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Isoxazoline-carbocyclic aminols for nucleoside synthesis through aza-Diels–Alder reactions

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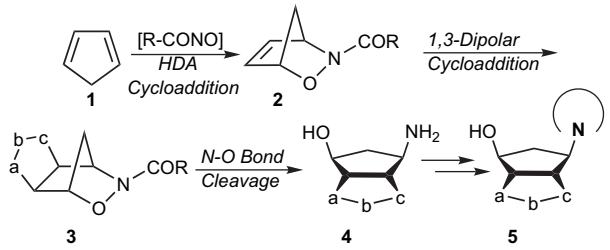
Abstract—A novel approach to useful aminols for the synthesis of carbocyclic nucleosides is reported starting from a convenient source, the 2-azanorborn-5-enes. These are readily available through the Grieco cycloaddition of cyclopentadiene with iminium salts and are reactive dipolarophiles toward nitrile oxides. The prolific elaboration of the isoxazoline cycloadducts allowed preparation of the target aminols through the unmasking of the hydroxymethylene group at the C3 level of the azanorbornene structure.

1. Introduction

The preparation of carbocyclic and heterocyclic nucleoside analogues has been extensively pursued due to the importance in the development of new anti-viral drugs.[1] Most of the nucleoside analogues refer to a general structure defined by the presence of a five-membered ring (furanose ring in natural compounds) of a carbocyclic or heterocyclic nature, which holds a hydroxymethylene group cis-related to the heterobase needed for enzyme or nucleic acid recognition.[2] Great interest has also risen in the so-called nor-derivatives where the hydroxymethylene substituent is replaced by an OH function.[3]

In this context, we have recently developed a synthesis of the isoxazoline-carbocyclic nucleosides **5** by the linear construction of the desired purine and pyrimidine bases on the regioisomeric aminols **4** (Scheme 1) obtained through elaboration of the hetero-Diels–Alder (HDA) cycloadducts **2** of cyclopentadiene **1** with the nitrosocarbonyl intermediates (RCONO).[4] These fleeting intermediates are generated traditionally by periodate oxidation of hydroxamic acids[5] or by oxidation of nitrile oxides with *N*-methylmorpholine *N*-oxide (NMO),[6] and are promptly trapped with dienes to afford HDA cycloadducts in high yields. The HDA cyclopentadiene cycloadducts **2** have proved to be highly reactive dipolarophiles toward nitrile oxides, affording the 1,3-dipolar cycloadducts of type **3**, which are converted quantitatively by detachment of the acyl moiety and reductive cleavage of the N–O bond into the stereodefined *anti* aminols **4**.[7] Starting from these, by the linear construction of the heterobases, we have detailed the first synthesis of a class of racemic purine- and pyrimidine-carbocyclic nucleosides **5** containing a fused isoxazolinic ring and lacking a methylene group in the side chain in the carbocyclic unit.[4]



Scheme 1.

For direct access to the nucleoside analogues carrying the hydroxymethylene moiety on the carbocyclic unit, in order to compare the role of the elongation of the side chain on the biological activity of isoxazoline-nucleosides, the 2-azabicyclo[2.2.1]hept-5-en-3-one **6** looked promising for this purpose (Fig. 1). This lactam **6** has found wide applications in carbocyclic nucleoside synthesis[2,8] because of the easy access to the required aminols by easy cleavage of the lactam moiety. The preparation of the starting azaheptenone **6** is however affected by some problems; it can be prepared through cycloaddition of cyclopentadiene to tosyl cyanide or methanesulfonyl cyanide, whose preparations require a potentially hazardous starting material (cyanogen chloride).[9] Although available from various chemical suppliers,

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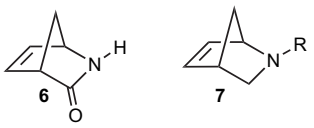


Figure 1.

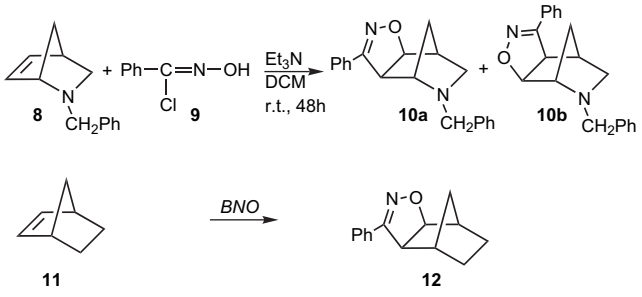
the cost of the racemic compound is too high for large-scale synthesis, and even more is that of the enantiomerically pure forms.[10]

Structurally similar to lactam **6** are Grieco's 2-azanorbornenes **7** that are derived from the cycloaddition of cyclopentadiene with iminium salts generated in situ under Mannich-like conditions, in a mild and convenient aqueous aza-Diels–Alder (ADA) reaction.[11] Despite their easy availability, no attempts have been made for their use in nucleosidic syntheses. To this purpose the aza-methylene bridge has to be modified, precisely the carbon C3 must be oxidized by appropriate unmasking procedures. Here we report the synthetic approach to novel isoxazoline-carbocyclic aminols bearing an hydroxymethylene functionality starting from the easy available 2-azanorbornenes of type **7**.

2. Results and discussion

2.1. The *N*-benzyl-2-azanorborn-5-ene 8 as dipolarophile

The *N*-benzyl-2-azanorborn-5-ene **8** was prepared by addition of freshly distilled cyclopentadiene to an aqueous solution of benzylamine hydrochloride and 37% aqueous formaldehyde in an ADA reaction according to the well-known procedure.[12] The 1,3-dipolar cycloaddition of benzonitrile oxide (BNO) with **8** was performed with the in situ procedure,[13] by adding the benzhydroximoyl chloride **9** to a dichloromethane (DCM) solution of a slight excess of *N*-benzyl-2-azanorborn-5-ene **8** (1.2 equiv) and a slight excess of Et_3N (1.1 equiv) (Scheme 2).



Scheme 2.

After stirring at room temperature for 48 h, the two regioisomeric isoxazoline cycloadducts **10a** and **10b** were isolated in 49% and 43% yields, respectively.

The structures rely upon their analytical and spectroscopic data. The ^{1}H NMR spectrum of **10a** showed the isoxazoline protons as doublets (J=8 Hz) at δ 4.03 and 4.83, while in regioisomer **10b** the isoxazoline doublets (J=8 Hz) were found at δ 3.74 and 4.94. The absence of appreciable coupling between the isoxazoline and bridge-head protons fully support the *exo* structures[7a,14] and is in line with the *exo*-selective addition to these dipolarophiles reported in literature for the dihydroxylation reactions of **8**.[15] The regiochemistry is however not clearly indicated by the spectra and an X-ray analysis of single crystal of **10b** allowed us to unequivocally attribute the correct regioisomeric structure. Figure 2 reports the ORTEP view of **10b**.

