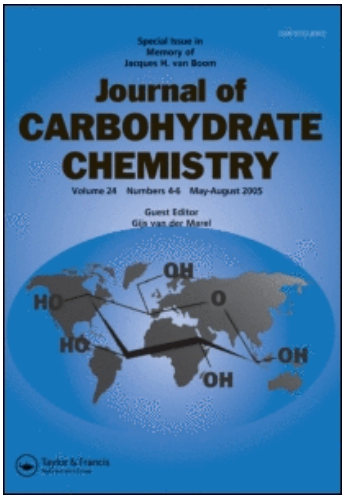

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Double Asymmetric Induction in 1,3-Dipolar Cycloaddition of Nitrones to 2,3-Unsaturated Sugar 1,5-Lactones†

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ABSTRACT

1,3-Dipolar cycloaddition of nitrones **1**–**3** to the α,β-unsaturated δ-lactones, non-chiral **4**, D-*glycero* **5**, DL-*glycero* **5/5ent**, D-*erythro* **6**, and D-*threo* **7**, provides an interesting example of a double asymmetric induction. In all cases, only the *exo* approach of reactants was observed. The high preference of *anti* addition of the nitrones to the terminal acetoxymethyl group in the lactones **5**–**7** is consistent with previous observations, and can be explained in terms of the axial approach of the nitrone oxygen atom. The 3-*t*-butoxy group of the nitrone plays a similar role. In the case of mismatched pairs, the location of the 4-acetoxy substituent in the lactone and that of the 4-*t*-butoxy one in the nitrone become decisive for the outcome of the addition. CD-spectroscopy proved to be an attractive tool to determine the absolute configuration of the cycloadducts.

Key Words: Sugar lactones; Nitrones; 1,3-Dipolar cycloaddition; Circular dichroism.

†This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

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INTRODUCTION

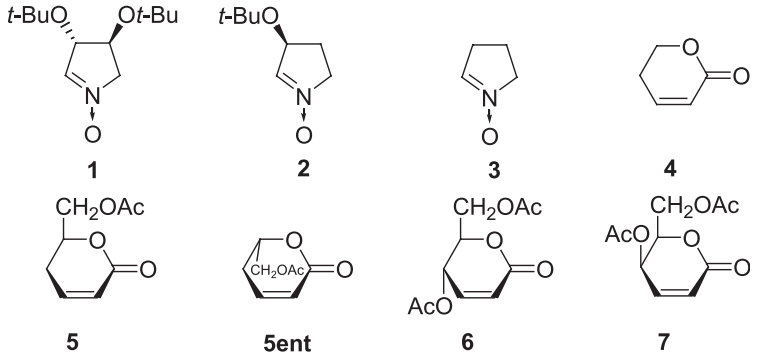
Recently, we have reported on the 1,3-dipolar cycloaddition of five membered cyclic nitrones **1** and **2** (Scheme 1), derived from L-tartaric[1,2] acid and (*S*)-malic acid,[3] respectively, to the α,β-unsaturated lactones, non-chiral **4**, enantio-pure D-*glycero* **5** and racemic mixture **5/5ent**.[4,5] It has been demonstrated that these reactions proceeded with a high stereoselectivity in the case of matched pairs, and with a significant kinetic resolution of the racemate **5/5ent** to yield the corresponding adducts **8–11** and **13–16** (Scheme 2). In all instances, only the *exo* approach of the dipoles **1** and **2** has been observed.[4,5]

Following subsequent hydrogenolysis of the N–O bond, adducts **8–10** and **13–16** may provide an entry to bicyclic iminosugars with indolizidine or pyrrolizidine skeletons.[6–8] Recently, the transformation of adduct **8** into 7-hydroxylentiginosine **18** and indolizidine **19**, structurally related to castanospermine (**20**), has been reported.[9]

The cycloaddition reactions between chiral nitrones **1** and **2**, and lactones **5** and **5ent** provided an interesting example of double asymmetric induction, where the chirality elements of each reactant may influence stereoselectivity either in concert or in opposition. To reach a more consistent picture of this reaction, we decided to expand the number of lactones and nitrones. We included the non-chiral nitrone **3**, as well as D-*erythro* **6**, and D-*threo* **7** lactones which are readily available from glucose and galactose, respectively. To provide a more solid and complete representation of cycloadditions, the previous[4,5] and the present results are discussed together.

RESULTS AND DISCUSSION

Due to the single asymmetric induction, cycloaddition of the non-chiral nitrone **3** to D-*glycero* **5**, D-*erythro* **6** and D-*threo* **7** lactones provides the basic information on the reaction. Reaction of nitrone **3** with lactone **6** gave cycloadducts **21** and **22** in a ratio of 4.2:1, respectively, as a result of an *exo* approach of the dipole to both sides of the dipolarophile. The configurations of adducts **21** and **22** were easily ascribed from values of $J_{1a,2}$ coupling constants. In the case of **21**, a small axial–pseudoequatorial



Scheme 1. Nitrones **1–3** and lactones **4–7** used for 1,3-dipolar cycloadition reactions.

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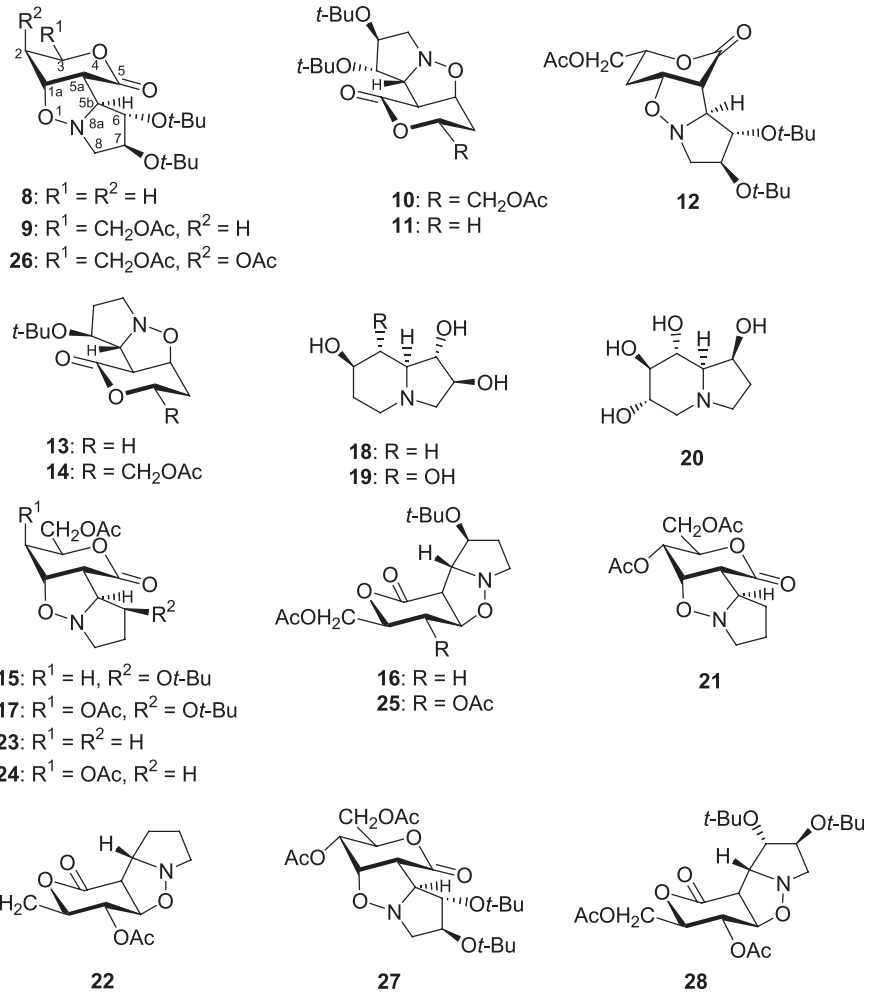

