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Synthesis of enantiomerically pure hydroxylated pyrroline *N*-oxides from D-ribose

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Abstract—A convenient way to obtain enantiomerically pure hydroxylated pyrroline *N*-oxides is reported. The key step is the formation of ω-oxo enoates from D-ribose and a subsequent 1,3-azaprotio cyclotransfer reaction of the resulting oximino alkenoate derivatives. The stereochemistry of the nitrones obtained is discussed in relation to that of the starting compounds.

1. Introduction

The cycloaddition reaction of nitrones with olefins is one of the most important methodologies for the synthesis of many complex organic molecules.[1] The concerted process of this reaction, usually accompanied by a high degree of regio- and stereoselectivity of the resulting isoxazolidine cycloadducts, allows the creation of multiple stereocenters in a single step, with complete control of their relative configuration. These adducts can be elaborated upon in a variety of ways, mainly originating by cleavage of the labile N–O bond under mild reducing conditions, leading to stereochemically well defined open chain adducts.

Of particular importance are the enantiomerically pure polyhydroxylated five- and six-membered cyclic nitrones and their cycloaddition reactions. These compounds, accessible either from sugars[2] or from other sources,[3] have found broad application in the synthesis of optically active nitrogenated compounds. In this respect, densely substituted pyrrolidines or piperidines can be obtained, by reacting a five- or six-membered cyclic nitrone and a suitable dipolarophile, followed by reductive cleavage of the resulting isoxazolidine ring. A further step toward the pyrrolizidine or indolizidine nucleus can be accomplished, by intramolecular cyclization of the resulting amino group and a proper functionality already existing on the starting nitrone or dipolarophile (e.g., an ester group). These intramolecular cyclizations, for example, *N*-alkylations, reductive aminations, lactam formations, etc. are of common use for the nitrogen bridgehead systems.[4]

The most general preparations of nitrones involve (i) condensation of *N*-substituted hydroxylamines with carbonyl compounds; (ii) oxidation of secondary amines or *N*,*N*-disubstituted hydroxylamines; and (iii) N-alkylation of oximes.[1e] The use of oximes as nitrone precursors has found considerable application, but one limitation is that a typical alkylation can be complicated by the formation of oximino ethers as by-products. However, an interesting variation of the alkylation process is the reaction of oximes with electron poor alkenes to give nitrones, a process that has been termed 1,3-azaprotio cyclotransfer by Grigg et al.,[5] who have also systematically studied many other electrophilic induced transformations of oximes to nitrones.[6] The intramolecular version of this transformation is given in Figure 1. *exo-trig* Cyclization is presumably the most favorable mode.[7] According to this protocol, the synthesis of a few chiral five- or six-membered cyclic nitrones has been reported.[2a–c] Another interesting variation starting from oximes and leading to chiral five-membered cyclic

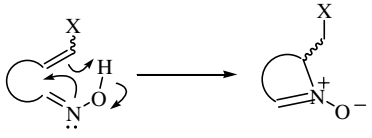

Figure 1. Intramolecular 1,3-azaprotio cyclotransfer of alkenyl oximes.

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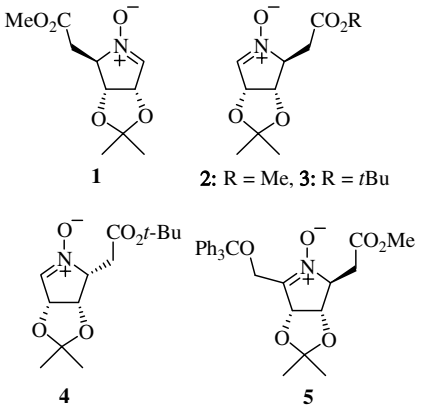
nitrones, involves an S_N2 type intramolecular cyclization of γ-mesyloxy or γ-iodo-*O*-silylated oxime derivatives.[2e–i]

The 1,3-azaprotio cyclotransfer process was also applied to the synthesis of nitrones **1**–**5** described in this paper. Nitrones **1** and **2** are in fact antipodes and their synthesis was planned on the basis of manipulation of the stereochemistry of the starting D-ribose. As regards the diastereomeric pair of nitrones **3** and **4**, their formation is related to the stereochemistry (*Z* or *E*) of the alkene precursors (Scheme 1).

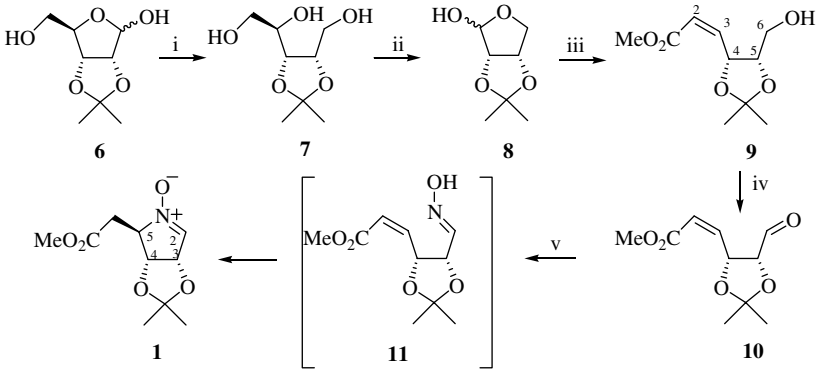


Scheme 1.

