Synthesis of novel pyrrolidine 3,4-diol derivatives as inhibitors of α-L-fucosidases†

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The stereoselective synthesis of new 3,4-dihydroxypyrrolidine derivatives starting from D-mannose, D-ribose and L-fucose is presented. Two synthetic strategies employing organometallic addition to hemiacetalic sugars followed by selective nucleophilic displacement or conjugate addition of ammonia to conjugate aldonic esters as key steps, are used. The new compounds were assayed for their inhibitory activity towards 13 commercially available glycosidases. Compounds that share the absolute configuration at C(2,3,4,5) of L-fucopyranosides and incorporate aromatic moieties are potent and selective inhibitors of α-L-fucosidases in the nM range.

Introduction

The role of glycosidases and glycosyltransferases in the biosynthesis of glycoproteins[1] and their control in recognition processes including cell/cell, cell/invader and inflammation,[2] has stimulated the development of their inhibitors. Many of them have shown great medicinal value as exemplified by the treatment of the influenza virus, non-insulin-dependent diabetes, or genetic disorders.[3,4] In particular α-L-fucosidases are enzymes that catalyze the hydrolysis of α-L-fucose units located on the cell surface oligosaccharides[5] and participate in a variety of biological processes.[6] The accumulation of fucose-containing glycoconjugates, because of the absence or deficiency of α-L-fucosidases leads to pathological modifications of normal cell behaviour such as inflammation,[7] tumor cell growth and formation of metastases,[8] neurovisceral disorders and cystic fibrosis.[9] α-L-Fucosidase activity is a diagnostic factor for several carcinomas.[10] α-L-fucosidases have been found in human seminal plasma and in the membranes of human sperm cells and facilitate sperm transport and sperm egg-interactions. Inhibitors of these enzymes can have anticonceptive properties.[11] Inhibitors of α-L-fucosidases have been also found to inhibit the cytophatic effect of HIV and reduce infection.[4]

Among the most powerful α-L-fucosidase inhibitors are derivatives of 1,5-dideoxy-1,5-iminoalditols, such as 1-deoxy-L-fuconojirimycin **1**,[12] homo-L-fuconojirimycin **2**[13] and L-fuconojirimycin (5-amino-5-deoxy-L-fucose) **3**.[14] 1,4-Dideoxy-1,4-iminoalditols are also an important class of glycosidase inhibitors, although their higher conformational flexibility reduces, in some instances, their selectivity.[15]

Iminoalditols having a carbon chain linked to the carbon adjacent to nitrogen, the so-called homoazasugars (aza-*C*-glycosides) have received special importance due to their stability towards chemical and enzymatic degradation, at the same time as retaining the same type of biological activity.[16] Homoazasugars bearing aminomethyl(ethyl), hydroxymethyl or 1,2-dihydroxyethylene groups as side chains, have been recently described.[17] With regard to their enzymatic inhibitory activity it has been reported that some homoanalogues of 1,5-dideoxy-1,5-iminoalditol derivatives are more active than the parent compounds.[18] Thus, β-homoanalogues **4**, **5** and **6**[19] have been described as potent α-L-fucosidase inhibitors in the nM range. Homoanalogues of 1,4-dideoxy-1,4-iminoalditol **7**[20] such as **8** and **9** are also potent inhibitors of α-L-fucosidases (**8**, K_i 1.4 μM),[21,22] (**9**, K_i 8 nM).[23] Compounds with an *R* configuration at C-5 (**10**[24,25] and **11**[22,24,26]) are inhibitors in the μM range (Fig. 1). Compounds with a spyrocyclopropyl moiety at C-5 have also been described as moderate inhibitors of α-L-fucosidases.[27] It has also been claimed that hydrophobic groups attached to the iminosugar improve their inhibitory activity through unspecific contributions to the binding with the enzyme.[28] The incorporation of aromatic moieties to L-fuconojirimycin derivatives increases the inhibitory activity remarkably[29] as in

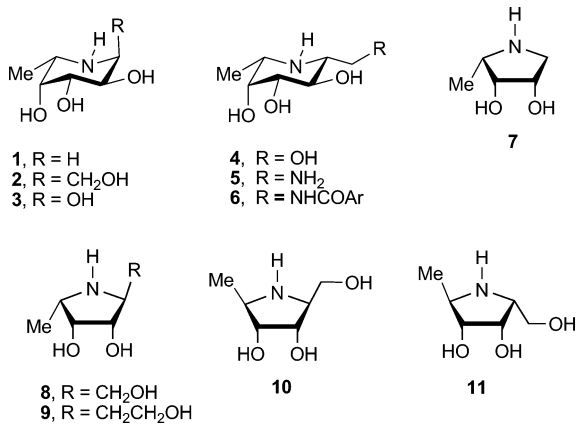

Fig. 1 α-L-Fucosidase inhibitors.

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† Electronic supplementary information (ESI) available: Further biological assays details and copies of ^{1}H- and ^{13}C-NMR spectra for compounds **19–21**, **24b**, **25b**, **39**, **40**, **42–47**, **49**,**50**,**54**, **59–61** and **63–66**. See DOI: 10.1039/b819867e

the case of amide **6**[30] with inhibitory activity in the pM range.

We and other authors have reported that the incorporation of aromatic moieties to the pyrrolidine framework greatly improves the activity and selectivity towards glycosidases.[31,32] In this regard, we have found that compounds **13** to **17** are better and more selective inhibitors than simple *meso*-pyrrolidine-3,4-diol (**12**) (Fig. 2). Recent work on the search of anti-cancer agents has shown that α-mannosidase inhibitors such as **13** have low cell membrane permeability and must be esterified to generate compounds with anti-cancer activity.[33] This suggests that less polar compounds than fuconojirimycin analogue **6** might be required to construct α-fucosidase inhibitors capable of penetrating cells. Thus, we have decided to explore the use of pyrrolidine-3,4-diol derivatives as templates for the creation of effective α-L-fucosidase inhibitors that could play a part in the development of potential drugs. With that aim a variety of 1,4-imino-*C*-heterocycles, aryl aminoalkyl pyrrolidines and related homoanalogues **18–21** were prepared by diversity oriented syntheses containing substitution or modification at C-2 and C-5 of the pyrrolidine framework.[34] It is believed that derivatives **18–21** with two hydroxyl groups should penetrate the cells more readily than compound **6** which has three hydroxyl groups. In addition, compound **18c** which bears a hydroxyethyl group on the pyrrolidine moiety and L-*fuco* configuration on C(2,3,4,5) is an interesting C-5 tethered imino-*C*-benzimidazole of interest for the preparation of affinity ligands for the purification of α-L-fucosidases.[35]

Our synthetic strategies start from isopropylidene protected hemiacetalic sugars (D-mannose, D-ribose and L-fucose) (Scheme 1). For the synthesis of compounds **18a**,**b** and **20a**,**b** the key intermediate is carbaldehyde **22** which is prepared by addition of methylmagnesium chloride as the key step, mesylation, chemoselective S_N2 and cyclization followed by acetal deprotection and glycol cleavage (pathway A). Compounds **18c**, **19a**, **19b**, **21a** and **21b** are prepared from ester derivatives **23**, **24** and **25** as

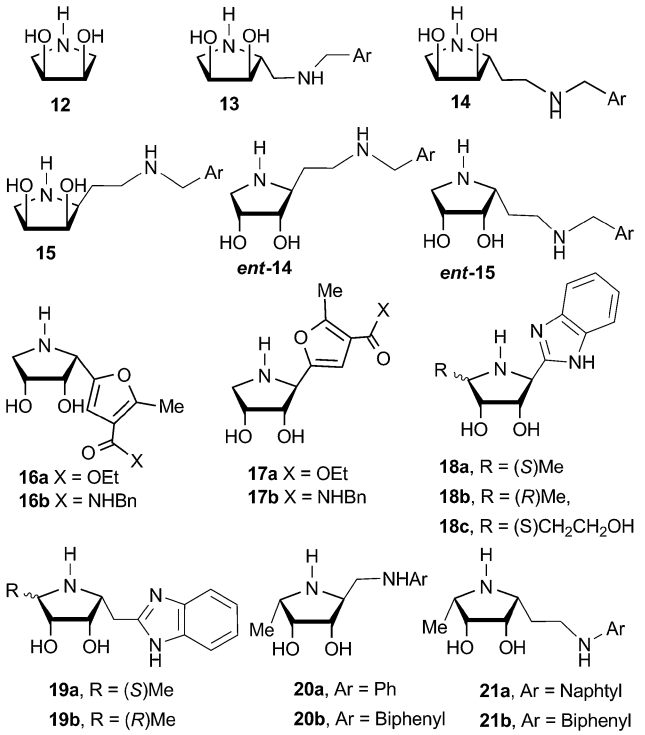
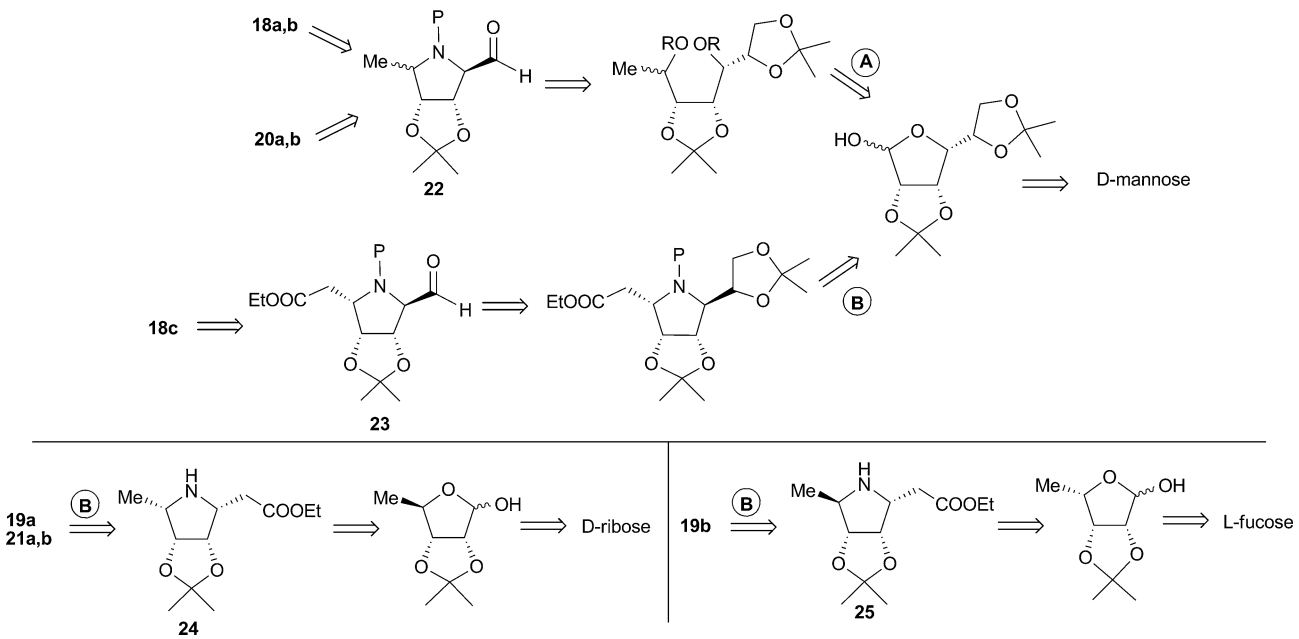


