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Highly stereoselective synthesis of imino-*C*-di- and trisaccharides as hydrolytically stable glycomimetics

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ABSTRACT

A new straightforward route to glycomimetics containing a piperidine unit is reported. The key step of the methodology is the intramolecular 1,3-dipolar cycloaddition of easily accessible glycosyl alkenyl nitrones. The reaction takes place in most cases with a complete selectivity in favor of the *exo*–*exo* adduct, which facilitates the synthesis of all-*cis* piperidines bearing the glycosyl units. The direct transformation of adducts into the final imino-*C*-di and trisaccharide analogues is achieved in one step using simple reagents. Inhibition properties against two glycosidases have been tested but no positive results have been found.

1. Introduction

Oligosaccharides are involved in a great number of physiological processes related to metabolism and energy storage.[1] They also help regulate several cellular processes through their interaction with membrane receptors and proteins.[2] Consequently the enzymes responsible for the synthesis and modification of oligosaccharides, such as glycosidases and glycosyltransferases,[3] are the object of many inhibitory studies.[4] Indeed, a lot of carbohydrate mimics, mainly optically active polyhydroxylated saturated nitrogen heterocycles have been synthesized and studied as glycosidase inhibitors.[5] On the other hand, to find or design potent and specific inhibitors of glycosyltransferases is more difficult probably because the active sites and structural motifs of those enzymes are heavily conserved.[6] Therefore, there is a considerable interest in the synthesis of glycomimetics for use in medicinal chemistry and drug development.[7]

A strategy that has demonstrated a high efficiency in designing more specific inhibitors of both glycosidases and glycosyltransferases consists of incorporating additional carbohydrate units to an iminosugar scaffold.[8] The scaffold can be designed in a similar way to known simple inhibitors and the additional carbohydrate units according to the corresponding binding site of the target enzyme. An example can be given by 1-deoxynojirimycin-derived glycomimetics **1** and **2**, which showed inhibitory activity against rat intestinal maltase (EC. 3.2.1.20) with IC_{50} values of 2.3 μM and 1.70 μM, respectively,[9] whereas 1-deoxynojirimycin alone showed an IC_{50} value of 28 μM against the same enzyme.[10] Following this approach a variety of imino di- and oligosaccharides have been prepared and tested as inhibitors of glycosidases and glycosyltransferases.[8] In addition to **1** and **2** examples are given by compounds **3** and **4** that competitively inhibited β-1,4-endoglucanases (Fig. 1).[11]

Similarly, compound **5** exhibited a potent inhibitor activity (K_i=25 μM) of human pancreatic α-amylase, whereas the iminosugar unit alone showed a modest activity (K_i=18 mM) against the same enzyme.[12] However, in several occasions iminodisaccharides are not ideal drug candidates due to their low metabolic stability toward endogenous glycosidases, which become into a poor bioavailability. This difficulty could be overcome by replacing the glycosidic bond with a C–C bond, which cannot be hydrolyzed. The resulting glycomimetics, called imino-*C*-disaccharides, should display high receptor affinity and selectivity in addition to enhanced metabolic stability and bioavailability.[13] In fact, considerable effort has been focused on the design and synthesis of those compounds, which often required dedicated approaches depending on the particular target.[14] In this context, we have described the synthesis of glycosyl pyrrolidines (Fig. 2, n=0), which can be considered pseudoimino-*C*-disaccharides (the two monosaccharide analogues

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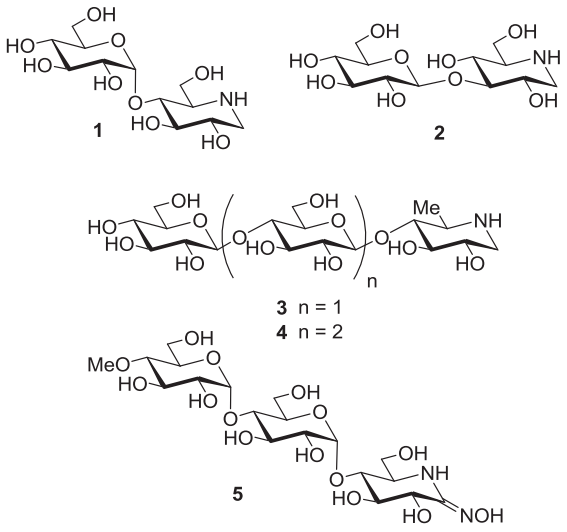


Fig. 1. Iminooligosaccharides.

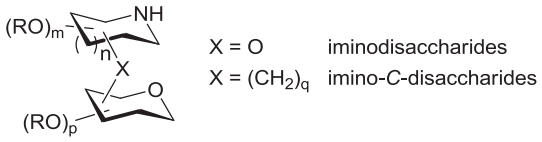
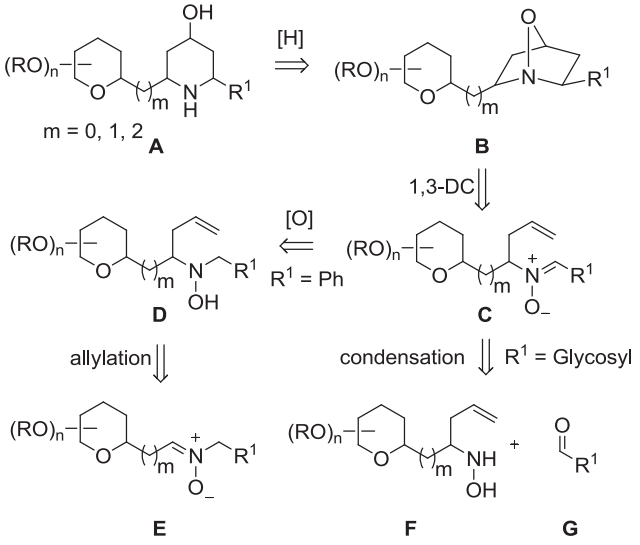


Fig. 2. Iminodisaccharides and C-analogues.

are directly linked; X=no atom) through inter-molecular 1,3-dipolar cycloaddition between *C*-glycosyl nitrones and methyl acrylate.[15]

In this paper we present full details[16] of a direct high-yielding approach to imino-*C*-disaccharides, based on an intramolecular cycloaddition of alkenyl glycosyl nitrones. Our retrosynthetic approach is presented in Scheme 1.

The first step illustrates the intention to create a hydroxyl group at the 4-position of the piperidine **A** after *N*,*O*-cleavage of adduct **B**. The key step of the approach is the intramolecular cycloaddition of alkenyl nitrones **C** to give adducts **B**. Nitrones **C** should be prepared by either condensation (from **F** and **G**) or oxidation (from **D**)



Scheme 1. Retrosynthetic analysis.

methods[17] from appropriate precursors depending on the nature of the substituent R. The *N*-disubstituted homoallylhydroxylamines **D** could be easily accessed in a stereoselective way from *C*-glycosyl nitrones **E** following our previously reported methodology on allylation of nitrones.[18] The *N*-monosubstituted homoallylhydroxylamines **F** would be obtained from nitrones of type **C** (R^1=Ph) through transoximation processes as reported.[19]

2. Results and discussion

2.1. Synthesis of nitrones

We selected several substrates bearing different sugar units in order to provide the methodology outlined in Scheme 1 with the required versatility. The sugar units and the nomenclature employed along this paper are presented in Chart 1.

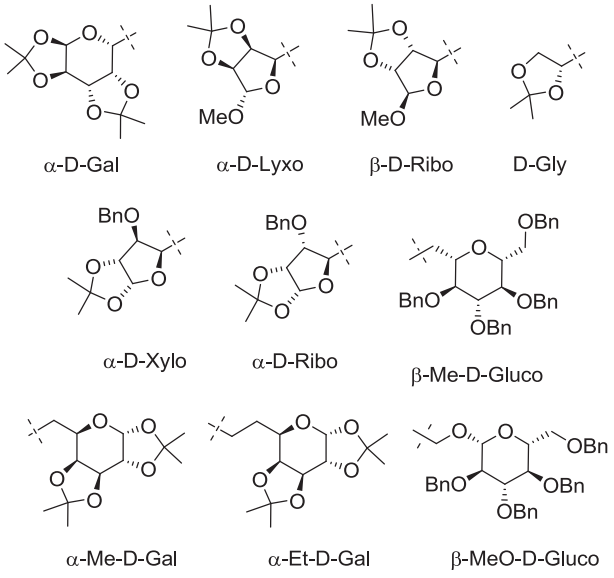
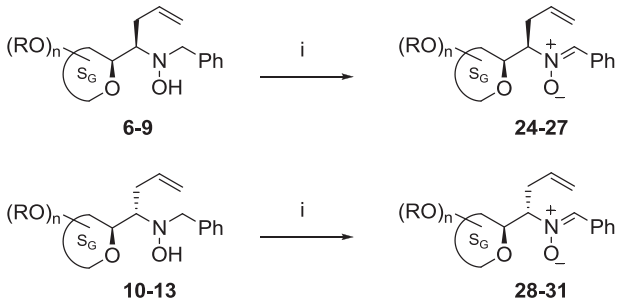


Chart 1. Sugar residues (S_G).

We reported that *N*-benzyl homoallylhydroxylamines **6**–**13** can be prepared through stereocontrolled allylation of *N*-benzyl nitrones in good yields and diastereoselectivities.[16,18] The required epimeric *C*-phenyl nitrones **24**–**27** and **28**–**31** were readily prepared from **6**–**9** and **10**–**13**, respectively, by oxidation with manganese(IV) oxide according to the method developed by Brandi and co-workers.[20] In all cases, the oxidation was completely regioselective and only the *C*-phenyl-*N*-homoallyl nitrones bearing a sugar unit at the nitrogen side were obtained as single isomers (Scheme 2, Table 1). The expected (*Z*)-configuration was confirmed



Scheme 2. Synthesis of *C*-(phenyl)-*N*-alkenylsugar nitrones. (i) MnO_2, CH_2Cl_2, rt, 6 h (for S_G see Table 1 and Chart 1).

Table 1
Synthesis of *C*-phenyl nitrones (Scheme 1)[a]

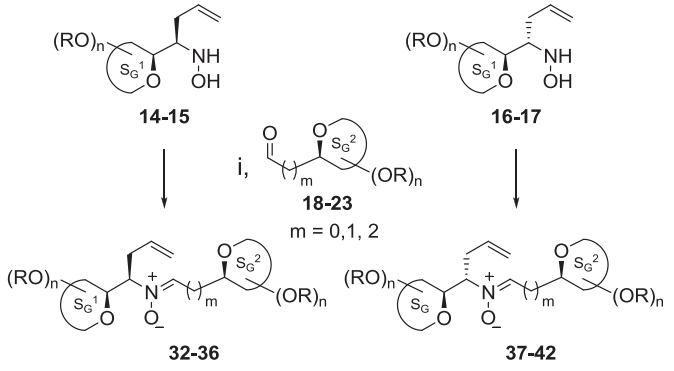
S_G	Hydroxylamine	Nitrone	Yield[b] (%)
α-D-gal	**6**	**24**	82
α-D-lyxo	**7**	**25**	80
α-D-xylo	**8**	**26**	78
α-D-ribo	**9**	**27**	81
β-D-ribo	**10**	**28**	82
α-D-lyxo	**11**	**29**	90
α-D-xylo	**12**	**30**	92
α-D-ribo	**13**	**31**	89

[a] For R^1 see Chart 1.
[b] Isolated yield.

by ^{1}H NMR 2D NOESY experiments and the previously described ASIS effect for nitrones.[21]

Nitrones bearing two glycosyl units were prepared from mono-substituted hydroxylamines **14**–**17**, easily accessible through trans-oximation of *C*-arylnitrones as reported by us[19] and other groups.[22] Condensation of **14**–**17** with aldehydes **18**–**23** provided access to nitrones **32**–**42** in good chemical yields (Scheme 3, Table 2).

Again, only the (*Z*)-isomer was obtained as confirmed by NMR experiments and in the case of **34** by X-ray crystallography.[23]



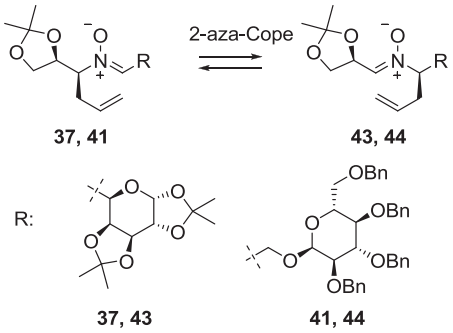
Scheme 3. Synthesis of nitrones bearing two glycosyl units. (i) $MgSO_4$, CH_2Cl_2, rt, 4 h (for S_G^1 and S_G^2 see Table 2 and Chart 1).

Nitrones **24**–**42** proved to be stable at room temperature with the exception of **37** and **41**, which were obtained as inseparable mixtures together with the corresponding rearranged nitrones **43** and **44** (Scheme 4). This result was not unexpected to us, since the 2-aza-Cope rearrangement of *N*-alkenyl nitrones with complete transfer of chirality had been reported from our laboratory for similar substrates.[24] In any case, this result does not affect to the

Table 2
Synthesis of nitrones bearing two sugar units (Scheme 2)[a]

S_G^1	S_G^2	Hydroxyl-amine	Aldehyde	Nitrone	Yield[b] (%)
D-gly	α-D-gal	**14**	**18**	**32**	78
D-gly	α-Me-D-gal	**14**	**19**	**33**	79
D-gly	α-Et-D-gal	**14**	**20**	**34**	81
α-D-gal	α-Et-D-gal	**15**	**21**	**35**	77
α-D-gal	$BnOCH_2$	**15**	**21**	**36**	76
D-gly	α-D-gal	**16**	**18**	**37**	88[c]
D-gly	α-Me-D-gal	**16**	**19**	**38**	73
D-gly	α-Et-D-gal	**16**	**21**	**39**	73
D-gly	β-Me-D-gluco	**16**	**22**	**40**	78
D-gly	β-MeO-D-gluco	**16**	**23**	**41**	75[c]
β-D-ribo	$BnOCH_2$	**17**	**21**	**42**	72

[a] For S_G^1 and S_G^2 see Chart 1.
[b] Isolated yield.
[c] Obtained as a mixture of rearranged nitrones (see text).

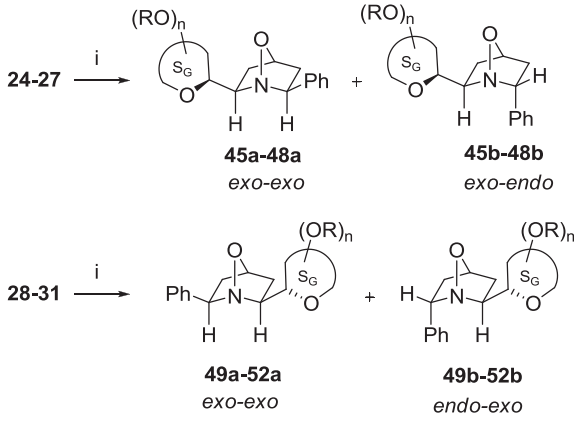


Scheme 4. 2-Aza-Cope rearrangement of nitrones **37** and **41**.

progress and applicability of the strategy since the same major adduct will be obtained in the intramolecular cycloaddition of couples **12e**/**13a** and **12i**/**13b**. Moreover, as discussed in previous reports[24] it cannot be discarded that a 2-aza-Cope rearrangement takes place during the next cycloaddition step (see below).[16]

2.2. Intramolecular cycloaddition

The intramolecular 1,3-dipolar cycloaddition of glycosyl *N*-alkenyl nitrones provides potentially useful stereoselectively functionalized bicyclic intermediates.[25] The scope of glycosyl nitrones **24**–**42** in the reaction was demonstrated by the following results. Heating of nitrones in toluene at 100 °C in a sealed tube for 72 h provided the corresponding cycloadduct in good yields. Under these conditions, the reaction of *C*-phenyl nitrones **24**–**31** proceeded smoothly to give adducts as mixtures of *exo*–*exo* and *endo*–*exo* (or *exo*–*endo*) isomers, the former being obtained predominantly (Scheme 5, Table 3).