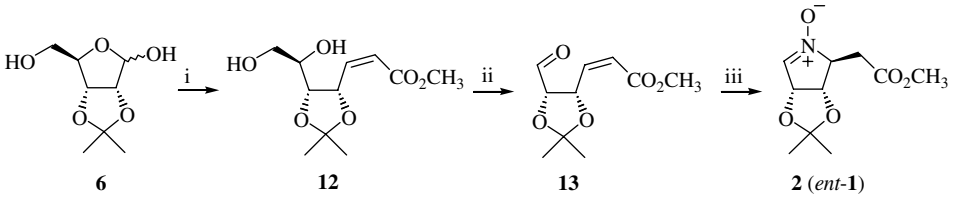
2. Results and discussion

The key step for the synthesis of all the nitrones in this study is the formation of the appropriate oxoenoates **10**, **13**, **17**, **18**, and **21** (Schemes 2–5) following conventional sugar transformations, all starting from the known D-ribose monoacetonide **6**.[8] It is worth mentioning that the alkene moiety, introduced by typical Wittig olefinations has predominantly the *Z*-form in accordance to other α-alkoxyaldehydes.[9] However, in one case (Scheme 4) an appreciable amount of the corresponding (*E*)-enoate was also obtained. This fact allowed us to gain insight regarding the influence of alkene form on the stereochemistry of the final nitrone. All oxoenoates upon treatment with hydroxylamine hydrochloride in the presence of $NaHCO_3$ afford the desired nitrones by a spontaneous cyclization of the non-isolable oxime derivatives.

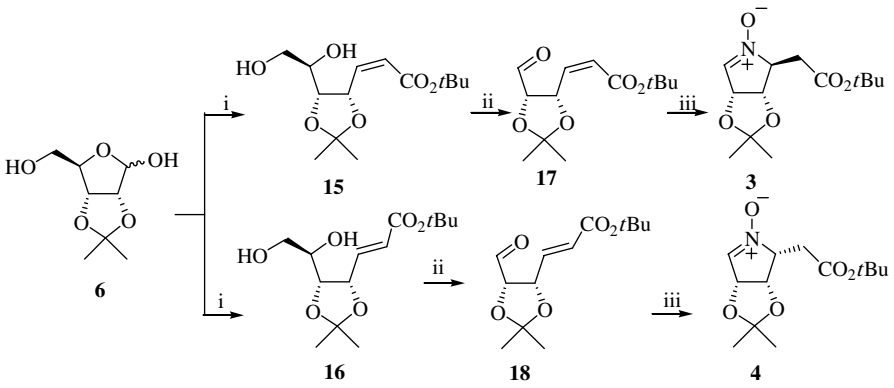
As outlined in Scheme 2, nitrone **1**[10] was obtained by a five-step reaction sequence starting from the D-ribose monoacetonide and following conventional sugar transformations, that is, $NaBH_4$ reduction to ribitol **7**[11] followed by periodate oxidation[12] to give L-erythrose monoacetonide **8**. Wittig olefination with the stable methoxycarbonyl methylenetriphenyl phosphorane ($Ph_3P{=}CHCOOCH_3$) followed by PDC oxidation[13] of the primary hydroxyl group of compound **9** gave the key oxoenoate **10**, which was finally transformed, by cyclization of the non-isolable aldoxime **11** to the desired nitrone **1** in 22% overall yield (based on the starting D-ribose). It is noteworthy that some problems have been encountered during the oxidation step of the primary hydroxyl group of compound **9**. Various approaches such as Swern oxidation ($DMSO/(COCl)_2/NEt_3$),[14] or Collins oxidation[15] have been tested, but the results were not satisfactory. Best results were obtained using pyridinium dichromate (PDC) in anhydrous acetic acid in the presence of molecular sieves 3 Å.



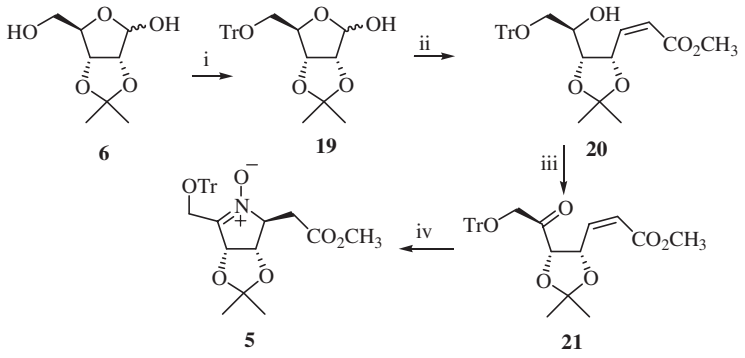
Scheme 2. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C, 1 h; (ii) $NaIO_4$, *t*-BuOH, H_2O, 25 °C; (iii) $Ph_3P{=}CHCO_2Me$, PhCOOH (cat.), CH_2Cl_2, reflux, 18 h; (iv) PDC, molecular sieves 3 Å (powder), dry AcOH, CH_2Cl_2, 25 °C, 30 min; (v) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH, 25 °C, 12 h.



Scheme 3. Reagents and conditions: (i) $Ph_3P{=}CHCO_2Me$, PhCOOH (cat.), CH_2Cl_2, reflux, 18 h; (ii) $NaIO_4$, *t*-BuOH, H_2O, 25 °C, 15 h; (iii) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH, 25 °C, 12 h.



Scheme 4. Reagents and conditions: (i) $Ph_3P{=}CHCOO$*t*-Bu **14**, PhCOOH (cat.), CH_2Cl_2, reflux, 18 h; (ii) $NaIO_4$, *t*-BuOH/H_2O, 25 °C, 17 h; (iii) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH, 25 °C, 12 h.



Scheme 5. Reagents and conditions: (i) Ph_3CCl, DMF, NEt_3, DMAP, 25 °C; (ii) $Ph_3P{=}CHCO_2CH_3$, PhCOOH (cat.), CH_2Cl_2, reflux, 18 h; (iii) PDC, molecular sieves 3 Å, dry AcOH, CH_2Cl_2, 25 °C, 0.5 h; (iv) $NH_2OH{\cdot}HCl$, $NaHCO_3$, EtOH, 25 °C, 2 h.

