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1,3-Dipolar cycloaddition of a nitrone derived from (*S*)-malic acid to α,β-unsaturated δ-lactones

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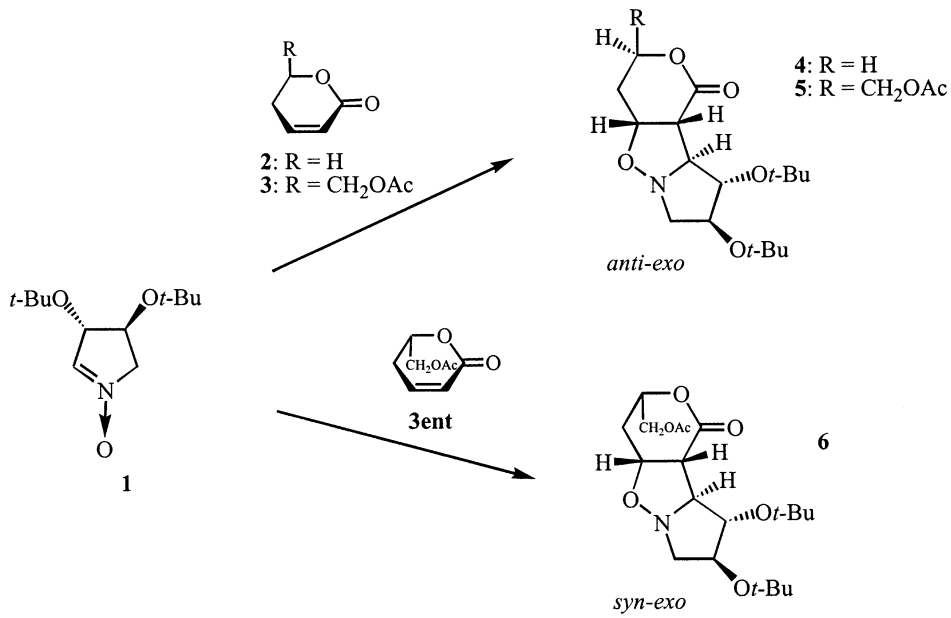
Abstract—1,3-Dipolar cycloaddition of nitrone **7** to α,β-unsaturated δ-lactones: non-chiral **2**, racemic mixture **3**/**3ent**, D-*glycero* **3** and D-*threo* **15** proceeds with high stereoselectivity in the case of **2** and **15**, and with a significant kinetic resolution in the case of the racemate **3**/**3ent**. The *endo* approach of reactants was not observed. CD-spectroscopy proved an attractive tool for determination of the absolute configuration of cycloadducts. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently we have reported on the 1,3-dipolar cycloaddition of five-membered cyclic nitrone **1**,[1] derived from tartaric acid, to α,β-unsaturated lactones such as non-chiral **2**, racemic mixture **3**/**3ent**, enantiopure D-*glycero* **3** and L-*glycero* **3ent** (Scheme 1).[2] It was found that these reactions proceed with high stereoselectivity in the



Scheme 1.

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case of **2**, **3** and **3ent** to yield corresponding adducts **4**–**6**. In the case of the racemate **3**/**3ent**, the cycloaddition proceeds with a significant kinetic resolution. In all cases only the *exo* approach of the dipole **1** has been observed since the high steric requirements of the *t*-butoxy groups precluded the *endo* geometry of the transition state.[2]

In continuation of this investigation we decided to examine similar 1,3-cycloaddition reactions involving the same lactones and the nitrone **7**,[3] derived from (*S*)-malic acid. The expected products, analogous to the previously obtained cycloadducts **4**–**6**, should provide convenient entry to the important iminosugars such as hydroxyindolizidines[4] via otherwise known methodology.[5,6]

A similar cycloaddition reaction involving enantiomeric oxazoline *N*-oxides **8** or **9** and (*R*)-lactone **10** has been recently reported.[7] Depending on whether the dipole and dipolarophile constitute the matched or mismatched pair, the *anti–exo* or *anti–endo* products, respectively, have been obtained. In contrast to nitrone **1**, which has two *t*-butoxy groups placed on both sides of the ring, nitrones **7**–**9** are substituted on one side of the five-membered ring only. Consequently, they should be able to approach the respective dipolarophile molecule (**2**, **3**, **3ent**, **10**) in an *endo*-fashion (Chart 1).