Scheme 5. Synthesis of bicyclic adducts bearing one glycosyl units. (i) Toluene, 100 °C, 72 h, sealed tube (for sugar unit see Table 3 and Chart 1).

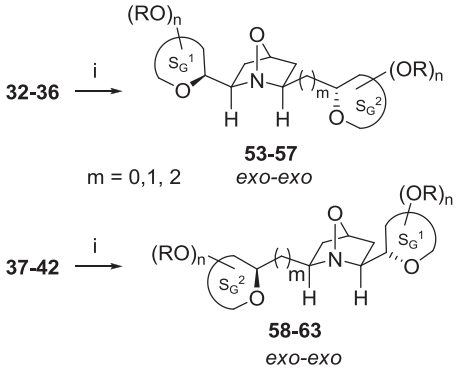
A marked effect of relative stereochemistry was observed on *endo*/*exo* selectivity with these nitrones. While slightly higher yields are observed for nitrones **28**–**31** (entries 5–8), better selectivities are obtained with nitrones **24**–**27** having a relative *syn*-disposition between the allyl group and the N^β stereogenic center (entries 1–4). Exceptions to this behavior are found with nitrones **26** (Table 3, entry 3) and **28** (Table 3, entry 5), which afforded the *exo*–*exo* isomer as the only product of the reaction.

A complete selectivity was obtained in all cases with nitrones **32**–**42** bearing two glycosyl units (Scheme 6, Table 4). Only the *exo*–*exo* isomer was detected in the crude reaction mixture. In the

Table 3
Cycloadducts with one sugar unit (Scheme 5)[a]

Entry	S_G	Nitrone	Adduct	dr (a/b)[b,c]	Yield[d] (%)
1	α-D-gal	**24**	**45**	82:18	82
2	α-D-lyxo	**25**	**46**	75:25	80
3	α-D-xylo	**26**	**47**	>95:5	78
4	α-D-ribo	**27**	**48**	76:24	81
5	β-D-ribo	**28**	**49**	>95:5	82
6	α-D-lyxo	**29**	**50**	66:34	90
7	α-D-xylo	**30**	**51**	59:41	92
8	α-D-ribo	**31**	**52**	68:32	89

[a] For S_G see Chart 1.
[b] Measured by integration of the corresponding ^{1}H NMR signals in the crude mixture.
[c] For adducts **45**–**48**, a and b series refer to *exo*–*exo* and *exo*–*endo* adducts, respectively. For adducts **49**–**52**, a and b series refer to *exo*–*exo* and *endo*–*exo* adducts, respectively.
[d] Isolated yield.



Scheme 6. Synthesis of bicyclic adducts bearing two glycosyl units. (i) Toluene, 100 °C, 72 h, sealed tube (for sugar unit see Table 4 and Chart 1).

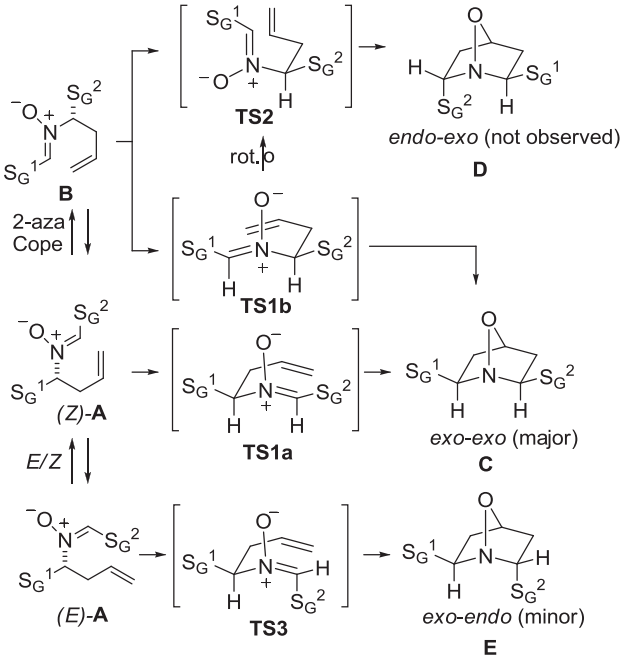
case of cycloadduct **53** (Table 4, entry 1) an abnormal low yield was obtained and the compound was accompanied by an unknown impurity that could not be separated by any chromatographic technique.

The relative *endo*/*exo* configuration of cycloadducts **45**–**63** was assigned on the basis of 1D and 2D NMR and NOE information. In particular NMR analysis of *exo*–*exo* adducts revealed an NOE between the two *endo* protons of the substituted carbons that can be accounted for only by such a configuration. Moreover, that effect was not observed for minor *endo*/*exo* (or *exo*/*endo*) isomers, when isolated. The absolute configuration was ascertained by X-ray crystallography.[23] Single crystals of **46a**, **48a**, **49a**, and **61** confirmed the assigned configuration to major compounds.[23] For minor adducts, X-ray analyses of **45b**, **46b**, and **51b** confirmed their absolute configuration as well as the existence of partial *E*/*Z* isomerization of nitrones during the cycloaddition step. In fact, the intramolecular cycloaddition of *N*-alkenyl nitrones **24**–**32** might be preceded by either an *E*/*Z* isomerization or a 2-aza-Cope rearrangement as suggested in previous reports (Scheme 7).[26]

Table 4
Cycloadducts with two sugar units (Scheme 6)[a]

S_G1	S_G2	Nitrone	Adduct	dr[b,c]	Yield[d] (%)
D-gly	α-D-gal	**32**	**53**	>95:5	36
D-gly	α-Me-D-gal	**33**	**54**	>95:5	89
D-gly	α-Et-D-gal	**34**	**55**	>95:5	82
α-D-gal	α-Et-D-gal	**35**	**56**	>95:5	70
α-D-gal	$BnOCH_2$	**36**	**57**	>95:5	80
D-gly	α-D-gal	**37**	**58**	>95:5	85
D-gly	α-Me-D-gal	**38**	**59**	>95:5	84
D-gly	α-Et-D-gal	**39**	**60**	>95:5	77
D-gly	β-Me-D-gluco	**40**	**61**	>95:5	75
D-gly	β-MeO-D-gluco	**41**	**62**	>95:5	80
β-D-ribo	$BnOCH_2$	**42**	**63**	>95:5	83

[a] For S_G^1 and S_G^2 see Chart 1.
[b] Measured by integration of the corresponding ^{1}H NMR signals in the crude mixture.
[c] Only the *exo*–*exo* adduct was obtained as the product of the reaction.
[d] Isolated yield.



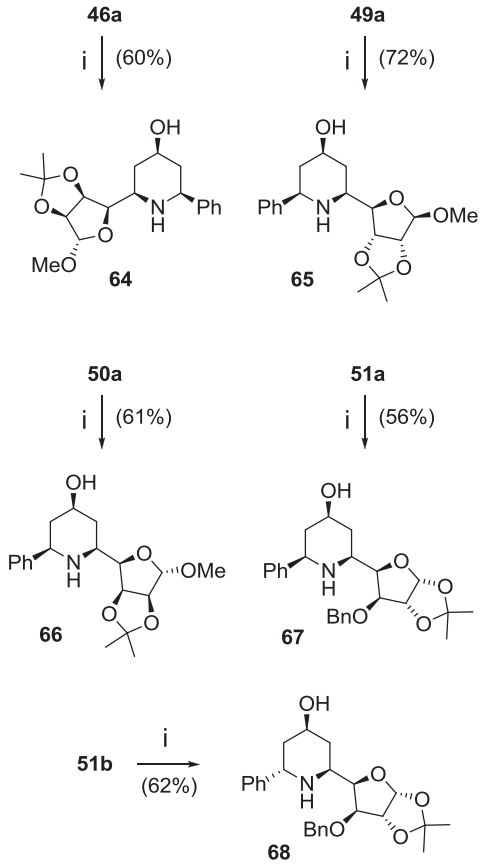
Scheme 7. *E*/*Z* isomerism and thermal-induced 2-aza-Cope rearrangement in *N*-alkenyl nitrones.

In several instances, *E*/*Z* isomerization of nitrones, which has been demonstrated to be a rotational process,[27] has been used to explain the stereochemical outcome of dipolar cycloadditions.[28] On the other hand, recent experimental and theoretical studies carried out in our laboratories[24] pointed out that the thermal 2-aza-Cope rearrangement of *N*-alkenyl nitrones is also possible. Both rearranged nitrones (*Z*)-**A** and **B** give rise to the same *exo*–*exo* major cycloadduct **C** through transition states **TS1a** and **TS1b**, respectively. The difference of the stereochemical outcome of the reaction arises from the minor adducts. In the case of racemic compounds[26a] it is not possible to determine the origin of the minor adduct (*E*/*Z* isomerization versus 2-aza-Cope rearrangement) because the two possible minor products are enantiomers. However, the presence of a homochiral sugar moiety (as in the case of nitrones **24**–**42**) converts the two minor adducts *endo*–*exo* and *exo*–*endo* being formed from nitrones **B** (through **TS2**) and (*E*)-**A** (through **TS3**), respectively, into distinguishable diastereomers. The X-ray-based determination of the absolute configuration of those minor adducts served as an ultimate confirmation of the existence of *E*/*Z* isomerism in the intramolecular dipolar cycloaddition of nitrones **24**–**42** since the elucidated structures corresponded to *exo*–*endo* adducts **E** and not *endo*–*exo* adducts **D**. This result is in a marked contrast to a similar reaction reported by us with D-glyceraldehyde derived nitrones, which only showed evidences of 2-aza-Cope rearrangement.[25]

2.3. Synthesis of imino-*C*-di- and trisaccharides

With the cycloadducts **45**–**63** successfully prepared in a very good diastereomeric ratio, the next step in the methodology

entailed the conversion of the bicyclic unit into a piperidine ring. The cleavage of the N–O bond can be carried out without affecting acid-sensitive protecting groups by using zinc in acetic acid under mild conditions.[25] Under these conditions, major *exo*–*exo* adducts **46a**, **49a**, **50a**, and **51a** were transformed into all-*cis* 2-glycosyl-4-hydroxy-6-phenyl piperidines **64**–**67** (Scheme 8). The same reaction conditions were applied to the minor adduct **51b** and glycosylpiperidine **68** was obtained in good yield, thus demonstrating a good scope for the methodology. Single crystals of **66** were



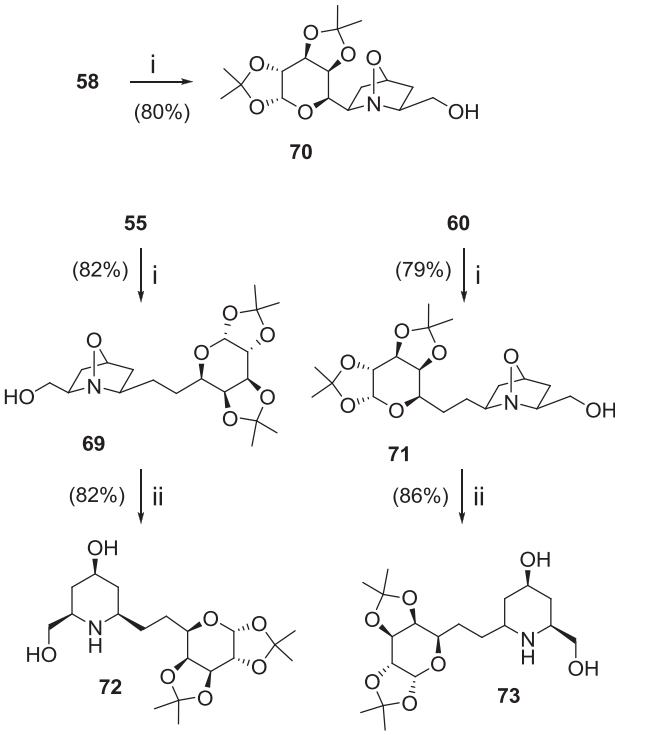
Scheme 8. Synthesis of 6-phenyl-4-hydroxy-*C*-glycosylpiperidines. (i) Zn, AcOH, 60 °C, 4 h.

obtained and the absolute configuration was ascertained by X-ray analysis,[23] thus confirming the assigned configuration to the precursor **50a**.

Moreover, it is also possible to carry out the conversion of the dioxolane moiety into a hydroxymethyl group prior to *N*,*O*-cleavage. The process involves the regioselective deprotection of the primary acetonide and oxidation of the resulting diol.

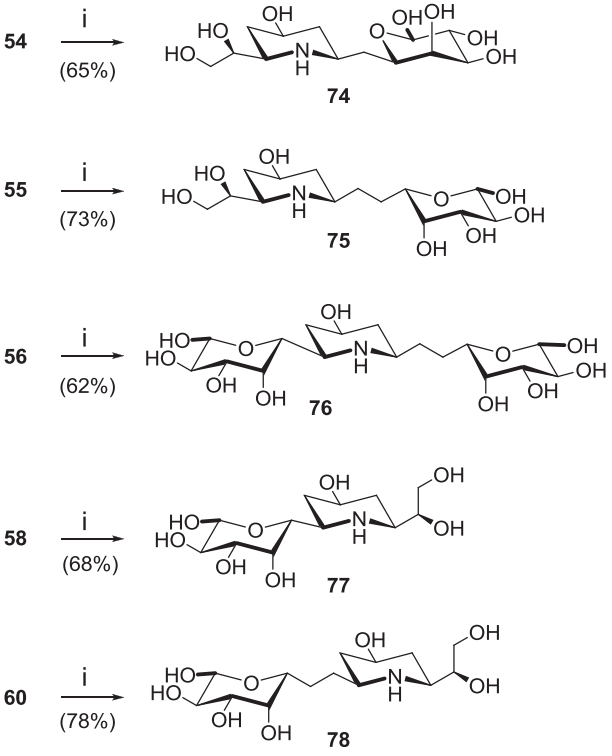
Acetonide hydrolysis was carried out with acetic acid and the resulting diol was cleaved by the action of sodium metaperiodate. The emerging aldehyde was reduced in situ with sodium borohydride to afford the final alcohol. By applying this variation *exo*–*exo* adducts **55a**, **58a**, and **60a** were converted into hydroxymethyl derivatives **69**–**71** (Scheme 9). Further *N*,*O*-cleavage of **69** and **71** was achieved by catalytic hydrogenation in the presence of Pearlman's catalyst that furnished 2-glycosyl-4-hydroxy-6-hydroxymethylpiperidines **72** and **73**, respectively.

The direct obtention of completely deprotected imino-*C*-di- and trisaccharides is also possible through a one-pot procedure. Starting from the corresponding cycloadducts **54a**, **55a**, **56a**, **58a**, and **60a**, compounds **74**–**78** were obtained (Scheme 10). The transformation was carried out by treating the cycloadducts with



Scheme 9. Synthesis of 6-hydroxymethyl-4-hydroxy-*C*-glycosylpiperidines. (i) 66% AcOH, rt, 14 h; then $NaIO_4$, SiO_2, CH_2Cl_2, rt, 1.5 h; then $NaBH_4$, 10:1 Et_2O/H_2O; (ii) H_2, $Pd(OH)_2/C$, MeOH, 100 bar, rt, 3 h.

aqueous trifluoroacetic acid, which guarantees the hydrolysis of all the acetonides. The remaining *N*,*O* bond was reduced by in situ catalytic hydrogenation in the presence of Pearlman's catalyst. The unprotected glycomimetics **74**–**78** were isolated in good chemical yields after purification by semipreparative HPLC (reverse phase).



