-type conformer in the reaction pathway of retaining β-glycosidases is shown schematically in Figure 2 for a β-glucuronidase. Guided by the pioneering work of Vasella and co-workers[9,13d,15] to use locked boat conformations as potential inhibitors we devised a novel bicyclic ketal: the dioxabicyclo[2.2.1]heptane derivative **5** should imitate the substrate in a conformation related to the transition state. The amino group in **5** is intended to mimic the positive charge of the oxonium ion.

The structure of the naturally occurring β-glucuronidase inhibitor siastatin B (**2**) served as a lead structure for the development of further two types of potential inhibitors (Figure 3). The change of the piperidine ring to a cyclopentylamine (dashed line in **2** of Figure 3) results in the cyclo-

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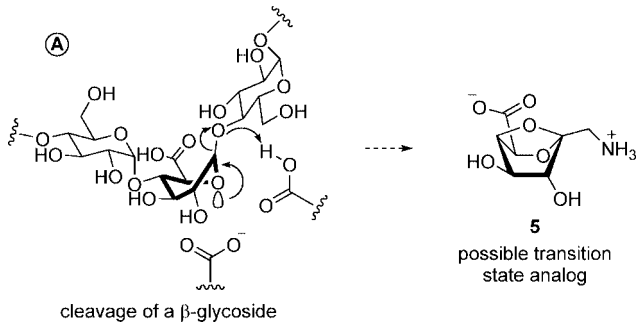


Figure 2. Section of the reaction pathway (A) for a retaining β-glucuronidase.

pentane **7**. If one assumes the imine **6** (or its iminium ion) as the biologically active form of siastatin B, then the 4,5-dihydroxynicotinic acid **8** might be another interesting candidate for glycosidase inhibition. The last scaffold evades on purpose stereochemical issues but offers the advantages of a rigid structure with a possible positive charge at the pyridine nitrogen atom (after *N*-protonation or *N*-alkylation).

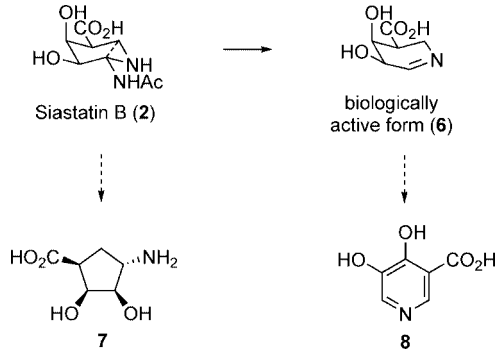
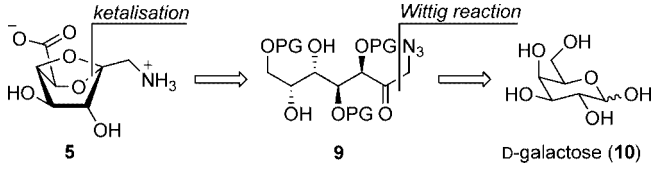


Figure 3. Siastatin B (**2**), a naturally occurring glycosidase inhibitor, as a lead structure for the inhibitor candidates **7** and **8**.

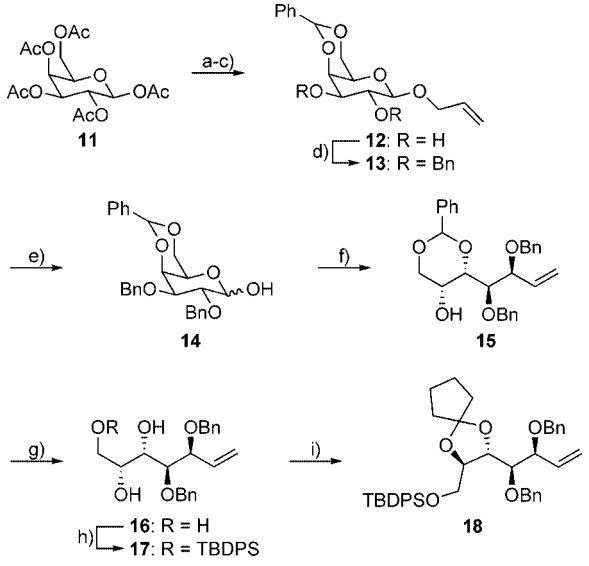
Synthesis of the Dioxabicyclo[2.2.1]heptane Scaffold

The synthetic plan for the bicyclic amino acid **5** relied on an intramolecular ketalisation of the open-chain dihydroxy ketone **9** as the key step (Scheme 1). Compound **9** should be available from D-galactose (**10**) by a C1 homologation, e.g., by a Wittig reaction.



Scheme 1. Retrosynthesis of bicyclic galacturonic acid derivative **5**.

According to this plan β-D-galactose pentaacetate[16] (**11**) was chosen as starting material (Scheme 2). By using allylic alcohol and boron trifluoride–diethyl ether[17] compound **11** was transformed into the corresponding anomeric allyl ether. After methanolysis of the remaining acetates with cat. NaOMe in MeOH,[18] the 4,6-diol was selectively protected as benzylidene acetal[19] to yield compound **12**. The benzylation of the two hydroxy groups in 2- and 3-position gave the fully protected galactose building block **13**. The subsequent selective cleavage of the allyl ether (**13** → **14**) could be achieved by its base-mediated (KO*t*Bu in DMSO, 100 °C) rearrangement into the corresponding enol ether and the cleavage of the latter with $HgCl_2$/HgO in acetone/water.[20]

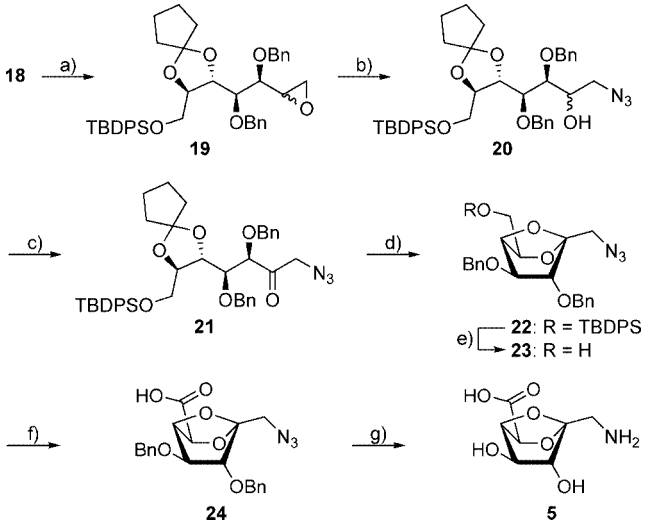


Scheme 2. a) CH_2CHCH_2OH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C → room temp., 24 h; b) NaOMe, MeOH, room temp., 18 h; c) $PhCH(OMe)_2$, CSA, MeCN, room temp., 1.5 h, 63% over three steps; d) NaH, BnBr, THF, room temp., 24 h, 93%; e) i. KO*t*Bu, DMSO, 100 °C, 20 min, ii. yellow HgO, $HgCl_2$, acetone/H_2O, 9:1, room temp., 15 h, 83%; f) $[Ph_3PMe]^+ Br^-$, *n*BuLi, THF, –30 °C → room temp., 24 h, 90%; g) $HS(CH_2)_3SH$, CSA, MeOH, room temp., 15 h, 97%; h) TBDPS-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C → room temp., 3 d, 83%; i) 1,1-dimethoxycyclopentane, CSA, MeCN, room temp., 25 min, 93%.

Next, a lactol Wittig reaction[21] (**14** → **15**) was performed in 90% yield by adding **14** to $[Ph_3PMe]^+Br^-$/*n*BuLi at –30 °C.[22] The subsequent cleavage of the benzylidene acetal **15** to the triol **16** with CSA in MeOH proceeded quantitatively only upon addition of 1,3-propanedithiol to trap the emerging benzaldehyde. The primary hydroxy function in **16** was protected selectively using TBDPS-Cl and TEA/DMAP to give the silyl ether **17**. The following choice of the protecting group for the remaining 1,2-diol was crucial for the final ketalisation. Initial attempts with an isopropylidene ketal suffered from problems in this key step. Thus, the more labile cyclopentylidene ketal[23] was chosen and compound **18** was obtained.

The final reaction sequence dealt with the introduction of the amino functionality and the construction of the bicyclic ketal (Scheme 3). First, the epoxidation of the alkene **18** led to the epoxide **19**. The opening of the epoxide with sodium azide at the less substituted position resulted in the azido alcohol **20**. A Swern oxidation converted the alcohol **20** into the ketone **21**. The following bicyclisation required the selective deprotection of the cyclopentylidene ketal without cleavage of the primary TBDPS ether. This was

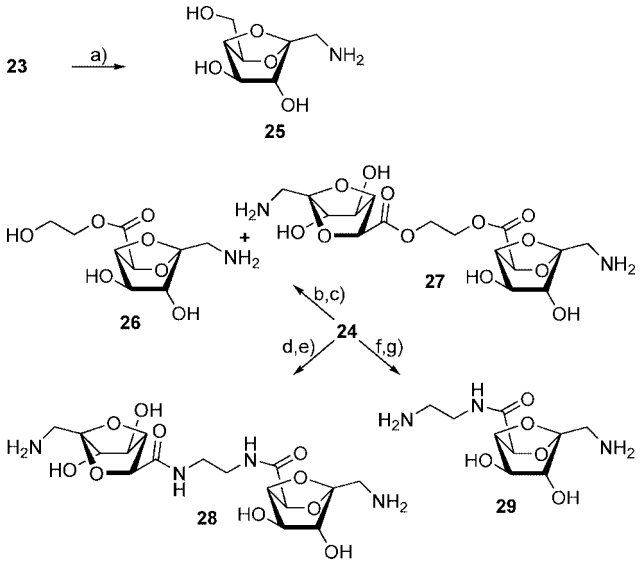
possible under anhydrous reaction conditions at 20 °C in a mixture of CH_2Cl_2 and TFA containing powdered molecular sieves. After chromatography the desired dioxabicyclo[2.2.1]heptane derivative **22** was obtained in 89% yield. The primary TBDPS ether was now cleaved with TBAF to afford the primary alcohol **23**. A subsequent one-step oxidation using diacetoxyiodobenzene and cat. TEMPO[24] led to the carboxylic acid **24**. The final deprotection of the benzyl ethers and the simultaneous reduction of the azide was accomplished by hydrogenation with $Pd(OH)_2/C$. The crude product was dissolved in MeOH and precipitated on addition of ethyl acetate to yield the target compound **5** as a colourless powder. The structure of **5** was confirmed by X-ray crystal structure analysis.[12]



Scheme 3. a) *m*CPBA, CH_2Cl_2, 0 °C → room temp., 60 h, 87%; b) NaN_3, NH_4Cl, EtOH, 78 °C, 45 h, 87% (98% based on conversion); c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 °C → room temp., 1.5 h, 83%; d) TFA/CH_2Cl_2 (1:1), MS (4 Å), room temp., 30 min, 89%; e) TBAF, THF, room temp., 1 h, 93%; f) $PhI(OAc)_2$, TEMPO, wet CH_2Cl_2, room temp., 90 min, 87%; g) H_2, $Pd(OH)_2/C$, EtOAc/MeOH, 2:1, room temp., 90 min, quant.

With an efficient route to the new scaffold in hand, a number of derivatives was prepared (Scheme 4). From **23** the amino alcohol **25** was obtained by reduction of the azide and simultaneous cleavage of the benzyl ethers. The azidocarboxylic acid **24** was the starting point for monomeric (**26**, **29**) and dimeric derivatives (**27**, **28**). Esterification of **24** with ethyleneglycol and subsequent azide reduction and benzyl ether cleavage yielded the monoester **26** and the diester **27**. Amide formation with ethylenediamine followed by hydrogenolysis led to the diamide **28**, while amide formation with Z-protected ethylenediamine and subsequent hydrogenolysis provided the monoamide **29**.

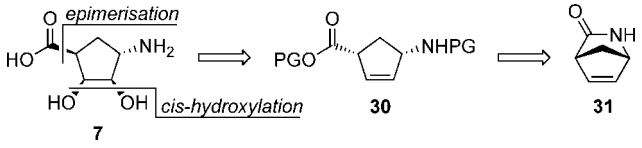
The synthetic routes described above allow an efficient elaboration of the novel dioxabicyclo[2.2.1]heptane scaffold in enantiopure form. The variability in the end game of the synthesis opens the possibility to a wide range of variations and derivative formation.



Scheme 4. a) H_2, $Pd(OH)_2/C$, EtOAc/MeOH, 2:1, room temp., 3 h, 99%; b) $HOCH_2CH_2OH$, EDC·HCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → room temp., 24 h, monomer: 22% (32% based on conversion), dimer: 12% (17% based on conversion); c) H_2, $Pd(OH)_2/C$, EtOAc/MeOH (2:1), room temp., 3–18 h, quant. monomer and 92% dimer; d) $H_2NCH_2CH_2NH_2$, HBTU, HOBt, *i*Pr_2NEt, CH_2Cl_2, room temp., 2 h, 40% (48% based on conversion); e) H_2, $Pd(OH)_2/C$, EtOAc/MeOH, 2:1, room temp., 18 h, 96%; f) $H_2NCH_2CH_2NHZ$, HATU, HOAt, *i*Pr_2NEt, CH_2Cl_2, room temp., 2 h, 78%; g) H_2, $Pd(OH)_2/C$, EtOAc/MeOH, 2:1, room temp., 3.5 h, 95%.

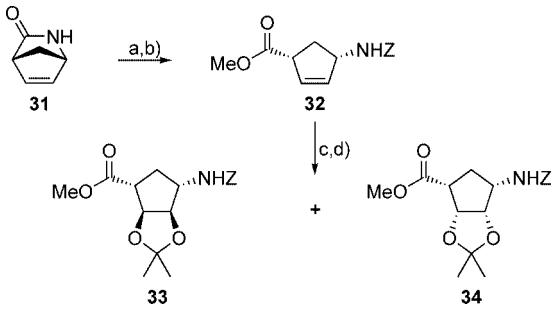
Synthesis of the Cyclopentane Scaffold

The synthetic strategy for the siastatin structure derived dihydroxycyclopentane amino acid **7** is shown in Scheme 5. A *cis*-dihydroxylation of an olefin precursor and the epimerisation of the carboxylic substituent leads to the *cis*-substituted precursor **30**, which should be accessible from the commercially available enantiopure lactam **31**. This approach should also lead to stereoanalogs of compound **7**.



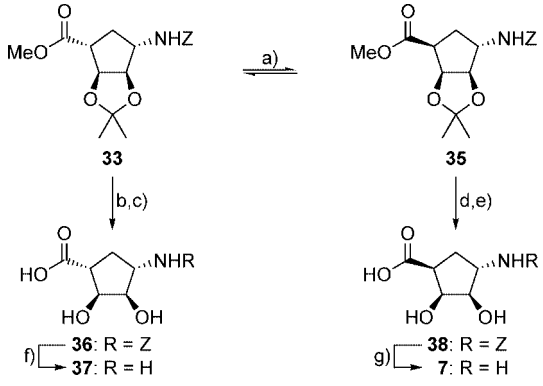
Scheme 5. Retrosynthesis of the dihydroxycyclopentane amino acid **7**.

The opening of the bicyclic lactam **31** in HCl/MeOH[25] gave the corresponding γ-amino methyl ester, whose amino group was directly Z-protected[26] to **32** (Scheme 6). The *cis* configuration of **32** was confirmed by the NOESY spectrum, and an epimerisation under the esterification conditions could be excluded.[27] The dihydroxylation of **32** with K_2OsO_4/NMO provided two diastereomeric *cis*-diols in a 1:1 ratio, which were in our hands not separable directly by silica gel chromatography. In contrast, the corresponding acetonides **33** and **34**, which were obtained from the diol mixture, were easily separated by flash column chromatography.



Scheme 6. a) $SOCl_2$, MeOH, 0 °C, 2 h; b) benzyl chloroformate, $NaHCO_3$, 1,4-dioxane/H_2O (4:3), room temp., 2 h, 93% over two steps; c) K_2OsO_4, NMO, acetone/H_2O (9:1), room temp., 40 h, 87%; d) 2,2-dimethoxypropane, CSA, MeCN, room temp., 30 min, 42% **33** and 49% **34**.

NaOMe in MeOH was a suitable base for the epimerisation **33** → **35**. Under these conditions the thermodynamically controlled deprotonation avoided β-elimination of the alkoxy substituent. Both epimeric esters **33** and **35** could be separated by chromatography and converted into the desired dihydroxy-γ-amino acids by microwave-assisted acetonide cleavage (**33** → **36**, **35** → **38**), ester hydrolysis and hydrogenolytic cleavage of the carbamate (**36** → **37**, **38** → **7**, Scheme 7).

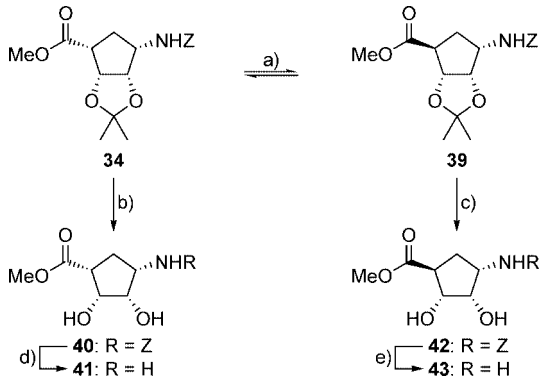


Scheme 7. a) NaOMe, MeOH, room temp., 100 min, 40% **35** and 45% **33**; b) AcOH/H_2O (4:1), 100 °C (microwave), 10 min; c) LiOH·H_2O, THF/H_2O (3:1), room temp., 18 h, 79% over two steps; d) AcOH/H_2O (4:1), 100 °C (microwave), 10 min; e) LiOH·H_2O, THF/H_2O (3:1), room temp., 1 h, 95% over two steps; f) H_2, $Pd(OH)_2$/C, MeOH, room temp., 90 min, 98%; g) H_2, $Pd(OH)_2$/C, MeOH, room temp., 1 h, 90%.

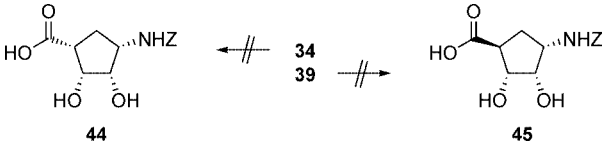
The diastereomeric acetonide ester **34** was epimerised to **39** (Scheme 8). Cleavage of the acetonide (**34** → **40**, **39** → **42**), and subsequent carbamate cleavage afforded the corresponding dihydroxy-γ-amino esters **41** and **43**.

As shown in Scheme 9, all attempts to hydrolyse the ester after cleavage of the acetonide failed for compounds **34** (→ **44**) and **39** (→ **45**). The *cis*-configured Z-protected amino alcohol led to an undesired oxazolidinone formation in these cases.

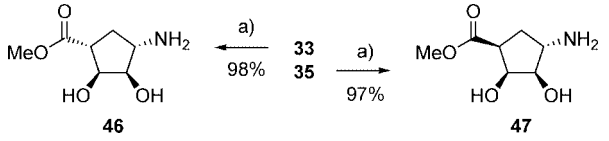
With compounds **33** and **35** the hydrogenolytic cleavage of the Z group after the acetonide cleavage was possible and resulted in the formation of the dihydroxy-γ-amino esters **46** and **47** (Scheme 10).



Scheme 8. a) NaOMe, MeOH, room temp., 3 h, 37% **39** and 58% **34**; b) AcOH/H_2O (1:1), 100 °C (microwave), 30 min, 90%; c) AcOH/H_2O (4:1), 100 °C (microwave), 10 min, 80%; d) H_2, $Pd(OH)_2$/C, MeOH, room temp., 1 h, 74%; e) H_2, $Pd(OH)_2$/C, MeOH, room temp., 1 h, 90%.



Scheme 9. Acetonide cleavage and subsequent saponification did not give the corresponding carboxylic acids **44** and **45**.

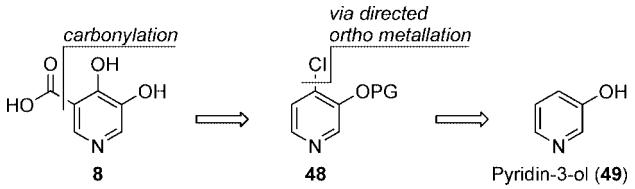


Scheme 10. a) i: AcOH/H_2O (4:1), 100 °C (microwave), 10 min; ii: H_2, $Pd(OH)_2$/C, MeOH, room temp., 90 min.

To summarise the synthesis of the cyclopentane scaffold, the choice of the enantiopure lactam **31**, combined with a stereodivergent approach, gave access to a series of dihydroxycyclopentane γ-amino acids (**7**, **37**) and esters (**41**, **43**, **46**, **47**).

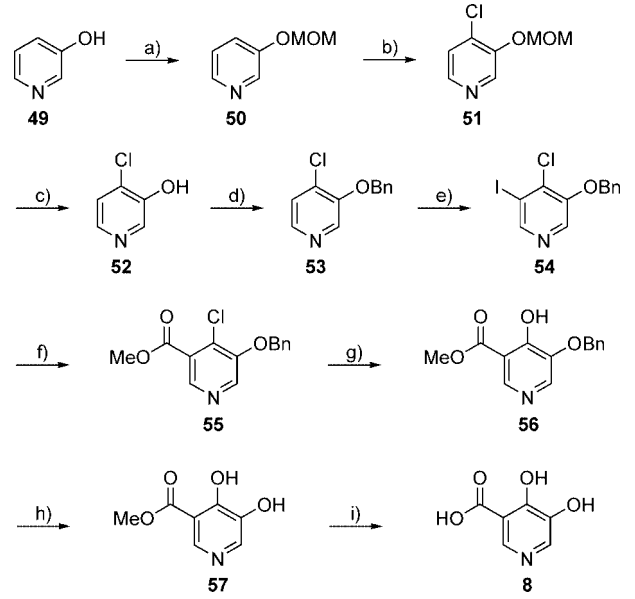
Synthesis of the 4,5-Dihydroxynicotinic Acid Scaffold

With no synthetic access to the 4,5-dihydroxynicotinic acid (**8**) known, we focused on the preparation of substituted heteroaromatics using directed *ortho*-metallation.[28] The retrosynthetic considerations of 4,5-dihydroxynicotinic acid (**8**) led to a route (Scheme 11) where the carboxylic group would be introduced at last by a carbonylation reaction. A properly *O*-protected 4-chloropyridin-3-ol **48** might be a precursor for this step. The latter should be available by 4-directed *ortho*-metallation from pyridin-3-ol (**49**). Various derivatives of compound **8** should be accessible according to this approach.



Scheme 11. Retrosynthesis of hydroxypyridine **8**.

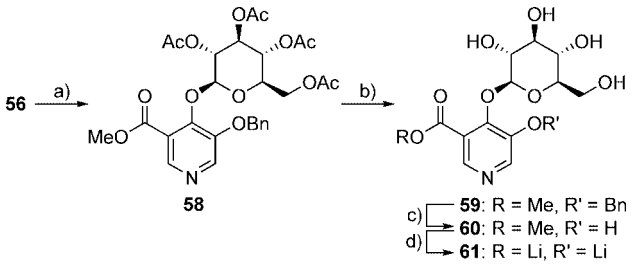
The synthesis of **8** commenced with the MOM protection of pyridin-3-ol (**49**). Compared to the literature procedure,[29] a better yield of **50** was achieved using DMF as solvent. The *ortho*-lithiation of **50** took place at –78 °C in Et_2O and after treatment with hexachloroethane, the chloropyridine **51** was obtained in 87% yield. In order to avoid a directing effect of the MOM group towards the 2-position in the next lithiation step, it was exchanged for a benzyl ether (**51** → **52** → **53**), which has the additional advantage of neutral (hydrogenolytic) cleavage conditions at the end of the synthesis. A selective lithiation of **51** at the 5-position with LDA at –78 °C was achieved. It should be noticed that with pyridines a halogen substituent can have a stronger metal-directing effect than an alkoxy substituent[28a] (Scheme 12).



Scheme 12. a) NaH, MOM-Cl, DMF, 0 °C, 90 min, 76%; b) *t*BuLi, C_2Cl_6, Et_2O, –78 °C → room temp., 2 h, 87%; c) TFA, CH_2Cl_2, 0 °C → room temp., 14 h, 94%; d) NaH, 15-crown-5, BnBr, DMF, 0 °C, 80 min, 55%; e) LDA, I_2, THF, hexanes, –78 °C, 75 min, 78% (83% based on conversion); f) CO, Et_3N, (*rac*-BINAP)$PdCl_2$, MeOH, 85 °C, 5 h, 95%; g) AcCl, MeOH, 85 °C, 16 h, 80%; h) H_2, $Pd(OH)_2$/C, TFE, room temp., 90 min, 98%; i) LiOH·H_2O, H_2O, 75 °C, 7 h, 92%.

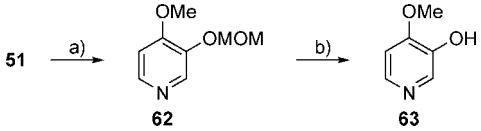
Preliminary experiments of quenching the pyridinyllithium intermediate from **53** with CO_2 (dry ice) gave only 47% yield of the desired carboxylic acid. A higher yield was achieved with the two-step procedure iodination/carbonylation (**53** → **54** → **55**). The use of CO in MeOH and (*rac*-BINAP)$PdCl_2$ as catalyst[30] gave the methyl ester **55** in 95% yield. The conversion of the 4-chloropyridine **55** to the 4-hydroxypyridine **56** was best accomplished with HCl/MeOH. A mechanistic rationale of this reaction consists of a nucleophilic aromatic substitution of chloride by methoxide and a subsequent S_N2 attack of chloride to yield the hydroxypyridine and methyl chloride which is converted into dimethyl ether.[31] An X-ray crystal structure analysis confirmed the constitution of **56**. The following debenzylation suffered from the low solubility of **56** in most common solvents. Trifluoroethanol was the only suitable solvent, which allowed a clean hydrogenolysis leading to **57**. Finally, the methyl ester was hydrolysed and the desired dihydroxynicotinic acid (**8**) was obtained.