Fig. 2 α-L-Fucosidase inhibitors containing aromatic moieties.

key intermediates, respectively. These intermediates are obtained through conjugate addition of ammonia to unsaturated aldonic esters derived by Wittig reaction from sugar hemiacetals and tandem cyclization (pathway B).

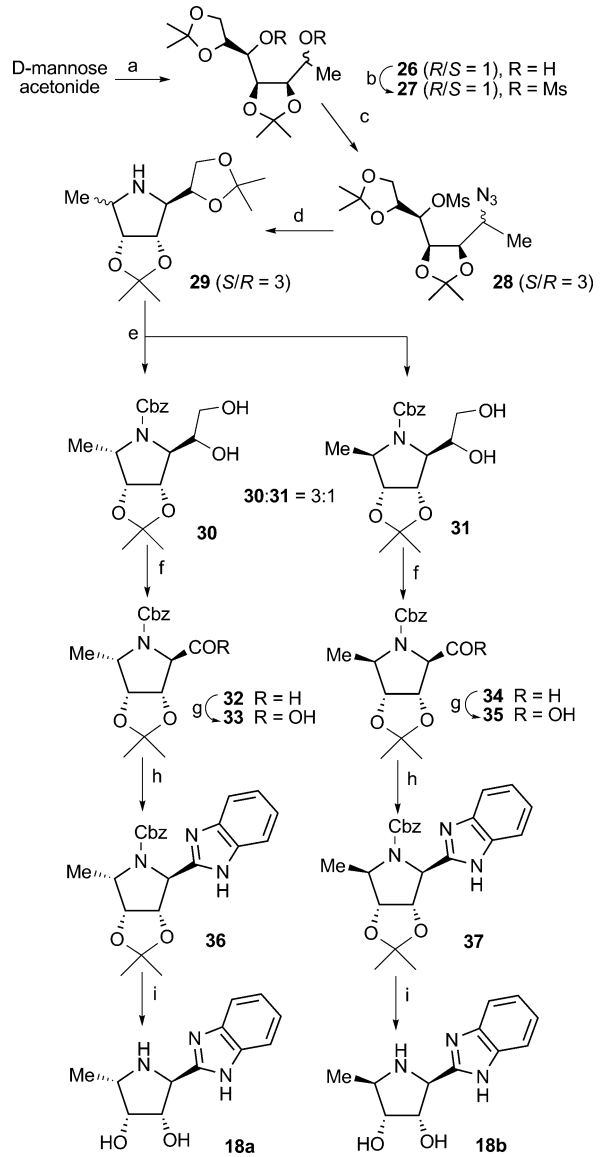
Results and discussion

Pathway A implies reaction of methylmagnesium chloride with commercially available D-mannose diacetonide which afforded



Scheme 1 Synthetic strategies.

a 1:1 mixture of diastereoisomeric diols (2*R*)-**26** and (2*S*)-**26** in 95% yield (Scheme 2). Standard mesylation of the diols provided a 1:1 mixture of dimesylates (2*R*)-**27** and (2*S*)-**27** in 75% yield, that after treatment with Me_3SiN_3 and Bu_4NF in DMF afforded a 3:1 mixture of azides (2*S*)-**28** and (2*R*)-**28** in 55% yield. This result indicates that the chemoselective S_N2 displacement of the mesyloxy group at C-2 of **27** is somehow faster with (2*R*)-**27** than with (2*S*)-**27**.[34]

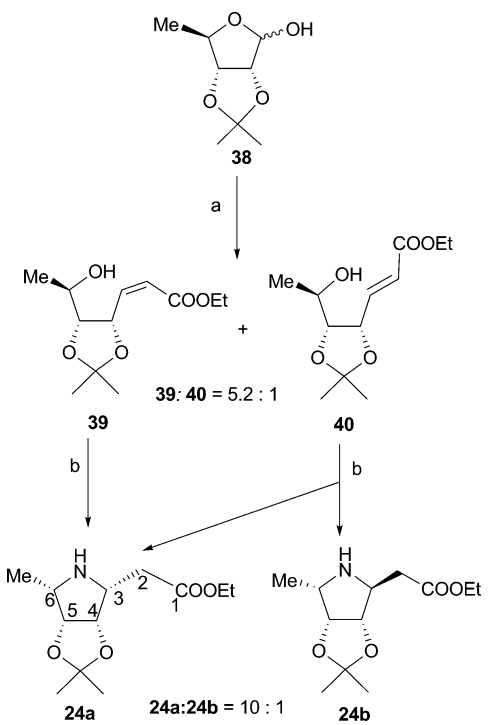


Scheme 2 *Reagents and conditions*: (a) MeMgCl, THF, r.t., 95%; (b) MsCl, pyridine, DMAP, 75%; (c) $TMSN_3$ (4 eq.)/TBAF (4 eq.), DMF, 90 °C, 4.5 h, 55% (74% from converted substrate); (d) (1) H_2, Pd/C, MeOH; (2) MeOH, DBU, 99% (1+2); (e) (1) CbzCl, $NaHCO_3$, EtOH/H_2O (1/1); (2) $Zn(NO_3)_2.6H_2O$, MeCN, 50 °C; (3) Flash chromatography; 58% (1+2+3); (f) $NaIO_4$, THF-H_2O; (g) $NaClO_2$, KH_2PO_4, Bu^tOH-H_2O; (h) (1) *o*-phenylenediamine, PyBOP, DIPEA, DMF, 65%; (2) AcOH, 50 °C, 100%; (i) (1) THF:HCl 1 M 1:1; (2) H_2, Pd/C, MeOH; 87% (1+2).

Catalytic hydrogenation of azides **28** gave a 3:1 mixture of primary amines that were not isolated but treated directly with DBU in MeOH. This promoted the intramolecular displacement of the mesyloxy group at C-5 giving a 3:1 mixture of (5*S*)-**29** and (5*R*)-**29** in quantitative yield. Amine protection as benzylcarbamate followed by selective hydrolysis of the least sterically hindered acetonides ($Zn(NO_3)_2$, H_2O/MeCN)[36] provided a 3:1 mixture of diols **30** and **31** that were readily separated by flash chromatography on silica gel (58% overall yield in three steps). Standard oxidative cleavage of the diols **30** and **31** with $NaIO_4$ furnished aldehydes **32** (92%) and **34** (100%), respectively.

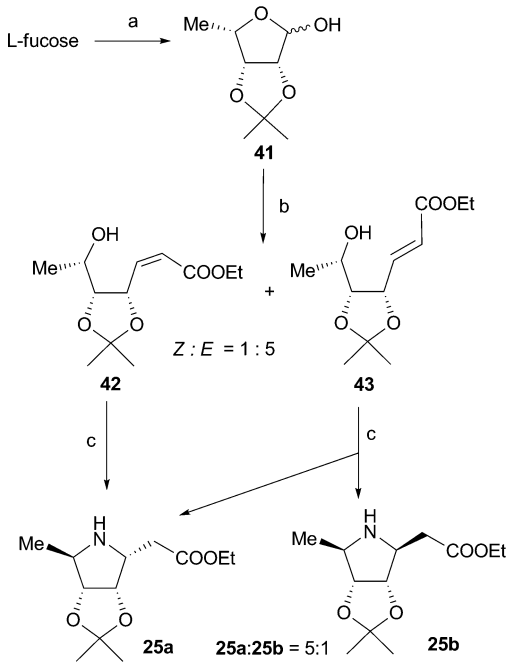
The structures of the 2,5-dideoxy-2,5-iminoalditol derivatives **30** and **31** were established by their spectral data and the relative configurations confirmed by NOE.[34] Oxidation of aldehyde **32** gave the corresponding carboxylic acid **33** (82% yield). Reaction with *o*-phenylenediamine in the presence of PyBOP and DIPEA and heating in AcOH at 50 °C followed by deprotection under standard conditions yielded benzimidazole derivative **18a** (Scheme 2). The same reaction sequence applied to aldehyde **34** provided benzimidazole **18b**.