Scheme 10. Synthesis of deprotected imino-*C*-di- and trisaccharides. (i) 9:1 TFA/H_2O, rt, 4 h; then H_2, $Pd(OH)_2/C$, MeOH, 100 bar, 3 h.

3. Biological studies

The iminoglycomimetics **74**–**78** have been evaluated for their inhibitory activities toward α-glucosidase from *Saccharomyces cerevisae* and β-glucosidase from almonds. Unfortunately low inhibition (20–50%) was observed at high concentration (1 mM) of compounds **74**–**78**. Affinity assays performed for these compounds against α-glucosidase from *S. cerevisae*, β-glucosidase from almonds, α-galactosidase from *green coffee bean*, β-galactosidase from *Escherichia coli* and α-L-fucosidase from *Bovine kidney* by STD-NMR ^{1}H experiments[29] showed no interaction.

4. Conclusions

The readily accessible alkenyl glycosyl nirones **24**–**42** have proven to be excellent and practical building blocks for the synthesis of a variety of imino-*C*-di- and trisaccharide analogues. The synthetic methodology consisting of an intramolecuar 1,3-dipolar cyloaddition and further elaboration of the resulting cycloadducts permitted synthetic manipulations to be applied to the dioxolane ring culminating in the obtention of hydroxymethyl derivatives. At the same time, it is also possible to transform the cycloadducts into completely deprotected glycomimetics in a straightforward way involving a one-pot procedure by using simple and easily accessible reagents. The scope and versatility of the methodology is demonstrated by the synthesis of di- and trisaccharide glycomimetics linked either directly or through flexible chains containing one or two carbon atoms, bearing in all cases a piperidine unit. Further studies directed at developing new syntheses of different iminoglycomimetics are currently undergoing in our laboratories.

5. Experimental section

5.1. General

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F_{254}; the position of the spots were detected with 254 nm UV light or by spraying with either 5% ethanolic phosphomolybdic acid or Mostain solution. Column chromatography was carried out in a Buchi 800 MPLC system or a Combiflash apparatus, using silica gel 60 microns and with solvents distilled prior to use. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 or 500 instrument in the stated solvent. Chemical shifts are reported in parts per million (δ) relative to $CHCl_3$ (δ=7.26) in $CDCl_3$. Optical rotations were taken on a JASCO DIP-370 polarimeter. Elemental analysis was performed on a Perkin Elmer 240B microanalyzer or with a Perkin–Elmer 2400 instrument.

5.2. General procedure for the synthesis of nitrones

Method A. A cooled (0 °C) solution of the corresponding hydroxylamine (1 mmol) in anhydrous dichloromethane (15 mL) was treated with activated manganese(IV) oxide (0.12 g, 1.4 mmol). The resulting mixture was stirred at 0 °C under an inert atmosphere for 6 h; the reaction mixture was then filtered through a short pad of Celite and dried over magnesium sulfate. The filtrate was evaporated under reduced pressure to give the crude product, which was purified by column chromatography in the stated eluent.

Method B. To a well-stirred solution of the corresponding aldehyde (2 mmol) in dichloromethane (25 mL) a solution of the corresponding hydroxylamine (2 mmol) was added in one portion. The resulting solution was treated with magnesium sulfate (2 mmol) and stirring was maintained at room temperature for 4 h. The reaction mixture was then filtered and the filtrate evaporated under reduced pressure to give the crude product, which was purified by column chromatography in the stated eluent.

*5.2.1. (R,Z)-N-(R,Z)-N-Benzylidene-1-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl) but-3-en-1-amine oxide (**24**).* Yield 0.662 g, 82%; white solid; mp 128–130 °C; R_f=0.65 (Hex/EtOAc 9:1); $[\alpha]_D^{25}$ −51 (*c* 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.23 (s, 3H), 1.33 (s, 3H), 1.47 (s, 3H), 1.59 (s, 3H), 2.69–2.76 (m, 1H), 2.84 (ddd, 1H, *J*=7.4, 10.7, 14.4 Hz), 4.05 (ddd, 1H, *J*=3.0, 9.6, 10.7 Hz), 4.24 (dd, 1H, *J*=1.5, 8.0 Hz), 4.27–4.30 (m, 2H), 4.56 (dd, 1H, *J*=2.3, 8.0 Hz), 5.02–5.05 (m, 1H), 5.17 (dd, 1H, *J*=1.7, 17.1 Hz), 5.55 (d, 1H, *J*=5.0 Hz), 5.76 (tdd, 1H, J=7.2, 10.1, 17.3 Hz), 7.39–7.50 (m, 4H), 8.24–8.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm) 24.3, 25.0, 26.0, 26.2, 33.3, 67.9, 70.1, 70.7, 70.8, 74.9, 96.6, 109.0, 109.2, 118.4, 128.5, 128.8, 130.4, 133.4, 136.2. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.68; H, 7.19; N, 3.60.

*5.2.2. (R,E)-N-Benzylidene-1-((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)but-3-en-1-amine oxide (**25**).* Yield 0.555 g, 80%; yellow oil; R_f=0.46 (Hex/EtOAc 8:2); $[\alpha]_D^{25}$ +29 (*c* 0.87, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.23 (s, 3H), 1.49 (s, 3H), 2.66–2.72 (m, 1H), 2.91–2.99 (m, 1H), 3.33 (s, 3H), 4.20 (ddd, 1H, *J*=3.0, 9.5, 10.8 Hz), 4.46 (dd, 1H, *J*=3.3, 9.5 Hz), 4.53 (d, 1H, *J*=5.8 Hz), 4.70 (dd, 1H, *J*=3.3, 5.8 Hz), 4.89 (s, 1H), 5.05–5.08 (m, 1H), 5.19 (ddd, 1H, *J*=1.3, 3.1, 17.1 Hz), 5.80 (tdd, 1H, *J*=7.2, 10.1, 17.2 Hz), 7.37 (s, 1H), 7.41–7.44 (m, 3H), 8.23–8.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm) 24.8, 26.2, 34.1, 54.5, 74.2, 79.1, 79.3, 85.1, 107.0, 112.5, 118.5, 128.4, 128.8, 130.3, 133.5, 136.0. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.51; H, 7.42; N, 3.89.

*5.2.3. (R,E)-N-Benzylidene-1-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-3-en-1-amine oxide (**26**).* Yield 0.661 g, 78%; colorless oil; R_f=0.23 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −11 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.43 (s, 3H), 1.63 (s, 3H), 2.77–2.83 (m, 1H), 3.05 (ddd, 1H, *J*=7.5, 11.0, 14.3 Hz), 4.18 (d, 1H, *J*=3.2 Hz), 4.28 (ddd, 1H, *J*=2.7, 9.4, 11.1 Hz), 4.34 (d, 1H, *J*=11.2 Hz), 4.72–4.75 (m, 2H), 4.81 (dd, 1H, *J*=3.1, 9.3 Hz), 5.13 (dd, 1H, *J*=1.6, 10.1 Hz), 5.26 (dd, 1H, *J*=1.5, 17.1 Hz), 5.79–5.90 (m, 1H), 6.07 (d, 1H, *J*=3.8 Hz), 7.26–7.52 (m, 9H), 8.16–8.18 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 26.3, 26.8, 34.4, 72.3, 73.9, 80.2, 81.9, 81.9, 105.1, 112.1, 118.6, 127.6, 128.0, 128.4, 128.5, 128.6, 130.1, 130.4, 133.2, 135.6, 137.0. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.98; H, 6.74; N, 3.51.

*5.2.4. (R,E)-N-Benzylidene-1-((3aR,5R,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-3-en-1-amine oxide (**27**).* Yield 0.686 g, 81%; white solid; mp 119–121 °C; R_f=0.2 (Hex/EtOAc 8:2); $[\alpha]_D^{25}$ +42 (*c* 0.95,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (s, 3H), 1.51 (s, 3H), 2.44 (ddd, 1H, *J*=4.4, 7.2, 14.6 Hz), 3.01 (ddd, 1H, *J*=7.3, 10.1, 15.0 Hz), 4.10 (td, 1H, *J*=4.1, 10.1 Hz), 4.24 (dd, 1H, *J*=3.8, 8.6 Hz), 4.34 (t, 1H, *J*=4.0 Hz), 4.40 (dd, 1H, *J*=4.3, 8.6 Hz), 4.65 (d, 1H, *J*=11.5 Hz), 4.71 (d, 1H, *J*=11.5 Hz), 4.96–5.01 (m, 1H), 5.11 (dd, 1H, *J*=1.6, 17.1 Hz), 5.54 (d, 1H, *J*=3.5 Hz), 5.71 (tdd, 1H, *J*=7.0, 10.2, 17.1 Hz) ,7.16–7.38 (m, 9H), 8.15–8.20 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 26.4, 26.9, 31.9, 72.5, 76.1, 78.0, 78.3, 78.8, 103.8, 113.1, 118.4, 127.8, 128.2, 128.3, 128.5, 128.7, 130.3, 130.4, 133.5, 136.2, 137.7 . Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.79; H, 6.81; N, 3.17.

*5.2.5. (S,E)-N-Benzylidene-1-((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)but-3-en-1-amine oxide (**28**).* Yield 0.570 g, 82%; syrup; R_f=0.7 (Hex/EtOAc 8:2); $[\alpha]_D^{25}$

−47 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.22 (s, 3H), 1.40 (s, 3H), 2.40–2.47 (m, 1H), 2.52–2.58 (m, 1H), 2.71 (td, 1H, *J*=4.2, 8.4 Hz, H_5), 3.36 (s, 3H), 3.73 (d, 1H, *J*=13.1 Hz), 4.03 (d, 1H, *J*=13.1 Hz), 4.29 (d, 1H, *J*=3.7 Hz), 4.48 (d, 1H, *J*=6.1 Hz), 4.61 (d, 1H, *J*=6.1 Hz), 4.96 (s, 1H), 5.02 (d, 1H, *J*=10.1 Hz), 5.10 (dd, 1H, *J*=1.4, 17.1 Hz), 5.75–5.85 (m, 1H), 6.27 (s, 1H), 7.17–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm) 25.0, 26.7, 29.1, 56.1, 62.3, 66.4, 83.5, 85.7, 87.9, 112.1, 112.5, 117.2, 127.3, 128.3, 129.1, 136.2, 138.1. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.43; H, 7.65; N, 4.30.

*5.2.6. (S,E)-N-Benzylidene-1-((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)but-3-en-1-amine oxide (**29**).* Yield 0.625 g, 90%; colorless oil; R_f=0.24 (Hex/EtOAc 8:2); $[\alpha]_D^{25}$ +72 (*c* 1.00,$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (s, 3H), 1.51 (s, 3H), 2.46–2.52 (m, 1H), 2.86 (ddd, 1H, *J*=7.2, 10.8, 13.9 Hz), 3.22 (s, 3H), 4.07 (ddd, 1H, *J*=2.9, 9.4, 10.7 Hz), 4.51 (dd, 1H, *J*=3.6, 9.2 Hz), 4.59 (d, 1H, *J*=5.9 Hz), 4.75 (dd, 1H, *J*=3.5, 5.8 Hz), 4.85 (s, 1H), 5.04–5.07 (m, 1H), 5.20 (ddd, 1H, *J*=1.3, 3.0, 17.0 Hz), 5.74–5.84 (m, 1H), 7.37 (s, 1H), 7.39–7.44 (m, 3H), 8.25–8.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 26.1, 32.2, 54.6, 76.4, 78.4, 79.4, 85.2, 106.5, 112.5, 118.5, 128.4, 130.0, 130.5, 132.9, 134.7. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.73; H, 7.38; N, 3.82.

*5.2.7. (S,E)-N-Benzylidene-1-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-3-en-1-amine oxide (**30**).* Yield 0.779 g, 92%; colorless oil; R_f=0.2 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −29 (*c* 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 3H), 1.51 (s, 3H), 1.99–2.05 (m, 1H), 2.78 (ddd, 1H, *J*=6.9, 10.9, 13.8 Hz), 3.98 (d, 1H, *J*=3.2 Hz), 4.10 (dt, 1H, *J*=2.9, 10.8 Hz), 4.48 (d, 1H, *J*=11.5 Hz), 4.69–4.75 (m, 3H), 5.01 (d, 1H, *J*=10.2 Hz), 5.07 (dd, 1H, *J*=1.4, 17.1 Hz), 5.70 (tdd, 1H, *J*=7.0, 10.1, 17.1 Hz), 5.92 (d, 1H, *J*=3.8 Hz), 7.35–7.44 (m, 9H), 8.21–8.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.4, 26.8, 32.0, 70.0, 71.8, 75.7, 78.9, 81.5, 104.9, 112.1, 118.4, 128.3, 128.4, 128.5, 128.7, 128.9, 130.0, 130.4, 132.8, 135.0, 136.7. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 71.05; H, 7.11; N, 3.04.

*5.2.8. (S,E)-N-Benzylidene-1-((3aR,5R,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-3-en-1-amine oxide (**31**).* Yield 0.754 g, 89%; white solid; mp 128–130 °C; R_f=0.10 (Hex/EtOAc 8:2); $[\alpha]_D^{25}$ +17 (*c* 1.04, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (s, 3H), 1.52 (s, 3H), 2.47–2.54 (m, 1H), 2.81–2.90 (m, 1H), 3.67 (dd, 1H, *J*=4.4, 9.0 Hz), 3.91 (td, 1H, *J*=5.3, 10.3 Hz), 4.35 (dd, 1H, *J*=5.4, 9.0 Hz), 4.45 (t, 1H, *J*=4.0 Hz), 4.54 (d, 1H, *J*=11.7 Hz), 4.76 (d, 1H, *J*=11.6 Hz), 4.97–5.03 (m, 1H), 5.09 (dd, 1H, *J*=1.5, 17.1 Hz), 5.62–5.73 (m, 2H), 7.19–7.36 (m, 9H), 8.13–8.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.6, 26.8, 33.4, 72.1, 77.3, 77.4, 77.6, 78.9, 103.8, 113.2, 118.6, 128.0, 128.2, 128.3, 128.4, 128.7, 130.1, 130.3, 132.8, 134.6, 137.2. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.72; H, 7.06; N, 3.49.