We previously found that 2-oxa-3-azanorbornenes of type **2** add BNO *exo*-selectively, and were 1.7 times more reactive than norbornene as a consequence of the higher relief of strain.[7,16] Similarly, we have performed a few competition experiments with *N*-benzyl-2-azanorbornene **8** and norbornene **11** in the cycloaddition with BNO. Table 1 gives the product distributions for the reactions conducted in a few representative solvents. These results show that the 2-azanorbornene **8** still remains a highly reactive dipolarophile but less than norbornene **11**. As an average, the reactivity of the 2-azanorbornene **8** is half that of norbornene **11** in apolar solvents (entries 1 and 2) and decreases to one third in more polar (entry 8) or polarizable (entries 5 and 6) solvents or in alcohols (entries 9 and 10). The lesser reactivity of the 2-azanorbornene **8** with respect to norbornene **11** could be attributed to the reduced strain in **8**. Replacement of the eclipsed dimethylene bridge of norbornene with the aminomethylene moiety causes a decrease in strain, in keeping with the reduced torsional barriers of amines with respect to alkanes.[17] The further decrease in reactivity in

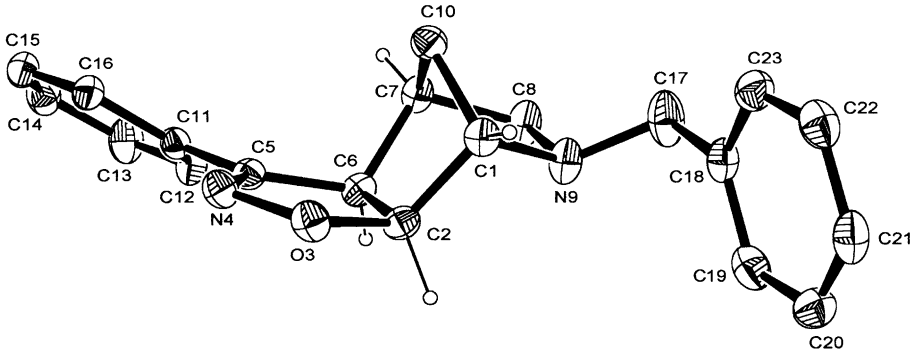


Figure 2. ORTEP plot of cycloadduct **10b** with atom labeling (ellipsoid at 25% probability). Hydrogen atoms are omitted for clarity with exception of C1, C2, C6, and C7.

Table 1. Competition experiments with *N*-benzyl-2-azanorbornene **8** and norbornene **11** in the cycloaddition to BNO and regioisomeric distribution[a,b]

No.	Solvent	**12** (%)	**10a** (%)	**10b** (%)	**10a+10b/12**	**10a/10b**
1	*n*-Hexane	66	19	13	0.48	59/41
2	Cyclohexane	65	17	12	0.45	59/41
3	THF	68	14	12	0.38	54/46
4	Acetone	73	13	11	0.33	54/46
5	C_6H_6	74	13	10	0.31	57/43
6	DCM	76	11	10	0.28	52/48
7	AcOEt	78	11	9	0.26	55/45
8	MeCN	76	10	8	0.24	56/44
9	MeOH	76	13	8	0.28	62/38
10	EtOH	75	13	8	0.28	62/38

[a] BNO generated in situ in the presence of a mixture of dipolarophiles **8** and **11**, 5 equiv each.
[b] Quantitative data are the average of HPLC analyses performed in duplicate from independent experiments.

polar or alcoholic solvents may be attributed to some complexation or hydrogen-bonding involving the nitrogen lone pair that increases the electron attracting power of the nitrogen and lowers the π orbital of the nearby C=C double bond. A decrease in reactivity in the cycloadditions of the mildly electrophilic nitrile oxides is then expected.[13]

The slight regiochemical preference of cycloadduct **10a** over **10b** compares well with previous results on the cycloadditions of BNO with 3-substituted cyclopentenes and can be attributed to the polarization of the double bond caused by the electronegative nitrogen allylic substitution.[13] Solvents affect slightly only the regiochemistry, which increases in alcohols but unexpectedly decreases in polar and polarizable solvents.

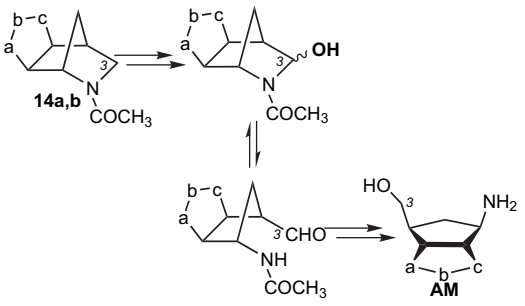
2.2. Synthesis of stereoisomeric aminols

Before attempting the cleavage step we have transformed the adducts into more convenient derivatives. Since the hydrogenolytic detachment of the *N*-benzyl moiety performed poorly, we found a convenient and high yielding alternative. The first step was the oxidation of **10a** and **10b**, which were converted into the corresponding *N*-oxides **13a** and **13b** by treating with 1.2 equiv of mCPBA in DCM at room temperature.[18] Conversion of the *N*-oxides into the amides **14a** and **14b** was achieved through the mild Polonovski rearrangement[19] of the amine *N*-oxides promoted by Ac_2O to afford the *N*-acetyl derivatives (Scheme 3).

The *N*-oxides **13a** and **13b** were isolated in quantitative yields and fully characterized spectroscopically. The *exo* position of the N–O bond was inferred by significative shifts of various signals due to the deshielding effect produced by the *N*-oxide group. In particular, the C3-H_{exo}, cis-related to the oxygen, is deshielded and occurs at δ 3.79 (dd, J=12, 5 Hz) in **13a** and at δ 3.75 (dd, J=12, 4 Hz) in **13b**, a typical behavior of *N*-oxides as reported in literature.[20]

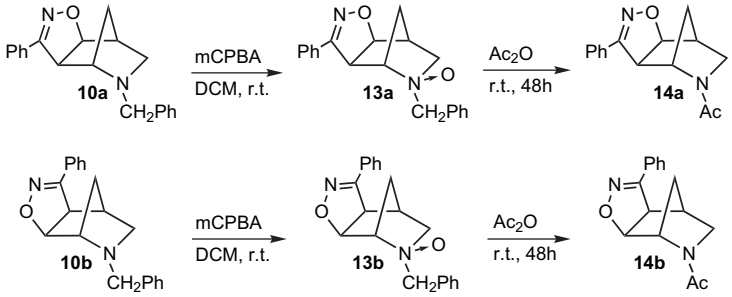
The Polonovski rearrangement of the *N*-oxides **13a** and **13b** was performed by dissolving the oxidized compounds in Ac_2O and leaving to react at room temperature for 48 h. The excess of Ac_2O was then decomposed with water overnight and, after adjustment of pH to 8, the water solutions were extracted with DCM. From the dried organic phase the *N*-acetyl derivatives **14a** and **14b** were isolated upon evaporation of the solvent as solid compounds in 94% and 85% yields, respectively. The structures rely upon the collected analytical and spectroscopic data. Besides little differences in the chemical shifts relative to the isoxazoline protons and those of the azanorbornene structure, the most relevant changes referred to the presence of the acetyl groups at δ 2.04 and 2.16, respectively for **14a** and **14b**.

Starting from the amides **14a** and **14b** we planned the oxidative strategy shown schematically in Scheme 4 for unmasking a hydroxymethylene group at the C3 of the amides.