The integration of the dihydroxynicotinic acid into a disaccharide mimic could be achieved by a glycosidic linkage to a sugar residue (Scheme 13). D-Glucose was chosen as the sugar moiety. The 4-hydroxypyridine **56** was allowed to react with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide under modified Koenigs–Knorr conditions[32] to yield the β-glucopyranoside **58** as the exclusive product. The *O*-glycosylation (no *N*-glycosylation was observed) was confirmed at a later stage of the deprotected compound **61**: in the HMBC spectrum the anomeric proton 1′-H showed a $^3J_{CH}$ coupling to C-4 of the pyridine. The deprotection proceeded in the following three steps. After methanolytic cleavage of the acetates in **58**, the tetraol **59** was obtained. The hydrogenolysis of the benzyl ether in **59** led to the 3-hydroxypyridine **60**. At last, the methyl ester could be hydrolysed to the corresponding carboxylic acid, which was stable as its lithium carboxylate **61**.



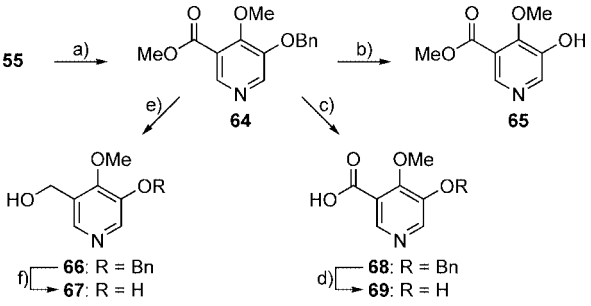
Scheme 13. a) 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide, AgOTf, 2,6-lutidine, MS (4 Å), CH_2Cl_2, room temp., 20 h, 78%; b) NaOMe, MeOH, room temp., 15 h, 94%; c) H_2, Pd black, EtOAc/MeOH (4:1), room temp., 150 min, quant.; d) LiOH·H_2O, THF/H_2O (3:1), room temp., 18 h, 93%.

For comparison, a dihydroxypyridine derivative lacking the carboxylic acid of the nicotinic acid was synthesised (Scheme 14). The 4-chloropyridine **51** was converted into the 3-methoxypyridine **62**, which after MOM cleavage afforded the 3-hydroxy-4-methoxypyridine (**63**).



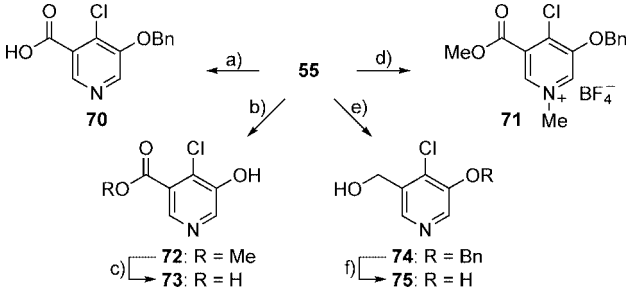
Scheme 14. a) NaOMe, MeOH, 80 °C, 32 h, 24%; b) TFA, CH_2Cl_2, 0 °C, 5 h, 87%.

To explore variations in the 4-position of the pyridine, a series of compounds with a 4-methoxy group was prepared (Scheme 15). Starting with the 4-chloronicotinic acid derivative **55**, a nucleophilic substitution by methoxide gave compound **64**. Hydrogenolytic cleavage of the benzyl ether resulted in **65**. The ester group in **64** was reduced to the corresponding alcohol **66**, which was deprotected to afford **67**. Hydrolysis of the ester group in **64** gave the carboxylic acid **68** and after debenzylation **69**.



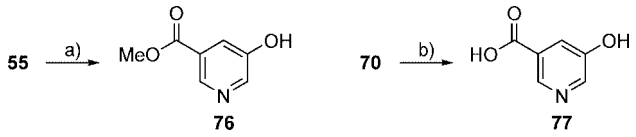
Scheme 15. a) NaOMe, MeOH, 85 °C, 24 h, 85%; b) H_2, Pd/C, MeOH, room temp., 2.5 h, 99%; c) LiOH·H_2O, THF/H_2O (3:1), room temp., 2 h, 90%; d) H_2, Pd/C, MeOH, room temp., 6 h, 95%; e) DIBAH, CH_2Cl_2, petroleum ether, –78 °C → room temp., 4 h, 89%; f) H_2, Pd/C, MeOH, room temp., 6 h, 96%.

The synthesis of 4-chloronicotinic acid derivatives is summarised in Scheme 16. While the synthesis of the compounds **70**, **72**, **73**, **74**, and **75** used similar reaction sequences as described for the 4-methoxy series, the access to the *N*-methylated pyridinium salt **71** deserves a comment. By using Meerwein's reagent the 4-chloronicotinic ester **55** could be *N*-alkylated at 20 °C to produce **71** with 78% yield.[33] The permanent positive charge was introduced to mimic the oxonium ion of the glycosidase mechanistic intermediate.



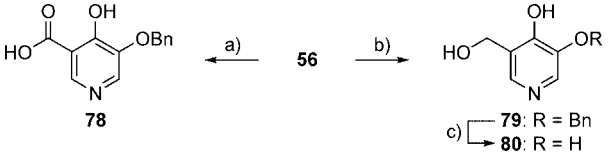
Scheme 16. a) LiOH·H_2O, THF/H_2O (3:1), room temp., 3.5 h, 98%; b) 1,4-cyclohexadiene, Pd black, MeOH, room temp., 30 min, 86%; c) LiOH·H_2O, THF/H_2O (3:1), room temp., 24 h, 96%; d) $Me_3O^+BF_4^-$, CH_2Cl_2, room temp., 6 h, 78%; e) DIBAH, CH_2Cl_2, –78 °C → room temp., 5 h, 85% (93% based on conversion); f) 1,4-cyclohexadiene, Pd black, MeOH, room temp., 3 h, 88%.

The Pd-mediated hydrogenolytic removal of the 4-chloro substituent led to the two 5-hydroxynicotinic acid derivatives **76** and **77** (Scheme 17).



Scheme 17. a) H_2, Pd/C, MeOH/DMF (5:1), room temp., 40 min, quant.; b) H_2, $Pd(OH)_2$/C, MeOH, room temp., 1 h, quant.

The 4-hydroxypyridines **78**, **79** and **80** were prepared from the common intermediate **56** (Scheme 18).



Scheme 18. a) LiOH·H_2O, THF/H_2O (3:1), room temp., 20 h, quant.; b) DIBAH, CH_2Cl_2, petroleum ether, –78 °C → room temp., 25 h, 75%; c) H_2, $Pd(OH)_2$/C, MeOH, room temp., 90 min, 88%.

The synthetic routes presented here allow an efficient access to 4,5-hydroxynicotinic acid scaffold with additional variation in the 4-position possible (R = OMe, Cl, H).

Glycosidase Inhibition Studies

Selected compounds of the three conceptually different inhibitor series were tested against commercially available β-glucuronidase, α- and β-glucosidase, α- and β-galactosidase, α-mannosidase and α-L-fucosidase. The rates of the enzymatic hydrolysis of appropriate substrates were determined spectrophotometrically in the absence and presence of the test compounds, while the quotient of both values gave the residual enzyme activity. In a preliminary screening the potential inhibitors were added at a concentration of 300 μm and compounds effecting an enzyme activity > 50% were regarded as inactive.

All tested substances of the bicyclic galacturonic acid series were not active towards the given glycosidases (IC_{50} > 500 μM). The cyclopentane series demonstrated the relevance of stereochemical issues. Only amino acid **7**, whose configuration derived from the natural β-glucuronidase inhibitor siastatin B, displayed a weak glycosidase inhibitory effect. However, inhibition was not selective as several glycosidases were affected. The three compounds **66**, **71** and **79** of the nicotinic acid series showed good and exclusive inhibition of β-glucosidase.

Enzyme inhibition of those compounds was measured at various inhibitor concentrations and the IC_{50} values were determined by non-linear regression. The results are compiled in Table 1.

Table 1. Glycosidase inhibition studies. Given are IC_{50} values in μM.

Compound	7	66	71	79
β-Glucuronidase (bovine liver)	300	–	–	–
α-Glucosidase (yeast)	277	–	–	–
β-Glucosidase (sweet almonds)	–	87	11	147
α-Galactosidase (green coffee beans)	–	–	–	–
β-Galactosidase (bovine liver)	–	–	–	–
α-Mannosidase (jack beans)	–	–	–	–
α-L-Fucosidase (bovine kidney)	305	–	–	–

The best inhibitor found was the *N*-methylated pyridine **71**, a good and selective β-glucosidase inhibitor. This result indicates that a permanent positive charge, which mimics the mechanistically relevant oxonium ion, makes a major contribution to the inhibitory properties of a nicotinic acid derivative. Moreover, it was shown that the exchange of the carboxylic acid residue by a hydroxymethyl group enhances the inhibitory effects of such molecules. Nicotinic alcohols **66** and **79** were found to be selective β-glucosidase inhibitors whereas the corresponding nicotinic acids **68** and **78** were completely inactive. These results serve as a basis for lead structure optimisation, and further exploration of possible structural modifications seem to be with good prospects.

Conclusions

We have described efficient syntheses of three novel scaffolds which are useful for the development of potent glycosidase inhibitors. Enzyme inhibition studies revealed, that especially *N*-alkylated hydroxypyridines are promising lead structures for the development of strong and selective β-glucosidase inhibitors.

Experimental Section

General Methods: All reactions sensitive to air or moisture were performed in flame-dried glassware under dry argon in dry solvents which were prepared as follows. THF was distilled from sodium/benzophenone. Et_2O was distilled from K/Na alloy. Toluene was distilled from sodium. MeOH was distilled from Mg turnings. DMF was distilled after drying with molecular sieves (4 Å) for 24 h and decanting. CH_2Cl_2 and Et_3N were distilled from CaH_2. Any other solvents, e.g., for extractions were rotary-evaporated prior to use. All starting materials and reagents were used as received unless noted otherwise. Thin layer chromatography was performed on glass plates coated with Merck silica gel 60 F_{254}. Spots were visualised with UV light and by heat staining with acidic cerium sulfate dip or basic potassium permanganate dip. Flash column chromatography was performed on Merck silica gel 60 (40–63 μm). Melting points were measured with a Stuart SMP10 apparatus and are not corrected. IR spectra were measured with a Bruker IFS 88 spectrometer. ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometers AC-300, AV-300, DRX-400, AMX-500, AV-500 and AV-600 at 25 °C in the indicated solvent. Spectra were calibrated with respect to the solvent signal or to an internal standard if specified. Optical rotations were determined with a Perkin–Elmer polarimeter 241, using a cuvette with 10-cm path length. Elemental analysis was performed with a Heraeus CHN rapid or Elementar Vario EL. HRMS were recorded by using either Finnigan LTQ FT (ESI) or Finnigan MAT 95S (ESI, EI) mass spectrometers. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene; CSA = (±)-camphor-10-sulfonic acid; DIBAH = diisobutylaluminium hydride; DMAP = 4-*N*,*N*-dimethylaminopyridine; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt = 1-hydroxy-7-azabenzotriazole; HOBt = 1-hydroxybenzotriazole; LDA = lithium diisopropylamide; *m*CPBA = 3-chloroperbenzoic acid; MOM = methoxymethyl; MTBE = *tert*-butyl methyl ether; room temp. = room temperature; TBDPS = *tert*-butyldiphenylsilyl; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin layer chromatography; Z = benzyloxycarbonyl.

Enzyme Inhibition Assays: Enzyme inhibition properties were determined for seven commercially available (Sigma) glycosidases. Selected compounds were tested against β-glucuronidase (bovine liver; G0501), α-glucosidase (yeast; G5003), β-glucosidase (almonds; G4511), α-galactosidase (green coffee beans; G8507), β-galactosidase (bovine liver; G1875), α-mannosidase (jack beans; M7257) and α-L-fucosidase (bovine kidney; F5884). As substrates were used phenolphthalein β-D-glucuronide for β-glucuronidase, *o*-nitrophenyl β-D-galactoside for β-galactosidase and appropriate *p*-nitrophenyl glycosides for the other enzymes. Siastatin B, 1-deoxynojirimycin, 1-deoxymannonojirimycin and 1-deoxygalactonojirimycin were used as positive control. Substrates and control inhibitors were purchased from Sigma except for siastatin B which was provided by Schering AG. A solution of the potential inhibitor (50 μL) in aqueous buffer (50 μL) was thermally equilibrated to the indicated temperature. Subsequently, an aqueous solution of the enzyme (50 μL) was added and the mixture was preincubated for 8 min. Then a solution of the corresponding substrate (50 μL) was added and the assay was incubated for an exact period of time (20–45 min). The enzymatic reaction was stopped by addition of glycine buffer (pH = 10.5, 0.5 M, 200 μL) and the amount of liberated phenolphthaleine or nitrophenol was determined spectrophotometrically with a Dynex MRX TC Revelation microplate reader by the change of optical density at 530 nm and 400 nm, respectively. Each experiment was carried out five times to average over the results. In a preliminary screening, residual enzymatic activities were determined at high concentrations of the test compounds (1 mm). Further experiments with various inhibitor concentrations were run for those compounds which caused less than 50% residual enzymatic activity at 1 mm concentration. The IC_{50} values were determined as concentration of inhibitor at 50% enzyme activity. Final assay concentrations and conditions were as follows: β-glucuronidase ([*E*] = 50 units/mL, [*S*] = 0.5 mm, 100 mm acetate buffer at pH = 5.0, 37 °C, 45 min); α-glucosidase ([*E*] = 0.05 units/mL, [*S*] = 0.5 mm, 50 mm phosphate buffer at pH = 6.8, 37 °C, 20 min); β-glucosidase ([*E*] = 0.02 units/mL, [*S*] = 0.5 mm, 50 mm acetate buffer at pH = 5.0, 37 °C, 20 min); α-galactosidase ([*E*] = 0.02 units/mL, [*S*] = 0.5 mm, 100 mm phosphate buffer at pH = 6.5, 25 °C, 20 min); β-galactosidase ([*E*] = 0.04 units/mL, [*S*] = 1.0 mm, 100 mm phosphate buffer at pH = 7.3, 37 °C, 20 min); α-mannosidase ([*E*] = 0.02 units/mL, [*S*] = 0.5 mm, 50 mm acetate buffer at pH = 4.5, 25 °C, 20 min); α-L-fucosidase ([*E*] = 0.01 units/mL, [*S*] = 0.25 mm, 50 mm acetate buffer at pH = 5.5, 25 °C, 30 min).

Allyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (12)

Allylation: A solution of β-D-galactose pentaacetate (**11**) (20.0 g, 51.2 mmol) and allyl alcohol (14.0 mL, 205 mmol) in CH_2Cl_2 (400 mL) was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (9.65 mL, 76.9 mmol) was added dropwise. The mixture was stirred at the same temperature for 1 h, then it was raised to room temp., and stirring was continued for 23 h. The solution was poured into ice-cold water (300 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (100 mL), satd. $NaHCO_3$ (100 mL) and H_2O (100 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. R_f = 0.24 (*n*-hexane/MTBE, 1:1) for the tetraacetate and R_f = 0.09 (*n*-hexane/MTBE, 1:1) for the triacetate.

Acetate Deprotection: The crude allyl galactoside was dissolved in MeOH (200 mL) and treated with NaOMe (1.0 M in MeOH, 2.56 mL, 2.56 mmol). After stirring at room temp. for 18 h, the mixture was neutralised with ion exchange resin Amberlite IR-118, which was previously washed with MeOH, H_2O, 1 M HCl, H_2O and MeOH (2 × 2 mL of each). The resin was filtered off and the solvent was evaporated. R_f = 0.25 (CH_2Cl_2/MeOH/25% NH_3, 15:4:0.5).

Benzylidene Protection: The crude tetraol was suspended in MeCN (215 mL), and benzaldehyde dimethyl acetal (14.0 mL, 93.0 mmol) and CSA (540 mg, 2.32 mmol) were added which effected slow dissolution of the substrate. The reaction was quenched after 1.5 h by addition of Et_3N (5 mL), and the solvents were removed in vacuo. The solid residue was recrystallised from boiling MeOH (20 mL) to give the desired galactoside **12** (9.89 g, 32.1 mmol, 63% over three steps). R_f = 0.35 (CH_2Cl_2/MeOH, 9:1); m.p. 170 °C; $[\alpha]_D^{20}$ = –37.9 (*c* = 3.70, in $CHCl_3$/MeOH, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (br. s, 2 H, OH), 3.48 (s, 1 H, 5-H), 3.71 (br. s, 1 H, 3-H), 3.79 (dd, *J* = 9.3, 7.6 Hz, 1 H, 2-H), 4.09 (dd, *J* = 12.5, 1.9 Hz, 1 H, 6-H^a), 4.15 (dd, *J* = 12.7, 6.5 Hz, 1 H, OC*H*^{a}H^{b}CH), 4.22 (d, *J* = 3.6 Hz, 1 H, 4-H), 4.31–4.38 (m, 2 H, 1-H, 6-H^b), 4.45 (dd, *J* = 12.5, 5.3 Hz, 1 H, OCH^a*H*^{b}CH), 5.23 (d, *J* = 10.2 Hz, 1 H, CHC*H*^{a}H^b), 5.33 (dd, *J* = 17.2, 1.5 Hz, 1 H, CHCH^a*H*^{b}), 5.56 (s, 1 H, PhC*H*), 5.97 (m, 1 H, C*H*CH$_2$), 7.33–7.40 (m, 3 H, CH$_{ar}$), 7.46–7.54 (m, 2 H, CH$_{ar}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.8 (C-5), 69.3 (C-6), 70.3 (O*C*H$_2$CH), 71.9 (C-2), 72.9 (C-3), 75.5 (C-4), 101.6 (Ph*C*H), 101.8 (C-1), 118.1 (CH*C*H$_2$), 126.6 (2 C), 128.4 (2 C), 129.3 (CH$_{ar}$), 134.0 (*C*HCH$_2$), 137.7 (C$_{q,ar}$) ppm. IR (KBr): $\tilde{\nu}$ = 3487 (br. m), 2978 (w), 2865 (w), 1647 (w), 1452 (w), 1402 (m), 1368 (m), 1345 (w), 1251 (w), 1219 (w), 1171 (s), 1101 (s), 1079 (s), 1054 (s), 1012 (s), 998 (s), 929 (w), 901 (w), 860 (w), 822 (w), 768 (w), 737 (m), 697 (m), 650 (w), 624 (w), 603 (w), 556 (w), 418 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{20}NaO_6$: 331.1152; found: 331.1156 [M + Na]$^+$.

Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (13): NaH (60% in mineral oil, 5.28 g, 132 mmol) was washed with *n*-pentane (8 mL) and added to a solution of the diol **12** (5.10 g, 16.5 mmol) in THF (130 mL). The evolution of hydrogen ceased within 20 min, then benzyl bromide (7.87 mL, 66.2 mmol) was added. The mixture was stirred for 24 h. MeOH (20 mL) was added slowly to quench the reaction, and the solvents were removed in vacuo. The residue was taken up in $CHCl_3$ (250 mL), H_2O (250 mL) was added, and the phases were separated. The aqueous phase was extracted with $CHCl_3$ (3 × 100 mL), the combined organic layers were washed with H_2O (2 × 100 mL), dried with $MgSO_4$, and the solvent was evaporated to dryness. The residue was subjected to flash column chromatography (250 g silica, *n*-pentane/MTBE, 1.5:1 → 1:1.5) to provide the benzyl ether **13** (7.52 g, 15.4 mmol, 93%) as colourless solid. R_f = 0.17 (*n*-hexane/MTBE, 2:1); m.p. 127 °C; $[\alpha]_D^{25}$ = +29.6 (*c* = 3.03, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.30 (br. d, *J* = 0.8 Hz, 1 H, 5-H), 3.55 (dd, *J* = 9.7, 3.7 Hz, 1 H, 3-H), 3.87 (dd, *J* = 9.7, 7.8 Hz, 1 H, 2-H), 4.01 (dd, *J* = 12.3, 1.8 Hz, 1 H, 6-H^a), 4.10 (d, *J* = 3.2 Hz, 1 H, 4-H), 4.14 (dddd, *J* = 13.0, 6.0, 1.4, 1.4 Hz, 1 H, OC*H*^{a}H^{b}CH), 4.30 (dd, *J* = 12.3, 1.4 Hz, 1 H, 6-H^b), 4.44 (d, *J* = 7.8 Hz, 1 H, 1-H), 4.45 (dddd, *J* = 12.9, 5.2, 1.4, 1.4 Hz, 1 H, OCH^a*H*^{b}CH), 4.74 (d, *J* = 12.4 Hz, 1 H, PhC*H*$_2$), 4.78 (d, *J* = 10.6 Hz, 2 H, PhC*H*$_2$), 4.94 (d, *J* = 10.8 Hz, 1 H, PhC*H*$_2$), 5.18 (ddd, *J* = 10.5, 2.6, 1.1 Hz, 1 H, CHC*H*^{a}H^b), 5.33 (ddd, *J* = 17.3, 3.2, 1.6 Hz, 1 H, CHCH^a*H*^{b}), 5.49 (s, 1 H, PhC*H*), 5.96 (m, 1 H, C*H*CH$_2$), 7.23–7.41 (m, 13 H, CH$_{ar}$), 7.53–7.58 (m, 2 H, CH$_{ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 66.6 (C-5), 69.4 (C-6), 70.3 (O*C*H$_2$CH), 72.2 (Ph*C*H$_2$), 74.2 (C-4), 75.5 (Ph*C*H$_2$), 78.6 (C-2), 79.4 (C-3), 101.5 (Ph*C*H), 102.8 (C-1), 117.3 (CH*C*H$_2$), 126.7 (2 C), 127.7, 127.8, 127.9 (2 C), 128.26 (2 C), 128.27 (2 C), 128.4 (2 C), 128.5 (2 C), 129.1 (2 C, CH$_{ar}$), 134.4 (*C*HCH$_2$), 138.1, 138.7, 139.1 (C$_{q,ar}$) ppm. IR (KBr): $\tilde{\nu}$ = 3033 (w), 2861 (m), 1497 (w), 1454 (m), 1399 (w), 1367 (m), 1343 (w), 1186 (w), 1118 (s), 1095 (s), 1062 (s), 1027 (m), 1010 (s), 736 (s), 696 (s) cm^{-1}. $C_{30}H_{32}O_6$ (488.57): calcd. C 73.75, H 6.60; found C 73.76, H 6.49.

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranose (14): A solution of the allyl acetal **13** (1.40 g, 2.87 mmol) in dry DMSO (30 mL) was treated with KO*t*Bu (322 mg, 2.87 mmol) and the reaction flask was placed in an oil bath at 100 °C. After stirring for 20 min, the dark yet hot reaction mixture was poured onto ice-cold water (100 mL) and extracted with Et_2O (4 × 80 mL). The combined organic layers were washed with H_2O (2 × 40 mL), satd. NH_4Cl (40 mL) and brine (40 mL), and the solvents were evaporated to give a yellow solid. TLC indicated complete conversion to a slightly more polar compound. It was dissolved in acetone/H_2O (9:1 v/v, 35 mL), yellow HgO (776 mg, 3.58 mmol) was added, and a solution of $HgCl_2$ (778 mg, 2.87 mmol) in acetone/H_2O (9:1 v/v, 15 mL) was added dropwise. The mixture was stirred for 15 h, then the suspension was filtered through a short column of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in Et_2O (100 mL), washed with H_2O (50 mL), KI (10% in H_2O, 3 × 50 mL) and brine (50 mL) and dried with $MgSO_4$. The volume was reduced in vacuo to approx. 1/3 which induced crystallisation of the product. It was filtered off after standing at room temp. for 3 h. The mother liquor was concentrated to dryness, taken up in CH_2Cl_2, and Et_2O was added to gain more product. The desired protected galactose **14** (1.07 g, 2.38 mmol, 83%) was obtained as a mixture of the α/β anomers in the form of a colourless microcrystalline material. R_f = 0.35 for **14α** and R_f = 0.27 for **14β** (*n*-hexane/MTBE, 1:9); m.p. 158 °C; $[\alpha]_D^{20}$ = +81.4 (*c* = 2.84, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 3.16 (d, *J* = 1.5 Hz, 1 H, OH, **14α**), 3.25 (s, 1 H, 5-H, **14β**), 3.53 (dd, *J* = 9.6, 3.5 Hz, 1 H, 3-H, **14β**), 3.62 (d, *J* = 7.2 Hz, 1 H, OH, **14β**), 3.75–3.80 (m, 2 H, 5-H, **14α**, 2-H, **14β**), 3.92–3.98 (m, 3 H, 6-H^a, **14β**, 3-H, 6-H^a, **14α**), 4.03 (dd, *J* = 9.9, 3.3 Hz, 1 H, 2-H, **14α**), 4.07 (d, *J* = 3.2 Hz, 1 H, 4-H, **14β**), 4.15 (d, *J* = 2.9 Hz, 1 H, 4-H, **14α**), 4.18 (d, *J* = 12.3 Hz, 1 H, 6-H^b, **14α**), 4.27 (d, *J* = 12.3 Hz, 1 H, 6-H^b, **14β**), 4.61 (t, *J* = 7.4 Hz, 1 H, 1-H, **14β**), 4.65–4.89 (m, 8 H, PhC*H*$_2$), 5.34 (br. s, 1 H, 1-H, **14α**), 5.46 (s, 1 H, PhC*H*, **14α**), 5.47 (s, 1 H, PhC*H*, **14β**), 7.24–7.42 (m, 26 H, CH$_{ar}$), 7.50–7.56 (m, 4 H, CH$_{ar}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.8 (C-5, **14α**), 66.7 (C-5, **14β**), 69.4 (C-6, **14β**), 69.6 (C-6, **14α**), 71.9 (Ph*C*H$_2$, **14α**), 72.0 (Ph*C*H$_2$, **14β**), 73.85 (C-4, **14β**), 73.90 (Ph*C*H$_2$, **14α**), 74.4 (C-4, **14α**) 75.3 (Ph*C*H$_2$, **14β**), 75.8, 75.9 (C-2, C-3, **14α**), 79.5 (C-3, **14β**), 80.0 (C-2, **14β**), 92.5 (C-1, **14α**), 97.6 (C-1, **14β**), 101.1 (Ph*C*H, **14α**), 101.2 (Ph*C*H, **14β**), 126.4, 126.5, 127.7, 127.75, 127.78, 127.82, 127.85, 127.92, 128.1, 128.22, 128.25, 128.4, 128.47, 128.51, 128.95, 129.01 (30C,

CH_{ar}), 137.9, 138.0, 138.39, 138.45, 138.7, 138.8 ($C_{q,ar}$) ppm. IR (KBr): $\tilde{\nu}$ = 3416 (br. m), 3065 (w), 3033 (w), 2862 (m), 1497 (w), 1453 (m), 1402 (w), 1368 (m), 1341 (w), 1253 (w), 1222 (w), 1140 (m), 1098 (s), 1084 (s), 1058 (s), 1028 (m), 1011 (m), 996 (m), 823 (w), 801 (w), 778 (w), 733 (s), 696 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{28}NaO_6$: 471.1778; found: 471.1781 $[M + Na]^+$. $C_{27}H_{28}O_6$ (448.51): calcd. C 72.30, H 6.29; found C 72.05, H 6.10.