2. Results and discussion

Reaction of lactone **2** with nitrone **7** gave the almost pure adduct **11** (89% yield) as a result of an *exo* approach of the dipole to the *si–si* side of the dipolarophile (Scheme 2). The configuration of the adduct **11** was proven by the NOESY experiments which did not detect any spin–spin interactions between C(5a) and C(5b) protons. The stereochemical pathway of cycloaddition of **7** to **2** resembles that of the reaction between **1** and **2**.[2]

Reaction of nitrone **7** with D-*glycero* lactone **3**[8] furnished two cycloadducts **12** and **13** in a ratio of about 2:3, respectively.

The structure of cycloadduct **13** was established by the X-ray crystallography (Figure 1), whereas the structure of isomeric compound **12** was assigned on the basis of the apparent analogy to the structure of the related crystalline compound **16**, which was determined by the X-ray crystallographic analysis (Figure 2). Cycloaddition of nitrone **7** to 1 equiv. of the racemate **3**/**3ent**[9]

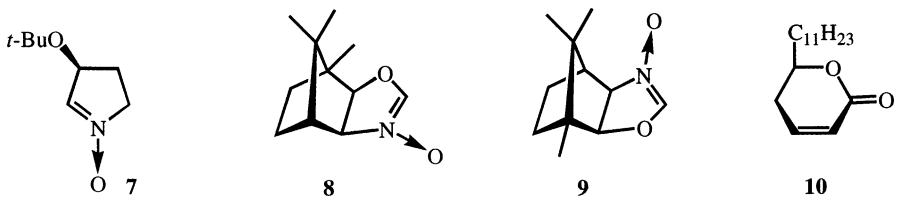
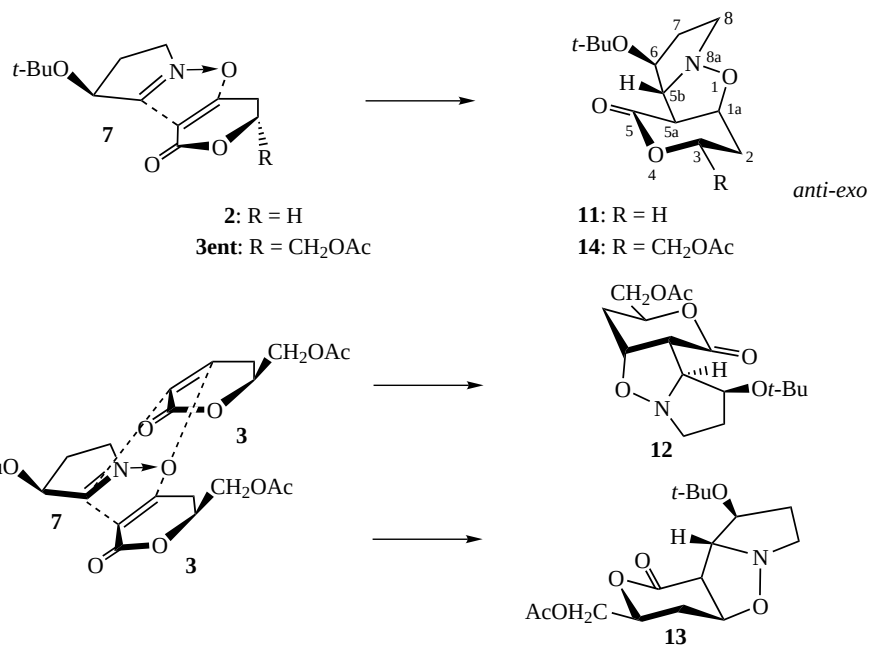


Chart 1.



Scheme 2.

