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Conversion of a nitrosocarbonyl hetero Diels–Alder cycloadduct to useful isoxazoline-carbocyclic aminols

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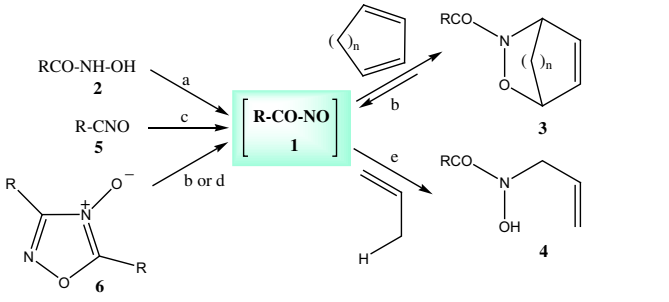
ABSTRACT

A new approach to useful precursors for the synthesis of isoxazoline-carbocyclic nucleosides is detailed, starting from the readily available *N*-benzoyl-2,3-oxazanorborn-5-ene and introducing more polar and hydrophilic functionalities through 1,3-dipolar cycloaddition of carbethoxyformonitrile oxide, generated either from the corresponding hydroximoyl chloride or, more conveniently, by catalyzed condensation with ethyl nitroacetate.

1. Introduction

Nitrosocarbonyls (R-CONO) **1** are fleeting intermediates which gained wide acceptance as dienophiles because of their high dienophilic activity and the synthetic potential of their hetero Diels–Alder (HDA) cycloadducts.[1] They are also reactive enophiles allowing for easy allylic amination and amidation with a variety of olefins.[2] Traditionally, nitrosocarbonyls are generated through periodate oxidation of hydroxamic acids **2** and instantly trapped by dienes (Scheme 1).[3]



a. IO_4^-; b. Δ; c. NMO; d. hv; e. only for **1** generated under non-oxidative (b-d) conditions

Scheme 1.

Other oxidative conditions have been developed[4–6] while the thermal cycloreversion of the HDA adducts **3** offers an alternative source of these intermediates.[7]

Recently, we developed two alternative entries to nitrosocarbonyls through the mild oxidation of nitrile oxides **5** with *N*-methylmorpholine-*N*-oxide (NMO)[8] and the clean photolysis and thermolysis of 1,2,4-oxadiazole-4-oxides **6**.[9] The mild oxidation of nitrile oxide with NMO is well compatible with the HDA and also with the Ene route, which works fine with tetra- and tri-substituted alkenes.[10] The photochemical cleavage of **6** is the softest route to nitrosocarbonyls. It was applied to the first and unique detection of nitrosocarbonyls through the laser photolysis of 1,2,4-oxadiazole-4-oxides **4**[11] and applies successfully to the HDA and Ene routes affording the corresponding adducts in high yields because of the absence of any interfering reactions aside from the nitrosocarbonyl dimerization and the subsequent rearrangement of the fleeting dimers.[12]

The HDA cycloadducts of nitrosocarbonyl intermediates allow for a flexible introduction of multiple functionality[13] as shown, for example by the various feasible manipulations of the 2,3-oxazanorborn-5-ene structure **3a** deriving from the HDA cycloaddition of nitrosocarbonyl benzene with cyclopentadiene. The *N*-acyl substituent can be detached under mild conditions[14] and the C=C double bond can be oxidized or reduced.[15] Several methods are available to selectively cleave the *N*–O tether including the use of amalgams [Na(Hg), Al(Hg)],[14i–k,15a–c] metals in acids (Zn/HCl, Zn/AcOH) or catalytic hydrogenation.[14f,g]

We found that the 2,3-oxazanorborn-5-ene **3a** is a highly reactive dipolarophile in cycloadditions with benzonitrile oxide (BNO) or mesitonitrile oxide (MNO) affording *exo*-selectively the

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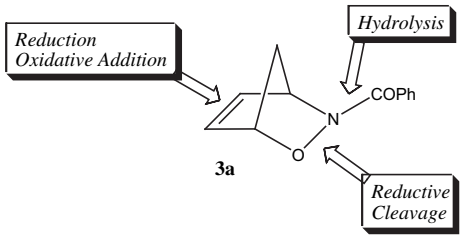
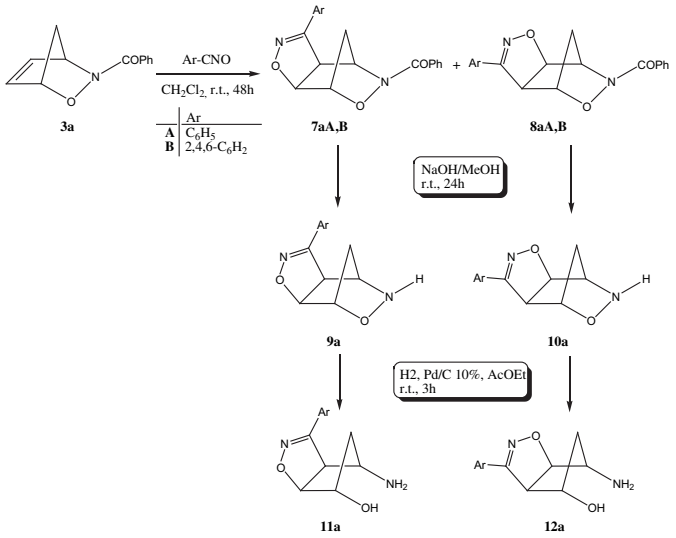


