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Asymmetric nitrone cycloadditions and their application to the synthesis of enantiopure pyrrolidine and pyrrolizidine derivatives

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Abstract—The cycloaddition reactions of a pair of chiral pyrroline-*N*-oxides derived from D-ribose with some typical mono and disubstituted alkenes are reported. In all these reactions with monosubstituted alkenes as well as with dimethyl maleate the preferred stereochemical outcome of the cycloaddition step comes from a 5-*exo-anti* transition state whereas stereoisomers from the 5-*exo-syn* transition state are also present as minor adducts. In the reaction with dimethyl fumarate the major adduct comes from a *4-exo-5-endo-syn* transition state. The further behavior of the obtained isoxazolidines upon reductive ring opening conditions depends on the kind and the geometry of the preexisting substituents and they are transformed to enantiomerically pure pyrrolidine or pyrrolizidinone derivatives.

1. Introduction

Many chiral polyhydroxylated pyrrolidines, piperidines and the closely related pyrrolizidines, and indolizidines have biologically important properties as glycosidase inhibitors mimicking the structure of monosaccharides.[1] These alkaloidal sugar mimics, also known as azasugars are attractive synthetic targets as possible therapeutic agents against various metabolic disorders or infections like diabetes, influenza, AIDS or cancer.[2]

During the past decade a large number of elegant and efficient routes for azasugars has been developed.[1] Among them the nitrone-olefin 1,3-dipolar cycloaddition, an important methodology for the synthesis of many complex organic compounds, seems to be of particular importance.[3] The concerted process of this reaction accompanied by the usually high degree of regio and stereoselectivity allows the creation of multiple stereocenters in a single step, with complete control of their relative configuration. The resulting isoxazolidine cycloadducts may be elaborated in a variety of ways. For example, the labile N–O bond can be cleaved under mild reducing conditions followed by an intramolecular cyclization of the liberated amino group and the preexisting functionalities from either the nitrone or the dipolarophile. Various cyclization modes may proceed, such as N-alkylation, reductive amination, lactame formation, etc. depending on the nature of these functionalities. In this way pyrrolidines, piperidines, or even larger ring systems may be obtained. Accordingly, starting from cyclic nitrones, bicyclic nitrogen bridgehead rings like pyrrolizidine or indolizidine, etc. derivatives can be obtained. In this respect early attempts at the synthesis of pyrrolizidine alkaloids such as dl-sunipidine,[4] dl-retronecine,[5] or isoretronecanol[6] are noteworthy. Applying chiral nitrones and/or dipolarophiles the corresponding chiral aza heterocycles may be obtained. In particular, chiral polyhydroxy nitrones with stereochemistry closely related to that of monosaccharides and suitable alkenes may give the corresponding azasugar derivatives.

Special notice should be given to enantiomerically pure polyhydroxylated five or six-membered cyclic nitrones. These compounds accessible either from sugars,[7] or from other sources[8] are of particular importance and have found broad application in the synthesis of many nitrogenated sugar derivatives. In this way the stereochemistry of the starting nitrone is directly transferred to the final products.

As a continuation of our studies on the use of chiral 1,3-dipolar cycloadditions to gain access to azasugars[9] we have recently published the synthesis of the enantiomerically pure cyclic nitrones **1** and **2** (*ent*-**1**) starting from D-ribose.[10]

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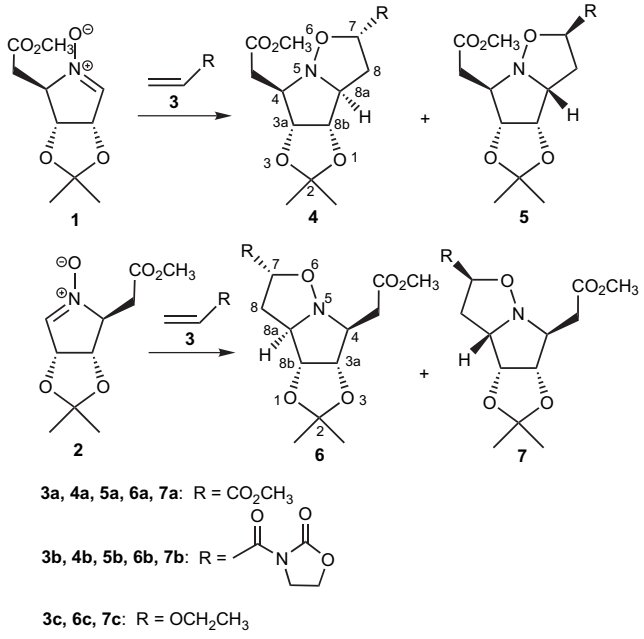
In this paper we present their cycloaddition reactions with both mono and disubstituted alkenes and the reductive transformations of the appropriate isoxazolidine cycloadducts to pyrrolidines and/or pyrrolizines.

2. Results and discussion

For the purposes of our study we used the monosubstituted alkenes methyl acrylate, acryloyloxazolidinone, ethyl vinyl ether, and the disubstituted alkenes dimethyl fumarate and dimethyl maleate. All these dipolarophiles are commercially available except for acryloyl oxazolidone, which has been prepared by a known way.[11]Methyl acrylate and ethyl vinyl ether were used in a large excess serving also as solvents while a two molar excess of the dipolarophile in dry chloroform was used in all other cases. All these reactions were carried out by refluxing under an argon atmosphere and they were monitored by TLC until the disappearance of the starting nitrone. The reactions with methyl acrylate (**3a**) and acryloyloxazolidinone (**3b**) were performed with both the enantiomeric nitrones **1** and **2** affording the diastereomeric 5-substituted isoxazolidines **4**, **5**, and **6** (*ent*-**4**), **7** (*ent*-**5**), respectively, in a ratio 3:1 for the reactions with methyl acrylate and 2:1 for the reactions with acryloyloxazolidinone and 80–90% total yield (Scheme 1).

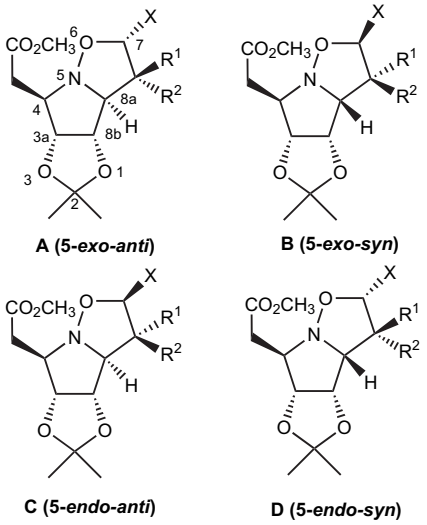


Scheme 1.

The structural elucidation of the obtained cycloadducts was mainly based on their spectral data, in connection with some chemical modifications. The structure of compound **5b** was unambiguously determined by an X-ray crystal structure analysis.

The proposed regiochemistry is in accordance with the well established regiochemistry of cycloadditions of nitrones with monosubstituted alkenes as dipolarophiles where the formation of 5-substituted isoxazolidines predominates[12] and it is strongly supported by the chemical shift of the 7-H proton next to isoxazolidine oxygen, which appears as a triplet or doublet of doublets at the higher δ value.

For 5-substituted isoxazolidines there are four possible diastereomers arising from the 5-X *exo*/*endo* approach of dipolarophile and also from the *syn* and the *anti* face of the reacting nitrone as depicted in Scheme 2 (R^1=R^2=H) for the nitrone **1**. Among these four possible diastereomeric structures the major products **4/6** were assigned as 5-*exo*-*anti* cycloadducts whereas the minor products **5/7** as 5-*exo*-*syn* cycloadducts. The observed low value (J=3.4 Hz) for the coupling constant between 8a-H and 8b-H of compounds **4b/6b** is indicative for their trans arrangement. Furthermore the significant NOE enhancement observed between 7-H and 8b-H (8% enhancement of 7-H upon saturation of 8b-H and 6% enhancement of 8b-H upon saturation of 7-H) supports strongly the proposed structure since among the four possible diastereomeric structures shown in Scheme 2 only structure A with a ladle arrangement of the three rings having the 7-H and 8b-H at the same site permits a close proximity between them.



Scheme 2.

