Preparation and Biological Evaluation of Pyrrolidinediols and Pyrrolidine *N*-Oxides from D-Ribose Using the Nitrone Approach[‡] [‡‡]

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The transformation of 3,4-isopropylidenedioxy-5-methylpyrrolidine 1-oxides with various 2-substituents into the free diols and, by reduction, into the corresponding pyrrolidinediols (iminoglycitols) is described. The pyrrolidine *N*-oxides were derived from D-ribose via unsaturated hydroxylamines, with the key steps of nitrone addition and Cope–House cyclization as described earlier. The biological activity of these compounds with respect to glycosidase inhibition was examined; while all the tested pyrrolidine *N*-oxides proved inactive, some of the new iminopolyols showed moderate activity against α-L-fucosidases and α-D-glucosidases, with K_i values of 30–40 μM.

Introduction

Many polyhydroxypyrrolidines (1,4-iminoglycitols) exhibit biological activity towards glycosidases, inhibiting the enzymatic degradation of oligosaccharides and polysaccharides.[3−14] This is explained by their ability to mimic the *exo*-protonated glycoside or transition states adopted by the natural substrate in the course of the hydrolysis.[13−21]

Glycosidases are also responsible for the catabolism of glycoproteins.[22] Since the ligand-receptor interaction between glycoconjugates located on the cell surface and certain proteins regulates important biological processes[23] − such as cell-cell recognition,[24] inflammation[25] and cell infection[24] − glycosidase inhibitors might also constitute powerful tools in the treatment of certain diseases.[15,22−27] In particular, inhibitors of fucosidases might be of therapeutic value, since the α-L-fucopyranosyl fragment **A** (6-deoxy-L-galacto) is present in numerous oligosaccharides and glycoconjugates.[25,28,29] Recognition of the α-L-fucoside moiety in these glycoconjugates by specific lectins is of great importance for pathological modifications of normal cell behaviour, such as tumour growth, formation of metastases[30] or exaggerated leukocyte recruitment during inflammatory diseases.[25] High activity of fucosidases and enrichment of fucosyl-containing structures in cancer cells has been observed.[28]

Consequently, much effort has been devoted towards the synthesis and structure-activity analysis of fucosidase inhibitors, and a variety of such compounds have been found (see Figure 1). The piperidine 1-deoxy-L-fuconojirimycin (DFJ, **B**), the imino analogue of the natural substrate, is the most potent inhibitor known so far, displaying highly selective, competitive inhibition.[31−34]

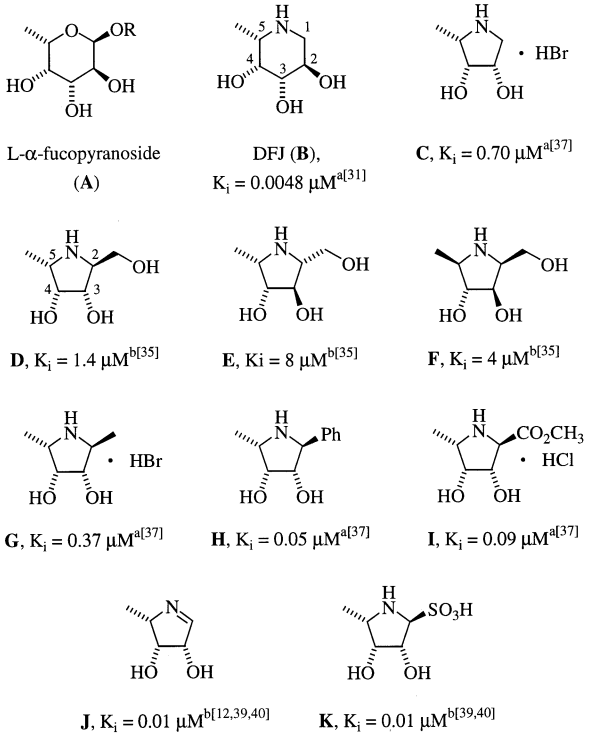

Figure 1. α-L-Fucopyranoside (6-deoxy-L-*galacto*, **A**) and fucosidase inhibitors **B**−**K**; K_i values refer to inhibition of α-L-fucosidase derived from either [a]bovine epididymis or [b]bovine kidney

In contrast to DFJ (**B**) and related piperidine inhibitors, where epimers often show a total loss of inhibitory activity, polyhydroxypyrrolidine inhibitors retain their activity and a variety of configurations is tolerated (Figure 1). Wong and co-workers have developed a chemo-enzymatic syn-

[‡] Synthesis of Glycosidase-Inhibiting Iminopolyols by Cope−House Cyclization of Unsaturated Hydroxylamines, IV. − Part III, II and I: See ref.[2]

[‡‡] See Ref.[1]

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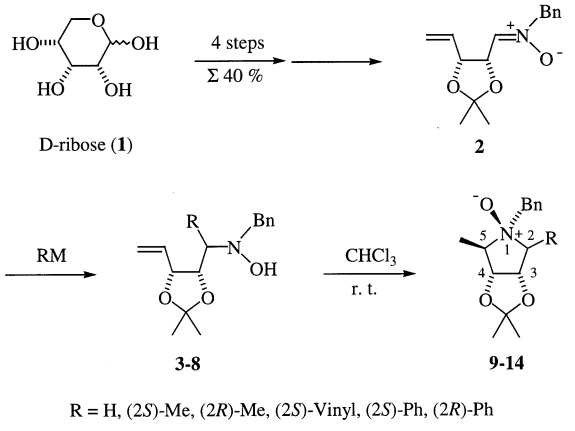
thesis for the iminopolyols **D**−**F** and have interpreted the differing activities in terms of lower steric demand, as compared to that of the six-membered counterparts.[35] Recently, several highly active pyrrolidines and *N*-hydroxypyrrolidines have been found both in our group[36−38] and by Defoin and co-workers.[39,40] These iminopolyols **G**−**K** constitute the most powerful fucosidase inhibitors of the pyrrolidine series known so far, and likewise show that the imine **J**, and its hydrogensulfite adduct **K**, or lipophilic groups at the 2-position are more effective than the "usual" hydroxymethyl substituent (cf. **D**, **E**, **F**). Concerning the configuration, the most active pyrrolidine structures in terms of fucosidase inhibition exhibit the "natural" all-*cis* orientation of the substituents at positions 3, 4, and 5.[37−40]

In the preceding paper of this series, we have presented stereoselective syntheses of 3,4-dihydroxypyrrolidine 1-oxides such as **9**−**14** (Scheme 1), taking advantage of substituent variation in the nitrone addition step and of the Cope−House cyclization of the corresponding unsaturated hydroxylamines **3**−**8** derived from D-ribose (**1**, Scheme 1).[41] Since this reaction gives access to 4,5-*trans*-pyrrolidine 1-oxides (e.g., **9**−**14**), it provides a valuable tool with which to address the question of whether this all-*cis* relationship is a necessary prerequisite for fucosidase inhibition, as well as for further evaluation of 2-substituents.



Scheme 1. Synthesis of pyrrolidine *N*-oxides **9**−**14** from D-ribose (**1**) using nitrone addition/Cope−House cyclization as key steps[41]

Here, we report on our findings concerning the transformation of these pyrrolidine *N*-oxides into new candidates for glycosidase inhibition assays (Figure 2) and on the results of these biological tests:

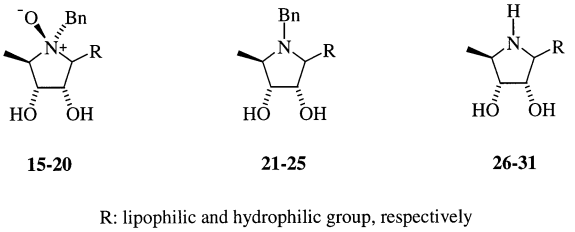


Figure 2. Pyrrolidine *N*-oxides **15**−**20** and pyrrolidinediols **21**−**31**: target structures and new candidates for glycosidase inhibition assays

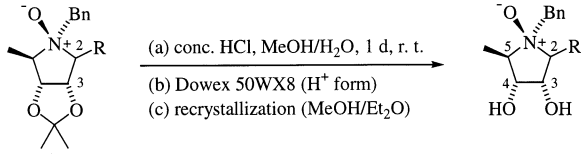
(i) We were interested in the preparation of various 3,4-dihydroxypyrrolidine 1-oxides **15**−**20** (R = H, Me, vinyl, Ph), in order to test the hypothesis that these compounds might constitute a new class of glycosidase inhibitors.[36] This idea relates to the fact that these *N*-oxide structures not only show all properties necessary for effective glycosidase inhibition − that is, (i) a basic heteroatom that may be protonated and mimic the intermediates occurring in the course of the hydrolysis, and (ii) ring substituents analogous to those in the natural substrate − but also possess an additional function (*N*-oxy) that might produce improved hydrogen bonding with the respective amino acids of the active site of the enzyme.

(ii) In order to determine the inhibitory activity of (3*S*,4*R*,5*R*)-3,4-dihydroxy-5-methylpyrrolidines, we sought access to compounds **21**−**31**, bearing a variety of 2-substituents: R = H (parent), R = methyl, vinyl, phenyl (lipophilic), R = hydroxymethyl, carboxy (hydrogen donor-acceptor properties), methoxycarbonyl (electron-withdrawing, still lipophilic). It was intended to synthesize both 2-epimers of the 2-methyl- and 2-carboxypyrrolidines **22** and **23** (**30** and **31**, respectively), in order to evaluate the influence of the orientation of these substituents on both the activity and the selectivity of glycosidase inhibition. The preparation of the *N*-debenzylated analogues **26** and **27** [R = H, (2*S*)-methyl] was also planned, to estimate the contribution of this lipophilic group to the biological activity of these compounds.

Results and Discussion

Preparation of 3,4-Dihydroxy-5-methylpyrrolidine 1-Oxides 15−20 and Pyrrolidines 21−27 with Lipophilic 2-Substituents

The acetonide protecting groups in the pyrrolidine *N*-oxides **9**−**14**[41] were removed using aqueous hydrochloric acid in methanol (Scheme 2). The 3,4-dihydroxypyrrolidine 1-oxides **15**−**20** were obtained as hydrochlorides, each in the form of an oil. After purification using acidic ion exchange resin (Dowex 50WX8, H^+ form), however, crystalline samples of the pyrrolidine *N*-oxides **15**−**20** were isolated. The reduction of the pyrrolidine *N*-oxides **9**−**13** was effected with acid-activated zinc dust and is summarized in

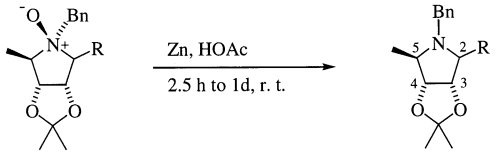


9 R = H
10 R = (2*S*)-Me (*meso*)
11 R = (2*R*)-Me
12 R = (2*S*)-Vinyl
13 R = (2*S*)-Ph
14 R = (2*R*)-Ph

15 R = H	71 %
16 R = (2*S*)-Me	84 %
17 R = (2*R*)-Me	63 %
18 R = (2*S*)-Vinyl	57 %
19 R = (2*S*)-Ph	81 %
20 R = (2*R*)-Ph	68 %

Scheme 2. Preparation of 3,4-dihydroxy-5-methylpyrrolidine 1-oxides **15**−**20** [(2*S*) derivatives: 2,3-*trans*; (2*R*) derivatives: 2,3-*cis*; numbering does not apply to **9** and **15**]

Scheme 3; the corresponding, analytically pure 3,4-isopropylidenedioxypyrrolidines **32**−**36** were obtained in 49−84% yield.