corresponding 1,3-dipolar cycloadducts **7** and **8** in fair yields (Scheme 2).[8d] These *exo*-cycloadducts **7** and **8** were almost quantitatively converted into aminols with the aid of the transformation shown in Scheme 2. Alkaline hydrolysis of the cycloadducts **7** and **8** takes place easily at room temperature affording the cyclic hydroxylamines **9** and **10**, which were converted into the aminols **11** and **12** by catalytic hydrogenation.



Scheme 2.

Starting from the aminols **11** and **12**, through the linear construction of the heterobases, we have recently detailed the syntheses of conformationally locked[16] racemic purine- and pyrimidine-carbocyclic nucleosides lacking a methylene group in the side chain in the carbocyclic unit.[8e–g] In the planned efforts to expand upon the versatility of **3**[17] and in the search for more hydrophilic and less cytotoxic structures, we were interested in replacing the aromatic rings on the isoxazoline moiety with hydrophilic groups. We report here the studies regarding the conversion of 2,3-oxazanorborn-5-ene **3a** into isoxazolinic moieties carrying ester and alcoholic functions by cycloaddition of **3a** with carbethoxyformonitrile oxide and nitronates.

2. Results

2.1. Cycloaddition of carbethoxyformonitrile oxide generated from the corresponding hydroximoyl chloride to the 2,3-oxazanorborn-5-ene and the nitronate approach

The 1,3-dipolar cycloaddition of **3a** with carbethoxyformonitrile oxide was performed with the in situ procedure,[17] by adding the corresponding hydroximoyl chloride **13** (1.2 equiv), prepared according to the reported protocol,[18] to a CH_2Cl_2 solution of the dipolarophile at 0 °C in the presence of a slight excess of Et_3N (1.3 equiv) (Scheme 3).

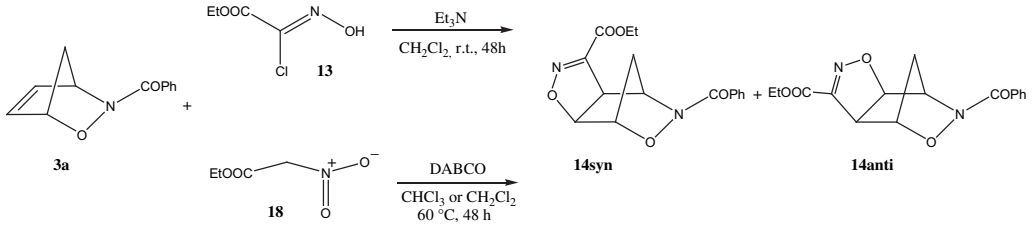
After chromatography, the two regioisomeric *exo*-cycloadducts **14syn** and **14anti** were isolated in 55% and 38% yields, respectively, as well as the furoxan deriving from the dimerization of the excess carbethoxyformonitrile oxide. The **syn** and **anti** descriptors refer here to the relative location of the ring oxygens.

The structures were secured from their analytical and spectroscopic data. The ^{1}H NMR spectrum of **14syn**, the only crystalline compound, showed the isoxazoline proton H5 at δ 5.12 (dt, J=8.6, 1.5 Hz), coupled with the H4 proton at δ 4.09 (d, J=8.6 Hz) and with the more deshielded of the two methylene protons at δ 2.04 through a ^4J=1.5 Hz ('W-coupling').[17] The regioisomer **14anti** is an oil and its ^{1}H NMR spectrum showed the isoxazoline proton H5 at δ 5.22 (dt, J=8.6, 1.5 Hz), coupled with the H4 proton at δ 3.99 (d, J=8.6 Hz) and with the more deshielded of the two methylene protons at δ 2.08 through a ^4J=1.5 Hz ('W-coupling'). The presence of the 'W-coupling' in both the cycloadducts as well as the absence of appreciable coupling between the isoxazoline and the bridgehead protons, found as singlets in both cases, fully support the *exo* structures of the 1,3-dipolar cycloadducts and is in line with the *exo*-selective addition to these dipolarophiles reported in the literature for other 1,3-dipoles and for the dihydroxylation reaction.[19] The regiochemical assignment was firmly established with an X-ray structure on a rearranged product obtained in the alkaline hydrolysis of the cycloadduct **14syn** reported later in Scheme 4.

