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Synthesis and Comparative Study of Homoisofagomines and Analogues as Glycosidase Inhibitors

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The synthesis of polyhydroxyazepanes and their corresponding lactams has been carried out by use of Grubbs cyclisation, to yield the azepane scaffolds, as a key step. A comparative study of glycosidase inhibition by the azepanes and the corresponding lactams with varying stereochemical dispositions, number of hydroxy groups, and side chain structures was carried out.

Introduction

The marketing of glycosidase-inhibitor-based drugs[1] such as miglustat (**1**, Figure 1), against Gaucher's disease, and miglitol (**2**), against type 2 diabetes, has provided great incentive for the design and synthesis of better glycosidase inhibitors.[2,3] Design of glycosidase inhibitors is based on mimicking the half-chair conformation and the charge on the oxocarbenium ion at the glycosidase active site.[4] Many of these glycosidase inhibitors are piperidine- and pyrrolidine-derived molecules and are referred to as azasugars (or iminosugars).[5]

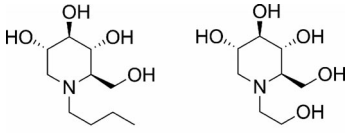

Figure 1. Examples of marketed drugs.

Almost all synthetic endeavours pertaining to azasugars have been directed towards pyrrolidines, piperidines and their conjugates.

These studies have led to a number of excellent enzyme inhibitors, such as isofagomine (**3**, Figure 2) and the amide counterparts **4** and **5**.[3g] Higher analogues of piperidines in the form of polyhydroxyazepanes **6**,[4h] **7**[4k] and **8**[4i,4j] have also been reported to be good glycosidase inhibitors.[4]

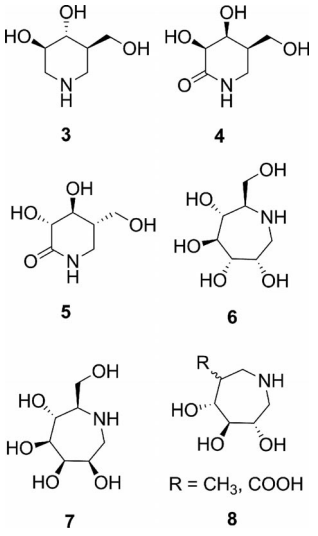

Figure 2. Examples of isofagomines, lactam counterparts and higher analogues.

Although the synthesis of tetrahydroxylated and trihydroxylated azepanes was reported[4a] as early as 1967, glycosidase inhibition studies have been carried out only in the last two decades. Enzyme inhibition studies on polyhydroxylated azepanes have recently grown in importance[6a,6b] as a consequence of the flexible azepane skeleton, which is believed to allow greater number of conformations and the formation of greater numbers of (and stronger) hydrogen bonds at the active sites of enzymes.[6c,6d] Polyhydroxyazepanes have also found use as DNA minor groove binding ligands (MGBLs).[7] This application has also been attributed to the greater flexibility of the azepane ring skeleton.

Here we report the synthesis of a number of polyhydroxylated azepanes and their lactam counterparts, together with a comparative inhibition study. To the best of

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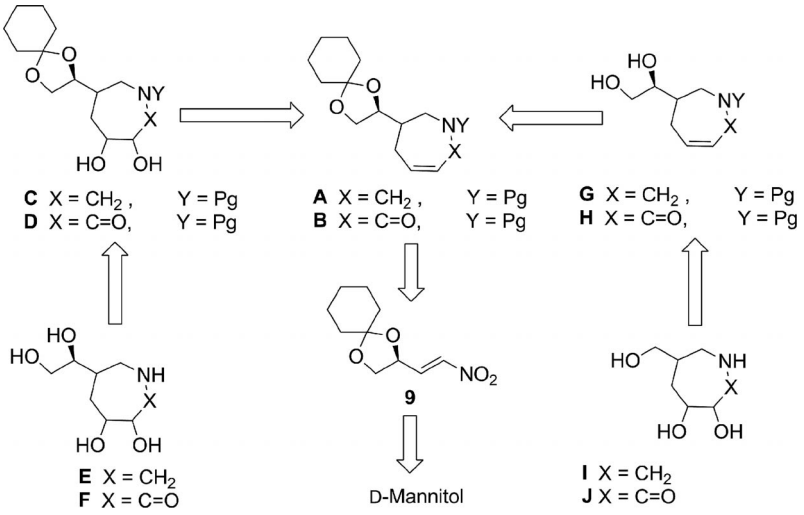

Scheme 1. Retrosynthesis of the planned polyhydroxyazepanes and their lactam counterparts.

our knowledge no such study directed towards comparing glycosidase inhibition by azasugars and by their lactam counterparts based on the same skeleton, with compounds possessing varying numbers and stereochemical dispositions of hydroxy groups, has been reported. For this purpose we chose to explore the inhibition profiles of higher congeners of the isofagomine-type skeleton. The excellent selective enzyme inhibition activity (against β-glucosidases) shown by isofagomine (**3**) was first reported by Bols et al.[8a] Syntheses of isofagomine and its analogues, including of their lactam counterparts,[8] have been reported in the literature; a few of these compounds have shown excellent inhibition profiles.

In this study we planned to keep the number of hydroxy groups the same as that in isofagomine, but on an azepane scaffold. The hydroxymethyl side chain has already been shown to be a moiety of importance, because it appears prominently in glycosidase inhibitors such as fagomine, isofagomine, its analogues and various aminocyclitols. We were interested in finding out how the molecules would behave if an extra $–CH_2OH$ group were attached to the already existing $–CH_2OH$ group. For this purpose we chose to use protected (*R*)-glyceraldehyde, derived from (+)-D-mannitol, as a precursor to the side chain on the azepanes and on the corresponding lactams. We planned to use the Michael adducts **10** and **11** (Scheme 2, below), obtained from glyceraldehyde-derived nitro olefin **9** (Scheme 1), as the common precursors to all of the azepanes and the corresponding lactams.

The retrosynthetic analysis is shown in Scheme 1. The final target molecules **E** and **F**, each with an extra $–CH_2OH$ group, and **I** and **J**, without one, should be obtainable from the common precursors **A** and **B**. The azepane skeletons should be accessible through ring-closing metathesis (RCM) of the corresponding dienes in the presence of the Grubbs catalysts. The dienes should be reachable from the nitro olefin **9** through sequential Michael addition of an allyl group, reduction of the nitro group to an amino group and base-mediated *N*-allylation/acryolylation. Further, the nitro olefin **9** was readily available from D-mannitol by a reported procedure.[9]

Results and Discussion

Michael addition of allylmagnesium chloride to the conjugated nitro olefin **9** at –30 °C led to the formation of a diastereomeric mixture of nitro olefins **10** and **11** (Scheme 2), which could not be easily separated at this stage. Reduction of the mixture of nitro olefins **10** and **11** and subsequent Boc protection furnished the chromatographically separable diastereomeric mixture of carbamates **12** and **13** in an approximate ratio of 1.6:1.

N-Allylation of carbamate **12** furnished the diene **14**, which underwent facile ring-closing metathesis in the presence of the first-generation Grubbs catalyst to provide the unsaturated azepene **16**. Similarly, the carbamate **13** furnished the cyclised product **17** via diene **15** in excellent yield.

The cyclised products **16** and **17** were each exposed to a catalytic amount of OsO_4 in the presence of NMO (Scheme 3) to yield diastereomeric *cis*-dihydroxylated azepane mixtures **18** and **19**, respectively. The diol moieties of the diastereomeric diol mixtures **18** and **19** were separately protected to form the corresponding acetonides: **20** and **21** from **18**, and **22** and **23** from **19**. On the other hand, non-hydroxylated azepenes **16** and **17** were hydrogenated in the presence of $Pd(OH)_2/C$ to yield the corresponding saturated products **24** and **25**, respectively.

The protected hydroxy azepanes **20**, **21**, **22**, **23**, **24** and **25** were hydrolysed in acidic medium to generate the corresponding free polyhydroxyazepanes **26**, **28**, **30**, **32**, **34** and **35** (Scheme 4) as their hydrochloride salts. These salts were neutralised by passage through basic resin (Dowex-50).

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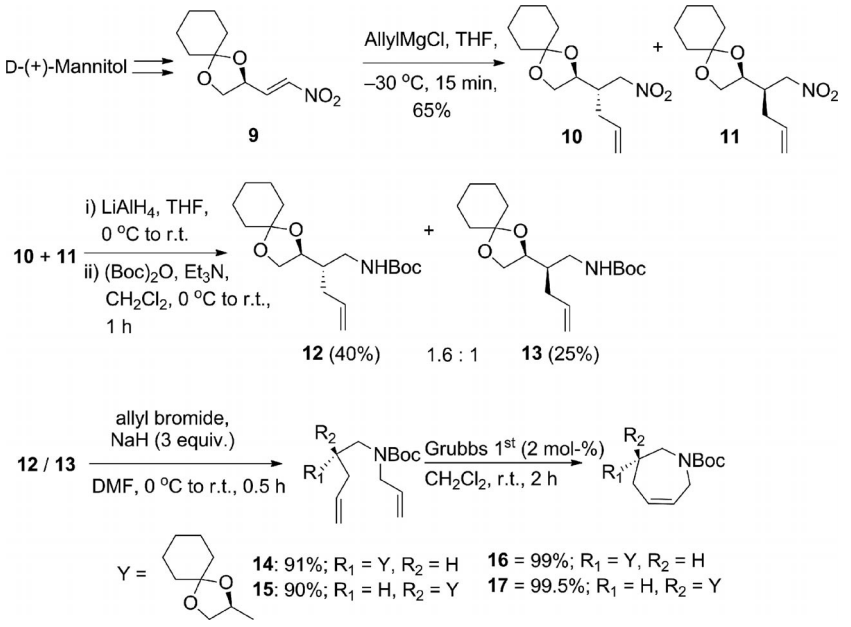
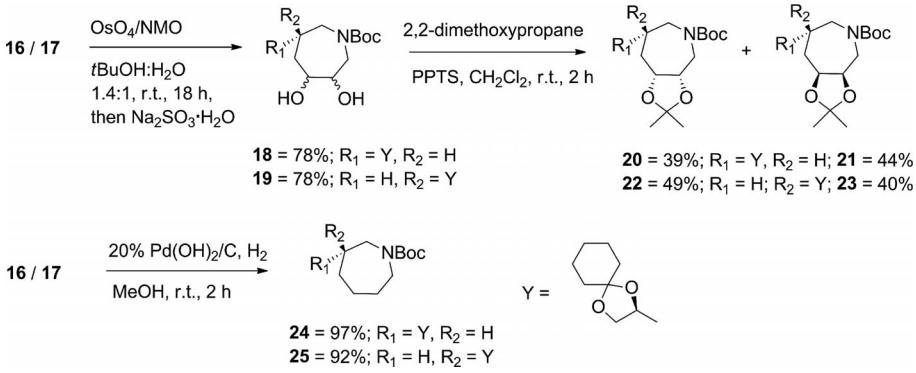


Scheme 2. Synthesis of azepane scaffolds.



Scheme 3. Dihydroxylation and reduction of polyhydroxyazepanes.

The relative stereochemistry at the newly generated chiral centres was confirmed by spectral analysis of the peracetylated products **27**, **29**, **31** and **33** obtained from **26**, **28**, **30** and **32**, respectively. The relative stereochemistry of the newly generated chiral centres (at C-3 and C-4) was determined through nOe irradiation studies. The absolute stereochemistry at the chiral centre C-6, on the other hand, was deduced on the basis of the crystal structure of the cyclised lactam **85** (Scheme 13 and Figure 6, below).

Irradiation of H-6 of compound **27** at δ = 2.18–2.28 ppm thus led to enhancement of the combined signals for H_b-7 and H_b-2 at δ = 3.65–3.72 ppm, whereas only negligible enhancement (1.2%) of the signal for H_a-7 (Figure 3) was observed. Irradiation of the H-3 signal at δ = 5.24 ppm led to 3.5% enhancement of the H_b-2 signal at δ = 3.65–3.72 ppm, whereas only 1.2% enhancement of the signal for H_a-2 at δ = 3.48 ppm was observed. The protons H-6, H_b-7, H_b-2, H-3, and H-4 are thus *syn*-oriented with respect to one another.