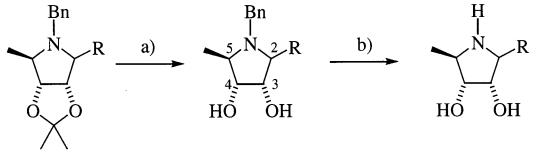


9 R = H
10 R = (2*S*)-Me
11 R = (2*R*)-Me
12 R = (2*S*)-Vinyl
13 R = (2*S*)-Ph

32 R = H 56 %
33 R = (2*S*)-Me 69 %
34 R = (2*R*)-Me 49 %
35 R = (2*S*)-Vinyl 84 %
36 R = (2*S*)-Ph 77 %

Scheme 3. Reduction of pyrrolidine *N*-oxides **9**−**13** [(2*S*) derivatives: 2,3-*trans*; (2*R*) derivatives: 2,3-*cis*; reverse numbering for **9**, **32**]

For preparation of the free iminopolyols, the acetonide groups on the above *N*-benzylpyrrolidines **32**−**36** were first removed with aqueous hydrochloric acid in methanol, furnishing the 3,4-dihydroxypyrrolidines **21**−**25** as hydrochlorides (Scheme 4). The iminopolyols **22**, **24**, and **25** were obtained as pure and crystalline hydrochloride salts from 2-propanol/diethyl ether; the diols **21** and **23** were purified using acidic ion exchange resin Dowex 50WX8. Next, the *N*-benzyl groups on the pyrrolidines **21** and **22** were split off by hydrogenation with Pearlman's catalyst,[42] to give **26** and **27**, respectively (Scheme 4).



R = H: **32** **21** 88 % **26** 50 %
R = (2*S*)-Me: **33** **22** 91 % **27** 87 %
R = (2*R*)-Me: **34** **23** 87 %
R = (2*S*)-Vinyl: **35** **24** 78 %
R = (2*S*)-Ph: **36** **25** 96 %

Scheme 4. Deprotection of iminopolyols **32**−**36**: (a) conc. HCl/MeOH/H_2O (1:8:8), room temp., 2−16 h; **21** and **23** purified with Dowex 50WX8 (H^+ form); (b) H_2 (4 bar), $Pd(OH)_2$/C, MeOH, room temp., 2−4 d; compound **26**: subsequent addition of HBr (48%). − Numbering does not apply to **21**, **26** and **32**. − **22**, **24**, **25**, and **27** isolated as hydrochloride, **26** as hydrobromide salt.

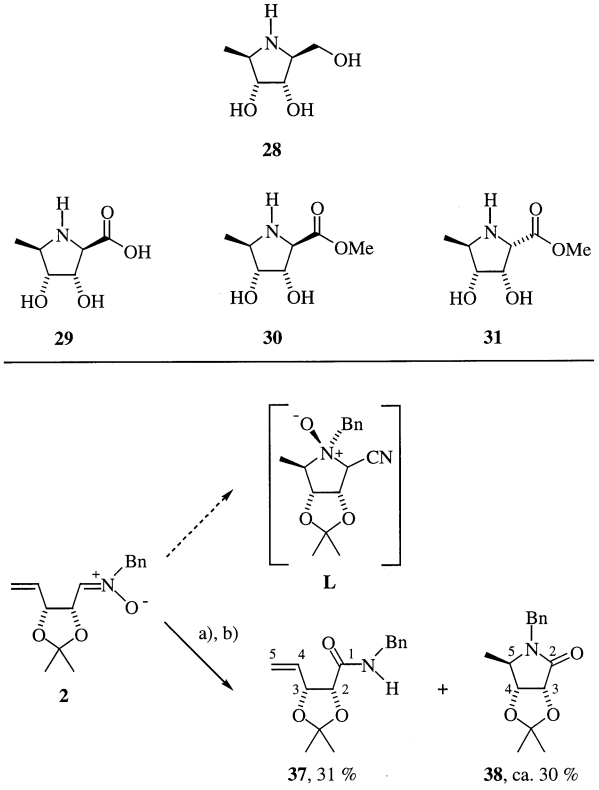
Preparation of 3,4-Dihydroxy-5-methylpyrrolidines with Hydrophilic 2-Substituents

The synthesis of the known fucosidase inhibitor **28**[43,44] and of the proline derivatives **29**[45] and **30** turned out to be more complicated. Moreover, the 2-epimer **31** was unexpectedly obtained instead of **30**. The two most obvious strategies for the synthesis of **29** and **30** were pursued first:

(i) Nucleophilic addition of cyanide to the *N*-benzyl nitrone **2**, followed by Cope−House cyclization of the intermediate unsaturated hydroxylamine (cf. Scheme 1).[41]

(ii) The use of the furyl ring as a carboxy equivalent,[46] by addition of furyllithium to the nitrone **2**,[41] reduction of the resulting pyrrolidine *N*-oxide, and cleavage of the furyl moiety using ruthenium trichloride/sodium periodate.[47−50]

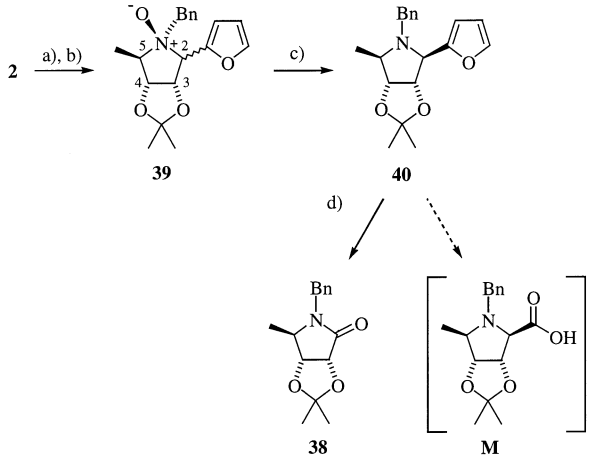
Route (i): Several cyanide sources (sodium cyanide, diethylaluminium cyanide, lithium cyanide) were employed to effect this addition to the nitrone **2**.[41] In each case, however, a complex reaction mixture resulted. When lithium cyanide was used, the amide **37** − probably formed by the known "Beckmann" rearrangement of nitrones[51] − and the lactam **38** were isolated in place of the expected 2-cyanopyrrolidine 1-oxide **L** (Scheme 5).



Scheme 5. Target structures with a hydrophilic 2-substituent **28**−**31** and first attempt ***(i)***; addition of lithium cyanide to the nitrone **2**: (a) LiCN, CH_2Cl_2, −20 °C, 5 h; (b) $CHCl_3$, room temp., 5 d

Route (ii): Addition of α-furyllithium to the *N*-benzyl nitrone **2**[41] with ensuing Cope−House cyclization of the intermediate unsaturated hydroxylamine afforded the pyrrolidine *N*-oxide **39** in high yield (89%) and with good selectivity [(2*S*)/(2*R*) = 92:8]. After zinc reduction of **39** to produce the *N*-benzylpyrrolidine **40**, none of the minor isomer could be detected. The furyl ring of the pyrrolidine **40** was cleaved with ruthenium tetroxide, generated in situ using a standard system consisting of ruthenium trichloride and sodium periodate.[47−50] However, the cyclic lactam **38** was formed rather than the expected proline derivative **M** (Scheme 6).

After these approaches had failed, the 2-vinylpyrrolidine **35** was selected as an alternative starting material. From this, the iminopolyol **28** and the proline derivative **29** should be readily accessible through a sequence of bis(hydroxylation), lead tetraacetate cleavage of the diol **41**, and reduction/oxidation of the corresponding aldehyde (Scheme 7).

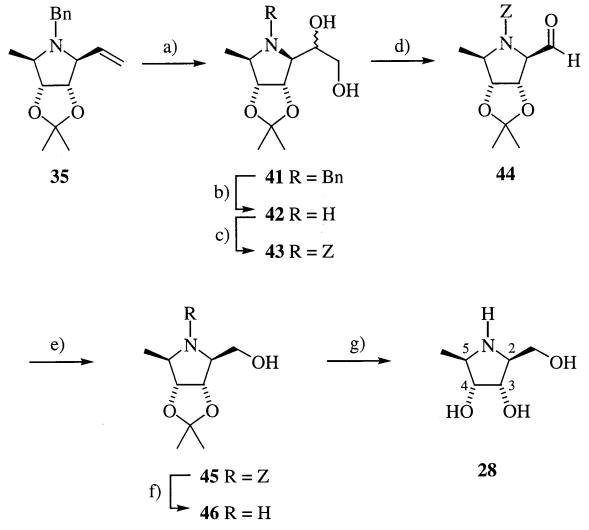


Scheme 6. Attempted preparation of the proline derivative **M** by nucleophilic addition of furyllithium to the nitrone **2**: (a) α-furylLi, THF, −80 °C, 75 min; (b) $CHCl_3$, room temp., 17 h, 89% [92:8]; (c) Zn, HOAc, room temp., 22 h, 75%; (d) $RuCl_3{\cdot}H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, room temp., 1 h, 43% of lactam **38**

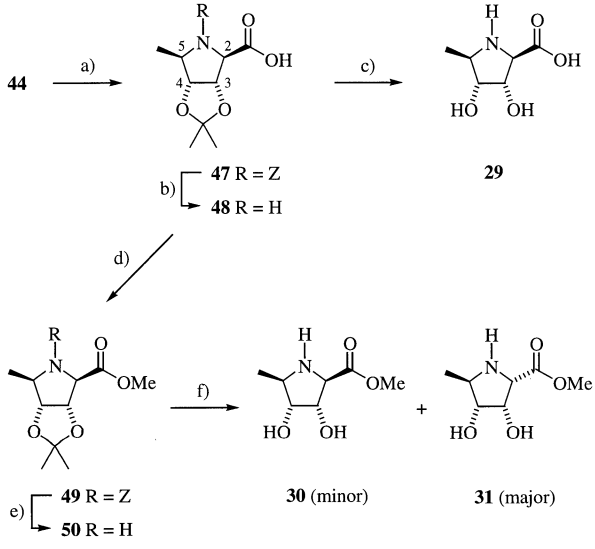
The first step proceeded as expected, to give a mixture of diastereomeric diols **41** (*dr* 60:40) in 83% yield. However, the *N*-benzyl-protected aldehyde obtained in the next step, by cleavage of the diol **41** with lead tetraacetate, turned out to be labile, and it was deemed necessary to replace the *N*-benzyl group by the more electron-poor benzyloxycarbonyl group. This was achieved by catalytic hydrogenation and treatment of the resulting pyrrolidine **42** with benzyl chloroformate. Indeed, lead tetraacetate cleavage followed by sodium borohydride reduction of the Z-protected diol **43** afforded the pyrrolidine **45**[44] in good yield. Both protecting groups of **45** were removed, firstly by hydrogenolysis to give **46** and subsequently with aqueous hydrochloric acid in methanol (Scheme 7). This afforded the fucosidase inhibitor **28** in 91% yield. The synthesis reported here thus comprises 13 steps and proceeds in 10.2% overall yield. In another synthesis of **28**, recently reported by Defoin and co-workers, sorbaldehyde dimethylacetal was used as starting material and an overall yield of 9.5% (13 steps) was reported.[43,44]

In order to secure the proline derivatives, the intermediate aldehyde **44** was oxidized to the carboxylic acid **47** with sodium chlorite (Scheme 8).[52,53] 3,4-Dihydroxy-5-methyl-D-proline (**29**) was then obtained by *N*,*O*-deprotection as above, by catalytic debenzylation of **47** to give **48**, followed by hydrolysis. The amino acid **29**, isolated as a spectroscopically pure hydrochloride, proved very hygroscopic (as seen with many of these iminopolyols), and was characterized by HRMS analysis. The route from D-ribose (**1**) to **29** takes 13 steps, with a 9.5% overall yield.