In view of a higher environmental sustainability, compounds **14syn** and **14anti** were also prepared from ethyl nitroacetate, according to a recently described catalytic cycloaddition condensation process involving the cycloaddition of a nitronic acid-base complex.[20] This method requires cheap and safe starting materials and affords the isoxazolines in excellent yields with a slight excess of nitroacetate. Thus, in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst (10 mol %), the condensation of commercially available ethyl nitroacetate **18** and 2,3-oxazanorborn-5-ene **3a** in chloroform or CH_2Cl_2 solutions kept at 60 °C for 48 h gave the cycloadducts **14syn** and **14anti**, in 50% and 46% yields, respectively.

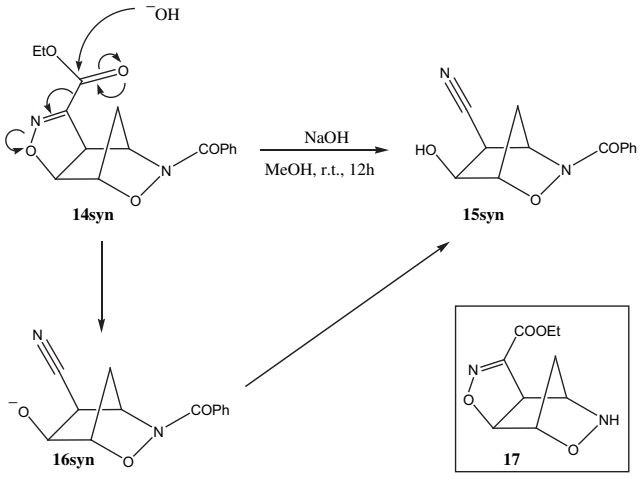
2.2. Alkaline hydrolysis of the esters 14

In order to achieve the aminol structures through the established synthetic route reported in Scheme 2, the alkaline hydrolysis of cycloadducts **14** was investigated. The hydrolysis of **14syn** took place easily in the presence of 1.1 equiv of NaOH in methanol



Scheme 3.

solution (Scheme 4). After stirring at room temperature for 12 h, the solvent was evaporated and the residue taken up with CH_2Cl_2 and washed with water.[8d]



Scheme 4.

A crystalline compound (**15syn**) was collected after evaporation of the CH_2Cl_2. The IR spectrum showed a broad and intense band at 3418 cm^{-1} resembling an OH group and a sharp band at 2241 cm^{-1}, in the typical range of C≡N absorptions. In addition to these, a band at 1652 cm^{-1} was consistent for an amide C=O group. These data did not fit with the expected hydroxylamine structure **17**. Moreover, the ^1H NMR spectrum showed two singlets at δ 5.17 and 4.69 attributable to the bridge-head protons of an oxazanorbornene structure. Two other protons are found at δ 4.46 (d, J=7 Hz) and at δ 3.49 (dd, J=7, 1.7 Hz), in a range quite shielded with respect to the chemical shifts commonly observed for isoxazoline protons. In the ^{13}C NMR the typical chemical shift of a C≡N group was found at δ 115.1. The overall picture suggests cleavage of the isoxazoline ring while the oxazanorbornene bicyclic structure survives.

The solution of this structural problem, which also confirms the regiochemical attribution of the starting compound **14syn**, was provided by single-crystal X-ray analysis which allowed for the unequivocal attribution of the structure of the β-hydroxy nitrile derivative **15syn**. The ORTEP view of compound **15syn** is reported in Figure 1.

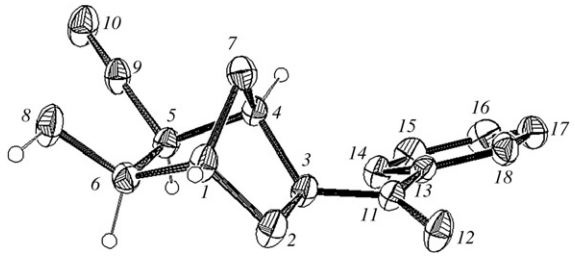
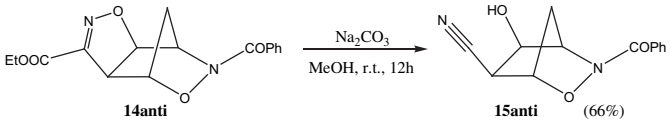


Figure 1. ORTEP plot of compound **15syn** with atom labeling (ellipsoid at 25% probability). Hydrogen atoms are omitted for clarity with the exception of those at the C1, C4, C5 and C6 atoms.