*5.2.9. (R,Z)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-N-(((3aR,5R,5a-S,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)methylene)but-3-en-1-amine oxide (**32**).* Yield 0.667 g, 78%; sticky foam; R_f=0.43 (Hex/EtOAc 1:1); $[\alpha]_D^{25}$ −86 (*c* 1.02, CH_2Cl_2). ^1H NMR (400 MHz, CD_2Cl_2) δ (ppm) 1.22 (s, 3H), 1.25 (s, 3H), 1.27 (s, 3H), 1.32–1.33 (m, 6H), 1.48 (s, 3H), 2.01 (ddd, 1H, *J*=3.2, 7.3, 14.1 Hz), 2.59 (ddd, 1H, *J*=6.8, 10.8, 14.2 Hz), 3.62 (ddd, 1H, *J*=3.3, 8.0, 11.0 Hz), 3.70 (dd, 1H, *J*=6.8, 8.6 Hz), 4.00 (dd, 1H, *J*=6.4, 8.6 Hz), 4.26 (dd, 1H, *J*=2.0, 5.0 Hz), 4.38 (dd, 1H, *J*=6.6, 14.5 Hz), 4.51–4.56 (m, 2H), 4.89 (dd, 1H, *J*=1.4, 5.2 Hz), 4.98–5.01 (m, 1H), 5.06 (dd, 1H, *J*=1.6, 17.0 Hz), 5.43 (d, 1H, *J*=5.0 Hz), 5.68 (tdd, 1H, *J*=7.1, 10.1, 17.1 Hz), 6.64 (d, 1H, *J*=5.3 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 24.5, 25.1, 25.5, 26.2, 26.3, 26.8, 32.8, 65.3, 66.5, 70.3, 70.8, 70.9, 75.1, 77.8, 96.6, 109.3, 109.6, 110.0, 118.7, 133.0, 136.7. Anal. Calcd for $C_{21}H_{33}NO_8$: C, 59.00; H, 7.78; N, 3.28. Found: C, 59.23; H, 7.61; N, 3.36.

*5.2.10. (R,Z)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-N-(2-((3aR,5-R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethylidene)but-3-en-1-amine oxide (**33**).* Yield 0.698 g, 79%; white solid; mp 109–111 °C; R_f=0.32 (EtOAc); $[\alpha]_D^{25}$ −34 (*c* 1.04, CH_2Cl_2). ^1H NMR (400 MHz, CD_2Cl_2) δ (ppm) 1.27 (s, 6H), 1.29 (s, 3H), 1.34 (s, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 2.01–2.08 (m, 1H), 2.56–2.74 (m, 3H), 3.60–3.66 (m, 1H), 3.75 (dd, 1H, *J*=6.1, 8.8 Hz), 3.95 (ddd, 1H, *J*=1.7, 4.6, 8.9 Hz), 4.02 (dd, 1H, *J*=6.4, 8.7 Hz), 4.09 (dd, 1H, *J*=1.8, 7.9 Hz), 4.25 (dd, 1H, *J*=2.4, 5.0 Hz), 4.37 (td, 1H, *J*=6.3, 8.1 Hz), 4.77 (dd, 1H, *J*=2.4, 7.9 Hz), 5.01–5.04 (m, 1H), 5.06–5.11 (m, 1H), 5.42 (d, 1H, *J*=5.0 Hz), 5.65 (tdd, 1H, *J*=7.1, 10.1, 17.1 Hz), 6.72 (dd, 1H, *J*=5.2, 6.0 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 26.1, 26.7, 27.0, 27.7, 27.8, 28.5, 29.8, 34.1, 66.4, 68.1, 72.4, 72.9, 74.6, 76.9, 79.0, 98.4, 110.5, 111.1, 111.3, 120.1, 134.8, 138.0. Anal. Calcd for $C_{22}H_{35}NO_8$: C, 59.85; H, 7.99; N, 3.17. Found: C, 59.97; H, 8.05; N, 3.01.

*5.2.11. (R,Z)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-N-(3-((3aR,5-R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)propylidene)but-3-en-1-amine oxide (**34**).* Yield 0.738 g, 81%; white solid; mp 122–124 °C; R_f=0.3 (EtOAc); $[\alpha]_D^{25}$ −43 (*c* 0.93, CH_2Cl_2). ^1H NMR (400 MHz, CD_2Cl_2) δ (ppm) 1.23–1.24 (m, 9H), 1.30 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.69 (dd, 1H, *J*=7.5, 14.8 Hz), 1.95–2.04 (m, 1H), 2.40–2.47 (m, 2H), 2.57–2.67 (m, 1H), 3.49–3.56 (m, 1H), 3.62–3.72 (m, 2H), 3.96–4.01 (m, 2H), 4.04 (dd, 1H, *J*=1.8, 7.9 Hz), 4.20 (dd, 1H, *J*=2.3, 5.1 Hz), 4.34 (td, 1H, *J*=6.4, 7.9 Hz), 4.49 (dd, 1H, *J*=2.3, 7.9 Hz), 4.97–5.09 (m, 2H), 5.39 (d, 1H, *J*=5.1 Hz), 5.60 (tdd, 1H, *J*=7.1, 10.1, 17.1 Hz), 6.62 (t, 1H, *J*=5.8 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 23.0 ,24.1, 24.7, 25.1, 25.8, 25.9, 26.1, 26.5, 32.1, 66.2, 67.4, 70.6, 70.9, 72.5, 75.0, 77.0, 96.5, 108.3, 108.9, 109.3, 118.2, 132.9, 139.1. Anal. Calcd for $C_{23}H_{37}NO_8$: C, 60.64; H, 8.19; N, 3.07. Found: C, 60.49; H, 8.33; N, 2.91.

*5.2.12. (R,Z)-1-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-N-(3-((3aR,5R,5a-S,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)propylidene)but-3-en-1-amine oxide (**35**).* Yield 0.887 g, 76%; white solid; mp 105–107 °C; R_f=0.14 (Hex/EtOAc 6:4); $[\alpha]_D^{25}$ −57 (*c* 1.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23–1.24 (m, 15H), 1.32 (s, 3H), 1.33 (s, 3H), 1.57–1.77 (m, 2H), 2.33–2.63 (m, 4H), 3.65 (ddd, 1H, *J*=1.7, 4.9, 8.7 Hz), 3.74 (ddd, 1H, *J*=3.1, 9.5, 10.5 Hz), 3.97–4.06 (m, 4H), 4.09 (dd, 1H, *J*=1.6, 8.0 Hz), 4.20 (dd, 3H, *J*=2.3, 5.0 Hz), 4.49 (dd, 2H, *J*=2.3, 7.9 Hz), 4.96–4.99 (m, 1H), 5.04 (ddd, 1H, *J*=1.3, 3.2, 17.1 Hz), 5.39–5.41 (m, 2H), 5.63 (tdd, 1H, *J*=7.2, 10.1, 17.1 Hz), 6.71 (t, 1H, *J*=6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 23.2, 24.4, 24.5, 25.1, 25.2, 26.1, 26.2, 26.3, 26.4, 26.5, 33.4, 67.6, 68.2, 70.5, 71.0, 71.1, 71.2, 71.4, 72.9, 73.4, 96.9, 96.9, 108.7, 109.3, 118.2, 134.1, 141.2. Anal. Calcd for $C_{29}H_{45}NO_{11}$: C, 59.68; H, 7.77; N, 2.40. Found: C, 59.81; H, 7.59; N, 2.67.

*5.2.13. (R,Z)-N-(2-(Benzyloxy)ethylidene)-1-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)but-3-en-1-amine oxide (**36**).* Yield 0.689 g, 77%; colorless oil; R_f=0.3 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −46 (*c* 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (s, 3H), 1.32 (s, 3H), 1.44 (s, 3H), 1.55 (s, 3H), 2.63–2.75 (m, 2H), 3.91 (dt, 1H, *J*=4.1, 9.6 Hz), 4.17 (dd, 1H, *J*=1.4, 9.4 Hz), 4.22 (dd, 1H, *J*=1.6, 8.0 Hz), 4.29 (dd, 1H, *J*=2.3, 5.0 Hz), 4.47 (d, 1H, *J*=4.5 Hz), 4.48 (d, 1H, *J*=4.5 Hz), 4.54–4.58 (m, 3H), 5.09 (dd, 1H, *J*=1.8, 10.1 Hz), 5.17 (dd, 1H, *J*=1.7, 17.1 Hz), 5.52 (d, 1H, *J*=5.0 Hz), 5.71 (tdd, 1H, *J*=7.2, 10.1, 17.2 Hz), 6.97 (t, 1H, *J*=4.4 Hz), 7.29–7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)

24.3, 24.9, 25.9 (2C), 32.0, 60.4, 66.9, 67.2, 69.90, 70.5, 70.8, 71.0, 96.5, 108.5, 109.1, 117.6, 127.6, 128.3, 131.2, 134.1, 135.3. Anal. Calcd for $C_{24}H_{33}NO_7$: C, 64.41; H, 7.43; N, 3.13. Found: C, 64.57; H, 7.28; N, 3.38.

*5.2.14. |(S,Z)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-N-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethylidene)but-3-en-1-amine oxide (**38**).* Yield 0.645 g, 73%; sticky foam; R_f=0.32 (EtOAc); $[\alpha]_D^{25}$ −23 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_2Cl_2) δ (ppm) 1.23–1.25 (m, 9H), 1.30 (s, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 2.40–2.46 (m, 1H), 2.59–2.67 (m, 3H), 3.55 (ddd, 1H, *J*=3.3, 8.1, 11.1 Hz), 3.78 (dd, 1H, *J*=4.8, 8.9 Hz), 3.91–3.96 (m, 2H), 4.05 (dd, 1H, *J*=1.8, 7.9 Hz), 4.22 (dd, 1H, *J*=2.4, 5.0 Hz), 4.31 (ddd, 1H, *J*=5.0, 6.0, 8.1 Hz), 4.52 (dd, 1H, *J*=2.4, 7.9 Hz), 4.98 (dd, 1H, *J*=1.8, 10.2 Hz), 5.06 (dd, 1H, *J*=1.7, 17.1 Hz), 5.38 (d, 1H, *J*=5.0 Hz), 5.68 (tdd, 1H, *J*=7.1, 10.1, 17.2 Hz), 6.71 (t, 1H, *J*=5.7 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 24.1, 24.8, 25.0, 25.8, 25.8, 26.7, 27.8, 33.3, 64.4, 66.4, 70.5,71.0, 72.7, 75.9, 76.4, 96.5, 108.6, 109.2, 109.7, 117.8, 133.6, 136.7. Anal. Calcd for $C_{22}H_{35}NO_8$: C, 59.85; H, 7.99; N, 3.17. Found: C, 60.01; H, 7.73; N, 3.03.

*5.2.15. (S,Z)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-N-(3-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)propylidene)but-3-en-1-amine oxide (**39**).* Yield 0.665 g, 73%; white solid; mp 93–95 °C; R_f=0.3 (EtOAc); $[\alpha]_D^{25}$ −47 (*c* 0.95, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_2Cl_2) δ (ppm) 1.26 (s, 3H), 1.27 (s, 6H), 1.33 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.65–1.81(m, 2H), 2.41–2.50 (m, 3H), 2.63–2.71 (m, 1H), 3.53 (ddd, 1H, *J*=3.3, 8.0, 10.7 Hz), 3.66 (ddd, 1H, *J*=1.7, 4.9, 8.6 Hz), 3.80 (dd, 1H, *J*=4.9, 8.9 Hz), 3.96 (dd, 1H, *J*=6.2, 8.9 Hz), 4.06 (dd, 1H, *J*=1.8, 7.9 Hz), 4.24 (dd, 1H, *J*=2.3, 5.1 Hz), 4.34 (ddd, 1H, *J*=5.0, 6.1, 8.0 Hz), 4.53 (dd, 1H, *J*=2.3, 7.9 Hz), 5.01–5.04 (m, 1H), 5.08 (ddd, 1H, *J*=1.4, 3.3, 17.1 Hz), 5.43 (d, 1H, *J*=5.1 Hz), 5.60–5.72 (m, 1H) , 6.68 (t, 1H, *J*=5.9 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 23.4, 24.5, 25.1, 25.4, 26.2, 26.3, 26.4, 27.1, 33.7, 66.9, 67.7, 70.9, 71.3, 72.9, 76.2, 76.6, 96.9, 108.6, 109.3, 110.0, 118.4, 133.9 , 139.7. Anal. Calcd for $C_{23}H_{37}NO_8$: C, 60.64; H, 8.19; N, 3.07. Found: C, 60.48; H, 8.31; N, 3.18.

*5.2.16. (S,Z)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-N-(2-((2R,3S,4R,5S,6S)-3,4,5,6-tetrakis(benzyloxy)tetrahydro-2H-pyran-2-yl)ethylidene)but-3-en-1-amine oxide (**40**).* Yield 1.125 g, 78%; white solid; mp 81–83 °C; R_f=0.25 (Hex/EtOAc 1:1); $[\alpha]_D^{25}$ +11 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_2Cl_2) δ (ppm) 1.23 (s, 3H), 1.29 (s, 3H), 2.43 (dddd, 1H, *J*=1.8, 3.3, 6.6, 11.2 Hz), 2.59–2.71 (m, 2H), 2.84 (ddd, 1H, *J*=3.9, 5.3, 17.1 Hz), 3.17–3.24 (m, 1H), 3.34 (td, 1H, *J*=3.0, 9.5 Hz), 3.43 (ddd, 1H, *J*=3.8, 7.6, 9.6 Hz), 3.53 (d, 1H, *J*=9.6 Hz), 3.58 (d, 1H, *J*=8.8 Hz), 3.61–3.63 (m, 2H), 3.76 (dd, 1H, *J*=5.0, 8.9 Hz), 3.92 (dd, 1H, *J*=6.2, 8.9 Hz), 4.26–4.33 (m, 1H), 4.41 (d, 1H, *J*=11.9 Hz), 4.49 (d, 1H, *J*=11.9 Hz), 4.57 (d, 1H, *J*=10.7 Hz), 4.74 (dd, 1H, *J*=7.1, 10.8 Hz), 4.81 (s, 2H), 4.97–5.00 (m, 2H), 5.05 (ddd, 1H, *J*=1.3, 3.0, 17.0 Hz), 5.59–5.69 (m, 1H), 6.71 (t, 1H, *J*=5.7 Hz), 7.10–7.13 (m, 2H), 7.16–7.28 (m, 18H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 25.4, 27.1, 29.4, 33.7, 66.8, 69.6, 73.8, 75.2, 75.6, 75.8, 76.2, 76.3, 76.9, 78.7, 79.4, 82.2, 87.2, 110.1, 118.5, 127.9, 128.0, 128.1 (2C), 128.2, 128.3 (2C), 128.4 (2C), 128.7 (2C), 134.0, 136.4, 138.7, 138.8 (2C), 139.2. Anal. Calcd for $C_{44}H_{51}NO_8$: C, 73.21; H, 7.12; N, 1.94. Found: C, 73.09; H, 6.92; N, 2.15.

*5.2.17. (S,Z)-N-(2-(Benzyloxy)ethylidene)-1-((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)but-3-en-1-amine oxide (**42**).* Yield 0.564 g, 72%; white solid; mp 72–74 °C; R_f=0.19 (Hex/EtOAc 6:4); $[\alpha]_D^{25}$ −36 (*c* 1.08, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (s, 3H), 1.41 (s, 3H), 2.20–2.28 (m, 1H), 2.69 (ddd, 1H, *J*=7.5, 10.6, 14.5 Hz), 3.28 (s, 1H), 3.50–3.67 (m, 3H), 4.42 (d, 1H, *J*=4.3 Hz), 4.45 (d, 1H, *J*=4.3 Hz), 4.47–4.53 (m, 4H), 4.59 (dd, 1H, *J*=1.4, 6.0 Hz), 4.90 (s, 1H), 5.03–5.13 (m, 2H), 5.60 (tdd, 1H, *J*=7.1, 10.1, 17.1 Hz), 6.72 (t, 1H, *J*=4.4 Hz), 7.21–7.30 (m, 5H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm) 25.3, 26.5, 32.5, 56.2, 65.3, 73.5, 77.0, 81.5, 85.3, 86.1, 109.7, 113.8, 119.0, 127.7, 127.9, 128.4, 132.1, 137.2, 138.4. Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.52; H, 7.66; N, 3.41.