As regards the other pair of cycloadducts **5b/7b** the relatively higher coupling constant between 8a-H and 8b-H (J=6.3 Hz) is indicative of their cis arrangement. Moreover this is also supported by NOE mutual enhancements between 8a-H and 8b-H (12% and 13% upon saturation of the respective protons). As regards the new stereogenic center at C-7, the observed NOE enhancements between 7-H and 4-H (8% enhancement of 4-H upon saturation of 7-H and 6% enhancement of 7-H upon saturation of 4-H) supports the concave arrangement of the rings, a fact, which is also supported by a substantial positive NOE (4%) developed on 7-H upon saturation of one of the dioxolane methyl groups. Moreover an X-ray crystal structure analysis carried out on compound **5b** confirms unequivocally its structure. An ORTEP drawing of compound **5b** is given in Figure 1.

As regards ^{1}H NMR data of compounds **4a/6a** and **5a/7a** are not sufficient to support the proposed structures since the most crucial structure elucidation peaks appear as superimposed multiplets. However, the structures of compounds

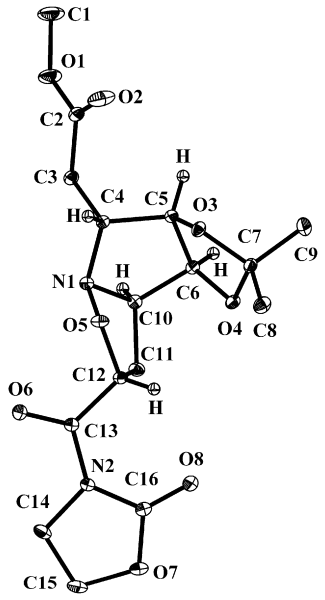
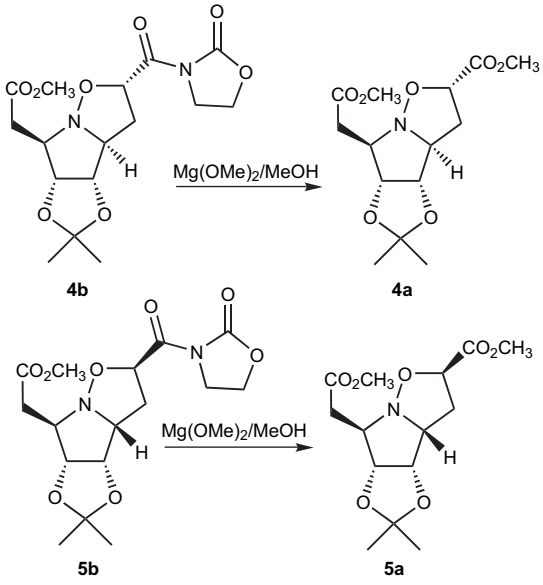


Figure 1. Labeled ORTEP plot for the molecular structure of compound **5b** at 30% thermal probability ellipsoids.

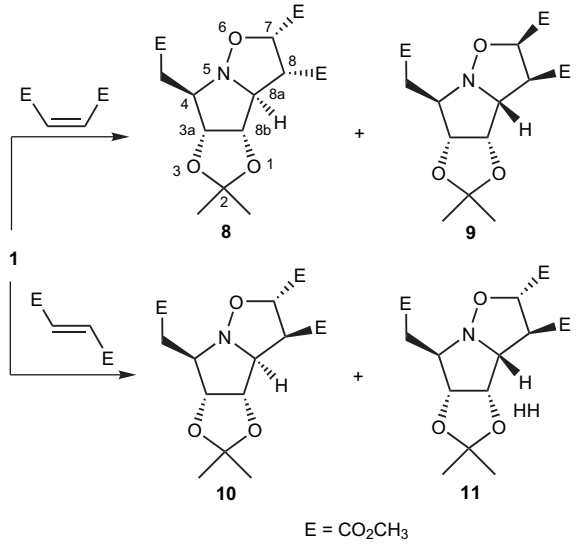
were secured by the conversion of **4b** and **5b** into **4a** and **5a**, respectively, upon treatment with $Mg(OMe)_2$ in accordance with analogous transformations of other similar carboximidic derivatives[13] (Scheme 3).



Scheme 3.

The cycloaddition reaction of nitrone **2** with ethyl vinyl ether also gave two diastereomeric cycloadducts **6c** and **7c** in a ratio ~2:1 and 94% total yield. Their structure elucidation was based on their spectral data. In particular, the low field chemical shift of 7-H for both compounds **6c** and **7c** at δ 5.02 and 5.15 ppm, respectively, confirms the proposed regiochemistry. The assignment of the proposed stereochemistry was made similarly to that of **4b/6b** and **5b/7b**. Thus, for the major isomer **6c** the relative low value of $J_{8aH-8bH}$=3.1 Hz is indicative for the trans arrangement of these protons. Additionally the significant positive NOE observed between 7-H and 8b-H (7% enhancement of 7-H upon saturation of 8b-H and 6% enhancement of 8b-H upon saturation of 7-H) strongly supports the proposed structure in which 7-H and 8b-H are in close proximity. For the minor diastereomer **7c** the relatively large value of coupling constant (J=7.9 Hz) between 8a-H and 8b-H is indicative of their cis arrangement as in compound **7b**. Furthermore the measurable coupling constants of the two 8-H give information for the trans geometry between 7-H and 8a-H. Thus one of 8-H at δ 2.31 (ddd, J=3.4, 6.2, and 13.1 Hz) is trans to 8a-H ($J_{81H-8aH}$=3.4 Hz) and cis to 7-H (J_{81H-7H}=6.2 Hz), whereas the other one at δ 2.83 (ddd, J=2.1, 7.9, and 13.1 Hz) is cis to 8a-H ($J_{82H-8aH}$=7.9 Hz) and trans to 7-H (J_{82H-7H}=2.1 Hz).

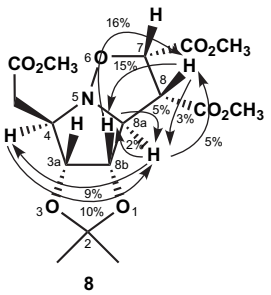
From the reaction of the nitrone **1** with dimethyl maleate an inseparable mixture was obtained, consisting of at least three components. Attempts at chromatographic separation failed, but the major diastereomer **8** was crystallized out from CH_2Cl_2/hexane leaving out an oily residue consisting mainly of the adduct **9** (Scheme 4).



Scheme 4.

The major isomer **8** was assigned as a *exo-anti* cycloadduct on the basis of its ^{1}H NMR data. The low value of the coupling constant of 8a-H with 8-H and 8b-H (J_{8aH-8H}=$J_{8aH-8bH}$=2.9 Hz) is indicative that 8a-H is trans to both 8H and 8b-H, which holds only in the *exo-anti* isomer between the four possible isomers (Scheme 2, structure A, X=R^2=CO_2CH_3, R^1=H). The proposed structure was further supported by NOE measurements made in C_6D_6 solution since in $CDCl_3$ most of the peaks were overlapped multiplets (Fig. 2).

The mutually significant NOE enhancements between 4-H and 8a-H show that these protons are at the same site as a result of the reaction of the *anti* face of the nitrone whereas the mutual large NOE enhancements between 8-H and 8b-H show their close proximity lying at the same site in a ladle arrangement of the three rings as a result of the *exo* approach of the dipolarophile to the *anti* face of the nitrone.

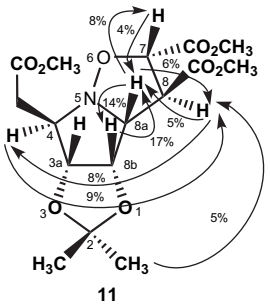


8

Figure 2. NOE enhancements measured on compound **8**.

The minor isomer from the reaction with dimethyl maleate was not isolated in a pure form. However, its proton NMR chemical shifts assigned by decoupling experiments from its crude mixture permit us to support structure **9** as a result of a *exo-syn* addition. The coupling constants of 8a-H with 8-H and 8b-H ($J_{8aH-8bH}$=$J_{8aH-8bH}$=5.8 Hz) are not very informative about their spatial arrangement. However, the substantial NOE enhancements between 8a-H and 8b-H (7% of 8b-H upon saturation of 8a-H and 10% of 8a-H upon saturation of 8b-H) and the absence of any measurable NOE between 8a-H and 8-H are indicative of cis and trans arrangements, respectively. Furthermore the proposed structure is supported by the remarkably positive NOE (4%) developed on both 7-H and 8-H upon saturation of one of the two dioxolane methyl groups. As is shown by molecular models the proximity of one of the methyl groups to 7-H and 8-H is possible only in the proposed structure with an *endo* position of the above hydrogens in a concave arrangement of the three rings.