For compound **29** (Figure 3), irradiation of either one of the protons H-4 and H-6 did not enhance the signals of the other, but irradiation of the signal for H-6 at δ = 2.45–2.57 ppm enhanced only the signal for H_b-7 at δ = 3.92–4.00 ppm and not that for H_a-7. Irradiation of the signal for H-4 at δ = 5.26 ppm, however, enhanced only the signal for H_a-7 at δ = 3.12 ppm and not that for H_b-7. The protons H-4 and H-6 are thus *anti*-oriented with respect to one another.

For diastereomer **31**, irradiation of either one of the signals for H-4 at δ = 5.24–5.26 ppm and H-6 at δ = 2.35–2.46 ppm did not enhance the signal of the other (Figure 3).

In the case of diastereomer **33**, however, irradiation of the H-6 signal at δ = 2.26–2.36 ppm led to enhancement of the H-4 signal at δ = 5.02 ppm. The absolute configurations of the stereocentres in **31** and **33** are thus as shown in Figure 3.

Further, the dihydroxyethyl side chains were cleaved to afford the corresponding trihydroxyazepanes. For this, se-

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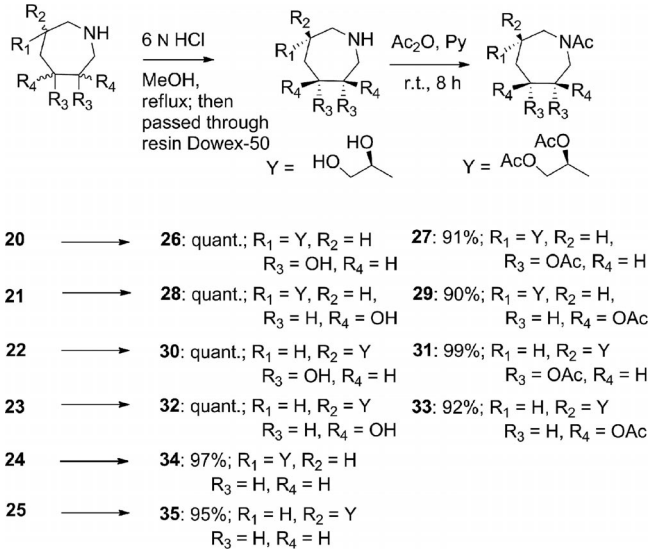


Scheme 4. Hydrolysis of polyhydroxyazepanes and their peracetylation.

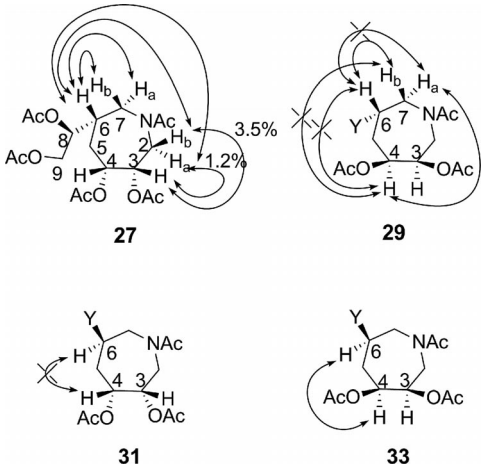


Figure 3. Representation of nOe correlations.

lective hydrolysis of the dioxolane ring of compound **16** with 40 mol-% *p*-toluenesulfonic acid (*p*TsA) in methanol was first performed to afford compound **36** (Scheme 5) in 99% yield (based on recovered starting material) after 8 h at room temperature. Other reported methods utilising camphorsulfonic acid,[9a] 0.1 N HCl in methanol[9b] or trifluoroacetic acid[9c] for the hydrolysis of the cyclohexylidene moiety proved futile because they also simultaneously effected the removal of the *N*-Boc protecting group. Oxidative cleavage of the dihydroxyethyl side chain with $NaIO_4$ gave the desired aldehyde **38** in excellent yield. Similarly, the other cyclised product **17** furnished **37** in 95% yield (based on recovered starting material), and this was converted into the corresponding aldehyde **39**. Reduction of these aldehydes with $NaBH_4$ yielded the alcohols **40** and **41**, respectively.

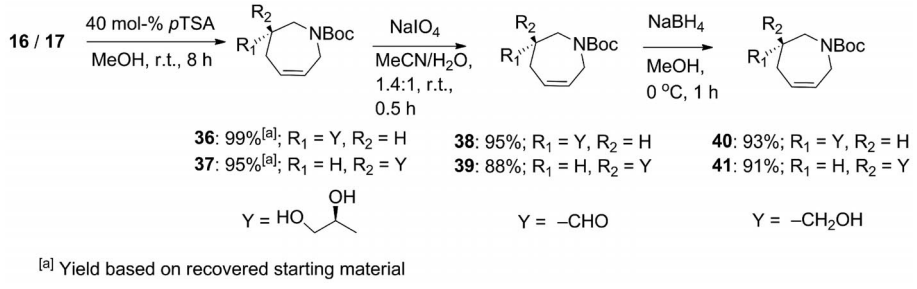
Acetylation of the alcohols **40** and **41** led to the acetates **42** and **43** (Scheme 6), which were dihydroxylated with OsO_4/NMO to yield **44** and **45**, respectively, each as an inseparable mixture of diastereomers. Protection of the diol systems as cyclohexylidene acetals led to the separation of the diastereomers **46** and **47** (from **44**) and of the diastereomers **48** and **49** (from **45**).

Non-hydroxylated azepanes **50** and **51** were obtained upon hydrogenation of **40** and **41**, respectively.

The newly generated hydroxyazepanes **46**, **47**, **48**, **49**, **50** and **51** underwent acidic hydrolysis to yield polyhydroxyazepanes **52**, **54**, **56**, **58**, **60** and **61** (Scheme 7), respectively. The relative stereochemistry of **52**, **54**, **56** and **58** at C-3 and C-4 was determined by spectral analysis (nOe) of the peracetylated products **53**, **55**, **57** and **59**, respectively. For compound **53** (Figure 4), irradiation of the signals for H-4 (δ = 4.96–5.01 ppm) and for H-6 (δ = 2.23–2.30 ppm) led in each case to enhancement of the signal of the other proton, whereas in **55**, irradiation of the H-4 signal (δ = 5.26–5.31 ppm) did not lead to enhancement of the H-6 signal (δ = 2.39–2.48 ppm). Protons H-4 and H-6 are thus *syn* oriented with respect to one another in **53** but *anti* oriented in **55**. Similarly, irradiation of the signals for H-4 (δ = 5.26–5.28 ppm) and H-6 (δ = 2.41–2.48 ppm) in **57** did not in either case show enhancement in the signal of the other proton, whereas for **59** they showed positive correlation between the protons H-4 (δ = 4.96–5.01 ppm) and H-6 (δ = 2.22–2.31 ppm).

The lactam counterparts of the polyhydroxyazepanes were also prepared by starting from the mixture of nitro olefins **10** and **11**. Reduction of the nitro functionality with $LiAlH_4$ and subsequent acryoylation led to amides **62** and **63** in a ratio of 1.6:1 (Scheme 8).

Surprisingly, cyclisation of the diene amides **62** and **63** failed in the presence of either the first- or the second-generation Grubbs catalysts. Use of $Ti(OiPr)_4$,[10] to reduce the electron density at the carbonyl group and thus allow cycli-



Scheme 5. Synthesis of side-chain-shortened azepanes.

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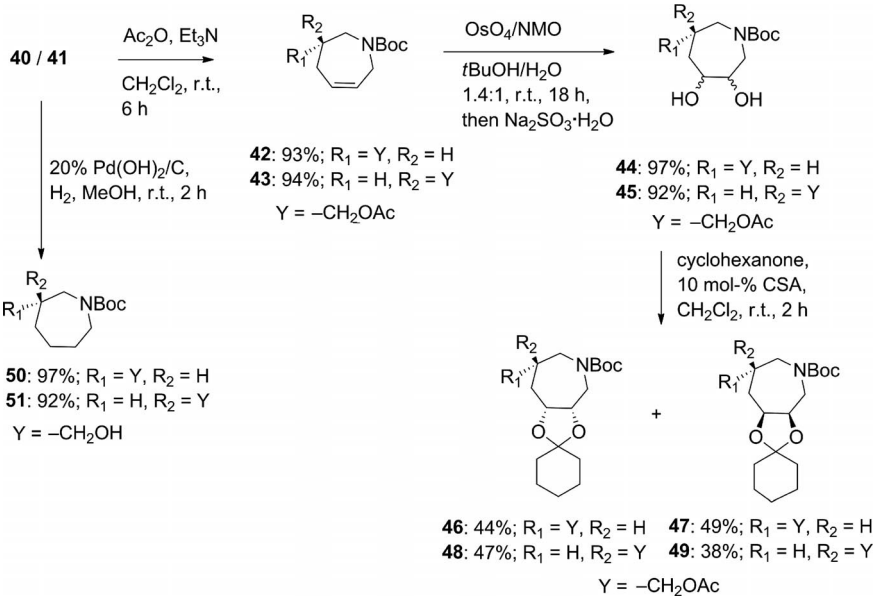
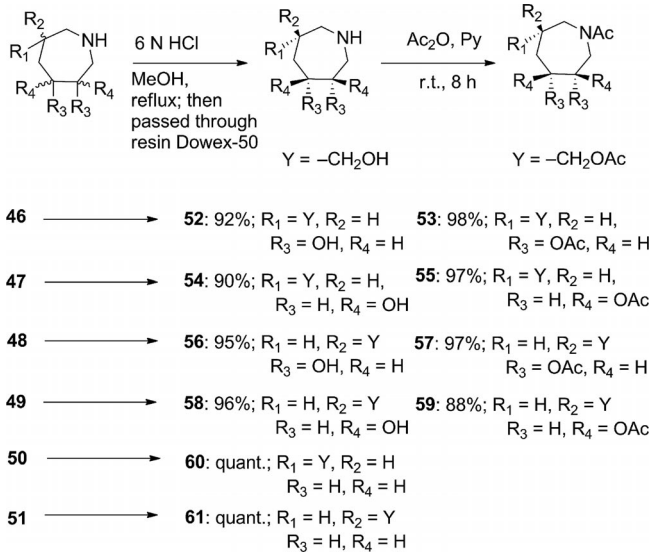


Scheme 6. Synthesis of side-chain-shortened azepanes.



Scheme 7. Synthesis of side-chain-shortened azepanes and their peracetylation.

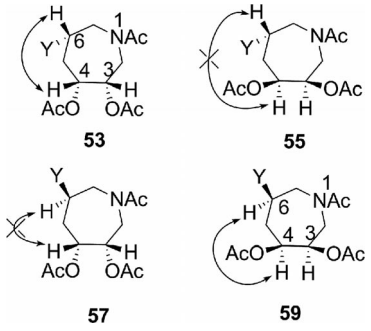
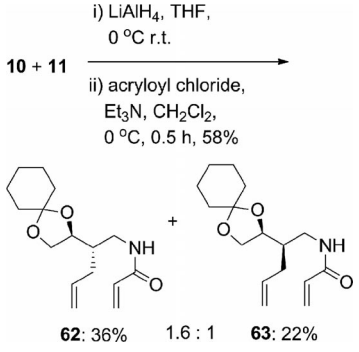


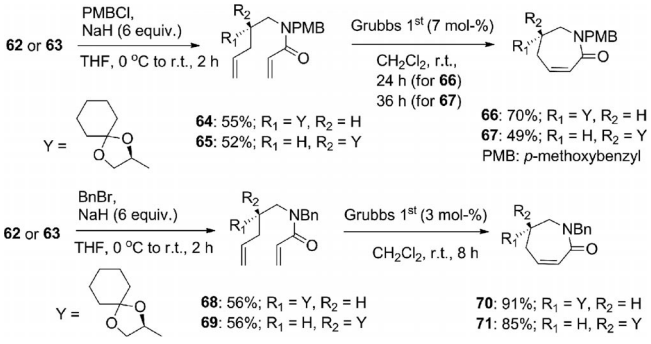
Figure 4. Representation of nOe correlations.

sation of the diene, also met with failure. Protection of the secondary amides **62** and **63** with *p*-methoxybenzyl groups



Scheme 8. Synthesis of diene amides.

led to the cyclised products **66** and **67**, respectively, but only in moderate yields (Scheme 9). However, when a less strongly electron-donating substituent (benzyl group) was used, the major diene **68** and minor diene **69** cyclised to give the unsaturated lactams **70** and **71**, respectively, in good yields.