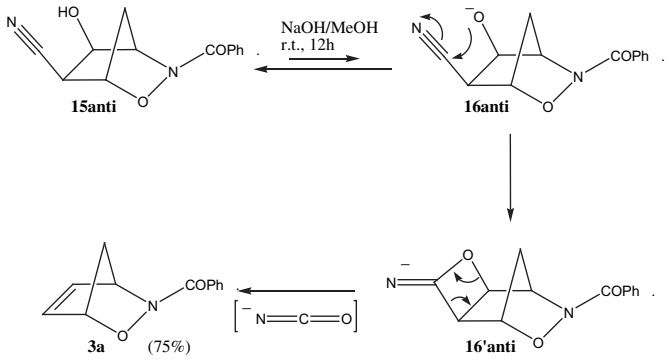
The results can be accounted for by a faster nucleophilic attack on the ester moiety with expulsion of the isoxazoline 3-anion, which fragments to the β-hydroxy nitrile as depicted in Scheme 4. This is a known mechanism for the alkaline fragmentation of 3-unsubstituted isoxazolines, i.e., fulminic acid cycloadducts,[21] as well as for reactions of nucleophiles with isoxazolines bearing $PhSO_2$-, EtOOC-,[22] TMS-[23] and HOOC-groups in the 3-position.[24] In all these cases, a base promotes the ring opening toward a β-hydroxy nitrile.

The cleavage of the cycloadduct **14syn** takes place easily even under milder conditions (Na_2CO_3, MeOH, rt, 12 h). Under these conditions cycloadduct **14anti** is also similarly converted into the β-hydroxy nitrile **15anti** (Scheme 5). After the usual work-up, a crystalline compound (66%) was isolated and identified as the desired β-hydroxy nitrile **15anti**. Similar spectroscopic data as for **15syn** were observed for **15anti**.



Scheme 5.

When using more drastic conditions (NaOH) the cycloadduct **14anti** enters an unexpected cycloreversion affording the starting oxazanorbornene **3a**. The β-hydroxy nitrile **15anti** is an intermediate in this formal cycloreversion process as shown by its easy elimination to **3a** by exposure to NaOH in MeOH. A conceivable mechanism for the ready elimination of **15anti** is depicted in Scheme 6. In the presence of NaOH the alcohol moiety of the anion **16anti** undergoes addition to the facing nitrile leading to a strained imino β-lactone anion **16′anti**. Cycloreversion of the latter affords then the oxa-azanorbornene **3a** and cyanate anion.



Scheme 6.

The mechanism is akin to that accepted for Wittig reaction starting from β-hydroxy phosphonium salts.[25] Treatment of the salts with a variety of bases at room temperature affords a betaine analogous to **16** with the phosphonium moiety in the place of nitrile. Closure to the four-membered oxaphosphetane and subsequent cycloreversion leads to the alkene and phosphine oxide.

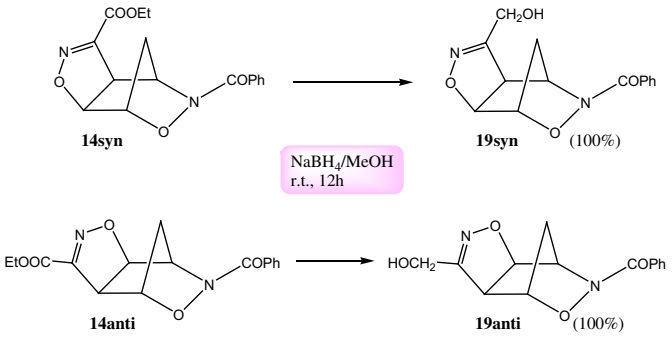
Surprisingly, the ready elimination of the OH and CN under basic conditions was never observed. Most studies dealt with acyclic β-hydroxy nitriles and the two groups adopt an *anti* stereochemistry making the here observed *syn* elimination more difficult.

The same reaction does not occur at room temperature in the case of the regioisomeric β-hydroxy nitrile **15syn**. Under more forcing conditions (NaOH, MeOH, 50 °C, 3 h) however either **15syn** or the adduct **14syn** afford **3a**, similarly.

2.3. Conversion to alcohols and related aminols

A viable alternative to the synthetic targets is provided by the conversion of the esters **14** to the related alcohols. The reductions of

the ester group of the 3-alkoxycarbonyl isoxazolines can be readily performed with $NaBH_4$ in methanol solution.[26] To methanol solutions of the compounds **14syn** and **14anti** a slight excess (1.1 equiv) of $NaBH_4$ was added portionwise and the solutions were stirred at room temperature for 12 h (Scheme 7).



Scheme 7.