Scheme 2. Cycloadducts **8–28** obtained *via* **1**,3-dipolar cycloaddition of nitrones **1–3** to lactones **4–7**.

coupling was found, whereas in the case of **22** a larger axial–pseudoaxial coupling was observed. Cycloaddition of the same nitrone **3** to lactones **5** and **7** yielded, in each case as a sole product, **23** and **24**, respectively. In the case of crystalline compounds **22** and **23**, the structure and configuration of both adducts were proven by their X-ray crystal structure analysis (Figures 1 and 2).[a]

The high preference for the *anti* addition of the nitrone **3** to the terminal acetoxymethyl group in lactones **5**–**7** is in agreement with our previous observations.[10,11]

[a]Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center, Cambridge, UK, as a supplementary publication: **22** (CCDC 203086), **23** (CCDC 203085).

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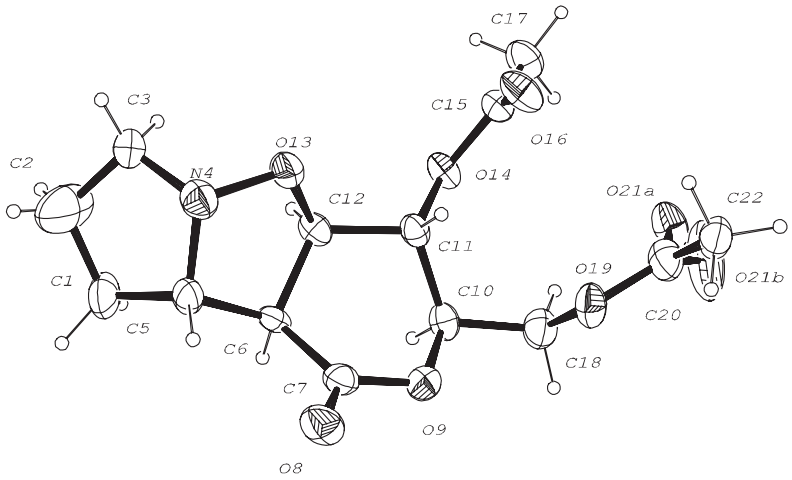

Figure 1. X-ray structure of compound **22** with crystallographic numbering scheme.

This phenomenon can be explained in terms of the axial approach of the nitrone oxygen atom[12,13] and, as a consequence, formation of the C–O bond prior to the C–C bond (Scheme 3). The terminal acetoxymethyl substituent serves as an anchor to stabilize the $^{o}H_5$ conformation. The preferred direction of the cycloaddition proceeds via a chair-like transition state. The lower stereoselectivity, observed in the case of addition of **3** to D-*erythro* lactone **6**, testified to some importance of the steric requirements involving the 4-*O*-acetyl substitutent of the lactone. Similar stereochemical preferences (cycloaddition to **5**–**7**) that favored the axial approach of the dipole, have also been observed for the cycloaddition of open chain nitrones[10,11] and nitrile oxide.[14]

The use of a chiral dipole created a double asymmetric induction system. Thus, addition of nitrone **1** to **5**,[4] or to **7**, proceeded with a high stereoselectivity to afford **9**[4] and **26**, respectively, as sole products. Reaction of **1** with D-*erythro* lactone **6**

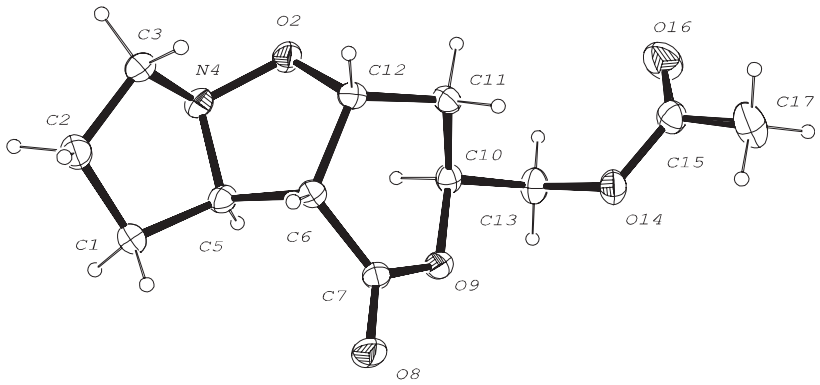

Figure 2. X-ray structure of compound **23** with crystallographic numbering scheme.

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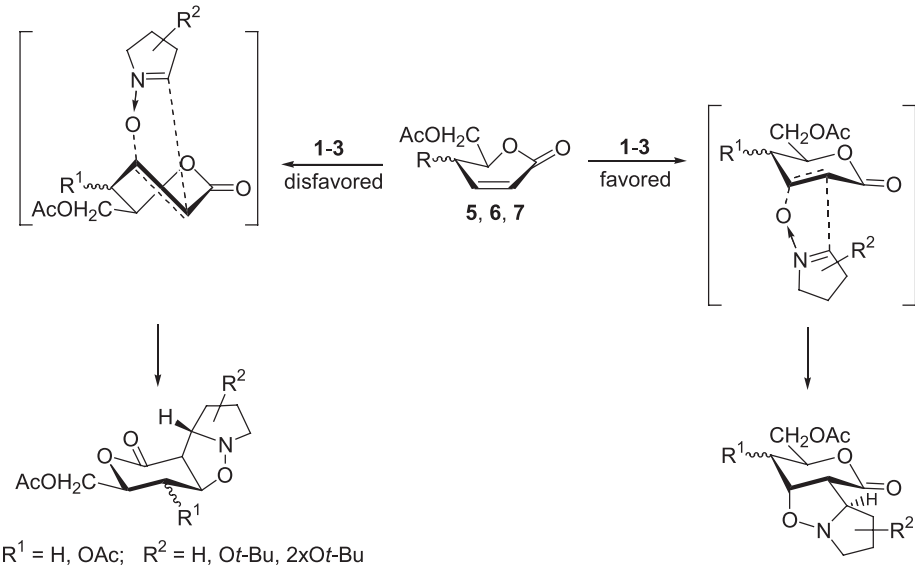


Scheme 3. Possible stereochemical pathway of 1,3-dipolar cycloaddition of nitrones **1–3** to lactones **4–7**.

