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Stereocontrolled synthesis of iminocyclitols with an ether bridge

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Abstract—Nor-tropane related bicyclic (6+5) iminocyclitols with an ether bridge and different substituents (hydroxymethyl, aminomethyl, and aminoethyl) on C-1 are prepared starting from a β-D-psicofuranosyl cyanide. The method involves an internal nucleophilic attack of a stabilized amide ion on a 5-mesyloxy derivative. The intermediate *N*-acetyl *O*-protected iminocyclitols present atropoisomerism due to restricted rotation of the N–CO amido bond. Conformational aspects of the prepared compounds are discussed.

1. Introduction

The iminocyclitols are a type of sugar analog in which the endocyclic oxygen atom has been substituted by a nitrogen atom. These compounds have biological and pharmaceutical importance as they are inhibitors of glycosidases and glycosyltransferases,[1] and consequently, they can be useful in the treatment of metabolic disorders and inflammatory processes.[1–5] The first iminocyclitols were discovered as natural products, although they were difficult to isolate, at least in multigram scale. In the last 15 years, much effort has been directed to the synthesis of five-, six-, and seven-membered monocyclic and bicyclic polyhydroxyalkyl iminocyclitols,[6,7] in many cases sugar derivatives being the starting materials for these syntheses. However, much less effort has been put into the synthesis of bicyclic iminocyclitols with an ether bridge (**1**) (Fig. 1), in spite of the restricted conformational properties of these compounds, which can be interesting for possible biological studies. A dihydroxy-3,6-anhydro iminoheptitol was prepared by Kilonda[8] starting from 1-amino-1-deoxy-D-glucitol; the same compound was later obtained starting from a dibenzyloxy-dihydroxy-perhydroazepane.[9] At the same time, the iminocyclitols **1** are structurally related with bicyclic alkaloids with nor-tropane skeleton (**2**), which have biological activity as competitive inhibitors of glycosidases.[10,11] Related bicyclic alkaloids having hydroxy(alkoxy)methyl groups instead of hydroxy groups have also been described.[12] Recently, we have described[13] the preparation of azasugar thioglycosides, using a cyclization reaction through an amide ion.

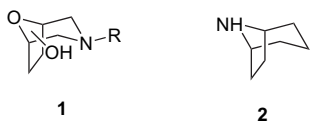

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Figure 1.

Now, we report the synthesis of the iminocyclitols with an ether bridge **9**, **13**, and **16** starting from the glycofuranosyl cyanide **3**.[14] Compounds **13** and **16** are homoaminoazasugars,[15] and can be useful for preparing azasugar-isothiocyanates, homonucleosides, and related compounds.[16]

2. Results and discussion

The 6-*O*-benzyl-2-cyanopsicofuranose derivative **3**,[14] which is easily prepared from 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose, was reduced with lithium aluminum hydride to obtain (Scheme 1) the amino derivative **4**, which was in situ acetylated to give **5** in 87% yield from **3**. The position 6 of **5** was debenzylated by hydrogenation (Pd–C) to get **6**, in which was introduced a good leaving group by treatment with mesyl chloride (→**7**).

Tables 1 and 2 show selected ^{1}H and ^{13}C NMR data of prepared compounds, respectively. The spectra of **5** showed signals for two acetyl groups (see also Section 3) and its ^{13}C NMR spectrum had no signal for a C≡N group. The resonance of C-6 in **6** showed a shielding of 7.5 ppm with respect to the same signal in **5**, indicative of the deprotection of the corresponding hydroxyl group. The presence of the mesyl group in **7** was evident from the signals at 3.09 (^{1}H) and

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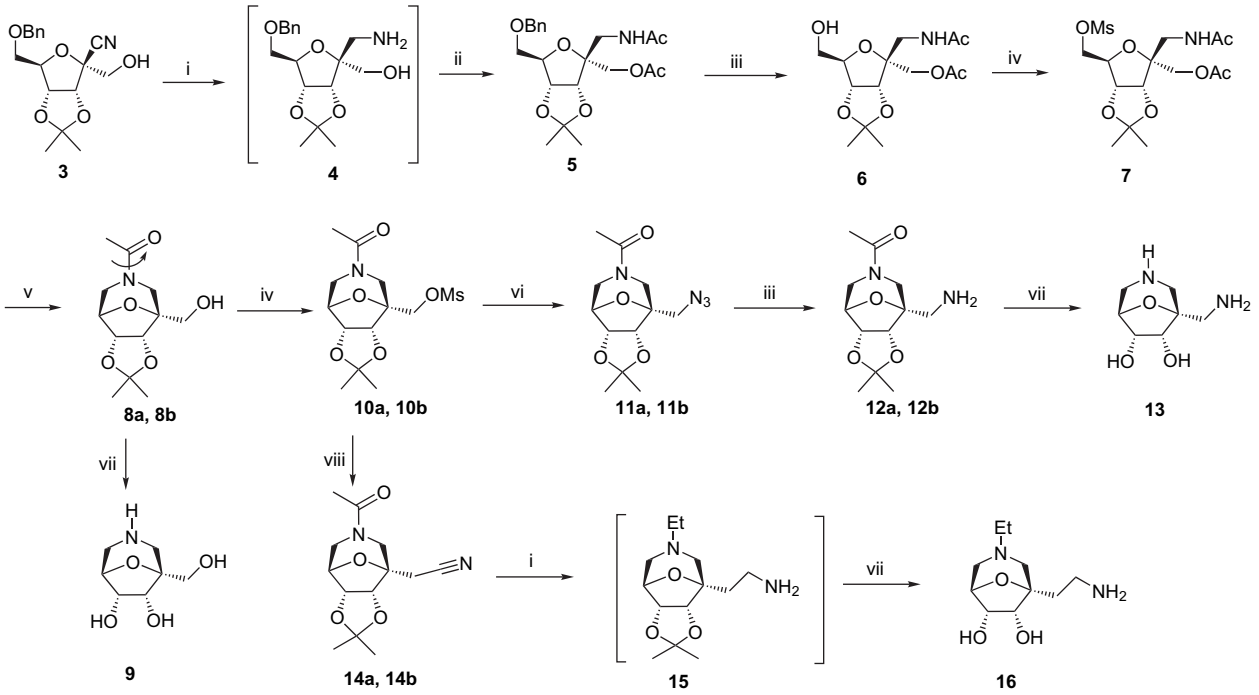


Scheme 1. Compounds showing atropoisomerism are indicated as **na** and **nb**. The major (*Z*, **na**) compound is showed. Reagents and conditions: (i) $LiAlH_4$, Et_2O; (ii) Ac_2O/Py; (iii) H_2, Pd–C, AcOEt; (iv) ClMs/Py, rt; (v) NaH, DMF; (vi) NaN_3, DMF; (vii) MeOH, HCl; (viii) KCN, DMF.

38.1 (^{13}C) ppm and from the deshielding of the signals for H6a and H6b (0.27–0.33 ppm) and C-6 (6.3 ppm).