Scheme 9. Synthesis of azepane lactam scaffolds.

Further, *cis* dihydroxylation of lactam **70** led to diols **72** and **73** in almost equal ratio (Scheme 10). However, *cis* dihydroxylation of **71** led to diastereomers **74** and **75**, which

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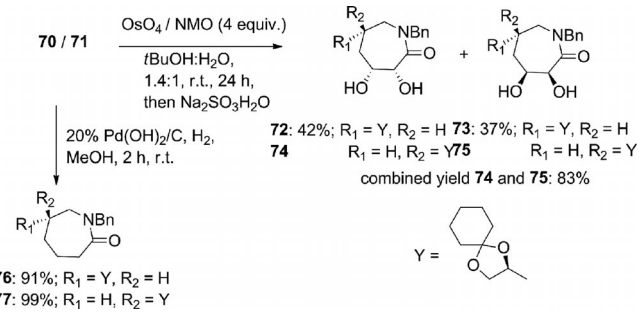
could only be partially separated chromatographically. Hydrogenation of **70** and **71** led to saturated lactams **76** and **77**, respectively, in excellent yields.



Scheme 10. Synthesis of polyhydroxyazepane lactams.

The relative stereochemistry of the newly generated chiral centres was determined by nOe irradiation. For compound **72** (Figure 5), irradiation of the H-6 signal (δ = 1.77–1.83 ppm) led to enhancement of the signals for H-4 (δ = 4.19 ppm) and for H-3 (δ = 4.50 ppm), whereas irradiation of the signals for H-4 and H-3 also led to the enhancement of the signal for H-6. For compound **73**, however, irradiation of signals for H-4 (δ = 4.09 ppm) and H-6 (δ = 1.83–1.87 ppm) did not in either case lead to enhancement of the signal of the other proton. The absolute configurations of the stereocentres are therefore as shown in Figure 5.

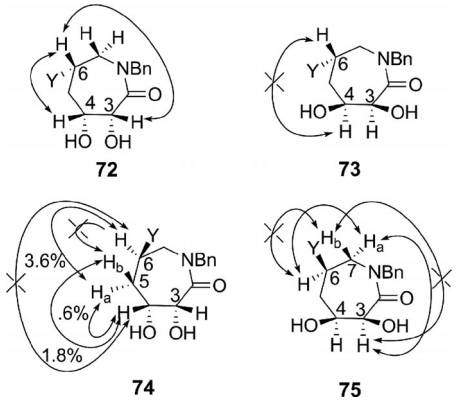
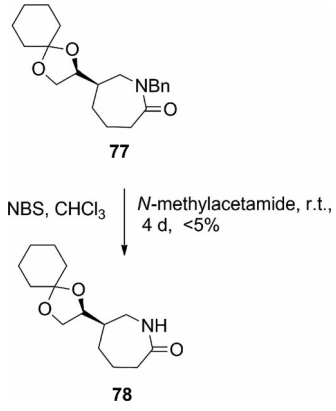


Figure 5. Representations of nOe correlations.

For compound **74** (Figure 5), irradiation of the H-4 signal (δ = 4.21 ppm) and the H-6 signal (δ = 1.88–1.99 ppm, combined signals for H-6 major rotamer, H-5 minor rotamer, H-6 minor rotamer) did not in either case lead to enhancement of the signal of the other proton. Irradiation of the signal for H-6 (combined signals for both rotamers) did, however, lead to a 3.6% enhancement in the signal for H_a-5 (δ = 2.16–2.20 ppm), whereas negligible enhancement was observed for the H_b-5 signal (δ = 1.54–1.59 ppm). Irradiation of the H-4 signal (δ = 4.13–4.18 ppm, combined signal for H-8 major rotamer, H-8 minor rotamer, H-4 minor rotamer) led to only 0.6% enhancement in the signal for H_a-5 but around 1.8% enhancement in the signal for H_b-5 (δ = 1.54–1.59 ppm). H-6 is thus oriented *syn* to H_a-5 but *anti* to H_b-5. Similarly, H-4 is oriented *syn* to H_b-5 but *anti* to H_a-5. Protons H-4 and H-6 are therefore oriented *anti* to one another.

For compound **75** (Figure 5), irradiation of the signal for H-6 (combined signals for H-6 and H-5) at δ = 1.88–1.98 ppm led to enhancement of the H_a-7 signal (δ = 3.49–3.55 ppm), whereas negligible enhancement was seen for the H_b-7 signal at δ = 3.79–3.84 ppm. Similarly, irradiation of the H-3 signal at δ = 4.45 ppm led only to enhancement of the signal for H_a-7 at δ = 3.49–3.55 ppm together with a small enhancement in the signal for H-6 at δ = 1.92–1.98 ppm. Protons H-3, H_a-7 and H-6 are therefore oriented *syn* with respect to one another.

Removal of the benzyl group under hydrogenolysis conditions[11a,11b,11c,11d] was also attempted, in the presence of 10% Pd/C or 20% $Pd(OH)_2$/C with or without acid; all met with failure. Apart from hydrogenolysis, other methods using conc. H_2SO_4, aq. HBr,[11e] *p*TsA,[11f] methanesulfonic acid,[11g] TFA (reflux)[11h,11i] or NBS[11j] were tried without any success. However, one recently reported procedure utilising NBS and *N*-methylacetamide[11k] as a radical source in $CHCl_3$ indeed furnished the debenzylated product **78** (Scheme 11) but only in <5% yield from **77**. It was therefore not possible to proceed further with such low yield.



Scheme 11. Radical-mediated debenzylation.

A recent report by Withers et al.[12] suggesting the interaction of the iminol tautomer of an amide group with the active site of the enzyme provided the required impetus to go further with the synthesis and enzyme assay, so we proceeded with the deprotection of the azepane lactams. The polyhydroxyazepanes **72**, **73**, **74**, **75**, **76** and **77** were hydrolysed in acidic medium to yield *N*-benzylated azepanes **79**, **80**, **81**, **82**, **83** and **84**, respectively (Scheme 12).

The side-chain lengths of the azepane lactams were reduced (Scheme 13) by use of a synthetic sequence similar to that employed for azepanes. The major and minor unsaturated azepane lactams **70** and **71** were hydrolysed under acidic conditions, leading to diols **85** and **86**, respectively (Scheme 13). The absolute stereochemistry at C-6 was determined with the aid of single-crystal X-ray crystallographic data for the free diol **85** (Figure 6). Oxidative cleav-

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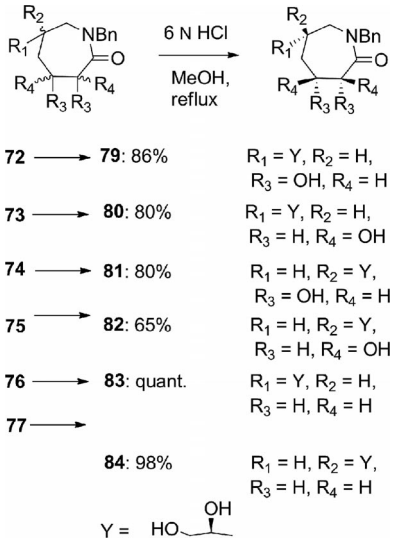


Scheme 12. Hydrolysis of azepane lactams.

age of the diols yielded aldehydes **87** and **88**, reduction of which to alcohols **89** and **90**, respectively, was carried out with $NaBH_4$.

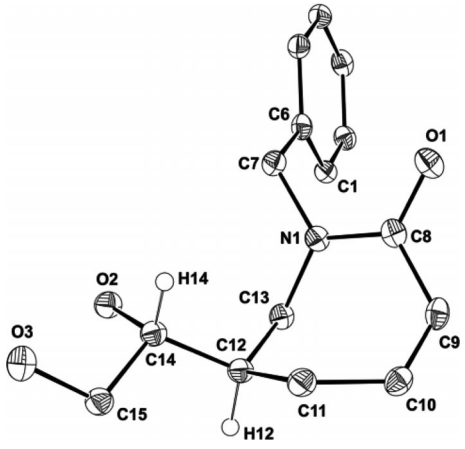
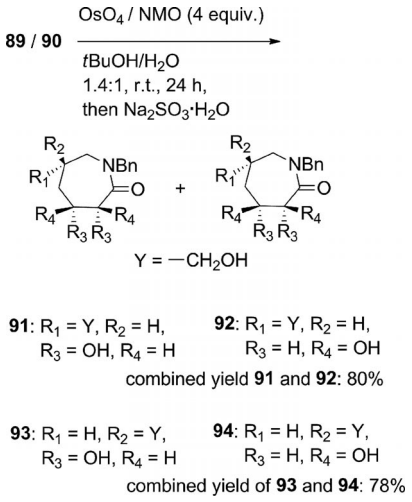


Figure 6. ORTEP diagram of compound **85**.[13]

cis Dihydroxylation of the unsaturated ring led to the partially separable diastereomeric pair of trihydroxyazepanes **91** and **92** from alcohol **89** (Scheme 14) and to another pair of trihydroxyazepanes **93** and **94** from alcohol **90**. The combined yield of **91** and **92** was found to be 80% whereas that for **93** and **94** was 78%.



Scheme 14. Dihydroxylation of azepane lactams.

The relative stereochemistry of the newly generated chiral centres was determined with the aid of nOe irradiation. For compound **91** (Figure 7), irradiation of the H-3 signal at δ = 4.46 ppm led to enhancement of the combined signals for H_b-5 and H-6 at δ = 1.95–2.04 ppm but did not show any enhancement for the H_a-5 signal at δ = 2.09–2.13 ppm. Irradiation of the H_a-5 signal, however, led to the enhancement of the signal for H-8 at δ = 3.64–3.67 ppm, but no enhancement for the H-3 signal at δ = 4.46 ppm was observed. In addition, irradiation of the combined signal of H_b-5 and H-6 led to enhancement of the H-3 signal. H_a-5 and H-8 are therefore oriented *syn* with respect to one an-

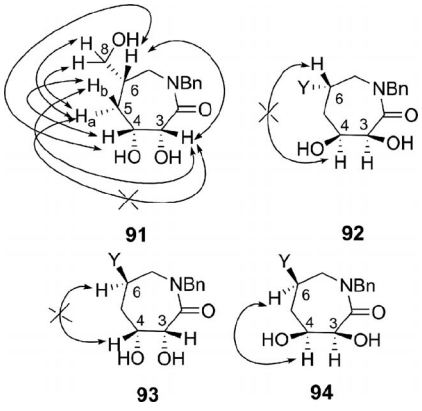
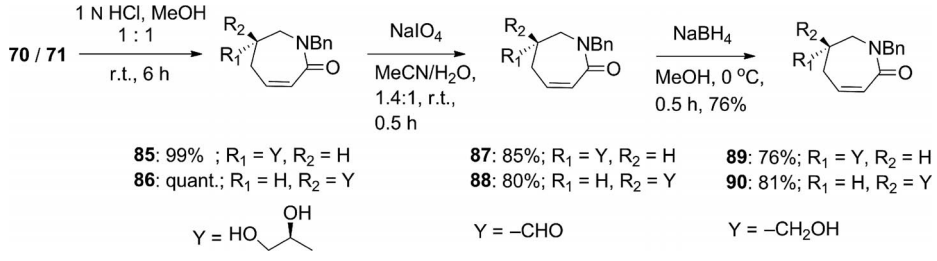


Figure 7. Representation of nOe correlations.



Scheme 13. Synthesis of side-chain-shortened azepane lactams.