In order to obtain the methyl ester of **29**, the protected imino acid **47** was treated with diazomethane (Scheme 8). The Z-protecting group in the resulting methyl ester **49** was removed by catalytic hydrogenation and the resulting pyrrolidine acetonide **50** was treated with dry hydrogen chloride in methanol. This caused acetal cleavage as expected, but also − surprisingly − partial epimerization at C-2. After a reaction time of 2.5 h at room temp., the two epimeric



Scheme 7. Synthesis of the 2-hydroxymethylpyrrolidine **28**: (a) OsO_4, *N*-methylmorpholine *N*-oxide, acetone/H_2O, room temp., 4.5 d, 83%; (b) H_2 (4 bar), $Pd(OH)_2$/C, MeOH, room temp., 3 d, quant.; (c) BnOCOCl, Na_2CO_3, dioxane/water, room temp., 2.5 h, 79%; (d) $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, room temp., 1 h; (e) $NaBH_4$, EtOH, 0 °C, 4 h, 77% for two steps; (f) H_2 (1 bar), Pd/C, MeOH, room temp., 5.5 h, 91%; (g) MeOH, HCl (1.5 N), room temp., 17 h, then Dowex 50WX8 (H^+ form), quant.



Scheme 8. Synthesis of the dihydroxyproline derivatives **29** and **31**: (a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, room temp., 5.5 h, 78% **47** based on the diol **43**; (b) H_2 (1 bar), Pd/C, MeOH, room temp., 4 h, quant.; (c) HCl (0.7 N), room temp., 4 h, quant.; (d) CH_2N_2, MeOH, 67% based on the diol **43**; (e) 1 bar H_2, Pd/C, room temp., 3 h, quant.; (f) MeOH/HCl (gas), room temp., 2.5 h, crude product with **30**/**31** = 29:71, 57% of **31** after crystallization; **29**, **30**, and **31** isolated as hydrochloride salt

dihydroxyproline esters **30** and **31** were obtained in a 29:71 ratio, as seen by ^1H and ^{13}C NMR analysis. A sample of the major epimer **31**, containing 6% of **30**, was isolated by recrystallization from isopropyl alcohol (57% yield). Thus, for the overall sequence from D-ribose to **31**, an overall yield of 4.9% over 14 steps is stated. A different approach to the racemic 3,4-dihydroxy-5-methylproline (±)-**29** was pub-

lished recently by Defoin and co-workers (9 steps, 8.8% total yield).[45]

Glycosidase Inhibition Assays

The biological activity of the compounds obtained here [the hydroxypyrrolidine *N*-oxides **15**−**20** (cf. Scheme 2) and the iminopolyols **21**−**29**, **31** (cf. Schemes 4, 7, 8)] was examined in glycosidase inhibition assays.[54,55] Each candidate was incubated with a set of 24 different enzymes. In order to evaluate the inhibitory activity, the rates of enzymatic cleavage of *p*-nitrophenyl glycoside ("substrate") were determined in the absence and in the presence of 1 mM of the potential inhibitor.[54,55] If a significant decrease in the rate of hydrolysis was observed, the inhibition activity of the compound was quantified by determination of IC_{50} and K_i values. The new compounds showing significant activity (> 70% inhibition) are included in Table 1.

Table 1. Inhibition activity of the 2-substituted iminopolyols obtained against various glycosidases (candidates **15**−**20**, **21**, **24**, **26**, **27** and **29** were found to be inactive)

Compound/ 2-substituent	Enzyme (source)[a]	% I[b]	IC_{50} [μM]	K_i [μM]
22/(2*S*)-Me	α-glucosidase (y. m.)	97	211	520
	α-glucosidase (b. y.)	93	246	618
23/(2*R*)-Me	α-L-fucosidase (b. k.)	85	242	236
25/(2*S*)-Ph	α-galactosidase (E. c.)	95	300	> 490
	α-glucosidase (y. m.)	95	131	363
	α-glucosidase (b. y.)	100	56	144
28/(2*S*)-CH_2OH	α-L-fucosidase (b. k.)	70	314	83 (120[44])
31/(2*S*)-CO_2Me	α-L-fucosidase (b. e.)	86	178	29
	α-L-fucosidase (b. k.)	80	316	37
	α-glucosidase (y. m.)	98	332	34
	α-glucosidase (b. y.)	95	205	44

[a] Enzyme sources: yeast, maltase (y. m.); baker's yeast (b. y.); bovine kidney (b. k.); *E. coli* (E. c.); bovine epididymis (b. e.). − [b] In the presence of 1 mM of inhibitor.

On the basis of these results, it is now possible to draw some conclusions as to structure-activity relationships:

(a) Since none of the pyrrolidine *N*-oxides **15**−**20** tested showed significant inhibition, it appears that the *N*-oxide function impedes activity. These observations are consistent with results reported by Wong and co-workers, indicating that the *N*-oxides of 1-deoxynojirimycin, 1,6-dideoxynojirimycin and castanospermine are weaker inhibitors than their *N*-methyl analogues.[56] This is explained by the ability of the *N*-oxide function to participate in intramolecular H-bonding and to interact in a repulsive manner with the carboxylate group of the enzyme; both are assumed to prevent the formation of a stable enzyme-inhibitor complex.[56]

(b) Comparison of the biological activities of the *trans*-2,3-dimethylpyrrolidines **22**, with an *N*-benzyl substituent, and of **27**, without one, suggests that the presence of an *N*-benzyl group might be useful, since compound **22** displays some activity (K_i in the 0.5 mM range) with two α-glycosidases, while the debenzyl compound **27** shows none.

(c) A substituent in the 2-position of the heterocycle seems to be crucial (the 2-unsubstituted pyrrolidines **21** and **26** were inactive). Furthermore, the configuration and nature of the group at C-2 affects both the selectivity and the strength of inhibition. Thus, the biological activity of the iminopolyols **22** (2-CH_3) and **25** (2-Ph), with 2,3-*trans* configurations, against certain α-D-glucosidases is lost when the lipophilic 2-residue is replaced by a polar group such as hydroxymethyl (**28**) or carboxy (**29**). In contrast, iminopolyols with 2,3-*cis* configurations and bearing either a lipophilic group such as 2-methyl (**23**) or a polar 2-substituent such as methoxycarbonyl (as seen in **31**) inhibit α-L-fucosidases to a weak to moderate extent.

No strict rule can be derived from these observations, though, as can be seen from the inhibition patterns of the iminopolyols **28** (2-hydroxymethyl; α-L-fucosidase inhibition) and **24** (2-vinyl; no activity). Nevertheless, it is noteworthy that the iminopolyols examined here show weak to moderate biological activity despite possessing the "wrong" D-configuration [(*R*)-5-methyl] as compared to the natural α-L-fucoside substrates. This supports the assumption that the configurational prerequisites for pyrrolidine inhibitors are less strict than those observed in the piperidine series.[15,35] However, the fact that the presence of the (5*R*) configuration in the new structures (D series) is responsible for a considerable loss of activity against α-L-fucosidases compared to the structures **C** and **G**−**K**, with "correct" 5-methyl group orientations (L series), can clearly be seen by comparison of the K_i values of the 5-epimers **D**[35] (1.4 μM) and **28**[44] (83−120 μM).

Conclusion

In summary, transformations of a series of (1*R*,3*S*,4*R*,5*R*)-1-benzyl-3,4-isopropylidenedioxy-5-methylpyrrolidine 1-oxides − obtained by Cope−House cyclization of unsaturated hydroxylamines derived from D-ribose[41] − into pyrrolidinediol structures of biological interest are reported. New syntheses of the known fucosidase inhibitor **28** and the 3,4-dihydroxy-5-methylproline derivative **29** have been developed. All the iminopolyols prepared in the course of this work were screened in glycosidase inhibition assays. Whereas none of the pyrrolidine *N*-oxides exhibited any activity, several of the iminopolyols turned out to be weak to moderate glycosidase inhibitors, with K_i values in the range from 30 to 500 μM. This supports the assumption that the configurational limitations affecting pyrrolidinepolyol inhibitors are less rigid than those for piperidinepolyol inhibitors. The (5*R*) configuration present in all structures of this series seems to impede effective inhibition of α-L-fucosidases. Nevertheless, as far as the 2-substituents are concerned, a distinct increase in activity is once again seen with a 2-methoxycarbonyl group (cf. ref.[37]).

Experimental Section

General Remarks: Melting points were determined with a Fisher Johns 4017 heating block and are uncorrected. − ^1H and ^{13}C NMR spectra were recorded with Bruker AC 250, ARX 300, or ARX 500 spectrometers using $SiMe_4$ as internal standard. C,H-COSY spec-

tra were recorded for the assignment of ^{13}C NMR signals. – IR spectra were recorded with a Perkin–Elmer 283 or a Bruker IFS 28 IR spectrometer. – Mass spectra and high-resolution mass spectra (HRMS) were measured with Finnigan Quadrupol-MS 4500/Finnigan MAT 95 mass spectrometers, respectively. – Optical rotations were determined with a Perkin–Elmer polarimeter 241MC. – A Parr (Moline, IL/USA) shaking apparatus was used for catalytic hydrogenation.

Materials: Solvents were purified and dried by standard methods.[57] For column chromatography, silica gel (40–63 μm, Merck) was used. Dowex 50WX8 acidic resin used for ion exchange purification was supplied by Fluka and was activated with HCl (1 N) prior to use. Commercial reagents were used throughout.

(1*S*,2*R*,3*R*,4*S*)-1-Benzyl-3,4-dihydroxy-2-methylpyrrolidine 1-Oxide (15): Compound **9**·H_2O (200 mg, 0.71 mmol)[41] was dissolved under nitrogen in a mixture of water (2 mL), MeOH (2 mL) and conc. HCl (0.25 mL). The clear solution was stirred for 1 d at room temp. The solvent was removed under reduced pressure, and the crude product, a colourless oil, was purified using 5 g of Dowex 50WX8 (H^+ form, by treatment of the resin with 1 N HCl and removal of excess acid by washing with water). The resin was charged with **15**·HCl, dissolved in MeOH, and first washed with 50-mL portions each of MeOH and water, before elution of **15** with 1 N NH_3 (100 mL). Concentration in vacuo afforded 158 mg of a colourless solid, which was recrystallized from MeOH/diethyl ether to give colourless crystals of **15** (112 mg, 71%), m.p. 172 °C (decomp.). – $[\alpha]_D^{20} = +17$ (*c* = 0.28, MeOH). – IR (KBr): $\tilde{\nu}$ = 3220 (br., OH), 2960, 2910, 1445, 1140, 1125, 1090 cm^{-1}. – ^1H NMR (MeOD, 500.1 MHz): δ = 1.48 (d, $J_{2,2\text{-Me}}$ = 6.4 Hz, 3 H, 2-CH_3), 3.37 (dq, $J_{2,3}$ = 8.8, $J_{2,2\text{-Me}}$ = 6.4 Hz, 1 H, 2-H), 3.48 (d, $J_{4,5}$ = 6.4 Hz, 2 H, 5-H), 4.08 (dd, $J_{2,3}$ = 8.8, $J_{3,4}$ = 6.4 Hz, 1 H, 3-H), 4.33 (s, 2 H, CH_2Ph), 4.37 (qu, $J_{3,4} = J_{4,5}$ = 6.4 Hz, 1 H, 4-H), 7.45 (m_c, 3 H, C_6H_5), 7.55 (m_c, 2 H, C_6H_5). – ^{13}C NMR (MeOD, 125.8 MHz): δ = 11.0 (2-CH_3), 67.0 (C-4), 70.5 (*C*H_2Ph), 73.3 (C-5), 74.7 (C-2), 75.1 (C-3), 129.8, 130.8, 131.5, 133.4 (C_6H_5). – $C_{12}H_{17}NO_3$ (223.3): calcd. C 64.55, H 7.67, N 6.27; found C 64.32, H 7.61, N 6.24.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-2,5-dimethylpyrrolidine 1-Oxide (16): Deprotection of **10**·H_2O (93 mg, 0.31 mmol)[41] and purification as described for the preparation of **15** yielded 75 mg of a colourless solid, which was recrystallized from MeOH/diethyl ether. The free diol **16** (62 mg, 84%) was obtained in the form of colourless needles, m.p. 186 °C (decomp.). – Optically inactive (*meso* compound). – IR (KBr): $\tilde{\nu}$ = 3190 (br., OH), 3050, 2980, 2940, 1495, 1455, 1445, 1430, 1365, 1165, 1135, 1090 cm^{-1}. – ^1H and ^{13}C NMR spectroscopic data for **16**: see Tables 2–4. – $C_{13}H_{19}NO_3$ (237.3): calcd. C 65.80, H 8.07, N 5.90; found C 65.66, H 8.10, N 5.91.