Treatment of the mesyloxy derivative **7** with sodium hydride in DMF produced the tricyclic compound **8**. The reaction involves O-deacylation and cyclization by intramolecular nucleophilic attack of a stabilized amide ion[13,17] (**17**, Scheme 2) on C-6. Reaction of **8** with HCl in methanol yielded the *N*- and *O*-unprotected target compound **9**. The NMR spectra (^{1}H and ^{13}C) of compound **8** showed two series of signals corresponding to two atropoisomers, **8a** and **8b**, by restricted rotation of the N–CO bond (see below). The 2D NOESY spectrum showed EXSY[18] peaks relating signals of the two different spin systems. No significant changes

Table 1. Selected ^{1}H NMR data (δ ppm, J Hz) for compounds **5**–**16** at 500 MHz in $CDCl_3$

	H1a	H1b	H3	H4	H5	H6a	H6b	CH_2NH		$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$
5	4.26	4.23	4.52	4.79	4.09	3.82	3.67	3.83, 3.17		6.0	6.0	0	2.5
6	4.39	4.17	4.66	4.97	4.11	3.79	3.64	3.81, 2.98		6.0	4.5	0	—
7	4.33	4.18	4.63	4.66	4.16	4.52	4.31	3.62, 3.36		6.5	5.0	2.5	3.5
	CH_2OH		H7	H6	H5	H4a	H4b	H2a	H2b	$J_{6,7}$	$J_{5,6}$	$J_{4a,5}$	$J_{4b,5}$
8a	3.60, 3.42		4.23	4.64	4.11	3.63	3.12	4.21	2.60	5.9	0	≈0[a]	2.5
8b	3.60, 3.45		4.50	4.38	4.15	4.03	2.62	3.68	3.16	5.9	0	≈0[a]	2.5
9	3.71, 3.60		4.30	4.25	4.02	2.84	2.73	2.87	2.83	6.5	0	2.5	1.4
	CH_2OMs		H7	H6	H5	H4a	H4b	H2a	H2b	$J_{6,7}$	$J_{5,6}$	$J_{4a,5}$	$J_{4b,5}$
10a	4.42, 4.23		4.32	4.73	4.24	3.67	3.16	4.20	2.71	5.8	0	≈0[a]	2.4
10b	4.42, 4.23		4.61	4.45	4.27	4.06	2.65	3.75	3.26	5.8	0	≈0[a]	2.4
	CH_2N_3		H7	H6	H5	H4a	H4b	H2a	H2b	$J_{6,7}$	$J_{5,6}$	$J_{4a,5}$	$J_{4b,5}$
11a	3.53		4.25	4.70	4.20	3.66	3.14	4.14	2.66	5.9	0	≈0[a]	2.5
11b	3.53		4.53	4.43	4.24	4.04	2.64	3.68	3.20	5.9	0	≈0[a]	2.5
	CH_2NH_2		H7	H6	H5	H4a	H4b	H2a	H2b	$J_{6,7}$	$J_{5,6}$	$J_{4a,5}$	$J_{4b,5}$
12a	2.80, 2.66		4.24	4.64	4.12	3.63	3.11	4.28	2.54	5.9	0	≈0[b]	2.5
12b	2.80, 2.66		4.50	4.38	4.15	4.03	2.61	3.79	3.07	5.9	0	≈0[b]	2.5
13	2.90, 2.84		4.28	4.26	4.03	2.81	2.70	2.76	2.64	6.5	0	2.5	≈0[b]
	CH_2CN		H7	H6	H5	H4a	H4b	H2a	H2b	$J_{6,7}$	$J_{5,6}$	$J_{4a,5}$	$J_{4b,5}$
14a	2.87, 2.71		4.43	4.60	4.34	3.57	3.39	4.48	2.94	5.5	0	≈0[b]	2.3
14b	2.81		4.44	4.61	4.36	4.33	2.87	3.75	3.40	5.5	0	≈0[b]	—
	$CH_2CH_2NH_2$		H7	H6	H5	H4a	H4b	H2a	H2b	$J_{6,7}$	$J_{5,6}$	$J_{4a,5}$	$J_{4b,5}$
16	3.18, 2.18, 1.86		4.18	4.26	4.12	2.76	2.11	2.73	2.01	6.3	0	≈0[b]	2.0

[a] The 2D COSY long range showed a correlation between H4a and H5, but this small coupling was not resolved in the ^{1}H NMR spectrum, precluding the determination of the value of $J_{4a,5}$.

[b] The lineshape of both, H-4a (H4b for **13**) and H-5, suggest the existence of a small coupling (<1 Hz) between these protons.

Table 2. Selected ^{13}C NMR data (125 MHz) for **5–14**, **16**

	C1	C2	C3	C4	C5	C6	CH_2NH
5	64.2	84.9	83.6	80.8	83.7	69.8	43.7
6	63.0	85.1	84.0	81.6	86.1	62.3	43.1
7	63.0	85.3	83.0	80.6	81.1	68.6	42.5
	CH_2OH	C1	C7	C6	C5	C4	C2
8a	60.5	83.3	81.8	82.5	77.7	47.1	45.5
8b	60.5	82.8	82.6	81.8	77.9	42.7	49.9
9	63.8	85.6	75.3	75.1	84.2	48.0	51.0
	CH_2OMs	C1	C7	C6	C5	C4	C2
10a	69.1	81.0	81.9	82.5	78.5	46.7	44.4
10b	69.3	80.6	82.0	82.6	78.8	42.2	48.7
	CH_2N_3	C1	C7	C6	C5	C4	C2
11a	51.4	82.4	81.9	82.6	78.2	46.7	45.1
11b	51.5	82.0	81.9	82.8	78.5	42.3	49.5
	CH_2NH_2	C1	C7	C6	C5	C4	C2
12a	42.7	83.2	81.9	82.6	77.9	47.1	45.9
12b	42.7	83.7	81.9	82.7	77.9	42.8	50.5
13	44.3	84.3	76.1	75.6	84.3	48.1	52.5
	CH_2CN	C1	C7	C6	C5	C4	C2
14a	21.3	80.8	82.4	83.5	79.1	47.4	46.9
14b	21.0	80.2	82.3	83.4	79.9	42.7	51.7
	$CH_2CH_2NH_2$	C1	C7	C6	C5	C4	C2
16	30.8, 37.0	84.6	76.0	75.7	83.7	55.5	61.7

were observed by comparison of the corresponding $^3J_{H,H}$ values (see Table 1 and Section 3) of **8a** and **8b**, which is indicative of no conformational changes in the tricyclic system. The ^1H and ^{13}C NMR spectra of *N*-acetyl derivatives **10–12** and **14** (see below) also show two series of signals, and their NOESY spectra also have EXSY peaks. However, the same spectra of the amino compounds **9**, **13**, and **16** have only one signal series and no EXSY peaks were observed; consequently the atropoisomerism is due to restricted rotation of the N–CO amido bond.