The reaction sequence to give nitrone **2** (*ent*-**1**) includes the Wittig olefination of **6** followed by periodate oxidation of the resulting diol group to the ω-oxoenoate **13** and subsequent transformation to the nitrone **2** upon treatment with hydroxylamine (Scheme 3). The overall yield, starting from D-ribose was 27%. It should be mentioned that a minor inseparable amount of the (*E*)-isomer of ester **12** was detected in the crude reaction mixture ($Z{:}E \sim 10{:}1$). Its ^{1}H NMR spectra show that besides the main peaks for the *cis* olefinic protons at δ 6.01 and 6.31 ($J_{2,3} = 11.7$ Hz) minor peaks appeared at δ 6.17 and 7.13 ($J_{2,3} = 15.7$ Hz), corresponding to the 2- and 3-H olefinic protons at trans position. Eventually only the (*Z*)-isomer of compound **13** was isolated.

An analogous reaction sequence to that for nitrone **2**, was followed by the synthesis of diastereomeric nitrones **3** and **4** (Scheme 4). However, it has been observed that the Wittig olefination of compound **6** with the stereochemically congested stable phosphorane **14**, gave appreciable amounts of both (*Z*)- and (*E*)-enoates **15** and **16** in a ~3:2 ratio. This was evidenced from the ^{1}H NMR of the crude reaction mixture, where besides the signals for the (*Z*)-isomer (see Experimental), showed also typical signals for the *trans* olefinic protons at δ 6.16 (dd, $J_{2,3} = 15.7$, $J_{2,4} = 1.5$ Hz) and 7.13 (dd, $J_{2,3} = 15.7$ and $J_{3,4} = 4.7$ Hz), corresponding to 2-H and 3-H of the (*E*)-isomer **16**. Since it was not possible to separate these isomers and only a small fraction of (*Z*)-isomer could be obtained in a pure state, their mixture was subjected to periodate oxidation to give the corresponding ω-oxoenoates **17** and **18**. Attempts to separate these compounds also failed and only a part of pure (*Z*)-enoate **17** but no pure (*E*)-enoate could be obtained. Fortunately, treatment of the original mixture with hydroxylamine gave the chromatographically separable nitrones **3** and **4**, in about the same ratio (~3:2) to that of the starting esters **15** and **16**. In an independent experiment carried out starting from pure (*Z*)-enoate **17** only nitrone **3** was formed. This fact along with the observed exclusive formation of *anti* nitrones **1** and **2** from the corresponding (*Z*)-enoates **10** and **13** (Schemes 2 and 3) strongly support that nitrone **4** was exclusively formed from (*E*)-enoate **18**.

In order to widen the scope of this study, the synthesis of the stereochemically congested nitrone **5** was also undertaken. This nitrone was obtained in 40% overall yield by an analogous four-step reaction sequence (Scheme 4), involving tritylation, Wittig olefination, PDC oxidation, and treatment with hydroxylamine. The *cis*-enoate **20** was exclusively formed affording finally the nitrone **5**.

The proton assignment of all nitrones was based on double resonance experiments, while their stereochemistry was proposed on the basis of the values of coupling

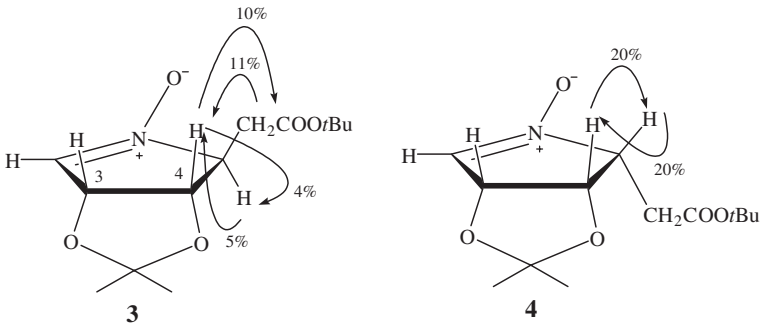


Figure 2. NOE results of nitrones **3** and **4**.

constants $J_{4,5}$ and also from NOE experiments. Thus for nitrones **1**–**3** and **5**, the observed coupling constants ($J_{4,5} = 1.0$ Hz) are in accordance with a trans-arrangement of 4-H and 5-H protons whereas the higher value $J_{4,5} = 5.9$ Hz in isomer **4** is in accordance with a cis-arrangement. Furthermore, NOE experiments carried out on compounds **3** and **4** showed that the saturation of 4-H and 5-H protons of compound **4** results in a strong mutual enhancement. On the contrary, in isomer **3** the observed enhancements are much smaller, whereas saturation of 4-H and CH_2 resulted in a strong mutual enhancement, supporting their *syn* proximity (Fig. 2).

The exclusive formation of *anti*-nitrones **1**, **2**, **3**, and **5**, when the pure (*Z*)-enoates **10**, **13**, **17**, and **21** were used, shows that the stereochemistry of the starting enoates determines the cyclization course. On the other hand, since both isomers **3** and **4** were obtained starting from the mixture of (*Z*)- and (*E*)-oxoenoates **17** and **18**, it is reasonable to assume that compound **17** is transformed exclusively to *anti* nitrone **3**, and compound **18** to the *syn* nitrone **4**.[16] Inspection of the possible transition states for the cyclization step of the intermediate (*Z*)- and (*E*)-oximes (Fig. 3) shows that for the (*Z*) derivatives the *syn*-isomer (TS **B**) is stereochemically congested, thus favoring the formation of *anti* isomer (TS **A**). On the other hand, both transition states **C** and **D** can be considered to have a similar stereochemical environment, although TS **C** leading to the nitrone **4**, may be considered as more kinetically controlled than TS **D** in accordance with other close related radical cyclizations.[17]

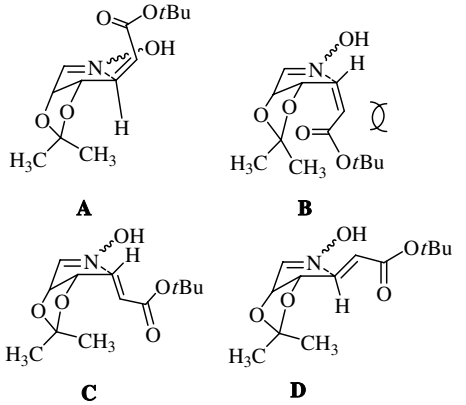


Figure 3. Possible transition states for the synthesis of nitrones **3** and **4**.