(2*R*,3*S*,4*R*,5*S*)-1,3-(Benzylidenedioxy)-4,5-dibenzyloxyhept-6-en-2-ol (15): A suspension of methyltriphenylphosphonium bromide (4.78 g, 13.4 mmol) in dry THF (70 mL) was cooled to –30 °C, and a solution of *n*BuLi (1.6 M in hexanes, 7.9 mL, 12.6 mmol) was added dropwise. The reaction mixture turned to a clear yellow solution within 20 min. At the same temperature a solution of lactol **14** (1.50 g, 3.34 mmol) in dry THF (30 mL) was added dropwise. The reaction mixture was stirred for 24 h while the temperature gradually came to room temp. The resulting orange suspension was quenched with H_2O (100 mL), and the layers were separated. The aqueous layer was neutralised with satd. NH_4Cl (100 mL) and extracted with MTBE (3 × 80 mL). The combined organic layers were washed with satd. NH_4Cl (2 × 50 mL), H_2O (50 mL) and brine (50 mL), dried with $MgSO_4$, and the solvents were evaporated. The remaining viscous yellow oil was purified by flash column chromatography (100 g silica, *n*-pentane/MTBE, 3:1 → 2:1) to give the corresponding alkene **15** (1.35 g, 3.02 mmol, 90%). The colourless oil solidified on standing overnight. R_f = 0.19 (*n*-hexane/MTBE, 3:1); m.p. 76 °C; $[\alpha]_D^{20}$ = +51.8 (*c* = 3.29, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 2.86 (d, *J* = 10.7 Hz, 1 H, OH), 3.76 (dd, *J* = 8.7, 2.4 Hz, 1 H, 4-H), 3.84 (br. d, *J* = 10.1 Hz, 1 H, 2-H), 4.05 (dd, *J* = 11.8, 1.1 Hz, 1 H, 5-H), 4.08 (dd, *J* = 6.8, 2.2 Hz, 1 H, 1-H^a), 4.19 (dd, *J* = 8.7, 1.0 Hz, 1 H, 3-H), 4.24 (dd, *J* = 11.9, 2.0 Hz, 1 H, 1-H^b), 4.34 (d, *J* = 12.1 Hz, 1 H, PhCH_2), 4.69 (d, *J* = 12.1 Hz, 1 H, PhCH_2), 4.70 (d, *J* = 10.9 Hz, 1 H, PhCH_2), 4.78 (d, *J* = 10.9 Hz, 1 H, PhCH_2), 5.27–5.38 (m, 2 H, 7-H_2), 5.40 (s, 1 H, PhC*H*), 5.96 (ddd, *J* = 17.5, 10.2, 7.5 Hz, 1 H, 6-H), 7.12–7.40 (m, 15 H, CH_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.4 (C-2), 70.6 (Ph*C*H_2), 72.8 (C-1), 75.6 (Ph*C*H_2), 77.8 (C-3), 78.3 (C-5), 79.9 (C-4), 101.2 (Ph*C*H), 118.6 (C-7), 126.0 (2 C), 127.7, 127.9, 128.2 (2 C), 128.3 (2 C), 128.39 (2 C), 128.42 (2 C), 128.6 (2 C), 129.0 (CH_{ar}), 136.1 (C-6), 137.9, 138.3, 138.5 ($C_{q,ar}$) ppm. IR (KBr): $\tilde{\nu}$ = 3472 (br. m), 3064 (m), 3031 (m), 2866 (m), 1496 (m), 1454 (s), 1396 (s), 1340 (m), 1308 (m), 1216 (s), 1089 (s), 1028 (s), 951 (w), 926 (m), 886 (w), 844 (w), 811 (w), 749 (s), 698 (s), 598 (w), 578 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{28}H_{30}NaO_5$: 469.1985; found: 469.1978 $[M + Na]^+$.

(2*R*,3*S*,4*S*,5*S*)-4,5-Dibenzyloxyhept-6-ene-1,2,3-triol (16): A mixture of acetal **15** (5.17 g, 11.6 mmol), CSA (537 mg, 2.31 mmol) and 1,3-propanedithiol (7.0 mL, 69.4 mmol) in MeOH (110 mL) was stirred at room temp. for 15 h. Et_3N (0.8 mL, 5.78 mmol) was added, and the solvents were evaporated. The residue was dissolved in $CHCl_3$ (200 mL) and washed with NaOH (2 M, 2 × 50 mL) and H_2O (50 mL). The solution was dried with $MgSO_4$, and the solvent was removed in vacuo. Flash column chromatography (250 g silica, *n*-pentane/acetone, 3:1 → 2:1) of the residue gave the triol **16** (4.01 g, 11.2 mmol, 97%) as colourless oil. R_f = 0.26 (MTBE); $[\alpha]_D^{20}$ = +81.4 (*c* = 2.84, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (dd, *J* = 8.5, 3.4 Hz, 1 H, 1-OH), 2.78 (d, *J* = 7.6 Hz, 1 H, OH), 3.55 (d, *J* = 3.7 Hz, 1 H, OH), 3.67 (ddd, *J* = 11.0, 8.5, 3.9 Hz, 1 H, 1-H^a), 3.71–3.80 (m, 2 H, 1-H^b, 4-H), 3.80–3.89 (m, 2 H, 2-H, 3-H), 4.15 (m, 1 H, 5-H), 4.39 (d, *J* = 11.9 Hz, 1 H, PhCH_2), 4.60–4.72 (m, 3 H, PhCH_2), 5.33–5.46 (m, 2 H, 7-H_2), 5.95 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1 H, 6-H), 7.22–7.44 (m, 10 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.5 (C-1), 69.9 (C-2/3), 71.1 (Ph*C*H_2), 72.3 (C-2/3), 74.3 (Ph*C*H_2), 79.7 (C-4), 80.4 (C-5), 119.6 (C-7), 128.0 (2 C), 128.1 (2 C), 128.2 (2 C), 128.56 (2 C), 128.63 (2 C, CH_{ar}), 134.3 (C-6), 137.6, 137.9 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3418 (br. s), 3088 (w), 3064 (m), 3031 (m), 2874 (s), 1640 (w), 1605 (w), 1586 (w), 1497 (m), 1454 (s), 1398 (m), 1345 (m), 1210 (m), 1067 (br. s), 1028 (m), 930 (m), 859 (w), 737 (s), 698 (s), 611 (w) cm^{-1}. $C_{21}H_{26}O_5$ (358.43): calcd. C 70.73, H 7.31; found C 70.42, H 7.11.

(2*R*,3*S*,4*S*,5*S*)-4,5-Dibenzyloxy-1-(*tert*-butyldiphenylsilyloxy)hept-6-ene-2,3-diol (17): A solution of the triol **16** (3.58 g, 9.99 mmol) in CH_2Cl_2 (90 mL) at 0 °C was mixed with TBDPS-Cl (2.60 mL, 9.99 mmol), Et_3N (1.38 mL, 9.99 mmol) and DMAP (61 mg, 499 mmol), and the mixture was stirred at room temp. for 3 d. Satd. NH_4Cl (100 mL) was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by flash column chromatography (200 g silica, *n*-pentane/MTBE, 6:1 → 3:1) to give the silyl ether **17** (4.96 g, 8.31 mmol, 83%) as colourless oil. R_f = 0.27 (*n*-hexane/MTBE, 3:1); $[\alpha]_D^{20}$ = +4.2 (*c* = 1.66, in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.06 [s, 9 H, $C(CH_3)_3$], 2.75 (d, *J* = 5.6 Hz, 1 H, OH), 3.06 (d, *J* = 5.3 Hz, 1 H, OH), 3.70–3.78 (m, 3 H, 1-H_2, 4-H), 3.94 (m, 2 H, 2-H, 3-H), 4.13 (dd, *J* = 7.4, 4.4 Hz, 1 H, 5-H), 4.40 (d, *J* = 11.9 Hz, 1 H, PhCH_2), 4.66 (d, *J* = 11.9 Hz, 2 H, PhCH_2), 4.74 (d, *J* = 11.4 Hz, 1 H, PhCH_2), 5.31–5.39 (m, 2 H, 7-H_2), 5.94 (ddd, *J* = 17.2, 10.4, 7.0 Hz, 1 H, 6-H), 7.26–7.45 (m, 16 H, CH_{ar}), 7.63–7.69 (m, 4 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 [*C*$(CH_3)_3$], 27.0 [3 C, C(*C*$H_3)_3$], 65.9 (C-1), 69.9, 70.1 (C-2, C-3), 70.9, 74.8 (Ph*C*H_2), 80.5 (C-5), 81.4 (C-4), 119.3 (C-7), 127.87 (6 C), 127.93 (2 C), 128.1 (2 C), 128.2 (2 C), 128.5 (2 C), 129.9 (2 C, CH_{ar}), 133.1, 133.3 ($C_{q,ar}$), 135.0 (C-6), 135.6 (2 C), 135.7 (2 C, CH_{ar}), 138.0, 138.2 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3482 (br. s), 3069 (m), 3031 (m), 2931 (s), 2858 (s), 1589 (w), 1497 (w), 1471 (m), 1454 (m), 1428 (s), 1391 (m), 1361 (m), 1307 (w), 1259 (w), 1210 (w), 1112 (br. s), 1028 (s), 998 (m), 933 (m), 867 (w), 824 (s), 739 (s), 701 (s), 613 (s), 506 (s) cm^{-1}. $C_{37}H_{44}O_5Si$ (596.83): calcd. C 74.46, H 7.43; found C 74.33, H 7.67.

(3*S*,4*R*,5*S*,6*R*)-3,4-Dibenzyloxy-7-(*tert*-butyldiphenylsilyloxy)-5,6-(cyclopentylidenedioxy)heptene (18): 1,1-Dimethoxycyclopentane (2.86 g, 27.4 mmol) and CSA (164 mg, 706 μmol) were added to a solution of diol **17** (4.96 g, 8.31 mmol) in MeCN (80 mL), and the mixture was stirred at room temp. for 25 min. The reaction was quenched by addition of Et_3N (200 μL, 1.45 mmol), and the solvents were evaporated. The residue was purified by flash column chromatography (250 g silica, *n*-pentane/MTBE, 11:1) to yield the ketal **18** (5.15 g, 7.77 mmol, 93%) as colourless oil. R_f = 0.42 (*n*-hexane/MTBE, 9:1); $[\alpha]_D^{20}$ = +21.7 (*c* = 3.10, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.05 [s, 9 H, $C(CH_3)_3$], 1.54–1.89 [m, 8 H, $(CH_2)_4$], 3.58–3.70 (m, 2 H, 4-H, 7-H^a), 3.84 (dd, *J* = 11.0, 1.5 Hz, 1 H, 7-H^b), 4.00 (dd, *J* = 7.0, 4.3 Hz, 1 H, 3-H), 4.09–4.20 (m, 2 H, 5-H, 6-H), 4.38 (d, *J* = 12.0 Hz, 1 H, PhCH_2), 4.61 (d, *J* = 11.0 Hz, 1 H, PhCH_2), 4.62 (d, *J* = 12.0 Hz, 1 H, PhCH_2), 4.76 (d, *J* = 11.2 Hz, 1 H, PhCH_2), 5.21–5.34 (m, 2 H, 1-H_2), 5.94 (ddd, *J* = 17.3, 10.1, 7.4 Hz, 1 H, 2-H), 7.16–7.45 (m, 16 H, CH_{ar}), 7.63–7.77 (m, 4 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 [*C*$(CH_3)_3$], 23.4, 23.7 ($C_qCH_2CH_2$), 26.9 [3 C, C(*C*$H_3)_3$], 37.4, 37.5 ($C_qCH_2CH_2$), 65.1 (C-7), 70.8, 75.1 (Ph*C*H_2), 75.6, 79.8 (C-5, C-6), 80.9 (C-3), 83.0 (C-4), 118.5 (C-1), 119.0 (C_qCH_2), 127.5, 127.67 (2 C), 127.71 (3 C), 128.0 (2 C), 128.2 (2 C), 128.3 (2 C), 128.4 (2 C), 129.7 (2 C, CH_{ar}), 133.6, 133.7 ($C_{q,ar}$), 135.8 (2 C), 135.89 (2 C, CH_{ar}), 135.94 (C-2), 138.3, 138.5 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3343 (br. w), 3069 (m), 3031 (m), 2931 (s), 2858 (s), 1589 (w), 1497 (w), 1472 (w), 1454 (m), 1428 (m), 1390 (m), 1361 (w), 1334 (m),

1206 (m), 1112 (s), 1028 (w), 999 (w), 824 (m), 739 (s), 701 (s), 612 (m), 505 (s), 490 (w) cm^{-1}. $C_{42}H_{50}O_5Si$ (674.94): calcd. C 76.09, H 7.60; found C 76.19, H 7.93.

(2*RS*,3*S*,4*R*,5*S*,6*R*)-3,4-Dibenzyloxy-7-(*tert*-butyldiphenylsilyloxy)-5,6-(cyclopentylidenedioxy)-1,2-epoxyheptane (19): Alkene **18** (1.44 g, 2.17 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with *m*CPBA (70% in H_2O, 588 mg, 2.39 mmol). The mixture was stirred for 18 h, then more *m*CPBA (70% in H_2O, 1.34 g, 5.44 mmol) was added, and it was stirred for further 42 h. The reaction was quenched by addition of semisatd. $Na_2S_2O_3$ (50 mL) with subsequent stirring for 5 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with satd. $NaHCO_3$ (20 mL) and H_2O (20 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (40 g silica, *n*-pentane/MTBE, 6:1) to provide the epoxide **19** (1.28 g, 1.89 mmol, 87%) as a 3:2 mixture of epimers in the form of a colourless oil. R_f = 0.52 (*n*-hexane/MTBE, 3:1); $[a]_D^{20}$ = +14.7 (*c* = 3.68, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.04 [s, 18 H, $C(CH_3)_3$], 1.52–1.89 [m, 16 H, $(CH_2)_4$], 2.50 (dd, *J* = 4.4, 2.2 Hz, 1 H, 1-H^a, **19b**), 2.58 (dd, *J* = 5.0, 2.3 Hz, 1 H, 1-H^a, **19a**), 2.65 (t, *J* = 4.0 Hz, 1 H, 1-H^b, **19b**), 2.78 (dd, *J* = 4.6, 4.2 Hz, 1 H, 1-H^b, **19a**), 3.15 (m, 1 H, 2-H, **19a**), 3.19–3.30 (m, 2 H, 2-H, 3-H, **19b**), 3.44 (dd, *J* = 6.2, 2.3 Hz, 1 H, 3-H, **19a**), 3.61–3.74 (m, 4 H, 4-H, 7-H^a), 3.80–3.90 (m, 2 H, 7-H^b), 4.04 (m, 1 H, 6-H, **19a**), 4.11–4.25 (m, 3 H, 5-H, **19a**, 5-H, 6-H, **19b**), 4.55–4.71 (m, 6 H, PhCH_2), 4.76 (d, *J* = 11.5 Hz, 1 H, PhCH_2, **19a**), 4.84 (d, *J* = 12.0 Hz, PhCH_2, 1 H, **19b**), 7.19–7.44 (m, 32 H, CH_{ar}), 7.64–7.73 (m, 8 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 [2 C, $C(CH_3)_3$], 23.5 (2 C), 23.7 (2 C, $C_qCH_2CH_2$), 26.9 [6 C, $C(CH_3)_3$], 37.5 (4 C, $C_qCH_2CH_2$), 43.4 (C-1, **19b**), 47.4 (C-1, **19a**), 51.0 (C-2, **19a**), 53.4 (C-2, **19b**), 64.9 (C-7, **19b**), 65.1 (C-7, **19a**), 72.6 (PhCH$_2$, **19b**), 73.5 (PhCH$_2$, **19a**), 74.5 (PhCH$_2$, **19b**), 74.6 (C-5, **19a**), 75.0 (PhCH$_2$, **19a**), 75.7 (C-5, **19b**), 78.6 (C-3, **19a**), 80.3 (C-6, **19b**), 80.7 (C-6, **19a**), 81.2 (C-4, **19a**), 81.4 (C-4, **19b**), 81.9 (C-3, **19b**), 119.1 (2 C, C_qCH_2), 127.6, 127.67, 127.71, 127.8, 127.9, 128.0, 128.07, 128.15, 128.3, 128.4, 128.50, 128.55, 129.65, 129.71 (32 C, CH_{ar}), 133.5, 133.6 (2 C), 133.7 ($C_{q,ar}$), 135.8, 135.86, 135.91 (8 C, CH_{ar}), 137.76, 137.83, 138.36, 138.39 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3068 (m), 3031 (m), 2931 (s), 2858 (s), 1589 (w), 1497 (w), 1472 (w), 1454 (m), 1428 (m), 1390 (w), 1335 (m), 1207 (m), 1112 (s), 1028 (m), 980 (m), 823 (m), 740 (s), 701 (s), 612 (m), 505 (s), 491 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{42}H_{50}NaO_6Si$: 701.3269; found: 701.3274 $[M + Na]^+$. $C_{42}H_{50}O_6Si$ (678.93): calcd. C 74.30, H 7.42; found C 74.24, H 7.31.

(2*RS*,3*S*,4*R*,5*S*,6*R*)-1-Azido-3,4-dibenzyloxy-7-(*tert*-butyldiphenylsilyloxy)-5,6-(cyclopentylidenedioxy)heptan-2-ol (20): A mixture of the epoxide **19** (4.15 g, 6.11 mmol), NH_4Cl (409 mg, 7.64 mmol) and NaN_3 (1.65 g, 25.4 mmol) in EtOH (65 mL) was heated to reflux for 45 h. Then the solvent was evaporated, and the residue was redissolved in MTBE (50 mL) and H_2O (50 mL). The aqueous phase was extracted with MTBE (2 × 30 mL), and the combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried with $MgSO_4$ and concentrated in vacuo. The residue was separated by flash column chromatography (130 g silica, *n*-pentane/MTBE, 5:1) to yield both the desired alcohol **20** (3.84 g, 5.32 mmol, 87%) as colourless oil and recovered starting material **19** (455 mg, 670 µmol, 11%). The yield of alcohol **20** with respect to 89% conversion was 98%. R_f = 0.30 (*n*-hexane/MTBE, 3:1); $[a]_D^{20}$ = –6.8 (*c* = 2.44, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 1.04 [s, 9 H, $C(CH_3)_3$, **20a**], 1.06 [s, 9 H, $C(CH_3)_3$, **20b**], 1.58–1.90 [m, 16 H, $(CH_2)_4$], 2.66 (br. s, 1 H, OH, **20b**), 2.81 (br. s, 1 H, OH, **20a**), 3.18 (dd, *J* = 12.4, 5.3 Hz, 1 H, 1-H^a, **20b**), 3.35 (dd, *J* = 12.5, 6.0 Hz, 1 H, 1-H^a, **20a**), 3.38 (dd, *J* = 11.5, 6.9 Hz, 1 H, 1-H^b, **20b**), 3.53 (dd, *J* = 12.6, 3.0 Hz, 1 H, 1-H^b, **20a**), 3.64 (dd, *J* = 6.1, 2.9 Hz, 1 H, 3-H, **20b**), 3.67–3.74 (m, 3 H, 3-H, **20a**, 7-H^a), 3.79 (t, *J* = 6.4 Hz, 1 H, 4-H, **20b**), 3.83 (dd, *J* = 8.0, 3.7 Hz, 1 H, 4-H, **20a**), 3.87 (dd, *J* = 11.0, 3.0 Hz, 1 H, 7-H^b, **20a**), 3.89 (dd, *J* = 13.4, 2.6 Hz, 1 H, 7-H^b, **20b**), 3.94–4.00 (m, 2 H, 2-H), 4.10–4.16 (m, 3 H, 5-H, **20b**, 6-H), 4.25 (dd, *J* = 8.0, 6.9 Hz, 1 H, 5-H, **20a**), 4.55 (d, *J* = 11.1 Hz, 2 H, PhCH_2), 4.61 (d, *J* = 11.2 Hz, 2 H, PhCH_2), 4.72 (d, *J* = 11.5 Hz, 1 H, PhCH_2, **20a**), 4.74 (d, *J* = 11.9 Hz, 1 H, PhCH_2, **20b**), 4.76 (d, *J* = 11.2 Hz, 1 H, PhCH_2, **20a**), 4.84 (d, *J* = 11.2 Hz, 1 H, PhCH_2, **20b**), 7.20–7.42 (m, 32 H, CH_{ar}), 7.64–7.71 (m, 8 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 [2 C, $C(CH_3)_3$], 23.47 (2 C), 23.55, 23.6 ($C_qCH_2CH_2$), 26.9 [6 C, $C(CH_3)_3$], 37.3, 37.4 (2 C), 37.5 ($C_qCH_2CH_2$), 53.6 (C-1, **20b**), 54.1 (C-1, **20a**), 64.6 (2 C, C-7), 70.5 (2C, C-2), 74.4, 74.5 (PhCH$_2$, **20a**), 74.7, 75.0 (PhCH$_2$, **20b**), 75.2 (C-5, **20a**), 76.2 (C-5, **20b**), 79.8 (C-3, **20a**), 80.0 (C-4, **20a**), 80.2 (C-4, **20b**), 80.4 (C-3, **20b**), 80.5 (C-6, **20b**), 80.7 (C-6, **20a**), 119.3 (C_qCH_2, **20a**), 119.5 (C_qCH_2, **20b**), 127.7, 127.95, 128.01, 128.1, 128.16, 128.22, 128.3, 128.55, 128.60, 129.7 (32 C, CH_{ar}), 133.4 (2 C), 133.5 (2 C, $C_{q,ar}$), 135.76, 135.82 (8 C, CH_{ar}), 137.67, 137.74, 137.8, 137.9 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3454 (br. m), 3069 (m), 3031 (m), 2931 (s), 2858 (s), 2103 (s), 1589 (w), 1497 (w), 1472 (m), 1454 (s), 1428 (s), 1391 (w), 1360 (w), 1335 (s), 1281 (br. m), 1209 (m), 1113 (s), 1028 (w), 824 (m), 738 (s), 701 (s), 613 (m), 506 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{42}H_{51}N_3NaO_6Si$: 744.3439; found: 744.3446 $[M + Na]^+$. $C_{42}H_{51}N_3O_6Si$ (721.96): calcd. C 69.87, H 7.12, N 5.82; found C 69.99, H 7.11, N 5.98.

(3*R*,4*S*,5*S*,6*R*)-1-Azido-3,4-dibenzyloxy-7-(*tert*-butyldiphenylsilyloxy)-5,6-(cyclopentylidenedioxy)heptan-2-one (21): A solution of oxalyl chloride (950 µL, 10.9 mmol) in CH_2Cl_2 (11 mL) was cooled to –60 °C and DMSO (1.55 mL, 21.8 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise, and the mixture was stirred for 5 min. Then alcohol **20** (3.15 g, 4.36 mmol) in CH_2Cl_2 (6.5 mL) was added slowly, and after 10 min the temperature was raised to –20 °C. The mixture was stirred for 1 h, then Et_3N (6.65 mL, 48.0 mmol) was added dropwise at –60 °C with subsequent warming to room temp. and further stirring for 10 min. Workup was performed by adding H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with H_2O (50 mL), dried with $MgSO_4$ and concentrated in vacuo. Flash column chromatography (250 g silica, *n*-pentane/MTBE, 7:1) yielded the heptanone **21** (2.62 g, 3.64 mmol, 83%) as colourless oil. R_f = 0.18 (*n*-hexane/MTBE, 9:1); $[a]_D^{20}$ = +42.0 (*c* = 2.78, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.04 [s, 9 H, $C(CH_3)_3$], 1.55–1.91 [m, 8 H, $(CH_2)_4$], 3.68 (dd, *J* = 11.1, 5.0 Hz, 1 H, 7-H^a), 3.85 (dd, *J* = 11.0, 2.4 Hz, 1 H, 7-H^b), 3.95 (dd, *J* = 8.3, 2.7 Hz, 1 H, 4-H), 3.99 (d, *J* = 19.5 Hz, 1 H, 1-H^a), 4.04–4.19 (m, 3 H, 1-H^b, 5-H, 6-H), 4.24 (d, *J* = 2.7 Hz, 1 H, 3-H), 4.45 (s, 2 H, PhCH_2), 4.55 (d, *J* = 11.5 Hz, 1 H, PhCH_2), 4.69 (d, *J* = 11.5 Hz, 1 H, PhCH_2), 7.10–7.44 (m, 16 H, CH_{ar}), 7.68 (m, 4 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 [$C(CH_3)_3$], 23.5 (2 C, $C_qCH_2CH_2$), 26.9 [3 C, $C(CH_3)_3$], 37.4, 37.5 ($C_qCH_2CH_2$), 57.2 (C-1), 64.7 (C-7), 74.6 (C-5), 74.7, 75.0 (PhCH$_2$), 80.8 (C-6), 82.3 (C-4), 84.8 (C-3), 119.6 (C_qCH_2), 127.70 (2 C), 127.74 (2 C), 128.18, 128.25 (2 C), 128.5 (3 C), 128.6 (2 C), 128.8 (2 C), 129.7 (2 C, CH_{ar}), 133.4, 133.5 ($C_{q,ar}$), 135.7 (2 C), 135.8 (2 C, CH_{ar}), 136.7, 137.0 ($C_{q,ar}$), 206.7 (C-2) ppm. IR (film): $\tilde{\nu}$ = 3442 (br. w), 3069 (w), 3032 (w), 2958 (s), 2932 (s), 2858 (s), 2106 (s), 1730 (s), 1589 (w), 1497 (w), 1472 (m), 1455 (m), 1428 (m), 1391 (w), 1335 (s), 1280 (m), 1206 (m), 1113 (s), 910 (m), 824 (m), 738 (s), 702 (s), 613 (m), 505 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{42}H_{49}N_3NaO_6Si$: 742.3283; found: 742.3283 $[M + Na]^+$.