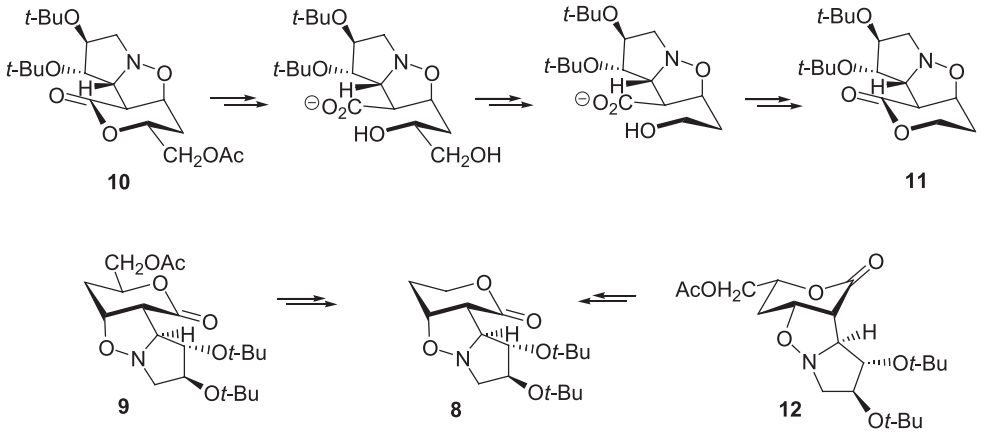
proceeded with only slightly lower asymmetric induction; the ratio of **27**:**28** being 10:1, respectively. In the ^{1}H NMR spectrum of a post-reaction mixture, the signals corresponding to diastereomer **28** were detectable. The configurations of adducts **26**–**28** were easily deduced by comparing their ^{1}H NMR spectra with those of adducts **8**,[4] **9**,[4] and **21**–**24**. Addition of the nitrone **1** to lactones **6** and **7** proceeded *anti* to both the terminal acetoxymethyl group in the lactone and the 3-*t*-butoxy group in the nitrone. The configuration at C-4 of the lactone played a minor role compared to the strongly disfavored *syn* addition to both the first-rank acetoxymethyl and 3-*t*-butoxy groups.

In the first paper of this series,[4] we have reported that the reaction of the mismatched pair **5ent** and **1** led to formation of a single product. Configuration of this product (which has never been isolated in a pure form) was previously erroneously assigned[4] based on the assumption that the addition should proceed *anti* to the *t*-butoxy group at C-3 of the nitrone. Reinvestigation of the cycloaddition of **1** to **5ent** (77.4% ee) revealed, in addition to **9** derived from **5**, the presence of two cycloadducts **10** and **12** in a ratio of about 2.5:1. These resulted presumably form the *exo* approach of the dipole to both sides of the dipolarophile. The configuration of the main product **10** may be established on the basis of the large *cis* vicinal coupling constant $J_{5b,6}$ = 6.9 Hz observed in its ^{1}H NMR spectrum. Due to the *trans* arrangement of both protons H-5b and H-6, the corresponding coupling constant value for the minor component **12** was below resolution. A small $J_{5b,6}$ was found for **9**. However, it should be noted that the structural assignments of adducts derived from lactones **5** and **5ent** are not straightforward since they usually do not form crystals suitable for X-ray analysis, and, at the same time, the ^{1}H NMR resonances of bridgehead protons H-5a and H-5b are not well resolved. Thus, in order to ascertain unequivocally, the spectral assignment

corresponding to structures **10** and **12**, both compounds were submitted to a four-step reaction sequence consisting of saponification of the lactone ring, glycolic cleavage of the free *vic*-terminal diol, reduction of the aldehyde to hydroxymethyl group, and lactonization. The product **11**, obtained from **10**, represented an alternative structure to the adduct **8** which was obtained by reaction of **1** and **4**. The analogous sequence of reactions, performed independently with **12** and **9**, provided in both cases the same known adduct **8** (Scheme 4). It should be pointed out that the very weak resonances corresponding to the adduct **11** have been found and reported[4] in the ^{1}H NMR spectrum of **8**.

The significant steric hindrance due to the 3-*t*-butoxy substitutent in nitrones **1** and **2** was demonstrated previously,[4,5] as high stereoselectivity of the cycloaddition of **1** and **2** to **4** resulted in the exclusive formation of **8** and **13**, respectively. Introduction of additional chirality elements to both reactants influences stereoselectivity depending on a matched or mismatched pair. This was illustrated by a significant kinetic resolution of the racemate in the reaction of two molar equiv of the lactone **5/5ent** with nitrones **1** and **2**. In the case of nitrone **2**, D-*glycero* lactone **5** was less reactive and could be isolated unreacted in 93% yield (81% ee).[5] In the case of the nitrone **1**, L-*glycero* lactone **5ent** is less reactive and can be isolated with 77.4% ee (86%).[4] In the case of reaction involving **1**, the *t*-butoxy substitutent at C-4 of the nitrone **1**, which introduces a secondary effect in the matched pair **1** and **5**, explains the lower kinetic resolution of the starting enantiomers **5/5ent**. The same secondary effect of the 4-*t*-butoxy group in the nitrone is very visible if one compares proportions of diastereomers in mismatched pairs **15**:**16** = 1:1.3 and **10**:**12** = 2.5:1, obtained in the case of the mismatched pairs **2**:**5**[5] and **1**:**5ent**, respectively.

Introduction of the additional acetoxy substitutent at position 4 of the lactone shifts the direction of the cycloaddition depending on the configuration at C-4 of the lactone. Indeed, addition of D-*erythro* lactone **6** to the nitrone **2** proceeded exclusively *syn* to the acetoxymethyl group to form adduct **25**, whereas addition of the D-*threo* lactone **7** to **2** was exclusively *anti* to the acetoxymethyl group to afford **17**[5] as a sole product.



Scheme 4. Chemical transformation of the adduct **10** into **11** and transformations of adducts **9** and **12** into **8**.

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These data demonstrated that the direction of asymmetric induction could be easily controlled by the proper selection of the substrate.

We have shown previously[5] that CD-spectroscopy is an attractive tool for the determination of the absolute configuration at newly formed stereogenic centers of adducts **8**, **9**, and **13**–**17**. A simple correlation between the sign of the n–π* Cotton effect (CE) and the O–C(=O)–C_α–C_β torsional angle based on the ''ring-chirality rule'' established by Legrand and Bucourt[15] makes possible a direct assignment of configuration at the C-5a atom. The determination of the absolute stereochemistry in these adducts was based on following assumptions:

- the lactone chromophoric system is planar;
- the conformation of the lactone ring is a major factor determining the sign of the n–π* transition;
- the positive (negative) sign of the CD band of the n–π* lactone transition corresponds to the negative (positive) sign of the O–C(=O)–C_α–C_β torsional angle.

On the basis of the CD data obtained for adducts **8**, **9**, and **13**–**17**, and additional X-ray, NMR results, and molecular modeling data, we can conclude that the ''ring-chirality rule'' is applicable in the case of our lactones, thus enabling the unambiguous stereochemical assignment of the cycloaddition products.[5] This assignment is made on the basis of the statement that the conformation of the six-membered ring depends mostly on the configuration at the bridgehead carbon atoms C-1a and C-5a. Thus, a negative sign of the n–π* CE can be connected with an (*R*) absolute configuration at the C-5a carbon atom whereas a positive sign of the same transition with a (5a*S*) configuration.

It was of interest to apply the inferences drawn from the available chiroptical spectra to all synthesized adducts. Our extended studies are focused on the proof of validity of the ''ring-chirality rule'' over a broad variety of adducts and, in particular, adducts differing in substitution within the nitrone ring. To achieve such a goal we have undertaken the chiroptical studies on the newly synthesized compounds **10**–**12** and **21**–**27**.

The CD and UV data of adducts **8**–**17** and **21**–**27** are collected in Table 1 and the CD spectra of some representative lactones are presented in Figure 3. As can be seen from Table 1, the studied compounds can be divided into two groups depending upon the sign of the long-wavelength CD band, most probably originating from the n–π* transition of the δ-lactone chromophore. The intensity of electronic absorption of this transition, however, appears to be relatively strong, suggesting the possible presence of a different electronic transition of approximately the same energy.