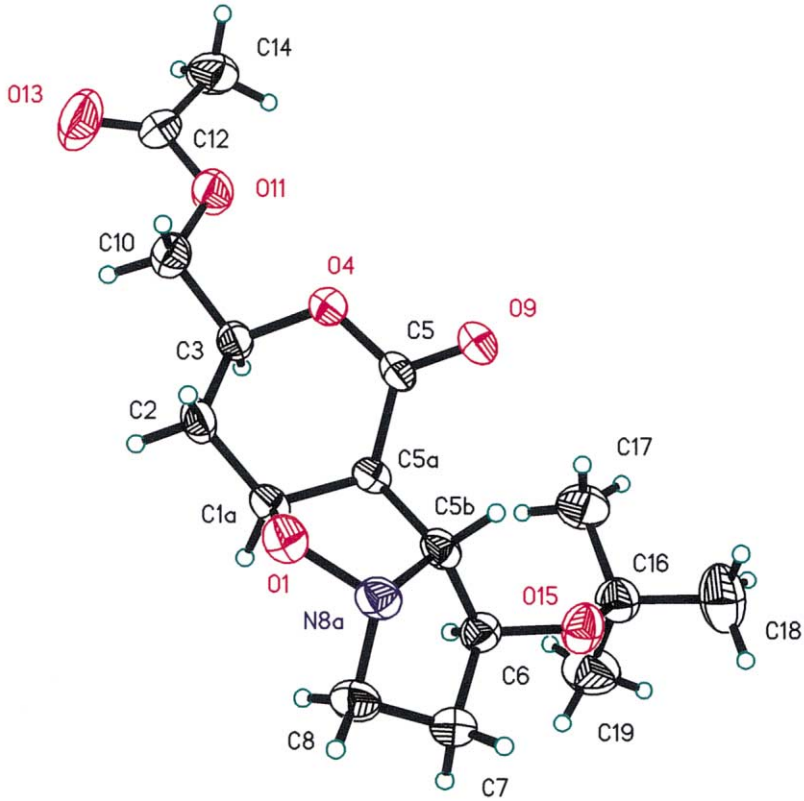


Figure 1. Crystal structure of compound **13** with the crystallographic numbering scheme. Thermal ellipsoids are shown at 30% probability level.

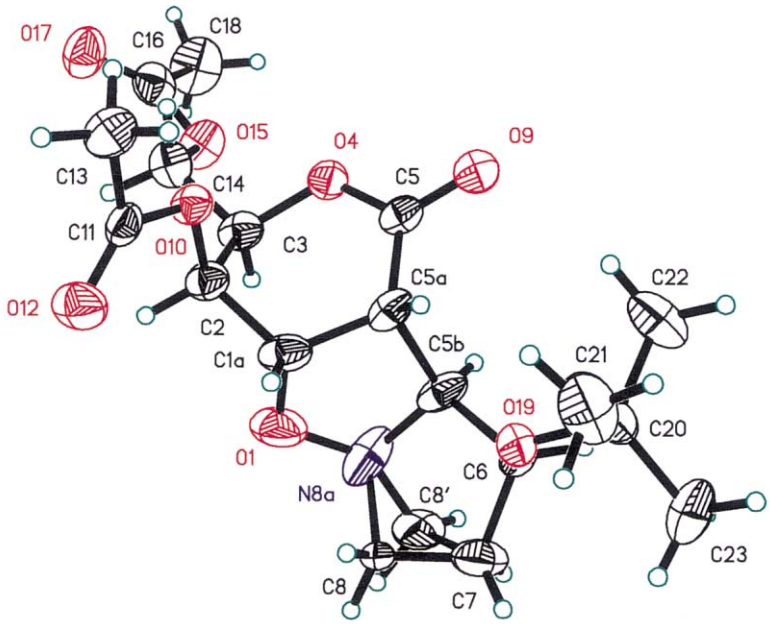


Figure 2. ORTEP diagram of compound **16** showing thermal ellipsoids at 30% probability level. Atom C8 is disordered between two positions of C8 (0.75):C8′ (0.25) occupancy ratio.

resulted in formation of a mixture of three products **12**, **13** and **14** in a ratio of about 2:3:5, respectively. The same reaction performed with 2 equiv. of the racemate **3**/**3ent** resulted in a significant kinetic resolution and yielded exclusively adduct **14** in 87% yield and unreacted D-*glycero* lactone **3** with 81% e.e., in 95% yield. Since the L-*glycero* lactone **3ent** is not easily available, such an exceptionally high kinetic resolution allows for treatment of the racemic mixture **3**/**3ent** as a source of enantiomerically pure **3ent** in the cycloaddition with **7**.

The less effective kinetic resolution observed during the reaction of nitrone **1** with **3**/**3ent** can be tentatively rationalized by the presence of an additional C(4) *t*-butoxy group in the nitrone **1** with associated additional steric hindrance to the *re* side of the nitrone ring.

