Synthesis of Glycaro-1,5-lactams and Tetrahydrotetrazolopyridine-5-carboxylates: Inhibitors of β-D-Glucuronidase and α-L-Iduronidase

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The known glucaro-1,5-lactam **8**, its diastereoisomers **9**–**11**, and the tetrahydrotetrazolopyridine-5-carboxylates **12**–**14** were synthesised as potential inhibitors of β-D-glucuronidases and α-L-iduronidases. The known 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactose (**16**) was transformed into the D-galactaro- and L-altraro-1,5-lactams **9** and **11** *via* the galactono-1,5-lactam **21** in twelve steps and in an overall yield of 13 and 2%, respectively. A divergent strategy, starting from the known tartaric anhydride **41**, led to the D-glucaro-1,5-lactam **8**, D-galactaro-1,5-lactam **9**, L-idaro-1,5-lactam **10**, and L-altraro-1,5-lactam **11** in ten steps and in an overall yield of 4–20%. The anhydride **41** was transformed into the L-threuronate **46**. Olefination of **46** to the (*E*)- or (*Z*)-alkene **47** or **48** followed by reagent- or substrate-controlled dihydroxylation, lactonisation, azidation, reduction, and deprotection led to the lactams **8**–**11**. The tetrazoles **12**–**14** were prepared in an overall yield of 61–81% from the lactams **54**, **28**, and **67**, respectively, by treatment with Tf_2O and NaN_3, followed by saponification, esterification, and hydrogenolysis. The lactams **8**–**11** and **40** and the tetrazoles **12**–**14** are medium-to-strong inhibitors of β-D-glucuronidase from bovine liver. Only the L-*ido*-configured lactam **10** (K_i = 94 μM) and the tetrazole **14** (K_i = 1.3 mM) inhibit human α-L-iduronidase.

Introduction. – β-D-Glucuronidases (EC 3.2.1.31, family 2)[1]) and α-L-iduronidases (EC 3.2.1.76, family 39) remove glycuronic acid residues from the non-reducing end of glycosaminoglycans such as chondroitin sulfate and hyaluronic acid. They are essential for the normal restructuring and turnover of extracellular matrix components [2], and play crucial roles in pathophysiological processes. Deficiency of β-D-glucuronidase and α-L-iduronidase in humans leads to mucopolysaccharidosis of type VII (*Sly* syndrome) [3][4] and of type I (*Hurler* syndrome) [5][6], respectively, while release of β-D-glucuronidase from cancer cells and breakdown of the basement membrane are required for metastasis of adenocarcinoma [7]. Induction of β-D-glucuronidase in the intestinal flora may also contribute to the pathogenesis of colon cancer [8][9]. In addition, β-D-glucuronidase and other lysosomal enzymes are released into the synovial fluid in inflammatory joint diseases like rheumatoid arthritis and contribute to their symptoms [10][11]. Strong and selective inhibitors of β-D-glucuronidase and α-L-iduronidase are thus of therapeutic interest. Siastatin B (**1**) [12] and its analogues **2**–**4** [13], the pipecolic acids **5** [14] and **6** [15], and glucarolactam **8** [16] inhibit β-D-glucuronidases. The idarolactone **7** [17] is the only known inhibitor of human α-L-iduronidase.

[1]) Glycosidases have been classified into families based on their sequence similarities [1]. A regularly updated database is available on the internet (http://afmb.cnrs-mrs.fr/CAZY/index.html).

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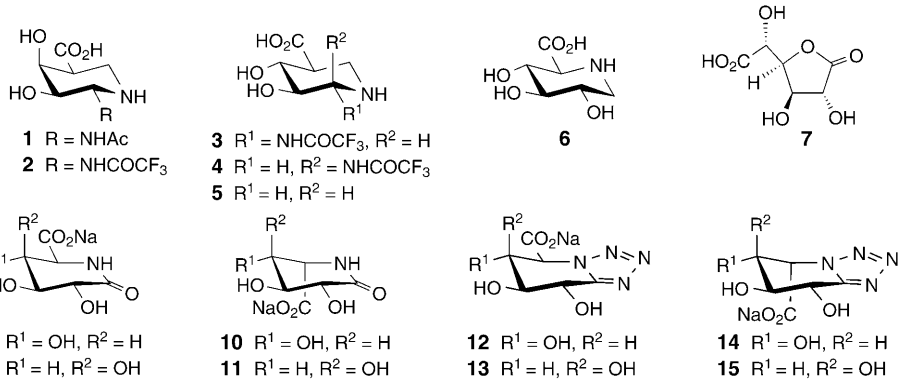

We wondered if β-D-glucuronidases and α-L-iduronidases act by similar mechanisms[2]) and, more specifically, about their configurational selectivity and the substrate distortion[3]) they induce. Based on the difference in the rates of hydrolysis of phenyl α-L-iduronide by partially purified β-D-glucuronidase and α-L-iduronidase in lysosomal extracts, *Weissmann* and *Santiago* have concluded that β-D-glucuronidase and α-L-iduronidase are distinct enzymes [23]. Although the three diastereoisomeric siastatins **2**–**4** [13] are equally potent inhibitors of β-D-glucuronidase from bovine liver, they were found to be unstable under the conditions of the enzyme assay [24], so that the question about the configurational selectivity of β-D-glucuronidase towards these inhibitors could not be answered. Not much is known about substrate distortion during the hydrolysis of glycuronides by β-D-glucuronidases and α-L-iduronidases beyond a hypothesis based on the similarity of α-L-iduronidases with the closely related β-D-xylosidases (family 39) [20]. We were interested in the configurational selectivity of the inhibition of β-D-glucuronidases and α-L-iduronidases by the diastereoisomeric lactams **8**–**11** and the corresponding tetrahydrotetrazolopyridine-5-carboxylates **12**–**15**.

Glycono-1,5-lactams and tetrahydrotetrazolopyridines are strong and selective inhibitors of β-glycosidases [21][25], mimicking a late transition state close to the (putative) oxocarbenium ion intermediate. The glucarolactam **8** [16], of interest as inhibitor of β-D-glucuronidases, was synthesised by catalytic oxidation of 5-amino-5-deoxyglucono-1,5-lactam (obtained from nojirimycin) using a rather expensive Pt catalyst loading (*ca.* 50 wt-%). The methyl ester of this benzyl (Bn)-protected glucarolactam was synthesised from methyl α-D-glucopyranoside in 14 steps and in an overall yield of 15% [26].

The requirement of all glycarolactams epimeric at C(4) and C(5) for the determination of configurational selectivity of β-D-glucuronidases and α-L-iduronidases suggested to either prepare these lactams from a common glycarolactam by epimerisation, or

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[2]) For structural and mechanistic aspects (active site residues) of β-D-glucuronidase, see [18] and of α-L-iduronidase, [19][20].

[3]) Substrate distortion during hydrolysis of glycosides possessing an equatorially oriented aglycon is required by the principle of stereoelectronic control. For some recent publications on the mechanism of glycoside hydrolysis, see [21][22].

from a *threo*-configured C(4) precursor corresponding to C(1) to C(4). We planned to first explore the synthesis of 5-amino-5-deoxy-D-galactaro-1,5-lactam (**9**) from D-galactose, and to either prepare the diastereoisomeric lactams **8**, **10**, and **11** from **9**, or from tartaric acid, depending on the results of the synthesis of **9**. In the event, the synthesis of **9** proved more difficult than anticipated, as described below. We have recently communicated the synthesis of the diastereoisomeric glycarolactams **8**–**11** from tartaric acid [27], and now provide a full account of this synthesis, of the transformation of the lactams **54**, **28**, and **67** to the tetrazoles **12**–**14**, and of their inhibition of β-D-glucuronidase from bovine liver and of human α-L-iduronidase.

Results and Discussion. – 1. *Synthesis of the* D-*Galactarolactam* **9** *and* L-*Altrarolactam* **11**. We planned to synthesise the benzylidene-protected galactonolactam **21** as a precursor of **9**, similarly to the corresponding tetrabenzyl glyconolactams [28][29]. The known 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactose **16** [30][31] (prepared from D-galactose in four steps and in an overall yield of 22% on a 50-g scale) was oxidised to the lactone **17** (96%), and then treated with NH_3 in MeOH to provide the hydroxy amide **18** (97%; *Scheme 1*). Oxidation of **18** turned out to be more difficult than expected. The hydroxy amide proved inert to the action of DMSO/Py·SO_3, *Dess–Martin* periodinane, CrO_3/pyridine, $RuO_2 \cdot H_2O/NaIO_4$, and pyridinium chlorochromate (PCC). This unusual stability correlates with a very strong intramolecular bifurcated H-bond of HO–C(5) to OC(4) and OC(6), and of NH to OC(5) and with the antiperiplanar orientation of H–C(5) to C(4 and 6)–O (*Scheme 1*). Finally, oxidation of **18** with DMSO and Ac_2O afforded a *ca.* 1:3 mixture of **19** and **20**[4]), which was treated with L-*Selectride* in THF to provide the D-galactonolactam **21** (61%) and the methylthiomethyl ether **19**[5]) (21%). All attempts to selectively reduce the benzylidene acetal **21** to the 4-*O*-benzylated primary alcohol under well-precedented conditions ($LiAlH_4$/$AlCl_3$, $PhBCl_2$ or Bu_2BOTf/Et_3SiH, $Bu_2BOTf/BH_3 \cdot THF$ [34]) lead to intractable mixtures. We, therefore, debenzylidenated **21** to the diol **22** (75%, besides 20% of **21**), silylated (^{t}BuMe$_2$SiCl) the diol to the monosilyl ether **23** (87%), methoxymethylated **23** to the acetal **24** (85%), and desilylated **24** to the selectively protected primary alcohol **25** (92%). *Jones* oxidation of **25** followed by treatment of the resulting acid with $TMSCH_2N_2$ yielded 60% of the methyl ester **26** besides 11% of the imide **27**. Oxidation with aqueous NaOCl, trichlorocyanuric acid, or $PhI(OAc)_2$ in the presence of TEMPO was less efficient.

Acetal hydrolysis of the methyl ester **26** (and of the corresponding acid) by conventional methods led to decomposition, while treatment of **26** with 1 equiv. of Tf_2O in MeCN afforded the alcohol **28** in 96% yield (*Scheme 2*). Using CH_2Cl_2 instead of MeCN lowered the yield. To the best of our knowledge, this is the first example of a deprotection of MOM ethers with Tf_2O. To test the generality of this method, we exam-

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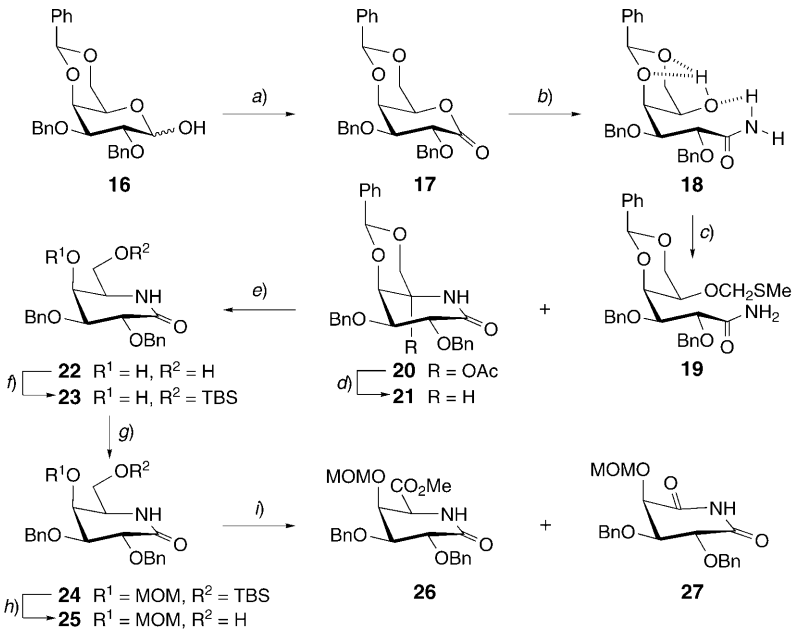
[4]) The structure **20** was tentatively assigned to the oxidation product. It showed an N*H* signal integrating for one H, a 3-H *s* at 1.97 ppm, an IR band at 1742 cm^{-1} in addition to the amide band at 1698 cm^{-1}, and no OH band.

[5]) For the formation of such products of a competing *Pummerer* rearrangement, see [32]. The S,O-acetal **19** was selectively deprotected (MeI and $NaHCO_3$) to the amide **18** (84%) [33].

Scheme 1



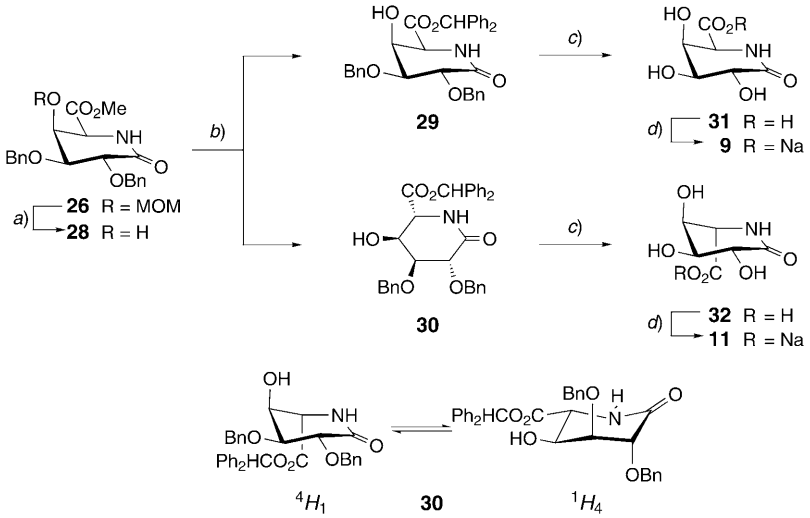
a) Ac_2O, DMSO; 96%. *b*) NH_3 in MeOH; 97%. *c*) Ac_2O, DMSO. *d*) L-*Selectride*, THF, −78°; 61% of **21** and 21% of **19**. *e*) CF_3CO_2H/H_2O 9:1; 75% of **22** and 20% of **21**. *f*) ^{t}BuMe$_2$SiCl, Et_3N, 4-(dimethylamino)pyridine (DMAP), DMF; 87%. *g*) Methoxymethyl chloride (MOMCl), ^{i}Pr$_2$NEt, Bu_4NI, 4-pyrrolidinopyridine, $ClCH_2CH_2Cl$, 80°; 85%. *h*) $Bu_4NF \cdot 3\,H_2O$, CH_2Cl_2/THF; 92%. *i*) 1. CrO_3, 1M H_2SO_4, acetone; 2. $Me_3SiCH_2N_2$, toluene/MeOH 4:1; 60% of **26** and 11% of **27**.

ined a few other MOM ethers and found that the HN-acyl group of **26** is essential for this transformation; it appears to react with Tf_2O and generate TfOH.

Most conditions tested for the saponification of **28** led to partial epimerisation (*ca.* 10%) at C(5), with the exception of the porcine liver esterase-catalysed transformation. However, this hydrolysis proceeded slowly, with only 40% conversion after 2 d. Hydrolysis with 0.1M H_2SO_4 led to decomposition. In view of these results, we saponified **28** with $LiOH \cdot H_2O$, and treated the mixture of the resulting C(5) epimeric acids with Ph_2CN_2 [35][36] to obtain the crystalline D-*galacto*- and L-*altro*-configured benzhydryl (=diphenylmethyl) esters **29** (83%) and **30** (10%), respectively, after a convenient separation by chromatography (*Scheme 2*). Hydrogenolysis of **29** and **30** (10% Pd/C, aq. MeOH, 6 bar H_2) gave the hydroxy acids **31** and **32** that were transformed into the configurationally stable sodium salts **9** and **11**, respectively, by passage through a column of *Dowex 50 W X2* (Na^+ form).

The hydroxy amide **18** in $CDCl_3$ adopts a conformation close to $^4C_1$. A network of intramolecular H-bonds (*Scheme 1*) is evidenced by *J*(2,3) and *J*(3,4) values of 9.3 and 1.9 Hz, respectively, and a HO–C(5) *d* resonating at 2.85 ppm with *J*(5,OH) = 11.5 Hz. The structure of **19** was deduced from the disappearance of the *d* corresponding to HO–C(5), the appearance of two *s*s at 4.72 (OCH_2S) and 2.20 (MeS) in the ^{1}H-NMR spectrum, a ^{13}C *t* at 68.02 (OCH_2S), and a *q* at 14.73 ppm (MeS). The configura-

Scheme 2



a) Tf_2O, MeCN; 96%. *b*) 1. $LiOH \cdot H_2O$, $MeOH/H_2O$ 1:1; 2. Ph_2CN_2, acetone; 83% of **29** and 10% of **30**. *c*) 10% Pd/C, H_2 (6 bar), $MeOH/H_2O$ 1:1; 98% of **31**; 98% of **32**. *d*) Ion exchange on *Dowex 50 W X2* (Na^+); 98% of **9**; 98% of **11**.

tion at C(5) and the $^4H_3$ conformation of **21** were assigned on the basis of $J(2,3) = 9.7$ and $J(3,4)$, $J(4,5)$, $J(5,6)$, and $J(5,6')$ of *ca.* 2 Hz. The structure of the galactonolactam **21** was established by X-ray crystal structure analysis[6]) (*Figure*).

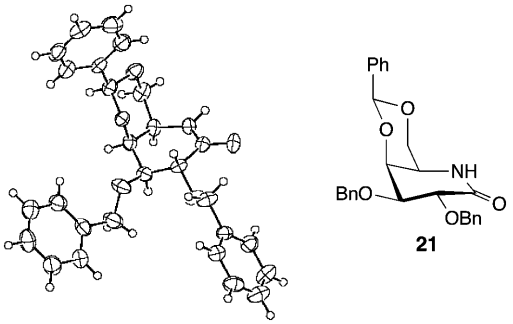


Figure. *ORTEP Representation of the crystal structure of the lactam* **21**

The C(2)–C(5) ^{13}C-NMR signals of the lactam **21** (*Table 3* in *Exper. Part*) were assigned on the basis of a HSQC-GRASP spectrum; those of the lactone **17**, the amides

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[6]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-256197. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

18 and **19**, the lactams **22**–**26**, and the imide **27** were assigned by analogy. Like the tetrabenzyl analogue [29], the galactonolactams **22**–**26** adopt a $^4H_3$ conformation in $CDCl_3$ as evidenced by large $J(2,3)$, and small $J(3,4)$ and $J(4,5)$ values (see *Table 2* in *Exper. Part*). The structure of the lactam **26** is confirmed by a ^{13}C *s* at 170.08 in addition to a C(1) signal at 168.19, a ^1H *s* at 3.27 (MeO), the disappearance of the $CH_2(6)$ signals, a downfield shift of 1.08 ppm for $H-C(5)$, and a strong C=O band at 1751 cm^{-1}. The structure of the imide **27** is supported by the disappearance of the $H-C(5)$ and $CH_2(6)$ signals, ^{13}C *s*s at 168.59 and 169.49 ppm, and strong C=O bands at 1745 and 1718 cm^{-1}. The $B_{2,5}$ conformation of **27** is evidenced by $J(2,3)$ and $J(3,4)$ values of 4.3 and 2.5 Hz, respectively.

2. *Synthesis of the Glycarolactams* **8**–**11** *from (*R,R*)-Tartaric Acid*. Considering the unsatisfactory route to **9** from D-galactose (16 steps, 3% overall yield), we decided to synthesise the diastereoisomeric glycarolactams **8**–**11** from the aldehyde **35** (*Scheme 3*). This aldehyde may be derived from tartaric acid, and although (*R*,*R*)- and (*S*,*S*)-tartaric acid (L- and D-threaric acid) and their derivatives are among the most extensively used starting materials of the chiral pool [37], there are only a few examples of syntheses of (chain-extended) carbohydrates and analogues from tartrates, such as the syntheses of deoxynojirimycin [38], castanospermine [39], polyhydroxy piperidines [40], conduritol [41], and a *myo*-inositol derivative [42].

We planned to synthesise the glycarolactams **8**–**11** by aminohydroxylation of the (*E*)- and (*Z*)-acrylates **33** and **34**, followed by cyclisation and deprotection. The unsaturated esters **33** and **34** should be obtained by diastereoselective olefination of the aldehyde **35** that is in equilibrium with the hydroxypyrrolidinone **36** (*Scheme 3*).

The known tartrimide **37** (prepared from diethyl L-tartrate in four steps and in an overall yield of 36% [43]) was reduced ($NaBH_4$) to the hydroxypyrrolidinone **36** (68%). *Wittig–Horner* olefination [44][45] proceeded well, but the resulting α,β-unsaturated ester cyclised rapidly to the 1,4-lactam **38** (74%)[7]). Hydrogenolytic debenzylation of **38** gave the dihydroxy ester **39** which was saponified. Ion-exchange chromatography gave the fully deprotected 1,4-lactam **40** in an overall yield of 97%.

Considering the ready cyclisation to **38**, we planned to substitute the amide **35** by the corresponding methyl ester **46**. Methanolysis of the readily available anhydride **41** (three steps from diethyl L-tartrate; 40% overall yield) [43] gave quantitatively the mono-ester **42**. An attempt to transform it to the aldehyde **46** by reduction of the corresponding acyl chloride with $Li(^tBuO)_3BH$ [46] led predominantly to the lactone **45**. The acid **42** was thus transformed to the mixed anhydride with MeOCOCl, and reduced with $NaBH_4$ to the alcohol **43** which was oxidised with TEMPO/trichlorocyanuric acid [47]. This gave, after chromatography, the aldehyde **46** (35–45%), the lactone **45** (12%), and the protected dimethyl tartrate **44** (18%) [48] besides 25% of the acid **42** (25%). Reduction of **42** with $BH_3\cdot THF$ was not advantageous. It was difficult to reproduce[8]) and yielded only 40% of the alcohol **43**. Reduction of the mixed anhydride with $Zn(BH_4)_2$ in Et_2O followed by oxidation led to the desired aldehyde **46** in a slightly increased yield of 60%.