(1*S*,3*R*,4*S*,5*S*,6*R*)-1-Azidomethyl-5,6-dibenzyloxy-3-(*tert*-butyldiphenylsilyloxymethyl)-2,7-dioxabicyclo[2.2.1]heptane (22): Powdered molecular sieves (4 Å, 2.30 g) were dried by heating in vacuo. Subsequently, dry CH_2Cl_2 (45 mL) and ketone **21** (2.30 g, 3.19 mmol) were added. After the starting material had dissolved, TFA (45 mL) was added in one portion at room temp. resulting in a yellow reaction mixture. TLC indicated complete conversion of the starting material within 25 min. The suspension was cooled to 0 °C, dry toluene (20 mL) was added, and the solvents were evaporated at the same temperature. The remaining solid was coevaporated twice with dry toluene (2 × 10 mL) to remove traces of TFA. The pale pink crude product was purified by flash column chromatography (200 g silica, *n*-pentane/MTBE, 7:1) to yield the bicyclic ketal **22** (1.80 g, 2.83 mmol, 89%) as colourless oil. R_f = 0.36 (*n*-hexane/MTBE, 3:1); $[\alpha]_D^{20}$ = –1.1 (*c* = 4.89, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 [s, 9 H, $C(CH_3)_3$], 3.40 (d, *J* = 13.7 Hz, 1 H, $CH^aH^bN_3$), 3.55 (d, *J* = 13.7 Hz, 1 H, $CH^aH^bN_3$), 3.57 (d, *J* = 9.4 Hz, 1 H, CH^aH^bOR), 3.61–3.66 (m, 2 H, CH^aH^bOR, 6-H), 3.80 (dd, *J* = 9.2, 4.6 Hz, 1 H, 3-H), 3.82 (t, *J* = 1.5 Hz, 1 H, 5-H), 4.45 (d, *J* = 11.9 Hz, 1 H, $PhCH_2$), 4.53 (d, *J* = 11.7 Hz, 1 H, $PhCH_2$), 4.55 (d, *J* = 12.4 Hz, 1 H, $PhCH_2$), 4.58 (d, *J* = 12.4 Hz, 1 H, $PhCH_2$), 4.74 (d, *J* = 1.6 Hz, 1 H, 4-H), 7.28–7.45 (m, 16 H, CH_{ar}), 7.63 (m, 4 H, CH_{ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.4 [$C(CH_3)_3$], 27.0 [3 C, $C(CH_3)_3$], 48.7 (CH_2N_3), 63.1 (CH_2OR), 71.4, 73.1 ($PhCH_2$), 77.2 (C-3), 81.1 (C-4), 83.6 (C-6), 87.4 (C-5), 106.9 (C-1), 127.88, 127.94 (2 C), 127.97 (2 C), 128.02 (2 C), 128.2, 128.3 (2 C), 128.68 (2 C), 128.74 (2 C), 129.8, 130.0 (2 C, CH_{ar}), 133.30, 133.35 ($C_{q,ar}$), 134.9, 135.6 (2 C, CH_{ar}), 137.4, 137.5 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3069 (w), 2930 (m), 2857 (m), 2104 (s), 1472 (w), 1428 (m), 1361 (w), 1283 (w), 1113 (s), 998 (w), 823 (m), 739 (m), 700 (s), 607 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{37}H_{41}N_3NaO_5Si$: 658.2708; found: 658.2701 [M + Na]$^+$. $C_{37}H_{41}N_3O_5Si$ (635.82): calcd. C 69.89, H 6.50, N 6.61; found C 70.10, H 6.79, N 6.31.

(1*S*,3*R*,4*S*,5*S*,6*R*)-1-Azidomethyl-5,6-dibenzyloxy-3-hydroxymethyl-2,7-dioxabicyclo[2.2.1]heptane (23): A solution of the silyl ether **22** (1.66 g, 2.61 mmol) in THF (22 mL) was treated with nBu$_4$N$^+$F$^-$ (1.0 M in THF, 5.22 mL, 5.22 mmol) and the mixture stirred for 1 h. The solvent was evaporated in vacuo, and the residue was purified by flash column chromatography (100 g silica, *n*-pentane/acetone, 3:1) to give the alcohol **23** (970 mg, 2.44 mmol, 93%) as colourless oil. R_f = 0.29 (*n*-pentane/acetone, 3:1); $[\alpha]_D^{22}$ = +12.9 (*c* = 3.60, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (t, *J* = 5.7 Hz, 1 H, OH), 3.46 (d, *J* = 13.7 Hz, 1 H, $CH^aH^bN_3$), 3.59–3.64 (m, 2 H, CH_2OH), 3.64 (d, *J* = 1.1 Hz, 1 H, 6-H), 3.68 (d, *J* = 14.0 Hz, 1 H, $CH^aH^bN_3$), 3.81 (t, *J* = 1.4 Hz, 1 H, 5-H), 3.86 (t, *J* = 5.6 Hz, 1 H, 3-H), 4.44 (d, *J* = 11.9 Hz, 1 H, $PhCH_2$), 4.54 (d, *J* = 11.9 Hz, 1 H, $PhCH_2$), 4.55 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.59 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.61 (d, *J* = 1.6 Hz, 1 H, 4-H), 7.28–7.41 (m, 10 H, CH_{ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.7 (CH_2N_3), 63.3 (CH_2OH), 71.6, 73.1 ($PhCH_2$), 77.4 (C-3), 81.3 (C-4), 83.7 (C-6), 87.5 (C-5), 107.1 (C-1), 128.0 (2 C), 128.2, 128.28 (2 C), 128.34, 128.7 (4 C, CH_{ar}), 137.3, 137.4 ($C_{q,ar}$) ppm. IR (film): $\tilde{\nu}$ = 3473 (br. m), 3064 (w), 3031 (m), 2927 (m), 2105 (s), 1497 (m), 1454 (s), 1359 (m), 1285 (m), 1209 (w), 1178 (w), 1110 (s), 983 (m), 950 (w), 851 (m), 801 (w), 752 (s), 699 (s), 665 (w), 605 (w), 557 (w), 537 (w), 463 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{23}N_3NaO_5$: 420.1530; found: 420.1533 [M + Na]$^+$.

(1*R*,3*S*,4*R*,5*S*,6*R*)-1-Azidomethyl-5,6-dibenzyloxy-2,7-dioxabicyclo[2.2.1]heptane-3-carboxylic Acid (24): To a solution of the alcohol **23** (136 mg, 342 μmol) in CH_2Cl_2 (4.3 mL) was added H_2O (25 μL, 1.39 mmol), $PhI(OAc)_2$ (253 mg, 786 μmol) and TEMPO (4.2 mg, 27 μmol). The mixture was stirred for 90 min and subsequently quenched by addition of semisatd. $NaHSO_3$ (15 mL). The phases were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with semisatd. $NaHSO_3$ (10 mL) and brine (10 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was subjected to flash column chromatography (17 g silica, $CHCl_3$/MeOH/HCO_2H, 20:1:0.1) to afford the carboxylic acid **24** (122 mg, 297 μmol, 87%) as colourless oil. It was coevaporated with MeOH/toluene (1:1 v/v, 2 × 2 mL) to remove traces of formic acid. R_f = 0.26 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.1); $[\alpha]_D^{20}$ = +58.1 (*c* = 3.75, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65 (d, *J* = 13.7 Hz, 1 H, $CH^aH^bN_3$), 3.71 (d, *J* = 1.1 Hz, 1 H, 6-H), 3.75 (d, *J* = 13.7 Hz, 1 H, $CH^aH^bN_3$), 3.80 (s, 1 H, 5-H), 4.27 (s, 1 H, 3-H), 4.44 (d, *J* = 11.7 Hz, 1 H, $PhCH_2$), 4.50 (d, *J* = 11.9 Hz, 1 H, $PhCH_2$), 4.55 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.58 (d, *J* = 11.7 Hz, 1 H, $PhCH_2$), 4.97 (d, *J* = 1.1 Hz, 1 H, 4-H), 7.26–7.40 (m, 10 H, CH_{ar}), 8.50 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.6 (CH_2N_3), 71.9, 73.2 ($PhCH_2$), 74.7 (C-3), 82.9 (C-6), 83.6 (C-4), 87.1 (C-5), 108.3 (C-1), 128.0 (2 C), 128.2 (2 C), 128.4, 128.5, 128.75 (2 C), 128.77 (2 C, CH_{ar}), 136.9 (2 C, $C_{q,ar}$), 171.3 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3030 (m), 2930 (s), 2107 (s), 1708 (m), 1609 (s), 1496 (w), 1433 (m), 1358 (w), 1281 (m), 1208 (w), 1179 (w), 1103 (s), 980 (w), 946 (w), 854 (w), 750 (m), 697 (m), 604 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{21}N_3NaO_6$: 434.1323; found: 434.1342 [M + Na]$^+$.

(1*R*,3*S*,4*R*,5*R*,6*R*)-1-Aminomethyl-5,6-dihydroxy-2,7-dioxabicyclo-[2.2.1]heptane-3-carboxylic Acid (5): Azide **24** (120 mg, 292 μmol) was dissolved in EtOAc/MeOH (2:1 v/v, 25 mL) under argon. $Pd(OH)_2$/C (20% Pd with 50% H_2O, 819 mg, 584 μmol) was added, and the flask was evacuated five times with subsequent hydrogen insertion. Complete conversion was achieved within 90 min. The reaction mixture was filtered through a short column of Celite which was washed with MeOH (5 × 5 mL). Concentration to dryness gave pure amino acid **5** (60 mg, 292 μmol, 100%) as colourless foam. In order to obtain a powder for better handling the foam was dissolved in MeOH (1 mL) and precipitated by slow addition of EtOAc (4 mL). The suspension was centrifuged and the supernatant was decanted. The resulting colourless solid was washed with Et_2O (4 mL) and dried in vacuo. R_f = 0.26 (*n*BuOH/H_2O/AcOH, 2:1:1); m.p. 140 °C (dec.); $[\alpha]_D^{20}$ = +45.1 (*c* = 0.35, in H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 3.59 (m, 2 H, CH_2NH_2), 3.89 (s, 1 H, 5-H), 4.00 (d, *J* = 1.2 Hz, 1 H, 6-H), 4.38 (s, 1 H, 3-H), 4.89 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O, MeCN): δ = 37.6 (CH_2NH_2), 75.6 (C-3), 78.1 (C-6), 82.7 (C-5), 87.3 (C-4), 106.7 (C-1), 175.0 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3401 (br. s), 2925 (m), 1602 (s), 1510 (w), 1429 (m), 1307 (w), 1170 (w), 1072 (m), 1035 (w), 958 (m), 824 (w), 696 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_7H_{12}NO_6$: 206.0659; found: 206.0660 [M + H]$^+$.

(1*S*,3*R*,4*R*,5*R*,6*R*)-1-Aminomethyl-3-hydroxymethyl-2,7-dioxabicyclo[2.2.1]heptane-5,6-diol (25): To a solution of the benzyl ether **23** (8.6 mg, 21.6 μmol) in EtOAc/MeOH (2:1 v/v, 2 mL) was added $Pd(OH)_2$/C (20% with 50% H_2O, 63.8 mg, 45.4 μmol). The flask was evacuated and ventilated with hydrogen five times, and the mixture was stirred for 3 h. Filtration through a short column of Celite and subsequent evaporation of the solvents gave pure amino alcohol **25** (4.1 mg, 21.3 μmol, 99%) as colourless solid. R_f = 0.09 (*n*BuOH/EtOH/H_2O/25% NH_3 4:1:1:1); $[\alpha]_D^{22}$ = +49.3 (*c* = 0.46, in MeOH). ^{1}H NMR (300 MHz, D_2O, MeCN): δ = 3.38 (s, 2 H, CH_2NH_2), 3.54 (dd, *J* = 11.8, 6.8 Hz, 1 H, CH^aH^bOH), 3.61 (dd, *J* = 11.8, 5.5 Hz, 1 H, CH^aH^bOH), 3.86 (t, *J* = 1.3 Hz, 1 H, 5-H), 3.93 (d, *J* = 1.0 Hz, 1 H, 6-H), 3.97 (dd, *J* = 6.6, 5.3 Hz, 1 H, 3-H), 4.56 (d, *J* = 1.3 Hz, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O, MeCN): δ = 38.4 (CH_2NH_2), 62.4 (CH_2OH), 77.6 (C-3), 78.5 (C-

6), 82.8 (C-5), 84.5 (C-4), 107.1 (C-1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_7H_{14}NO_5$: 192.0867; found: 192.0869 $[M + H]^+$.

2-Hydroxyethyl (1*R*,3*S*,4*R*,5*R*,6*R*)-1-Aminomethyl-5,6-dihydroxy-2,7-dioxabicyclo[2.2.1]heptane-3-carboxylate (26)

Esterification: To a solution of the carboxylic acid **24** (50 mg, 121 μmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added EDC·HCl (69.9 mg, 365 μmol), Et_3N (50.5 μL, 365 μmol) and DMAP (3.0 mg, 24.3 μmol). After stirring for 30 min, the temperature was raised to room temp. A solution of ethyleneglycol (3.4 μL, 60.8 μmol) in CH_2Cl_2 (1 mL) was added in 10 portions at 10 min intervals. After that, the mixture was stirred for further 22 h. $NaHSO_4$ (1 M, 10 mL) was added, and the phases were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 5 mL), and the combined extracts were washed with $NaHSO_4$ (5 mL), H_2O (5 mL) and brine (5 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was separated by flash column chromatography (5.5 g silica, $CHCl_3$/MeOH/HCO_2H, 100:0:0 → 100:1:0 → 100:1:0.5) which gave both recovered starting material **24** (15.4 mg, 37.4 μmol, 31%) and a mixture of the monomeric monoester and the dimeric diester. Subsequent flash column chromatography (2 g silica, $CHCl_3$/MeOH, 200:1 → 100:1) of the product mixture allowed the separation of the monoester (12.3 mg, 27.0 μmol, 22%) and the diester (6.4 mg, 7.5 μmol, 12%). Monomeric monoester: R_f = 0.24 ($CHCl_3$/MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (d, *J* = 13.9 Hz, 1 H, C*H*^{a}H^{b}N$_3$), 3.69 (d, *J* = 1.2 Hz, 1 H, 6-H), 3.78 (d, *J* = 14.2 Hz, 1 H, CH^a*H*^{b}N$_3$), 3.79–3.88 (m, 3 H, C*H*$_2$OH, 5-H), 4.22–4.40 (m, 2 H, C*H*$_2$OR), 4.29 (s, 1 H, 3-H), 4.45 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 4.53–4.60 (m, 3 H, PhC*H*$_2$), 4.95 (d, *J* = 1.2 Hz, 1 H, 4-H), 7.27–7.43 (m, 10 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.6 (CH_2N_3), 61.0 (CH_2OH), 67.4 (*C*H_2OR), 71.9, 73.2 (Ph*C*H_2), 75.1 (C-3), 83.4, 83.5 (C-4, C-6), 87.4 (C-5), 108.4 (C-1), 128.1 (2 C), 128.2 (2 C), 128.3, 128.4, 128.7 (2 C), 128.8 (2 C, CH_{ar}), 137.2, 137.3 ($C_{q,ar}$), 169.5 (CO) ppm.

Deprotection: The protected monoester (12.3 mg, 27.0 μmol) was dissolved in EtOAc/MeOH (2:1 v/v, 2 mL), and $Pd(OH)_2$/C (20% with 50% H_2O, 7.6 mg, 5.4 μmol) was added. The flask was evacuated and ventilated with hydrogen at atmospheric pressure five times. After 90 min of stirring, only reduction of the azide was determined by TLC (R_f = 0.40, in *n*BuOH/H_2O/AcOH, 4:1:1). More catalyst (66.0 mg, 47.0 μmol) was added to effect complete conversion within further 90 min. Filtration through a short column of Celite and solvent evaporation gave the deprotected monoester **26** (6.7 mg, 26.9 μmol, 100%) as an off-white solid. R_f = 0.11 (*n*BuOH/H_2O/AcOH, 4:1:1); $[\alpha]_D^{22}$ = +25.9 (*c* = 0.74, in MeOH). ^{1}H NMR (300 MHz, D_2O, MeCN): δ = 3.62 (s, 2 H, C*H*$_2$NH$_2$), 3.84 (m, 2 H, C*H*$_2$OH), 3.92 (s, 1 H, 5-H), 4.04 (d, *J* = 1.3 Hz, 1 H, 6-H), 4.31 (m, 2 H, C*H*$_2$OR), 4.61 (s, 1 H, 3-H), 5.01 (s, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, D_2O, MeCN): δ = 37.6 (CH_2NH_2), 59.9 (CH_2OH), 67.9 (*C*H_2OR), 75.1 (C-3), 77.9 (C-6), 82.7 (C-5), 87.1 (C-4), 107.1 (C-1), 171.4 (CO) ppm. HRMS (ESI): *m*/*z* calcd. for $C_9H_{16}NO_7$: 250.0921; found: 250.0923 $[M + H]^+$.

(1*R*,3*S*,4*R*,5*R*,6*R*)-Ethyleneglycol Bis(1-aminomethyl-5,6-dihydroxy-2,7-dioxabicyclo[2.2.1]heptane-3-carboxylate) (27)

Esterification: The dimeric diester was obtained from the esterification which was performed for the synthesis of the monoester **26**. R_f = 0.54 ($CHCl_3$/MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.46 (d, *J* = 13.9 Hz, 2 H, C*H*^{a}H^{b}N$_3$), 3.68 (d, *J* = 1.2 Hz, 2 H, 6-H), 3.76 (d, *J* = 13.9 Hz, 2 H, CH^a*H*^{b}N$_3$), 3.81–3.84 (m, 2 H, 5-H) 4.26 (s, 2 H, 3-H), 4.39–4.45 (m, 6 H, CH_2O, PhC*H*$_2$) 4.53–4.60 (m, 6 H, PhC*H*$_2$), 4.96 (d, *J* = 1.2 Hz, 2 H, 4-H), 7.27–7.39 (m, 20 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.5 (2 C, CH_2N_3), 63.0 (2 C, CH_2O), 71.7 (2 C), 73.1 (2 C, Ph*C*H_2), 74.9 (2 C, C-3), 83.3 (2 C), 83.4 (2 C, C-4, C-6), 87.1 (2 C, C-5), 108.4 (2 C, C-1), 128.1 (4 C), 128.16 (4 C), 128.24 (2 C), 128.3 (2 C), 128.70 (4 C), 128.73 (4 C, CH_{ar}), 137.30 (2 C), 137.35 (2 C, $C_{q,ar}$), 168.9 (2 C, CO) ppm.

Deprotection: The protected diester (6.4 mg, 7.5 μmol) was dissolved in EtOAc/MeOH (2:1 v/v, 1 mL), and $Pd(OH)_2$/C (20% with 50% H_2O, 31.8 mg, 22.6 μmol) was added. The flask was evacuated and ventilated with hydrogen at atmospheric pressure five times, and the mixture was stirred for 18 h. It was filtered through a short column of Celite, and the solvents were evaporated. The residue was dissolved in MeOH (0.25 mL) and precipitated on addition of EtOAc (1 mL). The suspension was centrifuged, and the supernatant was decanted. The deprotected diester **27** (3.0 mg, 6.9 μmol, 92%) was obtained as colourless solid. It contained the monoester **26** as impurity. R_f = 0.08 (*n*BuOH/H_2O/AcOH, 4:1:1); $[\alpha]_D^{22}$ = +29.3 (*c* = 0.28, in MeOH). ^{1}H NMR (300 MHz, D_2O): δ = 3.55–3.60 (m, 4 H, C*H*$_2$NH$_2$), 3.90 (s, 2 H, 5-H), 4.00 (d, *J* = 1.0 Hz, 2 H, 6-H), 4.45–4.51 (m, 4 H, CH_2O), 4.57 (s, 2 H, 3-H), 4.94 (s, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O, MeCN): δ = 37.7 (2 C, CH_2NH_2), 64.5 (2 C, *C*H_2OR), 75.1 (2 C, C-3), 78.0 (2 C, C-6), 82.8 (2 C, C-5), 87.2 (2 C, C-4), C-1 and CO not observed ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{25}N_2O_{12}$: 437.1402; found: 437.1428 $[M + H]^+$.

***N*,*N*′-(Ethane-1,2-diyl)bis[(1*R*,3*S*,4*R*,5*R*,6*R*)-1-aminomethyl-5,6-dihydroxy-2,7-dioxabicyclo[2.2.1]heptane-3-carboxyamide] (28)**

Amide Formation: Carboxylic acid **24** (44.0 mg, 107 μmol) was dissolved in CH_2Cl_2 (1.2 mL), and HOBt (18.1 mg, 134 μmol), *i*Pr_2NEt (55 μL 321 μmol), ethylenediamine (3.6 μL, 53.5 μmol) and HBTU (122 mg, 321 μmol) were added. After stirring for 2 h, the reaction mixture was diluted with $CHCl_3$ (10 mL) and subsequently washed with $NaHSO_4$ (1 M, 2 × 5 mL), $NaHCO_3$ (2 × 5 mL) and brine (5 mL). The solution was dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude product was separated by flash column chromatography (5.5 g silica, $CHCl_3$/MeOH/HCO_2H, 100:0:0 → 100:1:0 → 100:1:0.5) to give the desired protected diamide (18 mg, 21.3 μmol, 40%) as well as recovered starting material **24** (7.4 mg, 18.0 μmol, 17%). The yield was 48% based on 83% conversion. R_f = 0.39 ($CHCl_3$/MeOH, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.46 (m, 4 H, C*H*$_2$NH), 3.63–3.73 (m, 4 H, C*H*^{a}H^{b}N$_3$, 6-H), 3.74–3.86 (m, 4 H, CH^a*H*^{b}N$_3$, 5-H), 4.14 (s, 2 H, 3-H), 4.39 (d, *J* = 11.9 Hz, 2 H, PhC*H*$_2$), 4.45–4.65 (m, 6 H, PhC*H*$_2$), 5.00 (s, 2 H, 4-H), 7.12 (br. s, 2 H, NH), 7.24–7.42 (m, 20 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.4 (2 C, CH_2NH), 48.8 (2 C, CH_2N_3), 71.7 (2 C), 73.1 (2 C, Ph*C*H_2), 76.1 (2 C, C-3), 83.1 (2 C), 83.3 (2 C, C-4, C-6), 87.3 (2 C, C-5), 107.6 (2 C, C-1), 128.0 (4 C), 128.2 (6 C), 128.4 (2 C), 128.70 (4 C), 128.72 (4 C, CH_{ar}), 137.1 (2 C), 137.2 (2 C, $C_{q,ar}$), 170.2 (2 C, CO) ppm.

Deprotection: The protected diamide (8.7 mg, 10.3 μmol) was dissolved in EtOAc/MeOH (2:1 v/v, 2 mL), and $Pd(OH)_2$/C (20% with 50% H_2O, 54.8 mg, 39.2 μmol) was added. The flask was evacuated and ventilated with hydrogen at atmospheric pressure five times, and the mixture was stirred for 18 h. It was filtered through a short column of Celite, and the solvents were evaporated. The residue was coevaporated with MeOH/EtOAc (1:4 v/v, 2 mL) to give the diamide **28** (4.3 mg, 9.9 μmol, 96%) as colourless solid. R_f = 0.07 (*n*BuOH/H_2O/AcOH, 4:1:1); $[\alpha]_D^{22}$ = +37.8 (*c* = 0.45, in MeOH). ^{1}H NMR (300 MHz, D_2O, MeCN): δ = 3.11–3.27 (m, 2 H, C*H*$_2$NH), 3.61 (s, 4 H, C*H*$_2$NH$_2$), 3.61–3.74 (m, 2 H, C*H*$_2$NH), 3.91 (s, 2 H, 5-H), 3.99 (s, 2 H, 6-H), 4.34 (s, 2 H, 3-H), 4.99 (s, 2 H, 4-H) ppm. ^{13}C NMR (125 MHz, D_2O, MeCN): δ = 38.1 (2 C,

CH_2NH_2), 39.2 (2 C, CH_2NH), 76.0 (2 C, C-3), 78.0 (2 C, C-6), 82.7 (2 C, C-5), 86.6 (2 C, C-4), 107.8 (2 C, C-1), 172.0 (2 C, CO) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{27}N_4O_{10}$: 435.1722; found: 435.1742 $[M + H]^+$.