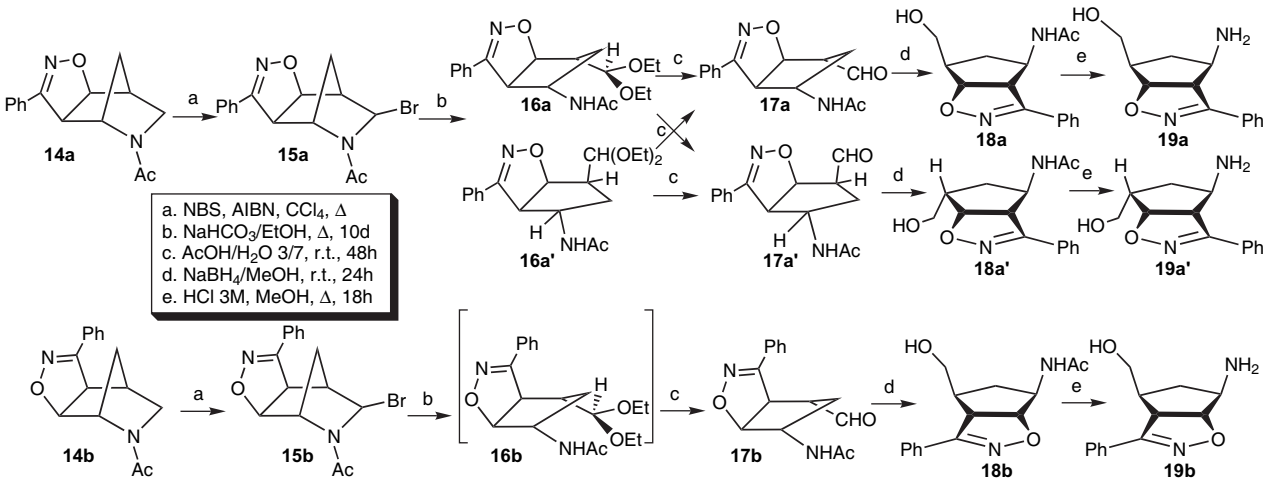


Scheme 4.

After a few attempts at a direct conversion of the C3 into a carbonyl function,[21] we found a convenient procedure for the oxidation of the regioisomeric *N*-acetyl derivatives **14a** and **14b** through NBS/AIBN bromination reaction (Scheme 5). Bromination of the cycloadducts **14a** and **14b** takes place easily in refluxing CCl_4 for 1–2 h. After filtration of succinimide and evaporation of the solvent, the residues were submitted to column chromatography on silica gel eluting with $CHCl_3$. The chromatographic separations afforded the expected *exo*-bromo derivatives **15a** and **15b** as the



Scheme 3.



Scheme 5.

major constituents, both obtained in 47% yield. Their structures rely upon the ^{1}H NMR spectra, which show the CH–Br signals as singlets at δ 5.37 and 5.45, respectively, for **15a** and **15b**. The lack of coupling with the bridge-head protons is consistent with the *exo* stereochemistry of bromine atom.[14]

In the case of the bromination of **14a**, chromatographic separation of the reaction mixtures also afforded more advanced intermediates toward the final aminol targets. Two epimeric diethoxy acetals **16a** and **16a′** and the corresponding aldehydes **17a** and **17a′** could be isolated, while in the case of the bromination of **14b** only the aldehyde **17b** was characterized. The formation of the acetals and the aldehydes can be attributed to the silica gel-promoted transformation of the bromo derivatives **15** due to the presence of ethanol as stabilizing agent in the chloroform used for the chromatographic separation. From **14a** in particular, two epimeric acetals **16a** (mp 140–142 °C) and **16a′** (mp 110–112 °C) were isolated as white solids in fair yields (16% and 12%, respectively). The structures rely upon careful spectroscopic analyses. The ring opening of the azanorbornene skeleton was indicated by the presence of a neat NH–Ac absorption in the FTIR spectrum (in **16a**, band at 3260 cm^{-1}; in **16a′**, band at 3271 cm^{-1}) and in the ^{1}H NMR spectra by the signals of two different OEt groups attributable to diastereotopic diethylacetal moieties. Moreover in these cleavage products, the flexible cyclopentane moiety allows couplings between the isoxazoline protons and the adjacent methines. In the retained product **16a** the H5-isoxazolinic proton occurs as a double doublet at δ 5.16 because of coupling with the H4-isoxazolinic proton at δ 4.09 (J=10 Hz) and the adjacent *trans* methine (J_{trans}=3 Hz) while in the epimeric product **16a′** the H5-isoxazolinic proton is a double doublet at δ 5.12 owing to the coupling with the H4-isoxazolinic proton at δ 4.23 (J=9 Hz) and the adjacent *cis* methine (J_{cis}=6 Hz).

NOESY experiments support the attributions showing diagnostic cross-peaks between the acetal proton and the H5-isoxazoline one in isomer **16a**. In the epimer **16a′** the NOESY cross-peaks occur between the acetal proton and one of the two different cyclopentane methylene protons and between the other methylene protons with the amide NH. By adapting the same procedure the bromide **15b** could be converted into the aldehyde **17b**. From the chromatographic separation an oily fraction was isolated containing presumably the acetal **16b** and related hemiacetal structures. The oil could not be purified but was directly hydrolyzed to the aldehyde. The formation of a single aldehyde **17b** in this case is probably due to the severe steric hindrance for substituents cis-located to the phenyl isoxazoline moiety, which offsets the epimerization.

The last compounds eluted are the aldehydes **17**. From **14a**, the two epimeric aldehydes **17a** and **17a′** were isolated as an oily mixture in comparable amounts in a combined yield of 18%. In the ^{1}H NMR spectrum of the mixture two singlets corresponding to the aldehyde groups were detected at δ 9.97 and 10.01, while the signal at δ 6.25 corresponded to the NH group, as the FTIR spectrum confirmed (NH band at 3297 cm^{-1} and the prominent aldehyde absorption). Since chromatographic separation of the two aldehydes was unsatisfactory, the mixture was submitted to the subsequent reductive step. From **14b** a single aldehyde **17b** was obtained as a crystalline compound (20% yield). It shows a neat NH absorption at 3520 cm^{-1} and the C=O band at 1716 cm^{-1} in the FTIR spectrum. In the ^{1}H NMR spectrum the aldehyde signal occurs as a sharp singlet at δ 9.79 while the NH is a broad singlet at δ 7.07.

The transformation of the bromides **15** into the acetals **16** and then into the aldehyde **17** could be optimized by adapting reported procedures. Thus refluxing the bromide **15a** in ethanol in the presence of an excess of $NaHCO_3$[22] allowed the complete conversion of **15a** into a 1:1 mixture of the two epimeric acetals **16a** and **16a′**, which were quantitatively hydrolyzed to the corresponding aldehydes **17a** and **17a′** upon treatment with AcOH/H_2O 3:7 at room temperature for 48 h.[23] Noteworthy and in accordance with expected enolization in acidic medium, from any single epimeric acetal **16a** or **16a′** the two epimeric aldehydes were obtained in a nearly 1:1 ratio and, as before, not separated but submitted to subsequent reduction. By applying the same procedure to the bromide **15b** a single aldehyde **17b** was obtained.