The synthesis of **19a** and **19b** was carried out following pathway B which starts from known hemiacetal **38** obtained from D-ribose by applying Bols' procedure.[37] Reaction of lactol **38** with ethoxycarbonylmethylene triphenylphosphorane in dichloromethane under reflux afforded a mixture of alkenes **39** and **40** in 90% yield and a ratio $Z:E = 5.2:1$. Mesylation of **39** and **40** followed by treatment with ammonia in ethanol furnished the corresponding pyrrolidines through tandem conjugate addition-internal S_N2 displacement. Starting from *Z*-alkene **39**, pyrrolidine **24a** was obtained as unique stereoisomer in 76% overall yield, whereas the same procedure applied to *E*-alkene **40** afforded a mixture of **24a** and **24b** in 60% overall yield, and a ratio, **24a**:**24b** = 10:1 (Scheme 3). The structures of **24a** and **24b** were based on their spectroscopic and analytical data.[34]



Scheme 3 *Reagents and conditions*: (a) $Ph_3P{=}CH_2COOEt$, CH_2Cl_2 reflux, 90%. (b) (i) MsCl, Py. (ii) NH_3, EtOH, 76% (from **39**), 60% (from **40**).

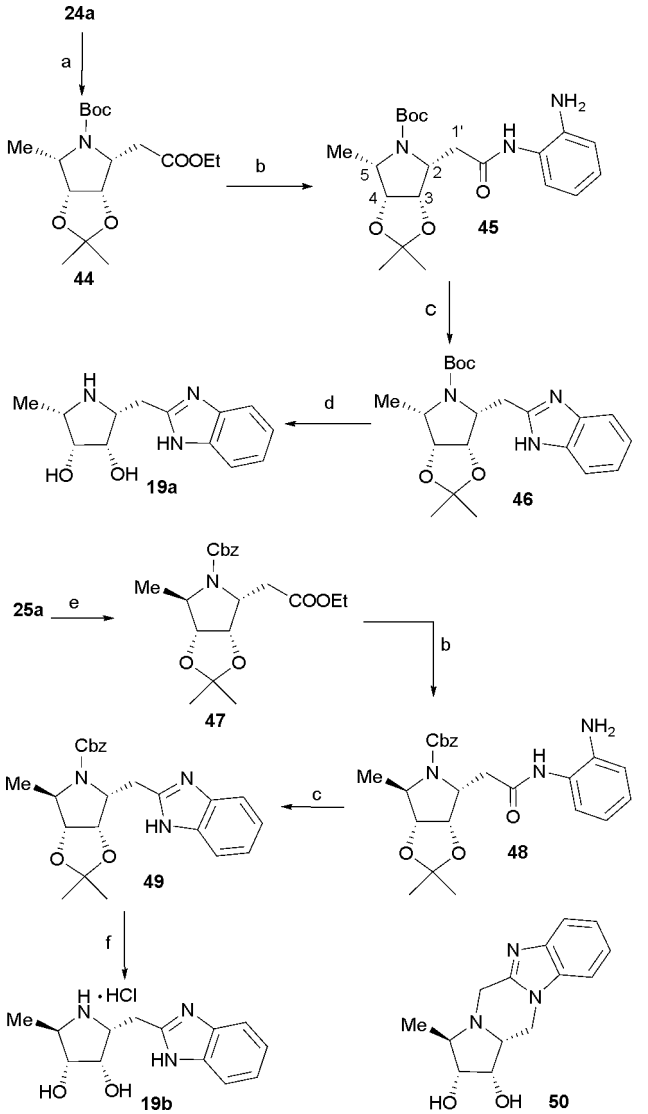
When a similar synthetic route was applied to L-fucose, pyrrolidines **25a** and **25b**, epimers at C-6 of **24a** and **24b**, were obtained. Thus, L-fucose acetonide formation followed by glycol cleavage, basic hydrolysis and neutralization gave lactol **41**. Subsequent Wittig olefination afforded alkenes **42** and **43** in 70% yield and a ratio *Z:E* = 1:5 (Scheme 4). The formation of pyrrolidines **25a** and **25b** from **42** and **43** followed the same stereochemical outcome than for the *ribo* series and is in accordance to that described for the *erythro* and *manno* series.[38] Pyrrolidine **25a** was obtained as a single diastereoisomer from *Z*-alkene **42** in 63% overall yield. The same reaction conditions applied to *E*- alkene **43** afforded a mixture of pyrrolidines **25a** and **25b** in a ratio **25a**:**25b** = 5:1. Their structures are based on their spectroscopic and analytical data. NOESY spectrum of **25a** showed NOEs between proton signals H3(δ = 3.44) and H4(δ = 4.66) and Me-6(δ = 1.05), indicating a *cis* relationship between H3 and H4 and *trans* relationship between H3 and H6. In the case of compound **25b** the NOESY spectrum showed NOEs between protons H2a(δ = 2.7), H4(δ = 4.29) and H2b(δ = 2.48), and between proton pairs H3(δ = 3.41) and H6(δ = 3.20), which indicates a *cis* relative configuration between H3 and H6 and *trans* relative configuration between H3 and H4.



Scheme 4 *Reagents and conditions*: (a) (i) 2,2-DMP, PTSA. (ii) $NaIO_4$, H_2O. (iii) NaOH. (iv) HCl, 65% (overall). (b) $Ph_3P{=}CH_2COOEt$, toluene, reflux, 70%. (c) (i) MsCl, Py. (ii) NH_3, EtOH, 63% (from **42**), 50% (from **43**).

The preparation of the benzimidazolyl derivative **19a** started from *N*-Boc protected pyrrolidine **44**. Saponification followed by reaction with *o*-phenylenediamine in the presence of PyBOP and DIPEA afforded amide **45** in 76% yield. Subsequent cyclization and acidic deprotection gave the target compound **19a** (Scheme 5).

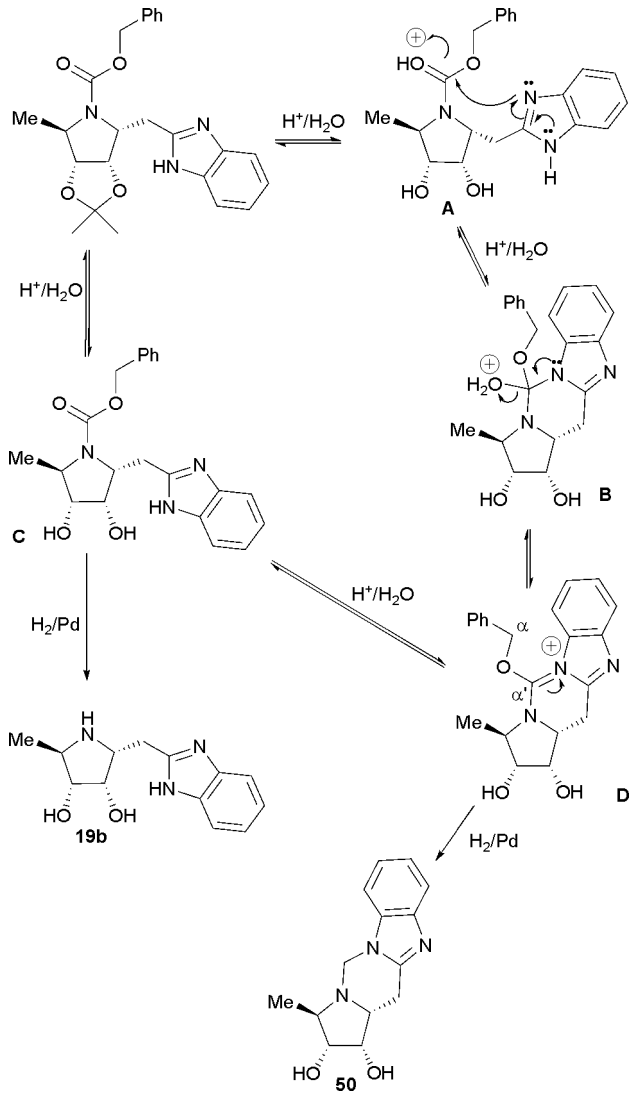
For the synthesis of the benzimidazolyl epimer **19b**, a similar synthetic route was applied but starting from benzyloxycarbonyl carbamate **47**. Cyclization of amide **48** in AcOH at 50 °C gave quantitatively protected benzimidazolyl derivative **49**. Elimination of the benzyloxycarbonyl and isopropylidene groups by



Scheme 5 *Reagents and conditions*: (a) Boc_2O, Py, 92%. (b) (i) NaOH, EtOH. (ii) *o*-phenylenediamine, PyBOP, DIEA, DMF, 76% (for **45**), 89% (for **48**). (c) AcOH, 50 °C, quant. (for **46** and **49**). (d) (i) HCl. (ii) NH_4OH, 64%. (e) CbzCl, EtOH, $NaHCO_3$, 90%. (f) (i) H_2, Pd/C, MeOH. (ii) HCl, THF, 58%.

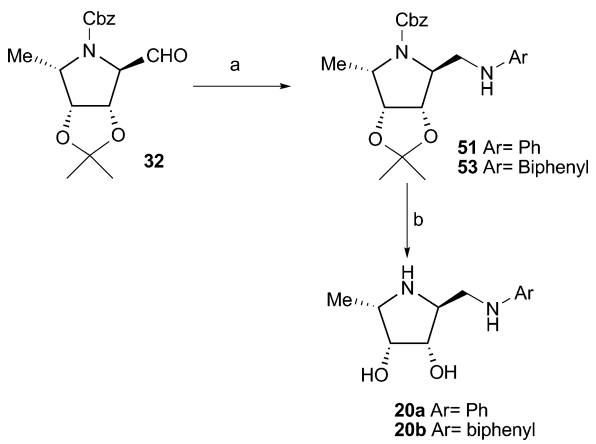
hydrogenolysis and acidic treatment gave **19b** in 58% overall yield (Scheme 5). However, in some instances, these deprotection steps applied over **49** afforded the unexpected compound **50**, isolated as the major product which was fully characterized by its spectral data (see Supporting Information). A possible mechanism for the formation of compounds **19b** or **50** is shown in Scheme 6. Nucleophilic attack by a nitrogen of the benzimidazole ring over the carbamate group under acidic conditions followed by hydrogenolysis of the Cα-O and Cα′-O bonds on intermediate **D**, affords compound **50** with a methylene bridge between pyrrolidine and benzimidazole nitrogens (Hα′a (δ = 5.26, d, $J_{\alpha'a,\alpha'b}$ = 12.6) and Hα′b (δ = 5.05, d)).