The reduction of the cycloadduct **14syn** afforded quantitatively the alcohol **19syn** whose IR spectrum showed an intense OH band at 3389 cm^{-1}. The same OH group gave a broad singlet in the ^1H NMR spectrum at δ 4.23, which disappears by adding D_2O. The ethoxy group signals are missing while an AB system centered at δ 4.44 corresponds to the CH_2–O group. The presence of the isoxazoline ring was confirmed since two doublets were found at δ 4.87 (J=8 Hz) and δ 3.98 (J=8 Hz), corresponding to the H5 and H4 isoxazoline protons. Finally, the bridge-head protons gave two singlets at δ 5.26 (CH–O) and at δ 4.85 (CH–N).

Reduction of regioisomer **14anti** afforded the alcohol **19anti** as an oil in quantitative yields.

After reducing the carbethoxy function the access to the related aminols was performed without problems (Scheme 8). The *N*-benzoyl removal from cycloadducts **19** took place easily in the presence of 1.1 equiv of NaOH in methanol solution. After stirring at room temperature for 12 h,[8d] the hydroxylamine derivatives **20** were obtained in high yields (95–98%) and fully characterized. The ^1H NMR spectra show the absence of any aromatic signal corroborating the benzoyl detachment and the presence of the NH signals as singlets at 6.24 and 6.25 δ, respectively for **20syn** and **20anti**.

Hydrogenolysis of derivatives **20syn** and **20anti** under standard conditions[8d] afforded quantitatively the desired target aminols **21syn** and **21anti** whose structures were proven from their analytical and spectroscopic data. In particular, in the IR spectra, intense bands corresponding to the OH and NH_2 groups are found for **21syn** and **21anti**. In the ^1H NMR spectra the NH signals disappeared while the isoxazoline structure survives: 3.59 (d, J=9 Hz, H4, 4.91 (d, J=9 Hz, H5) in **21syn** and 3.64 (d, J=8 Hz, H4), 4.86 (d, J=8 Hz, H5) in **21anti**.

3. Conclusions

In conclusion, useful precursors for the synthesis of isoxazoline-carbocyclic nucleosides are prepared from the readily available *N*-benzoyl-2,3-oxazanorborn-5-ene **3a** and introducing more polar and hydrophilic functionalities via a condensed carbethoxyisoxazoline nucleus. This polycyclic heterocycle is obtained from carbethoxyformhydroxymoyl chloride or, more conveniently, by catalyzed condensation with ethyl nitroacetate.

4. Experimental

4.1. General

Elemental analyses were done on a C. Erba 1106 elemental analyzer. IR spectra (Nujol mulls) were recorded on an FTIR Perkin–Elmer RX-1. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). Column chromatography and TLC: silica gel 60 (0.0630.200 mm) (Merck); eluant cyclohexane/ethyl acetate from 9:1 to 5:5.

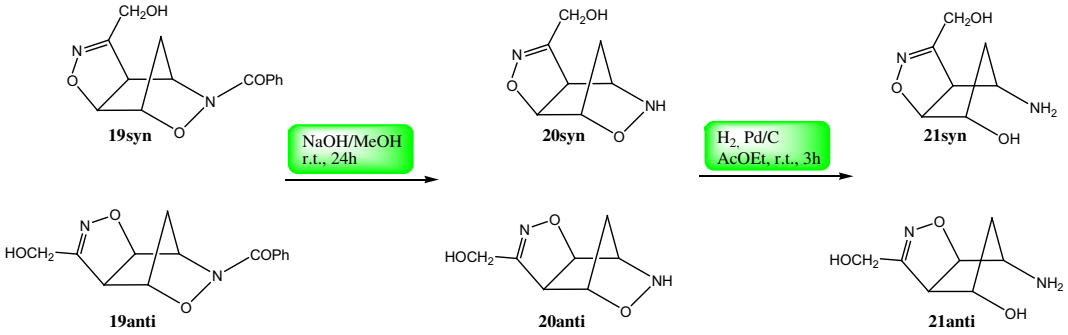
4.2. Materials

The hydroximoyl chloride, precursor of the carbethoxyformonitrile oxide, was obtained by treatment of commercially available (SIGMA–ALDRICH) glycine ethyl ester hydrochloride with sodium nitrite according to the reported method.[18] Ethyl nitroacetate and DABCO were Fluka products from SIGMA–ALDRICH. Chloroform (ethanol free) was filtered through a short pad of potassium carbonate just before the use.