In order to characterize the interconversion of the atropoisomers of **8**, a variable-temperature ^1H NMR study was performed. Ten experiments were carried out in DMSO-d_6 at different temperatures from 303 to 393 K. These spectra showed broadening of the signals with increasing temperature, and coalescence at different temperatures for different kinds of protons. At the highest temperature employed, some signals were still very broad, which suggests a high-energy barrier between the two atropoisomers. This observation is also supported by NOESY experiments carried out in $CDCl_3$ at 253 K. Under these conditions, no interchange (EXSY) peaks were observed, and δ and J values of the two series of signals were similar to those measured in the spectrum obtained at 303 K, indicating no conformational changes on decreasing the temperature. The energy barrier for the internal rotation was measured at the coalescence of H-5 (Fig. 2, T_c=333 K). Despite the small rotamer population difference (Δp=0.06), the data were treated as an exchange between two unequally populated sites.[19] The chemical shift separation at 303 K for this proton between the two rotamers is 17.7 Hz. From these data, the rate constants for the conversions **8a**→**8b** and **8b**→**8a** were calculated as 33.3 s^{-1} and 37.5 s^{-1}, respectively, and the substitution of these values into the Eyring equation[19] gave the values 17.3 and 17.2 kCal/mol for $\Delta G_a^{\neq}$ (**8a**→**8b**) and $\Delta G_b^{\neq}$ (**8b**→**8a**), respectively.

Treatment of **8** with mesyl chloride in pyridine gave the mesyl derivative **10a** (**10b**), which by reaction with sodium azide in DMF yielded **11a** (**11b**). Catalytic hydrogenation of **11** produced **12a** (**12b**), which by simultaneous deacetylation and deacetalation with HCl in methanol was transformed into the target methyl aminoazasugar **13**. The signals at 3.09 (3.07) (^1H) and 36.6 (36.7) ppm (^{13}C) in the NMR spectra of **10a** (and its rotamer **10b**), together with the deshielding in the resonances of the CH_2OMs group supported the presence of the mesyl group. The azido group of **11a** (**11b**) was evident from the IR absorption at 2105 cm^{-1}, which was not present in the IR spectrum of

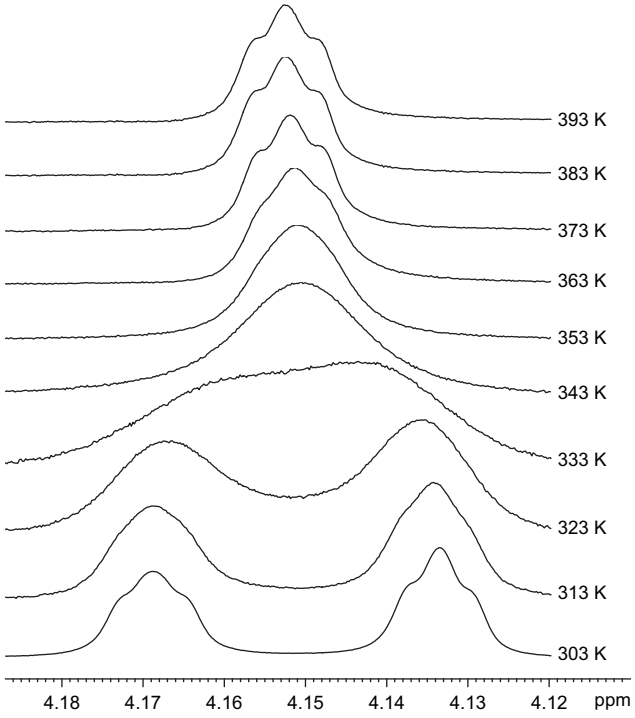
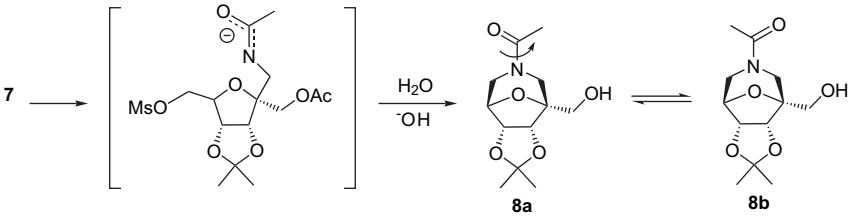


Figure 2. ^1H NMR peaks corresponding to H-5 in the two rotamers of **8** in DMSO-d_6 at various temperatures.



Scheme 2. Mechanism of the cyclization step.

12a (**12b**). The NMR spectra of **13** showed signals for only one spin system.

The reaction of the mesyl derivative **10** with potassium cyanide afforded in high yield the azasugar acetonitrile **14a** (**14b**), which was treated with lithium aluminum hydride to give **15**. During this reaction, the cyano and acetyl groups were simultaneously reduced. Compound **15** was directly *O*-deprotected to produce the azasugar ethylamino derivative **16** in 92% yield. The presence of C≡N group of **14a** (**14b**) was evident from the signals at 2300 cm^{-1} (IR spectrum) and 116.0 ppm (^{13}C NMR spectrum). The ^{13}C NMR spectrum of compound **16** had no signals for an isopropylidene group, the resonances for the *N*-ethyl group appeared at 52.8 (CH_2) and 12.0 (CH_3) ppm, and the signals for the amino-ethyl group were at 37.0 and 30.8 ppm.

The NOESY experiments were conclusive for the *Z*, *E* assignment of the *N*-acetyl derivatives **8a/8b**, **10a/10b**, **11a/11b**, **12a/12b**, and **14a/14b** (**a** is the major isomer and **b** the minor). In all cases, the observed NOEs for the methyl group of the *N*-Ac moiety were key for this determination. Thus, the observation of NOE interactions for this methyl group with protons H4a and H6, for the major atropoisomer (compounds **a**), and with protons H2a and H7 for the minor (compounds **b**), clearly indicates a *Z* and *E* configuration for the major and minor, respectively. Furthermore, these NOEs, together with those observed for H6 and H7, allowed the stereospecific assignment of the prochiral protons H4a/H4b and H2a/H2b. For these diastereotopic methylene protons, the most-deshielded signals in the ^1H NMR spectra, that is, H2a and H4a, correspond to the protons located in the concavity (*endo* protons) of the nor-tropane related part of the structure (H2a is the pro-*S* proton at C2 and H4a is the pro-*R* at C4). As an exception, only for **8a/8b** in $CDCl_3$ was the *E* isomer observed as the major product, at 303 K as well as at 253 K. This assignment is coherent with the observed chemical shifts in the ^1H and ^{13}C NMR spectra of these compounds, specially for the methylene groups located at the vicinal positions of the *N*-Ac (positions 2 and 4), from which we can deduce the opposite effect that the anisotropy of the carbonyl group exerts in these positions in both atropoisomers. Comparing the *Z* and *E* isomer, a shielding effect was constantly observed at C4 (approx. 4.5 ppm) in all cases, and a corresponding opposite effect at C2 (deshielding of approx. 4.5 ppm). Similarly, H4a for the *Z* isomer and H2a for the *E* isomer, were the protons most affected by the deshielding effect of the carbonyl, in agreement with a closer proximity of the carbonyl to these protons.