The synthesis of aminomethyl pyrrolidines **20a** and **20b** was carried out starting from aldehyde **32**. Reductive amination of **32** with aniline provided derivative **51** (75%), which after deprotection under standard conditions, afforded diamine **20a** in quantitative



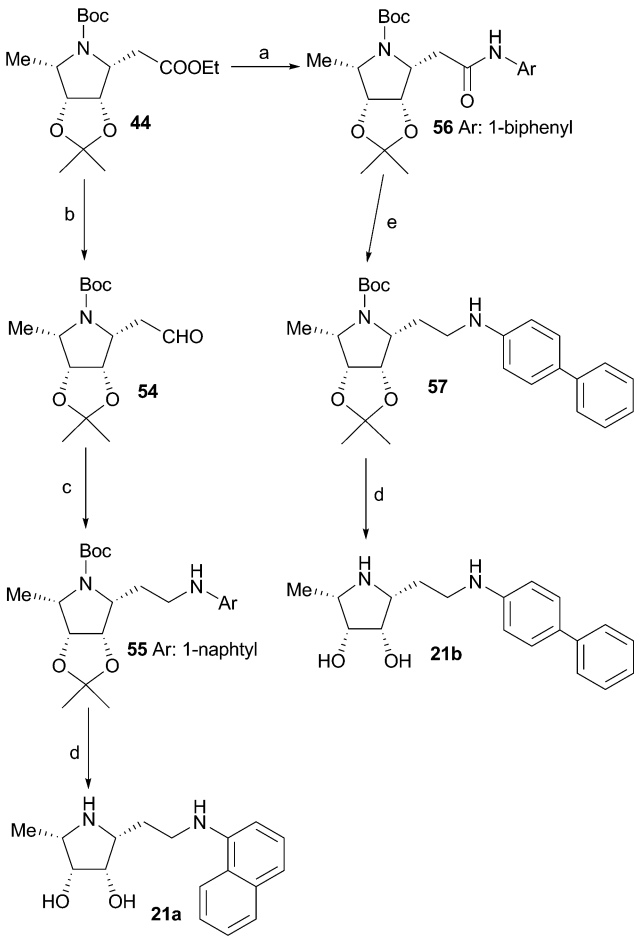
Scheme 6 Proposed mechanism for the formation of **50**.

yield. Following a similar synthetic route and using biphenyl-4-amine for the condensation with the aldehyde **32**, derivative **20b** was obtained (Scheme 7).



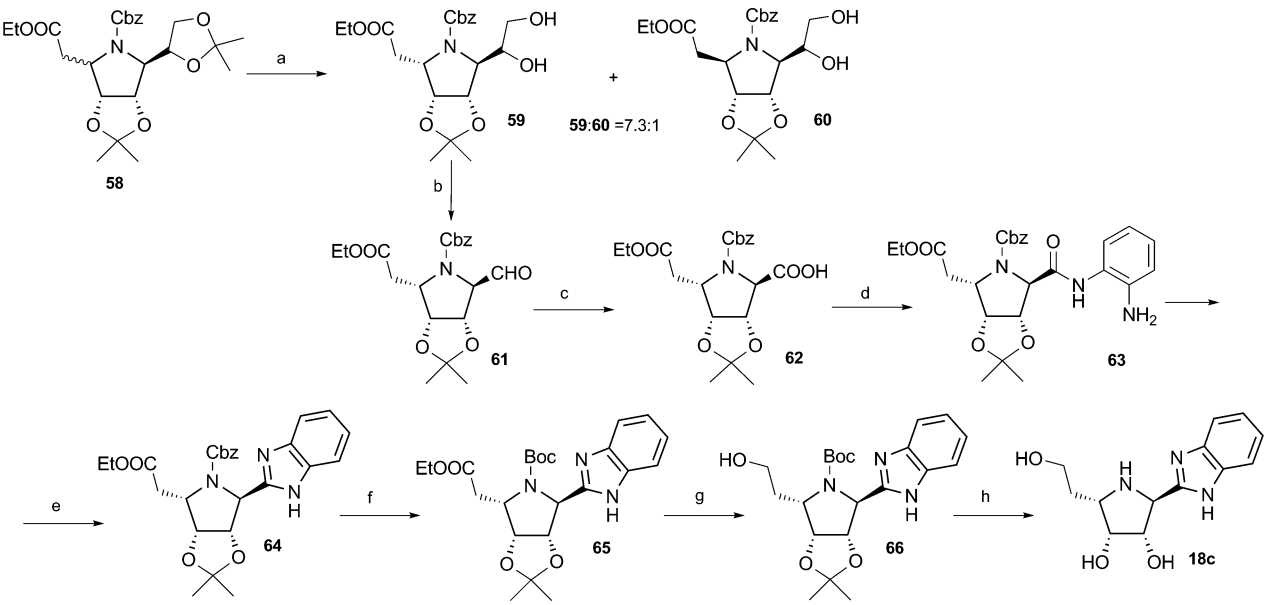
Scheme 7 *Reagents and conditions*: (a) $ArNH_2$, $NaBH(AcO)_3$, 66–75%. (b) (i) HCl (1M). (ii) H_2, Pd/C, MeOH, quant.

The synthesis of naphthalene-1-amino ethyl pyrrolidine **21a** was carried out by the reductive amination of aldehyde **54** with naphthalene-1-amine (85%) followed by acidic deprotection. Carbaldehyde **54** was obtained from **44** by reduction with DIBALH in 74% yield (Scheme 8). Biphenylaminoethyl pyrrolidine **21b** was prepared starting from ethyl ester **44**. Saponification and reaction with biphenyl-4-amine in the presence of PyBOP and DIPEA gave amide **56** in 71% yield. Reduction with $BH_3.SMe_2$ afforded diamine **57**, from which acidic deprotection gave **21b** in 84% overall yield (from **56**).



Scheme 8 *Reagents and conditions*: (a) (i) NaOH, EtOH. (ii) Ar-NH_2, PyBOP, DIEA, DMF, 71%. (b) DIBALH, CH_2Cl_2, −78 °C, 74%. (c) $ArNH_2$, $NaBH(AcO)_3$, 85%. (d) (i) HCl (1M), THF. (ii) NH_4OH, 62% (for **21a**), 97% (for **21b**). (e) BH_3, Me_2S, THF, 89%.

The synthesis of **18c** was carried out in a similar way (Scheme 9). Thus, starting from a mixture 12:1 of pyrrolidines **58**,[38] selective acetonide hydrolysis followed by chromatographic purification, allowed for the separation of pyrrolidines **59** and **60**. Oxidative cleavage of major derivative **59** and subsequent coupling reaction of the corresponding carboxylic acid **62** with *o*-phenylenediamine followed by cyclization afforded benzimidazole derivative **64**. Protecting group manipulation followed by reduction of the ester moiety and final deprotection afforded benzimidazole derivative **18c**.



Scheme 9 *Reagents and conditions*: (a) $Zn(NO_3)_2 \cdot 6H_2O$, MeCN, 50 °C, 75%. (b) $NaIO_4$, THF-H_2O, 93%. (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 87%. (d) *o*-phenylenediamine, PyBOP, DIEA, DMF, 88%. (e) AcOH, 50 °C, 96%. (f) H_2, Pd/C, $(Boc)_2O$, MeOH, 80%. (g) $LiAlH_4$, THF, 0 °C, 96%. (h) (i) HCl (4M). (ii) NH_4OH, 92%.

Biological evaluation of 3,4-dihydroxypyrrolidine derivatives towards glycosidases

The new compounds **18a–c**, **19a–b**, **20a–b** and **21a–b** have been assayed for their inhibitory activity towards 13 commercially available glycosidases.[39] At 1 mM concentration and under enzyme optimal pH they did not inhibit the β-galactosidases from *Aspergillus niger* and *Escherichia coli*, α-glucosidases from yeast and rice, α-mannosidases from Jack beans, β-mannosidases from snail, β-xylosidases from *Aspergillus niger* and β-acetylglucosaminidase from Jack beans and from bovine kidney. Table 1 summarises the inhibitory activity measured towards α-L-fucosidase from bovine kidney, β-galactosidase from bovine liver, amyloglucosidase from *Aspergillus niger* and β-glucosidase from almonds. Apart from the benzimidazole derivatives **18a** and **18c** that inhibit only α-L-fucosidases at 1 mM concentration, the other 5-methyl-3,4-dihydroxypyrrolidine derivatives present weak inhibitory activity toward β-galactosidase from bovine liver, but not towards other β-galactosidases. The former enzyme is known to be poorly selective and to be inhibited by almost any amine, so the results of Table 1 should not be taken as a lack of α-L fucosidase selectivity of pyrrolidines **18b**, **19a**, **19b**, **20b**, **21a** and **21b**. As expected, the best inhibitory activities and selectivities towards α-L-fucosidases were observed for pyrrolidines **18a** (K_i = 80 nM) and **20b** (K_i = 40 nM) that share the same absolute configuration than C(2,3,4,5) of α-L-fucopyranosides.