The reduction of the aldehydes **17** to the desired primary alcohols **18** was performed with $NaBH_4$ in MeOH solution. From the diastereomeric aldehydes **17a** and **17a′**, the

corresponding alcohols **18a** and **18a′** were obtained in quantitative yields and could be easily separated by column chromatography as colorless solids. The structures rely upon their analytical and spectroscopic data. Besides the signals attributable to the cyclopenta-isoxazoline skeleton, the ^{1}H NMR spectrum of the alcohols **18** showed the significant presence of the OH and the diastereotopic protons of the hydroxymethylene group as multiplets at δ 3.73 and 3.84 in **18a** and at δ 3.71 and 3.86 in **18a′**. The stereochemistry relies upon the vicinal coupling of the H5-isoxazolinic protons and the methines. In the retained product **18a** the H5-isoxazolinic proton at δ 5.13 (dd, J=9.6, 4 Hz) is coupled with the smaller J_{trans} with the adjacent *trans* methine while in the epimeric product **18a′** the H5-isoxazolinic proton at δ 5.20 (dd, J=9, 5 Hz) is coupled with the larger J_{cis} with the analogous type of proton.

The NOESY experiment carried out on **18a** confirmed the stereochemistry due to the existence of cross-peaks correlating the hydroxymethylene protons with the H5-isoxazoline proton at δ 5.13 and the NH proton with the H4-isoxazoline one at δ 4.11. In the epimer **18a′** the NOESY experiment confirmed the *anti* relationship between the alcoholic function and the acetamide group because of the sole presence of a cross-peak correlating the H5-isoxazoline proton at δ 5.20 and the *CH*–CH_2OH proton, while the CH_2OH shows no NOE cross-peaks. The spectra of the regioisomeric alcohol **18b** show the hydroxymethylene protons at δ 3.74 and 3.83; the H5-isoxazolinic proton at δ 4.99 (dd, J=9 Hz with the H4-isoxazolinic proton at δ 4.18) is trans coupled with the *CH*–NHAc (J=2 Hz) at δ 4.39.

Finally, the three regio- and stereoisomeric alcohols **18** were definitively and quantitatively hydrolyzed to the corresponding aminols **19** by boiling a methanolic solution with HCl 3 M overnight (Scheme 5). Table 2 summarizes the main physical and spectroscopic data of the target compounds. Very sharp bands were found in the FTIR spectra between 3250–3370 cm^{-1} corresponding to the NH_2 groups while the OH bands are somewhat broad and at lower frequencies because of strong intra- and inter-molecular hydrogen bonds. In the ^{1}H NMR spectra the hydroxymethylene groups gave AB systems at the expected chemical shifts and the isoxazoline protons were also in their typical range.

Table 2. Physical and spectroscopic data of the aminols **19**

Entry	**19**	Mp °C[a]	FTIR (cm^{-1})		^{1}H NMR (δ)		
			ν_{OH}	ν_{NH_2}	CH_2OH	H4-isoxaz.	H5-isoxaz.
1	**a**	116–118	3176	3334, 3266	3.70	4.02	5.21
2	**a′**	154–156	3158	3330, 3257	3.67, 3.87	4.03	5.28
3	**b**	130–131	3176	3370, 3291	3.70	4.26	4.79

[a] White solids from benzene/ethanol.

3. Conclusions

In the search of a new and convenient synthetic route to isoxazoline-carbocyclic aminols with a primary hydroxy group useful for nucleoside preparations, we took advantage of the easily available *N*-benzyl-2-azanorbornene, which underwent 1,3-dipolar cycloaddition with BNO to afford the regioisomeric cycloadducts **10a** and **10b** in good yields. Replacement of the benzyl group was easily achieved through *N*-oxidation and a successive Polonovski rearrangement leading to the *N*-acetyl derivatives, which proved to be convenient intermediates for the activation of the C3 position of the azanorbornene structure. Upon treatment with NBS and solvolysis[24] of the bromo derivatives **15a** and **15b**, the aldehydes **17a** and **17b** were obtained. The straightforward reduction of the latters gave the target aminols.

In conclusion, we have proposed a novel approach to useful aminols for the synthesis of carbocyclic nucleosides starting from the readily available 2-azanorbornenes and unmasking the hydroxymethylene group at the C3 level of the azanorbornene structure.

The aminols will be used for the linear construction of purine and pyrimidine carbocyclic nucleosides whose activities as anti-viral agents will be compared with those of the previously synthesized compounds.

4. Crystal structure analyses

The ORTEP view of compound **10b** with the atomic numbering is shown in Figure 2. The crystal and collection data as well as the structure refinements of the cycloadduct are given in Table 3. Table 4 reports the bond lengths and angles while Table 5 the torsion angles.

Table 3. Crystal data, collection data, and structure refinements of cycloadduct **10b**

	10b
Formula	$C_{20}H_{20}N_2O$
CCD deposit no.	291,467
MW	304.38
Crystal size, mm	0.52×0.42×0.28
Temperature, K	293(2)
Crystal system	Monoclinic
Space group	$P2_1/n$
a, Å	12.622(2)
b, Å	9.687(1)
c, Å	13.348(1)
β	96.01(1)
V, Å^3	1623.1(3)
Z	4
D_{calcd}, g/cm^3	1.246
Abs coeff., μ, cm^{-1}	0.774
Radiation	Mo Kα
λ	0.071073
F(000)	648
Range (°) for data coll.	$2.1\leq\theta\leq30.0$
Index range	$-17<h<17$, $0<k<13$, $0<l<18$
Reflection no.	4723
Unique refl.	4656
Correction applied	Lorentz polarization
Absorption correction	Semi-empirical from psi-scan
Absorption factors T	0.998, 0.973
No. of obsd refl. $I>2\sigma(I)$	1610
Refinement method	Full-matrix least-squares on F^2
Variables no.	288
Weights	0.0474, 0.003
Goodness-of-fit	0.923 (No refl. 4656)
R_1	0.064 (No refl. 1610)
wR_2	0.143 (No refl. 4656)
($\Delta\rho$) max, min, eÅ^{-3}	0.220, −0.110

Table 4. Bond lengths (Å) and angles (°) with Esd's in parentheses of cycloadducts **10b**

	10b
Bond lengths	
C1–C2	1.521(3)
C1–N9	1.481(3)
C1–C10	1.526(4)
C2–O3	1.454(3)
C2–C6	1.534(4)
O3–N4	1.420(3)
N4–C5	1.278(3)
C5–C6	1.496(3)
C5–C11	1.464(3)
C6–C7	1.542(3)
C7–C8	1.524(4)
C7–C10	1.522(4)
C8–N9	1.493(4)
N9–C17	1.430(4)
Bond angles	
C2–C1–N9	103.9(2)
C2–C1–C10	102.8(2)
N9–C1–C10	104.6(2)
C1–C2–O3	112.5(2)
C1–C2–C6	102.7(2)
O3–C2–C6	105.2(2)
C2–O3–N4	109.5(2)
O3–N4–C5	109.6(2)
N4–C5–C6	114.5(2)
N4–C5–C11	120.0(2)
C6–C5–C11	125.5(2)
C2–C6–C5	101.2(2)
C2–C6–C7	102.9(2)
C5–C6–C7	114.4(2)
C6–C7–C8	107.1(2)
C6–C7–C10	101.9(2)
C8–C7–C10	100.8(2)
C7–C8–N9	103.4(2)
C1–N9–C8	104.0(2)
C1–N9–C17	116.1(2)
C8–N9–C17	111.7(1)
C1–C10–C7	93.0(2)

In the azanorbornane ring the sum of the angles at N9 [331.8(2)°] is consistent with sp^3 hybridization. The heights of the pyramids with the nitrogen atom at the apex and the three atoms connected to it at the base is 0.459(2) Å. In the isoxazoline rings the angle at N4 of **10b** is consistent with sp^2 hybridization of N4 whereby the 2pz lone pair takes part in π-bonding within a part of the heterocyclic rings. Indeed the bond distances N4–C5 show a double bond character: 1.278(3) Å. The internal angles at the nitrogen atoms, O3–N4–C5 109.6(2)°, C1–N9–C8 104.0(2)° differ by 5.6°, justified by the different types of nitrogen; the narrower angle C1–N9–C8 is caused by the lone pair.