3. Conclusion

A convenient way for the synthesis of polyhydroxylated chiral five-membered cyclic nitrones has been reported. Based on the intramolecular 1,3-azaprotio cyclotransfer reaction of appropriate oximino alkenoates, it has been established that the nature of the alkene moiety (*Z*- or *E*-form) determines the course of the cyclization step. In this way, it is possible to manipulate the stereo chemistry of the newly generated asymmetric center of the nitrone nucleus, by controlling the stereochemistry of the alkene part, so affording stereochemically defined pyrrolidine derivatives. Further work is planned to widen the scope of this process.

4. Experimental

4.1. General remarks

All melting points are uncorrected and were 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 NMR spectra, reported in δ units, were obtained in deuteriochloroform solutions, with tetramethylsilane as internal standard, and recorded with a Brucker AM 300 spectrometer, operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). The mass spectra were measured with a VG TS-250 spectrometer with ionization energy of 70 eV. Elemental analyses were performed with a Perkin–Elmer CHN 2400 automatic analyzer. Optical rotations were measured with an A. KRÜSS Optronic P3002, operating at 589 nm ($l = 1$ dm, 25 °C). Several intermediates were not obtained in analytically pure form, so that when it was possible, they were characterized only by their NMR data.

4.2. Synthesis of nitrone 1

4.2.1. 2,3-*O*-Isopropylidene-D-ribofuranose 6. This was prepared following standard procedure[8] from D-ribose (12.5 g, 83 mmol), dry acetone (125 mL), and sulfuric acid (0.3 mL). Yield 15.3 g (97%).

4.2.2. (3a*S*,6a*S*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-ol 8. To a cooled (ice bath) solution of D-ribose monoacetonide **6** (30.76 g, 0.162 mol) in reagent grade MeOH (200 mL), $NaBH_4$ (9.18 g, 0.24 mol) was added in small portions with stirring. Stirring was continued for an additional hour, then the reaction mixture concentrated to give the crude ribitol derivative **7**, which was used in the next step without further purification.

To a stirred solution of compound **7** in *t*-BuOH/H_2O (300/200 mL), $NaIO_4$ (139.1 g, 0.65 mol) was added in portions. Stirring was continued overnight at rt, then CH_2Cl_2 (500 mL) was added and the reaction mixture neutralized with solid $NaHCO_3$. The solids were filtered off, and the aqueous phase extracted with CH_2Cl_2. The resulting organic phase was dried over Na_2SO_4, concentrated, and chromatographed on a silica gel column (eluent hexane/EtOAc, 3:1) to give pure compound **8** (20.5 g, 79% from the starting compound **6**) as an oil. Spectral data are in agreement with the literature values.[11]

4.2.3. Methyl (*Z*)-3-[(4*R*,5*S*)-5-(hydroxy methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenoate 9. A solution of compound **8** (20.5 g, 0.128 mol), methoxycarbonylmethylenetriphenylphosphorane (59.8 g, 0.179 mol) and benzoic acid (1 g) in dry CH_2Cl_2 was refluxed for 18 h. The solvent was removed in vacuo and the residue chromatographed on a silica gel, column eluting with hexane/EtOAc (8:1) to give compound **9** (16.58 g, 60%) as analytically pure solid.

Data for compound **9**: Mp 27–29 °C (from CH_2Cl_2/hexane). $[\alpha]_D^{25} = -140$ (*c* 1.2, $CHCl_3$). IR (Nujol): 3480 (br), 1700, 1630 cm^{-1}. ^1H NMR: δ, 1.41 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.17 (br s, 1H, OH), 3.46 (dd, 1H, $J = 5.1$, 11.7 Hz, CH_2OH), 3.61 (dd, 1H, $J = 3.6$, 11.7 Hz, CH_2OH), 3.74 (s, 3H, $COOCH_3$), 4.58 (ddd, 1H, $J = 7.1$, 5.1, 3.6 Hz, 5-H), 5.6 (dt, 1H, $J = 7.1$, 1.6 Hz, 4-H), 5.97 (dd, 1H, $J = 11.6$, 1.6 Hz, 2-H), 6.41 (dd, 1H, $J = 7.1$, 11.6 Hz, 3-H). ^{13}C NMR: δ, 24.6, 27.3, [C(CH_3)$_2$], 51.6 (OCH_3), 61.4 (C-6), 74.8 (C-5), 78.8 (C-4), 108.9 (O*C*Me$_2$O), 120.5 (C-2), 147.6 (C-3), 166.4 (C-1). MS: *m*/*z* (%): 216 (14) [M^+]. Anal. Calcd for $C_{10}H_{16}O_5$ (216.23): C, 55.55; H, 7.46. Found: C, 55.41; H, 7.37.