The stereochemistry of products obtained as a result of these cycloadditions strongly indicates the preferred geometry of the transition state. The *exo* approach of nitrone dipole to the *si–si* side of lactones **2** and **3ent** results in matched pairs. The cycloaddition of nitrone **7** to the D-*glycero* lactone **3** creates, however, a mismatched pair. In consequence, two products are obtained, both having a significantly higher activation energy than that necessary for the formation of **14**. This is manifested by the kinetic resolution of the racemate **3**/**3ent** by the nitrone **7**. Unexpectedly, the formation of two *exo*-products **12** and **13** for the mismatched pair **7** and **3** differentiate this reaction from that of **9** and **10** where only the *endo–anti* adduct was obtained.[7]

In the light of our results, one can expect that the additional substituent at C(4) of the lactone **3**, located *cis* to the terminal C(6) carbon atom (for example the D-*threo* lactone **15**) should shift the reaction towards exclusive formation of the cycloadduct *anti* to both substituents of the lactone. Indeed, the cycloaddition of **7** and **15** resulted in formation of only one product **16**. The structure of adduct **16** was established by the X-ray structure analysis (Figure 2). Unequivocal assignment of the structure of **16** also helped to establish the structure of related adduct **12**. In the case of Langlois et al.[7] the *endo* approach of reactants in the mismatched pair (**9** and **10**) was explained by the presence of a stabilizing secondary interaction between the *endo* cyclic oxygen and the lactone carbonyl group.[10]

Hydrogenolysis of the N–O bond in adducts **11**–**14** over Pd/C in acetic anhydride–acetic acid mixture led to compounds **17**–**20**, respectively. Similarly to the analogous compounds obtained from nitrone **1**, the C(3) hydroxyl group in products **17**–**20** was not acetylated under the reaction conditions. Hydrogenation of adduct **14** in ethyl acetate solution resulted in opening of the five-membered ring and formation of compound **21**. The reaction probably proceeds via β-elimination followed by hydrogenation of the double bond (Chart 2).

3. CD-Spectra of adducts 4–6, 11–14 and 16

Direct assignment of the absolute configuration of cycloaddition products of Brandi's nitrones **1** and **7** to the unsaturated δ-lactones **2**, **3**, **3ent**, **15** is not straightforward since these adducts do not usually form crystals suitable for the X-ray diffractometry. In addition, in standard solvents the ^{1}H NMR resonances of bridgehead protons C(5a)H and C(5b)H are frequently overlapped. These difficulties prompted us to investigate the CD-spectra of adducts in question, all possessing a saturated lactone chromophore incorporated into the six-membered ring.

The CD and UV data of compounds **4**–**6**, **11**–**14** and **16** are collected in Table 1 and the CD spectra of representative compounds are presented in Figure 3. As can be seen in Table 1, in most cases the compounds investigated display well developed absorption maxima in the 206–216 nm spectral range. These maxima most probably originate from the n–π* transition of the lactone chromophore. However, the intensity of this absorption appears to be relatively strong for the n–π* transition