The cycloaddition of nitrone **1** with dimethyl fumarate afforded two well resolved chromatographic bands in a ratio ~3:7. The fast moving band was a mixture of more than one diastereoisomer, which could not be further purified with compound **10** as the main component whereas the second band consisted of pure **11**. Structure **10**, which comes from a 4-*exo*-5-*endo-anti* approach is proposed on the basis of its proton chemical shifts as they were assigned in its crude mixture. Particularly 8a-H appears as a broad singlet with almost zero coupling constants with both 8-H and 8b-H, a fact that strongly supports its trans arrangement with these protons. Among the four possible diastereoisomers from the reaction of **1** with dimethyl fumarate (Scheme 2, X=R^1=CO_2CH_3, R^2=H) this arrangement holds only in structure C. The major product **11** was assigned as a 4-*exo*-5-*endo-syn* cycloadduct on the basis of NOE measurements as depicted in Figure 3. Since in $CDCl_3$ solution the peaks overlapped the measurements were made in $CDCl_3/C_6D_6$ (1:1) solution where fortunately all the peaks of diagnostic values appeared separately.



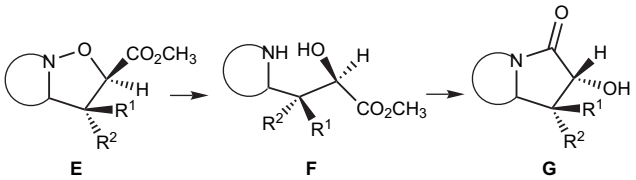
11

Figure 3. NOE enhancements measured on compound **11**.

The large enhancements between 8a-H and 8b-H strongly support their cis-arrangement whereas the comparatively much smaller enhancements between 8a-H and 8-H are indicative of their trans arrangement. Since 8a-H is trans to 8-H it lies on the same site of the ring with 7-H and a substantial positive NOE is developed between them. Furthermore the significant NOE enhancements between 8-H and 4-H show their close proximity, which is possible only in a concave arrangement of the three rings with 8-H in an *endo* position. This arrangement is further supported by the positive NOE of 8-H upon saturation of one of the dioxolane methyl groups.

The observed diastereoselectivity of the reactions of nitrones **1** and **2** is in accordance with molecular model predictions. Thus, with the exception of the reaction with dimethyl fumarate in all cases the stereochemically favored 5-*exo* adducts are formed with predominance of the 5-*exo-anti* adduct, which comes from the less sterically hindered transition state. In the reaction with dimethyl fumarate the more crucial steric hindrance caused by the 4-substituent favors the formation of the 4-*exo* adducts, which have the 5-substituent in an *endo* position. Futhermore due to favorable secondary interactions of the 5-*endo* substituent the *endo-syn* cycloadduct predominates. These findings are also in line with the well documented behavior of cyclic nitrones to react via *exo* transition states.[7b,7c,14]

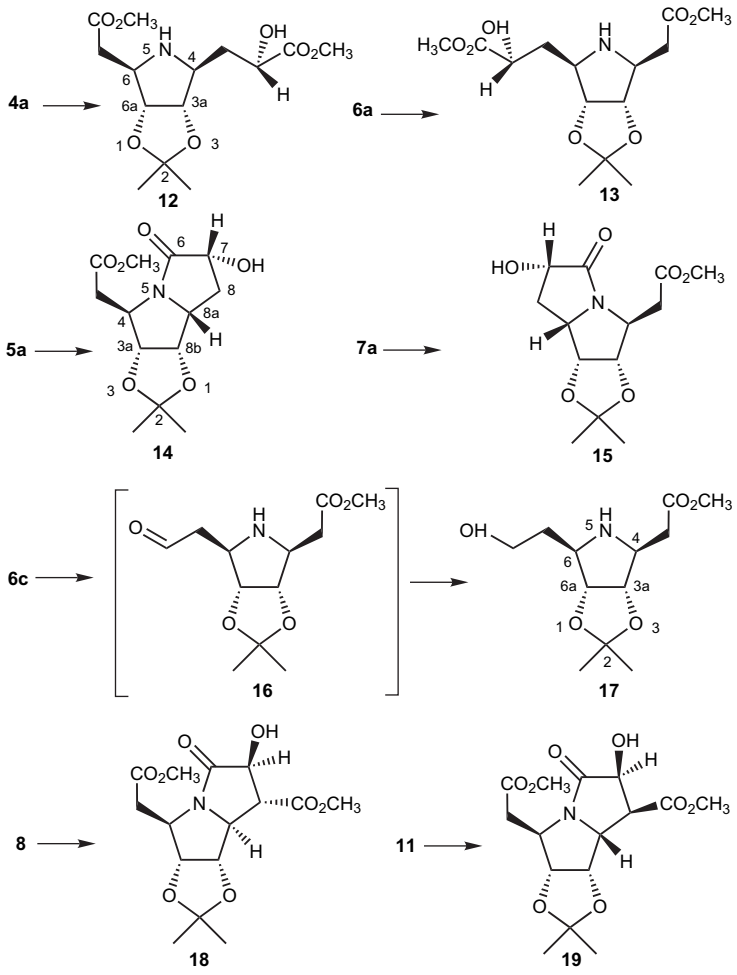
As has already been mentioned isoxazolidines are valuable intermediates for the synthesis of many nitrogenated heterocycles including those of nitrogen bridgeheaded bicyclic systems. In our case a reductive cleavage of the isoxazolidine ring may result in the formation of a pyrrolidine ring system containing an ester group at the desired position for the formation of a new lactam ring via an intramolecular cyclization. Thus the obtained 5-carboxymethyl isoxazolidines can be transformed to bicyclic lactams (**G**) via the intermediate amino derivatives (**F**) according to Scheme 5. During this process the stereochemistry of the starting nitrone and the stereogenic centers created during the cycloaddition step is transferred to the final products as is well documented in many cases by us and others.[15]



E F G

Scheme 5.

The reduction of the obtained isoxazolidines was made smoothly with Raney/Ni in a hydrogen atmosphere at room temperature and gave the open chain amino derivatives (**F**) or cyclization products (**G**) in moderate to good yields (45–77%) as shown in Scheme 6 for each case. Hydrogenolysis of the two enantiomeric isoxazolidines **4a** and **6a** gave the



Scheme 6.

two enantiomeric pyrrolidines **12** and **13**, respectively. Despite the presence of the 5-CO_2CH_3 these compounds were not further cyclized to bicyclic lactams derivatives even after prolonged heating. A reasonable explanation for this behavior could arise from the stereochemistry of the starting cycloadducts resulting in structures **12** and **13** where both the $CH_2CO_2CH_3$ group at C-5 and the open chain substituent generated after the cleavage of the isoxazolidine ring are on the same side probably in conformations that do not favor the cyclization step. On the contrary isoxazolidines **5a** and **7a** resulting in intermediates with the $CH_2CO_2CH_3$ group and side chain in trans position gave the cyclization products **14** and **15**. Isoxazolidine **6c** gave the pyrrolidine **17** probably by further reduction of the intermediate aldehyde **16**. The isoxazolidines **8** and **11** the main products of the cycloaddition of **1** with dimethyl maleate and dimethyl fumarate gave the pyrrolizidine derivatives **18** and **19** through cyclization of intermediate amines of the type **F**. The formation of compound **18** through an intermediate amine with a cis disposition of the $CH_2CO_2CH_3$ group and the resulting side chain as in compounds **12/13** is rather unexpected after the failure of **12/13** to give cyclization products. It seems that the presence of a second carboxymethyl group at the 8-position plays a not fully understandable role to a stabilization of a conformation favoring the cyclization step.