The *N*-benzoyl-2,3-oxazanorborn-5-ene **3a** was prepared in 68% yield by the mild oxidation of BNO[27] with NMO (1.3 equiv) in CH_2Cl_2 in the presence of an excess of freshly distilled cyclopentadiene (2 equiv) according to the published procedure.[8c]

4.3. Cycloaddition of carbethoxyformonitrile oxide to the 2,3-oxazanorborn-5-ene 3a

To a stirred solution of the dipolarophile 2,3-oxazanorborn-5-ene **3a** (4.02 g, 20 mmol) in anhydrous CH_2Cl_2 (100 mL) and triethylamine (3.65 mL, 26 mmol), a solution of carbethoxymethylen-hydroximoyl chloride (20 g, 132 mmol) in the same solvent (20 mL) was added dropwise under stirring at 0 °C over a 0.5 h period. After keeping the reaction mixture for 2 days at rt, the organic phase was washed twice with water and dried over Na_2SO_4. The filtrate was evaporated under reduced pressure leaving a residue which was separated by column chromatography, using cyclohexane/ethyl acetate from 9:1 to 5:5 as eluant, to give the stereoisomeric cycloadducts **14syn** and **14anti**, which were fully characterized.



Scheme 8.

Compound **14syn**: 3.5 g (55%), mp 134–135 °C, colorless crystals from ethyl acetate/diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.35 (t, 3H, J=7 Hz, CH_3), 1.87 (d, 1H, J=12 Hz, H–CH), 2.04 (dt, 1H, J=12, 1.5 Hz, HC–H), 4.09 (d, 1H, J=8.6 Hz, H4 isox.), 4.34 (m, 1H, CH_2–O), 4.94 (s, 1H, CH–N), 5.12 (dt, 1H, J=8.6, 1.5 Hz, H5 isox.), 5.19 (s, 1H, CH–O), 7.51 (m, 3H, arom.), 7.75 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=15.3, 34.1, 56.2, 61.0, 63.8, 81.7, 86.4, 129.6, 130.2, 133.5, 133.9, 151.8, 160.8, 172.6 ppm. IR: ν=1732 (C=O), 1676 (C=N) cm^{-1}. $C_{16}H_{16}O_5N_2$ (316.31): C 60.75, H 5.10, N 8.86; found C 60.7, H 5.0, N 8.9.

Compound **14anti**: 2.4 g (38%), pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.36 (t, 3H, J=7 Hz, CH_3), 1.91 (d, 1H, J=12 Hz, H–CH), 2.08 (dt, 1H, J=12, 1.5 Hz, HC–H), 3.99 (d, 1H, J=8.6 Hz, H4 isox.), 4.34 (m, 1H, CH_2–O), 5.07 (s, 1H, CH–N), 5.15 (s, 1H, CH–O), 5.22 (dt, 1H, J=8.6, 1.5 Hz, H5 isox.), 7.45 (m, 3H, arom.), 7.76 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.9, 32.6, 56.1, 61.4, 62.4, 79.9, 84.6, 128.2, 128.8, 132.0, 132.4, 150.2, 159.6, 170.3 ppm. IR: ν=1719 (C=O), 1664 (C=N) cm^{-1}. $C_{16}H_{16}O_5N_2$ (316.31): C 60.75, H 5.10, N 8.86; found C 60.6, H 4.9, N 8.7.

4.4. Alkaline hydrolysis of cycloadducts 14

To a stirred solution of the cycloadducts **14** (0.30 g, 0.95 mmol) in methanol (50 mL), 1.1 equiv of solid ground Na_2CO_3 were added portionwise at room temperature. After keeping the reaction mixture overnight at rt, the solvent was evaporated and the residues were taken up with CH_2Cl_2 and washed twice with a saturated solution of $NaHCO_3$ to adjust the pH at 7. A further wash with water was made and finally the organic phases were dried over Na_2SO_4. The evaporation of the CH_2Cl_2 left solid compounds which were purified by recrystallization from the appropriate solvents to give the β-hydroxy nitriles **15syn** in quantitative yields and **15anti** in 66% yield.

Compound **15syn**: 0.23 g (100%), mp 167–168 °C, colorless crystals from ethanol. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.14 and 2.46 (m, 2H, CH_2), 3.49 (dd, 1H, J=7, 1.7 Hz, CH–CN), 4.46 (d, 1H, J=7 Hz, CH–OH), 4.69 (s, 1H, CH–N), 5.17 (s, 1H, CH–O), 7.46 (m, 2H, arom.), 7.55 (m, 1H, arom.), 7.76 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=30.8, 34.3, 40.1, 59.0, 70.4, 80.9, 115.1, 128.2, 128.7, 129.0, 132.3, 176.0 ppm. IR: ν=3418 (OH), 2241 (CN), 1652 (C=O) cm^{-1}. $C_{13}H_{12}O_3N_2$ (244.24): C 63.92, H 4.95, N 11.47; found C 63.8, H 5.0, N 11.5.