5.3. Intramolecular 1,3-dipolar cycloaddition. General procedure

A solution of the corresponding nitrone (1.5 mmol) in toluene (15 mL) was heated in a sealed tube at 100 °C for 72 h at which time the solvent was evaporated under reduced pressure to give the crude product, which was analyzed by ^{1}H NMR for determining the diastereoselectivity and purified by column chromatography in the stated eluent.

*5.3.1. (2S,4S,6R)-2-Phenyl-6-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**45a**).* Yield 0.413 g, 66%; white solid; mp 179–181 °C; R_f=0.69 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ −92 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) s 1.32 (s, 3H), 1.33 (s, 3H), 1.45 (s, 3H), 1.51 (s,3H), 1.80 (dd, 1H, *J*=7.8, 12.0 Hz) , 1.90–1.96 (m, 1H), 1.98–2.04 (m, 1H), 2.17 (dd, 1H, *J*=8.4, 11.6 Hz), 3.32 (ddd, 1H, *J*=4.3, 7.7, 10.4 Hz), 3.59 (dd, 1H, 0.8, 10.3 Hz), 4.02 (dd, 1H, *J*=4.7, 8.3 Hz), 4.27 (dd, 1H, *J*=2.1, 4.9 Hz) ,4.58 (dd, 1H, *J*=2.1, 8.0 Hz), 4.68 (dd, 1H, *J*=1.3, 8.1 Hz), 4.98 (t, 1H, *J*=4.8 Hz), 5.51 (d, 1H, *J*=4.9 Hz), 7.20–7.22 (m, 1H), 7.30–7.34 (m, 2H) , 7.40–7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.2, 25.0, 26.0, 26.1, 36.8, 42.3, 65.5, 69.7 (2C), 70.6, 71.1, 71.2, 79.4, 96.6, 108.6, 108.8, 126.6 (2C), 128.3, 144.2. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.68; H, 7.18; N, 3.65.

*5.3.2. (2R,4S,6R)-2-Phenyl-6-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**45b**).* Yield 0.091 g, 15%; white solid; mp 177–179 °C; R_f=0.5 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ −92 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.14 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.50 (s, 3H), 1.68 (dd, 1H, *J*=7.8, 11.8 Hz), 1.77–1.86 (m, 2H), 2.29–2.36 (m, 1H), 3.26 (ddd, 1H, *J*=4.8, 7.8, 10.1 Hz), 3.55 (dd, 1H, *J*=1.3, 10.1 Hz), 4.20 (dd, 1H, *J*=2.1, 4.9 Hz), 4.52 (dd, 1H, *J*=2.1, 8.0 Hz), 4.59 (dd, 1H, *J*=1.5, 8.0 Hz), 4.70 (dd, 1H, *J*=6.3, 10.1 Hz), 5.03 (t, 1H, *J*=5.2 Hz), 5.41 (d, 1H, *J*=4.9 Hz), 7.28–7.33 (m, 2H), 7.41–7.42 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.1, 25.0, 25.7, 26.1, 35.3, 38.8, 58.7, 70.2, 70.3 (2C), 70.5, 70.7, 71.0, 81.8, 96.3, 108.4, 127.4, 128.0, 128.9, 136.0. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.72; H, 7.43; N, 3.58.

*5.3.3. (2R,4S,6S)-2-((3aS,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**46a**).* Yield 0.302 g, 58%; white solid; mp 153–155 °C; R_f=0.63 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ +5 (*c* 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.30 (s, 3H), 1.45 (s, 3H), 1.89 (dd, 1H, *J*=7.9, 11.5 Hz), 2.00–2.05 (m, 2H), 2.20 (dd, 1H, *J*=8.4, 11.3 Hz), 3.30 (s, 3H), 3.49 (ddd, 1H, *J*=4.3, 8.0, 9.7 Hz), 3.86 (dd, 1H, *J*=3.3, 9.7 Hz), 4.05 (dd, 1H, *J*=4.5, 8.3 Hz), 4.54 (d, 1H, *J*=5.8 Hz),4.84 (s, 1H), 4.88 (dd, 1H, *J*=3.4, 5.8 Hz), 5.00 (t, 1H, *J*=4.9 Hz), 7.32–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.8, 26.2, 36.9, 42.2, 54.4, 64.8, 69.8, 79.3, 79.5, 81.9, 85.1, 107.0, 112.1, 126.6, 126.7, 128.3, 144.1. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.58; H, 7.36; N, 4.24.

*5.3.4. (2R,4S,6R)-2-((3aS,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**46b**).* Yield 0.099 g, 19%; white solid; mp 134–136 °C; R_f=0.3 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ +6 (*c* 1.00, $CHCl_3$). ^{1}H

NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.99 (s, 3H), 1.19 (s, 3H), 1.78 (dd, 1H, J=7.9, 11.7 Hz), 1.83 (dd, 1H, J=6.3, 11.7 Hz), 1.94–1.98 (m, 1H), 2.31–2.34 (m, 1H), 3.25 (s, 3H), 3.42 (ddd, 1H, J=4.6, 8.0, 9.4 Hz), 3.81 (dd, 1H, J=3.5, 9.5 Hz), 4.47 (d, 1H, J=5.9 Hz), 4.69–4.74 (m, 2H), 4.78 (dd, 1H, J=3.6, 5.9 Hz), 5.06 (t, 1H, J=5.2 Hz), 7.30–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.9, 25.6, 35.5, 38.685, 54.3, 58.2, 70.6, 79.3, 81.8, 82.5, 85.1, 106.8, 111.9, 127.6, 128.1, 129.2, 135.7. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.48; H, 7.32; N, 4.19.

*5.3.5. (2R,4S,6S)-2-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**47a**).* Yield 0.508 g, 80%; white solid; mp 151–153 °C; R_f=0.53 (CH_2Cl_2/Et_2O 97:3); $[\alpha]_D^{25}$ −32 (*c* 1.15,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 3H), 1.47 (s, 3H), 1.87 (dd, 1H, J=7.9, 11.9 Hz), 1.98–2.05 (m, 1H), 2.06–2.12 (m, 1H), 2.18 (dd, 1H, J=8.4, 11.7 Hz), 3.51 (ddd, 1H, J=4.4, 7.9, 10.1 Hz), 3.95 (dd, 1H, J=4.7, 8.3 Hz), 4.09 (dd, 1H, J=3.1, 10.1 Hz), 4.24 (d, 1H, J=3.1 Hz), 4.56 (d, 1H, J=11.9 Hz), 4.63 (d, 1H, J=3.8 Hz), 4.68 (d, 1H, J=11.9 Hz), 5.02 (t, 1H, J=4.9 Hz), 5.90 (d, 1H, J=3.8 Hz), 7.12–7.24 (m, 6H), 7.29–7.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.2, 26.7, 37.1, 42.5, 64.5, 70.1, 72.2, 79.5, 81.7, 82.8, 83.1, 104.8, 111.5, 126.6, 126.8, 127.5, 127.7, 128.3, 128.4, 137.6, 144.0. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 71.04; H, 7.18; N, 3.02.

*5.3.6. (2R,4S,6S)-2-((3aR,5R,6R,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**48a**).* Yield 0.400 g, 63%; white solid; mp 94–96 °C; R_f=0.31 (Hex/EtOAc 9:1); $[\alpha]_D^{25}$ +55 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (s, 3H), 1.51 (s, 3H), 1.62 (dd, 1H, J=8.6, 11.5 Hz), 1.93–1.99 (m, 1H), 2.01–2.06 (m, 1H), 2.09 (dd, 1H, J=8.4, 11.7 Hz), 3.19 (ddd, 1H, J=3.0, 5.2, 8.4 Hz), 3.86 (dd, 1H, J=4.6, 8.3 Hz), 3.96 (dd, 1H, J=3.0, 8.8 Hz), 4.00 (dd, 1H, J=5.1, 9.9 Hz), 4.42 (t, 1H, J=3.8 Hz), 4.55 (d, 1H, J=11.6 Hz), 4.67 (d, 1H, J=11.6 Hz), 4.87 (t, 1H, J=4.9 Hz), 5.66 (d, 1H, J=3.7 Hz), 7.11–7.16 (m, 1H), 7.18–7.25 (m, 5H), 7.29–7.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.5, 26.9, 34.9, 42.8, 67.4, 70.3, 72.3, 77.9, 78.5, 79.0, 79.5, 103.6, 112.6, 126.8 (2C), 127.7, 128.1, 128.2, 128.4, 138.1, 144.0 . Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.77; H, 6.73; N, 3.43.

*5.3.7. (2R,4S,6R)-2-((3aR,5R,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**48b**).* Yield 0.127 g, 20%; yellow oil; R_f=0.31 (Hex/EtOAc 9:1); $[\alpha]_D^{25}$ +53 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (s, 3H), 1.37 (dd, 1H, J=8.7, 11.2 Hz), 1.47 (s, 3H), 1.64 (dd, 1H, J=6.5, 11.5 Hz), 2.02 (dtd, 1H, J=2.5, 5.3, 10.9 Hz), 2.34 (dddd, 1H, J=2.6, 5.5, 10.3, 11.5 Hz), 3.31 (ddd, 1H, J=2.9, 5.8, 8.6 Hz), 3.86 (dd, 1H, J=2.9, 8.9 Hz), 3.93 (dd, 1H, J=4.3, 8.9 Hz), 4.37 (t, 1H, J=4.0 Hz), 4.51 (d, 1H, J=11.6 Hz), 4.60–4.64 (m, 2H), 4.89 (t, 1H, J=5.1 Hz), 5.66 (d, 1H, J=3.7 Hz), 7.18–7.31 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.4, 26.8, 35.7, 36.3, 59.2, 70.2, 72.3, 77.7, 78.6, 79.0, 80.8, 103.5, 112.6, 127.5 (2C), 127.8, 128.2, 128.4, 128.5, 136.5, 137.9. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.86; H, 6.88; N, 3.19.

*5.3.8. (2S,4R,6R)-2-((3aR,4R,6R,6aR)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**49a**).* Yield 0.474 g, 91%; white solid; mp 132–134 °C; R_f=0.62 (CH_2Cl_2/Et_2O 9:1); $[\alpha]_D^{25}$ −28 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.32 (s, 3H) 1.47 (s, 3H) 1.64–1.70 (m, 1H), 1.79 (dd, 1H, J=7.9, 11.6 Hz), 2.03–2.08 (m, 1H), 2.15 (dd, 1H, J=8.3, 11.7 Hz), 3.09 (ddd, 1H, J=4.7, 7.9, 11.0 Hz), 3.35 (s, 3H), 3.91 (dd, 1H, J=4.9, 8.1 Hz), 4.03 (d, 1H, J=10.6 Hz), 4.49 (d, 1H, J=5.9 Hz), 4.59 (d, 1H, J=6.0 Hz), 4.99 (t, 1H, J=4.9 Hz), 5.02 (s, 1H), 7.19–7.22 (m, 1H), 7.23–7.31 (m, 2H), 7.40–7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 25.5, 26.6, 36.0, 42.5, 54.6, 70.0, 70.4, 79.3, 81.4, 85.4, 88.8, 109.0, 112.8, 126.7, 126.8, 128.4, 143.8. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.62; H, 7.21; N, 4.10.

*5.3.9. (2S,4R,6R)-2-((3aS,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**50a**).* Yield 0.318 g, 61%; white solid; mp 125–127 °C; R_f=0.7 (CH_2Cl_2/Et_2O 9:1); $[\alpha]_D^{25}$ +72 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (s, 3H), 1.47 (s, 3H), 1.65–1.69 (m, 1H), 1.95 (dd, 1H, J=7.9, 12.0 Hz), 1.99–2.03 (m, 1H), 2.20 (dd, 1H, J=8.4, 11.6 Hz), 3.29–3.35 (m, 1H), 3.36 (s, 3H), 3.93 (dd, 1H, J=3.5, 9.4 Hz), 4.03 (dd, 1H, J=4.7, 8.3 Hz), 4.54 (d, 1H, J=5.9 Hz), 4.61 (dd, 1H, J=3.5, 5.9 Hz), 4.91–4.94 (m, 2H), 7.17–7.21(m, 1H), 7.27–7.30 (m, 2H), 7.40–7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.9, 26.1, 36.4, 42.3, 54.8, 67.7, 69.8, 78.5, 79.6, 82.0, 84.8, 107.3, 112.4, 126.6, 126.7, 128.2, 144.1. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.81; H, 7.16; N, 4.21.

*5.3.10. (2S,4R,6S)-2-((3aS,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**50b**).* Yield 0.168 g, 32%; syrup; R_f=0.3 (CH_2Cl_2/Et_2O 9:1); $[\alpha]_D^{25}$ +32 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (s, 3H), 1.19 (s, 3H), 1.58 (ddt, 1H, J=2.6, 5.0, 7.6 Hz), 1.71–1.79 (m, 2H), 2.39–2.46 (m, 1H), 3.38 (s, 3H), 3.43 (ddd, 1H, J=5.4, 8.0, 9.8 Hz), 3.86 (dd, 1H, J=3.7, 9.7 Hz), 4.49 (d, 1H, J=6.0 Hz), 4.54 (dd, 1H, J=3.7, 5.9 Hz), 4.76 (dd, 1H, J=6.3, 10.2 Hz), 4.86 (s, 1H), 4.97 (t, 1H, J=5.2 Hz), 7.23–7.27 (m, 1H), 7.32–7.36 (m, 2H), 7.41–7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 25.8, 36.4, 37.8, 54.8, 59.9, 70.1, 79.5, 80.1, 81.7, 84.9, 107.0, 112.4, 127.2, 128.3, 136.9. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.81; H, 7.40; N, 3.87.

*5.3.11. (2S,4R,6R)-2-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**51a**).* Yield 0.343 g, 54%; white solid; mp 102–104 °C; R_f=0.67 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ −16 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 3H), 1.40–1.47 (m, 1H), 1.50 (s, 3H), 1.70 (dd, 1H, J=8.0, 11.8 Hz), 1.96–2.02 (m, 1H), 2.13 (dd, 1H, J=8.4, 11.7 Hz), 3.32–3.38 (m, 1H), 3.85 (d, 1H, J=3.3 Hz), 3.97 (dd, 1H, J=4.8, 8.3 Hz), 4.18 (dd, 1H, J=3.3, 9.3 Hz), 4.42 (d, 1H, J=11.7 Hz), 4.62 (d, 1H, J=3.9 Hz), 4.69 (d, 1H, J=11.7 Hz), 4.87 (t, 1H, J=4.9 Hz), 5.99 (d, 1H, J=3.9 Hz), 7.15–7.19 (m, 1H), 7.25–7.28 (m, 3H), 7.32–7.40 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.3, 26.8, 36.0, 42.6, 67.4, 69.9, 71.6, 78.4, 81.3, 81.7, 82.4, 105.5, 111.5, 126.6 (2C), 128.0, 128.1, 128.2, 128.5, 137.2, 144.0. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.82; H, 6.85; N, 3.19.

*5.3.12. (2S,4R,6S)-2-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**51b**).* Yield 0.241 g, 38%; white solid; mp 151–153 °C; R_f=0.43 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ +10 (*c* 0.60,MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (s, 3H), 1.49 (s, 3H), 1.52 (dd, 1H, J=6.8, 10.4 Hz), 1.69 (dd, 1H, J=6.4, 11.4 Hz), 2.35–2.42 (m, 1H), 3.42 (ddd, 1H, J=5.2, 8.2, 8.9 Hz), 3.75 (d, 1H, J=3.3 Hz), 4.16 (dd, 1H, J=3.3, 9.4 Hz), 4.31 (d, 1H, J=11.9 Hz), 4.52 (d, 1H, J=3.9 Hz), 4.56 (d, 1H, J=11.9 Hz), 4.73 (dd, 1H, J=6.4, 10.3 Hz), 4.91 (t, 1H, J=5.1 Hz), 5.88 (d, 1H, J=3.8 Hz), 7.13–7.16 (m, 2H), 7.29–7.31 (m, 4H), 7.35–7.38 (m, 3H), 7.41–7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.4, 26.8, 36.1, 37.3, 59.8, 70.0, 71.3, 80.8, 81.2, 81.5, 82.5, 105.3, 111.6, 127.5, 127.6, 127.9, 128.4, 128.5, 128.7, 136.6. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.71; H, 7.11; N, 3.25.