4.2.4. Methyl (*Z*)-3-[(4*R*,5*R*)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenoate 10. To a solution of compound **9** (2.0 g, 9.26 mmol) in dry CH_2Cl_2 (50 mL) pyridinium dichromate (PDC) (5.2 g, 13.8 mmol), activated molecular sieves 3 Å (powder) (3.65 g) and dry acetic acid (0.46 mL) were successively added, under an argon atmosphere. The mixture was stirred at rt for 0.5 h, filtered under vacuum and the filtrate concentrated and passed over a silica gel column eluted with hexane/CH_2Cl_2/EtOAc (6:3:1) to obtain compound **10** (1.46 g, 74%) as an oil. Data for compound **10**: $[\alpha]_D^{25} = +16.3$ (*c* 0.65, $CHCl_3$). IR (film): 1700, 1650 cm^{-1}. ^1H NMR: δ, 1.45 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.76 (s, 3H, $COOCH_3$), 4.8 (dd, 1H, $J = 2.8$, 7.7 Hz, 5-H), 5.82 (ddd, 1H, $J = 1.7$, 6.7, 7.7 Hz, 4-H), 5.99 (dd, 1H, $J = 1.7$, 11.6 Hz, 2-H), 6.25 (dd, 1H, $J = 6.7$, 11.6 Hz, 3-H), 9.48 (d, 1H, $J = 2.8$ Hz, CH=O). ^{13}C NMR: δ, 27.3, 25.2 [C(CH_3)$_2$], 51.8 (OCH_3), 81.9, 75.8 (C-4, C-5), 111.5 (O*C*Me$_2$O), 122.6 (C-2), 143.8 (C-3), 165.9 (*C*OOCH$_3$), 199.3 (CH=O), MS: *m*/*z* (%): 214 (28) [M^+].

4.2.5. (3a*R*,4*R*,6a*S*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ium-5-olate 1. To a solution of **10** (13.0 g, 60.75 mmol) in reagent grade MeOH (150 mL) and H_2O (200 mL), $NH_2OH{\cdot}HCl$ (5.5 g, 79.1 mmol) and $NaHCO_3$ (7.65 g, 0.9 mmol) were added. The mixture was stirred at 25 °C for 12 h, extracted with CH_2Cl_2, the organic phase dried over Na_2SO_4, and the residue was chromatographed on a silica gel column (eluent EtOAc/hexane, 2:1) to give pure nitrone **1** (8.5 g, 66%) as an analytical pure colorless oil. Data for compound **1**: $[\alpha]_D^{25} = +11.0$ (*c* 1.46, $CHCl_3$). IR (film): 3030, 1715, 1565 cm^{-1}. ^1H NMR: δ, 1.39 (s, 3H, CH_3) 1.47 (s, 3H, CH_3), 2.99 (dd, 1H, $J = 4.1$, 17.6 Hz, CH_2COOCH$_3$), 3.13 (dd, 1H, $J = 6.2$, 17.6 Hz, CH_2COOCH$_3$), 3.71 (s, 3H, $COOCH_3$), 4.26 (ddd, 1H, $J = 4.1$, 6.2, 1.0 Hz, 5-H), 4.86 (dd, 1H, $J = 6.5$, 1.0 Hz, 4-H), 5.37 (d, 1H, $J = 6.5$ Hz, 3-H), 6.95 (s, 1H, 2-H). ^{13}C NMR: δ, 25.4, 26.9 [C(CH_3)$_2$], 32.9 (*C*H$_2$COOCH$_3$), 51.9 (OCH_3), 75.5 77.9, 78.7 (C-3, C-4, C-5), 112 (O*C*Me$_2$O), 133.2 (C-2), 170 (C=O), MS: *m*/*z* (%): 229 (89) [M^+]. Anal. Calcd for $C_{10}H_{15}NO_5$ (229.236): C, 52.40; H, 6.60; N, 6.11. Found: C, 52.70; H, 6.56; N, 6.25.

4.3. Synthesis of nitrone 2 *ent*-1

4.3.1. Methyl (*Z*)-3-{(4*S*,5*R*)-5-[(1*R*)-1,2-dihydroxyethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2-propenoate 12. A CH_2Cl_2 solution (~150 mL) of 2,3-*O*-isopropylidene-D-ribofuranose **6** (8.1 g, 43 mmol), methoxycarbonyl methylenetriphenyl phosphorane (15.5 g, 46.5 mmol), and benzoic acid (1 g) was refluxed for 18 h. The solvent was removed in vacuum and the residue was chromatographed on silica gel (eluent hexane/EtOAc, 2:1) to give compound **12** (10.5 g), contaminated with a minor amount of *E*-isomer and traces of triphenylphosphine oxide; this was used in the next step without further purification. A pure sample of compound **12** has the following spectral data: Data for compound **12**: IR (film): 3400 (br), 1715, 1635 cm^{-1}. ^1H NMR: δ, 1.38 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.63–3.76 (m, 3H, 6-H, 7-H), 3.74 (s, 3H, CO_2CH_3), 4.32 (dd, 1H, $J = 6.7$, 7.3 Hz, 5-H), 5.62 (dt, 1H, $J_{3,4} = J_{4,5} = 7.3$ Hz, $J_{2,4} = 1.1$ Hz, 4-H), 6.01 (dd, 1H, $J = 1.1$, 11.7 Hz, 2-H) 6.31 (dd, 1H, $J = 7.3$, 11.7 Hz, 3-H). ^{13}C NMR: δ, 25.2, 27.4 [C(CH_3)$_2$], 51.8 (OCH_3), 63.9, 70.2, 74.2, 78.7 (C-4, C-5, C-6, C-7), 109.3 (O*C*Me$_2$O), 121.6 (C-2),146 (C-3), 167.5 (C=O), MS: *m*/*z* (%): 246 (75) [M^+].