Table 1 Inhibitory activities of 3,4-dihydroxypyrrolidine derivatives **18**, **19**, **20** and **21** toward glycosidases. Percentage of inhibition at 1 mM, IC_{50} (in parentheses, μM) and K_i (bold, μM) if measured. Optimal pH, 35 °C[a,b,c]

	α-fucosidase	β-galactosidase	amyloglucosidase	β-glucosidase
18a	100%			
	K_i = 0.080 (C)	ni	ni	ni
18b	94%			94%
	K_i = 240 (C)	48%	ni	**K_i = 46 (NC)**
18c	85% (140)	ni	ni	ni
19a	95% (11)	62%	37%	32%
	K_i = 1.2 (C)			
19b	79%	45%	ni	59%
20a	99%	ni	ni	ni
	K_i = 0.237 (C)			
20b	99% (0.3)	47%	39%	ni
	K_i = 0.040 (C)			
21a	89% (24)	73%	ni	ni
	K_i = 2.4 (C)			
21b	95% (21)	83%	18%	ni
	K_i = 2.4 (C)			

[a] For conditions of measurements see ref. 39. [b] (C): competitive, (NC): non-competitive from Lineweaver-Burk plots, ni: no inhibition at 1 mM concentration of the inhibitor. [c] α-L-fucosidase from bovine kidney, β-galactosidase from bovine liver, Amyloglucosidase from *Aspergillus niger*, β-glucosidase from almonds.

Conclusions

New 3,4-dihydroxypyrrolidine derivatives have been obtained in a highly stereoselective manner starting from D-mannose, D-ribose and L-fucose. They have been assayed for their inhibitory activity towards 13 glycosidases. Compounds **18a** and **20b** with a (5*S*)-methyl group that share the absolute configuration of C(2,3,4,5) of L-fucopyranosides are potent and selective inhibitors of α-L-fucosidase from bovine kidney (K_i = 80 and 40 nM respectively). We have found that the (5*S*)-5-methylsubstituent (compounds **19a**, **20b**, **21a**, **21b**) leads to significantly better inhibitory activities than the (5*R*)-5-methyl substituent (compounds **18b**, **19b**) and that substitution at C(2) of the pyrrolidine ring by a (2*S*)-substituent (**18a**, **20b**) generates better inhibitors than the corresponding homoanalogues with (2*R*)-substituents (**19a**, **21b**).

Experimental

General methods

Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Perkin–Elmer 241MC spectropolarimeter. ^{1}H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$, [d_6]DMSO, CD_3OD and D_2O; J values are given in Hz and δ in ppm. All the assignments were confirmed by two-dimensional NMR experiments. The FAB mass spectra were obtained using glycerol or 3-nitrobenzyl alcohol as the matrix. TLC was performed on silica gel HF_{254} (Merck), with detection by UV light charring with H_2SO_4 or with Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography.

Experimental procedures and characterization data for the new compounds

(*Z*)- and (*E*)-Ethyl 2,3,7-trideoxy-4,5-*O*-isopropylidene-D-*ribo*-hept-2-enoate (39 and 40). To a solution of **38**[37] (0.886 g, 5.09 mmol) in dry CH_2Cl_2 (31 mL), ethoxycarbonyltriphenylmethylenephosphorane (2.66 g, 7.63 mmol) was added, and the mixture was heated under reflux for 6 h. After evaporation of the solvent, the residue was purified by column chromatography (ethyl acetate/petroleum ether 1:5) affording **39** (939 mg, 3.85 mmoles, 76%) and **40** (181 mg, 0.74 mmol, 14%) as oils. Data for **39**: $[\alpha]_D$ +47.5 (*c* 1.2 in CH_2Cl_2). IR (ν cm^{-1}) 3483 (OH), 2986, 2936, 1728 (C=O), 1646 (C=C), 1195, 1057, 871. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) δ 1.16 (3H, d, $J_{Me\text{-}6,6} = 6.0$, 6-Me), 1.28 (3H, t, $^2J_{H,H} = 7.5$, CH_2CH_3), 1.39, 1.51 (3H each, 2 s, $C(CH_3)_2$), 2.89 (1H, bs, OH), 3.74 (1H, dq, $J_{6,5} = 7.5$, 6-H), 4.14 (1H, dd, $J_{5,4} = 6.5$, 5-H), 4.19 (2H, qd, $J = 1.0$, CH_2CH_3), 5.54 (1H, ddd, $J_{4,2} = 1.0$, $J_{4,3} = 8.5$, 4-H), 6.00 (1H, dd, $J_{2,3} = 11.5$, 2-H), 6.28 (1H, dd, 3-H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ 14.3 (CH_2CH_3), 19.8 (6-Me), 25.6, 28.0 ($C(CH_3)_2$), 61.3 (CH_2CH_3), 66.7 (C-6), 76.9 (C-4), 83.2 (C-5), 109.4 ($C(CH_3)_2$), 122.0 (C-2), 146.8 (C-3), 167.2 (C=O). FABMS 267 [(M + Na)$^+$, 93%], 245 [(M + H)$^+$, 100%]. FABHRMS *m/z* found 267.1210, calcd. for $C_{12}H_{20}O_5Na$ (M + Na)$^+$: 267.1208. Data for **40**: $[\alpha]_D$ –4.0 (*c* 0.5 in CH_2Cl_2). IR (ν cm^{-1}) 3447 (OH), 2983, 2927, 1720 (C=O), 1371, 1302. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.27 (d, 3H, $J_{Me,6} = 6.3$, 6-Me), 1.28 (3H, t, $^2J_{H,H} = 7.2$, CH_2CH_3), 1.38, 1.49 (3H each, 2 s, $C(CH_3)_2$), 1.86 (1H, bs, OH), 3.75 (1H, dq, $J_{6,5} = 8.1$, 6-H), 4.00 (1H, dd, $J_{5,4} = 6.6$, 5-H), 4.19 (2H, q, CH_2CH_3), 4.81 (1H, m, 4-H), 6.09 (1H, dd, $J_{2,3} = 15.6$, $J_{2,4} = 1.5$, 2-H), 7.09 (1H, dd, $J_{3,4} = 5.4$, 3-H).^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 14.4 (CH_2CH_3), 21.1 (6-Me), 25.6, 27.7 ($C(CH_3)_2$), 60.7 (CH_2CH_3), 66.5 (C-6), 76.8 (C-4), 82.1 (C-5), 109.4 ($C(CH_3)_2$), 122.5 (C-2), 144.1 (C-3), 166.5 (C=O). FABMS 267 [(M + Na)$^+$, 100%]. FABHRMS *m/z* found 267.1207, calcd. for $C_{12}H_{20}O_5Na$ (M + Na)$^+$: 267.1208.

Ethyl 2,3,6,7-tetradeoxy-3,6-imino-4,5-*O*-isopropylidene-L-*galacto*-heptanoate ((2*R*,3*S*,4*R*,5*S*)-2-ethoxycarbonylmethyl-3,4-*O*-isopropylidene-5-methyl-pyrrolidine-3,4-diol) (24a). A solution of **39** (0.543 g, 2.23 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of MsCl (0.54 mL, 6.99 mmol) in dry pyridine (2.2 mL) cooled to 0 °C. After stirring at r.t. overnight, the mixture was cooled to 0 °C, H_2O (5 mL) was added and the reaction stirred for 15 min at r.t. The solvent was then evaporated, the crude was diluted with dichloromethane (30 mL) and washed with H_2O (2 × 30 mL) and brine (30 mL). The organic phase was dried, filtered and concentrated. The obtained residue was dissolved in absolute EtOH (20 mL), cooled to 0 °C and saturated with NH_3. After 5 days at r.t., the solvent was evaporated and the residue was treated with NH_4OH (25%, 30 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The organic phase was washed with satd. aq. sol. of $NaHCO_3$ (30 mL) and H_2O until neutral pH, dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by column chromatography (ether:acetone (5:1), Et_3N (1%)) to give pure **24a** (0.389 g, 76%). $[\alpha]_D$ –12.7 (*c* 1.2 in CH_2Cl_2). IR (ν cm^{-1}) 3444 (b, NH), 2981, 2934, 1734 (C=O), 1376, 1208, 1012. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.20 (3H, d, $J_{Me,6} = 6.6$, 6-Me), 1.26 (3H, t, $^2J_{H,H} = 7.1$, CH_2CH_3), 1.30, 1.44 (3H each, 2 s, $C(CH_3)_2$), 1.88 (1H, bs, NH), 2.57 (1H, dd, $^2J_{2a,2b} = 16.5$, $J_{2a,3} = 6.6$, 2a-H), 2.66 (1H, dd, $J_{2b,3} = 6.6$, 2b-H), 2.86 (1H, qd, $J_{6,5} = 4.0$, 6-H), 3.14 (1H, td, $J_{3,4} = 4.1$, 3-H), 4.15 (2H, qd, $J = 1.4$, CH_2CH_3), 4.47 (1H, dd, $J_{5,4} = 5.5$, 5-H), 4.62 (1H, dd, 4-H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 13.4 (CH_2CH_3), 14.3 (6-Me), 24.3, 25.8 ($C(CH_3)_2$), 33.6 (C-2), 57.7 (C-6), 58.8 (C-3), 60.7 (CH_2CH_3), 82.4 (C-4), 83.2 (C-5), 110.9 ($C(CH_3)_2$), 172.1 (C=O). CIMS 244 [(M + H)$^+$, 90%]. CIHRMS *m/z* found 244.1551, calcd. for $C_{12}H_{22}NO_4$ (M + H)$^+$: 244.1549. Anal. calcd. for $C_{27}H_{34}N_2O_5$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.75; H, 8.82; N, 5.61.