*5.3.13. (2S,4R,6R)-2-((3aR,5R,6R,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**52a**).* Yield 0.356 g, 56%; colorless oil;

R_f=0.27 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ +66 (*c* 0.70,$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (s, 3H), 1.61 (s, 3H), 1.74 (dd, 1H, *J*=8.4, 11.6 Hz), 2.01 (dtd, 1H, *J*=2.7, 4.8, 11.9 Hz), 2.16 (dd, 1H, *J*=8.4, 11.7 Hz), 1.99–2.05(m, 1H), 3.10 (td, 1H, *J*=5.2, 8.4 Hz), 3.85 (dd, 1H, *J*=4.6, 8.3 Hz), 3.95 (s, 1H), 4.01 (dd, 1H, *J*=5.1, 8.8 Hz), 4.55 (d, 1H, *J*=11.9 Hz), 4.62 (t, 1H, *J*=4.1 Hz), 4.81 (d, 1H, *J*=11.9 Hz), 4.97 (t, 1H, *J*=4.9 Hz), 5.81 (d, 1H, *J*=3.9 Hz), 7.19–7.34 (m, 1H), 7.26–7.31 (m, 5H), 7.35–7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.7, 26.8, 35.0, 42.3, 67.5, 70.4, 72.0, 77.0, 78.7, 79.1, 79.1, 103.9, 112.6, 126.7, 126.8, 127.9, 128.0, 128.2, 128.4, 137.5, 143.9. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.77; H, 7.12; N, 3.48.

*5.3.14. (2S,4R,6S)-2-((3aR,5R,6R,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenyl-7-oxa-1-azabicyclo[2.2.1]heptane (**52b**).* Yield 0.165 g, 26%; colorless oil; R_f=0.27 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ +67 (*c* 0.95,$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (s, 3H), 1.45 (s, 3H), 1.59 (dd, 1H, *J*=8.5, 11.4 Hz), 1.70 (dd, 1H, *J*=6.6, 11.6 Hz), 2.04–2.13 (m, 1H), 2.28 (dddd, 1H, *J*=2.6, 5.5, 10.2, 11.7 Hz), 3.11 (td, 1H, *J*=5.3, 8.4 Hz), 3.63 (dd, 1H, *J*=4.5, 8.8 Hz), 3.80 (dd, 1H, *J*=4.7, 8.8 Hz), 4.19 (d, 1H, *J*=11.2 Hz), 4.37 (d, 1H, *J*=11.2 Hz), 4.42 (t, 1H, *J*=4.2 Hz), 4.63 (dd, 1H, *J*=6.7, 10.0 Hz), 4.96 (t, 1H, *J*=5.1 Hz), 5.70 (d, 1H, *J*=3.8 Hz), 7.09–7.11 (m, 2H), 7.17–7.24 (m, 4H), 7.25–7.29 (m, 2H), 7.36–7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.7, 26.8, 35.1, 37.2, 70.6, 72.0, 77.3, 77.3, 79.6, 79.8, 81.2, 104.0, 112.6, 127.8, 127.8, 128.0, 128.2, 128.6, 128.9, 136.2, 137.5. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.65; H, 7.04; N, 3.41.

*5.3.15. (2R,4R,6S)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-((3aR,5-R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**53a**).* Yield 0.231 g, 36%; ^1H NMR (400 MHz, $CDCl_3$) selected signals: δ 1.30 (s, 3H), 1.34 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.45 (s, 3H), 1.49 (s, 4H), 1.67 (dd, 1H, *J*=7.7, 11.8 Hz), 1.84–1.92 (m, 1H), 2.00–2.07 (m, 1H), 3.43–3.49 (m, 1H), 3.58 (dd, 1H, *J*=1.2, 10.1 Hz), 3.70–3.78 (m, 2H), 4.00 (dd, 1H, *J*=5.8, 7.7 Hz), 4.13–4.21 (m, 1H), 4.24 (dd, 1H, *J*=2.1, 4.9 Hz), 4.56 (dd, 1H, *J*=2.0, 8.0 Hz), 4.63 (dd, 1H, *J*=1.5, 8.0 Hz), 4.89 (t, 1H, *J*=5.2 Hz), 5.49 (d, 1H, *J*=4.9 Hz).

*5.3.16. (2R,4S,6R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)methyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**54a**).* Yield 0.589 g, 89%; white solid; mp 159–161 °C; R_f=0.21 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −3 (*c* 0.99, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32–1.34 (m, 9H), 1.37 (s, 3H), 1.45 (s, 3H), 1.47–1.55 (m, 2H), 1.57–1.60 (m, 2H), 1.62 (s, 3H), 1.69 (ddd, 1H, *J*=1.4, 11.0, 14.7 Hz), 1.77 (dd, 1H, *J*=8.0, 11.4 Hz), 3.02–3.13 (m, 2H), 3.61 (t, 1H, *J*=8.0 Hz), 3.94 (dd, 1H, *J*=6.5, 8.2 Hz), 4.13–4.20 (m, 3H), 4.28 (dd, 1H, *J*=2.3, 4.9 Hz), 4.58 (dd, 1H, *J*=2.3, 7.8 Hz), 4.78 (t, 1H, *J*=4.8 Hz), 5.51 (d, 1H, *J*=4.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.2, 25.1, 25.2, 25.9, 26.5, 26.6, 34.5, 37.9, 40.0, 63.8, 65.6, 65.8, 68.8, 70.6, 70.8, 73.4, 77.2, 78.3, 96.3, 108.5, 108.8, 109.1. Anal. Calcd for $C_{22}H_{35}NO_8$: C, 59.85; H, 7.99; N, 3.17. Found: C, 59.97; H, 8.05; N, 3.28.

*5.3.17. (2R,4S,6R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**55a**).* Yield 0.560 g, 82%; sticky foam; R_f=0.23 (Hex/EtOAc 1:1); $[\alpha]_D^{25}$ −33 (*c* 0.97, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (s, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.47 (s, 5H), 1.51–1.71 (m, 5H), 1.80–1.89 (m, 1H), 2.82 (dq, 1H, *J*=4.7, 7.5 Hz), 2.93 (dt, 1H, *J*=4.7, 7.8 Hz), 3.62 (dd, 1H, *J*=6.8, 8.4 Hz), 3.64–3.71(m, 1H), 3.94 (dd, 1H, *J*=6.6, 8.4 Hz), 4.06–4.15 (m, 2H), 4.24 (dd, 1H, *J*=2.3, 5.1 Hz), 4.54 (dd, 1H, *J*=2.3, 7.9 Hz), 4.77 (t, 1H, *J*=4.8 Hz), 5.48 (d, 1H, *J*=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.3, 24.9, 25.1, 25.9, 26.0, 26.6, 26.7, 32.3, 34.7, 39.0, 65.7, 67.2, 67.5, 69.6, 70.4, 70.8, 72.4, 77.2, 78.7, 96.4, 108.2, 108.9, 109.3. Anal. Calcd for $C_{23}H_{37}NO_8$: C, 60.64; H, 8.19; N, 3.07. Found: C, 60.78; H, 8.00; N, 2.95.

*5.3.18. (2R,4S,6R)-2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**56a**).* Yield 0.613 g, 70%; white solid; mp 73–75 °C; R_f=0.39 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −47 (*c* 0.94, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (s, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.51 (s, 3H), 1.63–1.81 (m, 8H), 2.83–2.90 (m, 1H), 3.04–3.10 (m, 1H), 3.49 (d, 1H, *J*=10.1 Hz), 3.73–3.78 (m, 1H), 4.08 (dd, 1H, *J*=1.3, 8.0 Hz), 4.24 (dd, 1H, *J*=2.0, 4.9 Hz), 4.27 (dd, 1H, *J*=2.1, 5.1 Hz), 4.54–4.59 (m, 2H), 4.62–4.65 (m, 1H), 4.82 (t, 1H, *J*=4.7 Hz), 5.47 (d, 1H, *J*=4.9 Hz), 5.52 (d, 1H, *J*=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.2, 24.3, 24.9, 25.0, 26.0, 26.0, 26.1, 26.1, 26.7, 32.0, 36.8, 39.3, 69.8, 70.5, 70.6, 71.0, 71.1 (2C), 71.2 (2C), 72.9 (2C), 79.3, 96.5 (2C), 108.2, 108.5, 108.7, 108.9. Anal. Calcd for $C_{29}H_{45}NO_{11}$: C, 59.68; H, 7.77; N, 2.40. Found: C, 59.44; H, 7.59; N, 2.62.

*5.3.19. (2S,4S,6R)-2-(Benzyloxymethyl)-6-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**57a**).* Yield 0.537 g, 80%; sticky foam; R_f=0.42 (Hex/EtOAc 8:2); $[\alpha]_D^{25}$ −60 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (s, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.51 (s, 3H), 1.51–1.59 (m, 1H), 1.69–1.75 (m, 2H), 1.88 (tdd, 1H, *J*=3.9, 7.4, 9.0 Hz), 3.17–3.27 (m, 3H), 3.55 (dd, 1H, *J*=1.3, 10.3 Hz), 3.63 (dd, 1H, *J*=7.1, 9.5 Hz), 4.28 (dd, 1H, *J*=2.2, 5.0 Hz), 4.54 (d, 1H, *J*=11.8 Hz), 4.60 (dd, 1H, *J*=2.2, 8.0 Hz), 4.68 (dd, 1H, *J*=1.6, 8.0 Hz) , 4.72 (d, 1H, *J*=11.8 Hz), 4.86 (t, 1H, *J*=4.9 Hz), 5.51 (d, 1H, *J*=4.9 Hz), 7.27–7.31 (m, 1H), 7.32–7.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.1, 24.9, 25.9, 26.0, 36.4, 36.8, 65.2, 66.8, 69.6, 70.6, 71.0, 71.1, 72.9, 73.2, 78.9, 96.5, 108.5, 108.8, 127.5, 127.7, 128.3, 136.7. Anal. Calcd for $C_{24}H_{33}NO_7$: C, 64.41; H, 7.43; N, 3.13. Found: C, 64.58; H, 7.29; N, 3.36.

*5.3.20. (2S,4S,6R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-((3aR,5-R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**58a**).* Yield 0.545 g, 85%; white solid; mp 57–59 °C; R_f=0.41 (CH_2Cl_2/Et_2O 9:1); $[\alpha]_D^{25}$ −45 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (s, 3H), 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.69–1.78 (m, 2H), 1.80–1.92 (m, 2H), 2.84–2.89 (m, 1H), 3.14 (ddd, 1H, *J*=4.3, 7.7, 10.3 Hz) , 3.47 (d, 1H, *J*=10.4 Hz), 3.88 (ddd, 1H, *J*=4.7, 6.1, 9.3 Hz), 3.97 (dd, 1H, *J*=4.7, 8.6 Hz), 4.15 (dd, 1H, *J*=6.2, 8.6 Hz), 4.25 (dd, 1H, *J*=1.5, 5.0 Hz), 4.54–4.59 (m, 2H), 4.90 (t, 1H, *J*=4.8 Hz), 5.47 (d, 1H, *J*=4.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.1, 25.0, 25.1, 26.0, 26.1, 27.1, 36.7, 37.0, 65.5, 68.6, 69.6, 69.8, 70.5, 71.0, 71.1, 78.4, 79.8, 96.5, 108.5, 108.8, 109.1. Anal. Calcd for $C_{21}H_{33}NO_8$: C, 59.00; H, 7.78; N, 3.28. Found: C, 58.86; H, 7.63; N, 3.45.

*5.3.21. (2S,4R,6S)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)methyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**59a**).* Yield 0.556 g, 84%; not absolutely pure, only NMR signals are reported. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 6H), 1.33 (s, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 1.48–1.51 (m, 4H), 1.68–1.77 (m, 3H), 2.03–2.14 (m, 1H), 2.80 (dt, 1H, *J*=4.2, 8.4 Hz), 2.98–3.10 (m, 1H), 3.78–3.89 (m, 2H), 3.93 (dd, 1H, *J*=5.1, 8.5 Hz), 4.07–4.24 (m, 3H), 4.29 (dd, 1H, *J*=2.3, 5.1 Hz), 4.58 (dd, 1H, *J*=2.3, 7.9 Hz), 4.85 (t, 1H, *J*=4.8 Hz), 5.50 (d, 1H, *J*=5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 24.9, 25.3, 26.0, 26.0, 27.1, 36.6, 36.7, 39.2, 64.0, 64.5, 68.7, 69.8, 70.5, 70.8, 72.6, 78.7, 79.5, 96.5, 108.3, 108.9, 109.1.

5.3.22. (2S,4R,6S)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)-7-oxa-1-azabicyclo[2.2.1]

*heptane (**60a**).* Yield 0.526 g, 77%; white solid; mp 68–70 °C; R_f=0.26 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −41 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 6H), 1.34 (s, 3H), 1.39 (s, 3H), 1.44–1.51 (m, 9H), 1.65–1.77 (m, 4H), 1.83–1.89 (m, 1H), 2.71–2.78 (m, 2H), 3.70 (ddd, 1H, *J*=1.5, 3.4, 9.5 Hz), 3.84–3.90 (m, 1H), 3.98 (dd, 1H, *J*=4.7, 8.6 Hz), 4.10 (dd, 1H, *J*=1.7, 7.9 Hz), 4.14 (dd, 1H, *J*=6.0, 8.6 Hz), 4.27 (dd, 1H, *J*=2.3, 5.1 Hz), 4.56 (dd, 1H, *J*=2.3, 7.9 Hz), 4.83 (t, 1H, *J*=4.8 Hz), 5.51 (d, 1H, *J*=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.3, 24.9, 25.3, 26.0, 26.0, 27.2, 28.0, 33.3, 36.7, 39.8, 67.8, 68.0, 68.7, 69.8, 70.5, 70.9, 73.0, 78.7, 79.3, 96.5, 108.3, 108.9 (2C). Anal. Calcd for $C_{23}H_{37}NO_8$: C, 60.64; H, 8.19; N, 3.07. Found: C, 60.83; H, 8.31; N, 2.94.