These products have semirigid structures, whose most probable conformations are $^8C_3$ and $B^{8,3}$ (Scheme 3). There are various NMR data that allow us to distinguish between both conformations. For an $^8C_3$ conformation, a long-range coupling through a W pathway between H2a and H4a would be expected, as well as a 1,3-diaxial NOE between H2b and H4b, whereas for a $B^{8,3}$ conformation, the small coupling would be between H2b and H4b and the NOE would relate H2a and H4a. Despite all ^1H NMR spectra showing broadened signals for H2a and H4a, attributable to a hidden small coupling constant, in no case was the resolution enough to determine the value of this coupling constant. For compounds **8a/8b**, **10a/10b**, and **11a/11b**, the 2D COSY long-

Scheme 3. Conformations of the oxazine ring of compounds **8**, **10**–**12**, and **14**.

range experiments confirmed the expected coupling by the observation of a cross peak between H2a and H4a. These data clearly indicate an $^8C_3$ conformation. Unfortunately, the crucial 1,3-diaxial NOEs could not be detected in the NOESY spectra due to the proximity of these expected correlations to the more intense EXSY peaks. Only in the case of **8a/8b**, which was also studied in chloroform at low temperature (253 K), did the absence of exchange peaks in these conditions permit the observation of the NOE between H2b and H4b, confirming the $^8C_3$ conformation. Since the ^1H and ^{13}C NMR spectra of **8a/8b** indicate that there is no conformational change either by changing the solvent from DMSO-d_6 to $CDCl_3$, or by lowering the temperature from 303 K to 253 K in the latter solvent, we could expect the same $^8C_3$ conformation in all cases. Additionally, the aforementioned closer proximity of the carbonyl group to H2a and H4a for the *E* and the *Z* isomer, respectively, together with the observed NOEs between the methyl group of the *N*-Ac and H6 for the *Z* isomer and H7 for the *E* isomer, can be considered as an exclusive features of the $^8C_3$ conformation, since for the $B^{8,3}$ conformation the *N*-Ac group should be located far away from H6 and H7. The coupling pattern observed for H5 and the vicinal protons H4a and H4b is also in agreement with this conformation, since for the $B^{8,3}$ conformation we would expect a higher value for the $J_{4a,5}$ rather than lower and similar values observed for $J_{4a,5}$ and $J_{4b,5}$. Figure 3 shows the energy-minimized structure[20] of the major rotamer **8a**.

For the bicyclic compounds **9**, **13**, and **16** the NMR data were also in agreement with the $^8C_3$ conformation. In the case of the fully deprotected compounds **9** and **13**, the most noticeable difference in comparison with the other bi- or tricyclic compounds was the change in the order of appearance in the

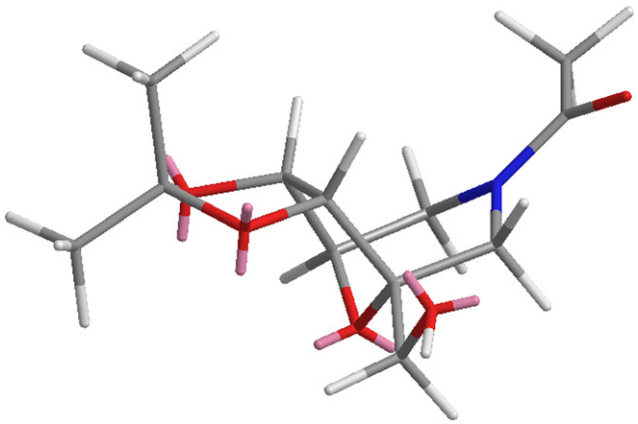


Figure 3. Main conformation (oxazine ring and amido bond) of rotamer **8a**.

^{1}H NMR spectra of the signals corresponding to the methylenes 2 and 4. Thus, in both compounds the pro-*R* proton at C4 is H-4b, instead of H-4a, and for **9** the pro-*S* proton at C-2 is H-2b, instead of H-2a. For all these bicyclic structures, and likewise the other studied compounds, the signals corresponding to the long-range coupled protons characteristic of the $^8C_3$ conformation (H2b/H4b for **9**, H2a/H4b for **13**, and H2a/H4a for **16**) presented a broadened lineshape, indicative of the presence of this small coupling. For compound **13**, a further confirmation was provided by the 2D NOESY spectrum, which showed a small correlation between H2b and H4a, the 1,3-diaxial interaction characteristic of the proposed conformation.

In conclusion, the glycosyl cyanide **3** is a suitable starting material to prepare conformationally restricted iminocyclitols with an ether bridge, with nor-tropane related structure, and different functionalizations on C-1. The key step is a cyclization reaction using a stabilized amide ion. All the reactions are highly stereoselective. The $^8C_3$ is the main conformation for prepared compounds in DMSO-d_6 and/or $CDCl_3$.

3. Experimental

3.1. General methods

Melting points were determined with a Gallenkamp apparatus and are uncorrected. A Perkin–Elmer Model 141 MC polarimeter, 1-cm tubes, and solutions in CH_2Cl_2, at 589 nm, were used for measurement of specific rotations. IR spectra were recorded for KBr discs on a Bomen–Michelson MB-120 FTIR spectrophotometer. Mass spectra (EI, CI, and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 keV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt. TLC was performed on Silica Gel HF_{254}, with detection by UV light or charring with H_2SO_4. Silica Gel 60 (Merck, 70–230 and 230–400 mesh) was used for preparative chromatography.

NMR experiments were recorded on a Bruker Avance 500 spectrometer (500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C) equipped with a 5 mm inverse detection probe. All experiments were performed at 303 K, except for the variable-temperature ^{1}H NMR study of **8**. The samples were thermically equilibrated at the corresponding temperature before measurement. The probe temperature was calibrated with a standard sample of 80% ethyleneglycol in DMSO-d_6. Sample concentrations were typically in the range 10–15 mg per 0.6 mL of the deuterated solvent. Chemical shifts are given in parts per million, using the residual protonated solvent signal as reference. ^{1}H and ^{13}C assignments were confirmed by 2D conventional COSY and HSQC experiments. 2D NOESY experiments were carried out by using conventional pulse sequence with a mixing time of 400 ms, a recycle delay of 2 s, and 2048 transients per spectrum in all cases.

3.1.1. 1-Acetyl-2-acetylaminomethyl-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranose (5). Lithium aluminum hydride (159 mg) was added at 0 °C to a solution of **2** (257 mg, 0.805 mmol) in super-dry diethyl ether (8.7 mL). The resulting suspension was stirred at room temperature for 3 h and afterward 414 μL of a 1 M solution of K_2CO_3 was carefully added. The reaction mixture was filtered through Celite, dried ($MgSO_4$), and evaporated to dryness. The obtained residue was dissolved in dry pyridine (3.3 mL) and cooled to 0 °C. Acetic anhydride (1.7 mL) was added and the mixture was kept stirred at 0 °C for 3 h. The solution was poured into ice water and extracted with CH_2Cl_2, the organic layer was separated, washed with 2 N H_2SO_4, saturated aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by column chromatography using ether/hexane 4:1 and ether as eluents to give a syrup. Yield 87%; $[\alpha]_D^{25}$ +33 (*c* 0.9, CH_2Cl_2); CIMS *m/z* 408 [(M+H)$^+$]; IR 3311, 3097, 2964, 2874, 1746, 1651, 1547, 1460, 1397, 1262, 1087, 880, 809 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.38 (m, 5H, Ph), 6.51 (m, 1H, N*H*Ac), 4.79 (t, 1H, $J_{3,4}$=$J_{3,4}$=6.0, H-4), 6.91 (d, 1H, J_{gem}=11.0, *H*CHPh), 4.52 (m, 2H, H-3, HC*H*Ph), 4.26, 4.23 (each d, each 1H, J_{gem}=12.0, H-1a, H-1b), 4.09 (m, 1H, H-5), 3.83 (dd, 1H, J_{gem}=14.0, J_{NH,CH_2}=9.0, *H*CHNH), 3.82 (d, 1H, $J_{6a,6b}$=11.0, H-6a), 3.67 (dd, 1H, $J_{5,6b}$=2.5, H-6b), 3.17 (dd, 1H, J_{NH,CH_2}=3.0, HC*H*NH), 2.09, 1.52 (each s, each 3H, CH_3CO), 1.50, 1.30 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.9, 170.8 (2CO), 137.7–127.9 (Ar), 114.1 ((CH$_3$)$_2$*C*), 84.9 (C-2), 83.7 (C-5), 83.6 (C-3), 80.8 (C-4), 74.2 (*C*H$_2$Ph), 69.8 (C-6), 64.2 (C-1), 43.7 (*C*H$_2$NH), 27.2, 25.4 (2(*C*H$_3$)$_2$C), 22.5, 21.0 (2*C*H$_3$CO); HRCIMS *m/z* obsd 408.2010 calcd for $C_{21}H_{30}NO_7$ 408.2022.