(1*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-2,5-dimethylpyrrolidine 1-Oxide (17): Deprotection of **11**·H_2O (88 mg, 0.30 mmol)[41] and purification as described for the preparation of **15** yielded a colourless solid (63 mg), which was recrystallized from MeOH/diethyl ether. Colourless crystals of **17** (45 mg, 63%) were obtained; m.p. 149–151 °C (decomp.). – $[\alpha]_D^{20} = -11$ (*c* = 0.13, MeOH). – IR (KBr): $\tilde{\nu}$ = 3600–2300 (OH), 1485, 1450, 1170, 1120 cm^{-1}. – ^1H and ^{13}C NMR spectroscopic data for **17**: see Tables 2–4. –

Table 2. ^1H NMR chemical shifts δ of pyrrolidine *N*-oxides **16**–**20**, **39**, 1-Bn-3,4-isopropylidenedioxypyrrolidines **33**–**36**, **40**, 1-*Z*-3,4-isopropylidenedioxypyrrolidines **45**, **47**, **49**, 3,4-isopropylidenedioxypyrrolidines **46**, **48**, **50**, *O*-deprotected iminopolyols **22**–**25**, and *N*,*O*-deprotected pyrrolidinediols **27**–**31** (δ [ppm]; 250.1, 300.1 or 500.1 MHz)

Compound [a]	2-H	3-H	4-H	5-H	5-CH_3	$C(CH_3)_2$	*N*-CH_2Ph or *N*-$COOCH_2$Ph	Others
16[b]	3.18	3.92	3.92	3.18	1.57	–	4.23 (CH_2), 7.47 (Ph)	1.57 (CH_3)
17[b]	3.73	3.93	4.19	3.73	1.58	–	4.23, 4.35 (CH_2), 7.39, 7.64 (Ph)	0.87 (CH_3)
18[b]	3.63	4.13	3.99	3.21	1.57	–	4.24 (CH_2), 7.47 (Ph)	5.59 (CH_EH_Z), 5.67 (CH_EH_Z), 6.43 (CH)
19[b]	4.15	4.49	4.09	3.51	1.52	–	4.06, 4.16 (CH_2), 7.45, 7.87 (2 Ph)	
20[b]	4.67	4.48	4.08	3.95	0.84	–	3.60, 4.44 (CH_2), 7.30–7.50, 8.01 (2 Ph)	
39[c]	4.84	5.30	4.84	4.29	1.59	1.33, 1.42	3.90, 4.29 (CH_2), 7.27, 7.32, 7.41	6.24, 6.43, 7.57 (furyl)
33[c]	2.66	4.14	4.14	2.66	1.18	1.29, 1.42	3.73 (CH_2), 7.26 (Ph)	1.18 (CH_3)
34[c]	3.19	4.29	4.56	2.89	1.13	1.33, 1.57	3.43, 3.87 (CH_2), 7.21, 7.29, 7.38 (Ph)	0.84 (CH_3)
35[c]	3.08	4.30	4.16	2.67	1.15	1.29, 1.43	3.61, 3.82 (CH_2), 7.25 (Ph)	5.35 (CH_EH_Z), 5.24 (CH_EH_Z), 5.76 (CH)
36[c]	3.59	4.34	4.22	2.78	1.21	1.25, 1.46	3.44, 3.78 (CH_2), 7.27 (2 Ph)	
40[c]	4.08	4.74	4.40	3.35	0.94	1.30, 1.55	3.36, 3.76 (CH_2), 7.26 (Ph)	6.37, 7.38 (furyl)
45[d,e]	3.91	4.69	4.38	3.95	1.18	1.25, 1.34	5.09 (CH_2), 7.32 (Ph)	3.37 (CH_aH_bOH), 3.55 (CH_aH_bOH), 4.77 (OH)
47[d,e]	4.32	4.87	4.45	4.10	1.19	1.27, 1.37	5.10 (CH_2), 7.31 (Ph)	
49[f,g]	4.96	4.79	4.22	4.56	1.36	1.28, 1.49	5.17, 5.24 (CH_2), 7.25 (Ph)	3.47 (OCH_3)
46[f–h]	3.39	4.56	4.17	3.34	1.23	1.44, 1.68	–	2.57 (NH, OH), 3.63 (CH_aH_bOH), 3.71 (CH_aH_bOH)
48[b]	4.08	5.22	4.68	3.95	1.36	1.37, 1.56	–	
50[c]	3.82	4.84	4.25	3.30	1.19	1.34, 1.53	–	2.37 (NH), 3.79 (OCH_3)
22[b,i]	3.59	3.92	3.92	3.59	1.33	–	4.48 (CH_2), 7.51, 7.58 (Ph)	1.33 (CH_3)
23[b]	3.19	4.02	3.71	2.95	1.08	–	3.69, 3.85 (CH_2), 7.22, 7.30, 7.38 (Ph)	1.03 (CH_3)
24[b,i]	3.97	4.16	3.94	3.66	1.27	–	4.37, 4.50 (CH_2), 7.49 (Ph)	5.48 (CH_EH_Z), 5.54 (CH_EH_Z), 6.00 (CH)
25[b,i]	4.48	4.48	4.13	3.73	1.49	–	4.48 (CH_2), 7.42 (2 Ph)	
27[b,i]	3.53	3.90	3.90	3.53	1.43	–	–	1.43 (CH_3)
28[b]	3.00	3.85	3.42	2.98	1.22	–	–	3.64 (CH_aH_bOH), 3.66 (CH_aH_bOH)
29[b,i]	4.24	4.43	3.83	3.64	1.46	–	–	
30[b,i]	4.27	4.44	3.86	3.65	1.46	–	–	3.89 (OCH_3)
31[b,i]	4.60	4.42	3.92	3.62	1.47	–	–	3.87 (OCH_3)

[a] Arrangement of compounds according to substance class (pyrrolidine *N*-oxide/pyrrolidine) and protecting group pattern for better comparison. – [b] In MeOD. – [c] In $CDCl_3$. – [d] In [D_6]DMSO. – [e] Measured at 353 K. – [f] In C_6D_6. – [g] Measured at 347 K. – [h] Major conformer, ratio 86:14 at 347 K. – [i] NMR-spectroscopic data of the hydrochloride.

Table 3. H,H-coupling constants *J* of pyrrolidine *N*-oxides **16**−**20**, **39**, 1-Bn-3,4-isopropylidenedioxypyrrolidines **33**−**36**, **40**, 1-*Z*-3,4-isopropylidenedioxypyrrolidines **45**, **47**, **49**, 3,4-isopropylidenedioxypyrrolidines **46**, **48**, **50**, *O*-deprotected iminopolyols **22**−**25**, and *N*,*O*-deprotected pyrrolidinediols **27**−**31** (*J* [Hz])

Compound [a]	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,5\text{-Me}}$	$^2J(CH_aH_bPh)$	Others
16[b]	–	–	–	6.4	–	$J(2\text{-}H,CH_3) = 6.4$
17[b]	8.7	4.9	3.9	7.2	12.3	$J(2\text{-}H,CH_3) = 6.7$
18[b]	8.1	7.5	7.5	6.4	–	$J(2\text{-}H,CH) = 8.1$, $J(CH{=}CH_EH_Z) = 10.6$, $J(CH{=}CH_EH_Z) = 17.6$, $^2J(CH_EH_Z) = 1.4$
19[b]	8.7	7.2	7.0	6.4	13.4	
20[b]	3.3	4.0	9.7	6.7	12.3	
39[c]	6.9	7.3	5.2	6.6	12.3	
33[c]	–	–	–	6.3	–	$J(2\text{-}H,CH_3) = 6.3$
34[c]	0.0	6.3	5.3	6.4	14.0	$J(2\text{-}H,CH_3) = 7.0$
35[c]	5.3	7.2	5.0	6.3	14.7	$J(2\text{-}H,CH) = 8.6$, $J(CH{=}CH_EH_Z) = 10.2$, $J(CH{=}CH_EH_Z) = 17.1$
36[c]	5.0	7.2	5.1	6.2	14.6	
40[c]	5.3	6.5	0.8	6.9	14.0	
45[d,e]	1.5	5.8	1.6	6.9	–	$J(2\text{-}H,CH_aH_bOH) = 7.2$, $J(2\text{-}H,CH_aH_bOH) = 3.8$, $^2J(CH_aH_bOH) = 10.8$, $J(CH_aH_bOH) = 5.7$, $J(CH_aH_bOH) = 4.7$
47[d,e]	2.0	5.7	0.8	7.0	–	$^4J(2\text{-}H,4\text{-}H) = 0.8$
49[f,g]	0.0	5.6	0.0	7.0	12.6	
46[f,g]	3.9	6.6	4.6	6.5		$J(2\text{-}H,CH_aH_bOH) = 5.4$, $J(2\text{-}H,CH_aH_bOH) = 4.5$, $^2J(CH_aH_bOH) = 10.8$
48[b]	1.9	5.6	1.4	7.4		
50[c]	3.8	6.6	3.8	6.8		
22[b,h]	–	–	–	7.0	–	$J(2\text{-}H,CH_3) = 7.0$
23[b]	6.2	6.2	4.6	6.6	13.6	$J(2\text{-}H,CH_3) = 6.6$
24[b,h]	7.4	4.6	4.6	7.0	13.1	$J(2\text{-}H,CH) = 9.3$, $J(CH{=}CH_EH_Z) = 10.3$, $J(CH{=}CH_EH_Z) = 16.9$, $^2J(CH_EH_Z) = 1.1$
25[b,h]	n. d.	n. d.	4.8	7.0	n. d.	
27[b,h]	–	–	–	7.1		$J(2\text{-}H,CH_3) = 7.1$
28[b]	4.9	6.2	7.1	6.4		$J(2\text{-}H,CH_aH_bOH) = 4.5$, $J(2\text{-}H,CH_aH_bOH) = 4.3$, $^2J(CH_aH_bOH) = 11.5$
29[b,h]	3.4	4.2	7.2	6.9		
30[b,h]	4.0	4.3	6.7	6.9		
31[b,h]	3.7	3.7	9.4	6.8		

[a] Arrangement of compounds according to substance class (pyrrolidine *N*-oxide/pyrrolidine) and protecting group pattern for better comparison. − [b] In MeOD. − [c] In $CDCl_3$. − [d] In [D_6]DMSO. − [e] Measured at 353 K. − [f] In C_6D_6. − [g] Measured at 347 K. − [h] Data of the hydrochloride.