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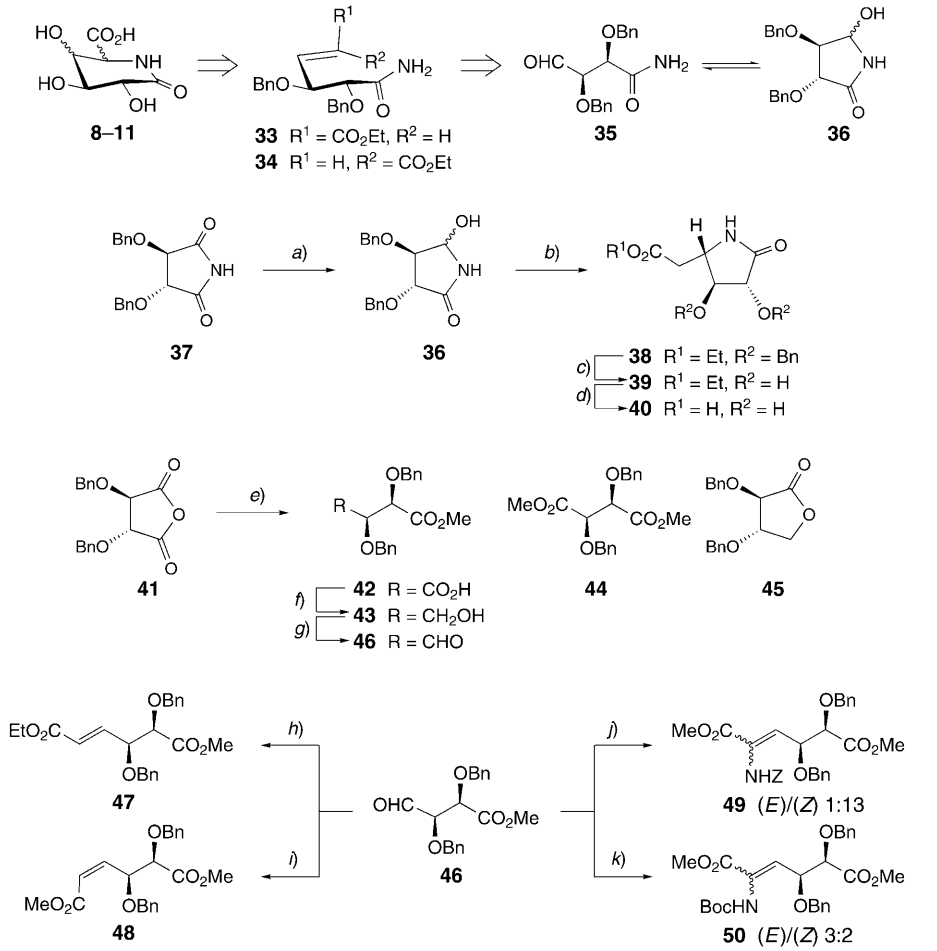
[7]) An attempt to olefinate the *N*-phenyl analogue of **31** did not affect the starting material.

[8]) The reaction had to be performed at a temperature between 15° and 18° where it proceeded slowly. Long reaction times led to the lactone **45** that was further reduced to 2,3-di-*O*-benzyl-L-threitol.

Scheme 3



a) $NaBH_4$, MeOH/CH_2Cl_2 2:1; 68% of **36** and 12% of **37**. *b*) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, $0 \rightarrow 23°$; 74%. *c*) H_2 (6 bar), 10% Pd/C, MeOH/AcOH 1:1; 99%. *d*) $LiOH \cdot H_2O$, EtOH/H_2O 1:1; 98%. *e*) MeOH; 99%. *f*) $ClCO_2Me$, $^iPr_2NEt$, THF, 0°, 2 h then $Zn(BH_4)_2$, Et_2O, $0 \rightarrow 10°$, 4 h. *g*) Trichlorocyanuric acid, 2,2,6,6-tetramethylpiperidinooxy (TEMPO), CH_2Cl_2, $-78 \rightarrow 0°$; 60% of **46**, 20% of **42** and 7% of **45** (from **42**). *h*) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°; 80%. *i*) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, potassium 1,1,1,3,3,3-hexamethyldisilazane (KHMDS), 18-crown-6, THF, −78°; 75%. *j*) $(MeO)_2P(O)CH(NHZ)CO_2Me$, 1,1,3,3-tetramethyl guanidine, THF, −78 to 25°; 85% ((*E*)/(*Z*) 1:13). *k*) $(MeO)_2P(O)CH(NHBoc)CO_2Me$, 1,8-diazabicylco[5.4.0]undec-7-ene (DBU), THF, 0–25°; 85% ((*E*)/(*Z*) 3:2).

Wittig–Horner olefination of **46** led to the (*E*)-alkene **47** (80%), and the *Still–Gennari* version [49] of the olefination provided the (*Z*)-alkene **48** (75%). The desired dehydroamino acids were prepared by olefination of **46** with the phosphonate derived from Z- or Boc-protected methyl glycinate [50]. This provided mixtures of the diaster-

eoisomeric Z-protected dehydro amino acids **49** (85%; (*E*)/(*Z*) 1:13) and of the Boc-protected analogues **50** (85%; (*E*)/(*Z*) 3:2), respectively.

As the planned aminohydroxylation of **47** did not affect the starting material[9]), we subjected **47** to a reagent-controlled dihydroxylation with OsO_4 in the presence of $NMO \cdot H_2O$ and $(DHQ)_2PHAL$, speculating that lactonisation would lead to selective protection of the *β*-OH group (*Scheme 4*). We indeed obtained selectively the L-idaro-1,4-lactone **51** (75%), while substrate-controlled dihydroxylation with OsO_4 and $NMO \cdot H_2O$ followed by lactonisation gave the D-galactaro-1,4-lactone **57** besides some **51** (98:2, 87%). To introduce the desired amino group, we prepared the triflate **52** (93%) from the L-idaro-1,4-lactone **51** and treated it with tetramethylguanidinium azide[10]) [51] to obtain almost quantitatively the D-*gluco* azido lactone **53**. Reduction of **53** should lead to the lactam **54**. Indeed, $Pd/CaCO_3$-catalysed hydrogenation in EtOH provided the protected D-glucarolactam **54** in 65% yield, while reduction of **53** with either Ph_3P, or propane-1,3-dithiol gave **54** in only 30–35%. Similarly as for **51**, triflation of **57** to **58** (94%) was followed by substitution with azide to give **59** (98%) that was reduced to the L-altrarolactam **60** (63%).

The D-galactaro- and L-idarolactams **28** and **67** were synthesised from the (*Z*)-acrylate **48** following the route described for the (*E*)-isomer **47** (*Scheme 5*). However, not surprisingly [52][53], substrate control of the dihydroxylation of the *(Z)*-acrylate was not selective, and treatment of **48** with OsO_4 and $NMO \cdot H_2O$ afforded an inseparable 1:1 mixture of the D-*gluco*- and L-*altro*-lactones **61** and **62** (78%). Triflation of this mixture resulted in a 1:2 mixture of triflates **63**/**64** (65%) besides unreacted D-*gluco*-lactone **61**[11]) (23%). The mixture **63**/**64** was transformed into the azides **65**/**66**. Hydrogenation followed by chromatography led to the D-galactarolactam **28** (41%) and the L-idarolactam **67** (21%).

Similarly as observed for the *galacto*-analogue **28**, saponification of the D-*gluco*-, L-*ido*-, and L-*altro*-lactams **54**, **67**, and **60**, respectively, with $LiOH \cdot H_2O$ led to partial epimerisation (*Schemes 4* and *5*), and the resulting impure acids were transformed to the crystalline benzhydryl esters **55** (85%), **68** (85%), and **30** (84%), containing minor amounts of the epimer **68**, **55**, or **29**, respectively.

The D-*gluco*- and L-*ido*-lactams **55** and **68** were debenzylated[12]), and the resulting acids **56**[13]) and **69**, respectively, were converted to the configurationally stable sodium salts **8** and **10** by passage through a column of *Dowex 50 W X2* (Na^+ form). This synthesis from tartaric anhydride **41** provides the D-glucaro-1,5-lactam **8**, D-galactaro-1,5-lactam **9**, L-idaro-1,5-lactam **10**, and L-altraro-1,5-lactam **11** in ten steps and in an overall yield of 18, 7, 4, and 20%, respectively.

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[9]) Similarly, attempted hydroboration of **49** and 1,4-addition of alcoholates to the dehydro amino acids **49** and **50** did not affect the starting material.

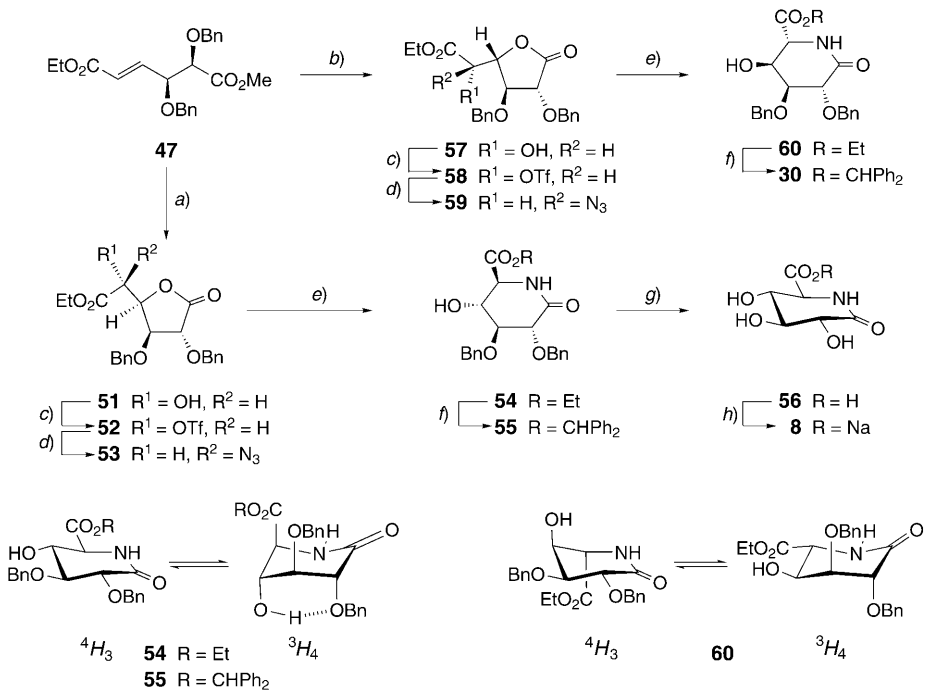
[10]) Similar yields were obtained when the triflate **52** was treated with Bu_4NN_3. Treatment of the triflate **52** with NaN_3 in DMF led to decomposition.

[11]) This allowed to transform the D-*gluco*-isomer **61** to the pure triflate **63** and azide **65**.

[12]) The deprotection of the D-galactarol-lactam **28** and D-altrarol-lactam **30** is discussed above.

[13]) The melting point of the known glucaro-1,5-lactam **56** is in agreement with the published data [16]; however, we have observed a specific rotation of +30.1 while *Niwa et al.* [16] have reported a value of +48.

Scheme 4

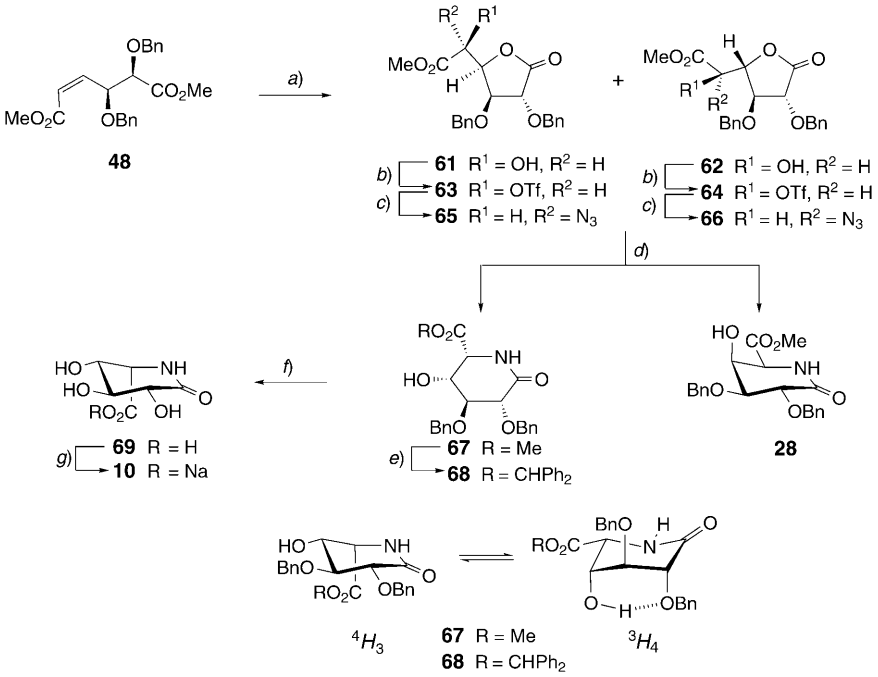


a) 2.5% OsO_4 in ^{t}BuOH, $K_3[Fe(CN)_6]$, $(DHQ)_2PHAL$, $MeSO_2NH_2$, K_2CO_3, ^{t}BuOH/H_2O 1:1, 0°; 75%. *b*) 2.5% OsO_4 in ^{t}BuOH, *N*-methylmorpholine *N*-oxide monohydrate (NMO·H_2O), acetone/H_2O (4:1); 87%. *c*) Tf_2O, 2,6-lutidine, CH_2Cl_2, $-78 \rightarrow 0°$; 93% of **52**; 94% of **58**. *d*) Tetramethylguanidinium azide, CH_2Cl_2, $-90 \rightarrow 10°$; 98% of **53**; 98% of **59**. *e*) 10% Pd/$CaCO_3$, H_2 (1 bar), EtOH, 4 h then N_2, 12 h; 65% of **54**; 63% of **60**. *f*) 1. LiOH·H_2O, MeOH/H_2O 1:1; 2. Ph_2CN_2, acetone; 85% of **55**; 84% of **30**. *g*) 10% Pd/C, H_2 (6 bar), MeOH/H_2O 2:1; 98% of **56**. *h*) Ion exchange on *Dowex 50W X2* (Na^+); 98% of **8**.

The (*E*)- and (*Z*)-configuration of the olefination products **47** and **48** was assigned on the basis of *J*(2,3) values of 15.9 and 11.5 Hz, respectively, while the configuration of the dehydro amino acids **49** and **50** was evidenced by the known deshielding effect of a vicinal, *cis*-oriented ester group on *H*–C(3) (and more weakly on *H*–C(4)) [54][55].

Formation of the 1,4-lactones **51**, **57**, and **61** is evidenced by strong IR bands at 1795–1799 cm^{-1} and by the disappearance of a MeO ^{1}H signal. The assignment of the L-*ido*- (**51** and **52**), D-*galacto*- (**57** and **58**), D-*gluco*- (**61** and **63**), and L-*altro*- (**62** and **64**) configuration to the 1,4-lactones is based on *J*(3,4) and *J*(4,5) values (see *Table 5* in *Exper. Part*), assuming a *cis*-dihydroxylation by OsO_4. The large *J*(2,3) and *J*(3,4) (6.5–8.1 Hz) values for the 1,4-lactones **51**–**53**, **57**–**59**, and **61**–**66**, respectively, show that **51–53** adopt predominantly a flattened ^4E conformation [56] where the substituents at C(29) and C(3) are pseudoequatorial (*J*(3,4) corresponding to an angle of *ca*. 20° for **51–53**, **61**, **63**, and **65**, and of *ca*. 150° for **57–59**, **62**, **64**, and **66**) (see *Table 5* in *Exper. Part*). The side chain adopts preferentially the *gg*-conformation. The D-

Scheme 5



a) 2.5% OsO_4 in ^{t}BuOH, *N*-methylmorpholine *N*-oxide monohydrate (NMO·H_2O), acetone/H_2O 4:1; 78% of **61**/**62** 1:1. *b*) Tf_2O, 2,6-lutidine, CH_2Cl_2, $-78 \rightarrow 0°$; 69% of **63**/**64** 1:2 and 23% of **61**. *c*) Tetramethylguanidinium azide, CH_2Cl_2, $-90 \rightarrow 10°$; 98% of **65**/**66** 1:2. *d*) 10% Pd/$CaCO_3$, H_2 (1 bar), THF, 4 h then N_2, 12 h; 21% of **67** and 41% of **28**. *e*) 1. LiOH·H_2O, MeOH/H_2O 1:1; 2. Ph_2CN_2, acetone; 85% of **68**. *f*) 10% Pd/C, H_2 (6 bar), MeOH/H_2O 1:1; 98% of **69**. *g*) Ion exchange on *Dowex 50W X2* (Na^+); 98% of **10**.

gluco- (**54** and **55**), L-*ido*- (**67** and **68**)[14]), and L-*altro*- (**60** and **30**) lactams in $CDCl_3$ are a *ca*. 1:1 mixture of the $^4H_3$ and $^3H_4$ conformers as evidenced by their medium J(2,3) and J(4,5) values (*Table 4* in *Exper. Part* and modeling with MM3*). The $^3H_4$ conformation of **54**, **55**, **67**, and **68** is favoured by a strong H-bond of HO–C(4) to C(2)–OBn (*Schemes 4* and *5*), as evidenced by the HO–C(4) *d*s with J(4,OH) = 6.5 to 8.7 Hz (see *Exper. Part*). The D-*galacto*-configuration and $^4H_3$ conformation of **28** and **29** agree well with J(2,3) = 7.8, J(3,4) = 2.5, J(4,5) = 2.8 Hz for **28**, and J(2,3) = 8.1, J(3,4) = 2.5, J(4,5) = 2.8 Hz for **29**. The lactams **56**, **31**, **69**, and **32**, and their sodium salts **8**–**11** prefer a $^4H_3$ conformation (*cf. Table 4* in *Exper. Part*).

3. *Synthesis of the Tetrazoles* **12**–**14**. We prepared the tetrazoles **70**–**72** (*Scheme 6*) by treating the glycarolactams with Tf_2O and NaN_3 according to the method of *Vonhoff* and *Vasella* [57]. Thus, the D-glucarolactam **54** was transformed into the tetrazole **70**, followed by saponification (LiOH·H_2O), esterification of the corresponding acid

[14]) J(2,3) and J(3,4) of **68**, and J(4, OH) of **67** were not determined due to signal overlap.

(Ph_2CN_2), and chromatography, to provide the D-*gluco*-tetrazole **73**[15]) (83%) and its L-*ido*-analogue **74** (6%). In a similar fashion, the L-idarolactam **67** provided the L-*ido*-tetrazole **71** which was transformed into the benzhydryl esters **74** (63%) and **73** (15%). The D-galactarolactam **28** yielded exclusively the D-*galacto*-tetrazole **76** (65%) *via* **72**. Surprisingly, the L-altrarolactam **60** was completely epimerised, and yielded exclusively the D-*galacto*-tetrazole **75**. Saponification and esterification of **75** gave **76** (65%). The ^{1}H-NMR spectrum of the crude tetrazole **75** established that epimerisation occurred during tetrazole formation and not during saponification. The preferred $^3H_4$ conformation of the intermediate L-*altro*-configured cyclic iminotriflate **81** (from **60** and Tf_2O) is destabilised by a $A_{1,3}$ strain between the substituents at C(1) and C(5) (*Scheme 6*). The readily occurring epimerisation of L-*altro* **81** to the D-*galacto*-isomer **80** is rationalised by the release of this $A_{1,3}$ strain. That the similar $A_{1,3}$ strain of the $^3H_4$ conformer of the L-*ido*-configured intermediate **83** did not lead to epimerisation to the D-*gluco*-isomer **82** is due to a H-bond between HO–C(4) and the ester C=O group. Treatment of the MOM-protected galactarolactam **26** with NaN_3 and Tf_2O led both to cleavage of the acetal and formation of the tetrazole **72** which was transformed into the benzhydryl ester **76** (58% from **26**). Each one of the tetrazoles **73**, **74**, and **76** was deprotected by hydrogenolysis, and the resulting acids **77**–**79** were converted to the sodium salts **12**, **14**, and **13**, respectively.

The tetrazoles **73**, **74**, and **76** are characterized by ^{13}C *s*s at 148.91 (**73**), 149.22 (**74**), and 151.44 ppm (**76**), disappearance of the strong IR amide bands and of the N*H* signals, and by $[M+H]^+$ signals in ESI-MS. The D-*gluco*- and L-*ido*-configured tetrazoles **73** and **74** adopt predominantly the $^7H_6$ conformation in $CDCl_3$ as evidenced by the coupling constants (see *Table 6* in *Exper. Part*). Similarly as discussed for **54** and **67**, the $^7H_6$ conformation is preferred due to a strong intramolecular H-bond from HO–C(4) to BnO–C(8) in the tetrazoles **73** (J(6,OH) = 8.7) and **74** (J(6,OH) = 9.6 Hz). The *galacto* tetrazole exists as a *ca.* 1:1 mixture of $^6H_7$ and $^7H_6$ conformers in $CDCl_3$ (see *Table 6* in *Exper. Part*). Although the $^7H_6$ conformation of the tetrazoles **72**, **75**, and **76** is destabilised by the 1,3-diaxial interaction between the substituents at C(5) and C(7), a combination of strain release (interaction of the substituent at C(5) with N(3)) and the strong bifurcated H-bond of HO–C(6) to the C=O group of the ester and OC(7) (see *Exper. Part*) stabilises the $^7H_6$ conformation and leads to the equilibrium between the $^6H_7$ and $^7H_6$ conformers (*Scheme 6*). The tetrazoles **12**–**14** in D_2O adopt the $^6H_7$ conformation (*cf. Table 6* in *Exper. Part*).