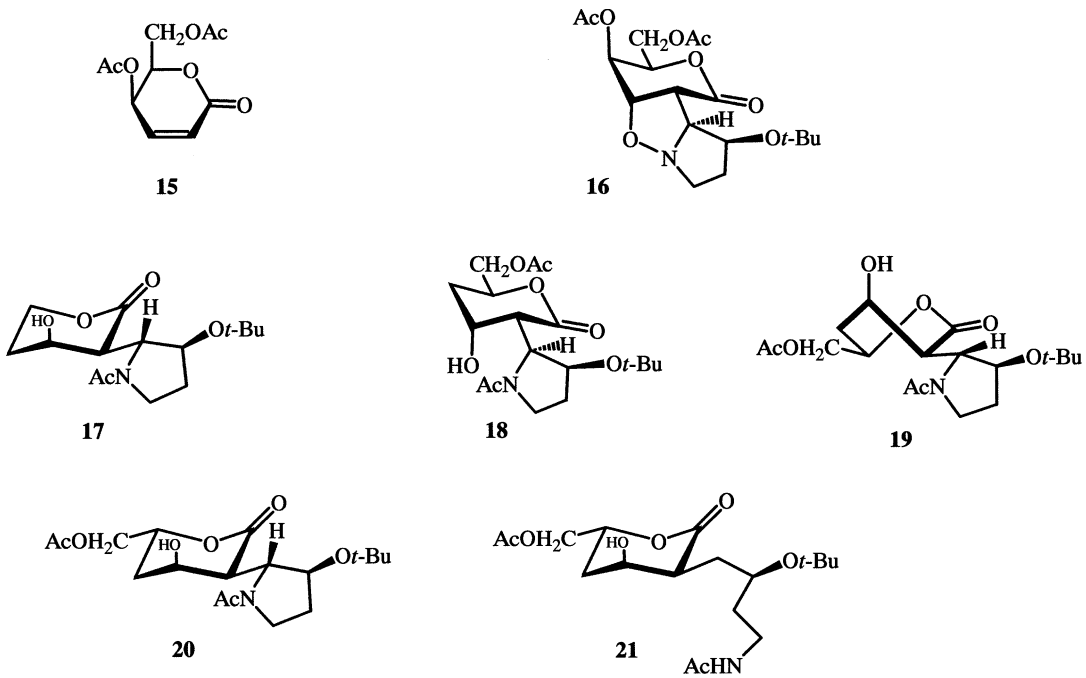


Chart 2.

Table 1. UV and CD data of compounds **4–6** and **11–16** recorded in acetonitrile. UV and CD values are given as ε (λ/nm) and $\Delta\varepsilon$ (λ/nm), respectively

Comp.	UV ε (λ)	CD $\Delta\varepsilon$ (λ)	
4	1200 (208)	−7.3 (188)	−2.42 (220.4)
5	750 (208)	−9.3 (188)	−1.89 (221.2)
6[a]	2100 (216[sh])	+0.6 (205)	−0.23 (224.0)
11	1000 (194[sh])	+0.4 (204[sh])	+1.32 (224.2)
12	710 (206)	−1.5 (203)	−0.41 (235.4)
13	580 (209)	−1.0 (194)	+2.54 (224.8)
14	520 (214)	+0.7 (204)	+1.09 (224.4)
16	205 (210[sh])	−0.6 (198)	+1.51 (218.0)

[a] Diastereomer ratio **5**:**6** = 1:3; sh, shoulder.

of the δ-lactone chromophore thus suggesting the presence of a different electronic transition of approximately the same energy.

As shown in Table 1 and Figure 3, two bands occur in the CD spectra of compounds **4–6**, **11–14** and **16**. The long wavelength band, most probably of an n–π* origin, appears in the 218–235 nm spectral range. The second band, occurring between 188–205 nm, may be a π–π* transition of the carboxylate unit.[11] Due to the insolubility of compounds of this series in common non-polar solvents, it was not possible to study systematically the solvent dependence of CD spectra. Thus, the origin of some electronic excitations could not be proved on the solvent dependence basis.

The assignment of absolute configuration for compounds **4–6**, **11–14**, and **16** is based on the 'ring-chirality rule' established by Legrand and Bucourt.[12] This rule, proposed for the five-, six-, and seven-membered lactones, states that the helicity of the lactone ring is a major factor determining the sign of the n–π* transition and it relates the sign of the CD band of the n–π* lactone transition to the sign of the O–C(=O)–C_α–C_β torsional angle. Recently, the ring chirality rule was successfully applied to the configurational and conformational assignments of various classes of lactones.[13–15]

In order to exclude possible solute–solvent interactions, that could affect CD spectra considerably due to conformational and/or vicinal effects, the CD curve for compound **13** was also measured in the solid state. The solid-state data are in a good agreement with the data recorded in solution (Figure 4, right). As expected, the shape of the spectra remain the same in both cases showing only a minor shift in the CD band maxima. The good agreement of the spectra in Nujol mull and acetonitrile indicates that the analysis of the CD data for the purpose of determination of the absolute configuration can be performed on the basis of chiroptical data measured in solution. In addition, the technique of low-temperature CD measurements has been used to study conformational equilibria. Investigation of compound **13** revealed (Figure 4, left) that the size of the n–π* CD does not change significantly between +20 and −180°C. Such temperature-independence of the CD spectra suggests that only one conformer is present exclusively or predominates strongly in the solution (the presence of two or more conformers with the same energy is less probable).