4.3.2. Methyl (*Z*)-3-[(4*S*,5*S*)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenoate 13. A mixture of the above crude compound **12** (10.0 g), *t*-BuOH (115 mL), water (85 mL) and $NaIO_4$ (18.3 g, 85.5 mmol) was stirred vigorously at rt for 18 h. The crude reaction mixture was triturated with excess of CH_2Cl_2, the solids were filtered off and the organic layer was washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. After

evaporation of the solvent the residue was chromatographed on a silica gel column (eluent hexane/EtOAc, 3:1) to give compound **13** (4.2 g, 46% from compound **7**) as an oil. Data for compound **13**: $[\alpha]_D^{25} = -15.5$ (*c* 0.7, $CHCl_3$). IR (film): 1700, 1650 cm^{-1}. ^1H NMR: δ, 1.45 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.76 (s, 3H, $COOCH_3$), 4.8 (dd, 1H, $J = 2.8$, 7.7 Hz, 5-H), 5.82 (ddd, 1H, $J = 1.7$, 6.7, 7.7 Hz, 4-H), 5.99 (dd, 1H, $J = 1.7$, 11.6 Hz, 2-H), 6.25 (dd, 1H, $J = 6.7$, 11.6 Hz, 3-H), 9.48 (d, 1H, $J = 2.8$ Hz, 6-H). ^{13}C NMR: δ, 25.2, 27.3 ($C(CH_3)_2$), 51.8 (OCH_3), 75.8, 81.9 (C-4, C-5), 111.5 ($OCMe_2O$), 122.6 (C-2), 143.8 (C-3), 165.9 (CO_2CH_3), 199.3 (CH=O). MS: *m/z* (%): 214 (28) [M^+].

4.3.3. (3a*S*,4*S*,6a*R*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ium-5-olate 2. To a solution of **9** (3.39 g, 15.85 mmol) in reagent grade MeOH containing $NaHCO_3$ (2 g, 23.76 mmol), $NH_2OH{\cdot}HCl$ (1.43 g, 20.6 mmol) was added. The mixture was stirred at 25 °C for 12 h, extracted with CH_2Cl_2, the organic phase dried over Na_2SO_4 and after evaporation of the solvent, the residue was chromatographed on a silica gel column, using a gradient from EtOAc/hexane 2:1 to pure EtOAc and gave the nitrone **2** (2.4 g, 66%) as an analytically pure colorless oil. Data for compound **2**: $[\alpha]_D^{25} = -12.4$ (*c* 1.55, $CHCl_3$). Anal. Calcd for $C_{10}H_{15}NO_5$ (229.23): C, 52.40; H, 6.60; N, 6.11. Found: C, 52.12; H, 6.57; N, 6.30. Spectral data are identical to that of nitrone **1**.

4.4. Synthesis of nitrones 3 and 4

4.4.1. (*Z*)- and (*E*)-*tert*-Butyl-3-{(4*S*,5*R*)-5-[(1*R*)-1,2-dihydroxyethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2-propenoates 15 and 16. These compounds were obtained as a mixture from the reaction of 2,3-*O*-isopropylidene D-ribofuranose **6** (1.98 g, 10.4 mmol) and phosphorane **14** (4.7 g, 12.5 mmol), according to the procedure described for the synthesis of compound **12** and purified by column chromatography (silica gel, hexane/EtOAc, 6:1) to give a mixture of both esters **15** and **16** (1.6 g, 70%) together with traces of Ph_3PO, which was used for the next step.

An analytically pure sample of *Z*-ester **15** was obtained as a colorless oil after repeated chromatographic separations of the mixture of esters **15** and **16**. Data of (*Z*)-ester **15**: $[\alpha]_D^{25} = +92.3$ (*c* 1.24, $CHCl_3$). IR (film): 3360–3260 (br), 1695 cm^{-1}. ^1H NMR: δ, 1.39 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 3.63–3.82 (m, 3H, 6-H, 7-H), 4.33 (dd, 1H, $J = 6.5$, 8.3 Hz, 5-H), 5.48 (ddd, 1H, $J = 1.0$, 6.5, 8.5 Hz, 4-H), 5.97 (dd, 1H, $J = 1.0$, 11.6 Hz, 2-H), 6.17 (dd, 1H, $J = 8.5$, 11.6 Hz, 3-H). ^{13}C NMR: δ, 26.0, 28.0 [$C(CH_3)_3$, $C(CH_3)_2$], 64.9, 70.5 (C-6, C-7), 75.4, 79.8 (C-4, C-5), 83.0 ($OCMe_3$), 110.2 ($OCMe_2O$), 124.0 (C-3), 145.0 (C-2), 167.5 (C=O). MS: *m/z* (%): 231 (M−*t*-Bu, 6). Anal. Calcd for $C_{14}H_{24}O_6$ (MW 288.34): C, 58.32; H, 8.39. Found: C, 58.19; H, 8.42.

4.4.2. (*Z*)- and (*E*)-*tert*-Butyl-3-[(4*S*,5*S*)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenoate 17 and 18. To a stirred solution of the above mixture of esters **15** and **16** (1.5 g, 5.2 mmol) dissolved in *t*-BuOH (40 mL) and water (20 mL), $NaIO_4$ (2.25 g, 10.5 mmol) was added in portions. Stirring was continued at rt for 17 h, then the mixture was neutralized ($NaHCO_3$), extracted with CH_2Cl_2, and dried over $MgSO_4$. After removal of the solvent the residue was quickly passed through a flash silica gel column eluting with hexane/EtOAc 4:1 to give a mixture of enoates **17** and **18** (0.9 g, 70%). An analytically pure sample of (*Z*)-enoate **17** (0.15 g, 75%) was obtained from the (*Z*)-ester **15** (0.2 g, 0.7 mmol), following the same procedure. Data for compound **17**: $[\alpha]_D^{25} = -6.35$ (*c* 1.98, $CHCl_3$). IR (film): 1720 (br), 1630 cm^{-1}. ^1H NMR: δ, 1.43 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.49 [s, 9H, $C(CH_3)_3$], 4.88 (dd, 1H, $J = 6.6$, 3.0 Hz, 5-H), 5.81 (ddd, 1H, $J = 6.6$, 8.0, 2.4 Hz, 4-H), 5.88 (dd, 1H, $J = 2.4$, 11.5 Hz, 2-H), 6.14 (dd, 1H, $J = 6.6$, 11.5 Hz, 3-H), 9.46 (d, 1H, $J = 2.4$ Hz, CH=O). ^{13}C NMR: δ, 25.0, 27.1, 28.0 ($C(CH_3)_2$, $C(CH_3)_3$), 75.5, 81.2, 81.7 ($OCMe_3$, C-4, C-5), 111.1 ($OCMe_2O$), 124.7 (C-3), 142.1 (C-4), 164.7 (CO_2t-Bu), 198.9 (CH=O). MS: *m/z* (%) 256 (11) [M^+]. Anal. Calcd for $C_{13}H_{20}O_5$ (256.29): C, 60.92; H, 7.89. Found: C, 60.67; H, 7.64.