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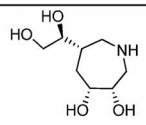
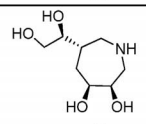
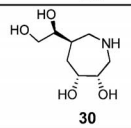
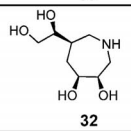
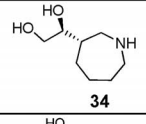
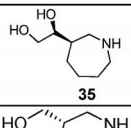
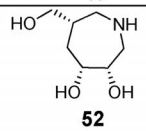
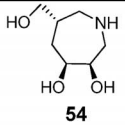
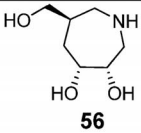
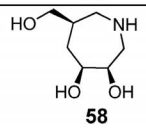
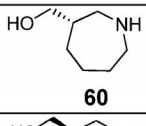
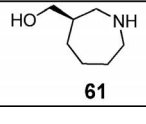
other whereas H-3 and H_a-5 are oriented *anti*. Moreover, H_b-5, H-6 and H-3 are oriented *syn* with respect to one another. The absolute configurations of the stereocentres are hence as shown in Figure 7.

In the case of compound **92** (Figure 7), however, irradiation of the signals for H-4 (δ = 4.19 ppm) and H-6 (δ = 1.98–2.04 ppm, combined signal for H_a-5 and H-6) did not in either case lead to enhancement of the signal of the other

Table 1. IC_{50} values (mM) of polyhydroxyazepanes.

Entry		α-Galactosidase (green coffee beans)	α-Glucosidase (yeast)	α-Glucosidase (rice)	β-Glucosidase (almonds)	α-Mannosidase (jack beans)	β-Galactosidase (bovine)
1	 **26**	2.32	n.i.	4.29	2.57	n.i.	n.i.
2	 **28**	1.78	n.i.	n.i.	2.25	1.55	n.i.
3	 **30**	2.69	n.i.	5.88	2.21	n.i.	n.i.
4	 **32**	1.51	n.i.	3.03	1.75	n.i.	5.65
5	 **34**	n.i.	1.7	1.76	n.i.	n.i.	0.71
6	 **35**	n.i.	n.i.	n.i.	n.i.	n.i.	1.2
7	 **52**	n.i.	3.2	3.3	n.i.	1.65	n.i.
8	 **54**	n.i.	0.102	4.65	n.i.	**0.082**	n.i.
9	 **56**	n.i.	n.i.	n.i.	n.i.	**0.054**	n.i.
10	 **58**	n.i.	n.i.	2.58	n.i.	**0.085**	n.i.
11	 **60**	n.i.	n.i.	n.i.	n.i.	n.i.	8.79
12	 **61**	n.i.	n.i.	5.43	n.i.	2.15	1.25

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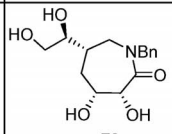
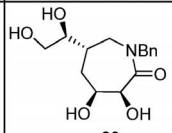
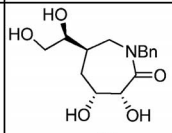
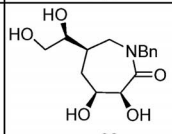
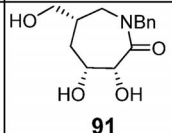
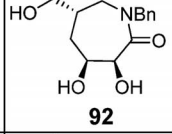
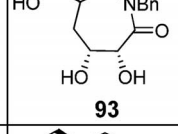
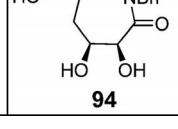
proton. For the pair of diastereomers **93** and **94**, irradiation of the H-6 signal at δ = 2.01–2.04 ppm (combined signal for H_b-5 and H-6) did not lead to enhancement in the signal of H-4 at δ = 4.20–4.24 ppm in the case of compound **93**, whereas irradiation of the H-6 signal at δ = 1.99–2.04 ppm (combined signal for H_a-5 major rotamer, H_a-5 minor rotamer, H-6 major rotamer) led to enhancement of the H-4 signal at δ = 4.19 ppm in the case of compound **94**. These observations led to the assignment of absolute configurations of compounds **93** and **94** as shown in Figure 7.

The fully deprotected polyhydroxyazepanes and the *N*-benzylated polyhydroxyazepane lactams were subjected to enzyme inhibition studies (Table 1 and Table 2) against the six commercially available enzymes α-galactosidase (green coffee beans), α-glucosidase (yeast), α-glucosidase (rice), β-glucosidase (almonds), α-mannosidase (jack beans) and β-galactosidase (bovine liver). Comparison of the IC_{50} values for the dihydroxyethyl azepanes **26**, **28**, **30** and **32** with those for the corresponding hydroxymethyl azepanes **52**, **54**, **56** and **58** (Table 1) shows that the latter group of compounds were better inhibitors than the former. Among them, azepanes **54**, **56** and **58** showed IC_{50} values of 0.082 mM, 0.054 mM and 0.085 mM, respectively, against α-mannosidase (jack beans).

The same trend of better inhibition activity of hydroxymethyl azepane lactams (**91**, **92**, **93** and **94**) could be observed on comparison with dihydroxyethyl azepane lactams (**79**, **80**, **81** and **82**) as shown in Table 2. It can thus

Table 2. IC_{50} values (mM) of polyhydroxyazepane lactams.

Entry		α-Galactosidase (green coffee beans)	α-Glucosidase (yeast)	α-Glucosidase (rice)	β-Glucosidase (almonds)	α-Mannosidase (jack beans)	β-Galactosidase (bovine)
1	 **79**	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
2	 **80**	n.i.	n.i.	n.i.	n.i.	1.22	n.i.
3	 **81**	n.i.	0.8	n.i.	n.i.	0.126	0.186
4	 **82**	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
5	 **91**	n.i.	0.832	n.i.	n.i.	0.234	0.173
6	 **92**	n.i.	n.i.	n.i.	n.i.	0.108	0.117
7	 **93**	n.i.	1.4	1.68	n.i.	0.546	0.894
8	 **94**	n.i.	n.i.	n.i.	n.i.	0.114	**0.074**

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be inferred that the dihydroxyethyl side chain is not only ineffective in enhancing the enzyme inhibition profile for azepanes but in fact lowers the activity of the hydroxymethyl azepanes (isofagomine homologues). Further, the IC_{50} values of compounds **54**, **56** and **58** were compared with the reported values[4k] for azepanes **95** and **96** (Figure 8), which have a close structural resemblance with an extra –OH group at C-5. Interestingly, the absence of the extra –OH group at C-5 both in **54** and in **58** made them better α-mannosidase inhibitors than **95** and **96**. On the other hand, **96** is a non-selective but strong inhibitor of α-galactosidase (coffee beans). Out of compounds **54**, **56** and **58**, azepane **56** is the most active and selective inhibitor of α-mannosidase. This suggests that better selectivity might possibly be achieved by changing the stereochemistry of the –OH and $–CH_2OH$ groups at C-3, C-4 and C-6.

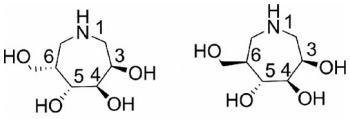

Figure 8. Structures of literature polyhydroxyazepanes.[4k]

The azepanes **34**, **35**, **60** and **61**, without hydroxy groups on their rings (Table 1), in general exhibit low affinities for enzyme inhibition. This may be attributed to the smaller extent of binding possible at the active sites of the glycosidases, due to the presence of fewer hydroxy groups. The hydroxymethyl azepanes **34** and **35** (Table 1) show very little inhibition, but the corresponding amides **83** and **84** were not soluble in water and so inhibition studies could not be done.

Of the lactams, only one compound – compound **94** (Table 2) – showed an inhibition value in the micromolar range (0.074 mM, Entry 8), for β-galactosidase (bovine liver). The same compound also showed inhibition very close to the micromolar range for α-mannosidase (jack beans). The other four lactams (**81**, **91**, **92** and **94**) also showed inhibitions close to the micromolar range (0.234 mM to 0.100 mM) both for α-mannosidase (jack beans) and for β-galactosidase (bovine liver). The azepanes reported in this paper thus appear not only to be better inhibitors than their lactam counterparts but also to be more selective.

Conclusions

In general it is found that the azepanes are better inhibitors than the corresponding azepane lactams, as well as being more selective. Further, the azepane-scaffold-based inhibitors (viz., **54**, **56** and **58**) were observed to be more active towards α-mannosidase (jack beans) than towards other glycosidases. This study also shows that the inhibition of glycosidases by tertiary amides is comparable to the inhibition profiles of azasugars. This might find utility in substitution of NH with some suitable substituent for the development of better inhibitors, as has already been observed in the cases of miglitol and miglustat.

Experimental Section

General Considerations: FT-IR spectra were recorded as thin films or as KBr pellets and are expressed in cm^{-1}. Proton (400 or 500 MHz) and ^{13}C (100 or 125 MHz) NMR spectra were recorded with $CDCl_3$ and/or D_2O as solvents. Chemical shifts are reported in δ values downfield from tetramethylsilane. Coupling constants are reported and expressed in Hz, and splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), q (quartet), m (multiplet). Optical rotations were measured with a polarimeter at 28 °C. Freshly distilled and dried solvents were used for all the reactions. The visualisation of spots on TLC plates was achieved by exposure to iodine or by spraying with H_2SO_4 (10%) followed by charring. Column chromatography was performed on silica gel (100–200 Mesh) with hexane and ethyl acetate as eluents. Mass spectra were obtained with a high-resolution ESI mass spectrometer.

General Procedure for Ring-Closing Metathesis (A): The first-generation Grubbs catalyst was added to a stirred solution of a diene (1 mmol) in dry CH_2Cl_2 (5 mL) and the mixture was stirred for the time interval given in the appropriate scheme. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using EtOAc/hexane [either 5–10% (for azepanes) or 30–50% (for lactams)].

General Procedure for Dihydroxylation (B): NMO (1.2 equiv. for azepanes and 4 equiv. for lactams) and a catalytic amount of OsO_4 dissolved in *t*BuOH were added to a stirred solution of an alkene (1 mmol) in a *t*BuOH/H_2O mixture (1.4:1, 6 mL) and stirring was continued for 18 h (for azepanes) or for 24 h (for lactams). At the end of the reaction, sodium sulfite (0.5 equiv. for azepanes or 3 equiv. for lactams) was added and the mixture was stirred for a further 30 min, followed by extraction with EtOAc (4 × 20 mL), washing with brine and drying over anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (50%).

General Procedure for Acetonide Protection (C): 2,2-Dimethoxypropane (1.1 mL, 9 mmol) was added at room temperature to a stirred solution of a diol (1 mmol) in dry acetone (10 mL), followed by PPTS (50 mg, 0.2 mmol), and the mixture was stirred for 2 h. Acetone was removed under reduced pressure and column chromatographic purification was carried out on silica gel with EtOAc/hexane (5–15%).

General Procedure for Hydrogenation (D): $Pd(OH)_2/C$ (20%, 15 mg) was added to a stirred solution of an alkene (1 mmol) in MeOH (5 mL) and the mixture was stirred under hydrogen at normal pressure for 2 h. The reaction mixture was filtered through celite pad and MeOH was removed under reduced pressure. The crude product was purified by silica gel column chromatography with EtOAc/hexane (5–10% for azepanes and 20–30% for lactams).

General Procedure for Hydrolysis (E): A solution of protected compound (1 mmol) in a mixture of 1 N HCl/MeOH (1:1, 2 mL) was stirred for 6 h. The solvent was removed under reduced pressure and the reaction mixture in MeOH was passed through Dowex-50 resin to obtain pure product.

General Procedure for Acetylation (F): Ac_2O (0.08 mL) and Et_3N (0.08 mL) were added to a stirred solution of an alcohol (1 mmol)

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in dry CH_2Cl_2 (3 mL) and stirring was continued for 6 h. CH_2Cl_2 was removed under reduced pressure and the crude product was purified by silica gel column chromatography with EtOAc/hexane (25%).

General Procedure for Peracetylation (G): Ac_2O (3 mL) was added to a solution of fully deprotected azepane (1 mmol) in pyridine (3 mL) and the mixture was stirred at room temperature for 8 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography with EtOAc/hexane (50–100%).