Bond lengths and angles in the condensed phenyl rings are reasonable, on weighted average,[25] 1.374(3) Å and 119.9(4)°. The phenyl ring attached to isoxazoline is nearly planar with maximum deviation 0.008(3) Å; this ring is tilted with respect to the isoxazoline moiety by 26.2(1)°, implying only a small conjugation between the double bond N4–C5 and the phenyl. The orientation is expressed by torsion angles given in Table 5. The deviations of atoms from the least-squares plane of the isoxazoline rings are in the range from −0.005(2) Å to 0.006(2) Å consistent with conformation *E* puckering parameters:[26] Q=0.010, ϕ=144.8° (ideal value 144°). The interplanar angle between the isoxazoline and the moiety C1–C2–C6–C7 is 117.98(9)°.

Table 5. Torsion angles (°) in compound **10b** with Esd's in parentheses

	10b
N4–C5–C11–C12	24.8(3)
N4–C5–C11–C16	−154.0(2)
C6–C5–C11–C12	−153.9(2)
C6–C5–C11–C16	27.3(3)

The six-membered ring of the azanorbornane is puckered with deviations by least-squares plane in the range −0.614(2) Å to 0.342(3) Å. These rings adopt boat conformation with parameters: Q=0.979, ϕ=62.4°, and θ=88.5° (ideal conformation ϕ=60° and θ=90°). The four chiral atoms C1, C2, C6, and C7 have the following configuration specified by the sequence rule:[27] *S*, *S*, *R*, *R* or *R*, *R*, *S*, *S* because of the centric space group. The molecular packing in the crystal is determined by van der Waal's contacts.

5. Experimental

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. IR spectra (Nujol mulls) were recorded on an FTIR Perkin–Elmer RX-1. ^{1}H and ^{13}C NMR spectra and NOESY experiments were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in parts per million from internal tetramethylsilane (δ). UV–vis spectra were recorded on an UV Perkin–Elmer LAMBDA 16 spectrophotometer using acetonitrile as solvent. HPLC analyses were carried out by means of a WATERS 1525 instrument equipped with an UV 2487 detector (λ=263 nm) both controlled by Breeze™ software and a RP C-18 Intersil ODS-2 column; a mixture of H_2O/CH_3CN 60:40 (1.0 mL/min) was used as an eluant. Column chromatography and TLC: silica gel 60 (0.063–0.200 mm) (Merck), eluants as specified. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

Materials. Benzhydroximoyl chloride **9** was prepared according to the well-known procedures.[28]

5.1. Cycloaddition of BNO with *N*-benzyl-2-azanorbornene

To *N*-benzyl-2-azanorbornene **8** (61.0 g, 327 mmol) dissolved in DCM (130 mL), Et_3N (42 mL, 300 mmol) was added and a solution of benzhydroximoyl chloride **9** (42.4 g, 273 mmol) in 150 mL of DCM was added dropwise under stirring at 0 °C. The reaction was continued for 48 h. The organic solution was washed with water and dried over anhydrous Na_2SO_4. The crude residue was then submitted to column chromatography to separate the cycloadducts **10a** and **10b**, which were isolated in 49% and 43% yields, respectively.

10a (33.8 g, 49%): As straw colored crystals from ethanol, mp 116–118 °C; [Found C, 78.9; H, 6.6; N, 9.1. $C_{20}H_{20}N_2O$ (MW=304.38) requires C, 78.92; H, 6.62; N, 9.20%]; ν_{max} (Nujol) 1590 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25–7.56 (10H, m, Ph), 4.83 (1H, dt, *J* 8, 1 Hz, H5-isoxaz.),

4.03 (1H, d, *J* 8 Hz, H4-isoxaz.), 3.79 (2H, AB syst., *J* 13 Hz, C*H*$_2$–Ph), 3.51 (1H, s, CH–N), 2.94 (1H, dd, *J* 10, 4 Hz, H3-*exo*), 2.78 (1H, br s, CH), 2.12 (1H, d, *J* 10 Hz, H3-*endo*), 1.64 (2H, m, CH$_2$); δ_C (75 MHz, $CDCl_3$) 156.4, 138.8, 129.7, 128.8, 128.6, 128.5, 128.4, 127.1, 126.6, 86.2, 61.8, 58.0, 53.3, 52.3, 44.4, 30.4.

10b (29.7 g, 43%): As straw colored crystals from ethanol, mp 119–121 °C; [Found C, 78.9; H, 6.7; N, 9.2. $C_{20}H_{20}N_2O$ (MW=304.38) requires C, 78.92; H, 6.62; N, 9.20%]; ν_{max} (Nujol) 1592 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.74 (4H, m, Ph), 7.25–7.56 (6H, m, Ph), 4.94 (1H, dt, *J* 8, 1.4 Hz, H5-isoxaz.), 3.78 (2H, s, C*H*$_2$–Ph), 3.74 (1H, d, *J* 8 Hz, H4-isoxaz.), 3.50 (1H, s, CH–N), 2.69 (1H, br s, CH); 2.63 (2H, m, H3); 1.58 (2H, m, CH$_2$); δ_C (75 MHz, $CDCl_3$) 156.7, 139.2, 129.8, 128.9, 128.7, 128.3, 127.0, 126.7, 85.8, 64.4, 59.5, 57.3, 55.7, 40.6, 28.8.

5.2. Competition experiments between norbornenes 8 and 11, and regioisomeric distribution of cycloadducts 10a and 10b

For the competition experiments, benzhydroximoyl chloride **9** (15 mg, 9.6 mmol) was added to a solution of *N*-benzyl-2-azanorbornene **8** and norbornene **11** in equimolecular amounts in 25 mL of the desired solvent along with 1.1 equiv of Et_3N. The mixtures were allowed to react at room temperature for 48 h. The solvents were evaporated and the crude residue was taken up in 25 mL of acetonitrile to be submitted to HPLC analyses.

For the determination of the regioisomeric distribution, the same quantities and procedure were followed in the absence of norbornene **11**.

The results are reported in Table 2.

5.3. Oxidation of the cycloadducts 10a and 10b with mCPBA

To DCM solutions of cycloadducts **10a** and **10b**, a slight excess (1.1 equiv) of mCPBA was added portionwise under stirring, cooling with a water bath the solutions if the temperature rises. The reactions were continued until the starting cycloadducts are consumed (TLC monitoring). Once the reactions were over, the solutions were neutralized with K_2CO_3 and were washed with water with final drying over anhydrous Na_2SO_4. Upon evaporation of the solvent, the crude *N*-oxides **13a** and **13b** were obtained in quantitative yields.