(1*R*,3*S*,4*R*,5*R*,6*R*)-*N*-(2-Aminoethyl)-1-aminomethyl-5,6-dihydroxy-2,7-dioxabicyclo[2.2.1]heptane-3-carboxamide (29)

Amide Formation: Carboxylic acid **24** (10.7 mg, 26.0 μmol) and mono-*Z*-protected ethylenediamine (6.0 mg, 26.0 μmol) were mixed in CH_2Cl_2 (1 mL). Subsequently, HOAt (10.6 mg, 78.0 μmol), *i*Pr_2NEt (17.7 μL, 104 μmol) and HATU (12.4 mg, 32.5 μmol) were added. The mixture was stirred for 2 h, then it was diluted with $CHCl_3$ (10 mL), and it was washed with $NaHSO_4$ (1 M, 2 × 5 mL), $NaHCO_3$ (2 × 5 mL) and brine (5 mL). The organic layer was dried with $MgSO_4$ and concentrated to dryness. Flash column chromatography (1.5 g silica, $CHCl_3$/MeOH, 100:1) of the residue yielded the corresponding protected monoamide (12.0 mg, 20.4 μmol, 78%) as colourless oil. R_f = 0.35 ($CHCl_3$/MeOH, 20:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.26–3.43 (m, 3 H, CH_2NH), 3.44–3.57 (m, 1 H, CH_2NH), 3.66 (d, *J* = 13.9 Hz, 1 H, C$H^aH^bN_3$), 3.70 (d, *J* = 1.3 Hz, 1 H, 5/6-H), 3.75 (s, 1 H, 5/6-H), 3.77 (d, *J* = 13.3 Hz, 1 H, C$H^aH^bN_3$), 4.13 (s, 1 H, 3-H), 4.41 (d, *J* = 11.6 Hz, 1 H, PhCH_2), 4.50 (d, *J* = 11.9 Hz, 1 H, PhCH_2), 4.57 (d, *J* = 10.3 Hz, 1 H, PhCH_2), 4.61 (d, *J* = 11.6 Hz, 1 H, PhCH_2), 4.95 (d, *J* = 1.3 Hz, 1 H, 4-H), 5.06 (d, *J* = 12.3 Hz, 1 H, Z-CH_2), 5.12–5.20 (m, 1 H, Z-N*H*), 5.13 (d, *J* = 12.3 Hz, 1 H, Z-CH_2), 7.11–7.20 (m, 1 H, NH), 7.22–7.42 (m, 15 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.7, 41.0 (CH_2NH), 48.8 (CH_2N_3), 67.0, 71.8, 73.2 (Ph*C*H_2), 76.0 (C-3), 83.0 (C-6), 83.4 (C-4), 87.4 (C-5), 107.6 (C-1), 128.0 (2 C), 128.2, 128.26 (3 C), 128.35, 128.5, 128.6, 128.77 (3 C), 128.79 (3 C, CH_{ar}), 136.6, 137.0, 137.1 ($C_{q,ar}$), 170.1 (CO) ppm.

Deprotection: The protected monoamide (8.5 mg, 14.5 μmol) was dissolved in EtOAc/MeOH (2:1 v/v, 2 mL), and $Pd(OH)_2$/C (20% with 50% H_2O, 81.3 mg, 57.9 μmol) was added. The flask was evacuated and ventilated with hydrogen at atmospheric pressure five times, and the mixture was stirred for 3.5 h. It was filtered through a short column of Celite, and the solvents were evaporated. The residue was coevaporated with MeOH/EtOAc (1:4 v/v, 2 mL) to give the monoamide **29** (3.4 mg, 13.8 μmol, 95%) as colourless solid. R_f = 0.02 (*n*BuOH/EtOH/H_2O/25% NH_3 4:1:1:1); $[\alpha]_D^{22}$ = +9.2 (*c* = 0.36, in MeOH). ^1H NMR (500 MHz, D_2O): δ = 3.17–3.26 (m, 2 H, CH_2N), 3.51–3.58 (m, 1 H, CH_2N), 3.63 (s, 2 H, 1-CH_2NH_2), 3.64–3.72 (m, 1 H, CH_2N), 3.98 (s, 1 H, 5-H), 4.06 (s, 1 H, 6-H), 4.45 (s, 1 H, 3-H), 4.96 (s, 1 H, 4-H) ppm. ^{13}C NMR (125 MHz, D_2O, MeCN): δ = 37.4 (1-*C*H_2), 38.1, 39.7 (CH_2N), 75.9 (C-3), 78.0 (C-6), 82.5 (C-5), 86.7 (C-4), 107.8 (C-1), 172.7 (CO) ppm. HRMS (ESI): *m*/*z* calcd. for $C_9H_{18}N_3O_5$: 248.1241; found: 248.1240 $[M + H]^+$.

Methyl (1*R*,4*S*)-4-Benzyloxycarbonylaminocyclopent-2-enecarboxylate (32)

Lactam Cleavage: A solution of 2-azabicyclo[2.2.1]hept-5-en-3-one (**31**) (869 mg, 7.96 mmol) in dry MeOH (75 mL) was cooled to 0 °C, and $SOCl_2$ (1.3 mL, 17.5 mmol) was added dropwise, which sometimes caused a vehement reaction. The mixture was stirred for 2 h, then the solvents were evaporated. Crystallisation of the hydrochloride was induced by addition of Et_2O (5 mL), which was subsequently removed in vacuo to give the desired methyl ester as colourless solid.

Amine Protection: The crude methyl ester was suspended in 1,4-dioxane (80 mL), and benzyl chloroformate (2.0 mL, 13.9 mmol) and a solution of $NaHCO_3$ (3.34 g, 39.8 mmol) in H_2O (60 mL) were added. After stirring for 2 h, the suspension was diluted with H_2O (300 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by flash column chromatography (100 g silica, *n*-pentane/MTBE, 2:1 → 1:1) to yield the protected amino acid **32** (2.04 g, 7.41 mmol, 93% over two steps) as colourless solid. R_f = 0.31 (*n*-hexane/MTBE, 1:1); m.p. 61 °C; $[\alpha]_D^{26}$ = +34.4 (*c* = 3.10, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.90 (dt, *J* = 13.9, 3.9 Hz, 1 H, 5-H^a), 2.50 (dt, *J* = 13.9, 8.4 Hz, 1 H, 5-H^b), 3.48 (dd, *J* = 8.4, 4.0 Hz, 1 H, 1-H), 3.69 (s, 3 H, CH_3), 4.85 (td, *J* = 8.5, 3.1 Hz, 1 H, 4-H), 5.09 (s, 2 H, PhCH_2), 5.24 (br. d, *J* = 8.5 Hz, 1 H, NH), 5.88 (m, 2 H, 2-H, 3-H), 7.27–7.40 (m, 5 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6 (C-5), 49.3 (C-1), 52.3 (CH_3), 56.4 (C-4), 66.7 (Ph*C*H_2), 128.1 (2 C), 128.2, 128.6 (2 C, CH_{ar}), 131.6, 134.6 (C-2, C-3), 136.7 ($C_{q,ar}$), 155.7 (OCONH), 174.9 (*C*O_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3303 (s), 3035 (w), 2953 (w), 1741 (s), 1681 (s), 1537 (s), 1454 (w), 1434 (w), 1328 (m), 1286 (m), 1258 (m), 1201 (m), 1177 (w), 1074 (m), 995 (w), 926 (w), 890 (w), 841 (w), 780 (w), 749 (w), 716 (m), 695 (m), 578 (w), 531 (w), 490 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{17}NNaO_4$: 298.1050; found: 298.1053 $[M + Na]^+$. The NMR spectroscopic data which were published for ***ent*-32** do not correspond to these results.[27] The *cis* arrangement of the substituents was proven by a NOESY experiment.

Methyl (1*R*,2*S*,3*R*,4*S*)-4-Benzyloxycarbonylamino-2,3-isopropylidenedioxycyclopentanecarboxylate (33) and Methyl (1*R*,2*R*,3*S*,4*S*)-4-Benzyloxycarbonylamino-2,3-isopropylidenedioxycyclopentanecarboxylate (34)

Dihydroxylation: To a solution of the cyclopentene **32** (957 mg, 3.48 mmol) in acetone/H_2O (9:1 v/v, 33 mL) were added K_2OsO_4 (6.4 mg, 17.4 μmol) and NMO (611 mg, 5.21 mmol). The solution was stirred at room temp. for 40 h, and then the reaction was quenched by addition of satd. $Na_2S_2O_3$ (50 mL). The mixture was extracted with $CHCl_3$ (5 × 50 mL), and the combined organic layers were washed with $Na_2S_2O_3$ (2 × 50 mL) and brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated to dryness, and the residue was purified by flash column chromatography (100 g silica, *n*-pentane/acetone, 2:1 → 1:1) to yield the desired *cis*-diol (933 mg, 3.02 mmol, 87%) as an inseparable mixture of diastereomers. R_f = 0.43 (*n*-pentane/acetone, 1:1).

Diol Protection: The isomeric mixture of the *cis*-diol (933 mg, 3.02 mmol) was dissolved in MeCN (30 mL), and 2,2-dimethoxypropane (1.24 mL, 10.1 mmol) and CSA (60.3 mg, 259 μmol) were added. The solution was stirred at room temp. for 30 min and was then quenched by addition of Et_3N (3 mL). The solvent was evaporated in vacuo, and the residue was separated by flash column chromatography (95 g silica, *n*-pentane/MTBE, 2:1 → 1:1) to afford the two protected *cis*-diol isomers **33** (440 mg, 1.26 mmol, 42%) and **34** (521 mg, 1.49 mmol, 49%), both as colourless solids. **33:** R_f = 0.29 (*n*-hexane/MTBE, 1:1); m.p. 106 °C; $[\alpha]_D^{21}$ = –20.8 (*c* = 2.40, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, C_qCH_3), 1.46 (s, 3 H, C_qCH_3), 1.96 (d, *J* = 14.0 Hz, 1 H, 5-H^a), 2.44 (dt, *J* = 14.0, 7.3 Hz, 1 H, 5-H^b), 3.02 (dt, *J* = 8.1, 1.8 Hz, 1 H, 1-H), 3.71 (s, 3 H, OCH_3), 4.17 (t, *J* = 6.4 Hz, 1 H, 4-H), 4.52 (d, *J* = 5.4 Hz, 1 H, 2/3-H), 4.83 (d, *J* = 5.6 Hz, 1 H, 2/3-H), 5.06 (d, *J* = 12.5 Hz, 1 H, PhCH_2), 5.12 (d, *J* = 12.5 Hz, 1 H, PhCH_2), 5.73 (d, *J* = 6.6 Hz, 1 H, NH), 7.28–7.42 (m, 5 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 26.8 (C_qCH_3), 31.9 (C-5), 50.8 (C-1), 52.6 (OCH_3), 57.5 (C-4), 66.8 (Ph*C*H_2), 83.3, 86.4 (C-2, C-3), 111.4 [$C_q(CH_3)_2$], 128.2 (2 C), 128.3, 128.6 (2 C, CH_{ar}), 136.7 ($C_{q,ar}$), 155.8 (OCONH), 176.0 (*C*O_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3353 (s), 2988 (m), 1730 (br. s), 1689 (s), 1540 (br. s), 1453 (m), 1437 (m),

1384 (m), 1301 (m), 1274 (m), 1254 (m), 1196 (m), 1069 (m), 1034 (m), 1004 (w), 867 (m), 756 (w), 724 (w), 697 (w), 657 (w), 516 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{23}NNaO_6$: 372.1418; found: 372.1433 $[M + Na]^+$. **34:** R_f = 0.15 (*n*-hexane/MTBE, 1:1); m.p. 106 °C; $[\alpha]_D^{20}$ = +3.7 (*c* = 3.31, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, C_qCH_3), 1.41 (s, 3 H, C_qCH_3), 1.95 (dd, *J* = 2.5, 12.3 Hz, 1 H, 5-H^a), 2.07 (dt, *J* = 12.3, 6.1 Hz, 1 H, 5-H^b), 2.68 (dd, *J* = 12.6, 6.1 Hz, 1 H, 1-H), 3.71 (s, 3 H, OCH_3), 3.91 (m, 1 H, 4-H), 4.52 (t, *J* = 5.2 Hz, 1 H, 3-H), 4.79 (t, *J* = 5.5 Hz, 1 H, 2-H), 5.08 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 5.12 (d, *J* = 12.1 Hz, 1 H, PhCH_2), 5.24 (d, *J* = 8.5 Hz, 1 H, NH), 7.28–7.40 (m, 5 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 25.7 (C_qCH_3), 29.6 (C-5), 46.0 (C-1), 52.0 (OCH_3), 52.4 (C-4), 67.0 (PhCH$_2$), 78.8 (C-3), 79.5 (C-2), 111.1 [$C_q(CH_3)_2$], 128.3 (2 C), 128.7 (3 C, CH_{ar}), 136.5 ($C_{q,ar}$), 155.9 (OCONH), 170.7 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3390 (br. m), 3035 (w), 2980 (m), 2928 (m), 1728 (br. s), 1701 (br. s), 1528 (br. s), 1456 (m), 1441 (w), 1374 (m), 1326 (w), 1281 (s), 1260 (m), 1243 (m), 1217 (m), 1172 (m), 1124 (m), 1105 (m), 1082 (m), 1030 (m), 1000 (m), 980 (w), 954 (w), 928 (w), 909 (w), 882 (w), 859 (w), 824 (w), 778 (w), 752 (w), 731 (w), 699 (m), 577 (w), 516 (w), 488 (w), 413 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{23}NNaO_6$: 372.1418; found: 372.1429 $[M + Na]^+$.

Methyl (1*S*,2*S*,3*R*,4*S*)-4-Benzyloxycarbonylamino-2,3-isopropylidenedioxycyclopentanecarboxylate (35): To a solution of methyl ester **33** (143 mg, 409 μmol) in dry MeOH (7 mL) was added NaOMe (0.5 M in MeOH, 0.82 mL, 409 μmol). The solution was stirred at room temp. for 100 min. It was neutralised by addition of ion exchange resin amberlite IR-120, which was washed with HCl (1 M, 2 × 2 mL), H_2O (2 × 2 mL) and MeOH (2 × 2 mL) prior to use. The solvent was removed in vacuo and the residue was separated by flash column chromatography (15 g silica, *n*-pentane/MTBE, 2:1 → 1:1) to afford the new epimer **35** (64.3 mg, 184 μmol, 45%) as colourless solid, as well as recovered starting material **33** (57.7 mg, 165 μmol, 40%). A minor amount of elimination product (6.6 mg, 22.7 μmol, 6%) was isolated as by-product. R_f = 0.14 (*n*-hexane/MTBE, 1:1); $[\alpha]_D^{18}$ = –36.2 (*c* = 3.15, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, C_qCH_3), 1.41 (s, 3 H, C_qCH_3), 1.78 (dd, *J* = 13.8, 6.0 Hz, 1 H, 5-H^a), 2.49 (td, *J* = 13.5, 6.1 Hz, 1 H, 5-H^b), 2.99 (dt, *J* = 12.9, 6.4 Hz, 1 H, 1-H), 3.73 (s, 3 H, OCH_3), 3.98 (t, *J* = 5.4 Hz, 1 H, 4-H), 4.48–4.62 (m, 2 H, 3-H, NH), 4.86 (t, *J* = 5.6 Hz, 1 H, 2-H), 5.10 (s, 2 H, PhCH_2), 7.28–7.42 (m, 5 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 26.0 (C_qCH_3), 30.5 (C-5), 47.6 (C-1), 52.0 (OCH_3), 56.3 (C-4), 67.1 (PhCH$_2$), 80.2 (C-2), 85.2 (C-3), 111.2 [$C_q(CH_3)_2$], 128.3, 128.4 (2 C), 128.7 (2 C, CH_{ar}), 136.3 ($C_{q,ar}$), 155.9 (OCONH), 171.0 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3336 (br. s), 2987 (m), 2851 (m), 1723 (br. s), 1531 (s), 1445 (m), 1374 (m), 1339 (m), 1305 (m), 1246 (s), 1210 (s), 1124 (m), 1050 (s), 1013 (m), 975 (w), 946 (w), 896 (w), 871 (w), 779 (w), 754 (w), 698 (w), 611 (w), 516 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{23}NNaO_6$: 372.1418; found: 372.1432 $[M + Na]^+$.

(1*R*,2*S*,3*R*,4*S*)-4-Benzyloxycarbonylamino-2,3-dihydroxycyclopentanecarboxylic Acid (36)

Ketal Cleavage: The protected diol **33** (130 mg, 372 μmol) was dissolved in AcOH (5.2 mL) and mixed with H_2O (1.3 mL). The solution was heated to 100 °C with microwaves in a sealed tube for 10 min. After removal of the solvents in vacuo, the solid residue was coevaporated with MeOH/toluene (1:1 v/v, 5 mL) to yield the crude diol. R_f = 0.33 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.5). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (dt, *J* = 13.5, 7.5 Hz, 1 H, 5-H^a), 2.47 (dt, *J* = 13.6, 8.3 Hz, 1 H, 5-H^b), 2.94 (m, 1 H, 1-H), 3.72 (s, 3 H, CH_3), 3.91–4.04 (m, 2 H, 4-H, 2/3-H), 4.28 (t, *J* = 4.3 Hz, 1 H, 2/3-H), 5.09 (d, *J* = 12.7 Hz, 1 H, PhCH_2), 5.13 (d, *J* = 12.3 Hz, 1 H, PhCH_2), 7.28–7.44 (m, 5 H, CH_{ar}) ppm.

Ester Cleavage: To a solution of the crude diol in THF/H_2O (3:1 v/v, 14 mL) was added LiOH·H_2O (47.0 mg, 1.12 mmol). The solution was stirred at room temp. for 18 h. It was then neutralised with ion exchange resin amberlite IR-120, which was washed with HCl (1 M, 2 × 2 mL), H_2O (2 × 2 mL) and MeOH (2 × 2 mL) prior to use. The solvents were removed in vacuo, and the residue was purified by flash column chromatography (12 g silica, $CHCl_3$/MeOH/HCO_2H, 20:1:0.1 → 10:1:0.1) to afford the carboxylic acid **36** (86.4 mg, 293 μmol, 79% over two steps) as colourless solid. R_f = 0.05 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.1); $[\alpha]_D^{25}$ = +3.7 (*c* = 2.88, in MeOH). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.45 (dt, *J* = 13.1, 8.9 Hz, 1 H, 5-H^a), 2.16 (dt, *J* = 13.0, 8.5 Hz, 1 H, 5-H^b), 2.56 (td, *J* = 9.1, 5.5 Hz, 1 H, 1-H), 3.59 (t, *J* = 5.9 Hz, 1 H, 3-H), 3.72 (dt, *J* = 1.5, 7.7 Hz, 1 H, 4-H), 3.97 (t, *J* = 5.3 Hz, 1 H, 2-H), 5.01 (s, 2 H, PhCH_2), 7.27–7.41 (m, 5 H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 30.5 (C-5), 47.6 (C-1), 55.6 (C-4), 65.1 (PhCH$_2$), 73.0 (C-2), 75.6 (C-3), 127.7 (3 C), 128.3 (2 C, CH_{ar}), 137.2 ($C_{q,ar}$), 155.7 (OCONH), 175.6 (CO_2H) ppm. IR (KBr): $\tilde{\nu}$ = 3459 (s), 3339 (s), 1735 (br. m), 1661 (m), 1550 (br. m), 1455 (w), 1414 (w), 1318 (w), 1284 (br. m), 1184 (m), 1026 (m), 838 (w), 762 (w), 726 (w), 694 (w), 547 (w), 493 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{17}NNaO_6$: 318.0948; found: 318.0952 $[M + Na]^+$.

(1*R*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxycyclopentanecarboxylic Acid (37): To a solution of carbamate **36** (49.4 mg, 167 μmol) in MeOH (3 mL) was added Pd(OH)$_2$/C (20% with 50% H_2O, 4.9 mg, 3.5 μmol). The flask was evaporated and flushed with hydrogen five times, and the reaction mixture was stirred at room temp. for 90 min. The catalyst was removed by filtration through a short column of Celite, and the solvent was evaporated in vacuo to afford the pure amino acid **37** (26.4 mg, 164 μmol, 98%) as colourless solid. R_f = 0.18 (*n*BuOH/H_2O/AcOH, 4:1:1); m.p. 209 °C (dec.); $[\alpha]_D^{25}$ = +4.4 (*c* = 0.88, in H_2O). ^1H NMR (300 MHz, D_2O): δ = 1.77 (dt, *J* = 13.7, 8.3 Hz, 1 H, 5-H^a), 2.47 (dt, *J* = 13.7, 8.6 Hz, 1 H, 5-H^b), 2.75 (td, *J* = 8.3, 3.7 Hz, 1 H, 1-H), 3.55 (quart, *J* = 8.1 Hz, 1 H, 4-H), 4.07 (dd, *J* = 7.4, 5.5 Hz, 1 H, 3-H), 4.23 (dd, *J* = 5.1, 4.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O, MeOH): δ = 29.2 (C-5), 51.6 (C-1), 55.7 (C-4), 74.5 (C-2), 75.5 (C-3), 181.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3267 (br. s), 1636 (m), 1558 (br. s), 1526 (br. s), 1416 (s), 1310 (w), 1264 (w), 1171 (w), 1093 (m), 1040 (w), 991 (w), 826 (w), 731 (w), 579 (w), 428 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_6H_{12}NO_4$: 162.0761; found: 162.0766 $[M + H]^+$.

(1*S*,2*S*,3*R*,4*S*)-4-Benzyloxycarbonylamino-2,3-dihydroxycyclopentanecarboxylic Acid (38)

Ketal Cleavage: The protected diol **35** (85.0 mg, 243 μmol) was dissolved in AcOH (6.4 mL) and mixed with H_2O (1.6 mL). The solution was heated to 100 °C by microwave irradiation in a sealed tube for 10 min. After removal of the solvents in vacuo, the solid residue was coevaporated with MeOH/toluene (1:1 v/v, 5 mL) to yield the crude diol. R_f = 0.24 (*n*-hexane/acetone, 1:1). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.63 (ddd, *J* = 14.0, 10.1, 6.9 Hz, 1 H, 5-H^a), 2.79 (m, 1 H, 5-H^b), 3.01 (br. s, 1 H, 2-OH), 3.08 (m, 1 H, 1-H), 3.75 (s, 3 H, CH_3), 3.95 (m, 1 H, 3-H), 4.03 (dtd, *J* = 10.7, 6.9, 4.2 Hz, 1 H, 4-H), 4.37 (t, *J* = 3.8 Hz, 1 H, 2-H), 4.43 (br. s, 1 H, 3-OH), 4.95 (br. s, 1 H, NH), 5.11 (s, 2 H, PhCH_2), 7.32–7.39 (m, 5 H, CH_{ar}) ppm.

Ester Cleavage: To a solution of the crude diol in THF/H_2O (3:1 v/v, 10 mL) was added LiOH·H_2O (27.1 mg, 645 μmol). The solution was stirred at room temp. for 1 h. It was then neutralised with ion exchange resin amberlite IR-120, which was washed with HCl (1 M, 2 × 2 mL), H_2O (2 × 2 mL) and MeOH (2 × 2 mL) prior to

use. The solvents were removed in vacuo, and the residue was purified by flash column chromatography (7 g silica, $CHCl_3$/MeOH/HCO_2H, 20:1:0.1 → 10:1:0.1) to give the carboxylic acid **38** (67.9 mg, 230 μmol, 95% over two steps) as colourless solid. R_f = 0.09 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.1); $[\alpha]_D^{20}$ = +17.4 (*c* = 3.58, in MeOH). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.34 (ddd, *J* = 13.5, 10.0, 6.2 Hz, 1 H, 5-H^a), 2.37 (dt, *J* = 12.9, 9.3 Hz, 1 H, 5-H^b), 2.85 (td, *J* = 9.0, 4.3 Hz, 1 H, 1-H), 3.70 (dd, *J* = 8.4, 3.5 Hz, 1 H, 3-H), 3.81 (quin, *J* = 7.6 Hz, 1 H, 4-H), 4.02 (t, *J* = 3.8 Hz, 1 H, 2-H), 5.01 (s, 2 H, PhC*H*$_2$), 7.27–7.42 (m, 6 H, NH, CH$_{ar}$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 29.3 (C-5), 44.2 (C-1), 54.9 (C-4), 65.1 (Ph*C*H$_2$), 72.8 (C-2), 77.5 (C-3), 127.8 (3 C), 128.3 (2 C, CH$_{ar}$), 137.2 (C$_{q,ar}$), 155.9 (OCONH), 173.2 (CO_2H) ppm. IR (KBr): $\tilde{\nu}$ = 3528 (s), 3311 (s), 2933 (br. m), 1730 (s), 1683 (br. s), 1551 (br. s), 1349 (w), 1279 (m), 1264 (m), 1239 (m), 1210 (m), 1118 (m), 1052 (m), 1018 (m), 970 (m), 930 (w), 861 (w), 830 (w), 760 (w), 722 (w), 696 (m), 620 (w), 573 (w), 528 (w), 469 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{17}NNaO_6$: 318.0948, found: 318.0952 [M + Na]$^+$.

(1*S*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxycyclopentanecarboxylic Acid (7): To a solution of carbamate **38** (58.8 mg, 199 μmol) in MeOH (4.5 mL) was added Pd(OH)$_2$/C (20% with 50% H_2O, 7.0 mg, 5.0 μmol). The flask was evaporated and flushed with hydrogen five times, and the reaction mixture was stirred at room temp. for 1 h. The catalyst was removed by filtration through a short column of Celite, and the solvent was evaporated in vacuo to afford the pure amino acid **7** (28.9 mg, 179 μmol, 90%) as colourless solid. R_f = 0.18 (*n*BuOH/H_2O/AcOH, 4:1:1); m.p. 215 °C (dec.); $[\alpha]_D^{26}$= +15.2 (*c* = 1.01, in H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.81 (ddd, *J* = 14.8, 10.0, 5.8 Hz, 1 H, 5-H^a), 2.58 (dt, *J* = 14.4, 9.9 Hz, 1 H, 5-H^b), 3.02 (td, *J* = 9.6, 4.0 Hz, 1 H, 1-H), 3.65 (ddd, *J* = 10.2, 8.7, 6.2 Hz, 1 H, 4-H), 4.08 (dd, *J* = 8.5, 3.8 Hz, 1 H, 3-H), 4.27 (t, *J* = 3.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O, MeOH): δ = 28.3 (C-5), 47.0 (C-1), 55.5 (C-4), 74.1 (C-2), 77.3 (C-3), 179.7 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3401 (br. s), 3129 (br. s), 1653 (m), 1557 (br. s), 1456 (m), 1394 (br. s), 1299 (m), 1252 (m), 1172 (m), 1119 (m), 1097 (m), 937 (w), 854 (w), 767 (w), 731 (w), 671 (w), 611 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_6H_{12}NO_4$: 162.0761; found: 162.0762 [M + H]$^+$.