All the obtained reduction products gave the expected chemical shifts in the proton and carbon NMR spectra. Concerning their stereochemistry in the open chain products **12/13** and **17** the values of $J_{3a–4}$ and $J_{6–6a}$ ranging between 3.4–4.7 Hz are sufficiently smaller than that of $J_{3a–6a}$ being 6.1–6.5 Hz and are in accordance with their trans arrangement as it comes out from their isoxazolidines precursors. As regards the stereochemistry of the pyrrolizones **14/15**, **18** and **19** it cannot be supported by *J* values and NOE measurements since the chemical shifts of the crucial hydrogens appear as superimposed multiplets. Their stereochemistry was proposed on the basis of the stereochemistry of their parent isoxazolidines, as it has been already described above, assuming preservation of the stereochemistry during the reduction and ring closure steps (Scheme 5). This generally accepted assumption[15] is also nicely proved in our case where starting from the two enantiomeric isoxazolidines **4a** and **6a** the two enantiomeric pyrrolidines **12** and **13** were obtained whereas the two enantiomeric isoxazolidines **5a** and **7a** give the two enantiomeric pyrrolizidones **14** and **15** as it comes out from the concurrence of the spectral data and the opposite optical rotations of **12/13** and **14/15**, respectively.

In conclusion, a pair of enantiomerically pure cyclic nitrones derived from D-ribose react diastereoselectively with mono

and disubstituted alkenes to give the corresponding isoxazolidines. With the exception of the reaction with dimethyl fumarate the preferred stereochemical process is governed by steric factors and comes from a 5-*exo-anti* transition state whereas stereoisomers from the 5-*exo-syn* transition state are also formed as minor adducts. In the reaction with dimethyl fumarate due to the compromise of steric factors and secondary interactions the major adduct comes from a *4-exo-5-endo-syn* transition state and the minor from a *4-exo-5-endo-syn* transition state. Reductive cleavage of the obtained isoxazolidines depends on the kind and geometry of the preexisting alkene substituent and can lead to pairs of enantiomerically pure pyrrolidine or pyrrolizidine derivatives.

3. Experimental

3.1. General

All melting points are uncorrected and they are obtained with a Kofler hot stage apparatus. The IR spectra were obtained with a Perkin–Elmer 297 spectrophotometer, as a thin film or Nujol mull as indicated. The nuclear magnetic resonance spectra, reported in δ units, were obtained in $CDCl_3$ solutions, unless otherwise stated, with tetramethylsilane as an internal standard, and recorded with a Brucker AM 300 spectrometer, operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). ^{1}H NMR assignments, where it was possible, were confirmed by double resonance experiments. The mass spectra were measured with VG TS-250 spectrometer with an ionization energy of 70 eV. Elemental analyses were performed with a Perkin–Elmer CHN 2400 automatic analyzer. Optical rotations were measured with a A. KRÜSS Optronic P3002, operating at 589 nm (l=1 dm, 25 °C).

3.2. Cycloaddition reactions of nitrones 1 and 2 (*ent*-1)

3.2.1. Reactions of nitrones 1 and 2 (*ent*-1) with methyl acrylate. A solution of the nitrone **1** (0.78 g, 3.4 mmol) and methyl acrylate (8 mL) was refluxed for 5 h. The crude product obtained after evaporating the excess of methyl acrylate was purified by column chromatography (silica gel, hexane/EtOAc, 2:1) to give the products **4a** (0.705 g) and **5a** (0.235 g). Following the same procedure nitrone **2** (*ent*-**1**) (1.2 g, 5.3 mmol) and methyl acrylate (12 mL) gave the products **6a** (*ent*-**4a**) (1.09 g) and **7b** (*ent*-**5a**) (0.380 g).

3.2.1.1. (3a*R*,4*R*,7*S*,8a*S*,8b*S*)-7-(Methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (4a). This compound was isolated in 66% yield as a colorless oil; R_f (hexane/EtOAc, 2:1) 0.54; $[\alpha]_D^{25}$ +93.2 (*c* 1.48, $CHCl_3$); IR (liquid film): ν_{max} 2985, 1725 cm^{-1}; ^{1}H NMR: δ 1.35 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.62–2.82 (2H, m, 8-H and C*H*$_2$CO$_2$CH$_3$), 2.86–3.04 (2H, m, 8-H and C*H*$_2$CO$_2$CH$_3$), 3.67–3.82 (8H, superimposed m and s, 4-H, 8a-H, and CH_3O), 4.48–4.57 (2H, m, 3a-H, 8b-H), 4.73 (1H, t, J=6.9 Hz, 7-H); ^{13}C NMR: δ 25.1 and 27.3 (CH_3), 34.5 and 37.8 (C-8 and *C*H$_2$CO$_2$CH$_3$), 51.7 and 52.3 (CH_3O), 69.4, 70.3, and 74.1 (C-4, C-7, and C-8a), 85.9 and 88.1 (C-3a and C-8b), 113.2 (*C*(CH$_3$)$_2$), 171.4 and 172.1 (C═O); MS: *m*/*z* 315 (56% M$^+$). Anal. calcd for $C_{14}H_{21}NO_7$ (315.33): C, 53.33; H, 6.71; N, 4.44. Found: C, 53.21; H, 6.56; N, 4.54.

3.2.1.2. (3a*R*,4*R*,7*R*,8a*SR*,8b*S*)-7-(Methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (5a). This compound was isolated in 22% yield as a colorless oil; R_f (hexane/EtOAc, 2:1) 0.37; $[\alpha]_D^{25}$ −46.2 (*c* 0.93, $CHCl_3$); IR (liquid film): ν_{max} 2980, 1725; ^{1}H NMR: δ 1.31 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.46–2.62 (2H, m, 8-H and C*H*$_2$CO$_2$CH$_3$), 2.68 (1H, dd, J=14.8, 5.6 Hz, C*H*$_2$CO$_2$CH$_3$), 2.93 (1H, ddd, J=12.8, 9.6, 3.3 Hz, 8-H), 3.70 (3H, s, CH_3O), 3.77 (3H, s, CH_3O), 3.84–3.93 (2H, m, 4-H and 8a-H), 4.64–4.70 (2H, m, 3a-H, 8b-H), 4.74 (1H, dd, J=9.6, 7.5 Hz, 7-H); ^{13}C NMR: δ 24.4 and 26.5 (CH_3), 33.8 and 36.8 (C-8 and *C*H$_2$CO$_2$CH$_3$), 51.8 and 52.3 (CH_3O), 67.1 and 67.8 (C-4, C-8a), 75.5, 80.9, and 85.7 (C-3a, C-7, and C-8b), 113.2 (*C*(CH$_3$)$_2$), 172.2 and 171.2 (C═O); MS: *m*/*z* 315 (84% M$^+$). Anal. calcd for $C_{14}H_{21}NO_7$ (315.33): C, 53.33; H, 6.71; N, 4.44. Found: C, 53.06; H, 6.48; N, 4.54.

3.2.1.3. (3a*S*,4*S*,7*R*,8a*R*,8b*R*)-7-(Methoxycarbonyl)-2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo-[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (6a). This compound was isolated in 65% yield as a colorless oil; R_f (hexane/EtOAc, 2:1) 0.54; $[\alpha]_D^{25}$ −93.2 (*c* 1.11, $CHCl_3$); spectral data are the same as for **4a**. Anal. calcd for $C_{14}H_{21}NO_7$ (315.33): C, 53.33; H, 6.71; N, 4.44. Found: C, 53.22; H, 6.50; N, 4.54.

3.2.1.4. (3a*S*,4*S*,7*S*,8a*S*,8b*R*)-7-(Methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (7a). This compound was isolated in 23% yield as a colorless oil; R_f (hexane/EtOAc, 2:1) 0.37; $[\alpha]_D^{25}$ +47.6 (*c* 0.54, $CHCl_3$); spectral data are the same as for **5a**. Anal. calcd for $C_{14}H_{21}NO_7$ (315.33): C, 53.33; H, 6.71; N, 4.44. Found: C, 53.18; H, 6.45; N, 4.63.

3.2.2. Reactions of nitrones 1 and 2 (*ent*-1) with *N*-acryloyl-1,3-oxazolidin-3-one. A solution of nitrone **1** (0.746 g, 3.25 mmol) and oxazolidinone **3b** (0.90 g, 6.5 mmol) in $CHCl_3$ (35 mL) was refluxed for 15 h. After evaporation of the solvent the crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:2) to give products **4b** (0.65 g) and **5b** (0.34 g). In the same way nitrone **2** (*ent*-**1**) and the oxazolidinone **3b** (same quantities) afford products **6b** (*ent*-**4b**) (0.63 g) and **7b** (*ent*-**5b**) (0.34 g).