General Procedure for Cyclohexylidene Deprotection (H): *p*TsA (40 mol-%, 69 mg) was added at room temperature to a stirred solution of protected compound (1 mmol) in MeOH (8.5 mL) and stirring was continued for 8 h. The reaction mixture was quenched with saturated Na_2CO_3 solution and extracted with EtOAc (5× 20 mL), washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (50–70%).

General Procedure for Vicinal Diol Cleavage (I): $NaIO_4$ (1.2 mmol) was added to an ice-cooled solution of a diol (1 mmol) in a MeCN/H_2O mixture (1.4:1, 4.5 mL) and the mixture was stirred for 30 min. The reaction mixture was filtered through a celite pad followed by extraction with EtOAc (3× 20 mL), washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (20%).

General Procedure for Aldehyde Reduction (J): $NaBH_4$ (1 mmol) was added to an ice-cooled solution of an aldehyde (1 mmol) in MeOH (2.5 mL) and the reaction mixture was stirred at this temperature for 30 min. Aqueous saturated NH_4Cl solution was added to the mixture, which was extracted with EtOAc (4× 20 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (30–50%).

General Procedure for Cyclohexylidene Protection (K): Cyclohexanone (2.5 mmol) was added to a stirred solution of diol (1 mmol) in dry CH_2Cl_2 (3 mL), followed by the addition of camphorsulfonic acid (10 mol-%), and the mixture was stirred for 2 h. Dichloromethane was removed under reduced pressure and the crude product was purified by silica gel column chromatography with EtOAc/hexane (5–10%).

General Procedure for Enzyme Inhibition: All the enzymes and their corresponding substrates (*p*-nitrophenyl glycosides) were procured from Sigma–Aldrich Chemical Co. The enzymes and substrate solutions were prepared as 0.025 M solutions in the appropriate pH buffer solutions of the corresponding enzyme. Solutions of compounds were made separately in water in the 1 to 5 mM range and added to enzyme solutions. The mixture of enzyme and compound was allowed to incubate at 37 °C for 1 h. An equal amount of the substrate solution was added to this mixture and incubation was continued for 10 min. Control experiments without the test compound were carried out simultaneously. The reaction was arrested by addition of excess 0.05 M borate solution. The percentage inhibition of the inhibitor for each enzyme was determined by comparing the absorption of the released nitrophenol in the test reaction and in the control reaction at 405 nm wavelength with a UV/Vis spectrophotometer (Perkin–Elmer Lambda-20). The IC_{50} values were calculated from the percentage inhibition, as the concentrations of the test compounds required to effect 50% inhibition of the enzyme.

(*S*)-2-[(*S*)-1-Nitropent-4-en-2-yl]-1,4-dioxaspiro[4.5]decane (10): Nitro olefin **9** (2 g, 9.4 mmol), dissolved in THF (2.5 mL), was added at –30 °C in a dropwise fashion over a period of 20 min to a suspension of allylmagnesium chloride (3 equiv.) in THF (6 mL). The reaction mixture was allowed to stir for 15 min and quenched by addition of satd. NH_4Cl solution. It was extracted with EtOAc (3× 30 mL), washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (1–4%). Compounds **10** and **11** were obtained in a combined yield of 1.55 g (65%), from which 380 mg of pure compound **10** was obtained as a colourless viscous oil. R_f = 0.75 in EtOAc/hexane (10%). $[\alpha]_D$ = +1.2 (*c* = 1.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.39–1.40 (m, 2 H), 1.56–1.63 (m, 8 H), 2.11–2.16 (m, 1 H), 2.27–2.31 (m, 1 H), 2.63–2.66 (m, 1 H), 3.65 (dd, *J* = 8.5, 6.8 Hz, 1 H), 4.03 (dd, *J* = 8.6, 6.6 Hz, 1 H), 4.20 (dd, *J* = 11.7, 6.6 Hz, 1 H), 4.32 (dd, *J* = 12.9, 6.3 Hz, 1 H), 4.47 (dd, *J* = 12.9, 6.8 Hz, 1 H), 5.11–5.15 (m, 2 H), 5.76–5.83 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7, 23.9, 25.1, 32.1, 34.3, 35.9, 39.4, 65.7, 74.8, 75.8, 109.9, 118.5, 134.2 ppm. IR (neat): $\tilde{\nu}$ = 2934, 1553, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{21}NO_2$ $[M + H]^+$ 256.1548; found 256.1549.

***tert*-Butyl (*S*)-2-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-enylcarbamate (12):** A mixture of compounds **10** and **11** (2 g, 7.84 mmol), dissolved in THF (7 mL), was added over a period of 30 min to an ice-cold suspension of $LiAlH_4$ (745 mg, 19.6 mmol) in THF (7 mL) and the reaction mixture was allowed to attain room temp. gradually and stirred at r.t. for 6 h. It was quenched at 0 °C with a mixture of EtOAc/H_2O (9:1), filtered through a celite pad and dried with anhydrous Na_2SO_4. The crude product was dissolved in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. Et_3N (1.3 mL, 9.1 mmol) and $(Boc)_2O$ (2.2 g, 10.3 mmol) were then added sequentially in dropwise fashion and the mixture was stirred at the same temperature for 1 h. Water (10 mL) was added and the compound was extracted with CH_2Cl_2 (3× 20 mL), washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (2–5%) to afford **12** as a colourless viscous oil, yield 1.01 g (40%); R_f = 0.6 in EtOAc/hexane (10%). $[\alpha]_D$ = –1.32 (*c* = 2.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (br. s, 11 H), 1.58–1.62 (m, 8 H), 1.70–1.73 (m, 1 H), 1.95–2.10 (m, 2 H), 3.10–3.16 (m, 1 H), 3.36–3.42 (m, 1 H), 3.64 (t, *J* = 7.8 Hz, 1 H), 3.96 (dd, *J* = 13.6, 7.6 Hz, 1 H), 4.07 (dd, *J* = 7.8, 6.1 Hz, 1 H), 5.04–5.09 (m, 2 H), 5.56 (br. s, 1 H), 5.72–5.82 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 23.9, 25.1, 28.4, 33.9, 35.0, 36.2, 42.0, 42.2, 67.9, 78.4, 78.8, 109.4, 117.2, 135.4, 156.1 ppm. IR (neat): $\tilde{\nu}$ = 3363, 2934, 1715, 1166 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{31}NO_4$ $[M + H]^+$ 326.2331; found 326.2336.

***tert*-Butyl (*S*)-2-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-enyl(allyl)carbamate (14):** NaH (553 mg, 3 mmol, 60% in oil) was added to an ice-cold solution of carbamate **12** (1.5 g, 4.6 mmol) in dry DMF (5 mL) and the mixture was stirred for 10 min, followed by the addition of allyl bromide (0.6 mL, 6.9 mmol) and further stirring for 30 min. Subsequently, H_2O (10 mL) was added and the reaction mixture was extracted with Et_2O (3× 20 mL), washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (5%) to give a light cream-coloured viscous oil; 1.53 g (91%); R_f = 0.8 in EtOAc/hexane (10%). $[\alpha]_D$ = –8.8 (*c* = 1.7, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (br. s, 2 H), 1.45 (br. s, 9 H), 1.56–1.60 (m, 8 H), 1.69–1.71 (m, 1 H), 1.91–2.04 (m, 2 H), 2.16–2.21 (m, 1 H), 3.28 (br. s, 2 H), 3.62–3.66 (m, 1 H), 3.75–3.87 (m, 2 H), 3.99–4.05 (m, 2 H), 5.00–5.13 (m, 4 H), 5.75–5.81 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 23.9, 25.2, 28.4, 32.9, 34.8, 36.2, 40.4, 47.2, 49.9, 66.9, 76.4, 79.6, 109.1, 116.6, 134.1, 136.2, 155.8 ppm. IR (neat): $\tilde{\nu}$ = 2975, 1695, 1163 cm^{-1}.

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HRMS (ESI): calcd. for $C_{21}H_{35}NO_4$ [M + H]$^+$ 366.2644; found 366.2641.

***tert*-Butyl (*S*)-3-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (16):** General Procedure **A** for ring-closing metathesis was followed with diene **14** (500 mg, 1.37 mmol) in the presence of the first-generation Grubbs catalyst (22 mg, 2 mol-%) over 2 h. Compound **16** was obtained as a colourless viscous oil, yield 455 mg (99%); R_f = 0.7 in EtOAc/hexane (10%). $[\alpha]_D$ = +6.08 (c = 1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamer ratio 2:1): δ = 1.39 (br. s, 4 H, 2 H major isomer, 2 H minor rotamer), 1.44 (br. s, 9 H minor rotamer), 1.47 (br. s, 9 H major rotamer), 1.56–1.61 (m, 16 H, 8 H major rotamer, 8 H minor rotamer), 1.99–2.17 (m, 6 H, 3 H major rotamer, 3 H minor rotamer), 3.32 (dd, J = 13.9, 7.8 Hz, 1 H major rotamer), 3.39 (dd, J = 12.0, 11.2 Hz, 1 H minor rotamer), 3.64–4.12 (m, 12 H, 6 H major rotamer, 6 H minor rotamer), 5.67 (br. s, 4 H, 2 H major rotamer, 2 H minor rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 23.9, 25.2, 27.8, 27.9, 28.5, 35.1, 36.4, 41.3, 42.3, 47.0, 49.1, 49.3, 67.3, 67.5, 77.7, 79.3, 79.5, 109.4, 127.8, 128.8, 128.9, 155.4 ppm. IR (neat): $\tilde{\nu}$ = 2934, 1695, 1165 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{31}NO_4$ [M + H]$^+$ 338.2331; found 338.2333.

***tert*-Butyl (*S*)-6-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]-3,4-dihydroxyazepane-1-carboxylate (18):** General Procedure **B** was used for dihydroxylation of diene **16** (590 mg, 1.75 mmol). Compound **18** was obtained as a colourless viscous oil, yield 507 mg (78%); R_f = 0.2 in EtOAc/hexane (50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (br. s, 4 H, 2 H major isomer, 2 H minor isomer), 1.46 (br. s, 18 H, 9 H major isomer, 9 H minor isomer), 1.56–1.61 (m, 16 H, 8 H major isomer, 8 H minor isomer), 1.91–1.96 (m, 2 H, 1 H major isomer, 1 H minor isomer), 2.15–2.20 (m, 2 H, 1 H major isomer, 1 H minor isomer), 2.34–2.42 (m, 2 H, 1 H major isomer, 1 H minor isomer), 2.63–2.76 (m, 2 H, 1 H major isomer, 1 H minor isomer), 3.10–3.21 (m, 2 H, 1 H major isomer, 1 H minor isomer), 3.35–3.48 (m, 4 H, 2 H major isomer, 2 H minor isomer), 3.52–3.56 (m, 1 H minor isomer), 3.63–3.69 (m, 3 H, 2 H major isomer, 1 H minor isomer), 3.78 (br. s, 1 H major isomer), 3.96–4.06 (m, 4 H, 1 H major isomer, 3 H minor isomer), 4.09 (br. s, 1 H major isomer) ppm. IR (neat): $\tilde{\nu}$ = 3433, 2934, 1689, 1164 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{33}NO_6$ [M + H]$^+$ 372.2386; found 372.2386.

***tert*-Butyl (3a*S*,7*S*,8a*R*)-7-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]azepine-5(4*H*)-carboxylate (20):** General Procedure **C** for acetonide protection was followed for **18** (300 mg, 0.81 mmol). This gave compound **20** as a colourless viscous oil, yield 130 mg (39%); R_f = 0.8 EtOAc/hexane (15%). $[\alpha]_D$ = +2.3 (c = 3.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, approximately rotamer ratio is 1:1.25): δ = 1.32–1.34 (m, 6 H, 3 H major rotamer, 3 H minor rotamer), 1.39 (br. s, 4 H, 2 H major rotamer, 2 H minor rotamer), 1.42–1.46 (m, 24 H, 12 H major rotamer, 12 H minor rotamer), 1.56–1.65 (m, 18 H, 9 H minor rotamer, 9 H minor rotamer), 1.71–1.79 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 2.48 (dd, J = 12.9, 10.7 Hz, 1 H major rotamer), 2.56 (dd, J = 13.1, 10.5 Hz, 1 H minor rotamer), 2.79 (dd, J = 13.2, 11.0 Hz, 1 H major rotamer), 2.88 (dd, J = 13.4, 10.5 Hz, 1 H minor rotamer), 3.63–3.71 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 3.79–3.84 (m, 1 H major rotamer), 3.86–3.91 (m, 1 H minor rotamer), 3.99–4.09 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 4.19–4.31 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 4.34–4.44 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 4.54–4.60 (m, 1 H major rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 23.9, 24.6, 25.1, 27.5, 28.4, 33.3, 33.9, 34.9, 36.2, 36.5, 39.6, 41.4, 48.0, 51.3, 52.8, 67.0, 67.4, 74.0, 74.9, 77.2, 78.1, 79.9, 108.9, 109.8, 154.7 ppm. IR (neat): $\tilde{\nu}$ = 2926, 1697, 1164 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{37}NO_6$ [M + H]$^+$ 412.2699; found 412.2697.