Enzymatic Tests and Discussion. – The lactams **8**–**11** and **40**, and the tetrazoles **12**–**14** were tested as inhibitors of bovine liver β-D-glucuronidase (acetate buffer, 30°, pH 5.0) and human α-L-iduronidase (2,2-dimethylglutarate buffer, 37°, pH 4.5) with 4-nitrophenyl β-D-glucuronide and 4-methylumbelliferyl α-L-iduronide as substrates, respectively. The inhibition data (K_i) and the pK values of the inhibitors are summarised in *Table 1*.

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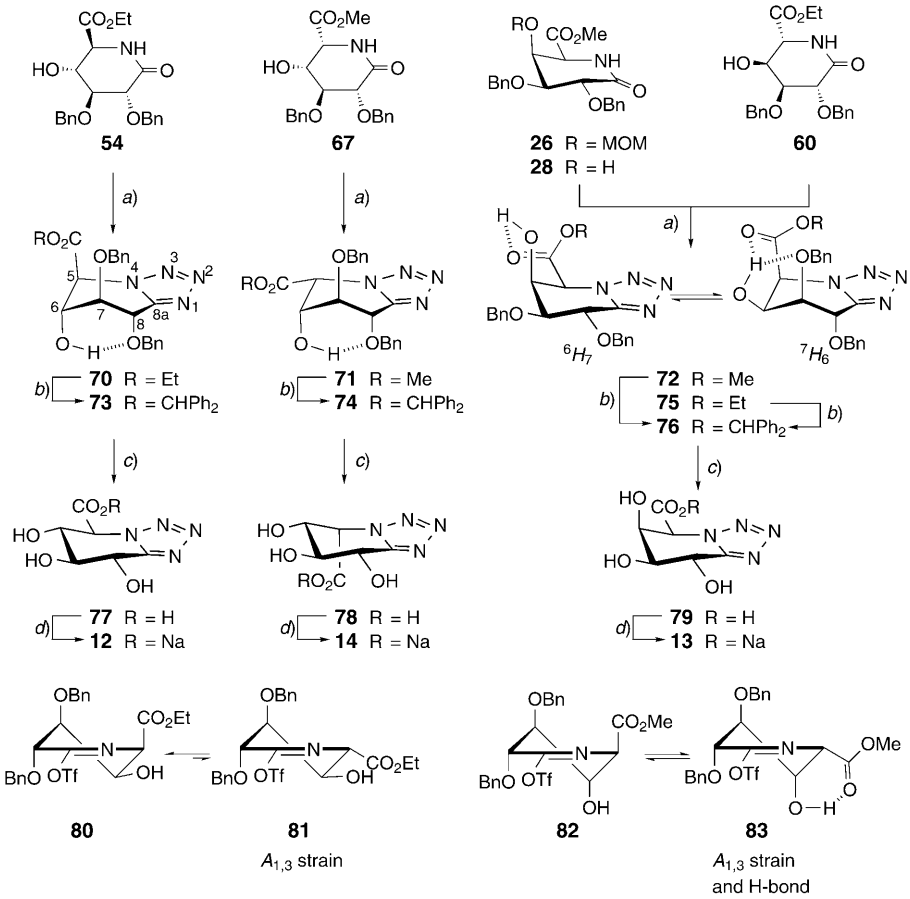
[15]) The direction of numbering of tetrazolopyridines (*cf.* **73** in *Scheme 6*) is opposite to that of pyranosides. Thus, the sides above and below the plane of the tetrazoles, as defined by clockwise and counterclockwise numbering, are interchanged relative to those defined by carbohydrate nomenclature.

Scheme 6



a) NaN_3, Tf_2O, MeCN, $-19 \rightarrow 0°$. *b*) 1. $LiOH \cdot H_2O$, $MeOH/H_2O$ 1:1; 2. Ph_2CN_2, acetone; 83% of **73** and 6% of **74** (from **54**); 63% of **74** and 15% of **73** (from **67**); 65% of **76** (from **28** or **60**); 58% of **76** (from **26**). *c*) 10% Pd/C, H_2 (6 bar), $MeOH/H_2O$ 1:1; 98% of **77**; 98% of **78**; 96% of **79**. *d*) Ion exchange on *Dowex 50W X2* (Na^+); 98% of **12**; 98% of **14**; 96% of **13**.

A comparison of the inhibition data for the lactams **8**–**11**[16]) and the tetrazoles **12**–**14** (*Table 1*) shows that bovine liver β-D-glucuronidase is not configurationally selective, while human α-L-iduronidase is, in accordance with earlier results based on the hydrolysis of diastereoisomeric phenyl glycuronides [23]. The lactams **8**–**11** and the tetrazoles **12**–**14** inhibit bovine liver β-glucuronidase in the μM to nM concentration range, while only the L-*ido*-configured lactam **10** inhibits human α-L-iduronidase ($K_i = 94$ μM). Surprisingly, the L-*ido*-configured tetrazole **14** is only a weak inhibitor ($K_i = 1.3$ mM) of human α-L-iduronidase. This weak inhibition might be due to an equi-

[16]) The inhibition constant of the known glucarolactam **8** is in agreement with the reported value [16].

Table 1. *Inhibition of β-D-Glucuronidase from Bovine Liver and Human α-L-Iduronidase by the 1,5-Lactams* **8**–**11**, *the Tetrazoles* **12**–**14**, *and the 1,4-Lactam* **40**

Inhibitor	pK_{HA}	K_i [μM] β-D-glucuronidase from bovine liver[a])	K_i [μM] human α-L-iduronidase[b])
8	2.6[c])	0.032[d]) (competitive)	[e])
9	–[f])	0.031 (noncompetitive)	[e])
10	3.5	0.6 ($\alpha=1.2$)	94 (competitive)
11	–[f])	1.6 (noncompetitive)	[e])
12	2.53	0.025 ($\alpha=1.9$)	>5 mM
13	2.52	6.3 ($\alpha=5.4$)	>5 mM
14	2.70	0.66 ($\alpha=2.2$)	1.3 mM
40	4.2	25 ($\alpha=7.1$)	[e])

[a]) At pH 5.0 and 30°. [b]) At pH 4.5 and 37°. [c]) Data taken from [16]. [d]) [16]: 0.039 μM. [e]) No inhibition at 2 mM. [f]) No inflection of the titration curve was observed between pH values of 2.0 and 7.0.

libration of the D-*gluco*-tetrazole **12** with the L-*ido*-isomer **14** under the enzymatic assay conditions. The tetrazoles **12**–**14** inhibit bovine liver β-D-glucuronidase to the same extent as the corresponding glycarolactams with the notable exception of the D-*galacto*-tetrazole **13** that is 200-fold less active than **9**. The 1,4-lactam **40** (*Scheme 3*) is a mixed-type inhibitor ($K_i=25$ μM) of bovine liver β-D-glucuronidase. The nature of the inhibition of β-D-glucuronidase by the glycaro-1,5-lactams depends on their configuration; the *gluco*-isomer **8** is a competitive and the *galacto*-isomer **9** a noncompetitive inhibitor.

The relatively weak inhibition of α-L-iduronidase by the L-*ido*-lactam **10** ($K_i=94$ μM) compared to the very strong inhibition of the β-D-glucuronidase by the D-*gluco*-lactam **8** ($K_i=0.032$ μM) suggests that the transition state for the hydrolysis of iduronides by α-L-iduronidase may be closer to that of the distorted conformers of the substrate, *e.g.*, a $^{2,5}B$, than to the flat oxocarbenium ion-type intermediate, considering that lactam-type inhibitors mimic a late transition state close to an oxocarbenium cation. A distorted substrate with a $^{2,5}B$ conformation was proposed for α-L-iduronidase by *Withers* and co-workers [20] on the basis of the sequence similarity between α-L-iduronidase and xylosidase.

We thank Dr. *B. Schweizer* for the crystal-structure determination, *M. Schneider* and *P. Kälin* for the pK_{HA} determinations, and Dr. *B. Bernet* for checking the *Exper. Part*. *J. P.* and *A. V.* thank the *Swiss National Science Foundation* and *F. Hoffmann La Roche*, Basel, for generous support.

Experimental Part

General. Solvents were distilled before use. Reactions were carried out under N_2, unless stated otherwise. Qual. TLC: precoated silica-gel plates (*Merck* silica gel *60 F_{254}*); detection by heating with 'mostain' (400 ml of 10% H_2SO_4 soln., 20 g of $(NH_4)_6Mo_7O_{24}\cdot 6\,H_2O$, 0.4 g of $Ce(SO_4)_2$). Normal workup implies pouring the reaction mixture into the indicated sat. aq. soln., extracting into the specified org. solvent, drying of the org. layer (Na_2SO_4), filtration, and evaporation of the volatiles. Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm). Prep. HPLC: *Kromasil* 100 Å, 5 μm, with a self-packed silica-

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the 1,5-Lactone* **17**, *the Amides* **18** *and* **19**, *the Protected 1,5-Lactams* **21** *and* **22**–**26**, *and the Imide* **27** *in $CDCl_3$*

	17	**18**	**21**	**19**	**22**
H–C(2)	4.54	4.05[a])	4.42	4.50	4.23
H–C(3)	3.89	4.32	3.82	4.15	3.78
H–C(4)	4.37	4.21	4.35	3.87	4.20
H–C(5)	4.10	3.81	3.26	4.27	3.45
H–C(6)	4.40	4.27	4.09	4.63	3.85
H′–C(6)	4.03	4.05[a])	4.01	3.93	3.82–3.75
J(2,3)	10.0	9.3	9.7	9.0	8.7
J(3,4)	2.5	1.9	2.2	1.2	2.5
J(4,5)	2.5	[b])	[b])	*ca.* 2.7	[b])
J(5,6)	1.5	1.9	1.6	1.5	6.2
J(5,6′)	1.5	[b])	[b])	1.2	5.3
J(6,6′)	12.8	11.8	12.8	12.8	11.5
	23	**24**	**25**	**26**	**27**
H–C(2)	4.23	4.26	4.25	4.25	4.08
H–C(3)	3.82–3.71	3.79	3.81	3.84	3.99
H–C(4)	4.13	4.16	4.21	4.09	4.78
H–C(5)	3.48–3.40	3.47	3.54	4.62	–
H–C(6)	3.82–3.71	3.74–3.69	3.73	–	–
H′–C(6)	3.82–3.71	3.74–3.69	3.73	–	–
J(2,3)	8.7	9.3	9.3	9.0	4.3
J(3,4)	2.3	2.2	2.2	1.9	2.8
J(4,5)	2.3	2.8	2.5	*ca.* 0.5	–
J(5,6)	7.5	8.1	6.5	–	–
J(5,6′)	4.7	5.6	6.5	–	–
J(6,6′)	[b])	[b])	[b])	–	–

[a]) Overlapping signals. [b]) Not assigned.

gel column (20×250 mm). M.p.: uncorrected. Optical rotations: 1-dm cell at 25°, 589 nm. FT-IR spectra: KBr or *ca.* 2% soln. in $CHCl_3/CH_2Cl_2$ or neat (ATR), absorption in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: chemical shifts δ in ppm rel. to TMS as external standard, and coupling constants J in Hz. HR-MALDI-MS: in gentisic acid (=2,5-dihydroxybenzoic acid, DHB) matrix. The pK_{HA} values were determined in H_2O by potentiometric titration with 0.1N NaOH at 25°. The β-D-glucuronidase from bovine liver (EC 3.2.1.31, *Fluka 49310*) and 4-nitrophenyl β-D-glucuronide (*Fluka 73677*) were used without further purification. 4-Methylumbelliferyl α-L-iduronide and human α-L-iduronidase (EC 3.2.1.76) were kindly provided by *Biomarin*.

2,3-Di-O-*benzyl-4,6*-O-*benzylidene*-D-*galactono-1,5-lactone* (**17**). A soln. of **16** (24 g, 53.5 mmol) in DMSO (150 ml) and Ac_2O (75 ml) was stirred at 23° for 15 h, and treated dropwise with H_2O (150 ml) over 30 min. The precipitate was filtered off and washed with Et_2O (2×250 ml). Trituration of the solid with Et_2O gave **17** (23 g, 96%). Colourless solid. R_f (AcOEt/toluene 1:1) 0.50. M.p. 118–120°. IR ($CHCl_3$): 3007*m*, 2930*m*, 2860*m*, 1744*s*, 1643*m*, 1496*m*, 1455*m*, 1368*m*, 1321*m*, 1248*s*, 1114*s*, 1035*m*, 927*m*, 873*m*, 839*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.50–7.25 (*m*, 15 arom. H); 5.54 (*s*, PhC*H*); 5.25 (*d*, *J*=10.6, PhC*H*); 4.84 (*d*, *J*=11.5, PhC*H*); 4.79 (*d*, *J*=10.9, PhC*H*); 4.75 (*d*, *J*=12.5, PhC*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 137.97, 137.92, 137.25 (3*s*); 129.67–126.51 (several *d*); 101.32 (*d*, Ph*C*H); 73.15, 72.86 (2*t*, 2 Ph*C*H_2). HR-MALDI-MS: 469.1659 (100, $[M+Na]^+$, $C_{27}H_{26}NaO_6^+$; calc. 469.1622).

2,3-Di-O-*benzyl-4,6*-O-*benzylidene*-D-*galactonamide* (**18**). A soln. of **17** (23 g, 51.5 mmol) in MeOH (100 ml) was treated with 7N NH_3 in MeOH (515 ml, 74 mmol), stirred at 23° for 1 h, and evaporated. Recrystallistion in AcOEt/cyclohexane gave **18** (23 g, 97%). Colourless crystals. R_f (AcOEt/cyclohexane 1:1) 0.21. M.p. 157–159°. $[\alpha]_D^{25} = +14.8$ ($c = 1.07$, $CHCl_3$). IR ($CHCl_3$): 3568*m*, 3512*m*, 3395*m*, 3037*m*, 2974*m*, 2927*s*, 2868*s*, 1689*s*, 1566*m,* 1495*m*, 1452*m*, 1391*s*, 1339*m*, 1220*m*, 1115*s*, 1082*s*, 1006*s*, 916*m*, 842*m*, 810*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.38–7.17 (*m*, 15 arom. H); 6.80 (br. *s*, exchange with D_2O, NH); 5.31 (*s*, PhCH); 5.94 (br. *s*, exchange with D_2O, NH); 4.75 (*d*, $J = 10.6$, PhC*H*); 4.68 (*d*, $J = 10.6$, PhC*H*); 4.65 (*d*, $J = 10.6$, PhC*H*); 4.45 (*d*, $J = 11.8$, PhC*H*); 2.85 (*d*, $J = 11.5$, exchange with D_2O, HO–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.16, 137.68, 137.03 (3*s*); 129.34–128.13 (several *d*); 126.13 (2*d*); 101.33 (*d*, Ph*C*H); 75.63, 74.26 (2*t*, 2 PhCH_2). HR-MALDI-MS: 486.1903 (100, $[M+Na]^+$, $C_{27}H_{29}NNaO_6^+$; calc. 486.1887). Anal. calc. for $C_{27}H_{29}NO_6$ (463.53): C 69.96, H 6.31, N 3.02; found: C 69.87, H 6.28, N 2.94.

Preparation of **19** *and* **21** *from* **18**. A soln. of **18** (23 g, 49.6 mmol) in DMSO (150 ml) and Ac_2O (75 ml) was stirred for 16 h at 23° and treated dropwise with H_2O (150 ml). The precipitate was filtered off and dried. A soln. of this solid in THF (500 ml) was cooled to −78°, treated with 1M L-*Selectride* in THF (54.5 ml, 54.5 mmol), stirred for 1 h, treated with sat. $NaHCO_3$ soln. (150 ml), and warmed to 0°. After separation of the layers, the aq. layer was extracted with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (AcOEt/cyclohexane 1:2) gave **19** (6.5 g, 21%) and **21** (13.5 g, 61%). Recrystallisation of **21** in ^{i}PrOH/CH_2Cl_2 gave colourless crystals.

Data of 2,3-Di-O-*benzyl-4,6*-O-*benzylidene-5*-O-*(methylthiomethyl)*-D-*galactonamide* (**19**). Colourless solid. R_f (AcOEt/cyclohexane 1:1) 0.43. M.p. 167–170°. $[\alpha]_D^{25} = -44.8$ ($c = 1.13$, $CHCl_3$). IR ($CHCl_3$): 3516*m*, 3397*m*, 3220*m* (br.), 3090*w*, 2925*m*, 2873*m*, 1954*w*, 1692*s*, 1564*m*, 1497*m*, 1454*m*, 1395*m*, 1361*m*, 1340*m*, 1302*m*, 1229*m*, 1214*m*, 1157*m*, 1118*m*, 1093*s*, 1070*s*, 1015*s*, 996*m*, 916*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.42–7.23 (*m*, 15 arom. H); 6.76 (br. *d*, $J = 3.4$, exchange with D_2O, NH); 5.65 (br. *d*, $J = 3.4$, exchange with D_2O, NH); 5.41 (*s*, PhC*H*); 4.83 (*d*, $J = 11.8$, PhC*H*); 4.74 (*d*, $J = 11.5$, PhC*H*); 4.72 (*s*, OCH_2S); 4.63 (*d*, $J = 11.5$, PhC*H*); 4.51 (*d*, $J = 11.5$, PhC*H*); 2.20 (*s*, MeS). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.36, 138.03, 137.22 (3*s*); 129.23–126.40 (several *d*); 101.55 (*d*, Ph*C*H); 74.54, 74.47 (2*t*, 2 PhCH_2); 68.02 (*t*, OCH_2S); 14.73 (*q*, MeS). HR-MALDI-MS: 546.1879 (100, $[M+Na]^+$, $C_{29}H_{33}NNaO_6S^+$; calc. 546.1921). Anal. calc. for $C_{29}H_{33}NO_6S$ (523.20): C 66.52, H 6.35, N 2.67, S 6.12; found: C 66.68, H 6.44, N 2.61, S 5.93.

Data of 5-Amino-2,3-di-O-*benzyl-4,6*-O-*benzylidene-5-deoxy*-D-*galactono-1,5-lactam* (**21**). R_f (AcOEt/cyclohexane 2:1) 0.20. M.p. 181–182°. $[\alpha]_D^{25} = +106.5$ ($c = 1.01$, $CHCl_3$). IR ($CHCl_3$): 3389*w*, 3066*m*, 3007*m*, 2872*m*, 1955*w*, 1680*s*, 1496*w*, 1452*m*, 1398*m*, 1363*m*, 1322*m*, 1111*s*, 1012*m*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.48–7.19 (*m*, 15 arom. H); 6.02 (br. *s*, NH); 5.50 (*s*, PhC*H*); 5.30 (*d*, $J = 10.6$, PhC*H*); 4.83 (*d*, $J = 11.2$, PhC*H*); 4.79 (*d*, $J = 12.4$, PhC*H*); 4.75 (*d*, $J = 12.4$, PhC*H*). ^{13}C-NMR (75 MHz, $CDCl_3$)[17]): see *Table 3*; additionally, 138.29, 137.98, 137.19 (3*s*); 129.36–126.39 (several *d*); 101.38 (*d*, Ph*C*H); 75.96, 72.73 (2*t*, 2 PhCH_2). HR-MALDI-MS: 469.1802 (30); 468.1761 (100, $[M+Na]^+$, $C_{27}H_{27}NNaO_5^+$; calc. 468.1781). Anal. calc. for $C_{27}H_{27}NO_5$ (445.19): C 72.79, H 6.11, N 3.14; found: C 72.98, H 6.32, N 3.15.

X-Ray Analysis of **21**. Orthorhombic $P2_12_12_1$; $a = 6.1462(2)$, $b = 18.3738(7)$, $c = 20.5926(9)$, $V = 2325.5(2)$ Å^3, $D_{calc} = 1.273$ Mg/m^3, $Z = 4$. The reflections were measured on a *Bruker Nonius-KappaCCD* diffractometer (graphite monochromator, MoK_α radiation, λ 0.71073) at 298 K. $R = 0.0671$, $R_w = 0.1571$. All the calculations were performed using maXus [58]. The non-H-atoms were refined anisotropically with SHELXL-97 [59]. The H-atoms were calculated at idealized positions and included in the structure-factor calculation with fixed isotropic displacement parameters.

5-Amino-2,3-di-O-*benzyl-5-deoxy*-D-*galactono-1,5-lactam* (**22**). A soln. of **21** (2.5 g, 5.61 mmol) in CH_2Cl_2 (60 ml) and H_2O (0.7 ml) was treated with CF_3CO_2H (4.3 ml, 56.1 mmol) and stirred at 23° for 24 h. Normal workup ($NaHCO_3$-soln./AcOEt) and FC (AcOEt/cyclohexane 1:1 → AcOEt/MeOH 95:5) afforded **21** (500 mg, 20%) and **22** (1.5 g, 75%).

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[17]) Assignments based on HSQC-GRASP spectrum.