Ethyl 2,3,6,7-tetradeoxy-3,6-imino-4,5-*O*-isopropylidene-L-*galacto*-heptanoate and ethyl 2,3,6,7-tetradeoxy-3,6-imino-4,5-*O*-isopropylidene-L-*talo*-heptanoate ((2*R* and 2*S*,3*S*,4*R*,5*S*)-2-ethoxycarbonylmethyl-3,4-*O*-isopropylidene-5-methyl-pyrrolidine-3,4-diol) (24a and 24b). Conventional mesylation of compound **40** (162 mg, 0.66 mmol) followed by NH_3 treatment and chromatographic purification as indicated for the preparation of **24a** afforded pyrrolidines **24a** (88.2 mg, 0.36 mmol, 55%) and **24b** (8.8 mg, 0.036 mmol, 5%). Data for **24b**: $[\alpha]_D$ +4.5 (*c* 0.7 in CH_2Cl_2). IR (ν cm^{-1}) 3448, (bs, NH), 2981, 2934, 1734 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.20 (d, 3H, $J_{Me,6} = 6.6$, 6-Me), 1.25 (3H, t, $^2J_{H,H} = 7.2$, CH_2CH_3), 1.30, 1.46 (3H each, 2 s, $C(CH_3)_2$), 1.97 (1H, bs, NH), 2.33 (1H, dd, $^2J_{2a,2b} = 15.3$, $J_{2a,3} = 7.8$, 2a-H), 2.41 (1H, dd, $J_{2b,3} = 7.8$, 2b-H), 3.07 (1H, qd, $J_{6,5} = 3.6$, 6-H), 3.59 (1H, t, 3-H), 4.16 (2H, q, CH_2CH_3), 4.46–4.52 (2H, m, 4-H, 5-H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 13.5 (6-Me), 14.3 (CH_2CH_3), 24.2, 26.2 ($C(CH_3)_2$), 36.8 (C-2), 56.2 (C-6), 60.7 (CH_2CH_3), 61.2 (C-3), 83.2, 86.5 (C-5, C-4), 111.2 ($C(CH_3)_2$), 171.5 (C=O). CIMS 244 [(M + H)$^+$, 47%]. CIHRMS *m/z* found 244.1548, calcd. for $C_{12}H_{22}NO_4$ (M + H)$^+$: 244.1549.

Ethyl *N*-(*tert*-butoxycarbonyl)-2,3,6,7-tetradeoxy-3,6-imino-4,5-*O*-isopropylidene-L-*galacto*-heptanoate ((2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-ethoxycarbonylmethyl-3,4-*O*-isopropylidene-5-methyl-pyrrolidine-3,4-diol) (44). To a solution of **24a** (0.306 g, 1.26 mmol) in dry pyridine (4.3 mL) was added a solution of Boc_2O (0.696 g, 2.99 mmol) in dry pyridine (2.9 mL). The mixture was left at r.t. for 3 h. After evaporation of the solvent, the residue was dissolved in AcOEt (25 mL) and washed twice with brine (25 mL). The dried organic phase was evaporated and the resulting residue was purified by column chromatography (ether:petroleum ether, 1:2) to give pure **44** (0.401 g, 93%) as a syrup. $[\alpha]_D$ –12.8 (*c* 1 in CH_2Cl_2). IR (ν cm^{-1}) 2981, 2937, 1736 (C=O), 1696 (C=O), 1383, 1171. ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm) δ 1.15 (3H, d, $J_{Me,6} = 7.0$, 6-Me), 1.19 (3H, t, $^2J_{H,H} = 7.2$, CH_2CH_3), 1.29 (3H, s,

C(CH_3)$_2$), 1.41 (9H, s, C(CH_3)$_3$), 1.45 (3H, s, C(CH_3)$_2$), 2.47 (1H, dd, $^2J_{2a,2b}$ = 16.0, $J_{2a,3}$ = 10.5, 2a-H), 2.67 (1H, dd, $J_{2b,3}$ = 4.5, 2b-H), 3.94 (1H, q, $J_{6,5}$ = 7.0, 6-H), 4.06 (2H, m, CH_2CH$_3$), 4.26 (1H, ddd, $J_{3,4}$ = 7.0, 3-H), 4.73 (1H, t, $J_{5,4}$ = 7.0, 5-H), 4.79 (1H, t, 4-H). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 13.5 (6-Me), 15.8 (CH$_2$CH_3), 24.2, 24.5 (C(CH_3)$_2$), 27.7 (C(CH_3)$_3$), 35.8 (C-2), 53.9 (C-6), 55.4 (C-3), 59.1 (CH_2CH$_3$), 78.1 (C-4), 78.7 (C(CH$_3$)$_3$), 79.2 (C-5), 111.3 (C(CH$_3$)$_2$), 153.0 (C=O of Boc), 170.0 (COOEt). CIMS 343 [(M)$^+$, 4%], 244 [(M − Boc + 2H)$^+$, 100%]. CIHRMS *m/z* found 343.1990, calcd. for $C_{17}H_{29}NO_6$ (M)$^+$: 343.1994.

(2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(2-aminophenylcarbamoylmethyl)-3,4-*O*-isopropylidene-5-methylpyrrolidine-3,4-diol (45). A solution of **44** (132 mg, 0.38 mmol) in 2:1 EtOH:NaOH (12 mL) was heated at 50 °C for 2 h. The mixture was then neutralized with IRA-120H$^+$, filtered and concentrated. The crude acid thus obtained was dissolved in DMF and *o*-phenylenediamine (45 mg, 0.42 mmol), DIPEA (130 μL, 0.76 mmol) and PyBOP (218 mg, 0.42 mmol) were added. The mixture was stirred overnight at r.t. Then, the solvent was evaporated and the residue dissolved in CH_2Cl_2 (40 mL) and washed with satd. aq. sol. of citric acid (2 × 30 mL) and brine (30 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The resulting crude was purified by column chromatography (CH_2Cl_2:MeOH, 30:1) to give pure **45** (132 g, 76%) as a white foam. [α]$_D$ −29.2 (*c* 0.9 in CH_2Cl_2). IR (ν cm^{-1}) 3545 (NH), 3365 (NH), 2981, 2935, 1689 (C=O), 1391, 1168. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.24 (3H, d, $J_{Me,5}$ = 7.2, 5-Me), 1.36 (3H, s, C(CH_3)$_2$), 1.47 (9H, s, C(CH_3)$_3$), 1.59 (3H, s, C(CH_3)$_2$), 2.73 (1H, dd, $^2J_{1'a,1'b}$ = 14.4, $J_{1'a,2}$ = 9.6, 1′a-H), 2.95 (1H, dd, $J_{1'b,2}$ = 4.8, 1′b-H), 4.07 (1H, q, $J_{5,4}$ = 7.2, 5-H), 4.48 (1H, ddd, $J_{2,3}$ = 7.2, 2-H), 4.75 (1H, t, $J_{4,3}$ = 7.2, 4-H), 4.91 (1H, t, 3-H), 6.72–6.77 (2H, m, H-arom.), 7.04 (1H, m, H-arom.), 7.15 (1H, m, H-arom.), 7.52 (1H, bs, CON*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 17.0 (5-Me), 24.9, 25.6 (C(*C*H$_3$)$_2$), 28.6 (C(*C*H$_3$)$_3$), 39.0 (C-1′), 55.2 (C-5), 56.4 (C-2), 80.3 (C-3, C-4), 80.5 (*C*(CH$_3$)$_3$), 112.9 (*C*(CH$_3$)$_2$), 117.5, 119.0, 123.8, 125.9, 127.4, 141.6 (6 C-Ar), 154.3 (C=O of Boc), 169.7 (*C*ONH). CIMS 406 [11%, (M + H)$^+$], 405 [(M)$^+$, 20%], 306 [(M − Boc + 2H)$^+$, 100%]. CIHRMS *m/z* found 405.2269, calcd. for $C_{21}H_{31}N_3O_5$ (M)$^+$: 405.2264.

(2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-(2-(1*H*-benzoimidazol-2-ylmethyl)-3,4-*O*-isopropylidene-5-methylpyrrolidine-3,4-diol (46). A solution of **45** (87.8 mg, 0.216 mmol) in glacial AcOH was stirred at 55 °C for 5 h. Then, the solvent was evaporated and the resulting residue was purified by column chromatography (CH_2Cl_2:MeOH, 25:1) to give pure **46** (83.6 mg, 100%) as a foam. [α]$_D$ +3.4 (*c* 1 in CH_2Cl_2). IR (ν cm^{-1}) 3464 (NH), 2980, 2934, 1691 (C=O), 1383, 1210, 1167, 1100, 1028, 868, 743. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.26 (3H, d, $J_{Me,5}$ = 6.9, 5-Me), 1.39 (3H, s, C(CH_3)$_2$), 1.43 (9H, s, C(CH_3)$_3$), 1.61 (3H, s, C(CH_3)$_2$), 3.28 (1H, dd, $^2J_{1'a,1'b}$ = 15.3, $J_{1'a,2}$ = 6.0, 1′a-H), 3.44 (1H, dd, $J_{1'b,2}$ = 7.2, 1′b-H), 4.13 (1H, q, $J_{5,4}$= 6.9, 5-H), 4.44 (1H, m, 2-H), 4.79 (1H, t, $J_{4,3}$ = 6.9, 4-H), 4.83 (1H, t, $J_{3,2}$ = 6.9, 3-H), 7.19 (2H, dd, *J* = 6.0, *J* = 3.0, H-arom.), 7.55 (2H, dd, H-arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 16.8 (5-Me), 25.0, 25.4 (C(*C*H$_3$)$_2$), 28.5 (C(*C*H$_3$)$_3$, 32.2 (C-1′), 55.0 (C-5), 57.5 (C-2), 79.4, 80.2 (C-3, C-4), 80.9 (*C*(CH$_3$)$_3$), 110.8 (*C*(CH$_3$)$_2$), 114.9, 122.1, 138.8, 152.7 (C-Ar), 154.8 (C=O). CIMS 388 [(M + H)$^+$, 76%], 387 [(M)$^+$, 33%], 288 [(M − Boc + 2H)$^+$, 100%], 287 [(M − Boc + H)$^+$, 15%]. CIHRMS *m/z* found 387.2154, calcd. for $C_{21}H_{29}N_3O_4$ (M)$^+$: 387.2158.