***tert*-Butyl (*S*)-3-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]azepane-1-carboxylate (24):** Hydrogenation of **16** (40 mg, 0.12 mmol) was performed as described in General Procedure **D**. Compound **24** was obtained as a colourless viscous oil, yield 39 mg (97%); R_f = 0.6 in EtOAc/hexane (10%). $[\alpha]_D$ = –2.7 (c = 0.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamer ratio 1:1.3): δ = 0.86 (t, J = 7.6 Hz, 1 H minor rotamer), 0.92 (t, J = 7.6 Hz, 1 H major rotamer), 1.14–1.43 (m, 6 H, 3 H major rotamer, 3 H minor rotamer), 1.46 (br. s, 9 H minor rotamer), 1.47 (br. s, 9 H major rotamer), 1.53–1.60 (m, 20 H, 10 H major rotamer, 10 H minor rotamer), 1.65 (br. s, 2 H, 1 H major rotamer, 1 H minor rotamer), 1.74–1.84 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 2.93 (dd, J = 14.5, 9.8 Hz, 1 H major rotamer), 3.02 (dd, J = 13.9, 10.2 Hz, 1 H minor rotamer), 3.15–3.28 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 3.36–3.48 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 3.59–3.69 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 3.80–3.91 (m, 3 H, 1 H major rotamer, 2 H minor rotamer), 3.94–4.05 (m, 2 H, 1 H major rotamer, 1 H minor rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8, 23.8, 23.9, 24.8, 25.2, 25.5, 27.8, 28.4, 28.5, 29.3, 29.6, 30.4, 34.9, 35.0, 36.3, 42.4, 43.5, 46.9, 47.5, 48.6, 48.7, 67.4, 67.7, 69.9, 72.2, 78.0, 78.2, 109.3, 155.5 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2861, 1694 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{33}NO_4$ [M + H]$^+$ 340.2488; found 340.2483.

(3*S*,4*R*,6*S*)-6-[(*S*)-1,2-Dihydroxyethyl]azepane-3,4-diol (26): Hydrolysis of **20** (120 mg, 0.29 mmol) was performed as described in General Procedure **E**. This gave compound **26** as a colourless viscous oil, yield 55 mg (quantitative). $[\alpha]_D$ = –17.3 (c = 2.3, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.56 (d, J = 13.9 Hz, 1 H), 1.67–1.77 (m, 1 H), 1.90–1.95 (m, 1 H), 3.00–3.06 (m, 2 H), 3.11–3.17 (m, 2 H), 3.34–3.39 (m, 1 H), 3.43 (dt, J = 11.7, 3.9 Hz, 1 H), 3.52–3.56 (m, 1 H), 3.64–3.68 (m, 1 H), 4.01 (br. s, 1 H) ppm. ^{13}C NMR (D_2O, 100 MHz): δ = 31.9, 34.4, 46.2, 47.2, 63.8, 68.1, 73.3, 74.8 ppm. IR (neat): $\tilde{\nu}$ = 3391, 2928 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{17}NO_4$ [M + H]$^+$ 192.1236; found 192.1237.

(3*S*,4*R*,6*S*)-1-Acetyl-6-[(*S*)-1,2-diacetoxyethyl]azepane-3,4-diyl Diacetate (27): General Procedure **G** was followed for peracetylation of **26** (25 mg, 0.13 mmol), and compound **27** was obtained as a colourless viscous oil, yield 48 mg (91%); R_f = 0.2 in EtOAc/hexane (50%). $[\alpha]_D$ = –4.2 (c = 1.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamer ratio 1:2): δ = 1.60–1.72 (m, 2 H, H_b-5 major rotamer, H_b-5 minor rotamer), 1.90–1.98 (m, 2 H, H_a-5 major rotamer, H_a-5 minor rotamer), 2.01–2.13 (series of singlets, 30 H, 8 OAc, 2 NAc), 2.13–2.19 (m, 1 H, H-6 minor rotamer), 2.18–2.28 (m, 1 H, H-6 major rotamer), 3.13–3.18 (m, 2 H, H_b-2 minor rotamer, H_a-7 minor rotamer), 3.33 (dd, J = 14.2, 8.3 Hz, 1 H, H_a-7 major rotamer), 3.48 (dd, J = 15.4, 4.6 Hz, 1 H, H_a-2 major rotamer), 3.65–3.72 (m, 3 H, H_b-7 minor rotamer, H_b-7 major rotamer, H_b-2 major rotamer), 4.04–4.07 (m, 2 H, H_b-9 major rotamer, H_b-9 minor rotamer), 4.28–4.38 (m, 3 H, H_a-9 major rotamer, H_a-9 minor rotamer, H_a-2 minor rotamer), 4.88–4.92 (m, 1 H, H-4 minor rotamer), 4.94–5.01 (m, 3 H, H-4 major rotamer, H-8 major rotamer, H-8 minor rotamer), 5.24 (br. s, 1 H, H-3 major rotamer), 5.34 (br. s, 1 H, H-3 minor rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 20.8, 21.1, 21.3, 28.9, 29.3, 35.5, 38.2, 46.2, 46.9, 49.6, 50.4, 62.7, 63.1, 70.6, 71.2, 71.8, 72.2, 72.5, 72.9, 169.7, 169.8, 169.9, 170.3, 170.5, 170.6 ppm. IR (neat): $\tilde{\nu}$ = 2926, 1742, 1647, 1242 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{27}NO_9$ [M + H]$^+$ 402.1764; found 402.1765.

***tert*-Butyl (*S*)-3-[(*S*)-1,2-Dihydroxyethyl]-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (36):** General Procedure **H** for cyclohexylid-

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ene deprotection of **16** (590 mg, 1.75 mmol) was followed. This gave **36** as a colourless viscous oil, yield 358 mg (99% based on recovery of starting material; 114 mg of starting material recovered); R_f = 0.2 in EtOAc/hexane (50%). $[\alpha]_D$ = –20.0 (c = 0.75, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz, approximate rotamer ratio 1:1): δ = 1.41 (br. s, 9 H), 1.43 (br. s, 9 H), 1.82–1.86 (m, 2 H), 2.21–2.26 (m, 4 H), 2.68 (br. s, 2 H), 3.05 (dd, J = 6.8, 3.6 Hz, 1 H), 3.07 (dd, J = 6.8, 3.6 Hz, 1 H), 3.34–3.42 (m, 2 H), 3.46–3.51 (m, 6 H), 3.67 (br. s, 2 H), 4.23–4.28 (m, 4 H), 4.79–4.82 (m, 2 H), 5.69–5.77 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 28.7, 39.7, 47.1, 49.4, 64.4, 71.2, 80.5, 129.0, 130.0, 156.7 ppm. IR (neat): $\tilde{\nu}$ = 3406, 2927, 1667 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{23}NO_4$ $[M + H]^+$ 258.1705; found 258.1706.

***tert*-Butyl (*S*)-3-Formyl-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (38):** General Procedure **I** was followed for vicinal diol cleavage of **36** (330 mg, 1.28 mmol). Compound **38** was obtained as a colourless viscous oil, yield 274 mg (95%); R_f = 0.6 in EtOAc/hexane (30%). $[\alpha]_D$ = +6.96 (c = 1.15, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz, rotamer ratio approximately 1:1): δ = 1.40 (br. s, 9 H), 1.41 (br. s, 9 H), 2.38–2.41 (m, 4 H), 2.71–2.82 (m, 2 H), 3.63 (dd, J = 14.7, 7.3 Hz, 1 H), 3.71 (dd, J = 14.2, 5.9 Hz, 1 H), 3.77–3.82 (m, 3 H), 3.89–3.97 (m, 2 H), 4.07–4.11 (m, 1 H), 5.55–5.60 (m, 2 H), 5.66–5.75 (m, 2 H), 9.68 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7, 24.5, 28.4, 45.3, 47.8, 50.9, 51.3, 80.0, 80.5, 126.3, 127.6, 129.1, 129.3, 155.1, 155.6, 202.2 ppm. IR (neat): $\tilde{\nu}$ = 2975, 1727, 1694 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{19}NO_3$ $[M + H]^+$ 226.1443; found 226.1443.

***tert*-Butyl (*S*)-3-(Hydroxymethyl)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (40):** General Procedure **J** was followed for reduction of aldehyde **38** (260 mg, 1.16 mmol). Compound **40** was obtained as a colourless viscous oil, yield 244 mg (93%); R_f = 0.2 in EtOAc/hexane (30%). $[\alpha]_D$ = –11.6 (c = 1.2, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz, rotamer ratio approximately 1:3): δ = 1.46 (br. s, 9 H), 1.48 (br. s, 9 H), 2.05–2.11 (m, 3 H, 1 H major rotamer, 2 H minor rotamer), 2.25–2.29 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 3.15 (dd, J = 14.4, 4.0 Hz, 1 H major rotamer), 3.34–3.39 (m, 2 H minor rotamer), 3.46–3.54 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 3.79–3.84 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 4.06–4.14 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 4.24–4.29 (m, 1 H major rotamer), 5.69–5.75 (m, 4 H, 2 H major rotamer, 2 H minor rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 28.7, 39.7, 40.7, 47.2, 47.3, 49.4, 63.4, 64.8, 80.2, 128.4, 128.7, 130.2, 156.6 ppm. IR (neat): $\tilde{\nu}$ = 3404, 2927, 1692, 1669, 1167 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{21}NO_3$ $[M + H]^+$ 228.1600; found 228.1608.

(3*S*,4*R*,6*S*)-6-(Hydroxymethyl)azepane-3,4-diol (52): General Procedure **E** was adopted for hydrolysis of **46** (60 mg, 0.16 mmol). It gave **52** as a colourless viscous oil, yield 23 mg (92%); R_f = 0.5 in MeOH/EtOAc (50%). $[\alpha]_D$ = –11.0 (c = 0.5, MeOH). ^1H NMR (D_2O, 500 MHz): δ = 1.48 (d, J = 13.0 Hz, 1 H), 1.56–1.63 (m, 1 H), 1.68–1.76 (m, 1 H), 2.35 (dd, J = 13.8, 10.0 Hz, 1 H), 2.64 (dd, J = 14.5, 6.0 Hz, 1 H), 2.71 (d, J = 18.0 Hz, 1 H), 2.76 (dd, J = 13.0, 5.5 Hz, 1 H), 3.25–3.30 (m, 2 H), 3.71 (d, J = 10.5 Hz, 1 H), 3.80 (br. s, 1 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 30.8, 37.6, 48.6, 49.6, 64.9, 71.6, 72.8 ppm. IR (neat): $\tilde{\nu}$ = 3373, 2930 cm^{-1}. HRMS (ESI): calcd. for $C_7H_{15}NO_3$ $[M + H]^+$ 162.1130; found 162.1130.