Methyl (1*S*,2*R*,3*S*,4*S*)-4-Benzyloxycarbonylamino-2,3-isopropylidenedioxycyclopentanecarboxylate (39): To a solution of methyl ester **34** (480 mg, 1.37 mmol) in dry MeOH (20 mL) was added NaOMe (0.5 M in MeOH, 2.75 mL, 1.37 mmol). The solution was stirred at room temp. for 3 h. It was neutralised by addition of ion exchange resin amberlite IR-120, which was washed with HCl (1 M, 2 × 2 mL), H_2O (2 × 2 mL) and MeOH (2 × 2 mL) prior to use. The solvent was removed in vacuo, and the residue was separated by flash column chromatography (50 g silica, *n*-pentane/MTBE, 2:1 → 1:1) to afford the new epimer **39** (176 mg, 504 μmol, 37%) as colourless solid, as well as recovered starting material **34** (276 mg, 790 μmol, 58%). R_f = 0.29 (*n*-hexane/MTBE, 1:1); m.p. 89 °C; $[\alpha]_D^{20}$ = –53.5 (*c* = 3.15, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, C$_q$C*H*$_3$), 1.43 (s, 3 H, C$_q$C*H*$_3$), 1.86 (td, *J* = 12.3, 8.0 Hz, 1 H, 5-H^a), 2.27 (dd, *J* = 12.7, 6.4 Hz, 1 H, 5-H^b), 2.89 (d, *J* = 7.9 Hz, 1 H, 1-H), 3.69 (s, 3 H, OCH_3), 4.14 (m, 1 H, 4-H), 4.57 (t, *J* = 5.3 Hz, 1 H, 3-H), 4.84 (d, *J* = 5.3 Hz, 1 H, 2-H), 5.09 (m, 2 H, PhC*H*$_2$), 5.19 (d, *J* = 8.5 Hz, 1 H, NH), 7.27–7.41 (m, 5 H, CH$_{ar}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 26.1 (C$_q$*C*H$_3$), 32.1 (C-5), 47.3 (C-1), 52.2 (OCH_3), 52.6 (C-4), 67.0 (Ph*C*H$_2$), 78.9 (C-3), 81.3 (C-2), 110.7 [*C*$_q$(CH$_3$)$_2$], 128.3, 128.4 (2 C), 128.6 (2 C, CH$_{ar}$), 136.6 (C$_{q,ar}$), 155.8 (OCONH), 173.3 (*C*O$_2$Me) ppm. IR (KBr): $\tilde{\nu}$ = 3394 (s), 3069 (w), 3038 (w), 2991 (m), 2981 (m), 2934 (m), 1719 (br. s), 1699 (br. s), 1521 (br. m), 1455 (m), 1382 (s), 1369 (m), 1349 (w), 1325 (m), 1288 (m), 1265 (m), 1242 (s), 1199 (s), 1175 (s), 1156 (m), 1107 (m), 1072 (m), 1047 (s), 1014 (s), 980 (m), 947 (w), 926 (w), 909 (m), 884 (m), 859 (w), 827 (w), 810 (w), 790 (w), 778 (w), 751 (m), 696 (m), 619 (w), 584 (w), 554 (w), 516 (w), 490 (w), 413 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{23}NNaO_6$: 372.1418; found: 372.1433 [M + Na]$^+$.

Methyl (1*R*,2*R*,3*S*,4*S*)-4-Benzyloxycarbonylamino-2,3-dihydroxycyclopentanecarboxylate (40): The protected diol **34** (142 mg, 406 μmol) was dissolved in AcOH (4 mL) and mixed with H_2O (4 mL). The solution was heated to 100 °C by microwave irradiation in a sealed tube for 30 min. The solvents were evaporated in vacuo and successively coevaporated with MeOH/toluene (1:1 v/v, 5 mL). The residue was purified by flash column chromatography (10 g silica, *n*-pentane/acetone, 1:1) to give the corresponding diol **40** (113 mg, 365 μmol, 90%) as colourless oil. R_f = 0.24 (*n*-hexane/acetone, 1:1); $[\alpha]_D^{21}$ = +0.4 (*c* = 7.02, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (ddd, *J* = 14.0, 9.3, 7.2 Hz, 1 H, 5-H^a), 2.29 (m, 1 H, 5-H^b), 2.86 (m, 1 H, 1-H), 3.57 (br. s, 2 H, OH), 3.70 (s, 3 H, CH_3), 3.96 (s, 1 H, 3-H), 4.09 (m, 1 H, 4-H), 4.30 (s, 1 H, 2-H), 5.08 (m, 2 H, PhC*H*$_2$), 5.61 (d, *J* = 7.6 Hz, 1 H, NH), 7.26–7.39 (m, 5 H, CH$_{ar}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.1 (C-5), 44.8 (C-1), 52.2 (C-4), 52.3 (CH_3), 67.0 (Ph*C*H$_2$), 73.0 (C-2), 73.2 (C-3), 128.2 (3 C), 128.6 (2 C, CH$_{ar}$), 136.5 (C$_{q,ar}$), 156.6 (OCONH), 174.0 (*C*O$_2$Me) ppm. IR (film): $\tilde{\nu}$ = 3402 (br. s), 3032 (w), 2952 (m), 1705 (br. s), 1521 (br. s), 1454 (m), 1438 (m), 1348 (m), 1212 (br. s), 1177 (m), 1111 (m), 1069 (m), 1028 (m), 917 (w), 742 (w), 699 (m), 578 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{19}NNaO_6$: 332.1105; found: 332.1109 [M + Na]$^+$.

Methyl (1*R*,2*R*,3*S*,4*S*)-4-Amino-2,3-dihydroxycyclopentanecarboxylate (41): To a solution of diol **40** (158 mg, 511 μmol) in MeOH (9 mL) was added Pd(OH)$_2$/C (20% with 50% H_2O, 15.8 mg, 11.2 μmol). The flask was evaporated and flushed with hydrogen five times, and the suspension was stirred at room temp. for 1 h. The catalyst was removed by filtration through a short column of Celite, and the solvent was evaporated in vacuo to afford the amine **41** (65.9 mg, 376 μmol, 74%) as yellowish solid. R_f = 0.33 (*n*BuOH/H_2O/HCO_2H, 4:1:1); m.p. 221 °C (dec.); $[\alpha]_D^{25}$ = +7.0 (*c* = 2.82, in H_2O). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.88–2.07 (m, 2 H, 5-H$_2$), 2.83 (td, *J* = 9.4, 4.9 Hz, 1 H, 1-H), 3.13–3.23 (m, 1 H, 4-H), 3.59 (s, 3 H, CH_3), 3.66 (dd, *J* = 5.9, 3.9 Hz, 1 H, 3-H), 4.03 (t, *J* = 4.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 31.4 (C-5), 45.3 (C-1), 51.2 (CH_3), 51.9 (C-4), 72.9 (C-3), 74.3 (C-2), 172.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3380 (br. s), 2956 (s), 1734 (br. s), 1637 (m), 1432 (w), 1344 (w), 1322 (w), 1244 (w), 1204 (m), 1172 (m), 1128 (w), 1086 (w), 1041 (w), 957 (w), 911 (w), 848 (w), 716 (w), 564 (w), 532 (w), 522 (w), 511 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_7H_{14}NO_4$: 176.0917; found: 176.0915 [M + H]$^+$.

Methyl (1*S*,2*R*,3*S*,4*S*)-4-Benzyloxycarbonylamino-2,3-dihydroxycyclopentanecarboxylate (42): The protected diol **39** (107 mg, 306 μmol) was dissolved in AcOH (6.4 mL) and mixed with H_2O (1.6 mL). The solution was heated to 100 °C by microwave irradiation in a sealed tube for 10 min. The solvents were evaporated in vacuo and successively coevaporated with MeOH/toluene (1:1 v/v, 5 mL). The residue was purified by flash column chromatography (11 g silica, *n*-pentane/acetone, 1:1) to afford the desired diol **42** (75.7 mg, 245 μmol, 80%) as colourless oil. R_f = 0.25 (*n*-hexane/acetone, 1:1); $[\alpha]_D^{21}$ = +8.4 (*c* = 7.93, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (ddd, *J* = 13.6, 11.4, 7.7 Hz, 1 H, 5-H^a), 2.23 (m, 1 H, 5-H^b), 2.94 (dt, *J* = 11.3, 6.9 Hz, 1 H, 1-H), 3.58 (s, 2 H, OH), 3.68 (s, 3 H, CH_3), 4.02 (m, 1 H, 3-H), 4.11 (m, 1 H, 4-H), 4.25 (m, 1 H, 2-H), 5.07 (m, 2 H, PhC*H*$_2$), 5.59 (d, *J* = 7.9 Hz, 1 H, NH), 7.27–7.37 (m, 5 H, CH$_{ar}$) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 32.1 (C-5), 47.8 (C-1), 51.8 (C-4), 52.3 (CH_3), 67.0 (PhCH_2), 73.4 (C-3), 75.5 (C-2), 128.2 (2 C), 128.3, 128.6 (2 C, CH_{ar}), 136.4 ($C_{q,ar}$), 156.4 (OCONH), 175.2 (CO_2Me) ppm. IR (film): $\tilde{\nu}$ = 3405 (br. s), 3033 (w), 2953 (m), 1716 (br. s), 1524 (br. m), 1455 (m), 1437 (m), 1290 (m), 1215 (s), 1176 (m), 1055 (m), 1011 (m), 966 (w), 866 (w), 776 (w), 740 (w), 698 (w), 578 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{19}NNaO_6$: 332.1105; found: 332.1109 $[M + Na]^+$.

Methyl (1*S*,2*R*,3*S*,4*S*)-4-Amino-2,3-dihydroxycyclopentanecarboxylate (43): To a solution of **42** (75.5 mg, 244 µmol) in MeOH (4.5 mL) was added $Pd(OH)_2$/C (20% with 50% H_2O, 7.5 mg, 5.4 µmol). The flask was evaporated and flushed with hydrogen five times, and the suspension was stirred at room temp. for 1 h. The catalyst was removed by filtration through a short column of Celite, and the solvent was evaporated in vacuo to afford the pure amine **43** (38.6 mg, 220 µmol, 90%) as yellowish oil. R_f = 0.29 (*n*BuOH/H_2O/HCO_2H, 4:1:1); $[\alpha]_D^{25}$ = +54.7 (*c* = 3.50, in H_2O). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.65 (ddd, *J* = 13.2, 11.3, 7.9 Hz, 1 H, 5-H^a), 1.84 (ddd, *J* = 13.5, 8.1, 5.8 Hz, 1 H, 5-H^b), 2.75 (dt, *J* = 11.5, 6.8 Hz, 1 H, 1-H), 3.10 (td, *J* = 8.1, 3.8 Hz, 1 H, 4-H), 3.47 (br. s, 3 H, NH, OH), 3.57 (t, *J* = 4.1 Hz, 1 H, 3-H), 3.59 (s, 3 H, CH_3), 3.95 (dd, *J* = 7.5, 3.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 34.3 (C-5), 48.0 (C-1), 51.4 (CH_3), 52.2 (C-4), 74.3 (C-3), 75.8 (C-2), 175.7 (CO) ppm. IR (film): $\tilde{\nu}$ = 3439 (br. s), 1720 (s), 1630 (s), 1561 (s), 1439 (m), 1400 (m), 1111 (m), 627 (w), 408 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_7H_{14}NO_4$: 176.0917; found: 176.0916 $[M + H]^+$.

Methyl (1*R*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxycyclopentanecarboxylate (46): The crude diol, which was described for the synthesis of carboxylic acid **36**, was purified by flash column chromatography (silica, *n*-pentane/acetone, 1:1) prior to use. To a solution of the pure diol (105 mg, 340 µmol) in MeOH (7 mL) was added $Pd(OH)_2$/C (20% with 50% H_2O, 10.5 mg, 7.5 µmol). The flask was evaporated and flushed with hydrogen five times, and the suspension was stirred at room temp. for 90 min. The catalyst was removed by filtration through a short column of Celite, and the solvent was evaporated in vacuo to afford amine **46** (58.1 mg, 332 µmol, 98%) as colourless oil. R_f = 0.29 (*n*BuOH/H_2O/HCO_2H, 4:1:1); $[\alpha]_D^{21}$ = –30.9 (*c* = 2.60, in H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.51 (dt, *J* = 13.5, 8.9 Hz, 1 H, 5-H^a), 2.37 (ddd, *J* = 13.6, 8.7, 8.1 Hz, 1 H, 5-H^b), 2.88 (td, *J* = 9.3, 6.0 Hz, 1 H, 1-H), 3.21 (td, *J* = 7.4, 6.8 Hz, 1 H, 4-H), 3.69–3.77 (m, 4 H, CH_3, 3-H), 4.27 (t, *J* = 5.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O, MeOH): δ = 31.7 (C-5), 48.4 (C-1), 53.2 (CH_3), 55.6 (C-4), 74.1 (C-2), 78.5 (C-3), 177.4 (CO) ppm. IR (film): $\tilde{\nu}$ = 3351 (br. s), 1720 (br. s), 1637 (m), 1559 (br. m), 1438 (m), 1204 (m), 1112 (m), 1042 (m), 824 (w), 749 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_7H_{14}NO_4$: 176.0917; found: 176.0917 $[M + H]^+$.

Methyl (1*S*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxycyclopentanecarboxylate (47): The crude diol, which was described for the synthesis of carboxylic acid **38**, was purified by flash column chromatography (silica, *n*-pentane/acetone, 1:1) prior to use. To a solution of the pure diol (106 mg, 343 µmol) in MeOH (7 mL) was added $Pd(OH)_2$/C (20% with 50% H_2O, 10.6 mg, 7.5 µmol). The flask was evaporated and flushed with hydrogen five times, and the suspension was stirred at room temp. for 1 h. The catalyst was removed by filtration through a short column of Celite, and the solvent was evaporated in vacuo to afford the amine **47** (58.4 mg, 333 µmol, 97%) as colourless solid. R_f = 0.37 (*n*BuOH/H_2O/HCO_2H, 4:1:1); m.p. 107 °C; $[\alpha]_D^{21}$ = +23.7 (*c* = 1.68, in H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.54 (ddd, *J* = 14.1, 10.5, 7.3 Hz, 1 H, 5-H^a), 2.49 (ddd, *J* = 14.1, 9.8, 8.0 Hz, 1 H, 5-H^b), 3.18–3.30 (m, 2 H, 1-H, 4-H), 3.68–3.75 (m, 4 H, CH_3, 3-H), 4.29 (t, *J* = 4.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O, MeOH): δ = 29.8 (C-5), 45.0 (C-1), 53.0 (CH_3), 54.7 (C-4), 74.1 (C-2), 80.3 (C-3), 175.6 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3380 (br. s), 2957 (s), 2883 (s), 1744 (br. s), 1617 (m), 1450 (m), 1427 (m), 1356 (m), 1333 (m), 1290 (m), 1257 (m), 1197 (s), 1175 (m), 1136 (m), 1104 (s), 1079 (s), 1046 (m), 997 (w), 960 (w), 919 (w), 829 (m), 796 (w), 733 (w), 676 (w), 542 (w), 427 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_7H_{14}NO_4$: 176.0917; found: 176.0917 $[M + H]^+$.

3-Methoxymethoxypyridine (50): NaH (60% in mineral oil, 9.25 g, 231 mmol) was washed with *n*-pentane (15 mL) and decanted. After short evacuation, DMF (450 mL) was added, and the suspension was cooled to 0 °C. Pyridin-3-ol (**49**) (20.0 g, 210 mmol) was added slowly with stirring. The solid material dissolved, and the evolution of hydrogen ceased within 10 min. After that, chloromethyl methyl ether (17.6 mL, 231 mmol) was slowly added dropwise into the dark yellow solution effecting an immediate precipitation of NaCl. The reaction mixture was stirred at 0 °C for further 90 min and was then quenched by addition of satd. aq. NH_4Cl (100 mL). Excess reagent and about 4/5 of the solvents were removed at 50 °C and high vacuum. The residue was poured into aqueous sodium carbonate buffer (1.0 M, pH = 10, 200 mL). The mixture was extracted with MTBE (8 × 75 mL), and the combined organic layers were washed with buffer (2 × 100 mL) and brine (100 mL), dried with $MgSO_4$, and the solvents were evaporated. The crude product was fractionally distilled (68 °C, 0.6 mbar) to afford the desired protected pyridinol **50** (22.2 g, 160 mmol, 76%) as a colourless oil. R_f = 0.26 (*n*-hexane/MTBE, 1:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45 (s, 3 H, CH_3), 5.16 (s, 2 H, CH_2), 7.18 (ddd, *J* = 8.6, 4.6, 0.5 Hz, 1 H, 5-H), 7.33 (ddd, *J* = 8.5, 2.9, 1.4 Hz, 1 H, 4-H), 8.23 (dd, *J* = 4.6, 1.5 Hz, 1 H, 6-H), 8.38 (d, *J* = 2.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.2 (CH_3), 94.7 (CH_2), 123.0 (C-4), 123.9 (C-5), 139.7 (C-2), 143.3 (C-6), 153.6 (C-3) ppm. IR (film): $\tilde{\nu}$ = 2957 (m), 2905 (m), 2828 (m), 1676 (w), 1575 (s), 1481 (s), 1427 (s), 1405 (w), 1307 (w), 1262 (s), 1229 (s), 1202 (s), 1154 (s), 1104 (w), 1082 (s), 1045 (s), 987 (s), 922 (m), 803 (s), 708 (s), 640 (w), 618 (w), 546 (w), 412 (w) cm^{-1}.

4-Chloro-3-methoxymethoxypyridine (51): The protected pyridinol **50** (4.49 g, 32.3 mmol) was dissolved in Et_2O (170 mL) and cooled to –78 °C. *t*BuLi (1.7 M in *n*-pentane, 19.9 mL, 33.9 mmol) was added dropwise by a syringe which gave a yellowish suspension. After further 30 min of stirring at –78 °C, hexachloroethane (9.17 g, 38.7 mmol) in Et_2O (17 mL) was added quickly to the reaction mixture; 30 min later, the temperature was raised to room temp. during 1 h. Then the reaction mixture was poured into aqueous carbonate buffer (1.0 M, pH = 10, 200 mL) and extracted with MTBE (3 × 100 mL). The organic layers were combined, washed with brine (50 mL) and dried with $MgSO_4$. The solvents were removed at room temp. under reduced pressure. Flash column chromatography (225 g silica, *n*-pentane/acetone, 4:1) of the crude product yielded the chloropyridine **51** (4.85 g, 27.9 mmol, 87%) as yellow oil. The product in neat form decomposes rapidly at room temp., but is stable for several weeks when stored in MTBE solution (ca. 50% v/v) at –28 °C. R_f = 0.28 (*n*-pentane/acetone, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.55 (s, 3 H, CH_3), 5.29 (s, 2 H, CH_2), 7.32 (d, *J* = 5.1 Hz, 1 H, 5-H), 8.20 (d, *J* = 5.1 Hz, 1 H, 6-H), 8.50 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.7 (CH_3), 95.8 (CH_2), 125.1 (C-5), 133.2 (C-4), 139.2 (C-2), 144.0 (C-6), 150.1 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3438 (br. w), 2959 (m), 2907 (m), 2829 (w), 1560 (s), 1486 (s), 1417 (m), 1397 (s), 1292 (s), 1243 (s), 1207 (m), 1188 (m), 1154 (s), 1083 (s), 1050 (s), 987 (s), 923 (m), 824 (s), 732 (w), 695 (s), 642 (w), 575 (m), 445 (w), 420 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_7H_8ClNO_2$: 173.0244;

found: 173.0237 $[M]^+$. $C_7H_8ClNO_2$ (173.60): calcd. C 48.43, H 4.64, N 8.07; found C 48.18, H 4.43, N 8.24.

4-Chloro-3-hydroxypyridinium Trifluoroacetate (52): The protected chloropyridinol **51** (4.84 g, 27.9 mmol) was dissolved in CH_2Cl_2 (210 mL), the solution was cooled to 0 °C, and TFA (20.7 mL, 279 mmol) was added with stirring. The temperature was kept for another 1.5 h; afterwards, the ice bath was removed, and the mixture was stirred for 12 h. Toluene (20 mL) was added, and the volume of the solvents was reduced to approx. 15 mL at 30 °C under reduced pressure. The rest was removed with a pipette from the precipitated crystalline material. After drying at 40 °C in high vacuum, the solid was washed once again with toluene (5 mL) and dried to remove traces of free TFA. The pyridinium salt **52** (6.38 g, 26.2 mmol, 94%) was obtained as colourless crystals in pure form. R_f = 0.35 (*n*-pentane/acetone, 2:1); m.p. 147 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.76 (d, J = 5.7 Hz, 1 H, 5-H), 8.18 (d, J = 5.5 Hz, 1 H, 6-H), 8.38 (s, 1 H, 2-H), 13.37 (s, 2 H, OH, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 115.8 (q, J = 291 Hz, CF_3), 126.2 (C-5), 133.0 (C-4), 134.9 (C-2), 137.4 (C-6), 151.6 (C-3), 158.7 (q, J = 36 Hz, *C*OCF$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2915 (br. m), 2559 (br. m), 1575 (s), 1478 (m), 1433 (s), 1315 (s), 1299 (s), 1210 (s), 1180 (m), 1083 (m), 1061 (s), 867 (w), 810 (s), 696 (s), 587 (w), 572 (w), 439 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for C_5H_4ClNO: 128.9981; found: 128.9971 $[M - TFA]^+$. $C_7H_5ClF_3NO_3$ (243.57): calcd. C 34.52, H 2.07, N 5.75; found C 34.47, H 1.94, N 5.69.

3-Benzyloxy-4-chloropyridine (53): NaH (60% in mineral oil, 1.12 g, 28.0 mmol) was washed with *n*-pentane (3 mL) and decanted. DMF (120 mL) was added, the resulting suspension was cooled to 0 °C, and the pyridinium salt **52** (3.10 g, 12.7 mmol) was added in small portions. After 5 min, the solid had completely dissolved, and 15-crown-5 (5.56 mL, 28.0 mmol) was added, then benzyl bromide (1.66 mL, 14.0 mmol) was added dropwise into the yellow solution which was kept at 0 °C for 80 min. The reaction mixture was poured into sodium carbonate buffer (1.0 M, pH = 10, 500 mL) and extracted with MTBE (4 × 100 mL). The organic layers were combined, dried with $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash column chromatography (110 g silica, *n*-pentane/MTBE, 1:3) which gave the desired benzyl ether **53** (1.54 g, 7.01 mmol, 55%) as yellow oil. The product in neat form decomposes rapidly at room temp., but is stable for several weeks when stored in MTBE solution (ca. 50% v/v) at –28 °C. R_f = 0.23 (*n*-hexane/MTBE, 1:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.24 (s, 2 H, CH_2), 7.33 (d, J = 5.0 Hz, 1 H, 5-H), 7.35 (pd, J = 7.2 Hz, 1 H, CH_{ar}), 7.40 (pt, J = 7.7 Hz, 2 H, CH_{ar}), 7.46 (pd, J = 7.5 Hz, 2 H, CH_{ar}), 8.16 (d, J = 4.9 Hz, 1 H, 6-H), 8.32 (s, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 71.7 (CH_2), 125.2 (C-5), 127.4 (2 C), 128.5, 128.9 (2 C, CH_{ar}), 132.9 (C-4), 135.9 ($C_{q,ar}$), 136.9 (C-2), 143.3 (C-6), 151.2 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3443 (br. w), 3035 (m), 2939 (w), 1559 (s), 1488 (s), 1454 (m), 1411 (s), 1384 (m), 1302 (s), 1252 (s), 1190 (w), 1081 (m), 1057 (m), 1001 (m), 914 (w), 821 (m), 737 (s), 702 (s), 636 (w), 570 (w), 526 (w), 461 (w), 443 (w), 412 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{12}H_{10}ClNO$: 219.0451; found: 219.0457 $[M]^+$. $C_{12}H_{10}ClNO$ (219.67): calcd. C 65.61, H 4.59, N 6.38; found C 65.47, H 4.91, N 6.46.

3-Benzyloxy-4-chloro-5-iodopyridine (54): *n*-Butyllithium (1.6 M in hexanes, 1.56 mL, 2.50 mmol) was added slowly to a solution of *i*Pr$_2$NH (0.372 mL, 2.65 mmol) in THF (3.07 mL) at –78 °C, and the mixture was stirred for 30 min. Meanwhile, a solution of chloropyridine **53** (463 mg, 2.11 mmol) in THF (15 mL) was cooled to –78 °C. The freshly prepared solution of LDA (0.5 M, 4.22 mL, 2.11 mmol) was added dropwise, and the mixture was stirred at this temperature for 30 min. Then I_2 (535 mg, 2.11 mmol) in THF (3.5 mL) was quickly added dropwise into the yellow solution; 15 min later, the cold reaction mixture was poured into a mixture of sodium carbonate buffer (1.0 M, pH = 10, 75 mL) and satd. $Na_2S_2O_3$ (75 mL), followed by extraction with MTBE (3 × 75 mL). The organic layers were washed with satd. $Na_2S_2O_3$ (2 × 30 mL) and brine (30 mL) and were dried with $MgSO_4$. Evaporation of the solvents and separation of the crude product by flash column chromatography (21 g silica, *n*-pentane/MTBE, 3:1 → 1.5:1 → 1:1) gave the iodo compound **54** (569 mg, 1.65 mmol, 78%) as colourless solid and recovered starting material (25.6 mg, 0.117 mmol, 6%). The yield was 83% based on 94% conversion. The product can be recrystallised from cyclohexane. R_f = 0.50 (*n*-hexane/MTBE, 1:3); m.p. 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.24 (s, 2 H, CH_2), 7.31–7.48 (m, 5 H, CH_{ar}), 8.21 (s, 1 H, 2-H), 8.56 (s, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.0 (CH_2), 98.7 (C-5), 127.4 (2 C), 128.7 (2 C), 128.9 (CH_{ar}), 135.1 (C-2), 135.4 ($C_{q,ar}$), 137.1 (C-4), 150.5 (C-6), 151.6 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 1546 (s), 1496 (w), 1441 (m), 1402 (m), 1375 (m), 1282 (s), 1150 (w), 1076 (w), 989 (s), 914 (w), 871 (w), 857 (m), 748 (m), 717 (m), 694 (m), 651 (w), 567 (w), 543 (w), 469 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{12}H_9ClINO$: 344.9417; found: 344.9410 $[M]^+$. $C_{12}H_9ClINO$ (345.56): calcd. C 41.71, H 2.63, N 4.05; found C 41.50, H 2.68, N 3.93.