$C_{13}H_{19}NO_3$ (237.3): calcd. C 65.80, H 8.07, N 5.90; found C 65.49, H 8.22, N 5.79.

(1*R*,2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-5-methyl-2-vinylpyrrolidine 1-Oxide (18): Deprotection of **12** (200 mg, 0.69 mmol),[41] purification and recrystallization (cf. preparation of **15**) afforded colourless crystals of **18** (98 mg, 57%), m.p. 151−152 °C (decomp.) − $[\alpha]_D^{20} = +13$ ($c = 0.53$, MeOH). − IR (KBr): $\tilde{\nu}$ = 3240, 2920, 1440, 1130, 1080 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **18**: see Tables 2−4. − $C_{14}H_{19}NO_3$ (249.3): calcd. C 67.45, H 7.68, N 5.62; found C 67.02, H 7.59, N 5.54.

(1*R*,2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-5-methyl-2-phenylpyrrolidine 1-Oxide (19): Deprotection of **13** (60 mg, 0.18 mmol),[41] purification using acidic resin, and recrystallization from MeOH/diethyl ether as described for **15** afforded colourless crystals of **19** (43 mg, 81%), m.p. 178−179 °C (decomp.). − $[\alpha]_D^{20} = +30$ (c = 0.51, MeOH). − IR (KBr): $\tilde{\nu}$ = 3200 (OH), 2940, 2910, 1442, 1140, 1125, 1080, 1040 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **19**: see Tables 2−4. − $C_{18}H_{21}NO_3$ (299.4): calcd. C 72.22, H 7.07, N 4.68, found. C 71.52, H 7.08, N 4.63.

(1*R*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-5-methyl-2-phenylpyrrolidine 1-Oxide (20): Deprotection of **14** (65 mg, 0.19 mmol)[41] and purification using acidic resin afforded the pyrrolidinediol *N*-oxide **20** (39 mg, 68%), m.p. 147−148 °C (decomp.) (> 90% purity according to ^1H NMR). − $[\alpha]_D^{20} = -40$ (c = 0.38, MeOH). − IR (KBr): $\tilde{\nu}$ = 3240 (b), 1485, 1445, 1355, 1195, 1140, 1120, 1080 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **20**: see Tables 2−4. − MS (Auto-CI, positive ion): *m*/*z* (%) = 300.2 (100) [MH^+], 284.1 (13), 212.1 (22), 132.1 (13), 91.0 (65). − HRMS (Auto-CI, positive ion): exact mass calcd. for $C_{18}H_{21}NO_3$ + H: 300.1600; found 300.1592.

(2*R*,3*R*,4*S*)-1-Benzyl-3,4-isopropylidenedioxy-2-methylpyrrolidine (32): A solution of the crude pyrrolidine *N*-oxide **9** (330 mg, 1.25 mmol, containing 8% of the 2-epimer)[41] in 6 mL of acetic acid was prepared under nitrogen in a heated flask. Activated Zn dust (1.23 g, 19 mmol) was added over a period of 45 min and the reaction mixture was stirred for 2.5 h at room temp. The mixture was filtered and the residue was washed with acetic acid. The filtrate was concd. in vacuo, diluted with water (10 mL), cooled to 0 °C and made basic (pH > 9) using 6 N NaOH. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried with $MgSO_4$ and concentrated to dryness. Flash chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) afforded pure **32** (colourless oil, 174 mg, 56% yield based on **2**). Additionally, 16 mg (5%) of the 2-epimer was obtained. − $[\alpha]_D^{20} = -63$ (c = 0.55, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2967, 2932, 2801, 1454, 1379, 1252, 1209, 1160, 1077, 1059 cm^{-1}. − ^1H NMR ($CDCl_3$, 500.1 MHz): δ = 1.15 (d, $J_{2,2\text{-Me}} = 6.4$ Hz, 3 H, 2-CH_3), 1.31, 1.52 [2 s, 6 H, $C(CH_3)_2$], 2.48 (dd, $J_{4,5a} = 3.9$, $^2J_{5a,5b} = 10.3$ Hz, 1 H, 5-H_a), 2.76 (dq, $J_{2,2\text{-Me}} = 6.4$, $J_{2,3} = 4.1$ Hz, 1 H, 2-H), 3.03 (dd, $J_{4,5b} = 6.1$, $^2J_{5a,5b} = 10.3$ Hz, 1 H, 5-H_b), 3.38 and 3.89 (2 d, $^2J = 13.1$ Hz, 2 H, CH_2Ph), 4.24 (dd, $J_{2,3} = 4.1$, $J_{3,4} = 6.9$ Hz, 1 H, 3-H), 4.62 (ddd, $J_{3,4} = 6.9$, $J_{4,5a} = 3.9$, $J_{4,5b} = 6.1$ Hz, 1 H, 4-H), 7.24, 7.30 (2m_c, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.9 (2-

Table 4. ^{13}C NMR chemical shifts δ of pyrrolidine *N*-oxides **16**−**20**, **39**, 1-Bn-3,4-isopropylidenedioxypyrrolidines **33**−**36**, **40,** 1-*Z*-3,4-isopropylidenedioxypyrrolidines **45**, **47**, **49**, 3,4-isopropylidenedioxypyrrolidines **46**, **48**, **50**, *O*-deprotected iminopolyols **22**−**25**, and *N*,*O*-deprotected pyrrolidinediols **27**−**31** (δ [ppm]; 62.9, 75.5 or 125.8 MHz)

Compound[a]	C-2	C-3	C-4	C-5	5-CH_3	$C(CH_3)_2$	CH_2Ph/ $COOCH_2Ph$	Others
16[b]	73.4[c]	73.5[c]	73.5[c]	73.4[c]	11.5		66.1 (CH_2), 130.4, 131.2, 132.9 (Ph)	11.5 (CH_3)
17[b,d]	81.9	71.7	76.2	74.1	13.2		69.6 (CH_2), 129.2, 130.2, 132.1, 133.8 (Ph)	9.7 (CH_3)
18[b,d]	81.5	72.7	74.5	74.0	12.1		67.8 (CH_2), 130.9, 131.5, 131.8, 133.8 (Ph)	124.7 (CH=*C*H_2), 132.4 (*C*H=CH_2)
19[b,d]	82.1	74.8	74.7	76.0	12.8		68.7 (CH_2), 130.0, 130.8, 131.2, 131.7, 131.8, 133.8, 134.2 (2 Ph)	
20[b,d]	89.2	73.4[c]	77.6	74.0	13.9		73.5[c] (CH_2), 129.7, 130.0, 130.8, 131.5, 132.7, 134.3, 134.4 (2 Ph)	
39[d,e]	84.4[c]	77.9	78.0[c]	74.1	12.3	24.1, 25.7, 114.5	66.2 (CH_2), 127.8, 128.9, 130.4, 132.3 (Ph)	110.9, 114.7, 143.7, 145.1 (furyl)
33[e]	64.3	84.8	84.8	64.3	18.2	25.5, 27.3, 113.1	53.4 (CH_2), 126.9, 128.1, 128.9, 138.1 (Ph)	18.2 (CH_3)
34[d,e]	59.5	85.0	81.8	57.9	12.7	25.7, 26.5, 111.4	50.5 (CH_2), 126.6, 128.1, 128.2, 139.9 (Ph)	10.1 (CH_3)
35[e]	72.7	83.2[c]	85.1[c]	63.6	18.2	25.4, 27.3, 113.3	53.1 (CH_2), 126.9, 128.0, 129.3, 138.5 (Ph)	118.7 (CH=*C*H_2), 137.4 (*C*H=CH_2)
36[d,e]	73.3	86.0	85.2	63.6	18.4	25.4, 27.4, 113.3	53.0 (CH_2), 126.8, 127.6, 127.9, 128.7, 129.3, 136.9, 141.0 (2 Ph)	
40[e]	58.3[c]	79.9[c]	85.2[c]	62.6[c]	10.4	25.3, 26.3, 112.1	50.7[c] (CH_2), 126.7, 128.1, 128.2, 139.2 (Ph)	109.4, 110.5, 141.5, 152.1 (furyl)
45[f,g]	67.6	82.6[c]	86.4[c]	61.3	19.8	25.8, 27.8, 112.1	67.5 (CH_2), 128.3, 128.9, 137.8 (Ph), 155.8 (CO)	63.9 (*C*H_2OH)
47[h,i]	67.1[c]	83.0[c]	85.7[c]	60.7	18.4	25.9, 27.8, 112.4	67.6[c] (CH_2), 126.3, 128.0, 128.5, 129.1, 137.7 (Ph), 154.6 (CO)	172.2 (COOH)
49[f,g]	67.4[c]	83.1[c]	86.2[c]	60.8	18.2	25.4, 27.4, 112.6	67.6[c] (CH_2), 128.0, 128.6, 137.5 (Ph)	51.8 (CO_2CH_3), 171.5 (CO_2CH_3)
46[f,g,j]	66.4	83.4[c]	87.7[c]	60.4	20.0	25.8, 28.0, 113.5		63.5 (*C*H_2OH)
48[b]	69.2	84.1[c]	86.2[c]	62.4	16.7	25.2, 27.4, 114.2		171.7 (COOH)
50[e]	66.6	84.0[c]	86.7[c]	60.1	18.8	25.1, 27.2, 113.8		52.5 (CO_2CH_3), 173.0 (CO_2CH_3)
22[b,k]	69.9	76.9	76.9	69.9	17.0		60.8 (CH_2), 131.9, 132.1, 132.8, 134.0 (Ph)	17.0 (CH_3)
23[b,d]	60.5	73.2	79.0	64.5	17.4		53.8 (CH_2), 128.7, 129.9, 130.5 (Ph)	10.9 (CH_3)
24[b,d,k]	75.9[c]	75.4	77.1[c]	70.2	17.3		60.3 (CH_2), 131.8, 132.8, 134.2 (Ph)	127.8 (CH=*C*H_2), 132.4 (*C*H=CH_2)
25[b,k]	74.3[c]	74.5[c]	74.8[c]	68.5	14.9		58.4 (CH_2), 129.6, 129.7, 129.9, 130.4, 130.6, 132.1 (2 Ph)	
27[b,k]	61.1	76.6	76.6	61.1	16.8			16.8 (CH_3)
28[b,d]	67.6	74.1	79.5	60.1	18.8			63.3 (CH_2OH)
29[b,d,k]	66.1	75.0	77.3	60.2	16.1			170.8 (COOH)
30[b,k]	65.8	74.8	77.2	60.7	16.0			54.9 (CO_2CH_3), 170.2 (CO_2CH_3)
31[b,d,k]	63.7	73.1	78.7	59.1	16.1			54.4 (CO_2CH_3), 168.6 (CO_2CH_3)

[a] Arrangement of compounds according to substance class (pyrrolidine *N*-oxide/pyrrolidine) and protecting group pattern for better comparison. − [b] In MeOD. − [c] Assignment may be reversed. − [d] Signal assignment based on C,H-COSY. − [e] In $CDCl_3$. − [f] In C_6D_6. − [g] Acquisition at 347 K. − [h] In [D_6]DMSO. − [i] Acquisition at 353 K. − [j] Major conformer, ratio 86:14 at 347 K. − [k] NMR-spectroscopic data of the hydrochloride.