***N*-{(*S*)-2-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-enyl}acrylamide (62):** A mixture of compounds **10** and **11** (2 g, 7.84 mmol) dissolved in THF (7 mL) was added over a period of 30 min to an ice-cooled suspension of $LiAlH_4$ (745 mg, 19.6 mmol) in THF (7 mL), allowed gradually to attain room temperature and stirred at r.t. for 6 h. The reaction mixture was quenched at 0 °C with a mixture of EtOAc/H_2O (9:1), filtered through a celite pad and dried with anhydrous Na_2SO_4. The crude product was dissolved in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. Et_3N (1.3 mL, 9.1 mmol) and acryloyl chloride (1.3 mL) were added sequentially in dropwise fashion and the mixture was stirred at the same temperature for 30 min. Water (10 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3× 20 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica gel column chromatography with EtOAc/hexane (20–30%) to provide compound **62** as a colourless viscous oil, yield 761 mg (36%); R_f = 0.2 in EtOAc/hexane (30%). $[\alpha]_D$ = +0.32 (c = 62.5, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40–1.44 (m, 2 H), 1.55–1.64 (m, 8 H), 1.73–1.81 (m, 1 H), 1.98–2.11 (m, 2 H), 3.22 (ddd, J = 13.8, 8.3, 3.9 Hz, 1 H), 3.65 (t, J = 8.0 Hz, 1 H), 3.73 (ddd, J = 13.8, 7.1, 3.9 Hz, 1 H), 4.01 (dt, J = 7.8, 6.1 Hz, 1 H), 4.11 (dd, J = 8.0, 6.1 Hz, 1 H), 5.06–5.07 (m, 1 H), 5.09–5.11 (m, 1 H), 5.62 (dd, J = 10.2, 1.5 Hz, 1 H), 5.77 (ddt, J = 17.1, 10.0, 7.3 Hz, 1 H), 6.06 (dd, J = 17.1, 10.2 Hz, 1 H), 6.24 (dd, J = 17.1, 1.2 Hz, 1 H), 6.66 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.9, 24.2, 25.1, 34.3, 35.0, 36.3, 41.6, 41.7, 68.2, 79.0, 109.6, 117.5, 125.5, 131.4, 136.0, 165.3 ppm. IR (neat): $\tilde{\nu}$ = 2935, 1659, 1551, 1102 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{25}NO_3$ $[M + H]^+$ 280.1912; found 280.1917.

***N*-{(*S*)-2-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-enyl}-*N*-(4-methoxybenzyl)acrylamide (64):** NaH (430 mg of 60% NaH) was added in a portionwise fashion to an ice-cold solution of **62** (500 mg, 1.79 mmol) in THF (6 mL), followed by dropwise addition of *p*-methoxybenzyl chloride (0.32 mL, 2.32 mmol), and the reaction mixture was allowed to attain room temperature gradually and stirred at r.t. for 2 h. The mixture was cooled to 0 °C; this was followed by addition of saturated aqueous NH_4Cl solution and extraction with EtOAc (3× 20 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. Column chromatographic purification of the crude product over silica gel with EtOAc/hexane (10%) gave compound **64** as a colourless viscous oil, yield 392 mg (55%); R_f = 0.7 in EtOAc/hexane (30%). $[\alpha]_D$ = –9.63 (c = 4, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz, rotamer ratio approximately 1:2): δ = 1.38 (br. s, 4 H, 2 H major rotamer, 2 H minor rotamer), 1.54–1.58 (m, 16 H, 8 H major rotamer, 8 H minor rotamer), 1.97–2.10 (m, 5 H, 3 H major rotamer, 2 H minor rotamer), 2.18–2.23 (m, 1 H minor rotamer), 3.31 (dd, J = 15.2, 8.5 Hz, 1 H minor rotamer), 3.47–3.58 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 3.64–3.69 (m, 1 H minor rotamer), 3.78 (br. s, 1 H major rotamer), 3.79 (s, 3 H major rotamer), 3.81 (s, 3 H minor rotamer), 3.90–3.96 (m, 1 H minor rotamer), 4.00–4.07 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 4.51–4.74 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 4.99–5.08 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 5.64–5.83 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 6.35–6.44 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 6.57 (dd, J = 16.7, 10.5 Hz, 1 H major rotamer), 6.70 (dd, J = 16.6, 10.5 Hz, 1 H minor rotamer), 6.83–6.89 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 7.08 (m, 2 H, 1 H, major rotamer, 1 H minor rotamer), 7.21 (d, J = 8.3 Hz, 1 H major rotamer), 7.29 (d, J = 8.3 Hz, 1 H minor rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 23.9, 25.2, 33.3, 34.8, 36.2, 40.3, 41.9, 47.2, 47.5, 48.8, 51.1, 55.2, 64.9, 67.1, 67.6, 76.4, 76.8, 109.1, 109.4, 113.9, 114.2, 116.7, 117.8, 127.7, 128.0, 128.1, 128.5, 128.9, 129.6, 134.7, 136.0, 159.1, 166.7, 167.3 ppm. IR (neat): $\tilde{\nu}$ = 2929, 1648, 1611, 1248 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{33}NO_4$ $[M + H]^+$ 400.2488; found 400.2486.

(*S*)-6-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]-1-(4-methoxybenzyl)-6,7-dihydro-1*H*-azepin-2(5*H*)-one (66): General Procedure **A** for ring-

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closing metathesis was followed with **64** (400 mg, 1.0 mmol) in the presence of the first-generation Grubbs catalyst (58 mg, 7 mol-%) and with stirring for 24 h. This gave compound **66** as a colourless viscous oil, yield 260 mg (70%); R_f = 0.2 in EtOAc/hexane (50%). $[\alpha]_D$ = –2.0 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38–1.41 (m, 2 H), 1.53–1.61 (m, 8 H), 1.94–2.01 (m, 2 H), 2.17–2.28 (m, 1 H), 3.34–3.46 (m, 3 H), 3.75–3.79 (m, 1 H), 3.79 (s, 3 H), 3.95 (dd, *J* = 8.0, 6.1 Hz, 1 H), 4.39 (d, *J* = 14.4 Hz, 1 H), 4.85 (d, *J* = 14.4 Hz, 1 H), 6.06 (d, *J* = 11.7 Hz, 1 H), 6.16–6.21 (m, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 25.1, 29.9, 34.9, 36.4, 44.8, 47.9, 50.5, 55.2, 67.4, 76.6, 109.6, 113.9, 127.4, 129.8, 129.9, 135.9, 159.1, 168.6 ppm. IR (neat): $\tilde{\nu}$ = 2931, 1654, 1609, 1512, 1246 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{29}NO_4$ [M + H]$^+$ 372.2175; found 372.2176.

***N*-{(*S*)-2-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]pent-4-enyl}-*N*-benzylacrylamide (68):** NaH (344 mg, 14.3 mmol of 60% NaH or 206 mg, 8.6 mmol of pure NaH) was added portionwise to an ice-cold solution of **62** (400 mg, 1.4 mmol) in THF (5 mL), followed by addition of $PhCH_2Br$ (0.22 mL, 1.86 mmol) in a dropwise fashion, and the reaction mixture was allowed to attain room temperature gradually and stirred at r.t. for 2 h. The reaction mixture was cooled to 0 °C, followed by addition of saturated NH_4Cl and extraction with EtOAc (3× 20 mL), washed with brine and dried with anhydrous Na_2SO_4. Column chromatographic purification of the crude product over silica gel with EtOAc/hexane (15%) gave compound **68** as a colourless viscous oil, yield 299 mg (56%); R_f = 0.6 in EtOAc/hexane (30%). $[\alpha]_D$ = –14.0 (*c* = 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamer ratio approximately 2:3): δ = 1.38 (br. s, 4 H, 2 H major rotamer, 2 H minor rotamer), 1.55–1.58 (m, 16 H, 8 H major rotamer, 8 H minor rotamer), 1.96–2.08 (m, 5 H, 2 H major rotamer, 3 H minor rotamer), 2.18–2.23 (m, 1 H major rotamer), 3.53–3.58 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 3.66–3.68 (m, 1 H major rotamer), 3.90–3.95 (m, 1 H minor rotamer), 4.03–4.08 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 4.58–4.71 (m, 3 H, 2 H major rotamer, 1 H minor rotamer), 4.79–4.82 (m, 1 H minor rotamer), 4.99–5.07 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 5.63–5.81 (m, 4 H, 2 H major rotamer, 2 H minor rotamer), 6.35–6.45 (m, 2 H, 1 H major rotamer, 1 H minor rotamer), 6.54 (dd, *J* = 16.7, 10.4 Hz, 1 H major rotamer), 6.72 (dd, *J* = 16.4, 10.7 Hz, 1 H minor rotamer), 7.15–7.34 (m, 10 H, 5 H major rotamer, 5 H minor rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7, 23.8, 23.9, 25.0, 25.1, 33.2, 33.3, 34.7, 34.9, 36.2, 40.3, 42.0, 47.6, 47.8, 49.5, 51.7, 67.1, 67.6, 76.3, 76.8, 109.2, 109.4, 116.9, 117.9, 126.4, 127.3, 127.6, 127.8, 128.1, 128.4, 128.5, 128.8, 134.7, 135.9, 137.0, 137.4, 166.8, 167.3 ppm. IR (neat): $\tilde{\nu}$ = 2935, 1650, 1613 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{31}NO_3$ [M + H]$^+$ 370.2382; found 370.2382.

Note: Strangely enough, during the benzylation (and also in the case of *p*-methoxybenzylation) the reactions needed 6 equiv. of NaH (60% in oil) to start, taking 2 h for completion. If done otherwise (i.e., by using the base in lesser equivalents initially and adding it subsequently to make it up to 6 equiv. or even more) there was only slight progress in the reaction, which never reached completion.

(*S*)-1-Benzyl-6-[(*S*)-1,4-dioxaspiro[4.5]decan-2-yl]-6,7-dihydro-1*H*-azepin-2(5*H*)-one (70): General Procedure **A** for ring-closing metathesis was followed with **68** (400 mg, 1.08 mmol) in the presence of the first-generation Grubbs catalyst (27 mg, 3 mol-%) and with stirring for 8 h. This gave compound **70** as a colourless viscous oil, yield 336 mg (91%); R_f = 0.2 in EtOAc/hexane (50%). $[\alpha]_D$ = –6.7 (*c* = 0.16, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36–1.40 (m, 2 H), 1.52–1.60 (m, 8 H), 1.95–2.03 (m, 2 H), 2.21–2.30 (m, 1 H), 3.41–3.45 (m, 3 H), 3.78 (q, *J* = 6.6 Hz, 1 H), 3.95 (dd, *J* = 8.0, 6.6 Hz, 1 H), 4.49 (d, *J* = 14.4 Hz, 1 H), 4.91 (d, *J* = 14.6 Hz, 1 H), 6.08 (d, *J* = 11.7 Hz, 1 H), 6.18–6.23 (m, 1 H), 7.26–7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8, 25.1, 29.7, 34.9, 36.3, 44.7, 48.8, 51.2, 67.4, 76.7, 109.7, 127.2, 127.5, 128.4, 128.6, 136.2, 137.7, 168.7 ppm. IR (neat): $\tilde{\nu}$ = 2933, 1654, 1607 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{27}NO_3$ [M + H]$^+$ 342.2069; found 242.2065.

(3*S*,4*S*,6*S*)-1-Benzyl-6-[(*S*)-1,4-dioxaspiro[4.5]decan-2-yl]-3,4-dihydroxyazepan-2-one (72): Dihydroxylation of **70** (100 mg, 0.29 mmol) was carried out by General Procedure **B**. Compound **72** was obtained as a colourless viscous oil, yield 47 mg (42%); R_f = 0.2 in EtOAc/hexane (60%). $[\alpha]_D$ = +8.33 (*c* = 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.41–1.44 (m, 2 H, cyclohexylidene), 1.49–1.56 (m, 6 H), 1.60–1.66 (m, 3 H, 2× cyclohexylidene, H-5), 1.77–1.83 (m, 1 H, H-6), 1.89–1.94 (m, 1 H, H-5′), 2.49 (br. s, OH), 3.18 (dd, *J* = 15.5, 9.9 Hz, 1 H, H-7), 3.36 (dd, *J* = 8.3, 6.5 Hz, 1 H, H-9), 3.53 (d, *J* = 15.3 Hz, 1 H, H-7′), 3.66 (dd, *J* = 13.6, 6.5 Hz, 1 H, H-8), 3.90 (dd, *J* = 8.2, 6.5 Hz, 1 H, H-9′), 4.19 (br. s, 1 H, H-4), 4.50 (br. s, 1 H, H-3), 4.61 (d, *J* = 14.5 Hz, 1 H, OCH_2Ph), 4.75 (br, OH), 4.78 (d, *J* = 15.0 Hz, 1 H, OCH_2Ph), 7.25–7.35 (m, 5 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.4, 27.4, 28.8, 38.3, 39.7, 40.3, 52.9, 56.1, 70.9, 74.3, 77.0, 113.4, 131.4, 132.1, 132.3, 139.9, 175.9 ppm. IR (neat): $\tilde{\nu}$ = 3402, 2925, 2854, 1650 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{27}NO_5$ [M + H]$^+$ 376.2124; found 376.2122.