Table 3. *Selected* ^{13}*C-NMR Chemical Shifts* [ppm] *of the 1,5-Lactone* **17**, *the Amides* **18** *and* **19**, *the Protected 1,5-Lactams* **21** *and* **22**–**26**, *the Imide* **27**, *the Protected 1,4-Lactones* **51**–**53**, **57**–**59**, **61**, **63**, *and* **65**, *the Protected 1,5-Lactams* **54**, **60**, **28**, **67**, **55**, **30**, **29**, *and* **68** *in* $CDCl_3$, *and the Deprotected 1,5-Lactams* **8**–**11** *in* D_2O

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
17	170.62	76.53	77.20	75.84	69.06	70.50
18	174.92	78.03	78.61	77.56	63.02	72.84
21[a])	172.12	77.22	78.19	73.28	46.99	69.56
19	174.92	77.64	78.94	77.64	68.00	73.31
22	171.40	76.60	79.67	67.73	54.04	63.11
23	170.67	77.15	79.96	66.58	54.50	63.46
24	170.57	77.32	80.13	70.75	55.30	63.61
25	171.34	77.17	79.34	71.69	54.96	62.33
26	168.19	77.30	80.04	72.27	56.25	170.08
27	169.49	75.18[b])	75.65[b])	72.24	168.59	–
51	172.95[b])	77.35[c])	79.12	77.10[c])	68.69	171.76[b])
52	171.20	77.72[b])	79.08	76.54[b])	75.91[b])	164.08
53	172.65	77.01[b])	78.99	76.69[b])	61.87	167.07
57	171.70	79.06[b])	79.35[b])	78.42[b])	68.31	170.78
58	170.27	78.55[b])	79.07	78.14[b])	77.18[b])	163.39
59	171.34	78.72[b])	78.54[b])	78.43[b])	61.90	166.00
61	173.00	77.55	79.56	77.55	70.45	170.69
63	171.57	78.23	80.19	76.37	75.24	164.27
65	171.94	77.23	78.61	76.66	61.10	167.81
54	169.03[b])	76.45	77.89	68.65	58.95	168.55[b])
60	169.78[b])	75.57	77.05	66.80	56.67	169.11[b])
28	170.03	76.57	79.01	67.04	55.93	168.85
67	169.41	74.89	76.82	67.75	56.95	167.85
55	168.27[b])	76.55[d])	78.70	68.32	59.55	168.13[b])
30	169.48[b])	77.44[d])	79.00	66.82	57.28	168.86[b])
29	169.96	76.69	79.11[d])	67.34	56.12	167.57
68	168.26	76.11[d])	78.73	67.31	57.34	167.27
8	176.02	70.64[b])	73.68	70.54[b])	60.23	172.50
9	174.43	69.36[b])	72.40	68.92[b])	58.64	172.73
10	174.30	71.78[b])	74.89	70.62[b])	59.90	172.72
11	176.18	70.03[b])	70.13[b])	69.49[b])	61.68	173.54

[a]) Assignments based on HSQC-GRASP spectrum. [b]) Assignments may be interchanged. [c]) Assignments may be interchanged. [d]) Assignments may be interchanged with the *d* of Ph_2CH (**55**: 76.07, **30**: 75.68, **29**: 79.04, **68**: 74.36 ppm).

Data of **22**. Colourless solid. R_f (AcOEt) 0.16. M.p. 133–134°. $[\alpha]_D^{25} = +108.3$ ($c = 1.07$, $CHCl_3$). IR (KBr): 3418*m* (br.), 3190*m*, 3108*m*, 3029*m*, 2895*m*, 1676*s*, 1497*w*, 1471*w*, 1453*m*, 1421*m*, 1387*w*, 1352*m*, 1305*m*, 1212*w*, 1169*m*, 1108*s*, 1066*s*, 1050*m*, 1028*m*, 980*w*, 944*w*, 918*w*, 878*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.43–7.26 (*m*, 10 arom. H); 6.39 (br. *s*, exchange with D_2O, NH); 5.21 (*d*, $J = 11.2$, PhC*H*); 4.80 (*d*, $J = 11.2$, PhC*H*); 4.74 (*d*, $J = 11.5$, PhC*H*); 4.67 (*d*, $J = 11.8$, PhC*H*); 2.86 (br. *s*, exchange with D_2O, 2 OH). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 137.94, 137.41 (2*s*); 128.47 (2*d*); 128.26 (4*d*); 128.00 (*d*); 127.82 (2*d*); 127.69 (*d*); 75.46, 72.77 (2*t*, 2 Ph*C*H_2). HR-MALDI-MS: 380.1478 (100, $[M + Na]^+$, $C_{20}H_{23}NNaO_5^+$; calc. 380.1468).

5-Amino-2,3-di-O-*benzyl-6*-O-*[(*tert*-butyl)dimethylsilyl]-5-deoxy*-D-*galactono-1,5-lactam* (**23**). A soln. of **22** (600 mg, 1.68 mmol) in DMF (6 ml) was treated with Et_3N (0.47 ml, 3.36 mmol), DMAP

(41 mg, 0.34 mmol), and (*t*-Bu)Me_2SiCl (278 mg, 1.85 mmol), and stirred at 23° for 16 h. Normal workup ($NaHCO_3$-soln./AcOEt), followed by FC (AcOEt/cyclohexane 1:2), gave **23** (690 mg, 87%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.25. $[\alpha]_D^{25} = +84.0$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3448*s*, 3191*m*, 3090*m*, 3065*m*, 3032*w*, 2959*m*, 2927*m*, 2887*m*, 2857*m*, 1682*s*, 1648*m*, 1495*w*, 1470*m*, 1453*m*, 1416*m*, 1395*m*, 1355*m*, 1338*m*, 1318*m*, 1300*w*, 1262*m*, 1251*m*, 1231*w*, 1206*w*, 1176*w*, 1114*s*, 1095*s*, 1026*m*, 986*m*, 928*w*, 903*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.26–7.46 (*m*, 10 arom. H); 5.79 (br. *s*, exchange with D_2O, NH); 5.26 (*d*, $J = 11.2$, PhC*H*); 4.82 (*d*, $J = 11.2$, PhC*H*); 4.77 (*d*, $J = 11.5$, PhC*H*); 4.68 (*d*, $J = 11.5$, PhC*H*); 2.43 (*t*, $J = 1.3$, exchange with D_2O, HO–C(4)); 0.89 (*s*, *t*-Bu); 0.08, 0.07 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.13, 137.52 (2*s*); 128.40 (2*d*); 128.21 (2*d*); 128.18 (2*d*); 127.91 (*d*); 127.89 (2*d*); 127.56 (*d*); 75.41, 72.75 (2*t*, 2 Ph*C*H_2); 25.92 (*q*, *Me*$_3$C); 18.30 (*s*, Me_3C); −5.29 (*q*, Me_2Si). HR-MALDI-MS: 494.2347 (100, $[M+Na]^+$, $C_{26}H_{37}NNaO_5Si^+$; calc. 494.2374). Anal. calc. for $C_{26}H_{37}NO_5Si$ (471.66): C 66.21, H 7.91, N 2.97; found: C 66.44, H 7.67, N 2.92.

5-Amino-2,3-di-O-*benzyl-6*-O-*[(*tert*-butyl)dimethylsilyl]-5-deoxy-4*-O-*(methoxymethyl)*-D-*galactono-1,5-lactam* (**24**). A soln. of **23** (1.2 g, 2.32 mmol) in $ClCH_2CH_2Cl$ (25 ml) was cooled to 0°, treated with ^{i}Pr_2NEt (2.4 ml, 13.92 mmol), Bu_4NI (171 mg, 0.46 mmol), 4-pyrrolidinopyridine (69 mg, 0.46 mmol), and MOMCl (0.53 ml, 6.96 mmol), and kept at 80° for 16 h. The soln. was cooled to 23°, diluted with CH_2Cl_2 (25 ml), and washed with $NaHCO_3$ soln. Drying (Na_2SO_4), filtration, and FC (AcOEt/cyclohexane 1:2) afforded **24** (1.1 g, 85%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.36. $[\alpha]_D^{25} = +64.4$ ($c = 1.07$, $CHCl_3$). IR ($CHCl_3$): 3391*w*, 3032*w*, 3008*w*, 2955*m*, 2931*m*, 2859*w*, 1673*s*, 1602*w*, 1497*w*, 1362*w*, 1311*w*, 1259*w*, 1224*m*, 1153*m*, 1108*s*, 1027*m*, 916*w*, 840*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.45–7.26 (*m*, 10 arom. H); 5.86 (br. *s*, NH); 5.23 (*d*, $J = 11.2$, PhC*H*); 4.93 (*d*, $J = 6.8$, OCHO); 4.81 (*d*, $J = 11.2$, PhC*H*); 4.70 (*s*, Ph*C*H_2); 4.61 (*d*, $J = 6.8$, OCHO); 3.36 (*s*, MeO); 0.89 (*s*, *t*-Bu); 0.07, 0.06 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.18, 137.75 (2*s*); 128.29 (2*d*); 128.16 (2*d*); 128.14 (2*d*); 127.64 (*d*); 127.56 (2*d*); 127.48 (*d*); 97.35 (*t*, OCH_2O); 75.33, 72.60 (2*t*, 2 Ph*C*H_2); 56.26 (*q*, MeO); 25.92 (*q*, *Me*$_3$C); 18.32 (*s*, Me_3C); −5.27 (*q*, Me_2Si). HR-MALDI-MS: 538.2591 (100, $[M+Na]^+$, $C_{28}H_{41}NNaO_6Si^+$; calc. 538.2595). Anal. calc. for $C_{28}H_{41}NO_6Si$ (515.71): C 65.21, H 8.01, N 2.72; found: C 65.25, H 8.04, N 2.53.

5-Amino-2,3-di-O-*benzyl-5-deoxy-4*-O-*(methoxymethyl)*-D-*galactono-1,5-lactam* (**25**). A soln. of **24** (1.1 g, 2.13 mmol) in CH_2Cl_2 (10 ml) was treated with 1M soln. of $Bu_4NF \cdot 3\,H_2O$ in THF (4.3 ml, 4.3 mmol) and stirred at 23° for 1 h. Normal workup ($NaHCO_3$-soln./CH_2Cl_2) and FC (AcOEt/cyclohexane 2:1 → AcOEt) gave **25** (0.79 g, 92%). Oil. R_f (AcOEt) 0.24. $[\alpha]_D^{25} = +57.0$ ($c = 0.90$, $CHCl_3$). IR ($CHCl_3$): 3389*m*, 3033*w*, 3010*m*, 2894*w*, 1677*s*, 1602*w*, 1497*w*, 1454*m*, 1359*w*, 1294*w*, 1110*s*, 1065*m*, 1029*s*, 915*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.45–7.26 (*m*, 10 arom. H); 6.64 (br. *s*, exchange with CD_3OD, NH); 5.20 (*d*, $J = 11.2$, PhC*H*); 4.92 (*d*, $J = 6.8$, OCHO); 4.79 (*d*, $J = 10.9$, PhC*H*); 4.73 (*d*, $J = 11.8$, PhC*H*); 4.68 (*d*, $J = 11.5$, PhC*H*); 467 (*d*, $J = 6.8$, OCHO); 3.40 (*s*, MeO); 3.25 (br. *s*, exchange with CD_3OD, HO–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.00, 137.64 (2*s*); 128.33 (2*d*); 128.17 (4*d*); 127.72 (*d*); 127.57 (3*d*); 97.91 (*t*, OCH_2O); 75.52, 72.80 (2*t*, 2 Ph*C*H_2); 56.36 (*q*, MeO). HR-MALDI-MS: 424.1730 (100, $[M+Na]^+$; $C_{22}H_{27}NNaO_6^+$; calc. 424.1731). Anal. calc. for $C_{22}H_{27}NO_6$ (401.45): C 65.82, H 6.78, N 3.49; found: C 65.80, H 6.88, N 3.73.

Preparation of Methyl Galactarate **26**. A soln. of **25** (120 mg, 0.3 mmol) in acetone (5 ml) was cooled to 0°, treated with a soln. of CrO_3 (100 mg, 0.9 mmol) in 1M H_2SO_4 (0.1 ml), warmed to 10°, and stirred for 4 h. The mixture was diluted with AcOEt (20 ml), washed with $NaHCO_3$ soln., dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:1) gave decarboxylation product **27** (12 mg, 11%) and **25** (10 mg, 8%). The aq. layer was acidified by slow addition of conc. H_2SO_4 and extracted with CH_2Cl_2 (2 × 20 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated to afford the free acid (75 mg, 61%). A soln. of the free acid in toluene/MeOH 6:1 (5 ml) was cooled to 0°, treated with 1M soln. of Me_3SiCHN_2 in hexane (60 µl), and stirred at 23° for 30 min. Normal workup (H_2O/AcOEt) and FC (AcOEt/cyclohexane 1:1) afforded **26** (77 mg, 60%).

Data of 2,3-Di-O-*benzyl-3*-O-*(methoxymethyl)*-L-*arabinarimide* (**27**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.54. IR ($CHCl_3$): 3365*w*, 3090*w*, 3068*w*, 3030*m*, 3014*m*, 2934*w*, 2903*w*, 1745*s*, 1718*s*, 1603*w*, 1497*w*, 1455*m*, 1396*m*, 1341*w*, 1310*m*, 1227*m*, 1205*m*, 1154*m*, 1121*m*, 1075*s*, 1056*s*, 1015*m*, 912*w*, 821*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 8.03 (br. *s*, exchange with D_2O, NH); 7.38–7.22 (*m*, 10 arom. H); 4.94 (*d*, $J = 6.5$, OCHO); 4.83 (*d*, $J = 12.1$, PhC*H*); 4.80 (*d*, $J = 6.8$, OCHO); 4.74 (*d*,

J = 12.1, PhC*H*); 4.63 (*d*, J = 12.1, PhC*H*); 4.61 (*d*, J = 11.8, PhC*H*); 3.42 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3* additionally, 136.88, 136.19 (2*s*); 128.48 (2*d*); 128.34 (2*d*); 128.22 (*d*); 128.12 (2*d*); 127.97 (*d*); 127.77 (2*d*); 96.64 (*t*, OCH_2O); 73.36, 73.14 (2*t*, 2 Ph*C*H_2); 56.10 (*q*, MeO). HR-MALDI-MS: 408.1423 (100, $[M+Na]^+$, $C_{21}H_{23}NNaO_6^+$; calc. 408.1418).

Data of 6-Methyl 5-Amino-2,3-di-O-*benzyl-5-deoxy-4*-O-*(methoxymethyl)*-D-*galactarate-1,5-lactam* (**26**). Colourless solid. R_f (AcOEt/cyclohexane 2:1) 0.42. $[\alpha]_D^{25} = +77.0$ (c = 1.02, $CHCl_3$). M.p. 126–127°. IR (KBr): 3309*s*, 3134*w*, 3064*w*, 3029*m*, 2994*w*, 2959*m,* 2929*m*, 2909*m*, 2861*m*, 2822*w*, 1751*s*, 1681*s*, 1664*s*, 1607*w*, 1585*w*, 1493*m*, 1474*m*, 1451*m*, 1409*m*, 1377*m*, 1363*m*, 1349*m*, 1316*m*, 1290*m*, 1268*m*, 1257*m*, 1227*s*, 1175*m*, 1146*s*, 1126*s*, 1109*s*, 1087*s*, 1056*m*, 1024*s*, 993*m*, 965*m*, 921*m*, 902*m*, 887*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.45–7.26 (*m*, 10 arom. H); 6.06 (br. *s*, NH); 5.25 (*d*, J = 11.2, PhC*H*); 4.89 (*d*, J = 6.8, OCHO); 4.83 (*d*, J = 10.9, PhC*H*); 4.76 (*d*, J = 11.8, PhC*H*); 4.70 (*d*, J = 11.5, PhC*H*); 4.63 (*d*, J = 6.8, OCHO); 3.84, 3.27 (2*s*, 2 MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3* additionally, 137.93, 137.45 (2*s*); 128.32 (2*d*); 128.25 (2*d*); 128.16 (2*d*); 127.74 (*d*); 127.59 (3*d*); 97.32 (*t*, OCH_2O); 75.60, 72.45 (2*t*, 2 Ph*C*H_2); 56.34 (*q*, MeO); 52.94 (*q*, MeO). HR-MALDI-MS: 452.1686 (100, $[M+Na]^+$, $C_{23}H_{27}NNaO_7^+$; calc. 452.1680). Anal. calc. for $C_{23}H_{27}NO_7$ (429.46): C 64.32, H 6.34, N 3.26; found: C 64.27, H 6.28, N 3.21.

6-Methyl 5-Amino-2,3-di-O-*benzyl-5-deoxy*-D-*galactarate-1,5-lactam* (**28**). A soln. of **26** (100 mg, 0.26 mmol) in MeCN (6 ml) was cooled to −19°, treated with Tf_2O (50 µl, 0.28 mmol), and stirred for 1 h. Normal workup (AcOEt/$NaHCO_3$-soln.) and FC (AcOEt/cyclohexane 1:1) afforded **28** (89 mg, 96%). Oil. R_f (AcOEt/cyclohexane 2:1) 0.21. $[\alpha]_D^{25} = +96.7$ (c = 0.68, $CHCl_3$). IR (CH_2Cl_2): 3576*w* (br.), 3389*w*, 3059*w*, 2985*w*, 2957*w*, 1752*s*, 1687*s*, 1605*w*, 1497*w*, 1455*w*, 1439*w*, 1421*w*, 1374*w*, 1335*w*, 1232*s*, 1174*w*, 1107*m*, 1076*m*, 1046*w*, 1028*w*, 956*w*, 896*w*, 841*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.43–7.29 (*m*, 10 arom. H); 6.09 (br. *s*, exchange with CD_3OD, NH); 5.19 (*d*, J = 11.2, PhC*H*); 4.79 (*d*, J = 11.2, PhC*H*); 4.73 (*d*, J = 11.5, PhC*H*); 4.68 (*d*, J = 11.5, PhC*H*); 3.80 (*s*, MeO); 2.80 (br. *d*, J = 2.8, exchange with CD_3OD, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3* additionally, 137.74, 137.18 (2*s*); 128.40 (2*d*); 128.24 (4*d*); 127.96 (*d*); 127.80 (2*d*); 127.72 (*d*); 75.23, 72.69 (2*t*, 2 Ph*C*H_2); 53.10 (*q*, MeO). HR-MALDI-MS: 408.1420 (100, $[M+Na]^+$, $C_{21}H_{23}NNaO_6^+$; calc. 408.1418). Anal. calc. for $C_{21}H_{23}NO_6$ (385.41): C 65.44, H 6.01, N 3.63; found: C 65.50, H 6.22, N 3.56.

Preparation of **29** *and* **30**. a) *From* **28**. A soln. of **28** (89 mg, 0.23 mmol) in MeOH/H_2O 1:1 (4 ml) was cooled to 0°, treated with $LiOH \cdot H_2O$ (10 mg, 0.23 mmol), and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (25 ml) and washed with ice-cold 1M HCl. The aq. layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. A soln. of the residue in acetone (6 ml) was treated dropwise with a soln. of Ph_2CN_2 (58 mg, 0.3 mmol) in acetone (2 ml) in portions, stirred for 4 h, and evaporated at 30°. FC (AcOEt/cyclohexane 1:4), followed by crystallization (AcOEt/hexane) of separated products, afforded **29** (103 mg, 83%) and **30** (12 mg, 10%).

b) *From* **60**. The lactam **60** (75 mg, 0.19 mmol) was transformed into **30** (85 mg, 84%) and **29** (12 mg, 12%) similarly as described for the preparation of **29**.

Data of 6-Diphenylmethyl 5-Amino-2,3-di-O-*benzyl-5-deoxy*-D-*galactarate-1,5-lactam* (**29**). Colourless solid. R_f (AcOEt/cyclohexane 1:1) 0.56. M.p. 105–107°. $[\alpha]_D^{25} = +72.7$ (c = 1.04, $CHCl_3$). IR (ATR): 3443*w*, 3310*w*, 3269*w*, 3062*w*, 3034*w*, 2900*w*, 1953*w*, 1757*m*, 1675*s*, 1601*w*, 1585*w*, 1496*m*, 1453*m*, 1400*w*, 1364*m*, 1333*w*, 1312*w*, 1221*s*, 1175*m*, 1146*m*, 1110*s*, 1079*m*, 1027*m*, 993*m*, 967*m*, 930*w*, 876*w*, 840*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.43–7.29 (*m*, 20 arom. H); 6.96 (*s*, Ph_2CH); 6.24 (br. *s*, exchange with CD_3OD, NH); 5.19 (*d*, J = 11.2, PhC*H*); 4.78 (*d*, J = 11.2, PhC*H*); 4.73 (*d*, J = 11.8, PhC*H*); 4.62 (*d*, J = 11.5, PhC*H*); 2.99 (br. *s*, exchange with CD_3OD, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.93, 138.85, 137.77, 137.36 (4*s*); 128.59–127.02 (several *d*); 79.04 (*d*, Ph_2CH); 75.27, 72.94 (2*t*, 2 Ph*C*H_2). ESI-MS: 538.2 (100, $[M+H]^+$). Anal. calc. for $C_{33}H_{31}NO_6$ (537.21): C 73.73, H 5.81, N 2.61; found: C 73.66, H 6.04, N 2.62.