3.1.2. 1-Acetyl-2-acetylaminomethyl-2-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranose (6). To a stirred solution of **5** (241 mg, 0.592 mmol) in ethyl acetate (40 mL), 10% Pd–C (40 mg) was added. The obtained solution was kept at room temperature and stirred under hydrogen atmosphere for 2.5 h. The mixture was filtered through Celite and evaporated to dryness. The resulting crude was purified by column chromatography on silica gel using dichloromethane/methanol 25:1 as eluent to give an amorphous solid. Yield 96%; $[\alpha]_D^{24}$ +18 (*c* 1.4, CH_2Cl_2); FABMS *m/z* 340 [(M+Na)$^+$]; IR 3451, 3285, 3090, 2986, 2938, 2901, 1740, 1651, 1572, 1443, 1377, 1292, 1211, 1072, 974, 864, 783 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, 1H, J_{NH,CH_2}=5.0, N*H*Ac), 4.97 (dd, 1H, $J_{3,4}$=6.0, $J_{4,5}$=4.5, H-4), 4.46 (d, 1H, H-3), 4.39 (d, 1H, $J_{1a,1b}$=11.0, H-1a), 4.23 (m, 1H, OH), 4.17 (d, 1H, H-1b), 4.11 (m, 1H, H-5), 3.81 (d, 1H, J_{gem}=14.0, *H*CHNH), 3.79 (d, 1H, $J_{6a,6b}$=14.5, H-6a), 3.64 (m, 1H, H-6b), 2.98 (dd, 1H, HC*H*NH), 2.12, 2.02 (each s, each 3H, CH_3CO), 1.53, 1.34 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.7, 171.6 (2CO), 113.9 ((CH$_3$)$_2$*C*), 86.1 (C-5), 85.1 (C-2), 84.0 (C-3), 81.6 (C-4), 63.0 (C-1), 62.3 (C-6), 43.1 (*C*H$_2$NH), 26.9, 25.2 (2(*C*H$_3$)$_2$C), 23.5, 21.2 (2*C*H$_3$CO); Anal. Calcd for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.87; H, 7.08; N, 4.34.

3.2. General procedure for the synthesis of compounds 7 and 10

Compound **6** or **8** (*m* mg) was dissolved in dry pyridine (*x* mL) and mesyl chloride (*y* mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for

24 h. The reaction crude was poured into saturated aqueous sodium hydrogencarbonate at 0 °C, and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness. The resulting residue was purified by silica gel column chromatography using dichloromethane/methanol 40:1 as eluent.

3.2.1. 1-Acetyl-2-acetylaminomethyl-2-deoxy-3,4-*O*-isopropylidene-6-*O*-mesyl-β-D-psicofuranose (7). *M*=234 mg (0.738 mmol), *x*=3.2 mL, *y*=280 μL, *z*=28 mL. Amorphous solid; yield 76%; $[\alpha]_D^{25}$ +37 (*c* 0.93, CH_2Cl_2); FABMS *m*/*z* 418 [(M+Na)$^+$]; IR 3420, 3079, 2928, 2856, 1752, 1657, 1561, 1521, 1466, 1371, 1116, 1069, 989, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (m, 1H, N*H*Ac), 4.66 (dd, 1H, $J_{3,4}$=6.5, $J_{4,5}$=5.0, H-4), 4.63 (d, 1H, H-3), 4.52 (dd, 1H, $J_{5,6a}$=2.5, $J_{6a,6b}$=11.5, H-6a), 4.33 (d, 1H, $J_{1a,1b}$=12.0, H-1a), 4.31 (dd, 1H, $J_{5,6b}$=3.5, H-6b), 4.18 (d, 1H, H-1b), 4.16 (m, 1H, H-5), 3.62 (dd, 1H, J_{gem}=14.5, J_{NH,CH_2}=8.0, *H*CHNH), 3.36 (dd, 1H, J_{NH,CH_2}=5.0, HC*H*NH), 3.09 (s, 3H, CH_3SO_2), 2.09, 2.01 (each s, each 3H, CH_3CO), 1.51, 1.31 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.0 (2CO), 115.1 ((CH$_3$)$_2$*C*), 85.3 (C-2), 83.0 (C-3), 81.1 (C-5), 80.6 (C-4), 68.6 (C-6), 63.0 (C-1), 42.5 (*C*H$_2$NH), 38.1 (*C*H$_3$SO$_2$), 26.8, 25.1 (2(*C*H$_3$)$_2$C), 23.2, 21.0 (2*C*H$_3$CO); Anal. Calcd for $C_{15}H_{25}NO_9S$: C, 45.56; H, 6.37; N, 3.54; S, 8.11. Found: C, 45.39; H, 6.33; N, 3.58; S, 7.86.