*5.3.23. (2S,4R,6S)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(((2R,3S,4R,5S,6S)-3,4,5,6-tetrakis(benzyloxy)tetrahydro-2H-pyran-2-yl)methyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**61a**).* Yield 0.812 g, 75%; white solid; mp 164–166 °C; R_f=0.25 (CH_2Cl_2/Et_2O 9:1); $[\alpha]_D^{25}$ −9 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (s, 3H), 1.33 (s, 3H), 1.39–1.45 (m, 1H), 1.61–1.71 (m, 3H), 1.81 (ddd, 1H, *J*=4.5, 7.0, 11.6 Hz), 1.93 (ddd, 1H, *J*=2.3, 10.5, 13.1 Hz), 2.68 (dt, 1H, *J*=4.2, 8.0 Hz), 3.08 (dq, 1H, *J*=4.2, 8.2 Hz), 3.20 (t, 1H, *J*=9.2 Hz), 3.36 (td, 1H, *J*=3.1, 9.6 Hz), 3.56–3.70 (m, 5H), 3.78–3.85 (m, 2H), 4.09–4.14 (m, 1H), 4.46–4.52 (m, 2H), 4.60 (dd, 1H, *J*=5.7, 11.7 Hz), 4.77–4.82 (m, 2H), 4.84 (s, 2H), 7.10–7.14 (m, 2H), 7.20–7.32 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.2, 27.0, 36.9, 38.5, 39.8, 63.6, 68.9, 69.0, 69.9, 73.3, 74.9, 75.0, 75.5, 77.0, 78.6, 78.6, 78.8, 79.2, 82.6, 87.1, 108.9, 127.6, 127.6, 127.7, 127.8 (2C), 127.9 (2C), 128.3 (2C), 128.4 (2C), 138.1, 138.2, 138.6 (2C). Anal. Calcd for $C_{44}H_{51}NO_8$: C, 73.21; H, 7.12; N, 1.94. Found: C, 73.01; H, 7.41; N, 2.13.

*5.3.24. (2S,4R,6R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(((2S,3R,4S,5S,6S)-3,4,5,6-tetrakis(benzyloxy)tetrahydro-2H-pyran-2-yloxy)methyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**62a**).* Yield 0.885 g, 80%; white solid; mp 120–122 °C; R_f=0.19 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ +35 (*c* 1.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (s, 3H), 1.33 (s, 3H), 1.39–1.45 (m, 1H), 1.61–1.71 (m, 3H), 1.81 (ddd, 1H, *J*=4 .5, 7.0, 11.6 Hz), 1.93 (ddd, 1H, *J*=2.3, 10.5, 13.1 Hz), 2.68 (dt, 1H, *J*=4.2, 8.0 Hz), 3.08 (dq, 1H, *J*=4.2, 8.2 Hz), 3.20 (t, 1H, *J*=9.2 Hz), 3.36 (td, 1H, *J*=3.1, 9.6 Hz), 3.56–3.70 (m, 5H), 3.78–3.85 (m, 2H), 4.09–4.14 (m, 1H), 4.46–4.52 (m, 2H), 4.60 (dd, 1H, *J*=5.7, 11.7 Hz), 4.77–4.82 (m, 2H), 4.84 (s, 2H), 7.10–7.14 (m, 2H), 7.20–7.32 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) 25.2, 27.0, 36.9, 38.5, 39.8, 63.6, 68.9, 69.0, 69.9, 73.3, 74.9, 75.0, 75.5, 77.0, 78.6 (2C), 78.8, 79.2, 82.6, 87.1, 108.9, 127.6 (2C), 127.7 (2C), 127.8 (2C), 127.9, 128.3 (2C), 128.4, 138.1, 138.2, 138.6 (2C). Anal. Calcd for $C_{44}H_{51}NO_9$: C, 71.62; H, 6.97; N, 1.90. Found: C, 71.81; H, 7.18; N, 2.11.

*5.3.25. (2R,4R,6S)-2-(Benzyloxymethyl)-6-((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**63a**).* Yield 0.487 g, 83%; white solid; mp 100–102 °C; R_f=0.33 (Hex/EtOAc 4:6); $[\alpha]_D^{25}$ +20 (*c* 0.98, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (s, 3H), 1.39 (s, 3H) ,1.47–1.55 (m, 2H), 1.58–1.64 (m, 2H), 2.83–2.89 (m, 1H), 3.00 (tt, 1H, *J*=6.2, 12.3 Hz), 3.15 (dd, 1H, *J*=6.2, 9.6 Hz), 3.29 (s, 3H), 3.58 (dd, 1H, *J*=7.6, 9.5 Hz), 3.90 (dd, 1H, *J*=1.1, 10.8 Hz), 4.36–4.41 (m, 2H), 4.50 (d, 1H, *J*=6.0 Hz), 4.56 (d, 1H, J=11.8 Hz), 4.77 (t, 1H, *J*=4.8 Hz), 4.94 (s, 1H), 7.15–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.4, 26.5, 35.8, 36.5 , 54.5, 67.0, 69.9, 73.1, 73.2, 78.8, 81.3, 85.3, 88.5, 108.9, 112.6, 127.4, 127.6, 128.2, 138.3 Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.57; H, 7.29; N, 3.73.

5.4. Cleavage of *N,O*-bond by reduction with Zn. Synthesis of compounds 64–68. General procedure

A solution of the corresponding bicycle (0.15 mmol) in a mixture of THF (1.5 mL), acetic acid (1.5 mL), and water (3 mL) is treated with Zn powder (1.3 g, 20 mmol) and the resulting mixture was stirred at 60 °C for 4 h, then filtered and the solid was washed with water. The filtrate was neutralized by addition of 5 M NaOH and then extracted with dichloromethane (3×50 mL). The combined organic extracts were washed sequentially with a saturated aqueous solution of EDTA and brine. The organic layer was separated, dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting crude product was purified by radial chromatography in the adequate eluent.

In order to obtain an acceptable reproducibility, the commercial Zn powder (5 g) was firstly stirred in HCl 0.5 N (12.5 mL) for 1 min, filtered, and washed with HCl 0.5 N, water (3×4 mL), EtOH 95% (2×8 mL), and Et_2O (8 mL). Then the metal was dried at vacuum overnight in presence of P_2O_5.

*5.4.1. (2R,4S,6S)-2-((3aS,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenylpiperidin-4-ol (**64**).* Yield 0.210 g, 60%; yellow solid; mp 62–64 °C; R_f=0.27 (CH_2Cl_2/Et_2O 3:7); $[\alpha]_D^{25}$ −7 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.28 (s, 3H), 1.38 (dd, 1H, *J*=5.5, 11.3 Hz), 1.45 (s, 3H), 1.46–1.57 (m, 1H), 2.06–2.16 (m, 3H), 2.42 (tdd, 1H, *J*=2.3, 4.5, 11.9 Hz), 3.14 (ddd, 1H, *J*=2.6, 8.8, 11.3 Hz), 3.33 (s, 3H), 3.75–3.93 (m, 3H), 4.57 (d, 1H, *J*=5.9 Hz), 4.71 (dd, 1H, *J*=3.6, 5.9 Hz), 4.90 (s, 1H) , 7.26–7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 25.2, 30.3, 39.1, 43.7, 54.6, 59.4, 69.1, 79.1, 82.9, 84.9, 106.5, 112.6, 126.8, 127.4, 128.5, 136.5. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.52; H, 7.89; N, 3.87.

*5.4.2. (2S,4R,6R)-2-((3aR,4R,6R,6aR)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenylpiperidin-4-ol (**65**).* Yield 0.252 g, 72%; white solid; mp 101–103 °C; R_f=0.43 (CH_2Cl_2/Et_2O 95:5); $[\alpha]_D^{25}$ +10 (*c* 0.6, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.24–1.36 (m, 4H), 1.43 (d, 1H, *J*=11.6 Hz), 1.49 (s, 3H), 1.80–20 (br s, 2H), 2.09 (ddt, 1H, *J*=1.9, 4.1, 11.6 Hz), 2.15 (ddt, 1H, *J*=1.9, 4.3, 11.9 Hz), 2.71 (ddd, 1H, *J*=2.2, 9.3, 11.4 Hz), 3.32 (s, 3H), 3.65 (dd, 1H, *J*=2.4, 11.4 Hz), 3.83 (ddd, 1H, *J*=4.5, 10.8, 15.5 Hz), 4.12 (dd, 1H, *J*=1.3, 9.2 Hz), 4.58 (d, 1H, *J*=6.0 Hz), 4.71 (dd, 1H, *J*=1.2, 6.0 Hz), 4.96 (s, 1H), 7.31–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 25.2, 26.6, 37.8, 44.0, 55.6, 57.7, 59.1, 69.6, 81.6, 85.4, 90.4, 109.6, 111.2 126.6, 127.3, 128.5, 143.8. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.46; H, 7.68; N, 4.12.

*5.4.3. (2S,4R,6R)-2-((3aS,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenylpiperidin-4-ol (**66**).* Yield 0.213 g, 61%; white solid; mp 87–89 °C; R_f=0.13 (CH_2Cl_2/Et_2O 3:7); $[\alpha]_D^{25}$ +7 (*c* 0.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25–1.34 (m, 3H), 1.43 (s, 3H), 1.46 (s, 3H), 1.58 (dd, 1H, *J*=2.5, 11.5 Hz), 1.90–2.13 (m, 3H), 2.17–2.22 (m, 1H), 3.11–3.18 (m, 1H), 3.26 (s, 3H), 3.73 (dd, 1H, *J*=2.0, 11.4 Hz), 3.86–3.94 (m, 2H), 4.55 (d, 1H, *J*=5.9 Hz), 4.72 (dd, 1H, *J*=3.5, 5.9 Hz), 4.84 (s, 1H), 7.25–7.28 (m, 1H), 7.31–7.35 (m, 2H), 7.39–7.45 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 24.7, 26.1, 29.7, 30.3, 25.5, 36.5, 43.2, 54.6, 54.6, 59.3, 69.3, 79.4, 82.9, 85.1, 106.9, 112.4, 125.5, 126.9, 127.4, 128.5. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.48; H, 7.63; N, 4.23.

*5.4.4. (2S,4R,6R)-2-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenylpiperidin-4-ol (**67**).* Yield 0.238 g, 56%; yellow solid; mp 128–130 °C; R_f=0.25 (CH_2Cl_2/Et_2O 3:7); $[\alpha]_D^{25}$ −8 (*c* 1.12, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (q, 1H, *J*=11.4 Hz), 1.24 (s, 3H), 1.40–1.49 (m, 4H), 1.54–1.58 (m, 2H), 1.97–2.03 (m, 2H), 3.07 (ddd, 1H, *J*=2.1, 9.2, 11.2 Hz), 3.61 (dd, 1H, *J*=2.2, 11.4 Hz), 3.63–3.72 (m, 1H), 3.86 (d, 1H, *J*=3.1 Hz), 4.01 (dd, 1H, *J*=3.1, 9.1 Hz), 4.39 (d, 1H, *J*=11.7 Hz), 4.56 (d, 1H, *J*=3.8 Hz), 4.65 (d, 1H, *J*=11.7 Hz), 5.84 (d, 1H, *J*=3.8 Hz), 7.14–7.34 (m, 10H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 26.2, 26.7, 36.4, 43.1, 54.0, 59.3, 69.3, 71.8, 81.2, 81.9, 83.3, 104.8, 111.7, 126.9, 127.3, 127.9,

128.1, 128.4, 128.6, 134.6 (2C). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.68; H, 7.52; N, 3.41.

*5.4.5. (2S,4R,6S)-2-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-6-phenylpiperidin-4-ol (**68**).* Yield 0.264 g, 62%; yellow solid; mp 60–62 °C; R_f=0.1 (CH_2Cl_2/Et_2O 3:7); $[\alpha]_D^{25}$ −18 (*c* 0.72, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (s, 3H), 1.30–1.37 (m, 1H), 1.46 (s, 3H), 1.79–1.85 (m, 2H), 2.11–2.16 (m, 2H), 3.39–3.45 (m, 2H), 3.86–3.93 (m, 2H), 4.33–4.39 (m, 2H), 4.53–4.62 (m, 3H), 5.88 (d, 1H, *J*=3.8 Hz), 7.15–7.33(m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.4, 26.9, 34.0, 39.4, 49.6, 51.3, 65.0, 71.7, 81.8, 82.3, 104.8, 111.8, 126.6, 126.9, 127.8, 128.0, 128.5, 128.6, 137.1 (2C). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.39; H, 7.49; N, 3.38.

5.5. Transformation of dioxolane ring into hydroxymethyl group. Synthesis of compounds 69–71. General procedure

A solution of the corresponding dioxolane (0.28 mmol) in 66% acetic acid (5 mL) was stirred at room temperature for 14 h and the solvent was evaporated under reduced pressure. The residue was taken-up in CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic extracts were dried over magnesium sulfate, and the solvent evaporated under reduced pressure to give the crude diol, which was used in the next step without further purification.

A suspension of silica gel (660 mg) in CH_2Cl_2 (5.5 mL) was treated with a solution of $NaIO_4$ (90 mg) in water (0.7 mL) and the resulting mixture was vigorously stirred at room temperature for 30 min at which time a solution of the diol obtained in the first step in CH_2Cl_2 (0.6 mL) was added, and the resulting mixture was stirred at room temperature for 1.5 h. After this time, the mixture was filtered through a short pad of Celite and the filtrate was evaporated under reduced pressure to give a residue, which was dissolved into 10:1 Et_2O/H_2O (0.55 mL). The resulting solution was treated with $NaBH_4$ (32 mg, 0.8 mmol) and the reaction mixture was stirred for 1 h at room temperature, at which time solid NH_4Cl (146 mg, 2.7 mmol) was added. When the gas evolution finished, the solution was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$ (25 mL) and washed with water (2×10 mL). The organic layer was dried over magnesium sulfate and evaporated under reduced pressure, to yield the crude product, which was purified by column chromatography in the stated eluent.

*5.5.1. ((2R,4S,6R)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)-7-oxa-1-azabicyclo[2.2.1]heptan-2-yl)methanol (**69**).* Yield 0.316 g, 82%; sticky foam; R_f=0.1 (Hex/EtOAc 1:1); $[\alpha]_D^{25}$ −50 (*c* 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 1.50 (s, 3H), 1.52–1.80 (m, 8H), 2.81 (ddd, 1H, *J*=4.6, 7.2, 14.2 Hz), 2.94 (ddd, 1H, *J*=4.3, 8.6, 13.1 Hz), 3.29–3.39 (m, 2H), 3.68–3.73 (m, 2H), 4.12 (dd, 1H, *J*=1.8, 7.9 Hz), 4.27 (dd, 1H, *J*=2.3, 5.1 Hz), 4.56 (dd, 1H, *J*=2.3, 7.9 Hz), 4.78 (t, 1H, *J*=4.9 Hz), 5.50 (d, 1H, *J*=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.4, 24.9, 26.0 (2C), 27.0, 32.4, 34.7, 39.5, 64.9, 66.9, 67.2, 68.7, 70.4, 70.8, 72.5, 78.7, 96.5, 108.2, 108.9. Anal. Calcd for $C_{19}H_{31}NO_7$: C, 59.20; H, 8.11; N, 3.63. Found: C, 59.39; H, 7.97; N, 3.49.

*5.5.2. ((2S,4S,6R)-6-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)-7-oxa-1-azabicyclo[2.2.1]heptan-2-yl)methanol (**70**).* Yield 0.286 g, 80%; sticky foam; R_f=0.12 (Hex/EtOAc 4:6); $[\alpha]_D^{25}$ −38 (*c* 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (s, 3H), 1.34 (s, 3H), 1.39–1.45 (s, 4H), 1.48 (s, 3H), 1.64 (dd, 1H, *J*=7.9, 11.6 Hz), 1.71 (dd, 1H, *J*=7.8, 12.1 Hz), 1.82–1.89 (m, 2H), 3.07 (ddd, 1H, *J*=4.8, 8.1, 12.8 Hz), 3.17 (ddd, 1H, *J*=4.3, 7.8, 10.2 Hz), 3.39–3.40 (m, 2H), 3.51 (d, 1H, *J*=10.2 Hz), 4.27 (dd, 1H, *J*=1.5, 5.0 Hz), 4.56–4.62 (m, 2H), 4.85 (t, 1H, *J*=4.9 Hz), 5.47 (d, 1H, *J*=5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.3, 25.0, 26.0, 26.0, 34.8, 37.0, 64.8, 65.0, 68.5, 69.7, 70.6, 70.9, 71.1, 79.1, 96.5, 108.6, 108.9. Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61; N, 3.92. Found: C, 57.28; H, 7.43; N, 4.19.