Data of 6-Diphenylmethyl 5-Amino-2,3-di-O-*benzyl-5-deoxy*-L-*altrarate-1,5-lactam* (**30**). Colourless solid. R_f (AcOEt/cyclohexane 1:1) 0.31. M.p. 138–140°. $[\alpha]_D^{25} = +57.1$ (c = 1.03, $CHCl_3$). IR (KBr): 3329*m* (br.), 3087*w*, 3064*m*, 3029*m*, 2931*w*, 2883*w*, 2848*w*, 1960*w*, 1883*w*, 1811*w*, 1737*s*, 1664*s*, 1585*w*, 1496*m*, 1452*m*, 1426*w*, 1396*w*, 1367*w*, 1326*m*, 1295*w*, 1260*m*, 1193*s*, 1180*s*, 1157*m*, 1125*s*, 1088*m*, 1070*s*, 1027*w*, 1003*w*, 984*w*, 943*s*, 907*w*, 880*w*, 845*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.36–7.28 (*m*, 18 arom. H); 7.27–7.20 (*m*, 2 arom. H); 6.93 (*s*, Ph_2CH); 6.17 (br. *s*, exchange with

Table 4. *Selected* ^{1}*H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Protected 1,5-Lactams* **54**, **60**, **28**, **67**, **55**, **30**, **29**, *and* **68** *in* $CDCl_3$ *and the Deprotected 1,5-Lactams* **56**, **32**, **31**, **69**, *and* **8**–**11** *in* D_2O

	54	**60**	**28**	**67**	**55**	**30**	**29**	**68**
H–C(2)	4.00	4.02	4.18	3.94	3.93	4.07	4.21	3.97–3.95
H–C(3)	3.86	3.89	3.86	3.90	3.80	3.76	3.84	3.97–3.95
H–C(4)	4.37	4.43	4.59	4.39	4.42	4.45	4.63	4.50–4.45
H–C(5)	4.21–4.05	4.22	4.11	4.37	4.25	4.25	4.09	4.45
J(2,3)	5.3	5.6	7.8	4.4	4.2	6.2	8.1	[a])
J(3,4)	5.4	2.5	2.5	3.4	5.2	2.5	2.5	[a])
J(4,5)	5.4	6.8	2.8	2.8	4.4	5.9	2.8	3.1
	56	**32**	**31**	**69**	**8**	**9**	**10**	**11**
H–C(2)	4.03	4.23	4.23	4.05	4.01	4.19	4.04	4.18
H–C(3)	3.74	3.81	3.99	3.80	3.71	3.99	3.81	3.78
H–C(4)	3.89	4.48	4.55	4.15	3.84	4.55	4.15	4.39
H–C(5)	3.82	4.26	4.42	4.09	3.74	4.42	4.08	3.98
J(2,3)	9.3	9.7	9.9	7.8	9.3	9.9	7.8	9.6
J(3,4)	8.4	2.5	2.7	5.4	9.0	2.7	5.3	2.8
J(4,5)	7.8	2.8	2.7	4.5	8.1	2.7	4.0	2.5

[a]) Not assigned.

CD_3OD, NH); 5.00 (*d*, *J* = 11.5, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.57 (*d*, *J* = 11.5, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 3.17 (*d*, *J* = 3.7, irradiation at 4.45 → br. *s*, exchange with CD_3OD, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 138.91, 138.69, 137.59, 137.27 (4*s*); 128.71–126.97 (several *d*); 75.68 (*d*, Ph_2CH); 74.08, 73.21 (2*t*, 2 PhCH_2). HR-MALDI-MS: 560.2037 (100, $[M+Na]^+$, $C_{33}H_{31}NNaO_6^+$; calc. 560.2044). Anal. calc. for $C_{33}H_{31}NO_6$ (537.21): C 73.73, H 5.81, N 2.61; found: C 73.70, H 5.96, N 2.56.

Hydrogenolysis of **29**. A suspension of **29** (46 mg, 0.086 mmol) and 10% Pd/C (15 mg) in MeOH/H_2O 2 : 1 (3 ml) was hydrogenated (6 bar) for 48 h. The mixture was filtered through *Celite*, and the filtrate was evaporated. A soln. of the residue in H_2O (10 ml) was washed with AcOEt (4×) and lyophilized to afford **31** (16 mg, 98%). A soln. of **31** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **9** (18 mg, 98%).

Data of 6-Hydrogen 5-Amino-5-deoxy-D-*galactaro-1,5-lactam* (**31**). M.p. 192–194°. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*.

Data of 6-Sodium 5-Amino-5-deoxy-D-*galactarate-1,5-lactam* (**9**). $[\alpha]_D^{25} = +14.1$ ($c = 0.79$, H_2O). IR (KBr): 3418*s* (br.), 2918*w*, 1655*s*, 1613*s*, 1398*m*, 1305*m*, 1160*w*, 1121*m*, 1096*m*, 1055*m*, 976*w*, 921*w*, 882*w*, 859*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*. ^{13}C-NMR (75 MHz, D_2O): see *Table 3*. ESI-MS (neg. mode): 190.2 (100, $[M-Na]^-$). Anal. calc. for $C_6H_8NNaO_6 \cdot 1.2\,H_2O$ (234.64): C 30.70, H 4.47, N 5.97; found: C 30.43, H 4.07, N 5.72.

Hydrogenolysis of **30**. The lactam **30** (40 mg, 0.074 mmol) was transformed into **32** (14 mg, 98%) similarly as described for the preparation of **31**. A soln. of **32** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **11** (16 mg, 98%).

Data of 6-Hydrogen 5-Amino-5-deoxy-L-*altraro-1,5-lactam* (**32**). ^{1}H-NMR (300 MHz, D_2O): see *Table 4*.

Data of 6-Sodium 5-Amino-5-deoxy-L-*altrarate-1,5-lactam* (**11**). M.p. 213–215°. $[\alpha]_D^{25} = +8.6$ ($c = 0.48$, H_2O). IR (KBr): 3424*s* (br.), 2926*w*, 2853*w*, 1666*s*, 1608*s*, 1473*w*, 1397*m*, 1322*m*, 1148*m*, 1112*m*, 1095*m*, 1058*m*, 970*w*, 929*w*, 886*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*. ^{13}C-NMR (75 MHz, D_2O): see *Table 3*. HR-MALDI-MS: 662.0660 (86, $[3M+Na]^+$, $C_{18}H_{24}N_3Na_4O_{18}^+$; calc. 662.0640),

449.0401 (25, $[2M+Na]^+$, $C_{12}H_{16}N_2Na_3O_{12}^+$; calc. 449.0391), 405.0752 (100, $[2M+2H-Na]^+$, $C_{12}H_{18}N_2NaO_{12}^+$; calc. 405.0752), 236.0140 (82, $[M+Na]^+$, $C_6H_8NNa_2O_6^+$; calc. 236.0142). Anal. calc. for $C_6H_8NNaO_6\cdot 1.3\ H_2O$ (236.44): C 30.47, H 4.52, N 5.92; found: C 30.33, H 4.66, N 5.75.

*3,4-Di-*O*-benzyl-*L*-threurono-4,1-lactam* (**36**). A soln. of **37** (1.0 g, 3.21 mmol) in MeOH/CH_2Cl_2 2:1 (24 ml) was cooled to −78°, treated with $NaBH_4$ (120 mg, 3.21 mmol), stirred for 1 h, and warmed to 0° over 3 h. The mixture was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:1) afforded **37** (120 mg, 12%) and **36** (680 mg, 68%). Oil. R_f (AcOEt/cyclohexane 2:1) 0.19. $[\alpha]_D^{25}=+68.4$ ($c=1.22$, $CHCl_3$). IR (ATR): 3279*m* (br.), 3087*w*, 3031*w*, 2994*w*, 1951*w,* 1876*w*, 1811*w*, 1703*s*, 1605*s*, 1585*w*, 1496*m*, 1453*m*, 1395*w*, 1356*m*, 1309*m*, 1267*m*, 1208*m*, 1107*s* (br.), 1055*s*, 1027*s*, 912*m*. ^{1}H-NMR (300 MHz, $CDCl_3$) (major/minor 70:30): 7.52 (br. *s*, exchange with CD_3OD, 0.7 H, NH); 7.39–7.24 (*m*, 10 arom. H); 4.96–5.01 (*m*, addition of CD_3OD → 5.00 *dd*, $J=5.0$, 1.2, 0.3 H, H−C(5), and 4.97 *d*, $J=3.1$, 0.7 H, H−C(5)); 4.96 (*d*, $J=10.3$, 0.3 H), 4.87 (*d*, $J=11.5$, 0.7 H), 4.75 (*d*, $J=12.8$, 0.3 H), 4.71 (*d*, $J=11.8$, 0.7 H), 4.64 (*d*, $J=11.8$), 4.55 (*d*, $J=11.8$, 0.3 H), 4.51 (*d*, $J=11.8$, 0.7 H) (2 PhCH_2); 4.32 (*d*, $J=7.2$, 0.3 H), 4.09 (*d*, $J=5.6$, irradiation at 3.98 → *s*, 0.7 H) (H−C(3)); 4.03 (*dd*, $J=7.2$, 5.0, 0.3 H), 3.98 (*dd*, $J=5.6$, 3.1, irradiation at 4.09 → *s*, 0.7 H) (H−C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): signals of major isomer: 172.38 (*s*, C=O); 137.18 (*s*); 136.90 (*s*); 128.51–127.75 (several *d*); 86.91 (*d*, C(5)); 81.58 (*d*, C(4)); 79.77 (*d*, C(3)); 72.81, 72.21 (2*t*, 2 Ph*C*H_2). ESI-MS: 649.2 (48, $[2M+Na]^+$), 336.2 (100, $[M+Na]^+$), 314.3 (90, $[M+H]^+$). Anal. calc. for $C_{18}H_{19}NO_4$ (313.13): C 69.00, H 6.11, N 4.47; found: C 68.70, H 6.01, N 4.59.

*6-Ethyl 4-Amino-2,3-di-*O*-benzyl-4,5-dideoxy-*L*-arabinarate-1,4-lactam* (**38**). A suspension of NaH (60% dispersion in oil, 128 mg, 3.19 mmol) in THF (10 ml) was cooled to 0°, treated with triethylphosphono acetate (0.7 ml, 3.35 mmol), stirred for 10 min, treated with a soln. of **36** (500 mg, 1.59 mmol) in THF (10 ml), and stirred at 23° for 24 h. The mixture was cooled to 0° and treated with 1M HCl (4 ml). Normal workup (H_2O/AcOEt), followed by FC (AcOEt/cyclohexane 1:2), afforded **38** (450 mg, 74%). Colourless solid. R_f (AcOEt/cyclohexane 2:1) 0.57. M.p. 72–73°. $[\alpha]_D^{25}=-0.7$ ($c=1.02$, $CHCl_3$). IR (KBr): 3205*w* (br.), 3110*w*, 2878*w*, 1956*w,* 1877*w*, 1724*s*, 1498*w*, 1455*w*, 1398*w*, 1376*w*, 1349*w*, 1335*m*, 1285*w*, 1264*w*, 1244*m*, 1208*m*, 1183*m*, 1151*m*, 1109*m*, 1065*w*, 987*w*, 913*w*, 861*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.43–7.23 (*m*, 10 arom. H); 6.14 (br. *s*, NH); 5.15 (*d*, $J=11.5$, PhC*H*); 4.80 (*d*, $J=11.5$, PhC*H*); 4.66 (*d*, $J=11.5$, PhC*H*); 4.52 (*d*, $J=11.5$, PhC*H*); 4.17 (*d*, $J=6.2$, H−C(2)); 4.15 (*q*, $J=7.2$, MeCH_2O); 3.82 (*t*, $J=5.9$, H−C(3)); 3.73 (*ddd*, $J=10.6$, 5.9, 3.1, H−C(4)); 2.76 (*dd*, $J=16.8$, 2.8, H−C(5)); 2.37 (*dd*, $J=16.8$, 10.6, H′−C(5)); 1.26 (*t*, $J=7.2$, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.66, 170.87 (2*s*, 2 C=O); 137.34, 137.15 (2*s*); 128.39–127.79 (several *d*); 83.49 (*d*, C(3)); 80.18 (*d*, C(2)); 72.65, 72.24 (2*t*, 2 Ph*C*H_2); 61.18 (*t*, Me*C*H_2O); 52.59 (*d*, C(4)); 38.87 (*t*, C(5)); 14.34 (*q*, *Me*CH_2O). HR-MALDI-MS: 406.1620 (100, $[M+Na]^+$, $C_{22}H_{25}NNaO_5^+$; calc. 406.1625). Anal. calc. for $C_{22}H_{25}NO_5$ (383.17): C 68.91, H 6.57, N 3.65; found: C 68.96, H 6.60, N 3.62.

*6-Ethyl 4-Amino-4,5-dideoxy-*L*-arabinarate-1,4-lactam* (**39**). A suspension of **38** (100 mg, 0.26 mmol) and 10% Pd/C (15 mg) in MeOH/AcOH 1:1 (6 ml) was hydrogenated at 6 bar for 24 h, filtered through *Celite*, and evaporated to afford **39** (52 mg, 99%). Solid. R_f (AcOEt/MeOH 4:1) 0.32. M.p. 112–114°. $[\alpha]_D^{25}=-29.7$ ($c=1.05$, $CHCl_3$). IR (KBr): 3499*w*, 3318*m* (br.), 3269*m* (br.), 2981*w*, 2917*w*, 2872*w*, 1692*s*, 1443*w*, 1399*m*, 1370*m*, 1342*m*, 1280*w*, 1235*m*, 1215*s*, 1186*m*, 1142*s*, 1089*s*, 1012*m*, 926*w*, 856*w*. ^{1}H-NMR (300 MHz, CD_3OD): 4.16 (*q*, $J=7.1$, MeCH_2O); 4.09 (*d*, $J=7.7$, H−C(2)); 3.78 (*t*, $J=7.3$, H−C(3)); 3.60 (*ddd*, $J=8.8$, 6.9, 4.1, H−C(4)); 2.80 (*dd*, $J=16.5$, 3.9, H−C(5)); 2.48 (*dd*, $J=16.5$, 8.8, H′−C(5)); 1.26 (*t*, $J=7.1$, *Me*CH_2O). ^{13}C-NMR (75 MHz, CD_3OD): 175.09, 171.42 (2*s*, 2 C=O); 79.04 (*d*, C(3)); 75.72 (*d*, C(2)); 60.82 (*t*, Me*C*H_2O); 53.85 (*d*, C(4)); 37.75 (*t*, C(5)); 13.28 (*q*, *Me*CH_2O). ESI-MS: 429.3 (15, $[2M+Na]^+$), 226.3 (100, $[M+Na]^+$). Anal. calc. for $C_8H_{13}NO_5$ (203.08): C 47.29, H 6.45, N 6.89; found: C 47.02, H 6.23, N 6.70.

*4-Amino-4,5-dideoxy-*L*-arabinaro-1,4-lactam* (**40**). A soln. of **39** (50 mg, 0.25 mmol) in EtOH/H_2O 1:1 (6 ml) was treated with LiOH·H_2O (10.6 mg, 0.253 mmol) and stirred for 1 h. The mixture was filtered through a column of *Dowex 50 W X2* (H^+ form). The filtrate was lyophilised to afford **40** (42 mg, 98%). Colourless powder. M.p. 222–224°. $[\alpha]_D^{25}=-34.3$ ($c=0.98$, H_2O). p$K_{HA}=4.2$. IR (KBr): 3410*w* (br.), 3247*m*, 3072*m* (br.), 2949*w*, 2923*w*, 2852*w*, 1726*s*, 1690*s*, 1453*w*, 1400*w*, 1349*w*, 1326*w*, 1272*w*, 1233*m*, 1217*w*, 1187*m*, 1139*m*, 1098*w*, 1081*w*, 937*w*. ^{1}H-NMR (300 MHz, D_2O): 4.33 (*d*, $J=8.1$,

H–C(2)); 3.95 (*t*, $J \approx 7.6$, H–C(3)); 3.73 (*ddd*, $J = 9.7, 7.5, 4.0$, H–C(4)); 2.89 (*dd*, $J = 16.8, 3.7$, H–C(5)); 2.63 (*dd*, $J = 16.8, 8.7$, H–C(5′)). ^{13}C-NMR (75 MHz, D_2O): 175.43, 175.01 (2*s*, 2 C=O); 78.44 (*d*, C(2)); 75.07 (*d*, C(3)); 53.22 (*d*, C(4)); 37.34 (*t*, C(5)). ESI-MS (neg. mode): 174.2 (100, $[M-H]^-$).

Preparation of **46**. *a*) A soln. of **41** (20 g, 64 mmol) in MeOH (200 ml) was stirred for 15 h, evaporated, co-evaporated with CH_2Cl_2 (2×), and dried under vacuum. A soln. of the crude (**42**) in THF (200 ml) was cooled to −15°, treated with $^iPr_2NEt$ (12.3 ml, 70.4 mmol), stirred for 10 min, treated with MeOCOCl (6.7 ml, 70.4 mmol), and warmed to 0° over 2 h. The white turbid soln. was treated with $NaBH_4$ (7.3 g, 192 mmol) in one portion and MeOH (200 ml) over 30 min, and stirred at 0° for 3 h. 1M HCl (200 ml) was added slowly (pH 2) until the mixture turned to a clear soln. Normal workup (H_2O/AcOEt) gave crude **43**. A soln. of crude **43** in CH_2Cl_2 was cooled to −70°, treated with trichloroisocyanuric acid (7.4 g, 32 mmol) and a soln. of TEMPO (300 mg, 1.92 mmol) in CH_2Cl_2 (150 ml), allowed to warm to −10°, stirred for 2 h, and filtered through *Celite*. The filtrate was washed with 1M HCl and brine, dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) afforded **45** (2.4 g, 12%), **44** (4.1 g, 18%), **46** (7.4 g, 35%)[18]), and **42** (5.0 g, 25%).

b) The mixed anhydride generated from **42** (1.0 g, 3.2 mmol) as described above was treated with 0.69M $Zn(BH_4)_2$ in Et_2O (9.2 ml) at 0°, stirred for 2 h, and treated with 1M HCl (10 ml). Normal workup (H_2O/AcOEt) and FC (AcOEt/cyclohexane 1:4) afforded **43**, which was converted to **45** (67 mg, 7%), **46** (630 mg, 60%), and **42** (200 mg, 20%) as described above.

*Data of 2,3-Di-*O*-benzyl-*L*-threono-1,4-lactone* (**45**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.58. $[\alpha]_D^{25} = +60.1$ ($c = 1.18$, $CHCl_3$). IR ($CHCl_3$): 3090*m*, 3068*m*, 3038*m*, 3007*m*, 2913*m*, 2873*m*, 1953*w*, 1793*s*, 1604*w*, 1587*w*, 1497*m*, 1479*m*, 1455*s*, 1371*m*, 1338*s*, 1310*m*, 1262*m*, 1178*s*, 1104*s*, 1027*s*, 913*m*, 889*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.47–7.26 (*m*, 10 arom. H); 5.05 (*d*, $J = 11.5$, PhC*H*); 4.80 (*d*, $J = 11.8$, PhC*H*); 4.65 (*d*, $J = 11.8$, PhC*H*); 4.55 (*d*, $J = 11.8$, PhC*H*); 4.41 (*dd*, $J = 8.8, 6.6$, H–C(4)); 4.34 (*q*, $J \approx 6.1$, H–C(3)); 4.25 (*d*, $J = 5.8$, H–C(2)); 4.07 (*dd*, $J = 8.8, 5.6$, H′–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.12 (*s*, C=O); 136.95, 136.69 (2*s*); 128.09 (2*d*); 128.54 (2*d*); 128.34 (2*d*); 128.22 (*d*); 128.19 (*d*); 127.83 (2*d*); 78.32 (*d*, C(3)); 77.38 (*d*, C(2)); 72.40, 72.15 (2*t*, 2 PhCH_2); 68.98 (*t*, C(4)).

*Data of 4-Methyl 2,3-Di-*O*-benzyl-*L*-threuronate* (**46**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.33. IR ($CHCl_3$): 3066*w*, 3034*w*, 2954*w*, 1757*s*, 1736*s*, 1605*w*, 1497*w*, 1455*m*, 1210*s*, 1099*s*, 1027*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.62 (*d*, $J = 1.2$, CHO); 7.33–7.25 (*m*, 10 arom. H); 4.80 (*d*, $J = 11.5$, PhC*H*); 4.75 (*d*, $J = 12.1$, PhC*H*); 4.60 (*d*, $J = 12.1$, PhC*H*); 4.42 (*d*, $J = 11.5$, PhC*H*); 4.36 (*d*, $J = 3.4$, H–C(2)); 4.13 (*dd*, $J = 3.4, 1.2$, H–C(3)); 3.71 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 201.22 (*s*, C(1)); 169.46 (*s*, C(4)); 136.33, 136.25 (2*s*); 128.44 (2*d*); 128.37 (2*d*); 128.31 (2*d*); 128.26 (3*d*); 128.09 (*d*); 82.83 (*d*, C(3)); 77.76 (*d*, C(2)); 73.63, 73.37 (2*t*, 2 PhCH_2); 52.30 (*q*, MeO). HR-MALDI-MS: 367.1159 (42, $[M+K]^+$, $C_{19}H_{20}KO_5^+$; calc. 367.0942); 351.1207 (100, $[M+Na]^+$, $C_{19}H_{20}NaO_5^+$; calc. 351.1203).