(2*R*,3*S*,4*R*,5*S*)-2-(1*H*-Benzoimidazol-2-yl-methyl)-5-methyl-pyrrolidine-3,4-diol (19a). A solution of **46** (47.2 mg, 0.122 mmol) in 4M HCl (3 mL) was stirred at r.t. for 8 h. The solvent was then evaporated and the resulting residue dissolved in H_2O (1 mL). NH_4OH (1 mL) was added and the mixture was left at r.t. for 2 h. Then, the solvent was evaporated and the resulting residue was purified by column chromatography (CH_2Cl_2:MeOH:NH_4OH, 5:1:0.1) to give pure **19a** (19.4 mg, 64%). [α]$_D$ +29.1 (*c* 1.3 in MeOH). IR (ν cm^{-1}) 3500–3200 (OH,NH), 2926, 1445. ^{1}H NMR (300 MHz, CD_3OD, δ ppm) δ 1.23 (3H, d, $J_{Me,5}$ = 6.6, 5-Me), 3.13 (1H, dd, $^2J_{1'a,1'b}$ = 15.3, $J_{1'a,2}$ = 8.4, 1′a-H), 3.22 (1H, m, 5-H), 3.35 (1H, m, 1′b-H), 3.71 (1H, td, $J_{2,1'b}$ = 8.4, $J_{2,3}$ = 6.0, 2-H), 4.09 (1H, t, $J_{4,3}$ = $J_{4,5}$ = 5.1, 4-H), 4.26 (1H, dd, 3-H), 7.21 (2H, dd, *J* = 6.0, *J* = 3.3, H-arom.), 7.51 (2H, dd, H-arom). ^{13}C NMR (75.4 MHz, CD_3OD, δ ppm) δ 13.9 (5-Me), 29.5 (C-1′), 57.7 (C-5), 60.7 (C-2), 73.5 (C-3), 73.8 (C-4), 115.5, 123.3, 139.6, 154.0 (C-Ar). CIMS 248 [(M + H)$^+$, 32%]. CIHRMS *m/z* found 248.1394, calcd. for $C_{13}H_{18}N_3O_2$ (M + H)$^+$: 248.1399.

Reductive amination: general procedure

To a solution of the corresponding aldehyde (0.10 mmol) in 1,2-dichloroethane (1 mL), the corresponding amine (0.11 mmol) and $NaBH(OAc)_3$ (0.14 mmol) were added. The reaction mixture was stirred at r.t. under N_2 for 3 h. Then, aq. sat. sol. of $NaHCO_3$ was added and the mixture extracted with AcOEt, dried (Na_2SO_4), filtered and evaporated in vacuo. Purification of the residue gave the corresponding amino pyrrolidines.

(2*S*,3*S*,4*R*,5*S*)-2-[2-(1,1′-Biphenyl-4-ylamino)methyl]-5-methyl-pyrrolidine-3,4-diol hydrochloride (20b). Reductive amination of **32**[34] with biphenyl-4-amine gave, after column chromatography on silica gel (ether:petroleum ether 1:1), protected derivative **53** (101 mg, 66%). A solution of **53** (70 mg, 0.148 mmol in MeOH (6 mL) was hydrogenated over Pd/C for 3 h. The mixture was filtered through celite and evaporated. The crude product was then treated with 4 N HCl (2 mL) and stirred at r.t. overnight. Evaporation of the solvent afforded **20b** (28 mg, 89%). [α]$_D$ −43.7 (*c* 0.67 in MeOH). ^{1}H NMR (300 MHz, CD_3OD, δ ppm) δ 1.43 (3H, d, $J_{Me,5}$ = 6.6, 5-Me), 3.76–3.86 (4H, m, 5-H, 2-H, 1′a-H, 1′b-H), 4.06 (1H, t, $J_{3,4}$ = $J_{3,2}$ = 2.7, 3-H), 4.22 (1H, m, 4-H), 7.31–7.34 (3H, m, H-arom.), 7.42 (2H, brt, *J* = 7.5, H-arom.), 7.59 (2H, brd, *J* = 7.9, H-arom.), 7.66 (2H, brd, *J* = 8.7, H-arom.). ^{13}C NMR (75.4 MHz, MeOD, δ ppm) δ 12.0 (5-Me), 48.1–49.8 (C-1′, under MeOD), 59.0, 60.1 (C-2, C-5), 72.9 (C-3), 76.0 (C-4), 119.7, 127.6, 128.3, 129.4, 129.9 (C arom.), 138.5, 141.4, 141.7 (*C*q arom.). CIMS 299 [(M + H)$^+$, 100%]. CIHRMS *m/z* found 299.1753, calcd. for $C_{15}H_{25}NO_5$ (M + H)$^+$: 299.1733.

(2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(1,1′-biphenyl-4-carbamoyl)methyl]-3,4-*O*-isopropylidene-5-methylpyrrolidine-3,4-diol (56). A solution of **44** (0.116 g, 0.337 mmol) in 2:1 EtOH: NaOH (12 mL) was heated at 50 °C for 2 h. The mixture was then neutralized with IRA-120H$^+$, filtered and concentrated. The crude acid thus obtained was dissolved in DMF and biphenyl-4-amine (68 mg, 0.40 mmol), DIPEA (0.13 mL, 0.78 mmol) and PyBOP (0.21 g, 0.40 mmol) were added. The mixture was stirred overnight at r.t. Then, the solvent was evaporated and the

residue dissolved in CH_2Cl_2 (30 mL) and washed with 1 M HCl (25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (CH_2Cl_2:MeOH, 60:1) afforded pure **56** (0.111 g, 71%) as a white foam. $[\alpha]_D$ −3.5 (*c* 1 in CH_2Cl_2). IR (ν cm^{-1}) 3466, 2981, 2934, 1692 (C=O), 1666 (C=O), 1529, 1392, 1168. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.24 (3H, d, $J_{Me,5} = 6.9$, 5-Me), 1.39 (3H, s, $C(CH_3)_2$), 1.48 (9H, s, $C(CH_3)_3$), 1.59 (3H, s, $C(CH_3)_2$), 2.86 (2H, m, 1′a-H, 1′b-H), 4.07 (1H, q, $J_{5,4} = 6.9$, 5-H), 4.44 (1H, m, 2-H), 4.77 (1H, t, $J_{4,3}$ =6.9, 4-H), 4.89 (1H, t, $J_{3,2} = 6.9$, 3-H), 7.32 (1H, m, H-arom.), 7.42 (2H, m, H-arom), 7.53–7.62 (6H, m, H-arom.), 8.21 (1H, brs, CONH). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 17.1 (5-Me), 24.9, 25.5 ($C(CH_3)_2$), 28.6 ($C(CH_3)_3$), 40.0 (C-1′), 55.1 (C-5), 56.2 (C-2), 79.7, 79.8 (C-3, C-4), 80.7 ($C(CH_3)_3$), 113.0 ($C(CH_3)_2$), 122.1, 126.9, 127.2, 127.7, 128.9, 136.9, 137.8, 140.8 (2Ph), 154.5 (C=O of Boc), 169.2 (CONH). CIMS 467 [(M + H)$^+$, 14%], 466 [(M)$^+$, 17%], 367 [(M − Boc + 2H)$^+$, 100%], 366 [(M − Boc + H)$^+$, 10%]. CIHRMS *m/z* found 466.2491, calcd. for $C_{27}H_{34}N_2O_5$ (M)$^+$: 466.2468. Anal. calcd. for $C_{27}H_{34}N_2O_5$: C, 69.50; H, 7.35; N, 6.00. Found: C, 69.40; H, 7.74; N, 5.62.

(2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[2-(1,1′-biphenyl-4-ylamino)ethyl]-3,4-*O*-isopropylidene-5-methylpyrrolidine-3,4-diol (57). To a 0 °C solution of amide **56** (94.3 mg, 0.20 mmol) in dry THF (5 mL), BH_3·SMe_2 (2 M in THF) (0.5 mL, 1 mmol) was added dropwise under argon atmosphere. The reaction mixture was then heated under reflux for 3 h. After cooling, the reaction was quenched by slow addition of MeOH (5 mL). After evaporation of the solvent, the residue was purified by column chromatography (ether:petroleum ether, 1:2) to give **57** (80.8 mg, 89%) as a foam. $[\alpha]_D$ +14.6 (*c* 0.9 in CH_2Cl_2). IR (ν cm^{-1}) 3402 (NH), 2979, 2916, 1689 (C=O), 1613, 1391. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.21 (3H, d, $J_{Me,5} = 6.6$, 5-Me), 1.39 (3H, s, $C(CH_3)_2$), 1.49 (9H, s, $C(CH_3)_3$), 1.57 (3H, s, $C(CH_3)_2$), 1.89 (1H, m, 1′a-H), 2.14 (1H, m, 1′b-H), 3.26 (2H, m, 2′a-H, 2′b-H), 4.04–4.13 (2H, m, 2-H, 5-H), 4.73 (1H, t, $J_{4,5} = 7.2$, 4-H), 4.79 (1H, t, $J_{2,3} = J_{3,4} = 7.2$, 3-H), 6.66 (2H, d, $J = 8.4$, H-arom.), 7.25 (1H, tt, $J = 7.2$, H-arom.), 7.36–7.46 (4H, m, H-arom.), 7.53 (2H, dd, $J = 8.4$, $J = 1.5$, H-arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 17.1 (5-Me), 25.0, 25.4 ($C(CH_3)_2$), 28.6 ($C(CH_3)_3$), 30.9 (C-1′), 42.1 (C-2′), 54.7, 56.7 (C-2, C-5), 79.8, 80.0 (C-3, C-4), 80.2 ($C(CH_3)_3$), 113.0 ($C(CH_3)_2$), 113.7, 126.2, 126.4, 128.1, 128.7, 130.7, 140.5, 147.1 (C-Ar), 154.6 (C=O of Boc). CIMS 453 [(M + H)$^+$, 48%], 452 [(M)$^+$, 65%], 353 [(M − Boc + 2H)$^+$, 100%], 352 [(M Boc + H) $^+$, 35%]. CIHRMS *m/z* found 452.2664, calcd. for $C_{27}H_{36}N_2O_4$ (M)$^+$: 452.2675. Anal. calcd. for $C_{27}H_{36}N_2O_4$: C, 71.65; H, 8.02; N, 6.12. Found: C, 71.23; H, 7.93; N, 5.96.