CH_3), 25.2, 27.1 [$C(CH_3)_2$], 56.4 (CH_2Ph), 57.9 (C-5), 63.7 (C-2), 77.8 (C-4), 86.3 (C-3), 112.7 [$C(CH_3)_2$], 126.9, 128.3, 128.7, 138.7 (C_6H_5). − $C_{15}H_{21}NO_2$ (247.3): calcd. C 72.84, H 8.56, N 5.66; found C 72.60, H 8.49, N 5.59.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-2,5-dimethylpyrrolidine (33): This compound was prepared as described for **32**; compound **10**·H_2O (159 mg, 0.54 mmol),[41] acetic acid (10 mL), Zn (0.70 g, 11 mmol), addition time 40 min, reaction time 1 d at room temp. Workup and flash chromatography as above afforded analytically pure **33** (colourless oil, 96 mg, 69%); optically inactive (*meso* compound). − IR (film): $\tilde{\nu}$ = 3423 (b), 2967, 2930, 1379, 1229, 1073 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **33**: see Tables 2−4. − $C_{16}H_{23}NO_2$ (261.4): calcd. C 73.53, H 8.87, N 5.36; found C 73.59, H 8.97, N 5.37.

(2*R*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-2,5-dimethylpyrrolidine (34): This compound was prepared as described for **32**; compound **11**·H_2O and its 5-epimer (116 mg, 0.39 mmol, *dr* 85:15),[41] acetic acid (5 mL), Zn (0.52 g, 8 mmol), addition time 30 min, reaction time 1 d at room temp. Workup as described above and flash chromatography (SiO_2; petroleum ether/ethyl acetate, 4:1) afforded **34** as a spectroscopically pure, colourless oil with a somewhat deviating analysis (50 mg, 49%) and another fraction containing equal amounts of **34** and its 5-epimer (29 mg, 28%). − $[\alpha]_D^{20}$ = −43 (*c* = 2.09, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2977, 2932, 1377, 1209, 1160, 1056 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **34**: see Tables 2−4. − $C_{16}H_{23}NO_2$ (261.4): calcd. C 73.53, H 8.87, N 5.36; found C 72.33, H 8.81, N 5.23.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methyl-2-vinylpyrrolidine (35): This compound was prepared as described for **32**; compound **12** (60 mg, 0.20 mmol),[41] acetic acid (3 mL), Zn (0.27 g, 4 mmol), addition time 20 min, reaction time 1 d at room temp. Workup as above and flash chromatography (SiO_2; petroleum ether/ethyl acetate, 4:1) afforded pure **35** as a colourless oil (47 mg, 84%). − $[\alpha]_D^{20}$ = −1 (*c* = 0.42, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2980, 2930, 1454, 1380, 1247, 1209, 1071 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **35**: see Tables 2−4. − $C_{17}H_{23}NO_2$ (273.4): calcd. C 74.69, H 8.48, N 5.12; found C 74.97, H 8.52, N 5.08.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methyl-2-phenylpyrrolidine (36): This compound was prepared as described for **32**; compound **13** (119 mg, 0.35 mmol),[41] acetic acid (8 mL), Zn (0.46 g, 7 mmol), addition time 45 min, reaction time 16 h at room temp. Workup and flash chromatography as above afforded analytically pure **36** as colourless crystals (88 mg, 77%), m.p. 63 °C. − $[\alpha]_D^{20}$ = +13 (*c* = 0.66, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2960, 2940, 2900, 2800, 1440, 1370, 1360, 1235, 1190, 1170, 1140, 1075, 1045 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **36**: see Tables 2−4. − $C_{21}H_{25}NO_2$ (323.4): calcd. C 77.99, H 7.79, N 4.33; found C 77.95, H 7.89, N 4.25.

(2*R*,3*R*,4*S*)-1-Benzyl-3,4-dihydroxy-2-methylpyrrolidine (21): The acetonide **32** (85 mg, 0.34 mmol) was dissolved under nitrogen in a mixture of MeOH (2 mL), water (2 mL) and conc. HCl (0.25 mL). The colourless reaction mixture was stirred for 16 h at room temp. Concentration to dryness and purification of the crude product using Dowex 50WX8 acidic resin (cf. preparation of **15**) afforded spectroscopically pure **21** with deviating elemental analysis (colourless oil, 63 mg, 88%). − $[\alpha]_D^{20}$ = −50 (*c* = 0.56, MeOH). − IR (film): $\tilde{\nu}$ = 3387, 2963, 2927, 1125 cm^{-1}. − ^1H NMR (MeOD,

300.1 MHz): δ = 1.22 ($J_{2,2\text{-Me}}$ = 6.2 Hz, 3 H, 2-CH_3), 2.27 (dd, $J_{4,5a}$ = 5.4, $^2J_{5a,5b}$ = 10.4 Hz, 1 H, 5-H_a), 2.47 (dq, $J_{2,3}$ = 7.2, $J_{2,2\text{-Me}}$ = 6.2 Hz, 1 H, 2-H), 3.13 (dd, $J_{4,5b}$ = 6.3, $^2J_{5a,5b}$ = 10.4 Hz, 1 H, 5-H_b), 3.32 and 3.98 (2 d, ^2J = 12.4 Hz, 2 H, CH_2Ph), 3.52 (dd, $J_{2,3}$ = 7.2, $J_{3,4}$ = 6.3 Hz, 1 H, 3-H), 4.01 (dt, $J_{3,4}$ = $J_{4,5b}$ = 6.3, $J_{4,5a}$ = 5.4 Hz, 1 H, 4-H), 7.27 (m_c, 5 H, C_6H_5). − ^{13}C NMR (MeOD, 75.5 MHz): δ = 17.8 (2-CH_3), 59.9 (CH_2Ph), 61.1 (C-5), 65.7 (C-2), 69.9 (C-4), 78.9 (C-3), 129.0, 129.9, 131.1, 139.7 (C_6H_5). − MS (FAB, positive ion): *m*/*z* (%) = 208.1 (100) [MH^+], 192.1 (10), 91.0 (48). − HRMS (FAB, positive ion): exact mass calcd. for $C_{12}H_{17}NO_2$ + H: 208.1338; found 208.1339. − $C_{12}H_{17}NO_2$ (207.3): calcd. C 69.54, H 8.27, N 6.76; found C 68.18, H 8.22, N 6.54.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-2,5-dimethylpyrrolidine Hydrochloride (22·HCl): Compound **33** (30 mg, 0.11 mmol) was deprotected as described for **21** (reaction time: 2 h). Concentration to dryness afforded a pale yellow solid (35 mg), which was recrystallized from MeOH/diethyl ether (1:6) and gave colourless crystals of pure **22**·HCl (27 mg, 91%), m.p. 177−178 °C; optically inactive (*meso* compound). − IR (KBr): $\tilde{\nu}$ = 3420, 3140, 2900, 2585, 1440, 1415, 1375, 1320, 1120, 1095, 1060, 1045, 1000 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data for **22**·HCl: see Tables 2−4. − $C_{13}H_{19}NO_2$·HCl (257.8): calcd. 60.58, H 7.82, N 5.43; found 60.21, H 7.73, N 5.30.

(2*R*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-2,5-dimethylpyrrolidine (23): Deprotection of **34** (37 mg, 0.14 mmol) as described above (reaction time: 3 h), and purification of the crude product using Dowex 50WX8 acidic resin (5 g, application of **23**·HCl dissolved in MeOH; washing with 70 mL each of MeOH and water; elution of **23** with 140 mL of 1 N NH_3) afforded spectroscopically pure **23** (27 mg, 87%, pale yellow oil). − $[\alpha]_D^{20}$ = −27 (*c* = 0.63, MeOH). − IR (film): $\tilde{\nu}$ = 3386, 2976, 1627, 1453, 1390 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data for **23**: see Tables 2−4.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-5-methyl-2-vinylpyrrolidine Hydrochloride (24·HCl): Deprotection of **35** (139 mg, 0.51 mmol) as described for **21** (reaction time: 3 h) and crystallization of the crude product from 2-propanol afforded colourless crystals of pure **24**·HCl (107 mg, 78%), m.p. 183−184 °C. − $[\alpha]_D^{20}$ = −13 (*c* = 0.53, MeOH). − IR (KBr): $\tilde{\nu}$ = 3320 (OH), 2910, 2760−2500, 1420, 1380, 1320, 1270, 1125, 1095, 1050 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data for **24**·HCl: see Tables 2−4. − $C_{14}H_{19}NO_2$·HCl (269.8): calcd. C 62.33, H 7.47, N 5.19; found C 62.28, H 7.50, N 5.12.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-dihydroxy-5-methyl-2-phenylpyrrolidine Hydrochloride (25·HCl): Deprotection of **36** (59 mg, 0.18 mmol) was performed as described for the preparation of **21**. Crystallization of the crude product from 2-propanol/diethyl ether yielded colourless crystals of pure **25**·HCl (56 mg, 96%), m.p. 181−183 °C. − $[\alpha]_D^{20}$ = −16 (*c* = 0.34, MeOH). − IR (KBr): $\tilde{\nu}$ = 3320, 2460, 1415, 1320, 1135, 1125, 1040 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data for **25**·HCl: see Tables 2−4. − $C_{18}H_{21}NO_2$·HCl (319.8): calcd. C 67.60, H 6.93, N 4.38; found C 67.50, H 6.94, N 4.25.

(2*R*,3*R*,4*S*)-3,4-Dihydroxy-2-methylpyrrolidine Hydrobromide (26·HBr): A solution of **21** (104 mg, 0.50 mmol) in MeOH (5 mL) was treated with Pearlman's catalyst [20% $Pd(OH)_2$ on charcoal, 20 mg] and was hydrogenated at a pressure of 4 bar.[42] After 2 d, the catalyst was removed by centrifugation and washed with MeOH. The crude product obtained from the combined solutes was treated with 48% HBr (0.25 mL) and crystallized from MeOH/diethyl ether (1:1), yielding pale-brown crystals of pure **26**·HBr (49 mg, 50%, m.p. 126−128 °C). − $[\alpha]_D^{20}$ = +45 (*c* = 0.41, MeOH). − IR (KBr): $\tilde{\nu}$ = 3320 (b), 3260, 2960, 2760, 1595, 1445, 1410, 1360, 1250, 1125, 1105, 1075, 1045 cm^{-1}. − ^{1}H NMR (MeOD, 500.1 MHz): δ = 1.43 (d, $J_{2,2\text{-Me}}$ = 6.9 Hz, 3 H, 2-CH_3), 3.21 (dd, $J_{4,5a}$ = 2.2, $^2J_{5a,5b}$ = 12.7 Hz, 1 H, 5-H_a), 3.49 (dd, $J_{4,5b}$ = 4.5, $^2J_{5a,5b}$ = 12.7 Hz, 1 H, 5-H_b), 3.53 (dq, $J_{2,3}$ = 8.3, $J_{2,2\text{-Me}}$ = 6.9 Hz, 1 H, 2-H), 3.85 (dd, $J_{2,3}$ = 8.3, $J_{3,4}$ = 4.2 Hz, 1 H, 3-H), 4.26 (ddd, $J_{3,4}$ = 4.2, $J_{4,5a}$ = 2.2, $J_{4,5b}$ = 4.5 Hz, 1 H, 4-H). − ^{13}C NMR (MeOD, 125.8 MHz): δ = 15.4 (2-CH_3), 50.6 (C-5), 58.2 (C-2), 70.7 (C-4), 77.7 (C-3). − $C_5H_{11}NO_2$·HBr (198.1): calcd. C 30.32, H 6.11, N 7.07; found C 30.66, H 6.15, N 7.00.