*1-Ethyl 6-Methyl (*E*)-4,5-Di-*O*-benzyl-2,3-dideoxy-*L*-*threo*-hex-2-enarate* (**47**). A suspension of NaH (60% suspension in oil, 200 mg, 5.02 mmol) in THF (20 ml) was cooled to 0°, treated with triethyl phosphonoacetate (1.1 ml, 5.48 mmol), stirred for 10 min, treated with a soln. of **46** (1.50 g, 4.57 mmol) in THF (20 ml), and stirred for 1 h. The mixture was treated with 1M HCl (5.5 ml) and extracted with AcOEt (2×50 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:5) afforded **47** (1.45 g, 80%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.56. $[\alpha]_D^{25} = +77.5$ ($c = 1.09$, $CHCl_3$). IR ($CHCl_3$): 3090*w*, 3067*w*, 3031*m*, 2955*m*, 2905*w*, 2875*w*, 1952*w*, 1879*w*, 1753*s*, 1717*s*, 1660*w*, 1604*w*, 1497*w*, 1455*m*, 1437*m*, 1394*w*, 1369*m*, 1345*m*, 1304*s*, 1279*s*, 1202*s*, 1181*s*, 1101*s*, 1072*m*, 1041*s*, 1028*s*, 984*m*, 912*w*, 864*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.33–7.25 (*m*, 10 arom. H); 6.90 (*dd*, $J = 15.9, 6.5$, irradiation at 6.05 → *d*, $J = 5.6$, irradiation at 4.33 → *d*, $J = 15.2$, H–C(3)); 6.05 (*dd*, $J = 15.9, 1.6$, irradiation at 6.90 → *d*, $J = 3.7$, irradiation at 4.33 → *d*, $J = 15.9$, H–C(2)); 4.83 (*d*, $J = 12.1$, PhC*H*); 4.67 (*d*, $J = 12.1$, PhC*H*); 4.46 (*d*, $J = 12.1$, PhC*H*); 4.38 (*d*, $J = 12.1$, PhC*H*); 4.33 (*ddd*, $J = 6.5, 4.1, 1.2$, irradiation at 6.05 → *dd*, $J = 6.2, 4.1$, irradiation at 4.01 → *dd*, $J = 6.5, 1.2$, H–C(4)); 4.24 (*q*, $J = 7.2$, MeCH_2O); 4.01 (*d*, $J = 3.7$, irradiation at 4.33 → *s*, H–C(5)); 3.67 (*s*, MeO); 1.32 (*t*, $J = 7.2$, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.89, 165.54 (2*s*, 2 C=O); 143.26 (*d*, C(3)); 137.12, 136.70 (2*s*); 128.28 (4*d*); 128.14 (2*d*); 128.03 (2*d*); 127.93, 127.84 (2*d*); 124.30 (*d*, C(2)); 79.59, 78.06 (2*d*, C(4), C(5)); 73.06, 71.70 (2*t*, 2

[18]) Starting from 1 g of **35**, **41** was obtained in 45% yield.

PhCH$_2$); 60.67 (*t*, MeCH$_2$O); 52.11 (*q*, MeO); 14.39 (*q*, MeCH$_2$O). HR-MALDI-MS: 421.1628 (100, $[M+Na]^+$, $C_{23}H_{26}NaO_6^+$; calc. 421.1622). Anal. calc. for $C_{23}H_{26}O_6$ (398.45): C 69.33, H 6.58; found: C 69.40, H 6.60.

*1,6-Dimethyl (*Z*)-4,5-Di-*O*-benzyl-2,3-dideoxy-*L*-*threo*-hex-2-enarate* (**48**). A soln. of $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (2.2 ml, 10.3 mmol) in THF (15 ml) was cooled to −78°, treated with KHMDS (80% suspension in oil, 2.2 g, 9.04 mmol), and 18-crown-6 (2.2 g, 8.22 mmol), stirred for 10 min, treated with a soln. of **46** (2.7 g, 8.22 mmol) in THF (15 ml), stirred for 1 h, treated with 1M HCl, and warmed to 0°. Normal workup (H_2O/AcOEt) and FC (AcOEt/cyclohexane 1:4) gave **48** (2.35 g, 75%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.54. $[\alpha]_D^{25} = +104.6$ (*c* = 1.23, $CHCl_3$). IR ($CHCl_3$): 3090*m*, 3067*m*, 3031*s*, 3013*s*, 2953*s*, 2905*w*, 1952*w*, 1876*w*, 1752*s*, 1720*s*, 1651*m*, 1606*w*, 1587*w*, 1497*m*, 1454*s*, 1438*s*, 1400*s*, 1341*m*, 1278*s*, 1229*s*, 1182*s*, 1136*s*, 1073*s*, 1027*s*, 1001*s*, 909*s*, 860*w*, 829*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.33–7.24 (*m*, 10 arom. H); 6.41 (*dd*, *J* = 11.5, 7.8, irradiation at 5.91 → *d*, *J* = 7.2, irradiation at 5.41 → *d*, *J* = 11.8, H–C(3)); 5.91 (*dd*, *J* = 11.5, 1.2, irradiation at 6.41 → *d*, *J* = 3.7, irradiation at 5.41 → *d*, *J* = 11.5, H–C(2)); 5.41 (*ddd*, *J* = 8.1, 3.4, 1.6, irradiation at 6.41 → *m*, irradiation at 5.91 → *dd*, *J* = 7.5, 3.4, irradiation at 4.27 → *dd*, *J* = 8.1, 1.6, H–C(4)); 4.87 (*d*, *J* = 12.1, PhC*H*); 4.61 (*d*, *J* = 11.8, PhC*H*); 4.40 (*d*, *J* = 11.8, PhC*H*); 4.36 (*d*, *J* = 11.5, PhC*H*); 4.27 (*d*, *J* = 3.4, irradiation at 5.41 → *s*, H–C(5)); 3.68, 3.65 (2*s*, 2 MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.01, 165.82 (2*s*, 2 C=O); 147.79 (*d*, C(3)); 137.50, 137.02 (2*s*); 128.24 (2*d*); 128.14 (4*d*); 128.06 (2*d*); 127.77, 127.67 (2*d*); 121.66 (*d*, C(2)); 79.58 (*d*, C(4)); 75.37 (*d*, C(5)); 73.14, 71.87 (2*t*, 2 PhCH$_2$); 51.98, 51.55 (2*q*, 2 MeO). HR-MALDI-MS: 407.1471 (100, $[M+Na]^+$, $C_{22}H_{24}NaO_6^+$; calc. 407.1465). Anal. calc. for $C_{22}H_{24}O_6$ (384.42): C 68.74, H 6.29; found: C 68.81, H 6.32.

*1,6-Dimethyl (*Z*)- and (*E*)-4,5-Di-*O*-benzyl-2-{[(benzyloxy)carbonyl]amino}-2,3-dideoxy-*L*-threo-hex-2-enarate* (**49**). A soln. of $(MeO)_2P(O)CH(NHZ)CO_2Me$ (1.77 g, 5.35 mmol) in THF (20 ml) was cooled to −78°, treated with 1,1,3,3-tetramethyl guanidine (0.6 ml, 4.87 mmol), stirred for 10 min, treated with a soln. of **46** (1.6 g, 4.87 mmol) in THF (20 ml), warmed to 23°, and stirred for 2 d. The mixture was diluted with AcOEt (50 ml) and washed with 1M HCl. The org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) gave (*E*)-**49**/(*Z*)-**49** 1:13 (2.2 g, 85%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.38. $[\alpha]_D^{25} = +55.1$ (*c* = 0.95, $CHCl_3$). IR (CH_2Cl_2): 3395*w*, 3065*w*, 3034*w*, 2954*m*, 2873*w*, 1954*w*, 1733*s*, 1661*w*, 1587*w*, 1497*s*, 1483*m*, 1455*m*, 1438*m*, 1311*m*, 1219*s*, 1135*m*, 1068*m*, 1050*m*, 1028*m*, 909*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): data of (*Z*)-**49**: 7.39–7.20 (*m*, 15 arom. H); 6.77 (br. *s*, NH); 6.30 (*d*, *J* = 8.1, H–C(3)); 5.11 (*d*, *J* = 12.4, PhC*H*); 5.06 (*d*, *J* = 12.1, PhC*H*); 4.82 (*d*, *J* = 11.8, PhC*H*); 4.58 (*d*, *J* = 12.1, PhC*H*); 4.54 (*dd*, *J* = 8.1, 3.4, irradiation at 6.30 → *d*, *J* = 3.4, H–C(4)); 4.44 (*d*, *J* = 11.8, PhC*H*); 4.30 (*d*, *J* = 12.1, PhC*H*); 4.23 (br. *d*, *J* = 3.1, H–C(5)); 3.80, 3.67 (2*s*, 2 MeO); data of (*E*)-**49**: 7.41–7.19 (*m*, 15 arom. H); 6.86 (br. *s*, NH); 6.22 (*d*, *J* = 8.1, H–C(3)); 5.11 (*d*, *J* = 12.4, PhC*H*); 4.67 (*d*, *J* = 11.5, PhC*H*); 4.59 (*d*, *J* = 11.5, PhC*H*); 4.56 (*dd*, *J* = 8.4, 6.5, H–C(4)); 4.46 (*d*, *J* = 11.8, PhC*H*); 4.40 (*d*, *J* = 11.8, PhC*H*); 4.10 (*d*, *J* = 6.5, H–C(5)); 3.77, 3.72 (2*s*, 2 MeO). ^{13}C-NMR (75 MHz, $CDCl_3$ (*E*)/(*Z*) 1:13): data of (*Z*)-**49**: 170.16, 164.37 (2*s*, 2 C–*C*=O); 153.91 (*s*, N–C=O); 137.08, 136.70, 135.61 (3*s*); 129.42 (*s*, C(2)); 128.42–127.75 (several *d*, including C(3)); 79.29 (*d*, C(5)); 75.00 (*d*, C(4)); 73.43, 71.33, 67.52 (3*t*, 3 PhCH$_2$); 52.76, 52.14 (2*q*, 2 MeO). HR-MALDI-MS: 556.1933 (100, $[M+Na]^+$, $C_{30}H_{31}NNaO_8^+$; calc. 556.1942). Anal. calc. for $C_{30}H_{31}NO_8$ (533.57): C 67.53, H 5.86, N 2.63; found: C 67.36, H 5.99, N 2.62.

*1,6-Dimethyl (*Z*)- and (*E*)-4,5-Di-*O*-benzyl-2-{[(*tert*-butoxy)carbonyl]amino}-2,3-dideoxy-*L*-threo-hex-2-enarate* (**50**). A soln. of $(MeO)_2P(O)CH(NHBoc)CO_2Me$ (2.2 g, 7.4 mmol) in THF (20 ml) was cooled to −78°, treated with DBU (1.1 ml, 6.7 mmol), stirred for 10 min, treated with a soln. of **46** (1.6 g, 6.7 mmol) in THF (20 ml), warmed to 23°, and stirred for 2 h. The mixture was diluted with AcOEt (50 ml) and washed with 1M HCl. The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) gave (*E*)-**50**/(*Z*)-**50** 3:2 (2.8 g, 85%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.47. IR (CH_2Cl_2): 3407*w*, 3067*w*, 3038*w*, 3006*w*, 2984*w*, 2954*w*, 2873*w*, 1952*w*, 1876*w*, 1810*w*, 1719*s*, 1659*w*, 1603*w*, 1480*m*, 1455*m*, 1438*m*, 1393*w*, 1369*m*, 1331*m*, 1242*s*, 1158*s*, 1095*m*, 1027*m*, 986*w*, 909*w*, 846*w*. ^{1}H-NMR (300 MHz, $CDCl_3$, (*E*)/(*Z*) 3:2)[19]): signals of (*Z*)-**50**: 7.35–7.22 (*m*, 10

[19]) Assignments based on DQFCOSY-GRASP spectrum.

arom. H); 6.52 (br. *s*, NH); 6.13 (*d*, *J* = 8.4, H–C(3)); 4.84 (*d*, *J* = 11.8, PhC*H*); 4.63 (*d*, *J* = 12.4, PhC*H*); 4.54 (*dd*, *J* = 8.4, 6.4, H–C(4)); 4.468 (*d*, *J* = 11.8, PhC*H*); 4.27 (*d*, *J* = 12.4, PhC*H*); 4.10 (*d*, *J* = 6.5, H–C(5)); 3.83, 3.63 (2*s*, 2 MeO); 1.40 (*s*, *t*-Bu); signals of (*E*)-**50**: 7.35–7.22 (*m*, 10 arom. H); 6.60 (br. *s*, NH); 6.25 (*d*, *J* = 8.4, H–C(3)); 4.68 (*d*, *J* = 11.5, PhC*H*); 4.62 (*d*, *J* = 11.8, PhC*H*); 4.51 (*dd*, *J* = 8.4, 3.4, H–C(4)); 4.475 (*d*, *J* = 11.8, PhC*H*); 4.41 (*d*, *J* = 11.8, PhC*H*); 4.10 (*d*, *J* = 6.5, H–C(5)); 3.81, 3.73 (2*s*, 2 MeO); 1.43 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$ (*E*)/(*Z*) 3:2)[20]: signals of (*Z*)-**50**: 170.24, 164.68 (2*s*, 2 C–*C*=O); 152.86 (*s*, N–C=O); 137.18, 136.85 (2*s*); 128.33–127.69 (several *d*, including *s* of C(2)); 125.65 (*s*, C(3)); 80.83 (*s*, Me_3C); 80.43 (*d*, C(5)); 75.57 (*d*, C(4)); 73.41, 71.03 (2*t*, 2 Ph*C*H_2); 52.64, 51.99 (2*q*, 2 MeO); 28.10 (*q*, *Me*$_3$C); signals of (*E*)-**50**: 170.54, 164.50 (2*s*, 2 C–*C*=O); 152.80 (*s*, N–C=O); 137.12, 136.32 (2*s*); 128.33–127.69 (several *d*, including *s* of C(2)); 126.59 (*s*, C(3)); 80.83 (*s*, Me_3C); 79.24 (*d*, C(5)); 74.76 (*d*, C(4)); 73.13, 71.54 (2*t*, 2 Ph*C*H_2); 52.49, 52.24 (2*q*, 2 MeO); 28.19 (*q*, *Me*$_3$C). HR-MALDI-MS: 522.2089 (100, $[M+Na]^+$, $C_{27}H_{33}NNaO_8^+$; calc. 522.2098). Anal. calc. for $C_{27}H_{33}NO_8$ (499.56): C 64.92, H 6.66, N 2.80; found: C 64.63, H 6.62, N 2.81.

*6-Ethyl 2,3-Di-*O*-benzyl-*L*-idarate-1,4-lactone* (**51**). A suspension of $(DHQ)_2PHAL$ (47 mg, 0.06 mmol), $K_3[Fe(CN)_6]$ (598 mg, 1.82 mmol), K_2CO_3 (249 mg, 1.80 mmol), and $MeSO_2NH_2$ (57 mg, 0.59 mmol) in ^{t}BuOH/H_2O 1:1 (20 ml) was cooled to 0°, treated with 2.5% soln. of OsO_4 in ^{t}BuOH (0.2 ml, 0.02 mmol), stirred for 1 h, treated with a soln. of **47** (240 mg, 0.60 mmol) in ^{t}BuOH (5 ml) over 30 min, and stirred at < 5° for 6 h. The mixture was treated with solid Na_2SO_3 (380 mg, 3.0 mmol), stirred for 10 min, and extracted with AcOEt (3 × 50 ml). The org. layers were washed with brine (50 ml), combined, dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) gave **51** (180 mg, 75%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.43. $[\alpha]_D^{25} = +98.5$ ($c = 1.04$, $CHCl_3$). IR (CH_2Cl_2): 3507*w*, 3090*w*, 3066*m*, 3034*m*, 2984*w*, 2930*w*, 2876*m*, 1955*w*, 1796*s*, 1738*s*, 1602*w*, 1586*w*, 1497*m*, 1454*m*, 1367*m*, 1331*m*, 1302*m*, 1228*s*, 1144*s*, 1104*s*, 1042*s*, 1028*s*, 910*m*, 864*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.41–7.26 (*m*, 10 arom. H); 5.14 (*d*, *J* = 11.5, PhC*H*); 4.78 (*d*, *J* = 12.4, PhC*H*); 4.72 (*d*, *J* = 11.5, PhC*H*); 4.64 (*d*, *J* = 12.1, PhC*H*); 4.30 (*q*, *J* = 6.9, MeCH_2O); 3.26 (*d*, *J* = 4.4, exchange with CD_3OD, HO–C(5)); 1.31 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 137.03, 136.93 (2*s*); 128.53 (2*d*); 128.44 (2*d*); 128.23 (2*d*); 128.13, 128.04 (2*d*); 127.84 (2*d*); 73.03, 72.91 (2*t*, 2 Ph*C*H_2); 62.96 (*t*, Me*C*H_2O); 14.26 (*q*, *Me*CH_2O). HR-MALDI-MS: 423.1412 (100, $[M+Na]^+$, $C_{22}H_{24}NaO_7^+$; calc. 423.1414). Anal. calc. for $C_{22}H_{24}O_7$ (400.42): C 65.99, H 6.04; found: C 65.91, H 6.07.

*6-Ethyl 2,3-Di-*O*-benzyl-5-*O*-[(trifluoromethyl)sulfonyl]-*L*-idarate-1,4-lactone* (**52**). A soln. of **51** (150 mg, 0.37 mmol) in CH_2Cl_2 (6 ml) was cooled to −78°, treated with Tf_2O (70 µl, 0.41 mmol), stirred for 5 min, treated dropwise with 2,6-lutidine (65 µl, 0.56 mmol) and warmed to 0° over 2 h. The mixture was washed with ice-cold 1M HCl and ice-cold $NaHCO_3$ soln. The org. layer was dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) afforded **52** (185 mg, 93%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.57. IR ($CHCl_3$): 3029*w*, 3015*w*, 1806*s*, 1773*m*, 1602*w*, 1455*w*, 1423*s*, 1138*s*, 1104*m*, 1076*m*, 1018*m*, 990*m*, 952*w*, 891*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.42–7.26 (*m*, 10 arom. H); 5.10 (*d*, *J* = 11.5, PhC*H*); 4.78 (*d*, *J* = 11.5, PhC*H*); 4.66 (*d*, *J* = 11.8, PhC*H*); 4.52 (*d*, *J* = 11.8, PhC*H*); 4.30, 4.29 (2*q*, *J* = 7.2, MeCH_2O); 1.31 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.18, 135.77 (2*s*); 128.55 (2*d*); 128.52 (2*d*); 128.47 (*d*); 128.44 (4*d*); 128.33 (*d*); 118.10 (*q*, ^1J(C,F) = 317, CF_3); 73.16, 72.95 (2*t*, 2 Ph*C*H_2); 63.53 (*t*, Me*C*H_2O); 13.91 (*q*, *Me*CH_2O). ^{19}F-NMR (282 MHz, $CDCl_3$): −73.74 (*s*, CF_3). HR-MALDI-MS: 555.0901 (76, $[M+Na]^+$, $C_{23}H_{23}F_3NaO_9S^+$; calc. 555.0907), 315. 0901 (100, $[M-TfOH-BnOH+H_2O+Na]^+$, $C_{15}H_{16}NaO_6^+$; calc. 315.0839).

*6-Ethyl 5-Azido-2,3-di-*O*-benzyl-5-deoxy-*D*-glucarate-1,4-lactone* (**53**). A soln. of **52** (185 mg 0.35 mmol) in CH_2Cl_2 (6 ml) was cooled to −90°, treated with tetramethylguanidinium azide (83 mg, 0.52 mmol), and warmed to 10° over 3 h. Normal workup (H_2O/CH_2Cl_2), followed by FC (AcOEt/cyclohexane 1:4), afforded **53** (145 mg, 98%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.57. $[\alpha]_D^{25} = +35.8$ ($c = 0.53$, $CHCl_3$). IR ($CHCl_3$): 3068*w*, 3032*m*, 3014*m*, 2930*w*, 2874*w*, 2125*s*, 1798*s*, 1745*s*, 1603*w*, 1497*w*, 1455*m*, 1395*w*, 1370*w*, 1331*m*, 1284*m*, 1263*m*, 1165*m*, 1104*s*, 1043*m*, 1028*s*, 911*w*, 857*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.37–7.20 (*m*, 10 arom. H); 5.06 (*d*, *J* = 11.8, PhC*H*); 4.69 (*d*, *J* = 11.3, PhC*H*); 4.59 (*d*, *J* = 11.8, PhC*H*); 4.50 (*d*, *J* = 11.8, PhC*H*); 4.12, 4.02 (2*q*, *J* = 7.2, MeCH_2O);

[20]) Assignments based on HSQC-GRASP spectrum.

Table 5. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Protected 1,4-Lactones* **51**–**53**, **57**–**59**, *and* **61**–**66** *in $CDCl_3$*

	51	**52**	**53**	**57**	**58**	**59**
H–C(2)	4.74	4.47	4.52	4.39	4.38	4.32
H–C(3)	4.49	4.55	4.41	4.58	4.33	4.45
H–C(4)	4.81	5.05	5.09	4.51	4.74	4.61
H–C(5)	4.51	5.44	4.39	4.25	5.27	4.38
J(2,3)	8.1	7.2	6.6	7.5	7.2	7.2
J(3,4)	8.1	7.6	4.4	7.8	7.2	7.0
J(4,5)	0.9	2.5	7.4	1.2	3.4	3.9
	61	**62**[a])	**63**	**64**[b])	**65**	**66**[c])
H–C(2)	4.63	4.37	4.42	4.37	4.51	4.51
H–C(3)	4.48	4.46	4.55	4.49	4.44	4.38
H–C(4)	5.01	4.59–4.47	5.28	4.65	5.00	4.64
H–C(5)	4.50	4.59–4.47	5.42	5.38	4.43	3.89
J(2,3)	7.5	7.2	7.8	7.8	6.5	6.5
J(3,4)	7.8	7.3	8.1	8.1	7.2	7.5
J(4,5)	2.5	[d])	3.1	2.5	3.4	2.8

[a]) From **61**/**62** 1:1. [b]) From **63**/**64** 1:2. [c]) From **65**/**66** 1:2. [d]) Not assigned.

1.19 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.91, 136.73 (2*s*); 128.80 (2*d*); 128.68 (2*d*); 128.61 (2*d*); 128.51, 128.39 (2*d*); 128.12 (2*d*); 73.19, 72.97 (2*t*, 2 Ph*C*H_2); 62.58 (*t*, Me*C*H_2O); 14.12 (*q*, *Me*CH_2O). HR-ESI-MS: 448.1473 (100, $[M+Na]^+$, $C_{22}H_{23}N_3NaO_6^+$; calc. 448.1479). Anal. calc. for $C_{22}H_{23}N_3O_6$ (425.43): C 62.11, H 5.45, N 9.88; found: C 62.45, H 5.88, N 9.32.