3.2.2. (1*R*,5*R*,6*R*,7*R*)-3-*N*-Acetyl-3-aza-7,8-(dimethylmethylenedioxy)-1-mesyloxymethyl-8-oxabicyclo[3.2.1]octane (10). *M*=166 mg (0.646 mmol), *x*=2.8 mL, *y*=245 μL, *z*=25 mL. Amorphous solid; yield 85%; mixture of two rotamers (**10a** and **10b**) in a ratio of 1.25:1; $[\alpha]_D^{24}$ −60 (*c* 0.92, CH_2Cl_2); FABMS *m*/*z* 358 [(M+Na)$^+$]; IR 2990, 2962, 2863, 1655, 1544, 1425, 1353, 1210, 1171, 1131, 1075, 980, 877, 829 cm^{-1}; NMR data for rotamer **10a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.73 (d, 1H, $J_{6,7}$=5.8, H-6), 4.42 (d, 1H, J_{gem}=11.0, *H*CHOMs), 4.32 (d, 1H, H-7), 4.24 (m, 1H, H-5), 4.23 (d, 1H, HC*H*OMs), 4.20 (d, 1H, $J_{2a,2b}$=13.4, H-2a), 3.67 (d, 1H, $J_{4a,4b}$=13.0, H-4a), 3.16 (dd, 1H, $J_{4b,5}$=2.4, H-4b), 2.71 (d, 1H, H-2b), 2.00 (s, 3H, CH_3CO), 1.38, 1.25 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 170.0 (CO), 111.2 ((CH$_3$)$_2$*C*), 82.5 (C-6), 81.9 (C-7), 81.0 (C-1), 78.5 (C-5), 69.1 (CH$_2$OMs), 46.7 (C-4), 44.4 (C-2), 36.6 (*C*H$_3$SO$_2$), 25.8, 24.3 ((*C*H$_3$)$_2$C), 21.3 (*C*H$_3$CO); NMR data for rotamer **10b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.61 (d, 1H, $J_{6,7}$=5.8, H-7), 4.45 (d, 1H, H-6), 4.42 (d, 1H, J_{gem}=11.0, *H*CHOMs), 4.23 (d, 1H, HC*H*OMs), 4.27 (m, 1H, H-5), 4.06 (d, 1H, $J_{4a,4b}$=13.3, H-4a), 3.75 (d, 1H, $J_{2a,2b}$=12.7, H-2a), 3.26 (d, 1H, H-2b), 2.65 (dd, 1H, $J_{4b,5}$=2.4, H-4b), 2.00 (s, 3H, CH_3CO), 1.38, 1.25 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 170.0 (CO), 111.2 ((CH$_3$)$_2$*C*), 82.6 (C-6), 82.0 (C-7), 80.6 (C-1), 78.8 (C-5), 69.3 (CH$_2$OMs), 48.7 (C-2), 42.2 (C-4), 36.7 (*C*H$_3$SO$_2$), 25.8, 24.3 ((*C*H$_3$)$_2$C), 21.2 (*C*H$_3$CO); HRFABMS calcd for $C_{13}H_{21}NO_7NaS$: 358.0936. Found: 358.0943. Anal. Calcd for $C_{13}H_{21}NO_7S$: C, 46.56; H, 6.31; N, 4.18; S, 9.56. Found: C, 46.47; H, 6.15; N, 4.19; S, 9.48.

3.2.3. (1*R*,5*R*,6*R*,7*R*)-3-*N*-Acetyl-3-aza-1-hydroxymethyl-7,8-(dimethylmethylenedioxy)-8-oxabicyclo[3.2.1]octane (8). Sodium hydride (60 mg, 60% in paraffin) was added to a solution of **7** (226 mg, 0.572 mmol) in dry DMF (6 mL) containing molecular sieves, and the mixture was stirred at room temperature for 12 h. The crude was poured into water and coevaporated to dryness with ethanol and toluene. The resulting residue was purified by column chromatography on silica gel using dichloromethane/methanol 30:1 as eluent to give **6** as a mixture of two rotamers (**8a** and **8b**) in a ratio of 1.25:1. Amorphous solid; yield 82%; $[\alpha]_D^{25}$ −55 (*c* 1.0, CH_2Cl_2); CIMS *m*/*z* 258 [(M+H)$^+$]; IR 3428, 2990, 2936, 2872, 1649, 1458, 1371, 1275, 1204, 1172, 1069, 878 cm^{-1}; NMR data for rotamer **8a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.80 (t, 1H, J_{OH,CH_2}=5.5, OH), 4.64 (d, 1H, $J_{6,7}$=5.9, H-6), 4.23 (d, 1H, H-7), 4.21 (d, 1H, $J_{2a,2b}$=13.5, H-2a), 4.11 (m, 1H, H-5), 3.63 (d, 1H, $J_{4a,4b}$=12.9, H-4a), 3.60 (m, 1H, CH$_2$OH), 3.42 (dd, 1H, J_{gem}=11.0, CH$_2$OH), 3.12 (dd, 1H, $J_{4b,5}$=2.5, H-4b), 2.60 (d, 1H, H-2b), 1.98 (s, 3H, CH$_3$CO), 1.35, 1.23 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.8 (CO), 110.5 ((CH$_3$)$_2$*C*), 83.3 (C-1), 82.5 (C-6), 81.8 (C-7), 77.7 (C-5), 60.5 (*C*H$_2$OH), 47.1 (C-4), 45.5 (C-2), 25.9, 24.4 ((*C*H$_3$)$_2$C), 21.3 (*C*H$_3$CO); NMR data for rotamer **8b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.83 (t, 1H, J_{OH,CH_2}=5.5, OH), 4.50 (d, 1H, $J_{6,7}$=5.9, H-7), 4.38 (d, 1H, H-6), 4.15 (m, 1H, H-5), 4.03 (d, 1H, $J_{4a,4b}$=13.3, H-4a), 3.68 (d, 1H, $J_{2a,2b}$=12.9, H-2a), 3.60 (m, 1H, CH$_2$OH), 3.45 (dd, 1H, J_{gem}=11.0, CH$_2$OH), 3.16 (d, 1H, H-2b), 2.62 (dd, 1H, $J_{4b,5}$=2.5, H-4b), 1.98 (s, 3H, CH$_3$CO), 1.35, 1.23 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.9 (CO), 110.6 ((CH$_3$)$_2$*C*), 82.8 (C-1), 82.6 (C-7), 81.8 (C-6), 77.9 (C-5), 60.5 (*C*H$_2$OH), 49.9 (C-2), 42.7 (C-4), 25.9, 24.4 ((*C*H$_3$)$_2$C), 21.3 (*C*H$_3$CO). HRCIMS calcd for $C_{12}H_{20}NO_5$: 258.1341. Found: 258.1339.

3.2.4. (1*R*,5*R*,6*R*,7*R*)-3-*N*-Acetyl-3-aza-1-azidomethyl-7,8-(dimethylmethylenedioxy)-8-oxabicyclo[3.2.1]octane (11). To a stirred solution of **10** (100 mg, 0.299 mmol) in dry DMF (7.5 mL), sodium azide (150 mg, 2.30 mmol) was added and the mixture was kept stirring for 2 h at 155 °C. The reaction was monitored by TLC using ethyl acetate as eluent. When the starting product was completely consumed, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The obtained residue was purified by silica gel column chromatography using ethyl acetate as eluent. Amorphous solid; yield 86%; $[\alpha]_D^{26}$ −77 (*c* 1.2, CH_2Cl_2); mixture of two rotamers (**11a** and **11b**) in a ratio of 1.25:1; CIMS *m*/*z* 283 [(M+H)$^+$]; IR 3416, 2995, 2931, 2105, 1644, 1422, 1374, 1358, 1215, 1112, 1072, 874 cm^{-1}; NMR data for rotamer **11a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.70 (d, 1H, $J_{6,7}$=5.9, H-6), 4.25 (d, 1H, H-7), 4.20 (m, 1H, H-5), 4.14 (d, 1H, $J_{2a,2b}$=13.0, H-2a), 3.66 (d, 1H, $J_{4a,4b}$=12.9, H-4a), 3.53 (m, 2H, CH_3N$_3$), 3.14 (dd, 1H, $J_{4b,5}$=2.5, H-4b), 2.66 (d, 1H, H-2b), 1.99 (s, 3H, CH_3CO), 1.38, 1.24 (each s, each 3H, (CH_3)$_2$C); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.9 (CO), 111.1 ((CH$_3$)$_2$*C*), 82.6 (C-6), 82.4 (C-1), 81.9 (C-7), 78.2 (C-5), 51.4 (*C*H$_2$N$_3$), 46.7 (C-4), 45.1 (C-2), 25.8, 24.4 ((*C*H$_3$)$_2$C), 21.3 (*C*H$_3$CO); NMR data for rotamer **11b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (d, 1H, $J_{6,7}$=5.9, H-7), 4.43 (d, 1H, H-6), 4.24 (m, 1H, H-5), 4.04 (d, 1H, $J_{4a,4b}$=13.4, H-4a), 3.68 (d, 1H, $J_{2a,2b}$=12.7, H-2a), 3.53 (m, 2H, CH_3N$_3$), 3.20 (d, 1H, H-2b), 2.64 (dd, 1H, $J_{4b,5}$=2.5, H-4b), 1.99 (s, 3H, CH_3CO), 1.38, 1.24