3.2.2.1. (3a*R*,4*R*,7*S*,8a*S*,8b*S*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-7-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]hexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (4b). This compound was isolated in 54% yield as a white solid, mp 157–160 °C (from EtOAc); R_f (hexane/EtOAc, 1:2) 0.43; $[\alpha]_D^{25}$ +71.4 (*c* 0.7, $CHCl_3$); IR (Nujol): ν_{max} 1775, 1720, 1700 cm^{-1}; ^{1}H NMR: δ 1.32 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.75–2.87 (3H, m, 8-H and C*H*$_2$CO$_2$CH$_3$), 2.99 (1H, dd, J=15.2, 8.5 Hz, 1H, C*H*$_2$CO$_2$CH$_3$), 3.62–3.71 (1H, m, 4-H), 3.74 (3H, s, CH_3O), 3.77–3.81 (1H, m, 8a-H), 3.96–4.05 (2H, m, –NC*H*$_2$CH$_2$O–), 4.43–4.52 (2H, m, –NCH$_2$C*H*$_2$O–), 4.61 (1H, dd, J=6.7, 3.4 Hz, 8b-H), 4.78 (1H, dd, J=6.7,

6.7 Hz, 3a-H), 5.38 (1H, dd, J=7.9, 6.0 Hz, 7-H); ^{13}C NMR: δ 25.0 and 27.3 (CH_3), 34.7 and 37.7 (C-8 and $CH_2CO_2CH_3$), 42.5 (–NCH_2CH_2O–), 51.8 (CH_3O), 62.7, 69.6, 70.5, 74.7, 86.0, and 88.2 (C-3a, C-4, C-7, C-8a, C-8b, and –NCH_2CH_2O–), 115.0 ($C(CH_3)_2$), 153.3, 170.9, and 171.5 (C=O); MS: m/z 370 (18% M^+). Anal. calcd for $C_{16}H_{22}N_2O_8$ (370.36): C, 51.87; H, 5.99; N, 7.56. Found: C, 51.97; H, 5.84; N, 7.55.

3.2.2.2. (3a*R*,4*R*,7*R*,8a*R*,8b*S*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-7-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]hexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (5b). This compound was isolated in 28% yield as white needles, mp 177–179 °C (from EtOAc); R_f (hexane/EtOAc, 1:2) 0.26; $[\alpha]_D^{25}$ −65.7 (c 0.67, $CHCl_3$); IR (Nujol): ν_{max} 1770, 1730, 1685 cm^{-1}; ^{1}H NMR: δ 1.30 (3H, s, CH_3), 1.55 (3H, s, CH_3), 2.42–2.55 (2H, m, 8-H and $CH_2CO_2CH_3$), 2.69 (1H, dd, J=15.9, 5.5 Hz, $CH_2CO_2CH_3$), 3.08 (1H, ddd, J=11.6, 9.1, 3.7 Hz, 8-H), 3.69 (3H, s, CH_3O), 3.85 (1H, ddd, J=8.1, 6.2, 3.7, 8a-H), 3.94 (1H, ddd, J=6.3, 5.5, 2.6 Hz, 4-H), 3.99–4.07 (2H, m, –NCH_2CH_2O–), 4.47 (2H, t, J=8.0 Hz, –NCH_2CH_2O–), 4.65 (1H, dd, J=6.2, 2.6 Hz, 3a-H), 4.75 (1H, dd, J=6.2, 6.2 Hz, 8b-H), 5.59 (1H, dd, J=9.1, 5.3, Hz, 7-H); ^{13}C NMR: δ 24.5 and 26.4 (CH_3), 33.7 and 36.8 (C-8 and $CH_2CO_2CH_3$), 42.5 (–NCH_2CH_2O–), 51.8 (CH_3O), 62.7, 67.2, 67.8, 75.6, 80.9, and 85.8 (C-3a, C-4, C-7, C-8a, C-8b, and –NCH_2CH_2O–), 113.4 ($C(CH_3)_2$), 153.0, and 170.2 (C=O); MS: m/z 370 (26% M^+). Anal. calcd for $C_{16}H_{22}N_2O_8$ (370.36): C, 51.87; H, 5.99; N, 7.56. Found: C, 51.63; H, 5.80; N, 7.48.

3.2.2.3. (3a*S*,4*S*,7*R*,8a*R*,8b*R*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-7-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]hexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (6b) (*ent*-4b). This compound was isolated in 52% yield as a white solid mp 163–164 °C (from EtOAc); R_f (hexane/EtOAc, 1:2) 0.43; $[\alpha]_D^{25}$ −72.7 (c 1.0, $CHCl_3$); spectral data are the same as compound **4b**. Anal. calcd for $C_{16}H_{22}N_2O_8$ (370.36): C, 51.87; H, 5.99; N, 7.56. Found: C, 52.18; H, 5.98; N, 7.54.

3.2.2.4. (3a*S*,4*S*,7*S*,8a*S*,8b*R*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-7-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]hexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (7b) (*ent*-5b). This compound was isolated in 28% yield as a white solid, mp 181–184 °C (from EtOAc); R_f (hexane/EtOAc, 1:2) 0.26; $[\alpha]_D^{25}$ +70.7 (c 1.0, $CHCl_3$); spectral data are the same as compound **5b**. Anal. calcd for $C_{16}H_{22}N_2O_8$ (370.36): C, 51.87; H, 5.99; N, 7.56. Found: C, 52.18; H, 6.06; N, 7.60.

3.2.3. Reaction of nitrone 2 with ethyl vinyl ether. A solution of nitrone **1** (0.230 g, 1.0 mmol) and ethyl vinyl ether (5 mL) was refluxed for 18 h. The crude product obtained after evaporating the solvent was purified by column chromatography (silica gel, hexane/EtOAc, 3:1) to give products **6c** (0.184 g) and **7c** (0.100 g).

3.2.3.1. (3a*S*,4*S*,7*R*,8a*R*,8b*R*)-4-(2-Methoxy-2-oxoethyl)-7-ethoxy-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (6c). This compound was isolated in 61% yield as a colorless oil; R_f (hexane/EtOAc, 3:1) 0.56; $[\alpha]_D^{25}$ −201 (c 2.13, $CHCl_3$); IR (liquid film): ν_{max} 1725 cm^{-1}; ^{1}H NMR: δ 1.13 (3H, t, J=7.1 Hz, CH_3CH_2O), 1.24 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.51–2.55 (2H, m, 8-H), 2.69 (1H, dd, J=15.1, 6.6 Hz, $CH_2CO_2CH_3$), 2.86 (1H, dd, J=15.1, 8.2 Hz, $CH_2CO_2CH_3$), 3.33–3.40 (1H, m, CH_3CH_2OHHH), 3.60–3.70 (5H, superimposed s and m, CH_3O, 4-H and CH_3CH_2O), 3.75 (1H, dt, J=6.3, 3.1 Hz, 8a-H), 4.65 (1H, t, J=6.9 Hz, 3a-H), 4.41 (1H, dd, J=6.9, 3.1 Hz, 8b-H), 5.02 (1H, dd, J=5.0, 1.7 Hz, 7-H); ^{13}C NMR: δ 14.8 (CH_3CH_2O), 24.9 and 27.2 (CH_3), 34.5 and 41.9 (C-8 and $CH_2CO_2CH_3$), 51.6 (CH_3O), 63.1, 69.0, 69.9, 88.5, and 85.7 (C-3a, C-4, C-8a, C-8b, and CH_3CH_2O), 100.1 (C-7), 114.5 ($C(CH_3)_2$), 171.0 (C=O); MS: m/z 301 (78% M^+). Anal. calcd for $C_{14}H_{23}NO_6$ (329.35): C, 55.80; H, 7.69; N, 4.65. Found: C, 55.95; H, 7.39; N, 4.85.