The CD data presented in Table 1 demonstrates that the investigated compounds can be divided into two groups depending upon the sign of the n–π* CD band

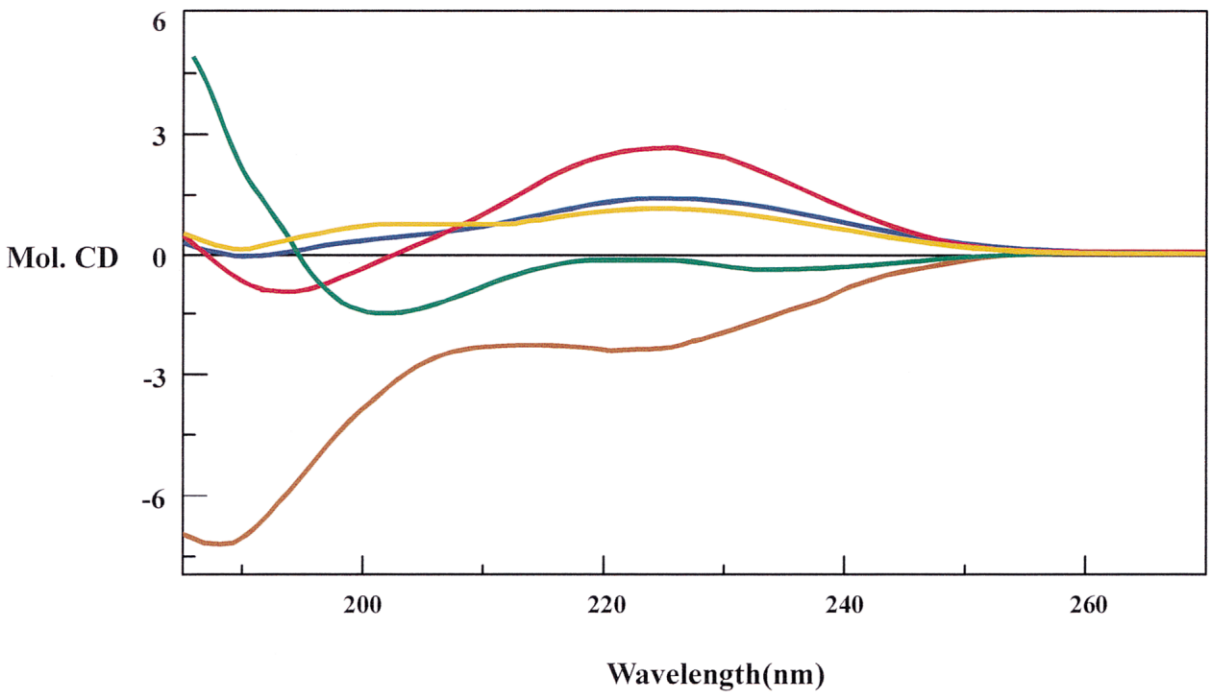


Figure 3. CD spectra of representative comnpounds **4** (brown line), **11** (blue line), **12** (green line), **13** (red line) and **14** (yellow line) taken in acetonitrile.