13a: White solid from ethanol, mp 122–124 °C; [Found C, 74.8; H, 6.1; N, 8.7. $C_{20}H_{20}N_2O_2$ (MW=320.38) requires C, 74.97; H, 6.29; N, 8.74%]; ν_{max} (Nujol) 1654 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.98 (2H, m, Ph), 7.00–7.60 (8H, m, Ph), 5.05 (1H, d, *J* 13 Hz, H5-isoxaz.), 4.97 (1H, d, *J* 8 Hz, C*H*$_2$–Ph), 4.45 (1H, d, *J* 13 Hz, H4-isoxaz.), 4.23 (1H, d, *J* 8 Hz, C*H*$_2$–Ph), 3.94 (1H, s, CH–N), 3.79 (1H, dd, *J* 12, 5 Hz, H3-*exo*), 3.56 (1H, dd, *J* 12, 1 Hz, H3-*endo*), 3.11 (1H, d, *J* 4 Hz, CH), 2.98 (1H, d, *J* 12 Hz, CH$_2$), 1.84 (1H, d, *J* 12 Hz, CH$_2$); δ_C (75 MHz, $CDCl_3$) 153.7, 131.2, 130.8, 130.4, 129.6, 128.9, 128.7, 127.1, 126.4, 84.5, 76.2, 74.8, 69.4, 52.9, 43.1, 29.9.

13b: White solid from ethanol, mp 144–146 °C; [Found C, 74.8; H, 6.2; N, 8.6. $C_{20}H_{20}N_2O_2$ (MW=320.38) requires C, 74.97; H, 6.29; N, 8.74%]; ν_{max} (Nujol) 1654 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (4H, m, Ph), 7.35 (6H, m, Ph), 5.83 (1H, d, *J* 8 Hz, H5-isoxaz.), 4.64 (1H, d, *J* 12 Hz, C*H*$_2$–Ph), 4.37 (1H, d, *J* 12 Hz, C*H*$_2$–Ph), 4.12 (1H, d, *J* 8 Hz, H4-isoxaz.), 3.86 (1H, s, CH–N), 3.75 (1H, dd, *J* 12, 4 Hz, H3-*exo*), 3.30 (1H, d, *J* 12 Hz, H3-*endo*), 2.80 (1H, d, *J* 14 Hz, CH), 2.78 (1H, d, *J* 12 Hz, CH$_2$), 1.69 (1H, d, *J* 12 Hz, CH$_2$); δ_C (75 MHz, $CDCl_3$) 156.8, 132.0, 130.6, 130.4, 129.4, 128.9, 128.4, 127.7, 126.8, 81.8, 76.0, 73.0, 67.8, 54.4, 40.3, 31.4.

5.4. Polonovski rearrangement

N-Oxides **13a** and **13b** were dissolved in pure Ac_2O (2.5 equiv) by controlling the temperature with an ice-bath. Stirring was continued at room temperature for 48 h. After this period of time, excess Ac_2O was decomposed by addition of water (leaving the mixtures overnight). To the solutions $NaHCO_3$ was added up to pH=8 and the solutions extracted with DCM. The organic phases were dried over anhydrous Na_2SO_4 and evaporation of the solvent afforded the crude *N*-acetyl derivatives **14a** and **14b** in nearly quantitative yields.

14a (94%): As straw colored crystals from benzene/*n*-hexane/drops of ethanol, mp 154–156 °C; [Found C, 70.3; H, 6.3; N, 10.9. $C_{15}H_{16}N_2O_2$ (MW=256.29) requires C, 70.29; H, 6.29; N, 10.93%]; ν_{max} (Nujol) 1630 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.85 (2H, m, Ph), 7.45 (3H, m, Ph), 4.91 (1H, m, H5-isoxaz.), 4.89 (1H, m, CH–N), 3.98 (1H, m, H4-isoxaz.), 3.47 (1H, dd, *J* 10, 4 Hz, H3-*endo*), 3.07 (1H, dd, *J* 10, 2 Hz, H3-*exo*), 3.04 (1H, s, CH), 2.04 (3H, s, CH$_3$), 1.76 (2H, m, CH$_2$); δ_C (75 MHz, $CDCl_3$) 168.9, 155.3, 130.2, 129.1, 128.9, 126.8, 85.5, 57.8, 56.4, 47.6, 44.4, 30.7, 21.7.

14b (92%): As straw colored crystals from benzene/*n*-hexane/drops of ethanol, mp 180–182 °C; [Found C, 70.2; H, 6.3; N, 11.0. $C_{15}H_{16}N_2O_2$ (MW=256.29) requires C, 70.29; H, 6.29; N, 10.93%]; ν_{max} (Nujol) 1622 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.73 (2H, m, Ph), 7.44 (3H, m, Ph), 4.83 (1H, d, *J* 8 Hz, H5-isoxaz.), 4.34 (1H, s, CH–N), 3.80 (1H, d, *J* 8 Hz, H4-isoxaz.), 3.27 and 3.40 (2H, AB syst., H3), 2.88 (1H, s, CH), 2.16 (3H, s, CH$_3$), 1.74 (2H, m, CH$_2$); δ_C (75 MHz, $CDCl_3$) 168.1, 156.2, 129.9, 129.7, 128.5, 126.4, 84.6, 61.2, 55.6, 49.6, 39.1, 31.8, 21.7.

5.5. Reactions with NBS/AIBN

N-Acetyl derivatives **14a** and **14b** were dissolved in CCl_4 (40 mL/g), using carefully CCl_4 washed glassware. To the suspensions 1 equiv NBS was added at room temperature along with 10% mol of AIBN. The mixtures were refluxed and the reaction status was monitored by TLC until the starting materials have disappeared. To ensure this, an additional half equivalent of NBS could be added. As the conversion of **14a** and **14b** was completed, the solutions were cooled down to ambient and then to lower temperature with an ice-bath to ensure the maximum separation of succinimide. From the filtrate, solvent was removed upon evaporation and the crude residues were submitted to chromatographic separation on

silica gel by eluting initially with $CHCl_3$ and $CHCl_3$/MeOH 9:1 afterwards. The bromo-cycloadducts **15a** and **15b**, the acetals **16a** and **16a′**, and the aldehydes **17a**, **17a′**, and **17b** were collected and characterized.

15a (47%): White solid from benzene/*n*-hexane, mp 212–215 °C; [Found C, 53.7; H, 4.5; N, 8.3. $C_{15}H_{15}N_2O_2Br$ (MW=335.20) requires C, 53.75; H, 4.51; N, 8.36%]; ν_{max} (Nujol) 1706, 1653 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, m, Ph), 7.47 (3H, m, Ph), 5.37 (1H, s, CH–Br), 5.08 (1H, d, *J* 8 Hz, H5-isoxaz.), 4.54 (1H, s, CH–N), 3.97 (1H, d, *J* 8 Hz, H4-isoxaz.), 2.97 (1H, s, CH), 2.63 (1H, m, CH_2), 2.24 (3H, s, CH_3), 1.77 (1H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 168.5, 154.4, 130.5, 129.1, 128.1, 126.3, 84.5, 64.6, 60.3, 59.5, 49.8, 28.2, 22.2.