3.2.3.2. (3a*S*,4*S*,7*S*,8a*S*,8b*R*)-4-(2-Methoxy-2-oxoethyl)-7-ethoxy-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (7c). This compound was isolated in 33% yield as a colorless oil; R_f (hexane/EtOAc, 3:1) 0.38; $[\alpha]_D^{25}$ +104.3 (c 0.82, $CHCl_3$); IR (liquid film): ν_{max} 1730 cm^{-1}; ^{1}H NMR: δ 1.22 (3H, t, J=6.1 Hz, CH_3CH_2O), 1.30 (3H, s, CH_3), 1.49 (s, 3H, CH_3), 2.31 (1H, ddd, J=13.1, 6.2, 3.4 Hz, 8-H), 2.41 (1H, dd, J=16.0, 8.7 Hz, $CH_2CO_2CH_3$), 2.68 (1H, dd, J=16.0, 5.6 Hz, $CH_2CO_2CH_3$), 2.83 (1H, ddd, J=13.1, 7.9, 2.1, 8-H), 3.43 (1H, dq, J=14.0, 7.0, Hz, CH_3CH_2O), 3.69 (3H, s, CH_3O), 3.77 (1H, dq, J=14.0, 7.0, Hz, CH_3CH_2O), 3.85 (1H, dt, J=7.9, 3.4 Hz, 8a-H), 3.97 (1H, dd, J=8.7, 5.6 Hz, 4-H), 4.66–4.72 (2H, m, 3a-H and 8b-H), 5.15 (1H, dd, J=6.2, 2.1 Hz, 7-H); ^{13}C NMR: δ 15.0 (CH_3CH_2O), 24.3 and 26.4 (CH_3), 36.7 and 36.9 (C-8 and $CH_2CO_2CH_3$), 51.8 (CH_3O), 63.4, 67.0, 67.8, 81.5, and 86.6 (C-3a, C-4, C-8a, C-8b, and CH_3CH_2O), 102.4 (C-7), 112.9 ($C(CH_3)_2$), 171.2 (C=O); MS: m/z 301 (93% M^+). Anal. calcd for $C_{14}H_{23}NO_6$ (329.35): C, 55.80; H, 7.69; N, 4.65. Found: C, 55.54; H, 7.42; N, 4.80.

3.2.4. Reaction of nitrone 1 with dimethyl maleate. A solution of nitrone **2** (0.605 g, 2.64 mmol) and dimethyl maleate (0.760 g, 5.28 mmol) in dry $CHCl_3$ (25 mL) was refluxed for 15 h. The crude product obtained after evaporating the solvent was purified by column chromatography (silica gel, hexane/ethylacetate/CH_2Cl_2, 3:1:1) to give a mixture of diastereomers as an oil. This was crystallized using a mixture of hexane/CH_2Cl_2 to give compound **8** as a white solid (0.380 g) whereas compound **9** was characterized as the main component of an oily residue (0.300 g).

3.2.4.1. (3a*R*,4*R*,7*S*,8*R*,8a*S*,8b*S*)-7,8-Di-(methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (8). This compound was isolated in 39% yield as a white solid, mp 115–119 °C (CH_2Cl_2/hexane); R_f (hexane/EtOAc/CH_2Cl_2, 3:1:1) 0.40; $[\alpha]_D^{25}$ +150 (c 0.1, $CHCl_3$); IR (Nujol): ν_{max} 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.75 (1H, dd, J=15.3, 7.4 Hz, $CH_2CO_2CH_3$), 2.98 (1H, dd, J=15.3, 7.1 Hz, $CH_2CO_2CH_3$), 3.68–3.77 (11H, superimposed s and m, OCH_3, 4-H and 8-H), 4.26 (1H, dd, J=2.9, 2.9 Hz, 8a-H), 4.55 (1H, dd, J=6.4, 2.8 Hz, 8b-H), 4.72–4.78 (2H, m, 3a-H, 7-H); ^{1}H NMR (C_6D_6): δ 1.13 (3H, s, CH_3), 1.35 (3H, s, CH_3), 2.67 (1H, dd, J=15.3, 6.7 Hz, $CH_2CO_2CH_3$), 2.95 (1H, dd, J=15.3, 7.3 Hz, $CH_2CO_2CH_3$), 3.01 (1H, dd, J=8.5, 3.7 Hz, 8-H), 3.30 (3H,

s, OCH_3), 3.32 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.82 (1H, ddd as q, J=7.3 Hz, 4-H), 3.95 (1H, dd, J=6.1, 2.4 Hz, 8b-H), 4.36–4.43 (2H, m, 3a-H, 7-H), 4.49 (1H, dd, J=3.7, 2.4 Hz, 8a-H); ^{13}C NMR: δ 25.3 and 27.4 (CH_3), 34.4 ($CH_2CO_2CH_3$), 51.8, 52.4, and 52.5 (CH_3O), 55.9 (C-8), 68.9, 72.1, 76.6, 85.5, and 87.5 (C-3a, C-4, C-7, C-8a, and C-8b), 114.8 ($C(CH_3)_2$), 169.2, 171.0, and 171.1 (C=O); MS: m/z 373 (70% M^+). Anal. calcd for $C_{16}H_{23}NO_9$ (373.35): C, 51.48; H, 6.21; N, 3.75. Found: C, 51.75; H, 6.27; N, 3.72.

3.2.4.2. (3a*R*,4*R*,7*R*,8*S*,8a*R*,8b*S*)-7,8-Di-(methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (9). This compound was obtained as the main component of an oily residue (31%, yield) and it was characterized only from its ^{1}H NMR spectrum; ^{1}H NMR: δ 1.32 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.60 (1H, dd, J=15.9, 7.2 Hz, C$H_2CO_2CH_3$), 2.72 (1H, dd, J=15.9, 5.5 Hz, C$H_2CO_2CH_3$), 3.64–3.78 (10H, superimposed s and m, OCH_3, 4-H), 4.09 (1H, dd, J=8.6, 5.8 Hz, 8-H), 4.29 (1H, dd, J=5.8, 5.8 Hz, 8a-H), 4.62 (1H, dd, J=6.0, 4.3 Hz, 3a-H), 4.82 (1H, dd, J=5.8, 5.8 Hz, 8b-H), 4.93 (1H, d, J=8.6 Hz, 7-H).

3.2.5. Reaction of nitrone 1 with dimethyl fumarate. A solution of nitrone **1** (0.738 g, 3.22 mmol) and dimethyl fumarate (0.928 g, 6.44 mmol) in $CHCl_3$ (30 mL) was refluxed for 15 h. The crude product obtained after evaporating the solvent was purified by column chromatography (silica gel, hexane/ethylacetate/CH_2Cl_2, 3:1:1). Two bands were separated in a ratio ~3:7. The first one (0.260 g) gave a mixture of diastereomers, an oil in which compound **10** was assigned as the main component and the second one (0.610 g) gave compound **11**, which was crystallized on standing.

3.2.5.1. (3a*R*,4*R*,7*R*,8*R*,8a*S*,8b*S*)-7,8-Di-(methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (10). This compound was obtained as the main component of an oily mixture (22%, yield) and it was characterized only from its ^{1}H NMR spectrum; ^{1}H NMR: δ 1.33 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.76 (1H, dd, J=16.0, 6.1 Hz, C$H_2CO_2CH_3$), 2.97 (1H, dd, J=16.0, 8.2 Hz, C$H_2CO_2CH_3$), 3.60–3.90 (11H, superimposed s and m, OCH_3, 4-H, 8-H), 4.15 (1H, br s, 8a-H), 4.65–4.85 (3H, m, 3a-H, 7-H, 8b-H).