(2*R*,3*S*,4*R*,5*S*)-2-[2-(1,1′-Biphenyl-4-ylamino)ethyl]-5-methylpyrrolidine-3,4-diol (21b). A solution of **57** (32.1 mg, 0.07 mmol) in 4 N HCl (2 mL) was stirred at r.t. overnight. The solvent was then evaporated, the residue dissolved in H_2O (1 mL), NH_4OH was added (1 mL) and the mixture stirred at r.t. for 2 h. After evaporation of the solvent, the resulting residue was purified by column chromatography (CH_2Cl_2:MeOH:NH_4OH, 5:1:0.1) to give pure **21b** (21.4 mg, 97%). $[\alpha]_D$ −3.7 (*c* 0.9 in MeOH). IR (ν cm^{-1}) 3310 (OH, NH), 2928, 1611, 1526. ^{1}H NMR (300 MHz, CD_3OD, δ ppm) δ 1.30 (3H, d, $J_{Me,5} = 6.6$, 5-Me), 1.92 (1H, m, 1′a-H), 2.15 (1H, m, 1′b-H), 3.29 (2H, m, 2′a-H, 2′b-H), 3.34–3.41 (2H, m, 5-H, 2-H), 4.17 (1H, dd, $J_{4,5} = 5.7$, $J_{4,3} = 5.1$, 4-H), 4.24 (1H, t, $J_{3,2} = 5.1$, 3-H), 6.75 (2H, d, $J = 8.7$, H-arom.), 7.20 (1H, tt, $J = 7.5$, H-arom.), 7.35 (2H, t, $J = 7.5$, H-arom.), 7.41 (2H, d, $J = 8.7$, H-arom.), 7.51 (2H, dd, $J = 8.4$, $J = 1.2$, H-arom.). ^{13}C NMR (75.4 MHz, CD_3OD, δ ppm) δ 13.6 (5-Me), 28.7 (C-1′), 42.1 (C-2′), 57.7, 60.4 (C-2, C-5), 72.9, 73.2 (C-3, C-4), 114.3, 126.9, 128.6, 129.7, 131.1, 142.7, 149.5 (C-Ar). CIMS 313 [(M + H)$^+$, 95%], 312 [(M)$^+$, 69%]. CIHRMS *m/z* found 313.1904, calcd. for $C_{19}H_{25}N_2O_2$ (M + H)$^+$: 313.1916.

***N*-(*tert*-Butoxycarbonyl)-2,3,6,7-tetradeoxy-3,6-imino-4,5-*O*-isopropylidene-L-*galacto*-2-heptose ((2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-formylmethyl-3,4-*O*-isopropylidene-5-methyl-pyrrolidine-3,4-diol) (54).** To a solution of **44** (165 mg, 0.48 mmol) in dry CH_2Cl_2 (2.3 mL) cooled to −78 °C, 1M DIBALH in CH_2Cl_2 (0.95 mL) was added dropwise under a nitrogen atmosphere. After stirring for 30 min, MeOH (1.5 mL) was added and the mixture slowly warmed up to r.t. Then, aqueous 1 M HCl (4 mL) was added in an ice-cold bath and the aqueous phase was extracted with CH_2Cl_2 (4×5 mL). The combined organic phases were washed with satd. aq. sol. of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The resulting crude was purified by column chromatography (ethyl acetate:petroleum ether, 1:4) to give pure **54** (106 mg, 74%). $[\alpha]_D$ −13.6 (*c* 0.9 in CH_2Cl_2). IR (ν cm^{-1}) 2981, 2936, 1724 (C=O), 1693 (C=O), 1384, 1169, 1028. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.20 (3H, d, $J_{Me,6} = 6.7$, 6-Me), 1.33 (3H, s, $C(CH_3)_2$), 1.44 (9H, s, $C(CH_3)_3$), 1.50 (3H, s, $C(CH_3)_2$), 2.80 (2H, m, 2a-H, 2b-H), 4.03 (1H, q, 6-H), 4.44 (1H, m, 3-H), 4.73 (1H, t, $J_{5,6} = J_{5,4} = 6.9$, 5-H), 4.82 (1H, t, $J_{4,3} = 6.9$, 4-H), 9.76 (1H, t, $J_{CHO,2a} = J_{CHO,2b} = 1.5$, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 16.7 (6-Me), 24.8, 25.3 ($C(CH_3)_2$), 28.5 ($C(CH_3)_3$), 46.0 (C-2), 54.9, 55.1 (C-3, C-6), 79.1 (C-5), 80.0 (C-4), 80.4 ($C(CH_3)_3$), 112.9 ($C(CH_3)_2$), 154.1 (C=O of Boc), 200.6 (CHO). CIMS 300 [(M + H)$^+$, 40%], 200 [(M − Boc + 2H)$^+$, 71%]. CIHRMS *m/z* found 300.1824, calcd. for $C_{15}H_{26}NO_5$ (M + H)$^+$: 300.1811.

(2*R*,3*S*,4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(2-naphthalen-1-ylamino)ethyl]-3,4-*O*-isopropylidene-5-methylpyrrolidine-3,4-diol (55). Reductive amination of **54** with naphthylamine gave, after column chromatography on silica gel (ether:petroleum ether 1:4), the protected derivative **55** (101.3 mg, 85%) as a white foam. $[\alpha]_D$ +18.6 (*c* 0.6 in CH_2Cl_2). IR (ν cm^{-1}) 3418 (NH), 2979, 1690 (C=O), 1390, 1168, 768. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.23 (3H, d, $J_{Me,5} = 6.9$, 5-Me), 1.45 (3H, s, $C(CH_3)_2$, 1.49 (9H, s, $C(CH_3)_3$), 1.63 (3H, s, $C(CH_3)_2$), 2.08 (1H, dq, $^2J_{1'a,1'b} = 13.8$, $J_{1'a,2'a} = J_{1'a,2'b} = J_{1'a,2} = 5.1$, 1′a-H), 2.32 (1H, m, 1′b-H), 3.38 (2H, m, 2′a-H, 2′b-H), 4.07–4.12 (2H, m, 5-H, 2-H), 4.76 (1H, t, $J_{4,5} = J_{4,3} = 7.2$, 4-H), 4.86 (1H, t, $J_{3,2} = 7.2$, 3-H), 6.58 (1H, d, $J = 7.5$, H-arom.), 7.18 (1H, d, $J = 8.1$, H-arom), 7.32 (1H, d, $J = 7.8$, H-arom), 7.36–7.43 (2H, m, H-arom), 7.77 (1H, dd, $J = 9.3$, $J = 1.8$ H-arom), 7.90 (1H, dd, $J = 8.1$, H-arom). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 17.2 (5-Me), 25.1, 25.6 ($C(CH_3)_2$), 28.6 ($C(CH_3)_3$), 30.5 (C-1′), 42.2 (C-2′), 54.7, 57.9 (C-2, C-5), 77.3 ($C(CH_3)_3$), 79.9, 80.0 (C-3, C-4), 113.1 ($C(CH_3)_2$), 113.7, 116.7, 120.5, 123.5, 124.4, 125.7, 126.9, 128.6, 134.5, 144.0 (Ar), 154.3 (C=O of Boc). CIMS 427 [(M + H)$^+$, 76%], 426 [(M)$^+$, 100%], 327 [(M − Boc + 2H)$^+$, 36%], 326 [(M − Boc + H)$^+$, 29%]. CIHRMS *m/z* found 426.2522, calcd. for $C_{25}H_{34}N_2O_4$ (M)$^+$: 426.2519. Anal. calcd. for $C_{25}H_{34}N_2O_4$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.26; H, 8.19; N, 6.43.

(2*R*,3*S*,4*R*,5*S*)-2-[(2-Naphthalen-1-ylamino)ethyl]-5-methylpyrrolidine-3,4-diol (21a). Conventional acidic deprotection of **55** (53.1 mg, 0.124 mmol) in 4 N HCl:THF (2:1, 3 mL), followed by neutralization with NH_4OH, gave after column chromatography (CH_2Cl_2/MeOH/NH_4OH 10:1:0.1→5:1:0.1) derivative **21a** (21.9 mg, 62%). $[\alpha]_D$ +10.9 (*c* 0.56 in MeOH). IR (ν cm^{-1}) 3377, 3049 (NH, OH), 2928, 1581, 1532, 1410. ^1H NMR (300 MHz, CD_3OD, δ ppm) δ 1.19 (3H, d, $J_{Me,5} = 6.9$, 5-Me), 1.90 (1H, m, 1′a-H), 2.17 (1H, m, 1′b-H), 2.94–3.05 (2H, m, 5-H, 2-H), 3.38 (2H, m, 2′a-H, 2′b-H), 4.02 (1H, t, $J_{4,5} = J_{4,3} = 5.4$, 4-H), 4.12 (1H, t, $J_{3,2} = 5.4$, 3-H), 6.61 (1H, d, $J = 7.5$, H-arom.), 7.13 (1H, d, $J = 8.4$, H-arom), 7.28 (1H, t, $J = 7.8$, H-arom), 7.35–7.42 (2H, m, H-arom), 7.72 (1H, m, H-arom), 8.00 (1H, m, H-arom). ^{13}C NMR (75.4 MHz, CD_3OD, δ ppm) δ 14.5 (5-Me), 29.4 (C-1′), 42.9 (C-2′), 57.5, 61.0 (C-2, C-5), 74.1, 74.4 (C-3, C-4), 104.9, 117.6, 121.9, 125.1, 125.3, 126.5, 127.7, 129.3, 135.9, 145.3 (Ar). CIMS 287 [$(M + H)^+$, 100%], 286 [$(M)^+$, 95%]. CIHRMS *m/z* found 287.1748, calcd. for $C_{17}H_{23}N_2O_2$ $(M + H)^+$: 287.1759.

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