Compound **15anti**: 0.15 g (66%), mp 43–45 °C, colorless crystals from diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.18 and 2.53 (d, 1H+1H, J=11 Hz, CH_2), 3.37 (d, 1H, J=7 Hz, CH–CN), 4.57 (d, 1H, J=7 Hz, CH–OH), 4.93 (s, 1H, CH–N), 4.99 (s, 1H, CH–O), 7.45 (m, 2H, arom.), 7.55 (m, 1H, arom.), 7.72 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=34.2, 41.5, 61.6, 69.5, 79.7, 114.9, 128.2, 128.8, 132.0, 132.1, 169.3 ppm. IR: ν=3392 (OH), 2248 (CN), 1652 (C=O) cm^{-1}. $C_{13}H_{12}O_3N_2$ (244.24): C 63.92, H 4.95, N 11.47; found C 63.9, H 4.9, N 11.4.

By using the standard procedure already tested (NaOH 1.1 equiv in MeOH at rt for 12 h) adduct **14syn** affords quantitatively the nitrile **15syn** while the adduct **14anti** or the β-hydroxy nitrile **15anti** yielded the 2,3-oxazanorborn-5-ene **3a** in fair yields.

Cycloadduct **14syn** and nitrile **15syn** afford in fair yields the 2,3-oxazanorbornen **3a** only under more forcing conditions (NaOH, MeOH, 50 °C, 3 h).

4.5. Reaction of ethyl nitroacetate with the 2,3-oxazanorborn-5-ene 3a in the presence of DABCO

Ethyl nitroacetate **18** (1.5 equiv) was added to a $CHCl_3$ or CH_2Cl_2 solution of the 2,3-oxazanorborn-5-ene **3a** (13.7 g, 68 mmol) in the presence of 0.1 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.76 g, 10% mol). The mixture was placed in a sealed flask and heated at 60 °C under stirring for 48 h. After this period of time, the solution was washed with water and the organic phase dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a residue which was submitted to chromatographic separation, using cyclohexane/ethyl acetate from 9:1 to 5:5 as eluant, to isolate the two cycloadducts **14syn** and **14anti** in 50% and 46% yields, respectively.

Compounds **14syn** and **14anti** prepared with the above described method were found identical (superimposable IR and ^{1}H NMR spectra) with authentic samples of the cycloadducts obtained from the cycloaddition of carbethoxyformonitrile oxide to the same dipolarophile.

4.6. Reduction of the cycloadducts 14

To a stirred solution of the cycloadducts **14** (0.4 g, 1.3 mmol) in methanol (70 mL), 1.1 equiv of $NaBH_4$ (0.06 g, 1.4 mmol) were added portionwise at room temperature and left overnight. After evaporation of the solvent, the residues were taken up with CH_2Cl_2 and washed twice with water and the organic phases dried over Na_2SO_4. The filtrates were evaporated under reduced pressure leaving the crude alcohols **19syn** and **19anti** in quantitative yields, which were purified and fully characterized.

Compound **19syn**: 0.35 g (100%), mp 100–102 °C, colorless crystals from diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.02 (m, 2H, CH_2), 3.98 (d, 1H, J=8 Hz, H4 isox.), 4.23 (br s, 1H, OH), 4.43 (d, 1H, J=16 Hz, CH_2–OH), 4.46 (d, 1H, J=16 Hz, CH_2–OH), 4.85 (s, 1H, CH–N), 4.87 (d, 1H, J=8 Hz, H5 isox.), 5.26 (s, 1H, CH–O), 7.42 (m, 2H, arom.), 7.52 (m, 1H, arom.), 7.75 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=32.6, 56.5, 56.7, 58.6, 80.9, 82.0, 128.1, 132.1, 132.2, 157.0, 170.0 ppm. IR: ν=3389 (OH), 1624 (C=X) cm^{-1}. $C_{14}H_{14}O_4N_2$ (274.27): C 61.31, H 5.15, N 10.21; found C 61.4, H 5.0, N 10.2.

Compound **19anti**: 0.34 g (100%), oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.87 and 2.04 (m, 2H, CH_2), 3.83 (br s, 1H, OH), 3.84 (d, 1H, J=17 Hz, CH_2–OH), 3.86 (d, 1H, J=17 Hz, CH_2–OH), 3.95 (d, 1H, J=8 Hz, H4 isox.), 5.03 (s, 1H, CH–N), 5.12 (s, 1H, CH–O), 5.19 (d, 1H, J=8 Hz, H5 isox.), 7.38 (m, 2H, arom.), 7.48 (m, 1H, arom.), 7.71 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=32.6, 53.0, 56.0, 61.3, 79.9, 84.6, 128.2, 128.8, 132.0, 132.4, 150.0, 160.0, 170.2 ppm. IR: ν=3482 (OH), 1625 (C=X) cm^{-1}. $C_{14}H_{14}O_4N_2$ (274.27): C 61.31, H 5.15, N 10.21; found C 61.2, H 5.0, N 10.1.