Following the above discussion it seems reasonable to assume that all compounds from Table 1 with a positive sign of their long-wavelength CD band appearing between 218 and 236 nm belong to the group with the (5a*S*) configuration. Consequently, the compounds from the second group, consisting of adducts **8**, **9**, **12**, **15**, **17**, **21**, **23**, **24**, **26** and **27** and characterized by the negative CD band in the same spectral region, belong to the (5a*R*) group. The X-ray data of adducts **22** and **23** (Figures 1 and 2), the only two compounds among the newly synthesized adducts **10**–**12** and **21**–**27**, which form suitable crystals for X-ray analysis, corroborate this statement unequivocally, showing a

Table 1. UV and CD data of adducts **8**–**17** and **21**–**27** recorded in acetonitrile. UV and CD data are given as ε (λ/nm) and Δε (λ/nm), respectively.

Comp.	Conf.	UV ε (λ)	CD Δε (λ)		
8	(5a*R*)	1200 (208)	−7.3 (188.4)		−2.42 (220.4)
9	(5a*R*)	750 (208)	−9.3 (188.2)		−1.89 (221.2)
10	(5a*S*)	560 (221^{sh})	−4.9 (186.0)	+1.29 (202.0)	+0.17 (236.0^{sh})
11	(5a*S*)	340 (225^{sh})	−6.7 (183.5)	+1.05 (201.5^{sh})	+1.93 (222.5)
12	(5a*R*)	2100 (216^{sh})	−3.3 (188.5)		−2.58 (222.0)
13	(5a*S*)	990 (194^{sh})	−0.1 (190.4)	+0.43 (204.0^{sh})	+1.33 (224.2)
14	(5a*S*)	520 (210)	−(a) (189.6)	+0.72 (204.0)	+1.09 (224.4)
15	(5a*R*)	710 (206)	+2.3 (189.4^{sh})	−1.46 (203.2)	−0.41 (235.4)
16	(5a*S*)	580 (209)	−0.95 (193.6)		+2.53 (224.8)
17	(5a*R*)	560 (216^{sh})	−0.55 (198.0)		+1.51 (218.0)
21	(5a*R*)	1100 (206^{sh})	+3.9 (184.5^{sh})	−0.79 (202.0^{sh})	−1.35 (226.0)
22	(5a*S*)	790 (214^{sh})	+2.8 (185.0^{sh})	−0.16 (207.0)	+0.98 (229.0)
23	(5a*R*)	790 (216^{sh})	+2.3 (185.0)	−1.33 (203.0)	−1.58 (223.5)
24	(5a*R*)	750 (218^{sh})	+1.8 (187.0^{sh})	+0.53 (208.0)	−0.49 (232.5)
25	(5a*S*)	710 (212^{sh})	−0.3 (198.5)	−0.33 (203.5)	+0.99 (228.5)
26	(5a*R*)	700 (216^{sh})	−6.5 (185.5)		−0.87 (222.0)
27	(5a*R*)	1300 (213^{sh})	−4.7 (188.5)		−1.39 (222.5)

a—Negative maximum; ^{sh}—shoulder.

(5a*S*) and (5a*R*) configuration respectively. In the case of compound **22**, however, the X-ray data demonstrate some degree of deviation of the lactone chromophore from planarity (the O═C–O–C torsional angle equals to + 10.9°). The non-planar lactone group has to be considered as an inherently chiral chromophore strongly contributing to the overall CD spectrum. Fortunately, this contribution seems to be of the same sign as

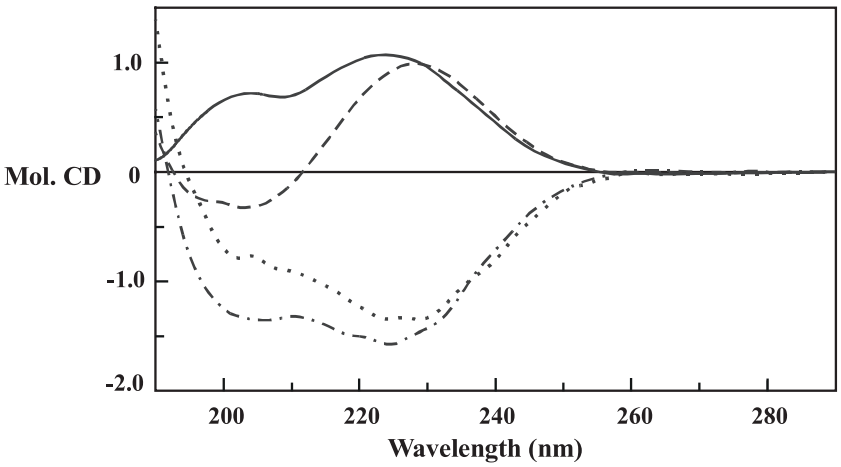

Figure 3. CD spectra of adducts **14** (———), **21** (– · – · – · –), **23** (· · · · · ·) and **25** (– – – –) recorded in acetonitrile.

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that of the lactone ring. Therefore, the ''ring-chirality rule'' should also apply to the CD of compound **22**.

Conversely, the lactone chromophoric system in adduct **23** is planar as evidenced by the O═C–O–C torsional angle value of −179.1°. In this case, however, the negative O–C(═O)–C_α–C_β torsional angle is in disagreement with the ''ring-chirality rule,'' which for a negative sign of the n–π* CE predicts a positive O–C(═O)–C_α–C_β torsional angle. On the other hand, the negative sign of the n–π* CE corresponds nicely to the (5a*R*) configuration confirmed by the X-ray data. The presence of different molecular species in the solid state and in solution may be a possible explanation of this discrepancy. To prove this assumption, the CD spectrum of lactone **23** was recorded in a KBr pellet. In comparison to the solution CD, there is an additional positive CE seen around 255 nm in the solid state spectrum (Figure 4). Assuming that in the KBr pellet all CD bands are red shifted by approximately 25 nm in comparison to the solution CD, the 255 nm CD band may be assigned to the n–π* excitation of the lactone chromophore. Thus, this sign change may give evidence for the above assumption in favour of the presence of a different molecular species in the solid state and solution. Moreover, the positive sign of the n–π* band nicely corresponds to the negative sign of the O–C(═O)–C_α–C_β torsional angle equal to −27.0° in the crystal and validates the ''ring-chirality rule'' for adduct **23** as well.

As mentioned above, in our previous paper[5] the absolute configuration at the C-5a carbon atom of the cycloaddition product of nitrone **1** to lactone **5ent** was incorrectly determined to be (*R*). This assignment was made, among others, also on the basis of the CD data. Although we believed at that time that the investigated product was a 1:3 mixture of adducts **9** and **10**, we showed in the present detailed study that indeed, three adducts were present, namely **9**, **10**, and **12**, in the mixture. Fortunately, this time we were able to isolate pure products. As can be seen in Table 1, the chiroptical data obtained for pure adducts **9**, **10**, and **12** fully agree with the stereochemical assignment made on the basis of other spectroscopic methods and the independently performed chemical correlation described above. It means, that the

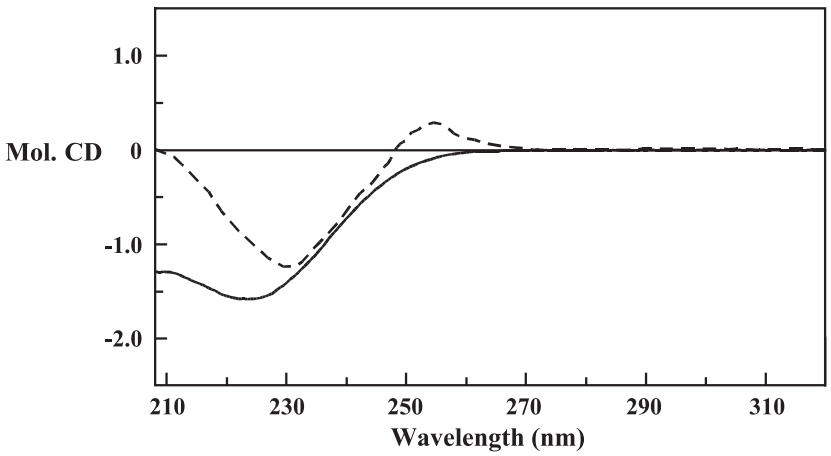

Figure 4. CD spectra of adduct **23** in acetonitrile (———), and in KBr pellet (– – – –).