(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-2,5-dimethylpyrrolidine Hydrochloride (27·HCl): The *N*-benzyl group of **22**·HCl (32 mg, 0.12 mmol) was removed by catalytic hydrogenation as described for **26**.[42] After a reaction time of 4 d and workup as above, the crude product, a colourless oil (22 mg), was crystallized from 2-propanol/diethyl ether (1:1). This afforded colourless needles of pure **27**·HCl (18 mg, 87%), m.p. 133 °C. − optically inactive (*meso* compound). − IR (KBr): $\tilde{\nu}$ = 3300 (br., OH), 2960, 2870, 2770, 2670, 2450, 1560, 1415, 1130, 1095, 1055, 1000 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data for **27**·HCl: see Tables 2−4. − $C_6H_{13}NO_2$·HCl (167.6): calcd. C 43.00, H 8.42, N 8.36; found C 42.54, H 8.41, N 8.04.

(2*R*,3*R*)-*N*-Benzyl-2,3-isopropylidenedioxy-4-penteneamide (37) and (3*R*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methylpyrrolidin-2-one (38): A solution of the nitrone **2** (200 mg, 0.77 mol)[41] in dry CH_2Cl_2 (8 mL) was treated at −20 °C with lithium cyanide (0.5 M in DMF, 2.30 mL, 1.2 mmol). Stirring was continued for 5 h; the reaction mixture turned red and a precipitate was formed. After addition of ammonium chloride (0.18 g) and water (10 mL), the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were washed with water (2 × 10 mL) and dried with $MgSO_4$. The residue obtained upon concentration in vacuo (219 mg) was dissolved in chloroform and stirred for 5 d at room temp. to effect Cope−House cyclization of the assumed intermediate hydroxylamine. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, ethyl acetate) yielding 150 mg of yellow oil that was rechromatographed (SiO_2; petroleum ether/ethyl acetate, 4:1, then 1:1). In this way, samples of the amide **37**, an analytically pure solid (63 mg, 31%), m.p. 33 °C, and of the lactam **38** (yellow oil, still containing impurities, 61 mg, ca. 30%) were obtained. − Amide **37**: $[\alpha]_D^{20}$ = +18 (*c* = 0.41, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3280 (b), 2970, 1665 (CO), 1525, 1205, 1080, 1030 cm^{-1}. − ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 1.40, 1.54 [2 s, $C(CH_3)_2$, 6 H], 4.41 and 4.53 (2 dd, ^2J = 15.0, $J_{CH,NH}$ = 6.0 Hz, 2 H, CH_2Ph), 4.68 (d, $J_{2,3}$ = 7.7 Hz, 1 H, 2-H), 4.89 (dd, $J_{2,3}$ = 7.7, $J_{3,4}$ = 6.6 Hz, 1 H, 3-H), 5.26 (dd, $J_{4,5E}$ = 10.3, $^2J_{5E,5Z}$ = 1.6 Hz, 1 H, 5-H_E), 5.42 (dd, $J_{4,5Z}$ = 17.0, $^2J_{5E,5Z}$ = 1.6 Hz, 1 H, 5-H_Z), 5.79 (ddd, $J_{3,4}$ = 6.6, $J_{4,5E}$ = 10.3, $J_{4,5Z}$ = 17.0 Hz, 1 H, 4-H), 6.82 (m_c, 1 H, NH), 7.28, 7.34 (2 m_c, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 25.1, 27.6 [$C(CH_3)_2$], 43.2 (CH_2Ph), 78.5 (C-2), 78.9 (C-3), 110.5 [$C(CH_3)_2$], 119.1 (C-5), 128.0, 128.1, 129.1, 138.2 (C_6H_5), 133.2 (C-4), 168.8 (CO). − MS (EI, 70 eV): *m*/*z* (%) = 261.1 (26) [M^+], 246.2 (11), 203.1 (100), 127.1 (37), 106.1 (31), 91.0 (82), 69.0 (60), 59.0 (34), 43.0 (18), 28.0 (18). − HRMS (EI, 70 eV): exact mass calcd. for $C_{15}H_{19}NO_3$: 261.1365; found 261.1361. − $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.32, N 5.36; found C 68.90, H 7.26, N 5.39. − Lactam **38**: ^{1}H NMR spectroscopic data identical to those given below.

(1*R*,2*S*,3*S*,4*R*,5*R*)-1-Benzyl-2-(2-furyl)-3,4-isopropylidenedioxy-5-methylpyrrolidine 1-Oxide (39): A solution of furan (0.17 mL, 2.3 mmol) in THF (10 mL) was placed under nitrogen in a flame-dried flask. After butyllithium (1.6 M in hexanes, 1.50 mL, 2.4 mmol) had been added at −80 °C, the solution was stirred for 2 h at 0 °C.

At this point, the nitrone **2** (200 mg, 0.77 mmol)[41] in THF (10 mL) was added over a period of 30 min at −80 °C. Stirring was continued for 75 min and the reaction mixture was then quenched with ammonium chloride (0.20 g) and water (10 mL). The aqueous phase was extracted with diethyl ether (4 × 10 mL). The organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residual orange oil (340 mg) was dissolved in chloroform (10 mL) and stirred for 17 h at room temp. After removal of the solvent, the crude product (**39** and its 2-epimer, *dr* 92:8) was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2, then 92:8). The pyrrolidine *N*-oxide **39** was obtained as a colourless oil containing 6−8% of the 2-epimer (224 mg, 89%). − $[\alpha]_D^{20} = -127$ (c = 0.51, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3385, 2988, 1382, 1209, 1097, 1021 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **39**: see Tables 2−4. − MS (EI, 70 eV): *m/z* (%) = 329.1 (28) [M^+], 271.1 (10), 202.0 (13), 150.0 (16), 91.0 (100). − HRMS (EI, 70 eV): exact mass calcd. for $C_{19}H_{23}NO_4$: 329.1627; found 329.1619.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-2-(2-furyl)-3,4-isopropylidenedioxy-5-methylpyrrolidine (40): As described for **32**; Zn dust (0.81 g, 12 mmol) added over 30 min to **39** (204 mg, 0.62 mmol, with ca. 8% of the 2-epimer) in acetic acid (10 mL); reaction time 22 h at room temp. Workup and chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) afforded the 2-(2-furyl)pyrrolidine **40** (146 mg, 75%) as a spectroscopically pure stereoisomer. *Note:* The pyrrolidine **40** proved sensitive towards oxidation by air and, after NMR measurement, was immediately subjected to the next step. − ^1H and ^{13}C NMR spectroscopic data for **40**: see Tables 2−4.

(3*R*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methylpyrrolidin-2-one (38): A solution of the acetonide **40** (129 mg, 0.41 mmol) in CCl_4 (2 mL), acetonitrile (2 mL), and water (3 mL) was treated with sodium periodate (1.32 g, 6.2 mmol) and $RuCl_3 \cdot H_2O$ (5 mg).[50] The solution turned dark, with formation of a colourless precipitate and gas evolution (carbon dioxide). After vigorous stirring for 1 h, the reaction mixture was extracted with CH_2Cl_2 (4 × 10 mL). The organic solutes were dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in diethyl ether and filtered through Celite. Column chromatography of the crude material obtained upon concentration of the filtrate (SiO_2; ethyl acetate/petroleum ether, 7:3) afforded colourless crystals of the pure lactam **38** (46 mg, 43%), m.p. 83−84 °C. − $[\alpha]_D^{20} = +69$ (c = 0.51, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2970, 2950, 2910, 1685 (CO), 1420 cm^{-1}. − ^1H NMR ($CDCl_3$, 500.1 MHz): δ = 1.18 (d, $J_{5,5\text{-Me}}$ = 6.9 Hz, 3 H, 5-CH_3), 1.36, 1.43 [2 s, 6 H, C(CH_3)$_2$], 3.53 (qu, $J_{5,5\text{-Me}}$ = 6.9 Hz, 1 H, 5-H), 3.95 and 5.03 (2 d, ^2J = 15.1 Hz, 2 H, CH_2Ph), 4.33 (d, $J_{3,4}$ = 5.7 Hz, 1 H, 3-H or 4-H), 4.76 (d, $J_{3,4}$ = 5.7 Hz, 1 H, 4-H or 3-H), 7.33 (m_c, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 17.6 (5-CH_3), 25.8, 27.2 [C(CH_3)$_2$], 44.1 (CH_2Ph), 56.2 (C-5), 77.2, 78.8 (C-3, C-4), 112.3 [C(CH_3)$_2$], 127.7, 128.0, 128.7, 135.4 (C_6H_5), 170.7 (CO). − $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.36; found C 68.75, H 7.36, N 5.36.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-2-(1′,2′-dihydroxyethyl)-3,4-isopropylidenedioxy-5-methylpyrrolidine (41): A solution of **35** (200 mg, 0.73 mmol) in 8 mL of acetone/water (1:1) was treated with *N*-morpholine *N*-oxide (NMO, 110 mg, 0.81 mmol) and OsO_4 (0.5 mL of a solution of 10 mg/mL OsO_4 in *tert*-butyl alcohol, 0.03 equiv.). The reaction mixture was stirred for 1 d at room temp., then treated with a further portion of NMO (110 mg) and OsO_4 solution (0.5 mL). After a total reaction time of 4.5 d, Na_2SO_3 (0.4 g) and silica gel (1 g) were added and the heterogeneous mixture was concentrated in vacuo. Flash chromatography (SiO_2, ethyl acetate) yielded the pure diol **41** as a mixture of epimers (colourless oil, 187 mg, 83%, *dr* 60:40). − $[\alpha]_D^{20} = -2$ (c = 0.59, CH_2Cl_2). − $C_{17}H_{25}NO_4$ (307.4): calcd. C 66.43, H 8.20, N 4.56; found C 66.41, H 8.32, N 4.62.