3.2.5.2. (3a*R*,4*R*,7*S*,8*S*,8a*R*,8b*S*)-7,8-Di-(methoxycarbonyl)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*b*]isoxazole (11). This compound was isolated in 51% yield as a white solid, mp 94–96 °C (EtOAc/hexane); R_f (hexane/EtOAc/CH_2Cl_2, 3:1:1) 0.38; $[\alpha]_D^{25}$ −28.1 (c 0.58, $CHCl_3$); IR (Nujol): ν_{max} 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.54 (1H, dd, J=15.9, 6.0 Hz, C$H_2CO_2CH_3$), 2.62 (1H, dd, J=15.9, 7.9 Hz, C$H_2CO_2CH_3$), 3.70 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.90 (1H, ddd, J=7.9, 6.0, 2.7 Hz, 4-H), 4.14 (1H, dd, J=5.0, 5.0 Hz, 8a-H), 4.19 (1H, dd, J=7.1, 5.0 Hz, 8-H), 4.66 (1H, dd, J=6.7, 2.7 Hz, 3a-H), 4.81–4.86 (2H, m, 7-H, 8b-H); ^{1}H NMR ($CDCl_3$/C_6D_6, 1:1): δ 1.18 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.34 (1H, dd, J=15.8, 7.0 Hz, C$H_2CO_2CH_3$), 2.44 (1H, dd, J=15.8, 6.4 Hz, C$H_2CO_2CH_3$), 3.46 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.53 (3H, s, OCH_3), 3.94 (1H, ddd, J=7.0, 6.4, 3.1 Hz, 4-H), 4.07 (1H, dd, J=5.9, 4.9 Hz, 8a-H), 4.27 (1H, dd, J=7.4, 4.9 Hz, 8-H), 4.44 (1H, dd, J=6.1, 3.1 Hz, 3a-H), 4.55 (1H, dd, J=6.1, 6.1 Hz, 8b-H), 4.87 (1H, d, J=7.4 Hz, 7-H); ^{13}C NMR: δ 24.4 and 26.0 (CH_3), 36.4 ($CH_2CO_2CH_3$), 50.8, 51.8, 52.6, and 52.7 (OCH_3 and C-8), 67.3, 70.9, 79.7, 81.3, and 85.4 (C-3a, C-4, C-7, C-8a, and C-8b), 113.8 ($C(CH_3)_2$), 169.5, 171.1, and 171.2 (C=O); MS: m/z 373 (16% M^+). Anal. calcd for $C_{16}H_{23}NO_9$ (329.35): C, 51.48; H, 6.21; N, 3.75. Found: C, 51.79; H, 6.27; N, 3.75.

3.3. Transformation of carboximidic derivatives 4b and 5b to the corresponding esters 4a and 5a

In an apparatus protected from moisture and under an argon atmosphere Mg turnings (0.032 g, 1.32 mmol) were treated with dry MeOH (0.7 mL) in the presence of CCl_4 (5–6 drops) at 0 °C with stirring. When all Mg had dissolved, compound **4b** (0.160 g, 0.43 mmol) in dry THF (3 mL) was added. The reaction mixture was stirred for ~15 min quenched with saturated NH_4Cl solution, extracted with EtOAc (2×20 mL), and dried. The crude product after evaporation of the solvent was purified by column chromatography (silica gel, hexane/EtOAc, 4:1) to give compound **4a** (0082 g, 60% yield) identical to that obtained from nitrone **1** and methyl acrylate. In the same way compound **5a** was obtained from **5b** (0.28 g, 0.75 mmol) and 2 mmol $Mg(OMe)_2$. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:1) to give the product in 80% yield.

3.4. Reductive cleavage of isoxazolidine derivatives

General procedure. A catalytic amount of Raney Ni (about 30 mg) was added to a previously degassed solution of isoxazolidine (1 mmol) in MeOH (5 mL) under a hydrogen atmosphere (balloon). The mixture was stirred for about 5 h and then the crude reaction mixture was passed through Celite, concentrated and purified by column chromatography on silica gel using the eluents indicated.

3.4.1. Methyl (2*S*)-3-[(3a*S*,4*S*,6*R*,6a*R*)-6-(2-methoxy-2-oxoethyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-2-hydroxypropanoate (12). This compound was obtained from **4a** in 66% yield as a colorless oil, after column chromatography (silica gel, hexane/EtOAc, 1:4); R_f (hexane/EtOAc, 1:4) 0.35; $[\alpha]_D^{25}$ −40.8 (c 0.59, $CHCl_3$); IR (liquid film): ν_{max} 3350 (br), 1720 cm^{-1}; ^{1}H NMR: δ 1.30 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.93–2.00 (2H, m, CH_2CH(OH)), 2.49 (1H, dd, J=16.3, 8.8 Hz, CH_2CO_2Me), 2.70 (1H, dd, J=16.3, 5.0 Hz, C$H_2CO_2CH_3$), 3.31 (2H, br, OH, NH), 3.42 (1H, ddd, J=8.4, 5.0, 3.4 Hz, 4-H), 3.51 (1H, ddd, J=8.8, 5.0, 4.2 Hz, 6-H), 3.69 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.34 (1H, dd, J=6.5, 4.2 Hz, 6a-H), 4.37–4.47 (2H, m, 3a-H, CH(OH)); ^{13}C NMR: δ 25.1 and 27.2 (CH_3), 36.4 and 38.7 ($CH_2CO_2CH_3$), CH_2CH(OH), 52.22 and 52.23 (OCH_3), 60.6, 61.5, and 69.5 (C-4, C-6, CH(OH)), 84.4 and 84.6 (C-3a, C-6a), 113.0 ($C(CH_3)_2$), 172.0 and 174.7 (C=O); MS: m/z 318 (100%, MH^+). Anal. calcd for $C_{14}H_{23}NO_7$ (317.34): C, 52.99; H, 7.31; N, 4.41. Found: C, 53.09; H, 7.06; N, 4.47.

3.4.2. Methyl (2*R*)-3-[(3a*R*,4*R*,6*S*,6a*S*)-6-(2-methoxy-2-oxoethyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-

***c*]pyrrol-4-yl]-2-hydroxypropanoate (13, *ent*-12).** This compound was obtained in the same way from **6a** in 77% yield as a colorless oil; R_f (hexane/EtOAc, 1:4) 0.35; $[\alpha]_D^{25}$ +38.7 (*c* 2.43, $CHCl_3$); spectral data are the same as above. Anal. calcd for $C_{14}H_{23}NO_7$ (317.34): C, 52.99; H, 7.31; N, 4.41. Found: C, 52.76; H, 7.28; N, 4.66.

3.4.3. Methyl 2-[(3a*R*,4*R*,7*R*,8a*R*,8b*S*)-7-hydroxy-2,2-dimethyl-6-oxohexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizin-4-yl]acetate (14). This compound was obtained from **5a** in 73% yield after column chromatography (silica gel, hexane/EtOAc, 1:2 to EtOAc) as a white solid, mp 85–87 °C; R_f (hexane/EtOAc, 1:2) 0.23; $[\alpha]_D^{25}$ +21.3 (*c* 0.57, $CHCl_3$); IR (Nujol): ν_{max} 3350, 1730, 1670 cm^{-1}; ^1H NMR: δ 1.30 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.00 (1H, br s, OH), 2.25 (1H, ddd, *J*=11.9, 8.6, 8.1, 8-H), 2.55 (1H, ddd, *J*=11.9, 8.6, 6.2, 8-H), 2.62–2.64 (2H, m, C*H*$_2$CO$_2$CH$_3$), 3.70 (3H, s, OCH_3), 4.02 (1H, ddd, *J*=8.1, 6.2, 4.8 Hz, 8a-H), 4.28 (1H, t, *J*=6.2 Hz, 4-H), 4.52 (1H, t, *J*=8.6 Hz, 7-H), 4.67 (1H, t, *J*=4.8 Hz, 8b-H), 4.83 (1H, d, *J*=4.8 Hz, 3a-H); ^{13}C NMR: δ 24.8 and 26.6 (CH_3), 29.7 and 36.2 (*C*H$_2$CO$_2$Me and C-8), 52.1 (OCH_3), 56.9 and 59.5 (C-4 and C-8a) 72.0, 79.4, and 86.8 (C-7, C-3a, and C-8b), 112.8 (*C*(CH$_3$)$_2$), 171.2 and 174.6 (C=O); MS: *m*/*z* 285 (56% M^+). Anal. calcd for $C_{13}H_{19}NO_6$ (285.30): C, 54.73; H, 6.71; N, 4.91. Found: C, 54.51; H, 6.53; N, 4.85.

3.4.4. Methyl 2-[(3a*S*,4*S*,7*S*,8a*S*,8b*R*)-7-hydroxy-2,2-dimethyl-6-oxohexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizin-4-yl]acetate (15, *ent*-14). This compound was obtained by an analogous way as above from **7a** in 76% yield as a white solid, mp 85–87 °C; R_f (hexane/ethyl acetate, 1:2) 0.23; $[\alpha]_D^{25}$ −21.3 (*c* 0.35, $CHCl_3$); spectral data are the same as above. Anal. calcd for $C_{13}H_{19}NO_6$ (285.30): C, 54.73; H, 6.71; N, 4.91. Found: C, 54.89; H, 6.77; N, 4.74.