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(5a*R*), (5a*S*), and (5a*R*) configuration determined for adducts **9**, **10**, and **12**, respectively, corresponds nicely with the negative, positive, and negative sign of the n–π* CD band, respectively. Thus, the CD results of adducts **9**, **10**, and **12** fully corroborate with the ''ring-chirality rule.''

Among all investigated adducts, the only exception regarding correlation between the negative sign of the n–π* CD band and the (5a*R*) configuration is presented by compound **17** which exhibits a positive n–π* CE for (5a*R*) configuration. In our previous report[5] this deviation from the rule was tentatively explained by the change of the lactone ring conformation induced by the presence of an axial acetoxy group at C-2 and the consequent repulsion between two bulky vicinal substituents. However, the CD data of compounds **24** and **26**, bearing the same substitution and stereochemistry within the lactone ring as compound **17**, do not uphold this explanation (Figure 5). As shown in Table 1, in both cases the n–π* CD band is negative in accordance with the ''ring-chirality rule.'' Having at our disposal only three examples of this kind, it was not easy to draw a definite conclusion allowing an unequivocal explanation of such a behavior. With reference to the available CD data, however, it seems reasonable to assume that the substitution of the nitrone ring may induce a deformation of the lactone ring conformation. In an extreme case, such a deformation may lead to an inversion of the ring conformation. In the present case, adducts **17** and **26** constitute local enantiomers regarding the O-*t*-Bu substituent at C-6, and at the same time their corresponding n–π* CD bands are of opposite sign. Therefore, it seems reasonable to assume that the stereochemistry of the substitution in the nitrone ring may influence the conformation of the six-membered lactone ring. Additional evidence in favor of such an assumption consists of the CD spectrum of adduct **24**, which is not substituted on the nitrone ring. In this case, the sign of the n–π* CE is indeed negative, however, its amplitude is approximately two-fold smaller than in the case of adduct **26**. Moreover, for **24** the n–π* CD band can be considered to be bisignate since a negative CE at 232 nm is preceded by a positive CE occurring at 208 nm (Table 1). From these data, it

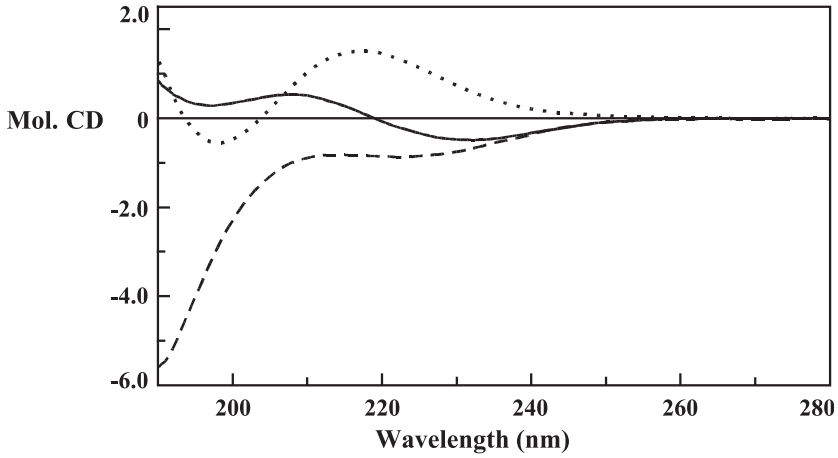

Figure 5. CD spectra of adducts **17** (· · · · · ·), **24** (———), and **26** (– – – –) recorded in acetonitrile.

may be suggested that the pseudoequatorial *O-t*-Bu substituent at C-6 stabilizes the conformation of the lactone ring with a positive O–C(═O)–C_α–C_β torsional angle (the case of adduct **26**), whereas the pseudoaxial *O-t*-Bu substituent at C-6 causes an inversion of the lactone ring conformation, most probably due to the presence of axial substituents suffering van der Waals repulsions (the case of adduct **17**). The lack of substituent at C-6 in adduct **24** seems to introduce some level of flexibility to the molecule characterized by a gradual distortion without inversion of the torsion angle variations. As a result, a weak n–π* CE with a negative sign accompanied by a positive CD band at shorter wavelength is observed. The above discussion is only an early attempt to explain the relationship between the structure of adducts and their respective chiroptical properties. More detailed and systematic studies on this subject are in progress in our laboratory.

CONCLUSIONS

Cycloaddition between **1**–**3** and **5**–**7** proceeds exclusively in the *exo* mode and shows high preference for *anti* addition to both the acetoxymethyl group of the lactone and the 3-*t*-butoxy group of the nitrone. In the case of mismatched pairs, the 4-acetoxy group of the lactone and 4-*t*-butoxy group of the nitrone begin to play a decisive role in the control of the stereochemical pathway of cycloaddition.

CD spectroscopy appears to be a convenient, sensitive and fast technique for the stereochemical assignment of products of cycloaddition between **1**–**3** and **5**–**7**. These assignments are based on the ''ring-chirality rule,'' which correlates the positive/negative sign of the n–π* CD band with the negative/positive sign of the O–C(═O)–C_α–C_β torsional angle. It is demonstrated that CD spectra are extremely sensitive to any changes of the conformation of the lactone ring. Moreover, they are also very sensitive to the substitution in the nitrone ring. These effects cannot be studied easily by any other spectroscopic method.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Brucker DRX 500 Avance Spectrometer. IR spectra were obtained on an FT-IR-1600 Perkin–Elmer spectrophotometer. The optical rotations were measured with a JASCO Dip-360 digital polarimeter. UV spectra were measured on a Cary 100 spectrophotometer in acetonitrile. CD spectra were recorded between 180–360 nm at rt with a *JASCO J-715* spectropolarimeter using acetonitrile solutions. Solutions with concentrations in the range 0.8×10^{-4} to 1.2×10^{-3} mol · dm^{-3} were examined in cells with a path length 0.1 or 1 cm. For the solid state CD measurements a crystalline compound (1–3 mg) and KBr (280–300 mg) were ground and formed into a disk which was rotated around the optical axis during the entire measurement using original JASCO equipment for this purpose.