4.7. Hydrolysis of the alcohols 19

To a stirred solution of the alcohols **19** (0.71 g, 2.6 mmol) in methanol (80 mL), 1.1 equiv of solid ground NaOH were added portionwise at room temperature. After keeping the reaction mixture overnight at rt, the solvent was evaporated and the residues were taken up with CH_2Cl_2 and washed twice with a saturated solution of $NaHCO_3$ to adjust the pH at 7. A further wash with water was made and finally the organic phases were dried over Na_2SO_4. The evaporation of the CH_2Cl_2 left solid compounds which were purified by recrystallization from proper solvents to give the hydroxylamines **20syn** and **20anti** in optimum yields.

Compound **20syn**: 0.43 g (98%), mp 143–145 °C, colorless crystals from diisopropyl ether. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ=1.73 and 1.87 (m, 2H, CH_2), 3.59 (d, 1H, J=8 Hz, H4 isox.), 4.11 (s, 1H, CH–N), 4.35 (d, 1H, J=15 Hz, CH_2–OH), 4.37 (d, 1H, J=15 Hz, CH_2–OH), 4.40 (m, 1H, OH), 4.42 (s, 1H, CH–O), 4.50 (d, 1H, J=8 Hz, H5 isox.), 6.24 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ=35.4, 57.6, 57.9, 60.2, 77.9, 84.2, 159.0 ppm. IR: ν=3225 (OH, NH), 1619 (C=N) cm^{-1}. $C_7H_{10}O_3N_2$ (170.16): C 49.41, H 5.92, N 16.46; found C 49.3, H 5.9, N 16.5.

Compound **20anti**: 0.42 g (95%), mp 98–100 °C, colorless crystals from diisopropyl ether+drops of ethanol. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ=1.77 and 1.88 (m, 2H, CH_2), 3.57 (d, 1H, J=8 Hz,

H4 isox.), 3.87 (s, 1H, CH–N), 4.30 (d, 1H, J=16 Hz, CH_2–OH), 4.32 (d, 1H, J=16 Hz, CH_2–OH), 4.68 (d, 1H, J=8 Hz, H5 isox.), 4.74 (s, 1H, CH–O), 6.25 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ=34.9, 57.4, 60.0, 62.2, 77.1, 84.3, 158.5 ppm. IR: ν=3392 (OH, NH), 1702 (C=N) cm^{-1}. $C_7H_{10}O_3N_2$ (170.16): C 49.41, H 5.92, N 16.46; found C 49.3, H 5.8, N 16.4.

4.8. Hydrogenolysis of hydroxylamines 20

Solutions of hydroxylamines **20** (2.2 mmol) and 10% Pd/C (115 mg) in ethyl acetate (80 mL) were submitted to catalytic hydrogenation at room temperature for 3 h until absorption of 1 equiv of hydrogen. The catalyst was filtered and the solutions evaporated to dryness to leave solid residues. Recrystallization from proper solvents afforded the desired aminols **21** in fair yields.

Compound **21syn**: 0.17 g (99%), mp 141–145 °C (dec), colorless crystals from diisopropyl ether. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ=1.73 (m, 2H, CH_2), 3.59 (d, 1H, J=9 Hz, H4 isox.), 4.10 (d, 1H, J=4 Hz, CH–N), 4.37 (d, 1H, J=16 Hz, CH_2–OH), 4.39 (d, 1H, J=16 Hz, CH_2–OH), 4.47 (d, 1H, J=4 Hz, CH–O), 4.91 (d, 1H, J=9 Hz, H5 isox.) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ=39.0, 57.6, 61.5, 65.2, 79.7, 93.0, 158.9 ppm. IR: ν=3357, 3284 (OH, NH_2), 1616 (C=N) cm^{-1}. $C_7H_{12}O_3N_2$ (172.18): C 48.83, H 7.03, N 16.27; found C 48.8, H 7.0, N 16.4.

Compound **21anti**: 0.16 g (98%), pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.86 and 2.14 (m, 1H+1H, CH_2), 3.64 (d, 1H, J=8 Hz, H4 isox.), 4.03 (s, 1H, CH–N), 4.42 (d, 1H, J=16 Hz, CH_2–OH), 4.44 (d, 1H, J=16 Hz, CH_2–OH), 4.79 (s, 1H, CH–O), 4.86 (d, 1H, J=8 Hz, H5 isox.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=34.4, 57.5, 58.6, 61.3, 76.2, 83.6, 156.6 ppm. IR: ν=3338 (OH, NH_2), 1677 (C=N) cm^{-1}. $C_7H_{12}O_3N_2$ (172.18): C 48.83, H 7.03, N 16.27; found C 48.7, H 6.9, N 16.3.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.10.062.

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