(each s, each 3H, $(CH_3)_2C$); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.9 (CO), 111.1 ($(CH_3)_2C$), 82.8 (C-6), 82.0 (C-1), 81.9 (C-7), 78.5 (C-5), 51.5 (CH_2N_3), 49.5 (C-2), 42.3 (C-4), 25.8, 24.4 ($(CH_3)_2C$), 21.2 (CH_3CO); HRCIMS calcd for $C_{12}H_{19}N_4O_4$: 283.1406. Found: 283.1407.

3.2.5. (1*S*,5*R*,6*R*,7*R*)-3-*N*-Acetyl-1-aminomethyl-3-aza-7,8-(dimethylmethylenedioxy)-8-oxabicyclo[3.2.1]octane (12). To a stirred solution of **11** (52 mg, 0.184 mmol) in ethyl acetate (5.3 mL), 10% Pd–C (18 mg) was added. The obtained suspension was kept at room temperature and stirred under hydrogen atmosphere for 3 h. The mixture was filtered through Celite and evaporated to dryness. Amorphous solid; yield 98%; $[\alpha]_D^{29}$ −71 (*c* 0.7, CH_2Cl_2); mixture of two rotamers (**12a** and **12b**) in a ratio of 1.25:1; FABMS *m*/*z* 279 [(M+Na)$^+$]; IR 3396, 2999, 2928, 2864, 1649, 1458, 1434, 1371, 1212, 1116, 1069, 1013, 870 cm^{-1}; NMR data for rotamer **12a**: ^1H NMR (500 MHz, DMSO-d_6) δ 4.64 (d, 1H, $J_{6,7}$=5.9, H-6), 4.28 (d, 1H, $J_{2a,2b}$=13.3, H-2a), 4.24 (d, 1H, H-7), 4.12 (m, 1H, H-5), 3.63 (d, 1H, $J_{4a,4b}$=12.9, H-4a), 3.23 (s, 2H, NH_2), 3.11 (dd, 1H, $J_{4b,5}$=2.5, H-4b), 2.80, 2.66 (each d, each 1H, J_{gem}=13.0, CH_2NH_2), 2.54 (d, 1H, H-2b), 1.98 (s, 3H, CH_3CO), 1.36, 1.24 (each s, each 3H, $(CH_3)_2C$); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.8 (CO), 110.6 ($(CH_3)_2C$), 83.2 (C-1), 82.6 (C-6), 81.9 (C-7), 77.9 (C-5), 47.1 (C-4), 45.9 (C-2), 42.7 (CH_2NH_2), 25.8, 24.4 ($(CH_3)_2C$), 21.4 (CH_3CO); NMR data for rotamer **12b**: ^1H NMR (500 MHz, DMSO-d_6) δ 4.50 (d, 1H, $J_{6,7}$=5.9, H-7), 4.38 (d, 1H, H-6), 4.15 (m, 1H, H-5), 4.03 (d, 1H, $J_{4a,4b}$=13.4, H-4a), 3.79 (d, 1H, $J_{2a,2b}$=12.9, H-2a), 3.23 (s, 2H, NH_2), 3.07 (d, 1H, H-2b), 2.80, 2.66 (each d, each 1H, J_{gem}=13.0, CH_2NH_2), 2.61 (dd, 1H, $J_{4b,5}$=2.5, H-4b), 1.98 (s, 3H, CH_3CO), 1.36, 1.24 (each s, each 3H, $(CH_3)_2C$); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.8 (CO), 110.6 ($(CH_3)_2C$), 83.7 (C-1), 82.7 (C-6), 81.9 (C-7), 77.9 (C-5), 50.5 (C-2), 42.8 (C-4), 42.7 (CH_2NH_2), 25.8, 24.4 ($(CH_3)_2C$), 21.3 (CH_3CO); HRFABMS: calcd for $C_{12}H_{20}N_2O_4Na$: 279.1321. Found: 279.1327.

3.2.6. (1*S*,5*R*,6*R*,7*R*)-3-*N*-Acetyl-3-aza-1-cyanomethyl-7,8-(dimethylmethylenedioxy)-8-oxabicyclo[3.2.1]octane (14). To a solution of **10** (110 mg, 0.328 mmol) in dry DMF (7.9 mL), KCN (165 mg, 2.53 mmol) and crown ether (18-crown-6) (175 mg, 0.656 mmol) were added. The mixture was stirred at 155 °C for 4 h and then poured into ice water, extracted with ethyl acetate, dried over $MgSO_4$, filtered, and evaporated to dryness. The obtained residue was purified by silica gel column chromatography using CH_2Cl_2/MeOH 40:1 as eluent to give **12** as a mixture of two rotamers (**14a** and **14b**) in a ratio of 1.2:1. Yield 85%; $[\alpha]_D^{20}$ −26 (*c* 2.2, CH_2Cl_2); CIMS *m*/*z* 267 [(M+H)$^+$]; IR 2919, 2840, 2300, 1654, 1443, 1374, 1358, 1266, 741 cm^{-1}; NMR data for rotamer **14a**: ^1H NMR (500 MHz, $CDCl_3$) δ 4.56 (d, 1H, $J_{6,7}$=5.9, H-6), 4.45 (d, 1H, J_{gem}=13.3, H-2a), 4.39 (d, 1H, H-7), 4.31 (m, 1H, H-5), 3.54 (d, 1H, J_{gem}=12.9, H-4a), 3.39 (dd, 1H, $J_{4b,5}$=2.4, H-4b), 2.91 (d, 1H, H-2b), 2.83 (d, 1H, J_{gem}=17.0, H-1′a), 2.67 (d, 1H, H-1′b), 2.09 (s, 3H, $COCH_3$), 1.48, 1.30 (each s, each 3H, $(CH_3)_2C$). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.5 (CO), 116.0 (CN), 113.1 ($(CH_3)_2C$), 83.5 (C-6), 82.4 (C-7), 80.8 (C-1), 79.1 (C-5), 47.4 (C-4), 46.9 (C-2), 25.9, 24.6 ($(CH_3)_2C$), 21.6 (CH_3CO), 21.3 (CH_2CN); NMR data for rotamer **14b**: ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (d, 1H, $J_{6,7}$=5.9, H-6), 4.41 (d, 1H, H-7), 4.33 (m, 1H, H-5), 4.29 (d, 1H, J_{gem}=12.9, H-4a), 3.72 (d, 1H, J_{gem}=12.6, H-2a), 3.36 (d, 1H, H-2b), 2.83 (d, 1H, H-4b), 2.77 (m, 2H, H-1′a and H-1′b), 2.10 (s, 3H, $COCH_3$), 1.48, 1.30 (each s, each 3H, $(CH_3)_2C$). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.5 (CO), 116.0 (CN), 113.1 ($(CH_3)_2C$), 83.4 (C-6), 82.3 (C-7), 80.2 (C-1), 79.9 (C-5), 51.7 (C-2), 42.7 (C-4), 25.9, 24.6 ($(CH_3)_2C$), 21.5 (CH_3CO), 21.0 (CH_2CN); HRCIMS calcd for $C_{13}H_{19}N_2O_4$: 267.1345 Found: 267.1330.