Column chromatography (CC) was performed using Merck silica gel 230–400 mesh. Racemic lactone **5/5ent** was obtained according to our earlier work.[16] Enantiomerically pure D-*glycero* lactone **5** was obtained according to Roth and Roark

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protocol.[17,18] Lactones **6** and **7** were obtained following a procedure described earlier,[19] and nitrone **3** was prepared following a known procedure.[20]

Cycloaddition of nitrones 1–3 to lactones 4–7. General procedure. The lactones and nitrones in the ratios reported in Table 2 were dissolved in dry toluene (3 mL) and stirred at rt for 48 h (entries 1, 2, 4, 6, 8, 11, 12, 14, 15, 16) or for 24 h and then under reflux for 0.5 h (entry 3) or under reflux for 1 h (entries 5, 7, 9, 10, 13). The progress of the reaction was monitored by TLC. After removal of the solvent, the residue was purified on a silica gel column to afford the corresponding cycloadducts. Yields are reported in Table 2.

(1a*S*,3*R*,5a*S*,5b*R*,6*S*,7*S*)-3-Acetoxymethyl-6,7-di-*tert*-butoxy-5-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (10). CC: hexane/Et_2O 1:1 v/v followed by toluene/acetone 15:1 v/v; $[\alpha]_D$ −4.8 (*c* 1.0, CH_2Cl_2); IR (film): 2975, 1745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 4.92 (m, 1H, *J* 2.5, 3.4, 5.2, 11.6 Hz, H-3), 4.45 (m, 1H, *J* 2.9, 3.0, 6.7 Hz, H-1a), 4.27 (dd, 1H, *J* 3.4, 12.2 Hz, C$H_A$$H_B$OAc), 4.18

Table 2. 1,3-Dipolar cycloaddition of nitrones **1–3** to lactones **4–7**. Entries 1–4, 8–11, 13 have been reported earlier, providing reaction conditions and analytical data of cycloadducts.

Entry	Lactone	Nitrone	Lactone:nitrone ratio (mmol/mmol)	Yield %	Proportion of stereoisomers (%)	Reaction conditions
1[4]	**4**	**1**	0.5:0.5	91	**8**(97):**11**(3)	rt, 48 h
2[4]	**5**	**1**	0.5:0.5	88	**9**(100)	rt, 48 h
3[4]	**5/5ent**	**1**	0.5:0.5	78	**9**(65):**10**(35)	rt, 24 h and reflux 0.5 h
4[4]	**5/5ent**	**1**	0.8:0.4	86	**9**(91):**10**(9)	rt, 48 h
5[#]	**5ent***	**1**	0.4:0.4	77	**9**(13):**10**(62):**12**(25)	reflux 1 h
6	**6**	**1**	0.4:0.6	68	**27**(92):**28**(8)	rt, 48 h
7	**7**	**1**	0.6:0.6	76	**26**(100)	reflux 1 h
8[5]	**4**	**2**	0.6:0.6	89	**13**(100)	rt, 48 h
9[5,¶]	**5**	**2**	0.6:0.6	75	**15**(42):**16**(58)	reflux 1 h
10[5,¶]	**5/5ent**	**2**	0.6:0.6	79	**14**(51):**15**(21):**16**(28)	reflux 1 h
11[5]	**5/5ent**	**2**	1.0:0.5	87	**14**(100)	rt, 48 h
12	**6**	**2**	0.2:0.3	62	**25**(100)	rt, 48 h
13[5]	**7**	**2**	0.6:0.6	81	**17**(100)	reflux 1 h
14	**5**	**3**	0.2:0.3	81	**23**(100)	rt, 48 h
15	**6**	**3**	0.6:0.6	83	**21**(74):**22**(26)	rt, 48 h
16	**7**	**3**	0.2:0.3	86	**24**(100)	rt, 48 h

[#]Revised reaction.
*Optical purity 77.4% ee.
[¶]In the previous paper (Ref. [5]) the ratio of diastereomers **15** and **16** in the Table 2 (entries 2 and 3) were reversed.
(From Refs. [4,5].)

(dd, 1H, *J* 5.2, 12.2 Hz, CH_AH_BOAc), 4.07 (dd, 1H, *J* 2.1, 6.9 Hz, H-5b), 3.98–4.06 (m, 2H, H-6,7), 3.69 (dd, 1H, *J* 2.1, 6.7 Hz, H-5a), 3.29 (dd, 1H, *J* 6.2, 13.2 Hz, H-8), 2.97 (dd, 1H, *J* 7.1, 13.2 Hz, H-8′), 2.09 (s, 3H, OAc), 2.04 (ddd, 1H, *J* 2.5, 2.9, 14.8 Hz, H-2), 1.94 (ddd, 1H, *J* 3.0, 11.6, 14.8 Hz, H-2′), 1.25, 1.17 (2s, 18H, 2O*t*–Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.0, 170.6, 76.6, 75.0, 73.8, 73.1, 72.8, 72.3, 65.2, 60.5, 48.5, 28.5, 28.5, 28.4, 20.7; HRMS (ESI) *m/z* $[M + H]^+$, Calcd for $C_{20}H_{34}NO_7$: 400.2330. Found: 400.2337.

(1a*R*,3*R*,5a*R*,5b*S*,6*S*,7*S*)-3-Acetoxymethyl-6,7-di-*tert*-butoxy-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (12). CC: hexane/Et_2O 1:1 v/v; $[\alpha]_D$ + 30.0 (*c* 1.0, CH_2Cl_2); IR (film): 2976, 1747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.74 (m, 1H, *J* 7.6, 8.7, 8.9 Hz, H-1a), 4.41 (m, 1H, *J* 1.8, 3.6, 6.0, 11.7 Hz, H-3), 4.26 (dd, 1H, *J* 3.6, 12.1 Hz, CH_AH_BOAc), 4.22 (dd, 1H, *J* 6.0, 12.1 Hz, CH_AH_BOAc), 4.04 (bs, 1H, H-6), 4.01 (bd, 1H, *J* 5.3 Hz, H-5b), 3.86 (m, 2H, H-7), 3.71 (dd, 1H, *J* 5.5, 13.2 Hz, H-8), 3.47 (dd, 1H, *J* 5.3, 8.9 Hz, H-5a), 2.86 (dd, 1H, *J* 3.1, 13.2 Hz, H-8′), 2.29 (ddd, 1H, *J* 1.8, 7.6, 14.0 Hz, H-2), 2.10 (s, 3H, OAc), 1.71 (ddd, 1H, *J* 8.7, 11.7, 14.0 Hz, H-2′), 1.23, 1.18 (2s, 18H, 2O*t*–Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 170.5, 81.0, 74.7, 74.3, 73.8, 73.5, 72.2, 65.0, 62.6, 50.3, 29.3, 28.4, 28.3, 20.7; HRMS (ESI) *m/z* $[M + H]^+$, Calcd for $C_{20}H_{34}NO_7$: 400.2330. Found: 400.2338.

(1a*S*,2*S*,3*R*,5a*R*,5b*S*)-2-Acetoxy-3-acetoxymethyl-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (21). CC: toluene/acetone 9:1 v/v; $[\alpha]_D$ + 138.6 (*c* 1.0, CH_2Cl_2); IR (film): 2960, 1743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.13 (ddd, 1H, *J* 1.9, 3.3, 10.1 Hz, H-3), 5.11 (dd, 1H, *J* 2.5, 10.1 Hz, H-2), 4.69 (dd, 1H, *J* 2.5, 7.0 Hz, H-2), 4.40 (dd, 1H, *J* 3.3, 12.7 Hz, CH_AH_BOAc), 4.28 (dd, 1H, *J* 1.9, 12.7 Hz, CH_AH_BOAc), 3.90 (m, 1H, H-5b), 3.51 (dd, 1H, *J* 1.9, 7.0 Hz, H-5a), 3.37 (ddd, 1H, *J* 4.3, 7.8, 13.5 Hz, H-8), 3.07 (dt, 1H, *J* 8.1, 8.1, 13.5 Hz, H-8′), 2.20 (m, 1H, H-7), 2.14, 2.07 (2s, 6H, 2OAc), 2.06 (m, 1H, H-6), 1.82 (m, 1H, H-7′), 1.71 (m, 1H, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4, 169.7, 168.7, 73.2, 72.2, 72.1, 66.7, 61.5, 56.7, 54.1, 30.0, 23.8, 20.8, 20.6; HRMS (ESI) *m/z* $[M + Na]^+$, Calcd for $C_{14}H_{19}NO_7Na$: 336.1054. Found: 336.1065.