3.4.5. Methyl [(3a*S*,4*S*,6*R*,6a*R*)-6-(2-hydroxyethyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]acetate (17). This compound was obtained from **6c** in 55% yield as a colorless oil after column chromatography (silica gel, EtOAc/MeOH/NH_4OH, 20:1:1); R_f (EtOAc/MeOH/NH_4OH, 20:1:1) 0.35; IR (liquid film): ν_{max} 3300 (br), 1720 cm^{-1}; ^1H NMR: δ 1.32 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.66–1.76 (1H, m, C*H*$_2$CH$_2$OH), 1.80–1.89 (1H, m, C*H*$_2$CH$_2$OH), 2.51 (1H, dd, *J*=16.4, 8.9 Hz, C*H*$_2$CO$_2$CH$_3$), 2.73 (1H, dd, *J*=16.4, 4.7 Hz, C*H*$_2$CO$_2$CH$_3$), 2.91 (2H, br, OH, NH), 3.32–3.38 (1H, m, 6-H), 3.48 (1H, apparent qn, *J*=4.7 Hz, 4-H), 3.70 (s, 3H, OCH_3), 3.73–3.88 (2H, m, C*H*$_2$OH), 4.33 (1H, dd, *J*=6.1, 4 Hz, 6a-H), 4.39 (1H, dd, *J*=6.1, 4.7 Hz, 4-H); ^{13}C NMR: δ 25.1 and 27.2 (CH_3), 34.7 and 38.5 (*C*H$_2$CO$_2$CH$_3$) and *C*H$_2$CHOH, 51.7 (OCH_3), 60.6, 61.2, and 63.7 (C-4, C-6, and CH_2OH), 84.4 and 84.6 (C-3a and C-6a), 113.6 (*C*(CH$_3$)$_2$), 172.1 (C=O); MS: *m*/*z* 260 (70% MH^+). Anal. calcd for $C_{12}H_{21}NO_5$ (259.30): C, 55.62; H, 8.16; N, 5.40. Found: C, 55.62; H, 8.23; N, 5.23.

3.4.6. Methyl (3a*R*,4*R*,7*S*,8*R*,8a*S*,8b*S*)-7-hydroxy-4-(2-methoxy-2-oxoethyl)-2,2-dimethyl-6-oxohexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine-8-carboxylate (18). This compound was obtained from **8** in 45% yield after column chromatography (silica gel, hexane/EtOAc/NEt_3, 33:66:1) as a white solid, mp 129–132 °C; R_f (hexane/EtOAc/NEt_3, 33:66:1) 0.25; $[\alpha]_D^{25}$ +2.0 (*c* 0.1, $CHCl_3$); IR (Nujol): ν_{max} 3340, 1730, 1680 cm^{-1}; ^1H NMR: δ 1.32 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.70 (1H, br s, OH), 2.95 (1H, dd, *J*=16.0, 5.0 Hz, C*H*$_2$CO$_2$CH$_3$), 3.07 (1H, dd, *J*=8.5, 8.5 Hz, 8-H), 3.49 (1H, dd, *J*=16.0, 7.0 Hz, C*H*$_2$CO$_2$CH$_3$), 3.70 (s, 3H, OCH_3), 3.84 (3H, s, OCH_3), 3.90–3.95 (2H, m, 4-H, 8a-H), 4.60–4.74 (3H, m, 3a-H, 7-H, and 8b-H); ^{13}C NMR: δ 25.4 and 27.5 (CH_3), 32.8 (*C*H$_2$CO$_2$CH$_3$), 51.9 and 52.1 (OCH_3), 54.1 and 58.2 (C-4 and C-8), 65.6 (C-8a), 75.0 (C-7), 81.7 and 86.6 (C-3a and C-8b), 114.0 (*C*(CH$_3$)$_2$), 167.5, 171.0, and 173.9 (C=O); MS: *m*/*z* 343 (34% M^+). Anal. calcd for $C_{15}H_{21}NO_8$ (343.34): C, 52.48; H, 6.17; N, 4.08. Found: C, 52.49; H, 6.18; N, 4.41.

3.4.7. Methyl (3a*R*,4*R*,7*S*,8*S*,8a*R*,8b*S*)-7-hydroxy-4-(2-methoxy-2-oxoethyl)-2,2-dimethyl-6-oxohexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine-8-carboxylate (19). This compound was obtained from **11** in 48% yield as a colorless oil after column chromatography (silica gel, hexane/EtOAc/NEt_3, 33:66:1); R_f (hexane/EtOAc/NEt_3, 33:66:1) 0.27; $[\alpha]_D^{25}$ −32.45 (*c* 0.36, $CHCl_3$); IR (liquid film): ν_{max} 3340, 1740, 1680 cm^{-1}; ^1H NMR: δ 1.25 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.80 (1H, br s, OH), 2.67 (2H, d, *J*=6.1 Hz, C*H*$_2$CO$_2$CH$_3$), 3.59 (1H, dd, *J*=6.6, 6.6 Hz, 8-H), 3.71 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.22 (1H, t, *J*=6.1 Hz, 4-H), 4.59–4.66 (2H, m, 7-H, 8a-H), 4.73 (1H, dd, *J*=5.0, 5.0 Hz, 8b-H), 4.84 (1H, d, *J*=5.0 Hz, 3a-H); ^{13}C NMR: δ 24.4 and 26.5 (CH_3), 35.8 (*C*H$_2$CO$_2$CH$_3$), 44.3 (C-8), 52.1 and 52.4 (OCH_3), 56.9 (C-4), 63.1 (C-8a), 74.3 (C-7), 78.3 and 87.4 (C-3a and C-8b), 112.7 (*C*(CH$_3$)$_2$), 169.7, 171.0, and 171.6 (C=O); MS: *m*/*z* 343 (75% M^+). Anal. calcd for $C_{15}H_{21}NO_8$ (343.34): C, 52.48; H, 6.17; N, 4.08. Found: C, 52.78; H, 6.29; N, 4.28.

3.5. Crystal data

3.5.1. Crystal structure determination of compound 5b. A colorless crystal was mounted on a glass fiber and transferred to the diffractometer. Diffraction measurements were made on a $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using Ni-filtered Cu Kα radiation. $\theta-2\theta$ scan, scan range 2.5 plus a_1a_2 separation, 3215 reflections measured ($2.1\leq\theta\leq65°$, $\pm h,-k,l$), 2969 unique (merging R=0.0115), giving 2856 with $I\geq2\sigma(I)$ and 2969, which were retained in calculations. Lorentz, polarization but no absorption corrections was applied using Crystal Logic software. The structure was solved by automatic direct methods[16a] (all non-H atoms) and refined by full-matrix least-squares technique[16b] on F^2 with all non-H atoms anisotropic. Hydrogen atoms were located from a ΔF synthesis and were refined isotropically. The weighting scheme $w^{-1}=[\sigma^2(F_o^2)+(0.0000P)^2+0.2529P]$, $P=1/3[\max(F_o^2,0)+2F_c^2]$ gave satisfactory analyses. Final R_1 [$I\geq2\sigma(I)$]=0.0266, wR_2 [all data]=0.0682, $S[F^2]$=1.042 for 324 refined parameters (R indices defined in Ref. 16b). An extinction correction[16b] refined to 0.025(1) and the final ΔF synthesis showed no peaks outside the range $-0.129\rightarrow+0.175$e $Å^{-3}$.

3.5.2. Crystal data.[17] $C_{16}H_{22}N_2O_8$, Orthorhombic, a=8.2234(6), b=10.3300(8), c=20.682(1) Å, V=1756.9(2) $Å^3$ (by least-squares refinement on diffractometer angles for 25 automatically centered reflections with $11\leq\theta\leq22°$,

λ=1.54180 Å, T=298 K), space group $P2_12_12_1$, Z=4, D_x=1.400 g cm^{-3}, colorless crystal 0.50×0.40×0.20 mm, μ(Cu Kα)=0.963 mm^{-1}.

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17. The authors have deposited the atomic coordinates for this structure to the Cambridge Crystallographic Data Centre, CCDC 615434.