4.4.3. (3a*S*,4*S*,6a*R*)-4-[2-(*tert*-Butoxy)-2-oxoethyl]-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ium-5-olate 3 and (3a*S*,4*R*,6a*R*)-4-[2-(*tert*-butoxy)-2-oxoethyl]-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ium-5-olate 4. To a stirred solution of the above mixture of (*Z*)- and (*E*)-esters **17** and **18** (0.54 g, 2.1 mmol) in methanol (15 mL), $NH_2OH{\cdot}HCl$ (0.2 g, 2.8 mmol), and $NaHCO_3$ (0.3 g, 3.2 mmol) were successively added, with stirring at rt. Stirring was continued for about 12 h, then the mixture extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, concentrated, and the residue was chromatographed on a silica gel column (eluent hexane/EtOAc, 1:4). Nitrone **3** (0.25 g) was eluted first, followed by the nitrone **4** (0.17 g) both as colorless oils. Total yield 70%. Following the same procedure from a pure sample of compound **17** (0.05 g, 0.18 mmol) nitrone **3** was exclusively isolated in 68% yield. Data for nitrone **3**: $[\alpha]_D^{25} = -3.1$ (*c* 3.4, $CHCl_3$). IR (film): 3070, 1720, 1560 cm^{-1}. ^1H NMR: δ, 1.39 (s, 3H, CH_3), 1.45 [s, 9H, $C(CH_3)_3$], 1.47 (s, 3H, CH_3), 2.94 (d, 2H, $J = 5.1$ Hz, CH_2CO_2t-Bu), 4.21 (t, 1H, $J = 5.1$ Hz, 5-H), 4.84 (d, 1H, $J = 6.5$ Hz, 4-H), 5.35 (d, 1H, $J = 6.5$ Hz, 3-H), 6.92 (s, 1H, 2-H). ^{13}C NMR: δ, 28.0, 27.1, 25.6 [$C(CH_3)_2$, $C(CH_3)_3$], 34.5 (CH_2CO_2t-Bu), 76.0, 78.2, 78.8, 82.0 ($OCMe_3$, C-3, C-4, C-5), 112.0 ($OCMe_2O$), 133.0 (C=N), 168.8 (CO_2t-Bu). MS: *m/z* (%): 271 (6) [M^+]. Anal. Calcd for $C_{13}H_{21}NO_5$ (271.31): C, 57.55; H, 7.80; N, 5.16. Found: C, 57.68; H, 7.75; N, 4.96.

Data for nitrone **4**: $[\alpha]_D^{25} = -62.1$ (*c* 1.76, $CHCl_3$). IR (film): 3100, 1710, 1575 cm^{-1}. ^1H NMR: δ, 1.38 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 2.77 (dd, 1H, $J = 9.9$, 17.1 Hz, CH_2CO_2t-Bu), 3.22 (dd, 1H, $J = 4.6$, 17.1 Hz, CH_2CO_2t-Bu), 4.40–4.47 (m, 1H, 5-H), 5.0 (dd as t, 1H, $J = 5.9$ Hz, 4-H), 5.28 (d, 1H, $J = 5.9$ Hz, 3-H), 6.87 (s, 1H, 2-H). ^{13}C NMR: δ, 25.7, 26.9, 27.8, 27.9 [$C(CH_3)_2$, $C(CH_3)_3$], 32.0 (CH_2CO_2t-Bu), 71.5, 74.9, 77.7, 81.2 ($OCMe_3$, C-3, C-

4, C-5), 111.9 (O*C*Me$_2$O), 131.4 (C=N), 169.6 (C=O). MS: *m*/*z* (%): 271 (22) [M$^+$]. Anal. Calcd for $C_{13}H_{21}NO_5$ (271.31): C, 57.55; H, 7.80; N, 5.16. Found: C, 57.66; H, 7.65, N, 4.86.

4.5. Synthesis of nitrone 5

4.5.1. (3a*R*,6*R*,6a*R*)-2,2-Dimethyl-6-[(trityloxy)methyl]-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol 19. To a cooled (0 °C) solution of compound **6** (7.0 g, 36.84 mmol) in dry DMF (47 mL), dry NEt$_3$ (10 mL), DMAP (230 mg, 1.89 mmol) and trityl chloride (11.4 g, 41 mmol) were successively added with stirring under an argon atmosphere. Stirring was continued at rt for 24 h, then the crude mixture poured on ice-water (200 mL), extracted with CH_2Cl_2, the organic phase was washed with a saturated NH_4Cl solution, then with water, dried over Na_2SO_4, and evaporated. Column chromatography on silica gel (eluent hexane/EtOAc, 6:1) of the residue gave compound **19** (11 g, 69%) as an oil; this was used without further purification in the next step.