Methyl 5-Benzyloxy-4-chloronicotinate (55): A mixture of iodopyridine **54** (1.50 g, 4.34 mmol), (*rac*-BINAP)$PdCl_2$[34] (69.5 mg, 86.9 μmol), MeOH (40 mL) and Et_3N (1.21 mL, 8.69 mmol) was placed in a high-pressure reactor, and CO (0.4 MPa) was inserted. The reactor was sealed and heated to 85 °C for 5 h. Then the vessel was cooled to room temp., and the mixture was filtered through a short column of Celite and concentrated. The crude product was purified by flash column chromatography (96 g silica, *n*-pentane/MTBE, 1:1 → 1:1.5), and the methyl nicotinate **55** (1.14 g, 4.11 mmol, 95%) was isolated as a pale pink solid. R_f = 0.33 (*n*-hexane/MTBE, 1:3); m.p. 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, CH_3), 5.26 (s, 2 H, CH_2), 7.31–7.48 (m, 5 H, CH_{ar}), 8.39 (s, 1 H, 6-H), 8.62 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9 (CH_3), 72.0 (CH_2), 127.0 (C-3), 127.4 (2 C), 128.6, 128.9 (2 C, CH_{ar}), 133.0 (C-4), 135.4 ($C_{q,ar}$), 138.6 (C-6), 144.3 (C-2), 151.4 (C-5), 164.6 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3063 (w), 2955 (w), 1727 (s), 1556 (m), 1499 (w), 1467 (m), 1421 (m), 1389 (w), 1317 (s), 1240 (w), 1209 (w), 1175 (w), 1078 (w), 1055 (m), 889 (w), 802 (w), 779 (m), 726 (m), 691 (w), 661 (w), 568 (w), 463 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{14}H_{12}ClNO_3$: 277.0506; found: 277.0491 $[M]^+$. $C_{14}H_{12}ClNO_3$ (277.70): calcd. C 60.55, H 4.36, N 5.04; found C 60.42, H 4.40, N 5.08.

Methyl 5-Benzyloxy-4-hydroxynicotinate (56): Dry MeOH (70 mL) was treated with acetyl chloride (1.02 mL, 14.4 mmol). After 10 min, the chloronicotinate **55** (2.00 g, 7.20 mmol) was added in one portion. The mixture was heated to 85 °C in a sealed tube for 16 h. The solution was concentrated to dryness, and the residue was coevaporated with MeOH (10 mL). Purification of the crude product by flash column chromatography (110 g silica, $CHCl_3$/MeOH, 40:1 → 10:1) and subsequent coevaporation with hot MeOH (10 mL) yielded the hydroxynicotinate **56** (1.49 g, 5.75 mmol, 80%) as colourless solid. R_f = 0.24 ($CHCl_3$/MeOH, 10:1); m.p. 226 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO/10 eq TFA): δ = 3.82 (s, 3 H, CH_3), 5.20 (s, 2 H, CH_2), 7.32–7.37 (m, 1 H, CH_{ar}), 7.40 (pt, J = 7.4 Hz, 2 H, CH_{ar}), 7.47 (pd, J = 7.3 Hz, 2 H, CH_{ar}), 8.18 (s, 1 H, 6-H), 8.53 (s, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO/10 equiv. TFA): δ = 52.4 (CH_3), 71.5 (CH_2), 115.7 (C-3), 125.0 (C-6), 128.3 (2 C), 128.5, 128.6 (2 C, CH_{ar}), 135.7 ($C_{q,ar}$), 139.4 (C-2), 148.1 (C-5), 164.1 (CO), 164.6 (C-4) ppm. IR (KBr):

$\tilde{\nu}$ = 2925 (br. m), 1705 (s), 1637 (m), 1573 (m), 1546 (m), 1510 (m), 1438 (w), 1345 (w), 1299 (m), 1256 (w), 1222 (w), 1198 (w), 1154 (w), 1110 (m), 1013 (w), 988 (w), 969 (w), 904 (w), 887 (w), 858 (w), 807 (m), 755 (w), 704 (w), 654 (w), 617 (w), 597 (w), 512 (w), 420 (w) cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{14}H_{13}NO_4$: 259.0845; found: 259.0841 $[M]^+$. $C_{14}H_{13}NO_4$ (259.26): calcd. C 64.86, H 5.05, N 5.40; found C 64.50, H 4.86, N 5.34.

Methyl 4,5-Dihydroxynicotinate (57): Benzyl ether **56** (80.9 mg, 312 µmol) was dissolved in CF_3CH_2OH (8 mL), and $Pd(OH)_2/C$ (20% with 50% H_2O, 8.8 mg, 6.24 µmol) was added, followed by fivefold evacuation and subsequent hydrogen insertion at atmospheric pressure. The product precipitated in the course of the reaction. After a reaction time of 90 min, the solid material was collected by filtration. The residue was then suspended in DMSO (3 mL), and dissolution was effected by addition of a few drops of TFA. The catalyst was removed by filtration through a short column of Celite. Evaporation of the solvents yielded the diol **57** (51.8 mg, 306 µmol, 98%) as an off-white powder. R_f = 0.30 (*n*BuOH/H_2O/HCO_2H, 4:1:1); m.p. 259 °C (dec.). ^1H NMR (300 MHz, 5% (v/v) TFA in [D_6]DMSO): δ = 3.79 (s, 3 H, CH_3), 7.76 (s, 1 H, 6-H), 8.34 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO/D_2O/TFA, 82:1 (v/v/v)):: δ = 54.0 (CH_3), 115.0 (C-3), 127.9 (C-6), 138.0 (C-2), 147.4 (C-5), 163.3 (C-4), 165.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3049 (br. m), 1703 (s), 1662 (w), 1588 (m), 1557 (m), 1506 (s), 1440 (m), 1375 (m), 1299 (s), 1261 (w), 1196 (w), 1157 (w), 1128 (w), 1095 (m), 1020 (w), 914 (w), 862 (w), 801 (m), 748 (w), 637 (m), 560 (w), 504 (w), 422 (w) cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_7H_7NO_4$: 169.0375; found: 169.0380 $[M]^+$.

4,5-Dihydroxynicotinic Acid Dilithium Salt (8): A solution of methyl ester **57** (60.2 mg, 356 µmol) and $LiOH\cdot H_2O$ (29.9 mg, 712 µmol) in H_2O (7 mL) was warmed to 75 °C for 7 h. The mixture was concentrated to dryness, and the resulting solid was coevaporated with MeOH. The lithium salt **8** (54.8 mg, 328 µmol, 92%) was obtained in pure form as colourless powder. R_f = 0.12 (EtOH/H_2O/25% NH_3, 7:2:1); m.p. >300 °C. ^1H NMR (300 MHz, D_2O): δ = 7.53 (s, 1 H, 6-H), 8.01 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 113.2 (C-3), 122.5 (C-6), 136.9 (C-2), 148.0 (C-5), 166.5 (CO), 171.6 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3251 (br. m), 2732 (br. m), 1657 (m), 1617 (m), 1587 (s), 1505 (s), 1438 (w), 1410 (m), 1388 (m), 1342 (w), 1310 (m), 1228 (w), 1198 (m), 1113 (w), 912 (w), 874 (w), 851 (w), 816 (s), 644 (s), 568 (w), 524 (m), 445 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_6H_4NO_4$: 154.0140; found: 154.0137 $[M - Li]^-$.

Methyl 5-Benzyloxy-4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosidyl)nicotinate (58): Molecular sieves (4 Å, 110 mg) were dried by heating in vacuo. Dry ethanol-free CH_2Cl_2 (11 mL) and pyridone **56** (110 mg, 424 µmol) were added, and the mixture was stirred for 30 min. Then silver triflate (131 mg, 509 µmol), 2,6-lutidine (59 µL, 509 µmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[35] (209 mg, 509 µmol) were added. The suspension was stirred at room temp. for 20 h under the exclusion of light. The reaction mixture was filtered through a short column of Celite, and the filter cake was washed with $CHCl_3$ (2×10 mL). The combined organic phases were washed with satd. $Na_2S_2O_3$ (15 mL) and brine (15 mL) and dried with $MgSO_4$. Flash column chromatography (30 g silica, *n*-pentane/MTBE/acetone, 1:1:0 → 1:3:0 → 2:0:1 → 1:0:1) yielded the glucoside **58** (195 mg, 331 µmol, 78%) as a colourless foam. R_f = 0.16 (*n*-pentane/acetone, 2:1); m.p. 44 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.87 (s, 3 H, CH_3), 2.002 (s, 3 H, CH_3), 2.005 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 3.40 (ddd, *J* = 9.3, 4.4, 2.2 Hz, 1 H, 5′-H), 3.78 (dd, *J* = 12.5, 2.3 Hz, 6′-H^a), 3.90 (s, 3 H, OCH_3), 4.13 (dd, *J* = 12.5, 4.3 Hz, 6′-H^b), 5.09–5.16 (m, 2 H, 3′-H, 4′-H), 5.18 (s, 2 H, PhCH_2), 5.22 (m, 1 H, 2′-H), 5.38 (d, *J* = 7.6 Hz, 1 H, 1′-H), 7.37–7.47 (m, 5 H, CH_{ar}), 8.44 (s, 1 H, 6-H), 8.56 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 20.6, 20.7 (2 C, CH_3), 52.6 (OCH_3), 61.5 (C-6′), 68.0 (C-4′), 71.9 (C-2′), 72.2 (C-5′), 72.4 (PhCH_2), 73.0 (C-3′), 99.9 (C-1′), 122.7 (C-3), 128.0 (2 C), 129.0, 129.1 (2 C, CH_{ar}), 135.6 ($C_{q,ar}$), 140.2 (C-6), 145.4 (C-2), 147.2 (C-5), 150.1 (C-4), 165.0 (CO_2Me), 169.4 (2 C), 170.4, 170.6 (MeCO) ppm. IR (KBr): $\tilde{\nu}$ = 2956 (br. w), 1758 (br. s), 1566 (w), 1486 (w), 1423 (w), 1374 (m), 1315 (m), 1232 (br. s), 1155 (w), 1037 (br. s), 906 (w), 849 (w), 780 (w), 751 (w), 699 (w), 598 (w), 479 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{31}NNaO_{13}$: 612.1688; found: 612.1702 $[M + Na]^+$. $C_{28}H_{31}NO_{13}$ (589.54): calcd. C 57.04, H 5.30, N 2.38; found C 56.86, H 5.34, N 2.24.

Methyl 5-Benzyloxy-4-β-D-glucopyranosidylnicotinate (59): The tetraacetate **58** (507 mg, 860 µmol) was dissolved in dry MeOH (23 mL) and treated with NaOMe (0.5 M in MeOH, 120 µL, 60 µmol) at room temp. After stirring for 15 h, silica (2 g) was added, the solvent was evaporated, and the residue was directly subjected to flash column chromatography (36 g silica, $CHCl_3$/MeOH, 20:1 → 10:1). Tetraol **59** (342 mg, 812 µmol, 94%) was obtained as a colourless foam. R_f = 0.35 ($CHCl_3$/MeOH, 5:1); m.p. 108 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.95 (dd, *J* = 7.8, 5.8 Hz, 1 H, 6-OH), 2.69 (d, *J* = 2.8 Hz, 1 H, OH), 2.87 (d, *J* = 1.5 Hz, 1 H, OH), 3.07 (dt, *J* = 9.3, 3.9 Hz, 1 H, 5′-H), 3.44–3.68 (m, 5 H, 2′-H, 3′-H, 4′-H, 6′-H_2), 3.95 (s, 3 H, CH_3), 4.95 (d, *J* = 2.5 Hz, 1 H, OH), 5.00 (d, *J* = 7.4 Hz, 1 H, 1′-H), 5.16 (d, *J* = 11.0 Hz, 1 H, PhCH^aH^b), 5.21 (d, *J* = 11.0 Hz, 1 H, PhCH^aH^b), 7.36–7.48 (m, 5 H, CH_{ar}), 8.49 (s, 1 H, 6-H), 8.53 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.2 (CH_3), 61.7 (C-6′), 69.6 (C-2′/3′/4′), 72.6 (PhCH_2), 74.0 (C-2′/3′/4′), 75.9 (C-2′/3′/4′), 76.4 (C-5′), 104.1 (C-1′), 121.3 (C-3), 128.3 (2 C), 129.1 (3 C, CH_{ar}), 135.3 ($C_{q,ar}$), 140.5 (C-6), 144.9 (C-2), 147.2 (C-5), 151.6 (C-4), 166.6 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3403 (br. s), 2919 (w), 1714 (s), 1582 (m), 1487 (s), 1455 (w), 1425 (m), 1380 (w), 1317 (s), 1248 (m), 1205 (w), 1158 (w), 1054 (br. s), 897 (w), 850 (w), 792 (w), 750 (m), 699 (w), 577 (w), 525 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}NNaO_9$: 444.1265; found: 444.1265 $[M + Na]^+$.

Methyl 4-β-D-Glucopyranosidyl-5-hydroxynicotinate (60): Pd black (5.1 mg, 47.8 µmol) was added to a solution of benzyl ether **59** (50.4 mg, 120 µmol) in EtOAc/MeOH (4:1 v/v, 10 mL), and the argon was replaced by hydrogen at ambient pressure. The reaction was accurately monitored by TLC and the undesired concurrent cleavage of the glycosidic bond was revealed by using EtOH/H_2O/25% NH_3 (7:2:1) as eluent. After 150 min, the mixture was filtered through a short column of Celite, and the solvents were evaporated at room temp.; EtOAc was removed by coevaporation with MeOH (2×3 mL). Pyridinol **60** (39.7 mg, 120 µmol, 100%) was obtained as colourless solid. The crude unstable compound was used immediately for the next step. R_f = 0.19 ($CHCl_3$/MeOH, 3:1). ^1H NMR (600 MHz, [D_6]DMSO): δ = 3.10–3.18 (m, 2 H, 4′-H, 5′-H), 3.19–3.27 (m, 2 H, 2′-H, 3′-H), 3.31 (br. s, 2 H, OH), 3.45 (dd, *J* = 11.7, 4.8 Hz, 1 H, 6′-H^a), 3.60 (d, *J* = 10.6 Hz, 1 H, 6′-H^b), 3.81 (s, 3 H, CH_3), 4.29 (br. s, 1 H, OH), 4.99 (d, *J* = 7.3 Hz, 2 H, 1′-H, OH), 5.10 (br. s, OH), 8.19 (s, 1 H, 2-H), 8.28 (s, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 52.2 (CH_3), 60.6 (C-6′), 69.5 (C-4′), 73.8 (C-2′), 76.1 (C-3′), 77.3 (C-5′), 102.9 (C-1′), 122.5 (C-3), 141.3 (C-2), 142.0 (C-6), 146.4 (C-5), 148.1 (C-4), 165.3 (CO) ppm.

Dilithium Salt 61: Methyl 4-β-D-glucopyranosidyl-5-hydroxynicotinate (**60**, 39.7 mg, 120 µmol) was dissolved in THF/H_2O (3:1 v/v, 10 mL) and treated with $LiOH\cdot H_2O$ (10.1 mg, 240 µmol) directly after its preparation. The clear solution was stirred for 18 h. The solvents were evaporated to dryness, and the residue was coevapo-

rated with MeOH/toluene (1:1 v/v, 2 × 2 mL) for the removal of H_2O. The solid was dissolved in MeOH (4 mL), and the solution was cleared by filtration through a syringe filter (0.2 μm). The product was precipitated from MeOH solutions (1 mL) by addition of firstly EtOAc (5 mL) and secondly Et_2O (5 mL). Each time the supernatant was decanted after centrifugation. Finally, the solid was washed with Et_2O (5 mL) and dried in vacuo to give the nicotinic acid salt **61** (36.4 mg, 111 μmol, 93%) as colourless powder. R_f = 0.18 (*n*BuOH/EtOH/25% NH_3, 4:4:1); m.p. dec. >190 °C. ^{1}H NMR (600 MHz, D_2O): δ = 3.42–3.48 (m, 2 H, 4′-H, 5′-H), 3.48 (d, J = 7.8 Hz, 1 H, 2′-H), 3.54 (dd, J = 9.0, 9.0 Hz, 1 H, 3′-H), 3.74 (dd, J = 12.4, 4.5 Hz, 1 H, 6′-H[a]), 3.89 (dd, J = 12.5, 1.9 Hz, 1 H, 6′-H[b]), 4.97 (d, J = 7.7 Hz, 1 H, 1′-H), 7.66 (s, 1 H, 2-H), 7.90 (s, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 60.1 (C-6′), 68.8 (C-4′), 72.6 (C-2′), 75.1 (C-3′), 75.8 (C-5′), 103.0 (C-1′), 130.4 (C-3), 132.5 (C-2), 141.8 (C-6), 147.9 (C-4), 155.4 (C-5), 174.1 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3366 (br. s), 1591 (s), 1557 (s), 1463 (m), 1398 (s), 1318 (m), 1236 (w), 1070 (s), 859 (w), 811 (w), 472 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{14}NO_9$: 316.0669; found: 316.0665 $[M - Li]^-$.

4-Methoxy-3-methoxymethoxypyridine (62): Chloropyridine **51** (54.5 mg, 314 μmol) was dissolved in NaOMe solution (0.5 M in MeOH, 2.00 mL, 1.00 mmol), and the mixture was heated to 80 °C in a sealed tube. After 32 h, silica gel (300 mg) was added, the solvent was removed, and the resulting solid was directly subjected to flash column chromatography (5 g silica, *n*-pentane/acetone, 2:1 → 1:1 → 1:3). Methoxypyridine **62** (12.8 mg, 75.7 μmol, 24%) was isolated as colourless oil. R_f = 0.23 (*n*-hexane/acetone, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.52 [s, 3 H, (CH_2OCH_3)], 3.91 (s, 3 H, 4-OCH_3), 5.21 (s, 2 H, CH_2), 6.82 (d, J = 5.5, 1 H, 5-H), 8.22 (d, J = 5.5 Hz, 1 H, 6-H), 8.35 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8 (4-OCH_3), 56.6 (CH_2OCH_3), 96.3 (CH_2), 107.1 (C-5), 139.4 (C-2), 143.5 (C-3), 145.7 (C-6), 156.2 (C-4) ppm. IR (film): $\tilde{\nu}$ = 2956 (m), 2842 (w), 1585 (s), 1513 (s), 1443 (m), 1417 (m), 1298 (s), 1251 (m), 1228 (m), 1201 (m), 1180 (s), 1152 (s), 1086 (s), 1064 (s), 1025 (s), 984 (s), 922 (m), 824 (m), 766 (w), 644 (w), 598 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_8H_{11}NO_3$: 169.0739; found: 169.0741 $[M]^+$.

3-Hydroxy-4-methoxypyridinium Trifluoroacetate (63): A solution of the MOM-protected pyridinol **62** (53.2 mg, 314 μmol) in CH_2Cl_2 (2.5 mL) at 0 °C was treated with TFA (0.23 mL, 3.14 mmol) for 5 h. Then toluene (3 mL) was added, and the solvents were concentrated to a volume of approx. 0.5 mL at 40 °C under reduced pressure. The rest of the liquid was removed from the precipitate with a pipette and the colourless crystalline material was washed with toluene (1 mL), dried in vacuo and coevaporated with toluene (2 mL) once again to give pure pyridinol **63** (65.8 mg, 275 μmol, 87%). A sample of the free pyridine was obtained for NMR spectroscopy by coevaporation with DMSO (0.5 mL). R_f = 0.12 (*n*-hexane/acetone, 1:3); m.p. 147 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 4.07 (s, 3 H, CH_3), 7.54 (d, J = 6.6 Hz, 1 H, 5-H), 8.23 (d, J = 1.1 Hz, 1 H, 2-H), 8.39 (dd, J = 6.6, 1.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 57.4 (CH_3), 109.2 (C-5), 127.7 (C-2), 136.0 (C-6), 145.6 (C-3), 160.4 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3082 (br. m), 2648 (br. m), 1671 (s), 1617 (m), 1574 (m), 1523 (s), 1463 (w), 1439 (s), 1304 (s), 1186 (s), 1163 (m), 1133 (s), 1008 (m), 879 (w), 843 (m), 823 (s), 795 (m), 775 (w), 725 (s), 598 (m), 554 (w), 507 (w), 441 (w), 419 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_6H_7NO_2$: 125.0477; found: 125.0476 $[M]^+$.

Methyl 5-Benzyloxy-4-methoxynicotinate (64): To a solution of chloropyridin **55** (104 mg, 375 μmol) in dry MeOH (6 mL) was added a solution of NaOMe (0.5 M in MeOH, 0.97 mL, 487 μmol). The mixture was heated to 85 °C in a sealed tube for 24 h. The solvent was removed, and satd. $NaHCO_3$ (20 mL) was added to the residue followed by extraction with MTBE (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and the solvent was evaporated. Flash column chromatography (9 g silica, CH_2Cl_2/acetone, 50:1 → 20:1) gave the methyl ether **64** (86.6 mg, 317 μmol, 85%) as colourless oil which solidified on standing at 4 °C. R_f = 0.36 (CH_2Cl_2/acetone, 20:1); m.p. 59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, CO_2CH_3), 4.04 (s, 3 H, 4-OCH_3), 5.18 (s, 2 H, CH_2), 7.31–7.46 (m, 5 H, CH_{ar}), 8.37 (s, 1 H, 6-H), 8.57 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.2 (CO_2CH_3), 61.7 (4-OCH_3), 72.3 (CH_2), 121.3 (C-3), 127.7 (2 C), 128.6, 128.9 (2 C, CH_{ar}), 135.9 ($C_{q,ar}$), 140.7 (C-6), 145.7 (C-2), 148.5 (C-5), 156.1 (C-4), 165.2 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3063 (w), 3006 (w), 2929 (w), 2832 (w), 1718 (s), 1607 (w), 1579 (w), 1492 (m), 1456 (m), 1424 (m), 1392 (w), 1321 (s), 1294 (m), 1245 (m), 1205 (m), 1157 (m), 1080 (m), 1056 (s), 1030 (w), 1009 (m), 901 (m), 825 (m), 801 (m), 780 (w), 748 (w), 730 (s), 694 (m), 613 (w), 576 (w), 468 (w), 427 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{15}H_{15}NO_4$: 273.1001; found: 273.0998 $[M]^+$. $C_{15}H_{15}NO_4$ (273.28): calcd. C 65.92, H 5.53, N 5.13; found C 65.88, H 5.37, N 5.24.

Methyl 5-Hydroxy-4-methoxynicotinate (65): Benzyl ether **64** (36.2 mg, 133 μmol) was dissolved in MeOH (4 mL), and Pd/C (5% with 50% H_2O, 4.3 mg, 1.01 μmol) was added. After fivefold evacuation and subsequent ventilation with hydrogen at atmospheric pressure, the suspension was stirred for 2.5 h. The mixture was filtered through a short column of Celite, and the filtrate was concentrated to dryness to give pure pyridinol **65** (24.2 mg, 132 μmol, 99%) as colourless solid. R_f = 0.25 (*n*-hexane/acetone, 1:1); m.p. 127 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, CO_2CH_3), 4.06 (s, 3 H, 4-OCH_3), 8.35 (s, 1 H, 6-H), 8.48 (s, 1 H, 2-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 52.7 (CO_2CH_3), 61.8 (4-OCH_3), 120.6 (C-3), 140.9 (C-6), 143.2 (C-2), 147.8 (C-5), 154.8 (C-4), 165.0 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2958 (br. w), 2572 (br. w), 1706 (s), 1594 (m), 1570 (m), 1511 (w), 1442 (m), 1427 (s), 1377 (w), 1333 (m), 1297 (s), 1251 (s), 1206 (m), 1143 (s), 1012 (w), 988 (s), 881 (m), 836 (m), 791 (m), 774 (w), 742 (w), 644 (w), 624 (w), 596 (w), 530 (w), 485 (w), 424 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_8H_{10}NO_4$: 184.0604; found: 184.0605 $[M + H]^+$.

5-Benzyloxy-4-methoxynicotinic Alcohol (66): A solution of methyl nicotinate **64** (33.0 mg, 121 μmol) in CH_2Cl_2 (1.5 mL) was cooled to –78 °C, and DIBAH (1.0 M in petroleum ether, 266 μL, 266 μmol) was added dropwise. The temperature was raised to room temp. during 3 h, and the mixture was stirred for another 1 h. The reaction was quenched by addition of satd. K/Na tartrate (5 mL) with subsequent vigorous stirring for 2 h. H_2O (10 mL) was added and, the phases were separated, followed by extraction with CH_2Cl_2 (4 × 3 mL). The combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. Flash column chromatography (2.2 g silica, *n*-pentane/acetone, 1:1 → 1:2) gave the desired nicotinic alcohol **66** (26.4 mg, 108 μmol, 89%) as colourless solid. R_f = 0.30 (*n*-hexane/acetone, 1:3); m.p. 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.07 (br. s, 1 H, OH), 4.04 (s, 3 H, CH_3), 4.69 (s, 2 H, CH_2OH), 5.14 (s, 2 H, $PhCH_2$), 7.31–7.45 (m, 5 H, CH_{ar}), 8.17 (s, 1 H, 2-H), 8.23 (s, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.9 (CH_2OH), 61.1 (CH_3), 72.1 ($PhCH_2$), 127.7 (2 C), 128.5, 128.8 (2 C, CH_{ar}), 129.5 (C-3), 136.2 ($C_{q,ar}$), 137.7 (C-6), 143.9 (C-2), 147.4 (C-5), 154.0 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3173 (br. m), 2943 (w), 1586 (m), 1501 (m), 1440 (m), 1425 (w), 1389 (w), 1376 (w), 1314 (s), 1271 (w), 1240 (m), 1159 (w), 1086 (w), 1071 (w), 1017 (s), 965 (w), 908 (w), 874 (w), 822 (m), 784 (w), 737 (m), 718 (w), 695 (m), 641 (w), 612 (w),

584 (w), 505 (w), 477 (m), 448 (w), 419 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{14}H_{15}NNaO_3$: 268.0944; found: 268.0946 $[M + Na]^+$.