(1a*R*,2*S*,3*R*,5a*S*,5b*R*)-2-Acetoxy-3-acetoxymethyl-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (22). CC: toluene/acetone 9:1 v/v; mp 101–102°C (Et_2O/hexane); $[\alpha]_D$ + 138.6 (*c* 1.0, CH_2Cl_2); IR (film): 2961, 1748 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.46 (dd, 1H, *J* 7.5, 9.4 Hz, H-2), 4.36 (dd, 1H, *J* 4.9, 12.5 Hz, CH_AH_BOAc), 4.04 (dd, 1H, *J* 2.7, 12.5 Hz, CH_AH_BOAc), 3.94 (dd, 1H, *J* 7.0, 9.0 Hz, H-1a), 3.84 (ddd, 1H, *J* 2.4, 6.9, 8.2 Hz, H-5b), 3.79 (ddd, 1H, *J* 2.7, 4.9, 9.4 Hz, H-3), 3.05 (ddd, 1H, *J* 3.8, 7.7, 13.6 Hz, H-8), 2.67 (dd, 1H, *J* 2.4, 9.0 Hz, H-5a), 2.57 (dt, 1H, *J* 7.9, 7.9, 13.5 Hz, H-8′), 1.66, 1.61 (2s, 6H, 2OAc), 1.69–1.52 (m, 2H, H-6,7), 1.26–1.14 (m, 2H, H-6′,7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 169.1, 168.8, 76.3, 74.9, 69.8, 66.6, 61.6, 56.1, 52.8, 30.4, 23.9, 20.8, 20.7; HRMS (ESI) *m/z* $[M + H]^+$, Calcd for $C_{14}H_{20}NO_7$: 314.1234. Found: 314.1242.

(1a*R*,3*S*,5a*R*,5b*S*)-3-Acetoxymethyl-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (23). mp 121–122.5°C (Et_2O/hexane); $[\alpha]_D$ + 72.8 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 2957, 1738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.95 (m, 1H, *J* 2.3, 3.4, 5.3, 11.7 Hz, H-3), 4.71 (m, 1H, H-1a), 4.29 (dd, 1H, *J* 3.4, 12.2 Hz,

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C*H*$_A$H$_B$OAc), 4.22 (dd, 1H, *J* 5.3, 12.2 Hz, CH$_A$*H*$_B$OAc), 3.87 (m, 1H, H-5b), 3.29 (dd, 1H, *J* 4.1, 7.7 Hz, H-5a), 3.18 (ddd, 1H, *J* 6.7, 7.6, 12.2 Hz, H-8), 3.12 (ddd, 1H, *J* 6.4, 7.8, 12.2 Hz, H-8′), 2.21 (m, 1H, H-6), 2.11 (s, 3H, OAc), 2.00–2.09 (m, 2H, H-2,7), 1.95–1.79 (m, 3H, H-2′,6′,7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5, 170.2, 73.2, 72.1, 71.3, 65.1, 55.2, 53.4, 29.6, 29.4, 22.9, 20.7; HRMS (EI) *m*/*z* $M^{+\cdot}$, Calcd for $C_{12}H_{17}NO_5$: 255.1107. Found: 255.1112.

Anal. Calcd for $C_{12}H_{17}NO_5$ (255.27): C, 56.46; H, 6.71; N, 5.49. Found: C, 56.26, H, 6.69; N, 5.37.

(1a*S*,2*R*,3*R*,5a*R*,5b*S*)-2-Acetoxy-3-acetoxymethyl-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (24). mp 88–91°C (Et_2O/hexane); $[\alpha]_D$ + 84.5 (*c* 0.5, CH_2Cl_2); IR (film $CHCl_3$): 2960, 1743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.15 (dd, 1H, *J* 1.2, 3.2 Hz, H-2), 5.11 (m, 1H, H-3), 4.49 (dd, 1H, *J* 3.2, 7.7 Hz, H-1a), 4.25 (dd, 1H, *J* 5.8, 11.7 Hz, C*H*$_A$H$_B$OAc), 4.23 (dd, 1H, *J* 6.8, 11.7 Hz, CH$_A$*H*$_B$OAc), 3.82 (dd, 1H, *J* 2.8, 6.0, 7.8 Hz, H-5b), 3.43 (dd, 1H, *J* 2.8, 7.7 Hz, H-5a), 3.25 (ddd, 1H, *J* 4.7, 7.9, 13.1 Hz, H-8), 3.08 (dt, 1H, *J* 7.9, 7.9, 13.1 Hz, H-8′), 2.19, ∼2.07, 1.80 (3m, 4H, H-6,6′,7,7′), 2.11, 2.08 (2s, 6H, 2OAc); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3, 169.4, 169.0, 74.0, 74.0, 71.9, 66.0, 62.0, 55.9, 51.9, 29.8, 23.3, 20.7, 20.6; HRMS (EI) *m*/*z* $M^{+\cdot}$, Calcd for $C_{14}H_{19}NO_7$: 313.1161. Found: 313.1164.

Anal. Calcd for $C_{14}H_{19}NO_7$ (313.31): C, 53.67; H, 6.11; N, 4.47. Found: C, 53.71; H, 6.07; N, 4.64.

(1a*R*,2*S*,3*R*,5a*S*,5b*R*,6*S*)-2-Acetoxy-3-acetoxymethyl-6-*tert*-butoxy-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (25). mp 116–117°C (Et_2O/hexane); $[\alpha]_D$ + 4.2 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): 2979, 1747 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.48 (dd, 1H, *J* 7.8, 9.4 Hz, H-2), 4.32 (dd, 1H, *J* 4.9, 12.5 Hz, C*H*$_A$H$_B$OAc), 4.03 (dd, 1H, *J* 2.6, 12.5 Hz, CH$_A$*H*$_B$OAc), 4.00 (t, 1H, *J* 3.4, 3.6 Hz, H-5b), 3.94 (dd, 1H, *J* 7.8, 8.8 Hz, H-1a), 3.83 (m, 1H, H-6), 3.79 (ddd, 1H, *J* 2.6, 4.9, 9.4 Hz, H-3), 3.03–3.06 (m, 2H, H-8,8′), 2.93 (dd, 1H, *J* 3.6, 8.8 Hz, H-5a), 1.94 (m, 1H, H-7), 1.66, 1.61 (2s, 6H, 2OAc), 1.43 (m, 1H, H-7′), 1.10 (s, 9H, O*t*–Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 169.0, 168.2, 77.3, 77.1, 76.3, 74.9, 74.0, 66.4, 61.6, 54.9, 51.1, 33.5, 28.5, 20.8, 20.7; HRMS (EI) *m*/*z* $M^{+\cdot}$, Calcd for $C_{18}H_{27}NO_8$: 385.1737. Found: 385.1725.