(*S*)-1-Benzyl-6-[(*S*)-1,4-dioxaspiro[4.5]decan-2-yl]azepan-2-one (76): Compound **76** was obtained by hydrogenolysis of compound **70** (70 mg, 0.21 mmol) as described in General Procedure **D**, as a colourless viscous oil, yield 64 mg (91%); R_f = 0.5 in EtOAc/hexane (50%). $[\alpha]_D$ = –1.6 (*c* = 2.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33–1.71 (m, 14 H), 1.84–1.90 (m, 1 H), 2.60–2.65 (m, 2 H), 3.32 (dd, *J* = 15.2, 8.6 Hz, 1 H), 3.45–3.53 (m, 2 H), 3.75 (dd, *J* = 15.0, 6.6 Hz, 1 H), 3.96 (dd, *J* = 8.0, 6.1 Hz, 1 H), 4.52 (d, *J* = 14.4 Hz, 1 H), 4.73 (d, *J* = 14.4 Hz, 1 H), 7.24–7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.2, 24.0, 24.2, 25.2, 32.7, 35.1, 36.5, 36.9, 42.8, 50.2, 51.2, 67.8, 76.4, 109.7, 127.4, 128.5, 128.6, 137.9, 175.8 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2857, 1646 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{29}NO_3$ [M + H]$^+$ 344.2225; found 344.2221.

(*R*)-6-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]azepan-2-one (78): NBS (124 mg, 0.69 mmol) was added at room temperature, together with *N*-methylacetamide (NMA, 2 mg, cat. amount), to a stirred solution of **77** (48 mg, 0.13 mmol) in $CHCl_3$ (2 mL) and the mixture was allowed to stir in the open air and in the presence of light for 4 d. The reaction mixture was then stirred with NaOH (0.1 N, 1 mL) for 5 min and extracted with CH_2Cl_2 (4× 10 mL), washed with brine and dried with anhydrous Na_2SO_4. Column purification of the crude product over silica gel with EtOAc/hexane (15–40%) gave compound **78** as a colourless viscous oil, yield 2 mg (< 5%); R_f = 0.2 in EtOAc/hexane (70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33–1.61 (m, 13 H), 2.00–2.04 (m, 2 H), 2.47–2.49 (m, 2 H), 3.12–3.20 (m, 3 H), 3.98–4.02 (m, 2 H), 5.81 (br. s, NH) ppm. IR (neat): $\tilde{\nu}$ = 3312, 2925, 1725, 1668 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{23}NO_3$ [M + H]$^+$ 254.1756; found 254.1753.

(3*S*,4*S*,6*S*)-1-Benzyl-6-[(*S*)-1,2-dihydroxyethyl]-3,4-dihydroxyazepan-2-one (79): General Procedure **E** was followed for hydrolysis of **72** (31 mg, 0.08 mmol). Compound **79** was obtained as a colourless viscous oil, yield 21 mg (86%); R_f = 0.6 in MeOH/EtOAc (20%). $[\alpha]_D$ = –37.0 (*c* = 0.7, MeOH). ^{1}H NMR (D_2O, 400 MHz, rotamer ratio approximately 1:2): δ = 1.78–1.82 (m, 1 H minor rotamer), 1.86–1.98 (m, 3 H, 1 H major rotamer; 2 H minor rotamer), 2.02–

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2.09 (m, 1 H major rotamer), 2.19–2.28 (m, 1 H major rotamer), 3.23–3.67 (m, 9 H, 5 H major rotamer, 4 H minor rotamer), 3.98–4.00 (m, 1 H minor rotamer), 4.21 (d, J = 15.2 Hz, 1 H minor rotamer), 4.42 (d, J = 15.2 Hz, 1 H major rotamer), 4.57–4.60 (m, 3 H, 1 H major rotamer, 3 H minor rotamer), 5.02 (d, J = 14.4 Hz, 1 H minor rotamer), 5.88 (d, J = 11.0 Hz, 1 H major rotamer), 6.34–6.40 (m, 1 H major rotamer), 7.18–32 (m, 10 H, 5 H major rotamer, 5 H minor rotamer) ppm. ^{13}C NMR (D_2O, 100 MHz): δ = 31.4, 34.5, 38.2, 43.8, 48.7, 49.4, 52.2, 52.9, 64.1, 64.6, 71.3, 72.1, 73.8, 128.8, 129.8, 137.5, 142.3, 171.9, 174.5 ppm. IR (neat): $\tilde{\nu}$ = 3372, 2923, 2853, 1641, 1592 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{21}NO_5$ $[M + H]^+$ 296.1498; found 296.1499.

(*S*)-1-Benzyl-6-[(*S*)-1,2-dihydroxyethyl]azepan-2-one (83): Hydrolysis of compound **76** (32 mg, 0.09 mmol) as described in General Procedure **E** led to compound **83** as a colourless viscous oil, yield 25 mg (quantitative); R_f = 0.3 in EtOAc. $[\alpha]_D$ = –3.7 (c = 0.12, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38–1.47 (m, 2 H), 1.53–1.62 (m, 1 H), 1.84–1.89 (m, 1 H), 1.94–2.01 (m, 1 H), 2.24 (br, OH), 2.55–2.64 (m, 2 H), 3.23 (d, J = 15.4 Hz, 1 H), 3.32–3.38 (m, 2 H), 3.47–3.53 (m, 2 H), 4.56 (d, J = 14.6 Hz, 1 H), 4.60 (d, J = 14.6 Hz, 1 H), 7.26–7.35 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 22.9, 31.1, 36.7, 42.2, 50.5, 50.9, 63.6, 74.1, 127.5, 128.5, 128.6, 137.5, 175.6 ppm. IR (neat): $\tilde{\nu}$ = 3392, 2928, 1615, 1451 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{21}NO_3$ $[M + H]^+$ 264.1600; found 264.1602.

(*R*)-1-Benzyl-6-[(*S*)-1,2-dihydroxyethyl]-6,7-dihydro-1*H*-azepin-2(5*H*)-one (86): Hydrolysis of **71** (213 mg, 0.62 mmol) as described in General Procedure **E** gave compound **86** as a colourless viscous oil, yield 163 mg (quantitative); R_f = 0.2 in EtOAc. $[\alpha]_D$ = –33.5 (c = 1.7, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.96 (br. s, 1 H), 2.32–2.36 (m, 2 H), 3.19 (d, J = 12.9 Hz, 1 H), 3.32–3.37 (m, 2 H), 3.46–3.49 (m, 2 H), 4.52 (d, J = 14.6 Hz, 1 H), 4.83 (d, J = 14.6 Hz, 1 H), 6.04 (d, J = 12.0 Hz, 1 H), 6.24–6.29 (m, 1 H), 7.29–7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.2, 42.9, 49.4, 51.1, 64.3, 73.3, 126.1, 127.6, 128.3, 128.7, 137.3, 138.4, 168.8 ppm. IR (neat): $\tilde{\nu}$ = 3389, 2924, 1648, 1591 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{19}NO_3$ $[M + H]^+$ 262.1443; found 262.1443.

(*S*)-1-Benzyl-7-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carbaldehyde (87): Compound **87** was obtained from **85** (270 mg, 1.03 mmol) by General Procedure **I** for vicinal diol cleavage as a colourless viscous oil, yield 200 mg (85%); R_f = 0.6 in EtOAc. $[\alpha]_D$ = +13.3 (c = 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.49–2.59 (m, 2 H), 2.70–2.77 (m, 1 H), 3.54–3.56 (m, 2 H), 4.44 (d, J = 14.6 Hz, 1 H), 4.94 (d, J = 14.4 Hz, 1 H), 6.13 (d, J = 11.7 Hz, 1 H), 6.25–6.31 (m, 1 H), 7.26–7.36 (m, 5 H), 9.46 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.5, 45.2, 50.9, 53.1, 127.9, 128.0, 128.5, 128.9, 135.2, 137.2, 168.7, 200.2 ppm. IR (neat): $\tilde{\nu}$ = 2927, 1723, 1647, 1600 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}NO_2$ $[M + H]^+$ 230.1181; found 230.1186.

(*S*)-1-Benzyl-6-(hydroxymethyl)-6,7-dihydro-1*H*-azepin-2(5*H*)-one (89): General Procedure **J** for aldehyde reduction with **87** (145 mg, 0.63 mmol) gave compound **89** as a colourless viscous oil, yield 111 mg (76%); R_f = 0.35 in EtOAc. $[\alpha]_D$ = –1.5 (c = 2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.98–2.10 (m, 2 H), 2.31 (dt, J = 16.5, 5.7 Hz, 1 H), 3.23–3.36 (m, 3 H), 3.41 (dd, J = 10.7, 5.4 Hz, 1 H), 4.55 (d, J = 14.6 Hz, 1 H), 4.77 (d, J = 14.6 Hz, 1 H), 6.03 (d, J = 11.9 Hz, 1 H), 6.21–6.25 (m, 1 H), 7.27–7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 30.2, 43.1, 48.4, 51.2, 64.3, 126.7, 127.5, 128.3, 128.6, 137.2, 137.6, 169.0 ppm. IR (neat): $\tilde{\nu}$ = 3389, 2922, 1648, 1593 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{17}NO_2$ $[M + H]^+$ 232.1337; found 232.1333.

(3*R*,4*R*,6*S*)-1-Benzyl-3,4-dihydroxy-6-(hydroxymethyl)azepan-2-one (91): Dihydroxylation of **89** (65 mg, 0.28 mmol) was performed as described in General Procedure **B**. This led to compounds **91** and **92** (60 mg, 80% combined yield). Column chromatographic purification was done with EtOAc/2% MeOH/EtOAc; pure compound **91** was obtained as a colourless viscous oil (although only 20 mg); R_f = 0.1 in EtOAc. $[\alpha]_D$ = –70 (c = 0.4, MeOH). ^{1}H NMR (D_2O, 500 MHz): δ = 1.70–1.75 (m, 1 H), 1.81 (br. s, 1 H), 1.87–1.94 (m, 1 H), 3.37 (dd, J = 10.9, 5.2 Hz, 1 H), 3.39–3.47 (m, 3 H), 3.94–3.95 (m, 1 H), 4.16 (d, J = 14.9 Hz, 1 H), 4.58 (br. s, 1 H), 4.91 (d, J = 15.2 Hz, 1 H), 7.16–7.29 (m, 5 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 34.0, 36.9, 47.9, 52.4, 62.8, 70.4, 127.7, 127.8, 128.9, 136.5, 173.8 ppm. IR (neat): $\tilde{\nu}$ = 3428, 2925, 1639 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{19}NO_4$ $[M + H]^+$ 266.1392; found 266.1394.

Compound 91: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.95–2.04 (m, 2 H, H-5, H-6), 2.09–2.13 (m, 1 H, H-5′), 3.41–3.51 (m, 2 H, H-7, H-7′), 3.64–3.67 (m, 1 H, H-8), 3.76–3.80 (m, 1 H, H-8′), 4.13 (br. s, 1 H, H-4), 4.19 (d, J = 14.9 Hz, 1 H, OCH_2Ph), 4.46 (br. s, 1 H, H-3), 4.73–4.75 (m, OH), 5.31 (d, J = 14.9 Hz, 1 H, OCH_2Ph'), 7.25–7.34 (m, 5 H, Ar-H) ppm.

Supporting Information (see footnote on the first page of this article): Experimental details and spectral data of new compounds; copies of ^{1}H and ^{13}C NMR spectra and additional NMR spectra for stereochemical analysis.

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[13] CCDC-956289 for compound **85** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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