5-Hydroxy-4-methoxynicotinic Alcohol (67): Benzyl ether **66** (19.2 mg, 78.3 μmol) was dissolved in MeOH (2.5 mL), and Pd/C (5% with 50% H_2O, 1.9 mg, 0.45 μmol) was added. The flask was evacuated five times and ventilated with hydrogen at atmospheric pressure thereafter. After stirring for 6 h, the suspension was filtered through a short column of Celite, and the solvent was removed giving the pyridinol **67** (11.7 mg, 75.4 μmol, 96%) as colourless solid. R_f = 0.18 ($CHCl_3$/MeOH, 5:1); m.p. 133 °C. ^1H NMR (500 MHz, [D$_4$]MeOH): δ = 4.03 (s, 3 H, CH_3), 4.64 (s, 2 H, CH_2), 7.99 (s, 2 H, 2-H, 6-H) ppm. ^{13}C NMR (75 MHz, [D$_4$]MeOH): δ = 58.2 (CH_2), 61.0 (CH_3), 131.6 (C-3), 138.9 (C-6), 141.3 (C-2), 148.5 (C-5), 154.3 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3102 (s), 2947 (s), 2808 (m), 1614 (w), 1586 (w), 1526 (w), 1461 (m), 1433 (s), 1387 (w), 1358 (m), 1323 (s), 1280 (w), 1259 (w), 1233 (w), 1160 (w), 1082 (m), 1008 (s), 972 (s), 868 (w), 826 (m), 765 (w), 725 (w), 626 (w), 593 (w), 481 (w), 418 (w) cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_7H_9NO_3$: 155.0582; found: 155.0587 $[M]^+$.

5-Benzyloxy-4-methoxynicotinic Acid (68): A solution of methyl ester **64** (34.5 mg, 126 μmol) in THF/H_2O (3:1 v/v, 3 mL) was treated with LiOH·H_2O (15.9 mg, 379 μmol) which induced the separation of two phases. The mixture was vigorously stirred for 2 h, then the solvents were removed in vacuo. The crude product was purified by flash column chromatography (2 g silica, $CHCl_3$/MeOH/HCO_2H, 25:1:0.5), and toluene (10 mL) was added to the product-containing fractions prior to solvent evaporation. The desired nicotinic acid **68** (29.4 mg, 113 μmol, 90%) was obtained as colourless solid. R_f = 0.21 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.5); m.p. 116 °C. ^1H NMR (500 MHz, [D$_4$]MeOH): δ = 4.06 (s, 3 H, CH_3), 5.24 (s, 2 H, CH_2), 7.34 (m, 1 H, CH_{ar}), 7.39 (pt, J = 7.5 Hz, 2 H, CH_{ar}), 7.47 (pd, J = 7.2 Hz, 2 H, CH_{ar}), 8.39 (s, 1 H, 6-H), 8.45 (s, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, [D$_4$]MeOH): δ = 62.1 (CH_3), 73.2 (CH_2), 124.4 (C-3), 129.0 (2 C), 129.5, 129.7 (2 C, CH_{ar}), 137.4 ($C_{q,ar}$), 139.2 (C-6), 144.8 (C-2), 150.1 (C-5), 157.9 (C-4), 167.7 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2946 (w), 2837 (w), 2490 (br. w), 1923 (br. w), 1701 (br. m), 1584 (m), 1489 (m), 1457 (w), 1434 (w), 1390 (w), 1311 (s), 1255 (m), 1148 (s), 1021 (s), 1001 (m), 903 (w), 883 (w), 849 (w), 833 (m), 798 (w), 757 (m), 698 (m), 590 (w), 534 (w), 489 (w), 419 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{14}H_{13}NO_4$: 260.0917; found: 260.0922 $[M + H]^+$.

5-Hydroxy-4-methoxynicotinic Acid (69): Benzyl ether **68** (21.2 mg, 81.8 μmol) was dissolved in MeOH (3 mL), and Pd/C (5% with 50% H_2O, 2.0 mg, 0.47 μmol) was added. After fivefold evacuation and subsequent ventilation with hydrogen at atmospheric pressure, the suspension was stirred for 6 h. The mixture was filtered through a short column of Celite, and the filtrate was concentrated to dryness to give pure pyridinol **69** (13.2 mg, 78.0 μmol, 95%) as colourless solid. R_f = 0.23 (*n*BuOH/EtOH/25% NH_3, 6:4:1); m.p. dec. >180 °C. ^1H NMR (400 MHz, [D$_4$]MeOH): δ = 4.08 (s, 3 H, CH_3), 8.15 (s, 1 H, 6-H), 8.28 (s, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, [D$_4$]MeOH): δ = 61.7 (CH_3), 125.2 (C-3), 138.7 (C-6), 141.8 (C-2), 149.3 (C-5), 156.4 (C-4), 168.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3080 (w), 2603 (br. m), 1621 (m), 1532 (m), 1473 (m), 1386 (s), 1313 (s), 1262 (s), 1117 (w), 989 (m), 876 (m), 820 (m), 801 (m), 764 (w), 740 (w), 636 (m), 580 (w), 561 (w), 475 (m), 453 (m) cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_7H_7NO_4$: 169.0375; found: 169.0373 $[M]^+$.

5-Benzyloxy-4-chloronicotinic Acid (70): A solution of methyl ester **55** (81.1 mg, 292 μmol) in THF/H_2O (3:1 v/v, 6 mL) was treated with LiOH·H_2O (36.8 mg, 876 μmol) which induced the separation of two phases. The mixture was vigorously stirred for 3.5 h, then silica gel (0.5 g) was added, and the solvents were removed in vacuo. The solid residue was subjected to flash column chromatography (8 g silica, $CHCl_3$/MeOH/HCO_2H, 25:1:0.5), and toluene (5 mL) was added to the product-containing fractions prior to solvent evaporation. The desired nicotinic acid **70** (75.1 mg, 285 μmol, 98%) was obtained as colourless solid. R_f = 0.35 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.5); m.p. 150 °C (dec.). ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 5.39 (s, 2 H, CH_2), 7.36 (t, J = 7.3 Hz, 1 H, CH_{ar}), 7.43 (t, J = 7.5 Hz, 2 H, CH_{ar}), 7.49 (t, J = 7.4 Hz, 2 H, CH_{ar}), 8.51 (s, 1 H, 2-H), 8.65 (s, 1 H, 6-H), 13.81 (br. s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 71.1 (CH_2), 127.7 (2 C), 128.2 (CH_{ar}), 128.3 (C-3), 128.5 (2 C, CH_{ar}), 129.8 (C-4), 135.9 ($C_{q,ar}$), 138.2 (C-6), 142.7 (C-2), 150.5 (C-5), 165.1 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3065 (w), 2479 (br. w), 1868 (br. w), 1573 (m), 1557 (m), 1497 (w), 1443 (w), 1385 (w), 1303 (s), 1278 (m), 1156 (m), 1082 (w), 1026 (m), 900 (w), 887 (w), 845 (w), 799 (m), 784 (w), 754 (w), 722 (w), 695 (m), 655 (w), 564 (w), 519 (w) cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{13}H_{10}ClNO_3$: 263.0349; found: 263.0345 $[M]^+$.

3-Benzyloxy-4-chloro-5-methoxycarbonyl-1-methylpyridinium Tetrafluoroborate (71): A solution of the nicotinate **55** (54.7 mg, 197 μmol) in CH_2Cl_2 (1.8 mL) was treated with trimethyloxonium tetrafluoroborate (29.1 mg, 197 μmol), and the mixture was stirred for 5 h. The clear reaction mixture containing the solid reagent became turbid soon. Pieces of reagent were ground with a glass bar, and the suspension was stirred for another 1 h. The product was filtered off, washed with CH_2Cl_2 (2 mL) and dried to give the pure pyridinium salt **71** (58.3 mg, 154 μmol, 78%) as colourless solid. It is a stable compound, but decomposes rapidly in DMSO. R_f = 0.48 (*n*BuOH/H_2O/HCO_2H, 4:1:1); m.p. 191 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 3.98 (s, 3 H, OCH_3), 4.38 (s, 3 H, NCH_3), 5.42 (s, 2 H, CH_2), 7.44 (t, J = 7.1 Hz, 1 H, CH_{ar}), 7.48 (t, J = 7.4 Hz, 2 H, CH_{ar}), 7.53 (d, J = 7.1 Hz, 1 H, CH_{ar}), 9.21 (s, 1 H, 2-H), 9.29 (s, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 48.5 (NCH_3), 53.8 (OCH_3), 73.1 (CH_2), 128.2 (2 C), 128.8 (2 C), 128.9 (CH_{ar}), 129.1 (C-3), 133.9 (C-6), 134.3 ($C_{q,ar}$), 139.2 (C-4), 140.4 (C-2), 153.6 (C-5), 161.0 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3121 (w), 2962 (w), 1740 (s), 1699 (w), 1628 (m), 1578 (w), 1499 (m), 1451 (s), 1399 (w), 1351 (s), 1299 (m), 1285 (m), 1229 (m), 1184 (w), 1094 (s), 1053 (br. s), 997 (m), 922 (w), 896 (m), 849 (m), 777 (m), 750 (m), 701 (w), 687 (w), 641 (w), 579 (w), 521 (w), 490 (w), 470 (w), 451 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{15}ClNO_3$: 292.0735; found: 292.0734 $[M - BF_4]^+$.

Methyl 4-Chloro-5-hydroxynicotinate (72): To a solution of benzyl ether **55** (87.2 mg, 314 μmol) in MeOH (6 mL) were added Pd black (16.7 mg, 157 μmol) and 1,4-cyclohexadiene (148 μL, 1.57 mmol). After stirring for 30 min, the reaction mixture was filtered through a short column of Celite, and the filtrate was concentrated to dryness. The residue was purified by flash column chromatography (6 g silica, *n*-pentane/acetone, 2:1) to yield pyridinol **72** (50.6 mg, 270 μmol, 86%) as colourless solid. R_f = 0.19 (*n*-hexane/acetone, 2:1); m.p. 117 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 3.87 (s, 3 H, CH_3), 8.38 (s, 1 H, 2-H), 8.40 (s, 1 H, 6-H), 11.21 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 52.7 (CH_3), 126.8, 127.5 (C-3, C-4), 140.8 (C-6), 141.0 (C-2), 150.7 (C-5), 164.2 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3420 (br. w), 3064 (m), 2954 (m), 2838 (m), 2654 (br. m), 1752 (s), 1719 (s), 1583 (w), 1565 (m), 1435 (s), 1425 (s), 1384 (w), 1317 (s), 1285 (s), 1238 (m), 1205 (s), 1167 (m), 1090 (w), 1080 (s), 1025 (m), 994 (w), 883 (w), 820 (m), 774 (m), 737 (m), 719 (w), 576 (w) cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_7H_6ClNO_3$: 187.0036; found: 187.0033 $[M]^+$.

4-Chloro-5-hydroxynicotinic Acid Dilithium Salt (73): Methyl ester **72** (17.9 mg, 95.4 μmol) was dissolved in THF (1.5 mL), then H_2O

(0.5 mL) and LiOH·H_2O (8.0 mg, 191 μmol) were added; 24 h later, the solvents were evaporated, and the residue was coevaporated with MeOH (2 mL). The crude product was dissolved in MeOH (1 mL) and precipitated by addition of Et_2O (5 mL). The suspension was centrifuged, the supernatant was decanted, and the solid was washed with Et_2O (2 mL) to yield the desired nicotinic acid **73** (17 mg, 91.7 μmol, 96%) as colourless solid. R_f = 0.20 (*n*BuOH/EtOH/25% NH_3, 6:4:1); m.p. >300 °C. ^{1}H NMR (300 MHz, [D_6]DMSO/D_2O, 7:1): δ = 7.23 (s, 1 H, 2-H), 7.49 (s, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO/D_2O, 7:1): δ = 126.0 (C-4), 130.2 (C-2), 138.7 (C-3), 139.4 (C-6), 160.5 (C-5), 170.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3386 (br. m), 1591 (s), 1552 (s), 1440 (s), 1394 (s), 1330 (m), 1253 (w), 1222 (w), 1154 (w), 1121 (w), 1072 (m), 997 (w), 831 (w), 800 (w), 727 (w), 613 (w), 575 (w), 430 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_6H_3ClNO_3$: 171.9801; found: 171.9796 [M – Li]$^-$.

5-Benzyloxy-4-chloronicotinic Alcohol (74): A solution of methyl nicotinate **55** (51.7 mg, 186 μmol) in CH_2Cl_2 (2 mL) was cooled to –78 °C, and DIBAH (1.0 M in petroleum ether, 410 μL, 410 μmol) was added dropwise. The mixture was stirred for 4 h, then it was warmed to room temp. and stirred for 1 h. The reaction was quenched by addition of satd. K/Na tartrate (5 mL) with subsequent vigorous stirring for 14 h. The phases were separated, and the aqueous phase was diluted with H_2O (10 mL), followed by extraction with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. Flash column chromatography (4.8 g silica, *n*-pentane/acetone, 2:1 → 1:1) gave the nicotinic alcohol **74** (39.4 mg, 158 μmol, 85%) as colourless solid as well as reisolated starting material **55** (4.7 mg, 16.9 μmol, 9%). The yield was 93% based on 91% conversion. R_f = 0.25 (*n*-hexane/acetone, 1:1); m.p. 100 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (br. s, 1 H, OH), 4.84 (s, 2 H, CH_2OH), 5.25 (s, 2 H, PhCH_2), 7.32–7.50 (m, 5 H, CH_{ar}), 8.29 (s, 1 H, 6-H), 8.34 (s, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.9 (CH_2OH), 71.8 (Ph*C*H_2), 127.4 (2 C), 128.6, 128.9 (2 C, CH_{ar}), 131.6 (C-4), 134.9 (C-3), 135.76 (C-6), 135.79 ($C_{q,ar}$), 142.7 (C-2), 150.9 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 3401 (br. m), 3186 (br. s), 2892 (m), 1562 (m), 1499 (w), 1458 (m), 1419 (m), 1388 (w), 1306 (s), 1166 (w), 1074 (w), 1026 (s), 970 (w), 940 (w), 913 (w), 864 (w), 847 (w), 792 (w), 777 (m), 745 (m), 695 (m), 563 (w), 485 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{13}H_{12}ClNO_2$: 249.0557; found: 249.0567 [M]$^+$.

4-Chloro-5-hydroxynicotinic Alcohol (75): To a solution of benzyl ether **74** (27.0 mg, 108 μmol) in MeOH (2 mL) were added Pd black (5.8 mg, 54 μmol) and 1,4-cyclohexadiene (51 μL, 540 μmol). After stirring for 3 h, the reaction mixture was filtered through a short column of Celite, and the filtrate was concentrated to dryness. A colourless solid was obtained which consisted of the desired pyridinol **75** (15.2 mg, 95.5 μmol, 88%) with 10% of 5-hydroxynicotinic alcohol (1.2 mg, 9.5 μmol, 9%) as by-product. This impurity could not be removed by flash column chromatography (1.6 g silica, *n*-pentane/acetone, 1:3 → 0:1). R_f = 0.30 (*n*-pentane/acetone, 1:3); m.p. 183 °C (dec.). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 4.56 (s, 2 H, CH_2), 5.39 (br. s, 1 H, OH), 8.10 (s, 1 H, 2-H), 8.16 (s, 1 H, 6-H), 10.61 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 58.7 (CH_2), 126.7 (C-3), 135.4 (C-4), 136.9 (C-6), 139.5 (C-2), 149.7 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 3097 (s), 2559 (br. m), 2082 (m), 1594 (w), 1552 (s), 1513 (s), 1456 (s), 1378 (w), 1326 (w), 1295 (m), 1064 (m), 988 (m), 871 (w), 827 (m), 770 (m), 715 (w), 676 (w), 591 (w), 553 (w), 439 (w), 409 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_6H_6ClNO_2$: 159.0087; found: 159.0083 [M]$^+$.

Methyl 5-Hydroxynicotinate (76): Benzyl ether **55** (48.8 mg, 176 μmol) was dissolved in MeOH/DMF (5:1 v/v, 12 mL), and Pd/C (5% with 50% H_2O, 4.9 mg, 1.15 μmol) was added. After fivefold evacuation and subsequent ventilation with hydrogen at atmospheric pressure, the suspension was stirred for 40 min. The mixture was filtered through a short column of Celite, and the filtrate was concentrated to dryness to give pure nicotinic acid as its hydrochloride **76·HCl** (quant.). The free base form **76** (20.6 mg, 135 μmol, 77%) could be obtained as colourless solid by flash column chromatography (3.5 g silica, *n*-pentane/acetone/MeOH, 2:1:0 → 0:0:1) of the hydrochloride with successive filtration through silica gel (0.5 g silica, *n*-pentane/acetone, 2:1). R_f = 0.30 (*n*-pentane/acetone, 2:1); m.p. 182 °C. ^{1}H NMR (hydrochloride, 300 MHz, [D_4]MeOH): δ = 4.01 (s, 3 H, CH_3), 8.35 (s, 1 H, 4-H), 8.55 (s, 1 H, 6-H), 8.82 (s, 1 H, 2-H) ppm. ^{1}H NMR (600 MHz, [D_4]MeOH): δ = 3.93 (s, 3 H, CH_3), 7.74 (dd, *J* = 2.7, 1.7 Hz, 1 H, 4-H), 8.28 (d, *J* = 2.9 Hz, 1 H, 6-H), 8.59 (d, *J* = 1.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, [D_4]MeOH): δ = 52.9 (CH_3), 124.3 (C-4), 128.5 (C-3), 141.8 (C-2), 142.6 (C-6), 155.7 (C-5), 166.9 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3428 (br. w), 2924 (m), 2848 (m), 2782 (m), 1730 (s), 1584 (m), 1500 (w), 1456 (m), 1435 (m), 1386 (w), 1312 (s), 1241 (s), 1160 (w), 1108 (m), 1025 (m), 996 (w), 930 (w), 880 (w), 802 (w), 765 (m), 691 (m), 561 (w), 443 (w), 415 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_7H_7NO_3$: 153.0426; found: 153.0429 [M]$^+$.

5-Hydroxynicotinic Acid Hydrochloride (77): A suspension of benzyl ether **70** (56.0 mg, 212 μmol) and $Pd(OH)_2$/C (20% with 50% H_2O, 5.6 mg, 3.4 μmol) in MeOH (10 mL) was evacuated and ventilated with hydrogen at ambient pressure five times. The substrate had dissolved completely after 10 min, and the mixture was stirred for further 50 min. The catalyst was filtered off through a short column of Celite, and the solution was concentrated to give pyridinium chloride **77** (37.0 mg, 211 μmol, 100%) as off-white solid. R_f = 0.32 (*n*BuOH/EtOH/25% NH_3, 6:4:1); m.p. (dec.). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.00 (dd, *J* = 2.6, 1.6 Hz, 1 H, 4-H), 8.49 (d, *J* = 2.7 Hz, 1 H, 6-H), 8.64 (d, *J* = 1.5 Hz, 1 H, 2-H), 11.41 (br. s, 1 H, NH/OH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 126.8 (C-4), 129.1 (C-3), 136.9 (C-2), 137.3 (C-6), 155.2 (C-5), 164.9 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3117 (s), 3050 (s), 2893 (m), 1728 (s), 1615 (m), 1528 (s), 1503 (w), 1400 (s), 1318 (w), 1268 (m), 1231 (w), 1213 (w), 1134 (m), 1108 (w), 1019 (w), 935 (w), 866 (w), 830 (m), 754 (m), 699 (w), 666 (w), 653 (w), 562 (w), 521 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_6H_5NO_3$: 139.0269; found: 139.0267 [M – HCl]$^+$.

5-Benzyloxy-4-hydroxynicotinic Acid (78): Methyl nicotinate **56** (72.6 mg, 280 μmol) was suspended in THF/H_2O (3:1 v/v, 4 mL). The solid dissolved upon addition of LiOH·H_2O (35.2 mg, 840 μmol), and the mixture was stirred for 20 h. Silica (500 mg) was added, the solvents were evaporated, and the residue was dried in vacuo. Flash column chromatography (7.5 g silica, $CHCl_3$/MeOH/HCO_2H, 20:1:0.2 → 10:1:0.2) and subsequent coevaporation with toluene (2 × 2 mL) and MeOH/toluene (1:1 v/v, 2 mL) afforded the nicotinic acid **78** (68.7 mg, 280 μmol, quant.) as pale yellow solid. R_f = 0.20 ($CHCl_3$/MeOH/HCO_2H, 10:1:0.5); m.p. dec. >230 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 5.10 (s, 2 H, CH_2), 7.32–7.50 (m, 5 H, CH_{ar}), 7.90 (s, 1 H, 6-H), 8.44 (s, 1 H, 2-H), 12.90 (br. s, 1 H, CO_2H), 16.32 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 70.8 (CH_2), 114.0 (C-3), 123.6 (C-6), 128.0 (2 C), 128.2, 128.5 (2 C, CH_{ar}), 136.1 ($C_{q,ar}$), 138.8 (C-2), 148.8 (C-5), 166.4 (CO), 172.3 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3227 (m), 3080 (m), 2932 (w), 1716 (s), 1636 (s), 1548 (s), 1455 (s), 1270 (s), 1157 (w), 1132 (w), 1113 (m), 1024 (s), 932 (w), 867 (w), 842 (w), 796 (m), 759 (w), 740 (m), 696 (m), 617 (w), 587 (w), 563 (w), 514 (w), 496 (m) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{13}H_{11}NO_4$: 245.0688; found: 245.0675 [M]$^+$.

5-Benzyloxy-4-hydroxynicotinic Alcohol (79): A suspension of methyl nicotinate **56** (44.4 mg, 171 μmol) in CH_2Cl_2 (5 mL) was cooled to –78 °C, and DIBAH (1.0 M in petroleum ether, 548 μL, 548 μmol) was added dropwise. After 10 min of stirring, the temperature was raised to room temp. causing a yellow colouration. To achieve complete conversion, more DIBAH (1.0 M in petroleum ether, 257 μL, 257 μmol) was added 24 h later, and the mixture was stirred for another 1 h. Then the reaction was quenched by addition of satd. K/Na tartrate (20 mL) with subsequent vigorous stirring for 14 h which caused decolourisation. The phases were separated, and the aqueous phase was diluted with H_2O (10 mL), followed by extraction with $CHCl_3$/*i*PrOH (5:1 v/v, 6×10 mL). The combined organic layers were concentrated to dryness. Flash column chromatography (5 g silica, $CHCl_3$/MeOH/*i*PrOH, 10:1:0 → 10:1:1 → 10:1:2) gave the nicotinic alcohol **79** (29.9 mg, 129 μmol, 75%) as colourless powder. R_f = 0.19 ($CHCl_3$/MeOH, 5:1); m.p. 180 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 4.33 (s, 2 H, CH_2OH), 4.89 (br. s, 1 H, OH), 5.00 (s, 2 H, PhCH_2), 7.31 (t, J = 7.0 Hz, 1 H, CH_{ar}), 7.37 (t, J = 7.6 Hz, 2 H, CH_{ar}), 7.41 (d, J = 7.4 Hz, 2 H, CH_{ar}), 7.46 (d, J = 4.4 Hz, 1 H, 2/6-H), 7.48 (d, J = 4.4 Hz, 1 H, 2/6-H), 11.25 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 57.3 (CH_2OH), 70.5 (PhCH_2), 122.6 (C-3), 127.7, 127.9 (2 C, CH_{ar}), 128.3 (2 C, CH_{ar}), 128.4 (C-2), 131.1 (C-6), 137.4 ($C_{q,ar}$), 146.5 (C-5), 170.9 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3360 (m), 3190 (m), 3059 (m), 2942 (m), 2877 (m), 1630 (m), 1580 (m), 1505 (s), 1459 (m), 1399 (m), 1334 (w), 1270 (s), 1198 (w), 1126 (w), 1061 (w), 1010 (m), 971 (w), 923 (w), 852 (w), 755 (w), 732 (m), 701 (w), 597 (w), 551 (w), 523 (w), 474 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{13}NNaO_3$: 254.0788; found: 254.0787 [M + Na]$^+$.

4,5-Dihydroxynicotinic Alcohol (80): To a solution of benzyl ether **79** (25.0 mg, 108 μmol) in MeOH (6 mL) was added $Pd(OH)_2$/C (20% with 50% H_2O, 2.5 mg, 1.8 μmol). The flask was evacuated and ventilated with hydrogen at ambient pressure five times, and the mixture was stirred for 90 min. Then it was filtered through a short column of Celite, and the solvent was evaporated to give pure alcohol **80** (13.4 mg, 95.0 μmol, 88%) as colourless solid. R_f = 0.34 (*n*BuOH/H_2O/HCO_2H, 4:1:1); m.p. 209 °C (dec.). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 4.36 (s, 2 H, CH_2), 7.37 (s, 1 H, 6-H), 7.46 (s, 1 H, 2-H), 11.28 (br. s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 57.1 (CH_2), 117.4 (C-6), 125.1 (C-3), 130.5 (C-2), 150.6 (C-5), 169.6 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3251 (br. s), 3048 (m), 2942 (s), 2823 (s), 1645 (s), 1561 (m), 1486 (s), 1455 (s), 1373 (w), 1306 (m), 1282 (m), 1207 (w), 1108 (w), 1036 (w), 997 (m), 962 (w), 847 (m), 788 (m), 721 (w), 613 (w), 555 (w), 507 (m), 489 (w) cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_6H_7NO_3$: 141.0426; found: 141.0428 [M]$^+$.

Acknowledgments

We thank the Schering AG, Berlin and the Fonds der Chemischen Industrie for the generous financial support of this work. A. E. thanks Dr. Eckhard Ottow and Professor Rainer Metternicht (both Schering AG) for support. M. R. and U. K. thank Dr. Stuart Ince (Schering AG) for a sample of siastatin B.

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Received: April 14, 2007
Published Online: July 3, 2007