4.5.2. Methyl (*Z*)-3-{(4*S*,5*R*)-5-[(1*R*)-1-hydroxy-2-(trityloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2-propenoate 20. Following the same procedure described for the synthesis of compound **9** this compound was obtained as an oil (1.54 g, 91%) from compound **19** (1.5 g, 3.47 mmol) and methoxycarbonylmethylenetriphenyl phosphorane (1.70 g, 5 mmol) and purified by column chromatography on silica gel (eluent hexane/CH_2Cl_2/EtOAc, 7:3:1). Data for compound **20**: IR (film): 3460 (br), 3080, 3050, 3020, 1715, 1640, 1590 cm^{-1}. ^{1}H NMR: δ, 1.33 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$), 2.69 (d, 1H, $J = 3.9$ Hz, OH), 3.28 (m, 2H, TrOC*H*$_2$), 3.69 (s, 3H, COOCH$_3$), 3.69–3.74 (m, 1H, 6-H), 4.41 (dd, 1H, $J = 6.5$, 7.5 Hz, 5-H), 5.69 (ddd, 1H, $J = 6.5$, 8.0, 1.5 Hz, 4-H), 5.92 (dd, 1H, $J = 1.5$, 10.5 Hz, 2-H), 6.18 (dd, 1H, $J = 8.0$, 10.5 Hz, 3-H), 7.2–7.46 (m, 15H, aromatic protons). ^{13}C NMR: δ, 27.5, 25.2 [C(*C*H$_3$)$_2$], 51.5 (OCH$_3$), 64.8, 69.7, 74.0, 78.6, 86.6 (Ph$_3$*C*O, TrO*C*H$_2$, C-4, C-5, CHOH), 109.0 (O*C*Me$_2$O), 121.5, 126.9, 127.7, 128.6, 143.7, 145.1 (C-2, C-3, C aromatic), 166.4 (CO$_2$Me). MS: *m*/*z* (%): 488 (14) [M$^+$]. Anal. Calcd for $C_{30}H_{32}O_6$ (488.58): C, 73.75; H, 6.60. Found: C, 73.41; H, 6.40.

4.5.3. Methyl (*Z*)-3-{(4*S*,5*S*)-2,2-dimethyl-5-[2-(trityloxy)-acetyl]-1,3-dioxolan-4-yl}-2-propenoate 21. This compound was obtained as oil in 72% yield according to the procedure described for the synthesis of compound **8** from compound **20** (0.98 g, 2 mmol), PDC (2.25 g, 6 mmol), activated molecular sieves 3 Å (powder) (2 g), dry acetic acid (0.3 mL) in dry CH_2Cl_2 (15 mL), and purified by column chromatography on a silica gel column (eluent hexane/EtOAc, 7:1). Data for compound **21**: ^{1}H NMR: δ, 1.33 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$) 3.70 (s, 3H, COOCH$_3$), 3.72 (d, 1H, $J = 18.0$ Hz, TrOC*H*$_2$), 4.00 (d, 1H, $J = 18.0$ Hz, TrOC*H*$_2$), 4.86 (d, 1H, $J = 7.8$ Hz, 5-H), 5.77–5.91 (m, 3H, 2-H, 3-H, 4-H, ABC system), 7.21–7.46 (m, 15H, aromatic protons). ^{13}C NMR: δ, 26.4, 24.8 [C(*C*H$_3$)$_2$], 51.6 (OCH$_3$), 69.0, 75.1, 81.0, 87.0 (*C*Ph$_3$, 4-C, 3-C, 7-C), 110.9 (O*C*OMe$_2$), 122.7, 127.2, 127.9, 128.5, 143.0, 143.3 (C-aromatic, C-2, C-3), 165.6 (COOCH$_3$), 203.7 (C=O). MS: *m*/*z* (%): 486 (23) [M$^+$]. Anal. Calcd for $C_{30}H_{30}O_6$ (486.56): C, 74.06, H, 6.21. Found: C, 74.40; H, 6.30.

4.5.4. (3a*S*,4*S*,6a*R*)-4-(2-Methoxy-2-oxoethyl)-2,2-dimethyl-6-[(trityloxy)methyl]-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ium-5-olate 5. This compound was obtained as oil in 90% yield, according to the procedure described for compound **1** from compound **22** (0.70 g, 1.44 mmol), NH$_2$OH·HCl (0.135 g, 1.94 mmol), NaHCO$_3$ (0.185 g, 2.2 mmol) in EtOH (20 mL) and purified by column chromatography on silica gel (eluent hexane/EtOAc, 3:1). Data for compound **5**: $[\alpha]_D^{25} = +5.0$ (*c* 0.38, CHCl$_3$). IR (film): 1740, 1600 cm^{-1}. ^{1}H NMR: δ, 1.45 (s, 3H, CH$_3$), 1.46 (s, 3H, CH$_3$), 2.87 (dd, 1H, $J = 6.9$, 17.4 Hz, C*H*$_2$COOCH$_3$), 2.96 (dd, 1H, $J = 4.3$, 17.4 Hz, C*H*$_2$COOCH$_3$), 3.68 (s, 3H, COOCH$_3$), 4.2 (s, 2H, TrOC*H*$_2$), 4.26 (unresolved multiplet, 1H, 5-H), 4.73 (dd, 1H, $J = 1.0$, 6.5 Hz, 4-H), 5.57 (d, 1H, $J = 6.5$ Hz, 3-H), 7.21–7.5 (m, 15H aromatic protons). ^{13}C NMR: δ, 25.8, 27.1 (C(*C*H$_3$)$_2$), 33.5 (*C*H$_2$COOCH$_3$), 52 (OCH$_3$), 58.7 (C-5), 75.6, 76.7, 79.9 (C*H*$_2$COOCH$_3$, C-3, C-4), 87.4 (*C*Ph$_3$), 112.0 (O*C*Me$_2$O), 127.2, 127.9, 128.7, 143.3, 144.6 (C=N, aromatic carbons) 170.1 (C=O). MS: *m*/*z* (%): 471 (100) [M$^+$−31]. Anal. Calcd for $C_{30}H_{31}NO_6$ (MW 501.57): C, 71.84; H, 6.23; N, 2.79. Found: C, 71.61; H, 6.15; N, 2.89.

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