15b (47%): White solid from benzene/*n*-hexane, mp 195–200 °C; [Found C, 53.8; H, 4.4; N, 8.4. $C_{15}H_{15}N_2O_2Br$ (MW=335.20) requires C, 53.75; H, 4.51; N, 8.36%]; ν_{max} (Nujol) 1700, 1661 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.74 (2H, m, Ph), 7.45 (3H, m, Ph), 5.45 (1H, s, CH–Br), 4.88 (1H, d, *J* 8 Hz, H5-isoxaz.), 4.51 (1H, s, CH–N), 3.97 (1H, d, *J* 8 Hz, H4-isoxaz.), 2.84 (1H, s, CH), 2.50 (1H, d, *J* 11 Hz, CH_2), 2.18 (3H, s, CH_3), 1.73 (1H, d, *J* 11 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.1, 155.8, 130.4, 129.0, 127.7, 126.8, 85.1, 68.0, 62.0, 54.6, 45.7, 29.7, 22.0.

16a (16%): White solid from benzene/*n*-hexane, mp 140–142 °C; [Found C, 65.8; H, 7.5; N, 8.1. $C_{19}H_{26}N_2O_4$ (MW=346.41) requires C, 65.87; H, 7.57; N, 8.09%]; ν_{max} (Nujol) 3260, 1651 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.87 (2H, m, Ph), 7.44 (1H, br s, NH), 7.42 (3H, m, Ph), 5.16 (1H, dd, *J* 10, 3 Hz, H5-isoxaz.), 4.68 (1H, d, *J* 5 Hz, O–CH–O), 4.44 (1H, m, CH–N), 4.09 (1H, dd, *J* 10, 3 Hz, H4-isoxaz.), 3.64 and 3.77 (4H, m, CH_2O), 2.57 (1H, m, CH), 2.05 (1H, m, CH_2), 1.91 (3H, s, CH_3), 1.74 (1H, m, CH_2), 1.24 (6H, t, CH_3); δ_C (75 MHz, CD_3COCD_3) 169.4, 158.5, 130.9, 130.6, 129.8, 128.4, 104.5, 89.2, 64.0, 63.5, 60.5, 55.7, 52.2, 33.9, 23.6, 16.1.

16a′ (12%): White solid from benzene/*n*-hexane, mp 110–112 °C; [Found C, 65.9; H, 7.6; N, 8.0. $C_{19}H_{26}N_2O_4$ (MW=346.41) requires C, 65.87; H, 7.57; N, 8.09%]; ν_{max} (Nujol) 3271, 1645 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.12 (2H, m, Ph), 7.50 (1H, br s, NH), 7.43 (3H, m, Ph), 5.12 (1H, dd, *J* 9, 6 Hz, H5-isoxaz.), 4.67 (1H, d, *J* 8.5 Hz, O–CH–O), 4.29 (1H, t, *J* 6 Hz, CH–N), 4.23 (1H, d, *J* 9 Hz, H4-isoxaz.), 3.61 (4H, m, CH_2O), 2.83 (1H, m, CH), 1.94 (3H, s, CH_3), 1.76 (1H, m, CH_2), 1.60 (1H, m, CH_2), 1.18 (6H, t, CH_3); δ_C (75 MHz, CD_3COCD_3) 170.6, 157.7, 130.9, 130.6, 129.8, 128.5, 104.5, 87.7, 63.6, 62.5, 60.8, 55.5, 50.4, 33.0, 23.3, 16.2.

17a/a′ (18%): White solid from benzene/ethanol, mp 119–122 °C; [Found C, 66.3; H, 5.8; N, 10.3. $C_{15}H_{16}N_2O_3$ (MW=272.29) requires C, 66.16; H, 5.92; N, 10.29%]; ν_{max} (Nujol) 3297, 1717, 1653 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.97 [10.01] (1H, s, CHO), 8.11 (2H, m, Ph), 7.46 (3H, m, Ph), 6.25 (1H, m, NH), 5.62 [5.65] (1H, d, *J* 8 Hz, H5-isoxaz.), 5.51 [5.54] (1H, s, CH–N), 4.49 [4.54] (1H, s, CH), 4.36 [4.42] (1H, d, *J* 8 Hz, H4-isoxaz.), 2.01 [2.06] (3H, s, CH_3), 1.89 [1.93] and 2.22 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 170.4, 156.4, 130.3, 128.8, 127.7, 127.5, 84.9 [84.5], 77.1 [77.3], 60.4 [62.0], 57.8 [60.2], 54.8 [55.7], 28.6 [30.0], 22.8 [23.3].

17b (20%): White solid from benzene/*n*-hexane, mp 162–164 °C; [Found C, 66.1; H, 5.9; N, 10.2. $C_{15}H_{16}N_2O_3$ (MW=272.29) requires C, 66.16; H, 5.92; N, 10.29%]; ν_{max} (Nujol) 3320, 1716 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 9.79 (1H, s, CHO), 7.69 (2H, m, Ph), 7.45 (3H, m, Ph), 7.07 (1H, br s, NH), 5.09 (1H, dd, *J* 9, 3 Hz, H5-isoxaz.), 4.73 (1H, dd, *J* 9, 3 Hz, H4-isoxaz.), 4.24 (1H, m, CH–N), 3.07 (1H, m, CH), 2.29 (2H, m, CH_2), 1.85 (3H, s CH_3); δ_C (75 MHz, CD_3COCD_3) 202.5, 170.6, 159.3, 131.2, 130.1, 129.5, 128.1, 91.7, 58.8, 56.8, 51.7, 32.0, 23.3.

5.6. Conversion of the bromo-cycloadducts 15a and 15b into the aldehydes 17a and 17b

To a solution in absolute EtOH of the bromo-cycloadducts **15a** and **15b**, an excess of $NaHCO_3$ was added and the mixtures were refluxed for several days, monitoring the evolution of the reactions by TLC until complete consumption of the starting materials. After filtration of the solid, the solvent was evaporated. The residues constituted a mixture of the acetals **16** and/or the aldehydes **17a** and **17b**. Complete transformation of the acetals into the aldehydes was secured by hydrolysis with AcOH/H_2O 3:7 at room temperature for 48 h. At the end of the reaction, the solution volumes were doubled with water and the pH adjusted at 7.5 with NaOH 20%. The water phases were extracted with DCM three times. The organic phases were dried over anhydrous Na_2SO_4 and evaporation of the solvent afforded the crude aldehydes **17**. From **15a**, the aldehydes **17a** and **17a′** were obtained as an epimeric mixture, not separated but submitted to the reduction step, while from **15b** the aldehyde **17b** was isolated and found identical to previously prepared sample.

5.7. Reduction of the aldehydes 17a and 17b

To a solution in MeOH of the aldehydes **17a** and **17b**, 2 equiv of $NaBH_4$ were added under stirring at room temperature. The reactions were carried on until complete consumption of the starting materials, monitoring by TLC. The reactions were subsequently quenched with water and saturated with salt. The water phases were extracted with DCM three times. The organic phases were dried over anhydrous Na_2SO_4 and evaporation of the solvent afforded the crude alcohols **18a** and **18b** in quantitative yields. Purification of the products was secured by column chromatography: from isomer **18a** the two stereoisomers **18a** and **18a′** were easily separated on silica gel by eluting with $CHCl_3$ initially and $CHCl_3$/MeOH 9:1 afterwards.