3.2.7. (1*S*,5*R*,6*R*,7*R*)-1-(2′-Aminoethyl-3-aza-7,8-(dimethylmethylenedioxy)-3-*N*-ethyl-8-oxabicyclo[3.2.1]-octane (15). Lithium aluminum hydride (100 mg) was added at 0 °C to a solution of **14** (50 mg, 0.188 mmol) in super-dry diethyl ether (7.0 mL). The resulting suspension was stirred at room temperature for 18 h and afterward 1 mL of a 1 M solution of K_2CO_3 was carefully added at 0 °C. The reaction mixture was filtered through Celite, dried ($MgSO_4$), and evaporated to dryness. The residue was used as obtained in the next reaction step. Amorphous solid; yield 64%; HRCIMS calcd for $C_{13}H_{25}N_2O_3$: 257.1865. Found: 257.1878.

3.3. Preparation of compounds 9, 13 and 16

To a solution of **8**, **12** or **15** (*m* mg) in methanol (*x* mL), concd HCl (*y* μL) was added. The resulting solution was stirred at 65 °C for 4 h and then evaporated to dryness. The obtained residue was purified by ion-exchange resin chromatography (Dowex50W8X) using 2 N aqueous ammonia as eluent.

3.3.1. (1*R*,5*R*,6*R*,7*S*)-3-Aza-6,7-dihydroxy-1-hydroxymethyl-8-oxabicyclo[3.2.1]octane (9). *M*=51 mg (0.198 mmol), *x*=5.2 mL, *y*=420 μL. Amorphous solid; yield 98%; $[\alpha]_D^{24}$ −23 (*c* 2.4, MeOH); CIMS *m*/*z* 176 [(M+H)$^+$]; IR 3420, 2928, 2856, 1649, 1450, 1355, 1116, 1045, 854, 767, 711 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 4.30 (d, 1H, $J_{6,7}$=6.5, H-7), 4.25 (d, 1H, H-6), 4.02 (m, 1H, H-5), 3.71, 3.60 (each d, each 1H, J_{gem}=11.5, CH_2OH), 2.87 (d, 1H, J_{gem}=12.5, H-2a), 2.84 (dd, 1H, J_{gem}=12.0, $J_{4a,5}$= 2.5, H-4a), 2.83 (d, 1H, H-2b), 2.73 (dd, 1H, $J_{4b,5}$=1.4, H-4b); ^{13}C NMR (125.7 MHz, MeOD) δ 85.6 (C-1), 84.2 (C-5), 75.3 (C-7), 75.1 (C-6), 63.8 (CH_2OH), 51.0 (C-2), 48.0 (C-4); HRCIMS calcd for $C_7H_{14}NO_4$: 176.0923. Found: 176.0919.

3.3.2. (1*S*,5*R*,6*R*,7*S*)-1-Aminomethyl-3-aza-6,7-dihydroxy-8-oxabicyclo[3.2.1]octane (13). *M*=42 mg (0.164 mmol), *x*=4.3 mL, *y*=348 μL. Amorphous solid; yield 98%; $[\alpha]_D^{29}$ −49 (*c* 1.5, MeOH); CIMS *m*/*z* 175 [(M+H)$^+$]; IR 3390, 2938, 2850, 1636, 1559, 1429, 1373, 1107, 1072, 866 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 4.28 (d, 1H, $J_{6,7}$=6.5, H-7), 4.26 (d, 1H, H-6), 4.03 (m, 1H, H-5), 2.90, 2.84 (each d, each 1H, J_{gem}=13.0, CH_2NH_2), 2.81 (dd, 1H, J_{gem}=13.0, $J_{4a,5}$=2.5, H-4a), 2.76 (d, 1H, J_{gem}=12.0, H-2a), 2.70 (d, 1H, H-4b), 2.64 (d, 1H, H-2b); ^{13}C NMR (125.7 MHz, MeOD) δ 84.3 (C-5), 84.3 (C-1), 76.1 (C-7), 75.6 (C-6), 52.5 (C-2), 48.1 (C-4), 44.3 (CH_2NH_2); HRCIMS calcd for $C_7H_{15}N_2O_3$: 175.1083. Found: 175.1079.

3.3.3. (1*S*,5*R*,6*R*,7*S*)-1-(2′-Aminoethyl)-3-aza-6,7-dihydroxy-3-*N*-ethyl-8-oxabicyclo[3.2.1]octane (16). *M*= 31 mg (0.164 mmol), *x*=5.2 mL, *y*=900 μL. Amorphous

solid; yield 92%; $[\alpha]_D^{20}$ −26 (*c* 0.8, MeOH); CIMS *m/z* 217 [(M+H)$^+$]; IR 3761, 3423, 2932, 2810, 1634, 1561, 1402, 1336, 1185, 1096, cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 4.26 (d, 1H, $J_{6,7}$=6.3, H-6), 4.18 (d, 1H, H-7), 4.12 (m, 1H, H-5), 3.18 (m, 2H, H-2′a and H-2′b), 2.76 (m, 1H, H-4a), 2.73 (d, 1H, J_{gem}=10.9, H-2a), 2.35 (q, 2H, $^3J_{H,H}$= 7.5, NCH_2CH$_3$), 2.18 (dt, 1H, J_{gem}=14.5, $J_{1'a,2'a}$= $J_{1'a,2'b}$=7.0, H-1′a), 2.11 (dd, 1H, J_{gem}=11.0, $J_{4b,5}$=2.0, H-4b), 2.01 (d, 1H, H-2b), 1.86 (dt, 1H, $J_{1'b,2'a}$=$J_{1'b,2'b}$=7.0, H-1′b), 1.06 (t, 3H, NCH$_2$CH_3); ^{13}C NMR (125.7 MHz, MeOD) δ 84.6 (C-1), 83.7 (C-5), 76.0 (C-7), 75.7 (C-6), 61.7 (C-2), 55.5 (C-4), 52.8 (NCH$_2$CH$_3$), 37.0 (C-2′), 30.8 (C-1′), 12.0 (NCH$_2$$CH_3$). HRCIMS calcd for $C_{10}H_{21}N_2O_3$: 217.1552. Found: 217.1553.

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