*5.5.3. ((2S,4R,6S)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)-7-oxa-1-azabicyclo[2.2.1]heptan-2-yl)methanol (**71**).* Yield 0.305 g, 79%; sticky foam; R_f=0.63 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25}$ −47 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 3H),1.34 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 1.49–1.83 (m, 8H), 2.30–2.41 (bs, 1H), 2.54 (s, 1H), 2.75–2.83 (m, 1H), 2.95 (ddd, 1H, *J*=4.4, 8.6, 12.8 Hz), 3.26–3.42 (m, 1H), 3.70 (ddd, 1H, *J*=1.6, 3.6, 9.4 Hz), 4.12 (dd, 1H, *J*=1.7, 7.9 Hz), 4.27 (dd, 1H, *J*=2.3, 5.1 Hz), 4.57 (dd, 1H, *J*=2.3, 7.9 Hz), 4.78 (t, 1H, *J*=4.9 Hz), 5.52 (d, 1H, *J*=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.3, 24.9, 26.0, 26.0, 27.9, 33.3, 34.7, 39.7, 65.0, 67.4, 67.8, 68.6, 70.5, 70.9, 73.0, 78.7, 96.5, 108.3, 109.0. Anal. Calcd for $C_{19}H_{31}NO_7$: C, 59.20; H, 8.11; N, 3.63. Found: C, 59.09; H, 8.03; N, 3.58.

5.6. Cleavage of *N,O*-bond by hydrogenation. Synthesis of compounds 72 and 73. General procedure

A solution of the corresponding alcohol (0.15 mmol) in MeOH (5 mL) was treated with a catalytic amount of Pearlamn's catalyst ($Pd(OH)_2$/C) and the resulting mixture was hydrogenated at 100 bar for 3 h. After this time, the mixture was filtered through a short pad of Celite, and the filtrate evaporated under reduced pressure, to obtain the crude product, which was purified by column chromatography in the stated eluent.

*5.6.1. (2R,4S,6R)-2-(Hydroxymethyl)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)piperidin-4-ol (**72**).* Yield 0.318 g, 82%; syrup; R_f=0.55 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25}$ −9 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD+D_2O) δ (ppm) 1.24 (s, 3H), 1.30 (s, 3H), 1.30–1.40 (m, 5H), 1.41 (s, 3H), 1.54–1.65 (m, 3H), 1.82–1.88 (m, 1H), 1.97 (ddd, 1H, *J*=1.9, 4.0, 11.0 Hz), 2.17 (ddd, 1H, *J*=2.0, 4.2, 10.9 Hz), 4.76 (br s, 3H, ex. D_2O), 3.05–3.16 (m, 2H), 3.51 (dd, 1H, *J*=6.3, 11.8 Hz), 3.64–3.71 (m, 2H), 3.74 (tt, 1H, *J*=4.4, 11.2 Hz), 4.08 (dd, 1H, *J*=1.8, 7.9 Hz), 4.25 (dd, 1H, *J*=2.4, 5.1 Hz), 4.52 (dd, 1H, *J*=2.3, 7.9 Hz), 5.40 (d, 1H, *J*=4.2 Hz). ^{13}C NMR (100 MHz, MeOD) δ (ppm) 24.6, 24.1, 26.4, 27.4, 31.1, 35.4, 38.6, 57.1, 58.7, 63.1, 66.8, 69.0, 70.9, 72.3 (2C), 74.1, 98.0, 109.8, 110.3. Anal. Calcd for $C_{19}H_{33}NO_7$: C, 58.90; H, 8.58; N, 3.61. Found: C, 59.15; H, 8.67; N, 3.46.

*5.6.2. (2S,4R)-2-(Hydroxymethyl)-6-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl)ethyl)piperidin-4-ol (**73**).* Yield 0.333 g, 86%; syrup; R_f=0.19 (Hex/EtOAc 7:3); $[\alpha]_D^{25}$ −25 (*c* 0.95, MeOH). ^{1}H NMR (400 MHz, MeOD+D_2O) δ (ppm) 1.34 (s, 6H), 1.41 (s, 3H), 1.51 (s, 3H), 1.56–1.88 (m, 6H), 2.01–2.08 (m, 1H), 2.18–2.23 (m, 1H), 3.09–3.19 (m, 2H), 3.58 (dd, 1H, *J*=6.9, 11.6 Hz), 3.73–3.78 (m, 3H), 4.18 (dd, 1H, *J*=1.7, 7.9 Hz), 4.36 (dd, 1H, *J*=2.4, 5.1 Hz), 4.63 (dd, 1H, *J*=2.3, 7.9 Hz), 4.76 (bs, 3H, ex. D_2O), 5.50 (d, 1H, *J*=5.1 Hz). ^{13}C NMR (100 MHz, MeOD) δ (ppm) 24.6, 25.1, 26.4, 26.7, 30.6, 35.1, 38.5, 56.4, 58.8, 62.8, 66.6, 68.5, 71.9, 72.3 (2C), 74.1, 98.0, 109.9, 110.4. Anal. Calcd for $C_{19}H_{33}NO_7$: C, 58.90; H, 8.58; N, 3.61. Found: C, 59.15; H, 8.41; N, 3.87.

5.7. Synthesis of unprotected glycomimetics. Synthesis of compounds (74–78). General procedure

A suspension of the corresponding bicycle (0.3 mmol) in TFA/water 9:1 (10 mL) was stirred at room temperature for 4 h. Then the solvent was evaporated, and the residue solved in MeOH (5 mL). A

catalytic amount of $Pd(OH)_2$ was added, and the mixture was hydrogenated at 100 bar for 3 h. After this time, the mixture was filtered through a short pad of Celite, and the solvent evaporated under reduced pressure, to obtain the crude product, which was purified by semipreparative HPLC (Atlantis dC18 OBD 5 μM 18×100 mm column; flow. 12.5 mL/min; H_2O), to give the pure products (mixture of anomers) as very hygroscopic foams. The detection was carried out by an UPLC-ELSD system, in the same conditions used in the purification step.

*5.7.1. (3R,4S,5R,6R)-6-(((2S,4S,6R)-6-((S)-1,2-Dihydroxyethyl)-4-hydroxypiperidin-2-yl)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (**74**).* Yield 0.063 g, 65%; white foam; $[\alpha]_D^{25}$ +26 (*c* 1, H_2O). ^1H NMR (500 MHz, D_2O) δ (ppm), mixture of anomers: 1.34–1.46 (m, 2H), 1.86–2.1 (m, 3.1H), 2.17–2.22 (m, 1H), 3.21–3.25 (m, 1H), 3.36 (dd, 0.7H, *J*=7.9, 9.9 Hz), 3.38–3.48 (m, 1H), 3.52 (dd, 0.7H, *J*=3.3, 9.9 Hz), 3.56–3.63 (m, 1H), 3.63–3.68 (m, 2.2H), 3.70–3.79 (m, 2.2H), 3.87 (ddd, 1H, *J*=4.3, 11.0, 15.5 Hz), 4.15 (dd, 0.3H, *J*=4.1, 8.1 Hz), 4.46 (d, 0.7H, *J*=7.9 Hz, β anomer), 5.13 (d, 0.3H, *J*=3.7 Hz, α anomer). ^{13}C NMR (125 MHz, D_2O), mixture of anomers: δ (ppm) 25.6, 28.7, 30.1, 36.0, 55.6, 55.7, 57.2, 57.2, 61.7, 65.3, 68.2, 69.2, 69.4, 70.0, 70.4, 70.8, 71.8, 72.9, 74.0, 92.2, 96.3. HRMS (ESI^+) *m*/*z* calcd for $C_{13}H_{25}NNaO_8$ ($M+Na^+$): 346.1467; found: 346.1475. Anal. Calcd for $C_{13}H_{25}NO_8$: C, 48.29; H, 7.79; N, 4.33. Found: C, 48.49; H, 7.93; N, 4.06.

*5.7.2. (3S,4R,5S,6S)-6-(2-((2R,4S,6R)-6-((S)-1,2-Dihydroxyethyl)-4-hydroxypiperidin-2-yl)ethyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (**75**).* Yield 0.074 g, 73%; white foam; $[\alpha]_D^{25}$ +27 (*c* 0.99, H_2O). ^1H NMR (500 MHz, D_2O), mixture of anomers: δ (ppm) 1.23–1.46 (m, 2H), 1.51–1.96 (m, 4.45H), 2.05–2.15 (m, 1H), 2.19–2.30 (m, 1H), 3.15–3.26 (m, 1.9H), 3.35 (dd, 0.75H, *J*=7.9, 9.9 Hz), 3.49–3.63 (m, 2.70H), 3.63–3.70 (m, 2.5H), 3.82–3.94 (m, 1.45H), 4.43 (d, 0.75H, *J*=7.9 Hz, β anomer), 5.13 (d, 0.25H, *J*=3.7 Hz, α anomer). ^{13}C NMR (125 MHz, D_2O), mixture of anomers: δ (ppm) 25.6, 28.7, 30.1, 36.0, 55.6, 55.7, 57.2, 57.2, 61.7, 65.3, 68.2, 69.2, 69.4, 70.0, 70.4, 70.8, 71.7, 72.9, 74.0, 92.2, 96.3. HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{27}NNaO_8$ ($M+Na^+$): 360.1580; found: 360.1585. Anal. Calcd for $C_{14}H_{27}NO_8$: C, 49.84; H, 8.07; N, 4.15. Found: C, 49.66; H, 8.25; N, 3.97.

*5.7.3. (3S,4R,5S,6S)-6-(2-((2R,4S,6R)-4-Hydroxy-6-((2R,3R,4S,5R)-3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-yl)piperidin-2-yl)ethyl) tetrahydro-2H-pyran-2,3,4,5-tetraol (**76**).* Yield 0.079 g, 62%; white foam; $[\alpha]_D^{25}$ +36 (*c* 1.05, MeOH). ^1H NMR (500 MHz, $CDCl_3$), mixture of anomers: δ (ppm) selected signals ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.44 (d, 1H, *J*=7.9 Hz, β anomer), 4.51 (d, 0.45H, *J*=7.7 Hz, β anomer), 4.53 (d, 0.37H, *J*=7.3 Hz, β anomer), 5.12 (d, 0.3H, *J*=3.8 Hz, α anomer), 5.19 (d, 0.32H, *J*=3.7 Hz, α anomer), 5.21 (d, 0.23H, *J*=2.8 Hz, α anomer), 5.21 (d, 0.3H, *J*=2.6 Hz, α anomer). ^{13}C NMR (125 MHz, $CDCl_3$), mixture of anomers: δ (ppm) 94.2 (β anomer), 94.3 (β anomer), 94.3 (β anomer), 94.4 (β anomer), 98.7 (α anomer), 98.7 (α anomer), 98.8, 98.9 (α anomer). HRMS (ESI^+) *m*/*z* calcd for $C_{17}H_{31}NNaO_{11}$ ($M+Na^+$): 448.1789; found: 448.1786. Anal. Calcd for $C_{17}H_{31}NO_{11}$: C, 47.99; H, 7.34; N, 3.29. Found: C, 48.17; H, 7.14; N, 3.41.

*5.7.4. (3R,4S,5R,6R)-6-((2R,4S,6S)-6-((S)-1,2-Dihydroxyethyl)-4-hydroxypiperidin-2-yl)tetrahydro-2H-pyran-2,3,4,5-tetraol (**77**).* Yield 0.063 g, 68%; white foam; $[\alpha]_D^{25}$ +18 (*c* 1, H_2O). ^1H NMR (500 MHz, D_2O), mixture of anomers: δ (ppm) 1.28–1.42 (m, 2H), 2.00–2.07 (m, 1H), 2.18–2.26 (m, 1H), 3.10–3.27 (m, 1H), 3.30–3.40 (m, 1H), 3.44 (dd, 1H, *J*=7.9, 10.0 Hz), 3.56 (dd, 0.6H, *J*=3.4, 10.0 Hz), 3.58–3.67 (m, 2.4H), 3.75–3.78 (m, 0.6H), 3.78–3.89 (m, 2H), 3.99–4.04 (m, 1H), 4.11–4.14 (s, 0.4H), 4.53 (d, 0.6H, *J*=7.9 Hz, β anomer), 5.22 (d, 0.4H, *J*=2.9 Hz, α anomer). ^{13}C NMR (125 MHz, D_2O), mixture of anomers: δ (ppm) 30.5, 30.6, 32.5, 32.5, 56.4, 56.5, 56.7, 61.7, 61.7, 64.8, 64.9, 67.1, 67.7, 68.4, 68.9, 69.2, 69.5, 71.1, 71.5, 72.0, 92.3, 96.4. HRMS (ESI^+) *m*/*z* calcd for $C_{12}H_{23}NNaO_8$ ($M+Na^+$): 332.1310; found: 332.1311. Anal. Calcd for $C_{12}H_{23}NO_8$: C, 46.60; H, 7.49; N, 4.53. Found: C, 46.71; H, 7.61; N, 4.38.

*5.7.5. (3R,4S,5R,6R)-6-(2-((2S,4R,6S)-6-((S)-1,2-Dihydroxyethyl)-4-hydroxypiperidin-2-yl)ethyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (**78**).* Yield 0.079 g, 78%; white foam; $[\alpha]_D^{25}$ +27 (*c* 0.99, H_2O). ^1H NMR (500 MHz, D_2O), mixture of anomers: δ (ppm) 1.27–1.39 (m, 1H), 1.43–1.61 (m, 3.6H), 1.64–1.82 (m, 3.5H), 2.01–2.07 (m, 1H), 2.18–2.28 (m, 1H), 3.16–3.27 (m, 1H), 3.28–3.38 (m, 1.7H), 3.49–3.58 (m, 3.7H), 3.65–3.93 (m, 1.7H), 3.82–3.93 (m, 2.5H), 4.44 (d, 0.7H, *J*=7.9 Hz, β anomer), 5.12 (d, 0.30H, *J*=3.8 Hz, α anomer). ^{13}C NMR (125 MHz, D_2O), mixture of anomers: δ (ppm) 25.6, 28.7, 30.1, 36.0, 55.6, 55.7, 57.2, 57.2, 61.7, 65.3, 68.2, 69.2, 69.4, 70.0, 70.4, 70.8, 71.7, 72.9, 74.0, 92.2, 96.3. HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{28}NO_8$ ($M+H^+$): 338.1809; found: 338.1824. Anal. Calcd for $C_{14}H_{27}NO_8$: C, 49.84; H, 8.07; N, 4.15. Found: C, 50.03; H, 8.16; N, 4.34.

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Supplementary data

ORTEP diagrams corresponding to X-ray analyses of compounds **34**, **45b**, **46a**, **46b**, **48a**, **49a**, **51b**, **61a**, **66**. ^1H and ^{13}C-APT NMR spectra of compounds **24**–**36**, **38**–**42**, **45**–**78**. HRMS mass spectra of compounds **74**–**78**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.05.126. These data include MOL files and InChiKeys of the most important compounds described in this article.

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23. The authors have deposited the atomic coordinates for the structures with the Cambridge Crystallographic Data Centre. Deposition numbers are as follows: **34**, CCDC 876853; **45b**, CCDC 749563; **46a**, CCDC 749564; **46b**, CCDC 749565; **48a** CCDC 876854; **49a**, CCDC 749567;**51b**, CCDC 876855; **61a**, CCDC 876856 and **66**, CCDC 749568. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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