Anal. Calcd for $C_{18}H_{27}NO_8$ (385.41): C, 56.10; H, 7.06; N, 3.63. Found: C, 56.16; H, 7.10; N, 3.79.

(1a*S*,2*R*,3*R*,5a*R*,5b*S*,6*S*,7*S*)-2-Acetoxy-3-acetoxymethyl-6,7-di-*tert*-butoxy-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (26). $[\alpha]_D$ + 35.8 (*c* 1.0, CH_2Cl_2); IR (film): 2976, 1749 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.18 (dd, 1H, *J* 1.2, 2.7 Hz, H-2), 4.76 (m, 1H, *J* 1.2, 6.1, 6.7 Hz, H-3), 4.44 (dd, 1H, *J* 2.7, 8.3 Hz, H-1a), 4.18 (bs, 1H, H-6), 4.11 (dd, 1H, *J* 6.7, 11.5 Hz, C*H*$_A$H$_B$OAc), 4.08 (dd, 1H, *J* 6.1, 11.5 Hz, CH$_A$*H*$_B$OAc), 3.84 (m, 2H, H-5b,7), 3.55 (dd, 1H, *J* 6.1, 11.9 Hz, H-8), 3.52 (dd, 1H, *J* 6.6, 8.2 Hz, H-5a), 2.67 (dd, 1H, *J* 5.3, 11.9 Hz, H-8′), 1.54, 1.51 (2s, 6H, 2OAc), 1.15, 0.93 (2s, 18H, 2O*t*–Bu); ^{13}C NMR (125 MHz, C_6D_6) δ: 169.5, 168.9, 168.1, 81.9, 78.3, 77.4 75.1, 74.9, 73.9, 73.6, 65.7, 61.6, 61.7, 50.1, 28.5, 28.2, 20.0, 19.8; HRMS (ESI) *m*/*z* $[M + H]^+$, Calcd for $C_{22}H_{36}NO_9$: 458.2385. Found: 458.2373.

(1a*S*,2*S*,3*R*,5a*R*,5b*S*,6*S*,7*S*)-2-Acetoxy-3-acetoxymethyl-6,7-di-*tert*-butoxy-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (27). $[\alpha]_D$ + 98.2 (*c* 1.05,

$CHCl_3$); IR (film $CHCl_3$): 2976, 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.26 (dd, 1H, *J* 3.0, 9.8 Hz, H-2), 4.95 (ddd, 1H, *J* 2.4, 3.6, 9.8 Hz, H-3), 4.81 (dd, 1H, *J* 3.0, 6.9 Hz, H-1a), 4.36 (dd, 1H, *J* 3.8, 12.6 Hz, CH_AH_BOAc), 4.26 (dd, 1H, *J* 2.4, 12.6 Hz, CH_AH_BOAc), 4.08 (bs, 1H, H-6), 3.86 (m, 1H, H-7), 3.74 (m, 2H, H-5a,5b), 3.68 (dd, 1H, *J* 5.6, 13.5 Hz, H-8), 2.89 (dd, 1H, *J* 2.9, 13.5 Hz, H-8′), 2.13, 2.08 (2s, 6H, 2OAc), 1.22, 1.71 (2s, 18H, 2O*t*–Bu); ^1H NMR spectrum of the crude post-reaction mixture of **27** showed the presence of **28** [(1a*R*,2*S*,3*R*,5a*S*,5b*R*,6*S*,7*S*)-2-acetoxy-3-acetoxymethyl-6,7-di-*tert*-butoxy-5-oxopyrrolidino [1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran; ∼7%], selected signals δ: 5.21 (dd, 1H, *J* 7.0, 9.3 Hz, H-2), 4.45 (ddd, 1H, *J* 2.7, 5.1, 9.3 Hz, H-3), 4.32 (dd, 1H, *J* 7.0, 8.8 Hz, H-1a), 4.23 (dd, 1H, *J* 2.7, 12.3 Hz, $CH_A\mathbf{H}_BOAc$), 3.94 (dd, 1H, *J* 2.0, 8.8 Hz, H-5a), 3.38 (dd, 1H, *J* 6.2, 14.0 Hz, H-8), 2.86 (dd, 1H, *J* 8.0, 14.0 Hz, H-8′), 2.11, 2.07 (2s, 6H, 2OAc). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4, 169.7, 168.8, 81.4, 77.4, 77.3, 75.0, 74.5, 72.8, 72.2, 65.7, 63.2, 61.5, 51.8, 28.4, 28.3, 20.7, 20.6. HRMS (ESI) *m*/*z* $[M + Na]^+$, Calcd for $C_{22}H_{35}NO_9Na$: 480.2204. Found: 480.2211.

Anal. Calcd for $C_{22}H_{35}NO_9$ (457.52): C, 57.75; H, 7.71; N, 3.06. Found: C, 57.68; H, 7.63; N, 2.77.

Transformation of lactones 9, 10, 12 into 8 and 11. A solution of lactone (**9**, **10**, **12**, 60 mg, 0.15 mmol) in MeOH (2 mL) was treated with 20% aq NaOH (1 mL) and stirred at rt. After disappearance of the substrate (about 0.5 h) the solution was saturated with CO_2, then sodium periodate (75 mg, 0.35 mmol) was added and solution was stirred for 1 h. Subsequently the reaction mixture was cooled in an ice-water bath and sodium borohydride (15 mg, 0.4 mmol) was added portionwise. After 1 h the mixture was neutralized with 2 M hydrochloric acid, and diluted with methanol (10 mL). The precipitate was filtered off and the filtrate was concentrated in vacuo to afford the crude product. It was lactonized upon reaction with DCC (31 mg, 0.15 mmol) and DMAP (18 mg, 0.15mmol) in CH_2Cl_2 for 3 h at rt. After removal of solvent the corresponding lactone was purified by chromatography to give product in a 50–55% yield.

Analytical data for **8** have been described previously.[4]

(1a*S*,5a*S*,5b*R*,6*S*,7*S*)-6,7-Di-*tert*-butoxy-5-oxopyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (11). mp 99–101.5°C (Et_2O/hexane); $[\alpha]_D$ + 6.7 (*c* 0.5, CH_2Cl_2); IR (film): 2974, 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.52 (ddd, 1H, *J* 3.2, 8.7, 11.3 Hz, H-3), 4.43 (m, 1H, H-1a), 4.23 (m, 1H, H-3′), 4.19 (dd, 1H, *J* 2.5, 7.2 Hz, H-5b), 4.05 (dd, 1H, *J* 5.9, 7.2 Hz, H-6), 3.95 (m, 1H, *J* 5.9, 6.7, 7.6 Hz, H-7), 3.65 (dd, 1H, *J* 2.5, 7.3 Hz, H-5a), 3.26 (dd, 1H, *J* 6.7, 13.4 Hz, H-8), 3.00 (dd, 1H, *J* 7.6, 13.4 Hz, H-8′), 2.16 (m, 1H, H-2), 1.97 (m, 1H, H-2′), 1.24, 1.17 (2s, 18H,2 O*t*–Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.2, 76.7, 76.1 74.9, 73.7, 73,4, 70.8, 64.5, 60.4, 48.7, 28.6, 28.5, 26.9; HRMS (EI) *m*/*z* $M^{+\cdot}$, Calcd for $C_{17}H_{29}NO_5$: 327.2046. Found: 327.2051.

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