(2*S*,3*S*,4*R*,5*R*)-2-(1′,2′-Dihydroxyethyl)-3,4-isopropylidenedioxy-5-methylpyrrolidine (42): A solution of **41** (343 mg, 1.12 mmol) in MeOH (10 mL) was hydrogenated with Pearlman's catalyst [70 mg, 20% $Pd(OH)_2$ on charcoal, 4 bar H_2].[42] After 3 d, the catalyst was removed by centrifugation and washed with MeOH. The MeOH phases were combined and concentrated to dryness, yielding analytically pure **42** (243 mg, 100%, *dr* 60:40), m.p. 62−63 °C. − $[\alpha]_D^{20} = +1$ (c = 0.97, MeOH). − $C_{10}H_{19}NO_4$ (217.3): calcd. C 55.28, H 8.81, N 6.45; found C 55.32, H 8.73, N 6.29.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyloxycarbonyl-2-(1′,2′-dihydroxyethyl)-3,4-isopropylidenedioxy-5-methylpyrrolidine (43): Na_2CO_3 (49 mg, 0.46 mmol) and benzyloxycarbonyl chloride (86 mg, 71 μL, 0.50 mmol) were added to a solution of the pyrrolidine **42** (100 mg, 0.46 mmol, *dr* 60:40) in 10 mL of dioxane/water, 1:1. After the reaction mixture had been stirred for 2.5 h at room temp., it was concentrated in vacuo, diluted with water (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic solution was dried with $MgSO_4$ and concentrated to dryness. The crude product (200 mg) was purified by flash chromatography (SiO_2; ethyl acetate), affording pure **43** as a colourless oil (127 mg, 79%, *dr* 60:40). − $C_{18}H_{25}NO_6$ (351.4): calcd. C 61.53, H 7.17, N 3.99; found C 61.20, H 7.19, N 3.93.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyloxycarbonyl-2-hydroxymethyl-3,4-isopropylidenedioxy-5-methylpyrrolidine (45): K_2CO_3 (704 mg, 5.09 mmol) was added to a solution of the pyrrolidine **43** (180 mg, 0.51 mmol, *dr* 60:40) in CH_2Cl_2 (5 mL). The resulting suspension was treated with a solution of lead tetraacetate (85%, 321 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) to give a yellow mixture, which was stirred for 1 h at room temp., filtered, and concentrated in vacuo. The resulting colourless oil (**44**, 175 mg) was dissolved in ethanol (6 mL) and $NaBH_4$ (39 mg, 1.03 mmol) was added at 0 °C. After 2.5 h, another portion of $NaBH_4$ (40 mg) was added. After 1.5 h at 0 °C, the reaction was quenched by addition of an aqueous solution of citric acid (0.25 M, 8 mL). The solution was neutralized using 6 N NaOH, concentrated by rotary evaporation until most of the ethanol was removed, and extracted with $CHCl_3$ (3 × 20 mL). The organic phase was dried with $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography (SiO_2; petroleum ether/ethyl acetate, 1:1) to give pure **45** as a colourless oil (126 mg, 77%). − $[\alpha]_D^{20} = +13$ (c = 0.52, CH_2Cl_2) {ref.[44] $[\alpha]_D^{20} = +13$ (c = 1.0, $CHCl_3$)} − IR (film): $\tilde{\nu}$ = 3458 (br., OH), 2986, 2938, 1694, 1681, 1454, 1415, 1380, 1359, 1329, 1241, 1213, 1064 cm^{-1} (identical with the data given in ref.[44]). − ^1H and ^{13}C NMR spectroscopic data for **45**: see Tables 2−4 (for NMR spectroscopic data in $CDCl_3$, 333 K, see ref.[44]). − $C_{17}H_{23}NO_5$ (321.4): calcd. C 63.54, H 7.21, N 4.36; found C 63.41, H 7.25, N 4.34.

(2*S*,3*S*,4*R*,5*R*)-2-Hydroxymethyl-3,4-isopropylidenedioxy-5-methylpyrrolidine (46): Removal of the Z group was achieved by hydrogenation (1 bar) of a solution of **45** (108 mg, 0.34 mmol) in MeOH (5 mL), using Pd catalyst (40 mg, 10% Pd on charcoal). After a reaction time of 5.5 h, the catalyst was removed by centrifugation and washed with MeOH. Concentration of the MeOH solution under reduced pressure afforded the acetonide **46** (63 mg, 91%) as a colourless oil. − ^1H and ^{13}C NMR spectroscopic data for **46**: see Tables 2−4.

(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-2-hydroxymethyl-5-methylpyrrolidine (28): Compound **46** (55 mg, 0.27 mmol) was dissolved under argon in a mixture of MeOH (3 mL), water (3 mL), and conc. HCl (0.45 mL). The colourless solution was stirred for 17 h at

room temp. Concentration to dryness afforded a brown oil (58 mg), which was purified using Dowex 50WX8 (1 g, cf. purification of **15**). The crude **28**·HCl in MeOH was loaded onto the resin, this was washed with MeOH (50 mL) and water (50 mL), and the pyrrolidine **28** was then eluted with 1 N NH_3 (50 mL). Removal of the solvent under reduced pressure yielded 40 mg (0.27 mmol, 100%) of the iminopolyol **28**, a spectroscopically pure, pale yellow solid with deviating analysis, m.p. 97−100 °C (ref.:[43,44] oil). − $[\alpha]_D^{20}$ = −1 (*c* = 1.50, MeOH) {ref.[43,44] $[\alpha]_D^{20}$ = −2 (*c* = 1.0, MeOH)}. − IR (KBr): $\tilde{\nu}$ = 3364 (br., OH), 2964, 2930, 1455, 1416, 1372, 1328, 1108 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **28**: see Tables 2−4 (for NMR spectroscopic data in D_2O cf. ref.[44]). − MS (Auto-CI): *m*/*z* (%) = 148.1 (16) [MH^+], 116.0 (100), 87.1 (22), 69.0 (68), 60.1 (10), 54.0 (14). − HRMS (Auto-CI): exact mass calcd. for $C_6H_{13}NO_3$ + H: 148.0974; found 148.0974. − $C_6H_{13}NO_3$ (147.2): calcd. C 48.96, H 8.90, N 9.52; found C 46.97, H 8.68, N 8.71.

(2*R*,3*S*,4*R*,5*R*)-1-Benzyloxycarbonyl-3,4-isopropylidenedioxy-5-methylproline (47): Lead tetraacetate cleavage of **43** (204 mg, 0.58 mmol) was performed as reported for **45**, yielding **44** (176 mg) as a colourless oil. This was dissolved in *tert*-butyl alcohol (2.5 mL) and 2-methyl-2-butene (1.5 mL).[53] An aqueous solution (0.75 mL) of $NaClO_2$ (79 mg, 0.87 mmol) and NaH_2PO_4 (105 mg, 0.87 mmol) was added over a period of 40 min. The reaction mixture was stirred for 5.5 h at room temp. and the pH was then adjusted to > 8 using 6 N NaOH. After most of the solvent had been removed in vacuo, water (15 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the pH was adjusted to 2 by addition of 1 N HCl. The organic phase collected on extraction of the aqueous phase with diethyl ether (3 × 15 mL) was dried with $MgSO_4$ and concentrated to dryness. The proline derivative **47** was isolated as a colourless resin (152 mg, 78%). − $[\alpha]_D^{20}$ = +15 (*c* = 1.90, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3660−2350 (br., COOH), 1753 (CO), 1708 (CO), 1419, 1356, 1212, 1064 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data of **47**: see Tables 2−4. − $C_{17}H_{21}NO_6$ (335.4): calcd. C 60.89, H 6.31, N 4.18; found C 60.27, H 6.39, N 4.02.

(2*R*,3*S*,4*R*,5*R*)-3,4-Isopropylidenedioxy-5-methylproline (48): The Z group was removed from **47** (75 mg in 5 mL of MeOH, 0.22 mmol) by catalytic hydrogenation (1 bar, 25 mg of 10% Pd on charcoal). After a reaction time of 4 h, the catalyst was removed by centrifugation and washed with MeOH (10 mL) and water (10 mL). The combined solutions were concentrated, yielding spectroscopically pure, colourless crystals of **48** (45 mg, 100%), m.p. 238−240 °C (decomp.). − $[\alpha]_D^{20}$ = −34 (*c* = 1.08, MeOH). − ^1H and ^{13}C NMR spectroscopic data for **48**: see Tables 2−4.

(2*R*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-methylproline Hydrochloride (29·HCl): Conc. HCl (0.25 mL) was added under nitrogen to an aqueous solution (4 mL) of **48** (52 mg, 0.26 mmol). After the colourless solution had been stirred for 4 h at room temp., it was concentrated to dryness. Drying over P_4O_{10} afforded 51 mg (100%) of spectroscopically pure **29**·HCl. The extremely hygroscopic solid deliquesced when exposed to air [ref.:[45] racemic mixture of neutral **29**, m.p. 115−116 °C (decomp.)]. − $[\alpha]_D^{20}$ = 0 (*c* = 0.24, MeOH). − IR (film): $\tilde{\nu}$ = 3680−2250 (br., COOH, NH, OH), 1732 (CO), 1626, 1392, 1233, 1126, 1075 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **29**·HCl: see Tables 2−4 (for NMR spectroscopic data of neutral **29** cf. ref.[45]) − $C_6H_{11}NO_4$·HCl (197.6): calcd. C 36.47, H 6.12, N 7.09; found C 34.91, H 6.04, N 6.31 [correct for M·HCl·$(H_2O)_{0.5}$]. − MS (FAB, positive ion, glycerol): *m*/*z* (%) = 162.1 (100) [MH^+]. − HRMS (FAB, positive ion, nitrobenzyl alcohol): exact mass calcd. for $C_6H_{11}NO_4$ + H: 162.0766; found 162.0762.

(2*R*,3*S*,4*R*,5*R*)-1-Benzyloxycarbonyl-3,4-isopropylidenedioxy-5-methylproline Methyl Ester (49): The carboxylic acid **47** was prepared from **43** (169 mg, 0.48 mmol) as described above. The crude product of **47** was dissolved in MeOH (5 mL) and treated with a 0.7 M solution of diazomethane in ether[58,59] until the yellow colour persisted. After concentration in vacuo, the crude ester was purified by flash chromatography (SiO_2; petroleum ether/ethyl acetate, 7:3) yielding the protected proline **49** (112 mg, 67%) as an analytically pure, colourless oil. − $[\alpha]_D^{20}$ = −19 (*c* = 0.15, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2987, 2952, 1753 (CO), 1707 (CO), 1412, 1207, 1063 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data of **49**: see Tables 2−4. − MS (EI, 70 eV): *m*/*z* (%) = 349.1 (14) [M^+], 290.1 (15), 246.1 (25), 91.1 (100), 28.1 (17), 18.0 (28). − $C_{18}H_{23}NO_6$ (349.4): calcd. C 61.88, H 6.64, N 4.01; found C 61.66, H 6.64, N 3.99.

(2*R*,3*S*,4*R*,5*R*)-3,4-Isopropylidenedioxy-5-methylproline Methyl Ester (50): Pd catalyst (10% Pd on charcoal, 30 mg) was added to a solution of the Z-proline derivative **49** (148 mg, 0.42 mmol) in MeOH (10 mL). The mixture was hydrogenated (1 bar) over a period of 3 h. The catalyst was removed by centrifugation and washed with MeOH. The combined MeOH phases were concentrated, yielding the proline ester **50** as a colourless oil (90 mg, 100%). − ^1H and ^{13}C NMR spectroscopic data for **50**: see Tables 2−4.

(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-methylproline Methyl Ester Hydrochloride (31·HCl): A solution of the proline derivative **50** (25 mg, 0.12 mmol) in MeOH (3.5 mL) was treated with MeOH saturated with HCl gas (0.5 mL) and stirred for 2.5 h at room temp. The residue obtained on concentration to dryness (ratio of 2-epimers **30**/**31** = 29:71) was crystallized from 2-propanol (1 mL), yielding almost analytically pure proline ester hydrochloride **31**·HCl (14 mg, 57%, **30**/**31** = 6:94), m.p. 189−191 °C. − $[\alpha]_D^{20}$ = +19 (*c* = 0.24, MeOH). − IR (KBr): $\tilde{\nu}$ = 2970, 2930, 2880, 1740 (CO), 1435, 1265, 1220, 1112, 1100, 1085 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data for **31**·HCl: see Tables 2−4. − MS (FAB, positive ion, nitrobenzyl alcohol): *m*/*z* (%) = 176.1 (100) [MH^+], 116.0 (10). − HRMS (FAB, positive ion, nitrobenzyl alcohol): exact mass calcd. for $C_7H_{13}NO_4$ + H: 176.0923; found 176.0919. − $C_7H_{13}NO_4$·HCl (211.6): calcd. C 39.72, H 6.67, N 6.62; found C 39.09, H 6.49, N 6.18.

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