6-Ethyl 5-Amino-2,3-di-O-*benzyl-5-deoxy*-D-*glucarate-1,5-lactam* (**54**). A suspension of **53** (145 mg, 0.34 mmol) and 10% $Pd/CaCO_3$ (20 mg) in EtOH (6 ml) was hydrogenated (1 bar) for 4 h and stirred under N_2 for 12 h. Filtration through *Celite*, evaporation, and FC (AcOEt/cyclohexane 1:1) gave **54** (88 mg, 65%). Colourless solid. R_f (AcOEt/cyclohexane 2:1) 0.29. M.p. 117–119°. $[\alpha]_D^{25} = +84.8$ ($c = 0.94$, $CHCl_3$). IR (KBr): 3428*m*, 3261*w*, 3063*w*, 3031*w*, 2980*w*, 2951*w*, 2897*w*, 1951*w*, 1870*w*, 1744*s*, 1684*s*, 1663*m*, 1496*w*, 1454*m*, 1397*w*, 1327*w*, 1255*m*, 1199*s*, 1143*w*, 1107*s*, 1072*m*, 1025*m*, 913*w*, 894*w*, 868*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.37–7.22 (*m*, 10 arom. H); 6.17 (br. *s*, exchange with CD_3OD, NH); 5.02 (*d*, *J* = 11.5, PhC*H*); 4.73 (*d*, *J* = 11.5, PhC*H*); 4.65 (*d*, *J* = 11.5, PhC*H*); 4.59 (*d*, *J* = 11.8, PhC*H*); 4.21–4.05 (*m,* Me*C*H_2O); 3.72 (*d*, *J* = 6.5, exchange with CD_3OD, HO–C(4)); 1.22 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 137.14, 136.75 (2*s*); 128.38 (2*d*); 128.33 (2*d*); 128.20 (2*d*); 128.01, 127.87 (2*d*); 127.61 (2*d*); 74.03, 73.22 (2*t*, 2 Ph*C*H_2); 62.23 (*t*, Me*C*H_2O); 14.11 (*q*, *Me*CH_2O). HR-MALDI-MS: 422.1576 (100, $[M+Na]^+$, $C_{22}H_{25}NNaO_6^+$; calc. 422.1574). Anal. calc. for $C_{22}H_{25}NO_6$ (399.43): C 66.15, H 6.31, N 3.51; found: C 66.27, H 6.60, N 3.45.

6-Ethyl 2,3-Di-O-*benzyl*-D-*galactarate-1,4-lactone* (**57**). A soln. of **47** (500 mg, 1.25 mmol) in acetone/H_2O 4:1 (15 ml) was treated with $NMO \cdot H_2O$ (507 mg, 3.75 mmol) and 2.5% soln. of OsO_4 in *t*BuOH (0.12 ml, 0.012 mmol), stirred for 36 h, treated with Na_2SO_3 (788 mg, 6.25 mmol), and stirred for 10 min. Normal workup (H_2O/AcOEt) and FC (AcOEt/cyclohexane 1:5) afforded **57** (437 mg, 87%). Oil. R_f (AcOEt/cyclohexane 1:2) 0.43. $[\alpha]_D^{25} = +13.3$ ($c = 1.08$, $CHCl_3$). IR (CH_2Cl_2): 3526*w* (br.), 3059*w*, 2873*w*, 1799*s*, 1742*s*, 1606*w*, 1497*w*, 1455*w*, 1419*w*, 1367*w*, 1208*m*, 1115*s*, 1047*m*, 896*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.41–7.26 (*m*, 10 arom. H); 5.08 (*d*, *J* = 11.5, PhC*H*); 4.78 (*d*, *J* = 11.5, PhC*H*); 4.71 (*d*, *J* = 11.5, PhC*H*); 4.60 (*d*, *J* = 11.5, PhC*H*); 4.29 (*q*, *J* = 7.2, Me*C*H_2O); 3.07 (*d*, *J* = 6.8, HO–C(5)); 1.30 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally,

136.93, 136.54 (2*s*); 128.50 (4*d*); 128.45 (2*d*); 128.23, 128 17 (2*d*); 127.87 (2*d*); 73.11, 71.47 (2*t*, 2 Ph*C*H$_2$); 62.83 (*t*, Me*C*H$_2$O); 14.23 (*q*, *Me*CH$_2$O). HR-MALDI-MS: 423.1418 (100, $[M+Na]^+$, $C_{22}H_{24}NaO_7^+$; calc. 423.1414). Anal. calc. for $C_{22}H_{24}O_7$ (400.42): C 65.99, H 6.04; found: C 66.18, H 6.33.

*6-Ethyl 2,3-Di-*O*-benzyl-5-*O*-[(trifluoromethyl)sulfonyl]-*D*-galactarate-1,4-lactone* (**58**). The alcohol **57** (445 mg, 1.11 mmol) was transformed into **58** (556 mg, 94%) similarly as described for the preparation of **52**. R_f (AcOEt/cyclohexane 1:2) 0.58. Yellowish solid. M.p. 81–82°. $[\alpha]_{365}^{25} = -0.3$ ($c = 1.08$, $CHCl_3$); $[\alpha]_{435}^{25} = +1.8$ ($c = 1.08$, $CHCl_3$); $[\alpha]_{546}^{25} = +1.5$ ($c = 1.08$, $CHCl_3$); $[\alpha]_{577}^{25} = +1.1$ ($c = 1.08$, $CHCl_3$); $[\alpha]_D^{25} = +0.5$ ($c = 1.08$, $CHCl_3$). IR (KBr): 3068*w*, 3037*w*, 2944*w*, 1801*s*, 1763*s*, 1606*w*, 1499*w*, 1468*w*, 1455*s*, 1422*s*, 1375*m*, 1364*m*, 1320*m*, 1284*m*, 1247*s*, 1220*s*, 1152*s*, 1097*s*, 1063*m*, 1027*s*, 1005*m*, 981*m*, 907*m*, 867*w*, 853*m*, 808*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.42–7.22 (*m*, 10 arom. H); 5.09 (*d*, $J = 11.5$, PhC*H*); 4.78 (*d*, $J = 11.5$, PhC*H*); 4.68 (*d*, $J = 10.9$, PhC*H*); 4.54 (*d*, $J = 10.9$, PhC*H*); 4.33, 4.28 (2*q*, $J = 7.2$, MeC*H*$_2$O); 1.31 (*t*, $J = 7.2$, *Me*CH$_2$O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.21, 135.96 (2*s*); 128.72 (2*d*); 128.63 (2*d*); 128.56 (2*d*); 128.52, 128.37 (2*d*); 127.98 (2*d*); 118.31 (*q*, ^1J(C,F) = 317, CF_3); 73.22, 72.64 (2*t*, 2 Ph*C*H$_2$); 63.80 (*t*, Me*C*H$_2$O); 13.96 (*q*, *Me*CH$_2$O). ^{19}F-NMR (282 MHz, $CDCl_3$): −73.71 (*s*, CF_3). HR-MALDI-MS: 555.0906 (100, $[M+Na]^+$, $C_{23}H_{23}F_3NaO_9S^+$; calc. 555.0907), 315.0838 (35, $[M - TfOH - BnOH + H_2O + Na]^+$, $C_{15}H_{16}NaO_6^+$; calc. 315.0839). Anal. calc. for $C_{23}H_{23}F_3O_9S$ (532.48): C 51.88, H 4.35, S 6.02; found: C 52.12, H 4.34, S 6.17.

*6-Ethyl 5-Azido-2,3-di-*O*-benzyl-5-deoxy-*L*-altrarate-1,4-lactone* (**59**). The triflate **58** (300 mg, 0.56 mmol) was transformed to **59** (235 mg, 98%) similarly as described for the preparation of **53**. Oil. R_f (AcOEt/cyclohexane 1:2) 0.58. $[\alpha]_D^{25} = +34.6$ ($c = 0.37$, $CHCl_3$). IR ($CHCl_3$): 3031*w*, 3014*w*, 2932*w*, 2118*s*, 1803*m*, 1749*m*, 1602*w*, 1497*w*, 1455*w*, 1371*w*, 1271*m*, 1206*m*, 1168*m*, 1115*s*, 1028*m*, 912*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.42–7.19 (*m*, 10 arom. H); 5.06 (*d*, $J = 11.5$, PhC*H*); 4.77 (*d*, $J = 11.5$, PhC*H*); 4.59 (*d*, $J = 11.0$, PhC*H*); 4.48 (*d*, $J = 11.0$, PhC*H*); 4.18, 4.12 (2*q*, $J = 7.1$, MeC*H*$_2$O); 1.19 (*t*, $J = 6.9$, *Me*CH$_2$O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*; additionally, 136.60, 136.29 (2*s*); 128.56 (4*d*); 128.37 (3*d*); 128.13 (*d*); 127.97 (2*d*); 73.01, 72.53 (2*t*, 2 Ph*C*H$_2$); 62.71 (*t*, Me*C*H$_2$O); 14.08 (*q*, *Me*CH$_2$O). HR-MALDI-MS: 448.1478 (100, $[M+Na]^+$, $C_{22}H_{23}N_3NaO_6^+$; calc. 448.1479). Anal. calc. for $C_{22}H_{23}N_3O_6$ (425.43): C 62.11, H 5.45, N 9.88; found: C 62.26, H 5.39, N 9.70.

*6-Ethyl 5-Amino-2,3-di-*O*-benzyl-5-deoxy-*L*-altrarate-1,5-lactam* (**60**). The azide **59** (170 mg, 0.40 mmol) was transformed to **60** (100 mg, 63%) similarly as described for the preparation of **54**. Oil. R_f (AcOEt/cyclohexane 2:1) 0.28. $[\alpha]_D^{25} = +52.6$ ($c = 0.36$, $CHCl_3$). IR (CH_2Cl_2): 3569*w*, 3391*m*, 3089*w*, 3064*m*, 3034*m*, 2985*w*, 2910*m*, 2875*m*, 1955*w*, *1880w*, 1743*s*, 1685*s*, 1605*w*, 1497*m*, 1455*m*, 1393*m*, 1371*m*, 1315*m*, 1274*s*, 1209*s*, 1158*m*, 1097*s*, 1076*s*, 1027*m*, 938*w*, 909*m*, 865*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.38–7.26 (*m*, 10 arom. H); 6.04 (br. *s*, exchange with CD_3OD, NH); 4.98 (*d*, $J = 11.5$, PhC*H*); 4.70 (*d*, $J = 11.5$, PhC*H*); 4.69 (*s,* PhC*H*$_2$); 4.24, 4.23 (2*q*, $J = 7.2$, addition of $CD_3OD \rightarrow q$, $J = 7.2$, MeC*H*$_2$O); 3.16 (*d*, $J = 3.4$, irradiation at 4.43 → *s*, exchange with CD_3OD, HO–C(4)); 1.29 (*t*, $J = 7.2$, *Me*CH$_2$O). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 137.47, 137.39 (2*s*); 128.42 (2*d*); 128.31 (2*d*); 128.06 (2*d*); 127.97 (*d*); 127.81 (3*d*); 74.03, 73.26 (2*t*, 2 Ph*C*H$_2$); 62.53 (*t*, Me*C*H$_2$O); 14.20 (*q*, *Me*CH$_2$O). HR-MALDI-MS: 422.1580 (100, $[M+Na]^+$, $C_{22}H_{25}NNaO_6^+$; calc. 422.1574). Anal. calc. for $C_{22}H_{25}NO_6$ (399.43): C 66.15, H 6.31, N 3.51; found: C 66.25, H 6.52, N 3.47.

Dihydroxylation of **48**. The (*Z*)-alkene **48** (3.0 g, 7.8 mmol) was transformed to a 1:1 mixture of **61** and **62** (2.4 g, 78%) similarly as described for the preparation of **57**.

*Data of 6-Methyl 2,3-Di-*O*-benzyl-*D*-glucarate-1,4-lactone* (**61**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.24. $[\alpha]_D^{25} = +47.4$ ($c = 1.11$, $CHCl_3$). IR (CH_2Cl_2): 3524*w*, 3065*w*, 3034*w*, 2956*w*, 2878*w*, 1795*s*, 1748*s*, 1606*w*, 1497*w*, 1445*m*, 1440*m*, 1395*w*, 1369*w*, 1334*w*, 1276*m*, 1248*m*, 1210*m*, 1162*s*, 1137*s*, 1104*s*, 1039*s*, 982*m*, 911*w*, 872*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.38–7.17 (*m*, 10 arom. H); 5.12 (*d*, $J = 11.2$, PhC*H*); 4.73 (*d*, $J = 11.2$, PhC*H*); 4.59 (*d*, $J = 11.8$, PhC*H*); 4.50 (*d*, $J = 11.2$, PhC*H*); 3.61 (*s*, MeO); 3.14 (*d*, $J = 5.6$, exchange with CD_3OD, HO–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.88, 136.60 (2*s*); 128.47 (2*d*); 128.39 (2*d*); 128.35 (2*d*); 128.12, 128.06 (2*d*); 127.71 (2*d*); 73.14, 72.71 (2*t*, 2 Ph*C*H$_2$); 52.73 (*q*, MeO). HR-MALDI-MS: 409.1265 (100, $[M+Na]^+$, $C_{21}H_{22}NaO_7^+$; calc. 409.1258). Anal. calc. for $C_{21}H_{22}O_7$ (386.39): C 65.28, H 5.74; found: C 65.29, H 5.97.

*Data of 6-Methyl 2,3-Di-*O*-benzyl-*L*-altrarate-1,4-lactone* (**62**). Oil. ^{1}H-NMR (300 MHz, $CDCl_3$, **61**/**62** 1:1): signals of **62**: see *Table 5*; additionally, 7.41–7.18 (*m*, 10 arom. H); 5.09 (*d*, *J* = 11.5, PhC*H*); 4.80 (*d*, *J* = 11.5, PhC*H*); 4.59–4.47 (*m*, overlapping with signals of **61**, 2 PhC*H*); 3.66 (*s*, MeO); 3.19 (*d*, *J* = 5.0, HO–C(5)).

Triflation of **61**/**62**. A 1:1 mixture of **61** and **62** (1.3 g, 3.36 mmol) was transformed into a 1:2 mixture of **63** and **64** (1.2 g, 69%), and **61** (305 mg, 23%) similarly as described for the preparation of **52**.

*Data of 6-Methyl 2,3-Di-*O*-benzyl-5-*O*-[(trifluoromethyl)sulfonyl]-*D*-glucarate-1,4-lactone* (**63**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.50. $[\alpha]_D^{25} = +49.0$ (*c* = 1.01, $CHCl_3$). IR (KBr): 3033*w*, 2957*w*, 2880*w*, 1803*m*, 1774*m*, 1749*m*, 1497*w*, 1455*w*, 1421*m*, 1365*w*, 1333*m*, 1298*m*, 1244*m*, 1207*s*, 1135*s*, 1101*s*, 1047*s*, 1012*s*, 960*s*, 897*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.38–7.19 (*m*, 10 arom. H); 5.10 (*d*, *J* = 11.2, PhC*H*); 4.72 (*d*, *J* = 11.2, PhC*H*); 4.60 (*d*, *J* = 11.5, PhC*H*); 4.50 (*d*, *J* = 11.5, PhC*H*); 3.51 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.41 (2*s*); 128.82 (3*d*); 128.66 (3*d*); 128.46 (*d*); 128.15 (3*d*); 118.49 (*q*, ^1J(C,F) = 318, CF_3); 73.29, 73.00 (2*t*, 2 Ph*C*H$_2$); 53.36 (*q*, MeO). ^{19}F-NMR (282 MHz, $CDCl_3$): −74.80 (*s*, CF_3). HR-MALDI-MS: 541.0744 (79, $[M+Na]^+$, $C_{22}H_{21}F_3NaO_9S^+$; calc. 541.0751), 301.0681 (100, $[M - TfOH - BnOH + H_2O + Na]^+$, $C_{14}H_{14}NaO_6^+$; calc. 301.0683).

*Data of 6-Methyl 2,3-Di-*O*-benzyl-5-*O*-[(trifluoromethyl)sulfonyl]-*L*-altrarate-1,4-lactone* (**64**). Oil. ^{1}H-NMR (300 MHz, $CDCl_3$, **63**/**64** 1:2): signals of **64**: see *Table 5*; additionally, 7.42–7.19 (*m*, 10 arom. H); 5.09 (*d*, *J* = 11.5, PhC*H*); 4.80 (*d*, *J* = 11.5, PhC*H*); 4.63 (*d*, *J* = 10.9, PhC*H*); 4.59 (*d*, *J* = 11.2, PhC*H*); 3.67 (*s*, MeO). ^{19}F-NMR (282 MHz, $CDCl_3$; **63**/**64** 1:2): −73.93 (*s*, 2.04 F, CF_3 of **64**); −74.27 (*s*, 0.96 F, CF_3 of **63**).

Azidation of **63**/**64**. A 1:2 mixture of **63** and **64** (285 mg, 0.55 mmol) was subjected to the same reaction conditions as described for the preparation of **53** to afford a 1:2 mixture of **65** and **66** (221 mg, 98%).

*Data of 6-Methyl 5-Azido-2,3-di-*O*-benzyl-5-deoxy-*L*-idarate-1,4-lactone* (**65**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.50. $[\alpha]_D^{25} = +129.3$ (*c* = 0.55, $CHCl_3$). IR ($CHCl_3$): 3030*m*, 3015*m*, 2125*s*, 1799*s*, 1749*m*, 1602*w*, 1497*w*, 1455*w*, 1313*w*, 1274*m*, 1104*m*, 1001*m*, 930*w*, 865*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.40–7.23 (*m*, 10 arom. H); 5.10 (*d*, *J* = 11.2, PhC*H*); 4.72 (*d*, *J* = 11.2, PhC*H*); 4.67 (*d*, *J* = 11.8, PhC*H*); 4.54 (*d*, *J* = 10.9, PhC*H*); 3.79 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.57, 136.38 (2*s*); 128.58 (2*d*); 128.52 (2*d*); 128.35 (2*d*); 128.32, 128.24 (2*d*); 127.95 (2*d*); 73.08, 72.77 (2*t*, 2 Ph*C*H$_2$); 53.28 (*q*, MeO). HR-MALDI-MS: 434.1324 (100, $[M+Na]^+$, $C_{21}H_{21}N_3NaO_6^+$; calc. 434.1323). Anal. calc. for $C_{21}H_{21}N_3O_6$ (411.41): C 61.31, H 5.14, N 10.21; found: C 61.45, H 5.26, N 10.19.

*Data of 6-Methyl 5-Azido-2,3-di-*O*-benzyl-5-deoxy-*D*-galactarate-1,4-lactone* (**66**). Oil. ^{1}H-NMR (300 MHz, $CDCl_3$, **65**/**66** 1:2): signals of **66**: see *Table 5*; additionally, 7.46–7.22 (*m*, 10 arom. H); 5.10 (*d*, *J* = 11.5, PhC*H*); 4.79 (*d*, *J* = 11.5, PhC*H*); 4.70–4.69 (overlapping *d*, PhC*H*); 4.54 (*d*, *J* = 11.5, PhC*H*); 3.82 (*s*, MeO).

Preparation of Lactams **28** *and* **67**. A 1:2 mixture of **65** and **66** (1.0 g, 2.43 mmol) was transformed into **67** (195 mg, 21%) and **28** (382 mg, 41%) similarly as described for the preparation of **54**.

*Data of 6-Methyl 5-Amino-2,3-di-*O*-benzyl-5-deoxy-*L*-idarate-1,5-lactam* (**67**). Oil. R_f (AcOEt/cyclohexane 2:1) 0.25. $[\alpha]_D^{25} = +39.5$ (*c* = 1.11, $CHCl_3$). IR (CH_2Cl_2): 3484*w* (br.), 3386*m*, 3062*w*, 3034*w*, 2957*w*, 1749*s*, 1679*s*, 1605*w*, 1497*s*, 1455*w*, 1438*m*, 1388*m*, 1374*m*, 1300*m*, 1273*m*, 1233*m*, 1160*m*, 1072*s*, 1028*m*, 1017*m*, 967*w*, 948*w*, 911*w*, 867*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.36–7.21 (*m*, 10 arom. H); 6.33 (br. *s*, exchange with CD_3OD, NH); 4.97 (*d*, *J* = 11.8, PhC*H*); 4.72 (*d*, *J* = 11.8, PhC*H*); 4.58 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 3.94 (br. *d*, *J* = 1.6, addition of CD_3OD → *d*, *J* = 4.4, H–C(2) and HO–C(4)); 3.83 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 136.79, 136.52 (2*s*); 128.46 (3*d*); 128.39 (2*d*); 128.27 (2*d*); 128.06 (*d*); 127.68 (2*d*); 73.67, 72.32 (2*t*, 2 Ph*C*H$_2$); 52.97 (*q*, MeO). HR-MALDI-MS: 408.1422 (100, $[M+Na]^+$, $C_{21}H_{23}NNaO_6^+$; calc. 408.1418). Anal. calc. for $C_{21}H_{23}NO_6$ (385.41): C 65.44, H 6.01, N 3.63; found: C 65.44, H 6.15, N 3.89.

Preparation of **55** *and* **68**. a) *From* **54**. A soln. of **54** (99 mg, 0.25 mmol) in MeOH/H_2O 1:1 (4 ml) was cooled to 0°, treated with LiOH·H_2O (12 mg, 0.27 mmol), and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (25 ml) and washed with ice-cold 1M HCl. The aq. layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. A soln. of the res-

idue in acetone (6 ml) was treated dropwise with a soln. of Ph_2CN_2 (58 mg, 0.3 mmol) in acetone (2 ml) in portions, stirred for 4 h, and evaporated at 30°. FC (AcOEt/cyclohexane 1:4), followed by crystallization (AcOEt/hexane) of separated products, afforded **55** (113 mg, 85%) and **68** (16 mg, 12%).

b) *From* **67**. A soln. of **67** (55 mg, 0.14 mmol) in MeOH/H_2O 1:1 (4 ml) was transformed to **68** (65 mg, 85%) and **55** (7.7 mg, 13%) similarly as described above.