18a (100%): White solid from acetone, mp 160–161 °C; [Found C, 65.6; H, 6.6; N, 10.2. $C_{15}H_{18}N_2O_3$ (MW=274.31) requires C, 65.67; H, 6.61; N, 10.21%]; ν_{max} (Nujol) 3535, 3297, 1653 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.89 (2H, m, Ph), 7.70 (1H, b, NH), 7.43 (3H, m, Ph), 5.13 (1H, dd, *J* 9.6, 4 Hz, H5-isoxaz.), 4.42 (1H, m, CH–N), 4.36 (1H, t, *J* 5 Hz, CH), 4.11 (1H, dd, *J* 9.6, 4 Hz, H4-isoxaz.), 3.73 and 3.84 (2H, m, CH_2–O), 2.38 (1H, m, OH), 2.13 (1H, m, CH_2), 1.89 (3H, s, CH_3), 1.62 (1H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 170.5, 155.9, 134.9, 130.8, 129.8, 128.4, 90.5, 64.2, 60.8, 55.7, 50.8, 36.0, 23.6.

18a′ (100%): White solid from acetone, mp 152–154 °C; [Found C, 65.6; H, 6.6; N, 10.1. $C_{15}H_{18}N_2O_3$ (MW=274.31) requires C, 65.67; H, 6.61; N, 10.21%]; ν_{max} (Nujol) 3316, 1676 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.11 (2H, m, Ph), 7.52 (1H, b, NH), 7.42 (3H, m, Ph), 5.20 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 4.29 (2H, m, CH–N and CH), 4.27 (1H, d, *J* 9 Hz, H4-isoxaz.), 3.71 and 3.86 (2H, m, OH and CH_2–O), 2.73 (1H, m, CH), 1.94 (3H, s, CH_3), 1.47 (2H, dd, *J* 13, 6 Hz, CH_2); δ_C (75 MHz, CD_3COCD_3) 170.7, 157.7, 130.9, 130.6, 129.8, 128.5, 87.6, 62.0, 60.9, 55.7, 49.4, 33.7, 23.3.

18b (100%): White solid from acetone, mp 142–145 °C; [Found C, 65.7; H, 6.7; N, 10.3. $C_{15}H_{18}N_2O_3$ (MW=274.31) requires C, 65.67; H, 6.61; N, 10.21%]; ν_{max} (Nujol) 3378, 3318, 1653 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.81 (2H, m, Ph), 7.50 (1H, b, NH), 7.45 (3H, m, Ph), 4.99 (1H, dd, *J* 9, 4 Hz, H5-isoxaz.), 4.53 (1H, t, *J* 5 Hz, OH), 4.39 (1H, m, CH–N), 4.18 (1H, dd, *J* 9, 4 Hz, H4-isoxaz.), 3.74 and 3.83 (2H, m, CH_2–O), 2.37 (1H, m, CH), 2.14 (2H, s, CH_2), 1.87 (3H, m, CH_3); δ_C (75 MHz, CD_3COCD_3) 169.6, 160.4, 130.9, 130.0, 129.8, 128.3, 93.8, 65.7, 58.0, 54.8, 47.9, 35.0, 23.5.

5.8. Hydrolysis of the alcohols 18a and 18b

To a solution in MeOH of the alcohols **18a**, **18a′**, and **18b**, an equivalent volume of HCl 3 M was added and the solutions were heated overnight under a nitrogen atmosphere. The solution volumes were doubled with water and the pH adjusted to 8 with $NaHCO_3$. The solutions were then saturated with salt and extracted with DCM three times. The organic phases were dried over anhydrous Na_2SO_4 and evaporation of the solvent afforded quantitatively the crude aminols **19a**, **19a′**, and **19b**, which were purified by crystallization.

19a (100%): White solid from benzene/ethanol, mp 116–118 °C; [Found C, 67.2; H, 6.9; N, 12.1. $C_{13}H_{16}N_2O_2$ (MW=232.27) requires C, 67.22; H, 6.94; N, 12.06%]; ν_{max} (Nujol) 3334, 3266, 3176, 1604 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.67 (2H, m, Ph), 7.44 (3H, m, Ph), 5.21 (1H, dd, *J* 9, 2 Hz, H5-isoxaz.), 5.16 (2H, b, NH_2), 4.02 (2H, m, CH–N and H4-isoxaz.), 3.70 (2H, AB syst., CH_2–O), 2.52 (1H, m, CH), 2.10 (2H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 158.8, 131.0, 130.8, 129.9, 128.2, 91.7, 66.2, 64.7, 62.2, 51.2, 37.8.

19a′ (100%): White solid from benzene/ethanol, mp 153–158 °C; [Found C, 67.3; H, 7.0; N, 12.1. $C_{13}H_{16}N_2O_2$ (MW=232.27) requires C, 67.22; H, 6.94; N, 12.06%]; ν_{max} (Nujol) 3329, 3257, 3158, 1591 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.66 (2H, m, Ph), 7.45 (3H, m, Ph), 5.28 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 4.03 (1H, d, *J* 9 Hz, H4-isoxaz.), 3.97 (1H, s, CH–N), 3.67 and 3.87 (2H, m, CH_2–O), 2.84 (1H, m, CH), 1.58 (2H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 158.6, 131.9, 130.1, 129.6, 128.0, 89.1, 65.4, 62.2, 62.1, 49.6, 36.3.

19b (100%): White solid from benzene/ethanol, mp 130–131 °C; [Found C, 67.1; H, 6.8; N, 12.0. $C_{13}H_{16}N_2O_2$ (MW=232.27) requires C, 67.22; H, 6.94; N, 12.06%]; ν_{max} (Nujol) 3370, 3291, 3176, 1594 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.83 (2H, m, Ph), 7.47 (3H, m, Ph), 5.26 (2H, b, NH_2), 4.79 (1H, d, *J* 9 Hz, H5-isoxaz.), 4.26 (1H, dd, *J* 9, 2 Hz, H4-isoxaz.), 4.13 (1H, d, *J* 6 Hz, CH–N), 3.70 (2H, AB syst., CH_2–O), 2.48 (1H, m, CH), 2.11 (2H, m, CH_2) 1.51 (1H, d, *J* 13 Hz, CH_2); δ_C (75 MHz, CD_3COCD_3) 160.5, 130.9, 130.8, 130.0, 128.2, 95.0, 68.0, 66.2, 55.2, 49.1, 37.5.

5.9. X-ray crystallography

Unit-cell dimensions for compound **10b** were obtained by least-squares fit of 2θ values for 25 reflections, using an Enraf–Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation at the Centro Grandi Strumenti (CGS) dell'Università, Pavia, Italy.

A summary of crystal data, data collection, and structure refinement for compounds **10b** is presented in Table 3. Table 4 reports the bond lengths and angles while Table 5 the torsion angles.

An approximate absolute scale factor and a mean thermal parameters of 3.31 Å was determined by Wilson's method.[29] The structure was solved by direct method and the E-map correctly revealed the non-hydrogen atoms in the molecules and refined anisotropically in subsequent three-cycle least-squares. The positions of the hydrogen atoms were located from a difference Fourier synthesis, and refined isotropically in the subsequent least-squares refinement. The program SHELXL[30] was used to solve the structure. The ORTEP[31] program was used for molecular graphics.

CCDC 291,467 contains the supplementary crystallographic data. These data can be obtained free of charge via the internet web site at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21EZ, UK, or deposit@ccdc.cam.ac.uk).

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