Data of 6-Diphenylmethyl 5-Amino-2,3-di-O-*benzyl-5-deoxy*-D-*glucarate-1,5-lactam* (**55**). Colourless solid. R_f (AcOEt/cyclohexane 1:1) 0.36. M.p. 107–109°. $[\alpha]_D^{25} = +67.6$ ($c = 0.94$, $CHCl_3$). IR (KBr): 3381*m* (br.), 3059*m*, 3031*m*, 2924*m*, 2852*w*, 1953*w*, 1884*w*, 1807*w*, 1742*s*, 1683*s*, 1496*m*, 1454*m*, 1353*w*, 1307*w*, 1242*m*, 1203*s*, 1182*m*, 1150*m*, 1075*s*, 1028*m*, 998*m*, 913*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.34–7.23 (*m*, 18 arom. H); 7.09–7.06 (*m*, 2 arom. H); 6.86 (*s*, Ph_2CH); 5.97 (br. *s*, NH); 4.97 (*d*, $J = 11.5$, PhC*H*); 4.69 (*d*, $J = 11.5$, PhC*H*); 4.39 (*d*, $J = 11.8$, PhC*H*); 4.26 (*d*, $J \approx 11.8$, PhC*H*); 3.70 (*d*, $J = 7.1$, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 139.05, 138.97, 136.90, 136.56 (4*s*); 128.55–126.92 (several *d*); 76.07 (*d*, Ph_2CH); 73.94, 72.73 (2*t*, 2 $PhCH_2$). HR-MALDI-MS: 576.1786 (100, $[M+K]^+$, $C_{33}H_{31}KNO_6^+$; calc. 576.1783), 560.2052 (70, $[M+Na]^+$, $C_{33}H_{31}NNaO_6^+$; calc. 560.2044). Anal. calc. for $C_{33}H_{31}NO_6$ (537.21): C 73.73, H 5.81, N 2.61; found: C 73.47, H 5.82, N 2.56.

Data of 6-Diphenylmethyl 5-Amino-2,3-di-O-*benzyl-5-deoxy*-L-*idarate-1,5-lactam* (**68**). Colourless solid. R_f (AcOEt/cyclohexane 1:1) 0.37. M.p. 43–44°. $[\alpha]_D^{25} = +20.3$ ($c = 0.82$, $CHCl_3$). IR (KBr): 3347*m*, 3033*w*, 2920*w*, 2852*w*, 1952*w*, 1882*w*, 1820*w*, 1743*s*, 1698*s*, 1496*w*, 1453*m*, 1424*w*, 1343*w*, 1294*w*, 1270*w*, 1225*s*, 1177*w*, 1162*w*, 1098*m*, 1081*m*, 1029*w*, 994*w*, 959*w*, 916*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.36–7.30 (*m*, 18 arom. H); 7.23–7.20 (*m*, 2 arom. H); 6.98 (*s*, Ph_2CH); 6.08 (br. *s*, NH); 4.96 (*d*, $J = 11.8$, PhC*H*); 4.73 (*d*, $J = 11.8$, PhC*H*); 4.60 (*d*, $J = 11.8$, PhC*H*); 4.49 (*d*, $J = 11.8$, PhC*H*); 3.64 (*d*, $J = 8.7$, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 139.01 (2*s*); 136.68, 136.36 (2*s*); 128.51–126.79 (several *d*); 74.36 (*d*, Ph_2CH); 73.75, 72.50 (2*t*, 2 $PhCH_2$). HR-MALDI-MS: 560.2038 (53, $[M+Na]^+$, $C_{33}H_{31}NNaO_6^+$; calc. 560.2044), 167.0854 (100, $[Ph_2C+H]^+$, $C_{13}H_{11}^+$; calc. 167.0855). Anal. calc. for $C_{33}H_{31}NO_6 \cdot 0.3\ H_2O$ (542.62): C 72.99, H 5.87, N 2.58; found: C 72.99, H 5.87, N 2.58.

Hydrogenolysis of **55**. A suspension of **55** (40 mg, 0.07 mmol) and 10% Pd/C (15 mg) in MeOH/H_2O 2:1 (3 ml) was hydrogenated (6 bar) for 48 h. The mixture was filtered through *Celite*, and the filtrate was evaporated. A soln. of the residue in H_2O (10 ml) was washed with AcOEt (4×) and lyophilized to afford **56** (18.7 mg, 98%). A soln. of **56** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **8** (16 mg, 98%).

Data of 6-Hydrogen 5-Amino-5-deoxy-D-*glucaro-1,5-lactam* (**56**). M.p. 180–183° (dec.) ([16]: 177–179°). $[\alpha]_D^{25} = +30.1$ ($c = 0.58$, H_2O; [16]: +48.0 (H_2O)). ^{1}H-NMR (300 MHz, D_2O): see *Table 4*.

Data of 6-Sodium 5-Amino-5-deoxy-D-*glucarate-1,5-lactam* (**8**). IR (KBr): 3419*s* (br.), 2923*w*, 2852*w*, 1658*s*, 1615*s*, 1399*m*, 1294*w*, 1116*m*, 1053*m*, 1011*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*. ^{13}C-NMR (75 MHz, D_2O): see *Table 3*. ESI-MS (neg. mode): 190.2 (100, $[M-Na]^-$).

Hydrogenolysis of **68**. The lactam **68** (45 mg, 0.084 mmol) was transformed into **69** (21.8 mg, 98%) similarly as described for the preparation of **56**. A soln. of **69** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **10** (17.5 mg, 98%).

Data of 6-Hydrogen 5-Amino-5-deoxy-L-*idaro-1,5-lactam* (**69**). $pK_{HA} = 3.5$. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*.

Data of 6-Sodium 5-Amino-5-deoxy-L-*idarate-1,5-lactam* (**10**). M.p. 186–187°. $[\alpha]_D^{25} = -37.8$ ($c = 0.33$, H_2O). $pK_{HA} = 3.5$. IR (KBr): 3390*s* (br.), 2923*w*, 2857*w*, 1666*s*, 1610*s*, 1399*m*, 1299*m*, 1127*w*, 1090*w*, 1061*m*, 1004*w*, 921*w*, 873*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*. ^{13}C-NMR (75 MHz, D_2O): see *Table 3*. HR-MALDI-MS: 662.0707 (7, $[3M+Na]^+$, $C_{18}H_{24}N_3Na_4O_{18}^+$; calc. 662.0640), 449.0420 (47, $[2M+Na]^+$, $C_{12}H_{16}N_2Na_3O_{12}^+$; calc. 449.0391), 405.0766 (70, $[2M+2\,H-Na]^+$, $C_{12}H_{18}N_2NaO_{12}^+$; calc. 405.0752), 236.0138 (82, $[M+Na]^+$, $C_6H_8NNa_2O_6^+$; calc. 236.0142). Anal. calc. for $C_6H_8NNaO_6 \cdot 1.7\ H_2O$ (243.64): C 29.57, H 4.71, N 5.75; found: C 29.44, H 4.46, N 5.58.

Preparation of **73** *and* **74**. a) *From* **54**. A soln. of **54** (90 mg, 0.22 mmol) in MeCN (5 ml) was cooled to −19°, treated with NaN_3 (52 mg, 0.79 mmol) and Tf_2O (0.19 ml, 1.12 mmol), and stirred for 1 h. The crude product obtained by normal workup ($NaHCO_3$-soln./AcOEt) was saponified with $LiOH \cdot H_2O$

Table 6. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *and ^{13}C-NMR Chemical Shifts* [ppm] *of the Protected Tetrazoles* **73**, **74**, *and* **76** *in $CDCl_3$, and the Deprotected Tetrazoles* **77**, **78**, *and* **12**–**14** *in D_2O*

	73	**74**	**76**	**77**	**78**	**12**	**13**	**14**
H–C(5)	5.59	5.39	5.53	5.19	5.59	4.84	5.19	5.35
H–C(6)	4.98	4.73	4.65	4.03	4.50	3.90	4.56	4.38
H–C(7)	4.06	4.27	3.95	4.47	4.22	4.21	3.89	4.22
H–C(8)	4.832	5.01	4.93	4.88	4.95	4.78	4.93	4.92
J(5,6)	1.9	4.4	5.6	5.2	6.2	6.9	2.5	5.9
J(6,7)	4.0	4.4	2.5	7.0	8.7	8.2	2.2	9.3
J(7,8)	2.5	3.4	5.3	5.2	7.2	7.2	8.5	7.2
J(6,8)	0.9	1.2	–	–	–	–	–	–
C(5)	63.65	61.98	61.81			65.13[a])	64.48	62.57
C(6)	67.16[a])	67.32[a])	68.08[a])			65.22[a])	66.63	65.55
C(7)	79.09	79.42	79.83			73.18	71.40[a])	71.77
C(8)	69.58[a])	68.83[a])	68.45[a])			70.54	71.29[a])	67.88
C(8a)	148.91	149.22	151.44			153.99	154.25	154.04
O=C–C(5)	164.18	164.18	165.05			172.25	171.27	171.48

[a]) Assignments may be interchanged.

(9.4 mg, 0.225 mmol) and treated with Ph_2CN_2 (65 mg, 0.34 mmol), as described for the preparation of **55**, to give **73** (106 mg, 83%) and **74** (7.5 mg, 6%), after separation by HPLC (prep. HPLC, AcOEt/hexane 1:3).

b) *From* **67**. The lactam **67** (40 mg, 0.104 mmol) was transformed to **74** (37 mg, 63%) and **73** (9 mg, 15%) similarly as described for the preparation of **73**.

*Data of Diphenylmethyl (5*R,*6*R,*7*S,*8*S*)-7,8-Di*-O-*(benzyloxy)-5,6,7,8-tetrahydro-6-hydroxytetrazolo[1,2-*a*]pyridine-5-carboxylate* (**73**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.33. $[\alpha]_D^{25} = +65.3$ ($c = 1.03$, $CHCl_3$). IR (KBr): 3460*m* (br.), 3085*w*, 3063*w*, 3031*w*, 2984*w*, 2869*w*, 1957*w*, 1886*w*, 1810*w*, 1747*s*, 1604*w*, 1586*w*, 1496*m*, 1454*s*, 1395*w*, 1357*w*, 1270*s*, 1246*m*, 1209*s*, 1185*m*, 1133*w*, 1086*s*, 1028*w*, 980*s*, 949*w*, 914*w*, 845*w*, 816*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*; additionally, 7.37–7.17 (*m*, 16 arom. H); 7.09–7.05 (*m*, 2 arom. H); 6.89–6.86 (*m*, 2 arom. H); 6.73 (*s*, Ph_2CH); 4.828 (*d*, $J = 11.8$, PhC*H*); 4.72 (*d*, $J = 12.1$, PhC*H*); 3.97 (*d*, $J = 12.4$, PhC*H*); 3.89 (*d*, $J = 8.7$, exchange with CD_3OD, HO–C(4)); 3.87 (*d*, $J = 12.4$, PhC*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 139.02, 138.84, 135.74, 135.11 (4*s*); 128.70–126.74 (several *d*); 73.07 (*d*, Ph_2CH); 72.27, 72.06 (2*t*, 2 $PhCH_2$). ESI-MS: 563.0 (100, $[M+H]^+$). Anal. calc. for $C_{33}H_{30}N_4O_5$ (562.22): C 70.45, H 5.37, N 9.96; found: C 70.34, H 5.61, N 9.80.

*Data of Diphenylmethyl (5*S,*6*R,*7*S,*8*S*)-7,8-Di*-O-*(benzyloxy)-5,6,7,8-tetrahydro-6-hydroxtetrazolo[1,2-*a*]pyridine-5-carboxylate* (**74**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.33. $[\alpha]_D^{25} = +53.0$ ($c = 1.07$, $CHCl_3$). IR (KBr): 3480*w* (br.), 3089*w*, 3062*w*, 3029*w*, 3007*w*, 2905*w*, 1953*w*, 1883*w*, 1810*w*, 1748*s*, 1604*w*, 1496*m*, 1456*m*, 1377*w*, 1354*w*, 1310*w*, 1276*w*, 1238*w*, 1208*s*, 1186*m*, 1137*m*, 1112*m*, 1094*m*, 1079*m*, 1054*m*, 1032*w*, 1004*w*, 976*m*, 926*w*, 873*w*, 839*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*; additionally, 7.38–7.30 (*m*, 18 arom. H); 7.15–7.12 (*m*, 2 arom. H); 7.07 (*s*, Ph_2CH); 4.82 (*d*, $J = 11.5$, PhC*H*); 4.70 (*d*, $J = 11.8$, PhC*H*); 4.57 (*d*, $J = 12.1$, PhC*H*); 4.48 (*d*, $J = 11.8$, PhC*H*); 3.99 (*d*, $J = 9.6$, exchange with CD_3OD, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 138.82, 138.78, 135.88, 135.05 (4*s*); 128.72–127.01 (several *d*); 74.00 (*d*, Ph_2CH); 73.04, 72.43 (2*t*, 2 $PhCH_2$). ESI-MS: 563.0 (100, $[M+H]^+$). Anal. calc. for $C_{33}H_{30}N_4O_5$ (562.22): C 70.45, H 5.37, N 9.96; found: C 70.35, H 5.62, N 9.76.

Preparation of **76**. a) *From* **28**. The lactam **28** (95 mg, 0.25 mmol) was transformed to **76** (90 mg, 65%) similarly as described for the preparation of **73**.

b) *From* **60**. The lactam **60** (100 mg, 0.25 mmol) was transformed to **76** (91 mg, 65%) similarly as described for the preparation of **73**.

c) *From* **26**. The lactam **26** (185 mg, 0.43 mmol) was transformed to **76** (102 mg, 58%) similarly as described for the preparation of **73**.

*Diphenylmethyl (5*R*,6*S*,7*S*,8*S*)-7,8-Di*-O-*(benzyloxy)-5,6,7,8-tetrahydro-6-hydroxytetrazolo[1,2-*a*]-pyridine-5-carboxylate* (**76**). Oil. R_f (AcOEt/cyclohexane 1:2) 0.33. $[\alpha]_D^{25} = +34.9$ ($c = 1.08$, $CHCl_3$). IR (ATR): 3363*w* (br.), 3062*w*, 3031*w*, 2970*w*, 2941*w*, 2872*w*, 1955*w*, 1884*w*, 1811*w*, 1746*s*, 1621*w*, 1601*w*, 1586*w*, 1496*m*, 1454*m*, 1366*m*, 1275*m*, 1216*s*, 1155*m*, 1092*s*, 1027*m*, 977*s*, 947*m*, 909*m*, 872*w*, 841*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*; additionally, 7.37–7.25 (*m*, 18 arom. H); 7.15–7.12 (*m*, 2 arom. H); 6.96 (*s*, Ph_2CH); 5.03 (*d*, $J = 11.5$, PhC*H*); 4.81 (*d*, $J = 11.8$, PhC*H*); 4.57 (*d*, $J = 11.5$, PhC*H*); 4.44 (*d*, $J = 11.5$, PhC*H*); 2.63 (*d*, $J = 5.6$, irradiation at 4.65 → *s*, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 138.54, 138.40, 136.54, 136.46 (4*s*); 128.65–126.84 (several *d*); 77.96 (*d*, Ph_2CH); 73.56, 72.87 (2*t*, 2 $PhCH_2$). ESI-MS: 563.2 (100, $[M+H]^+$). Anal. calc. for $C_{33}H_{30}N_4O_5 \cdot 0.3\ H_2O$ (567.62): C 69.78, H 5.43, N 9.86; found: C 69.77, H 5.60, N 9.86.

Hydrogenolysis of **73**. The tetrazole **73** (48 mg, 0.085 mmol) was transformed to **77** (18 mg, 98%) similarly as described for the preparation of **56**. A soln. of **77** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **12** (20 mg, 98%).

*Data of (5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxytetrazolo[1,2-*a*]pyridine-5-carboxylic Acid* (**77**). M.p. 172–174°. $pK_{HA} = 2.53$. ^{1}H-NMR (300 MHz, D_2O): see *Table 6*. Anal. calc. for $C_6H_8NO_5 \cdot 1.15\ H_2O$ (236.87): C 30.42, H 4.38, N 23.65; found: C 30.67, H 4.19, N 23.42.

*Data of Sodium (5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxytetrazolo[1,2-*a*]pyridine-5-carboxylate* (**12**). $[\alpha]_D^{25} = -22.1$ ($c = 0.95$, H_2O). $pK_{HA} = 2.53$. IR (KBr): 3404*s* (br.), 2923*w*, 2852*w*, 1633*s*, 1460*w*, 1391*m*, 1308*w*, 1272*w*, 1193*w*, 1164*w*, 1108*m*, 1060*m*, 1007*w*, 894*w*, 827*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 6*. ^{13}C-NMR (75 MHz, D_2O): see *Table 6*. ESI-MS (neg. mode): 453.1 (60, $[2M - Na]^-$), 215.1 (100, $[M - Na]^-$).

Hydrogenolysis of **74**. The tetrazole **74** (40 mg, 0.071 mmol) was transformed into **78** (15 mg, 98%) similarly as described for the preparation of **56**. A soln. of **78** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **14** (16.5 mg, 98%).

*Data of (5*S*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxytetrazolo[1,2-*a*]pyridine-5-carboxylic Acid* (**78**). $pK_{HA} = 2.70$. ^{1}H-NMR (300 MHz, D_2O): see *Table 6*. Anal. calc. for $C_6H_8NO_5 \cdot 0.95\ H_2O$ (233.27): C 30.89, H 4.28, N 24.02; found: C 31.06, H 4.10, N 23.71.

*Data of Sodium (5*S*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxytetrazolo[1,2-*a*]pyridine-5-carboxylate* (**14**). M.p. 139° (dec.). $[\alpha]_D^{25} = -54.3$ ($c = 0.63$, H_2O). IR (KBr): 3418*s* (br.), 2921*w*, 2855*w*, 1631*s*, 1465*w*, 1391*m*, 1324*m*, 1267*w*, 1232*w*, 1208*w*, 1169*w*, 1112*m*, 1063*m*, 1028*w*, 992*w*, 897*w*, 863*w*, 846*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 6*. ^{13}C-NMR (75 MHz, D_2O): see *Table 6*. ESI-MS (neg. mode): 215.3 (100, $[M - Na]^-$).

Hydrogenolysis of **76**. The tetrazole **76** (40 mg, 0.71 mmol) was transformed to **79** (15 mg, 96%) similarly as described for the preparation of **56**. A soln. of **79** in H_2O was passed through a column of *Dowex 50W X2* (Na^+ form). Lyophilisation gave **13** (16 mg, 96%).

*Data of (5*R*,6*S*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxytetrazolo[1,2-*a*]pyridine-5-carboxylic Acid* (**79**). M.p. 178–180°. $pK_{HA} = 2.52$. Anal. calc. for $C_6H_8NO_5 \cdot 0.53\ H_2O$ (225.70): C 31.93, H 4.05, N 24.82; found: C 31.78, H 4.05, N 24.53.

*Data of Sodium (5*R*,6*S*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxytetrazolo[1,2-*a*]pyridine-5-carboxylate* (**13**). $[\alpha]_D^{25} = +14.7$ ($c = 1.02$, H_2O). IR (KBr): 3411*s* (br.), 2925*w*, 2855*w*, 1634*s*, 1465*w*, 1386*m*, 1339*m*, 1258*w*, 1224*w*, 1110*m*, 1065*w*, 1012*w*, 920*w*, 854*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 6*. ^{13}C-NMR (75 MHz, D_2O): see *Table 6*. ESI-MS (neg. mode): 453.1 (60, $[2M - Na]^-$), 215.1 (100, $[M - Na]^-$).

Inhibition Studies. Determination of the inhibition constants (K_i) was performed with a range of inhibitor concentrations (typically 5–7 concentrations) which bracket the K_i value, and substrate concentrations which bracket the K_M value of each enzyme (typically 3–6 concentrations).

a) *Inhibition of β-*D*-Glucuronidase from Bovine Liver*. $K_M = 0.17–0.34$ ([16]: 0.3 mM). Inhibition constants (K_i) were determined at 30° at an enzyme concentration of 0.019 units/ml, using a 0.1M acetate buffer (pH 5.0) and 4-nitrophenyl β-D-glucuronopyranoside as the substrate. The enzymatic reaction was started after incubation of the enzyme (120 µl) in the presence of inhibitor (50 µl) during 30 min at

30°, by the addition of the substrate (30 µl). The enzyme reaction was quenched by addition of 0.5M NaOH (100 µl) after 10–20 min and the absorption at 405 nm was taken as rate for the hydrolysis of the substrate. K_i Values were determined by taking the slopes from the *Lineweaver–Burk* plots [60] and plotting them *vs.* the inhibitor concentrations [61]. After fitting a straight line to the data by linear regression, the negative [*I*]-intercept of this plot provided the appropriate K_i value.

b) *Inhibition of Human α-L-Iduronidase.* $K_M \approx 50$ µM. Inhibition studies were carried out at 37° at an enzyme concentration of 0.015 µg/ml (assuming an enzyme mass of *ca.* 82 kDa, as observed by MALDI-MS), using a 100 mM 2,2-dimethylglutarate buffer (pH 4.5), containing 0.1% BSA and 4-methylumbelliferyl α-L-iduronide as the substrate. Assay is performed by incubating the substate, enzyme and inhibitor (appropriate concentrations) in 200 µl of buffer at 37°. At 3, 6, and 9 min, separate 20 µl aliquots are taken and immediately diluted in 1 ml of 100 mM glycine buffer (pH 10.7). Fluorescence measurements are obtained immediately upon mixing, and the three points are plotted to obtain a linear initial rate. K_i Values were determined as described in *a*).

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