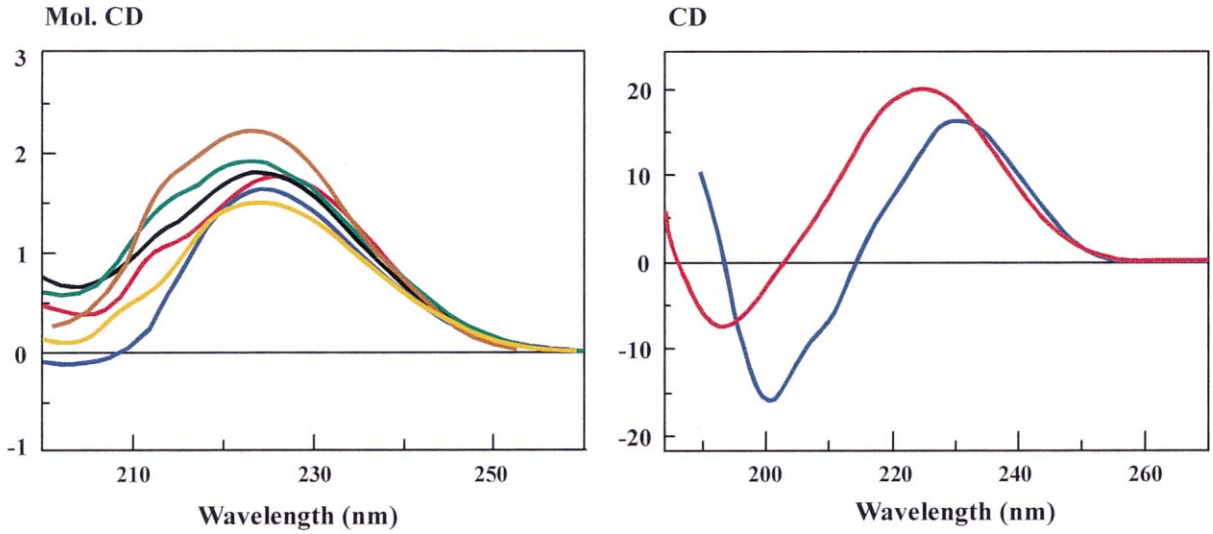


Figure 4. Solid state (blue line) {Nujol mull} and acetonitrile solution (red line) CD data (left) and low-temperature CD measurements of compound **13** (right): (yellow line) +20°C, (blue line) −20°C, (red line) −60°C, (black line) −100°C, (green line) −140°C, (brown line) −180°C.

occurring between 218–235 nm. According to the ring-chirality rule a negative (positive) n–π* band correlates with a positive (negative) O–C(=O)–C_α–C_β torsional angle. Thus, application of the rule to compound **13** with its positive n–π* band at 224 nm predicts a negative sign of the O–C(=O)–C_α–C_β torsional angle. This torsional angle is in fact negative and amounts to −39.4° as demonstrated by the X-ray diffraction data. On this basis it can be concluded that compounds **11** and **14** with a positive sign of the n–π* band, like compound **13**, have a negative sign of the O–C(=O)–C_α–C_β torsional angle and approximately the same conformation of the six-membered ring. This conclusion is additionally corroborated by MMX molecular modeling calculations showing the same skew-boat conformation of the lactone ring with a negative O—C(=O)–C_α–C_β torsional angle for the lowest energy conformers of these three compounds, approximately independently on the presence and configuration of the substituent at C(3) (Figure 5, top).[16] Thus, the absolute configuration at C(5a) for compounds **11** and **14** can be assigned to be (*S*), analogously to compound **13**.

A negative sign of the n–π* CD band for compounds **4**–**6** and **12** points to a mirror-image geometry of the lactone ring in comparison to that of compounds **11**, **13** and **14**. Consequently, the sign of the O–C(=O)–C_α–C_β torsional angle should be positive for **4**–**6** and **12**. The molecular modeling calculations indicate that this conclusion may be correct by predicting the lactone ring to be in an approximately the same distorted boat form and, for the low energy conformation of each compound, indicating a positive value of O–C(=O)–C_α–C_β torsional angle (Figure 5). Thus, the absolute configuration at C(5a) can be assigned as (*R*). The low magnitude of the n–π* CD band for compound **6** can be explained by its low diastereomeric purity since this compound was found to be a mixture of diastereomers **5** and **6** in a ratio 1:3, respectively.

Among the compounds investigated, the only exception is compound **16**. As stated before, cycloaddition of **7** and **15** leads exclusively to one product **16** with ascribed geometry *exo–syn* to the *t*-butoxy group. For such a geometry a negative sign of the n–π* CD band was expected. However, a positive n–π* CD is observed. Lactone **16**, in contrast to the other compounds, has an additional acetoxy substituent at C(2). The introduction of the second substituent may be responsible for the change of the lactone ring conformation in compound **16** in comparison with compounds **4**–**6** and **12**. Moreover, the interaction between two bulky substituents in vicinal positions may also cause configurational changes. The MMX calculation supports this conclusion showing that the preferred conformer (minimum energy conformation) of lactone **16** has a negative sign of the O–C(=O)–C_α–C_β torsional angle (Figure 5). Thus, 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 and validates the 'ring-chirality rule' for lactone **16** also. Unequivocal evidence for the configurational and conformational assignments was provided by the X-ray diffraction analysis of compound **16** (Figure 2). On this basis the (5a*R*) configuration can be unambiguously assigned for compound **16**.

4. Conclusions

In summary, we have demonstrated the effectiveness of 1,3-dipolar cycloaddition of the nitrone **7** to α,β-unsaturated δ-lactones in controlling the configuration of the stereogenic centers around the formed isoxazolidine ring. In particular, adducts **11** and **14**, with (*R*) configuration at the bridge-head carbon atom C(5b), offer an easy access to the swainsonine-related indolizidines. At the same time adduct **16**, with (*S*)-configuration at C(5b), may be regarded as a precursor for castanospermine-related indolizidines (Chart 3).

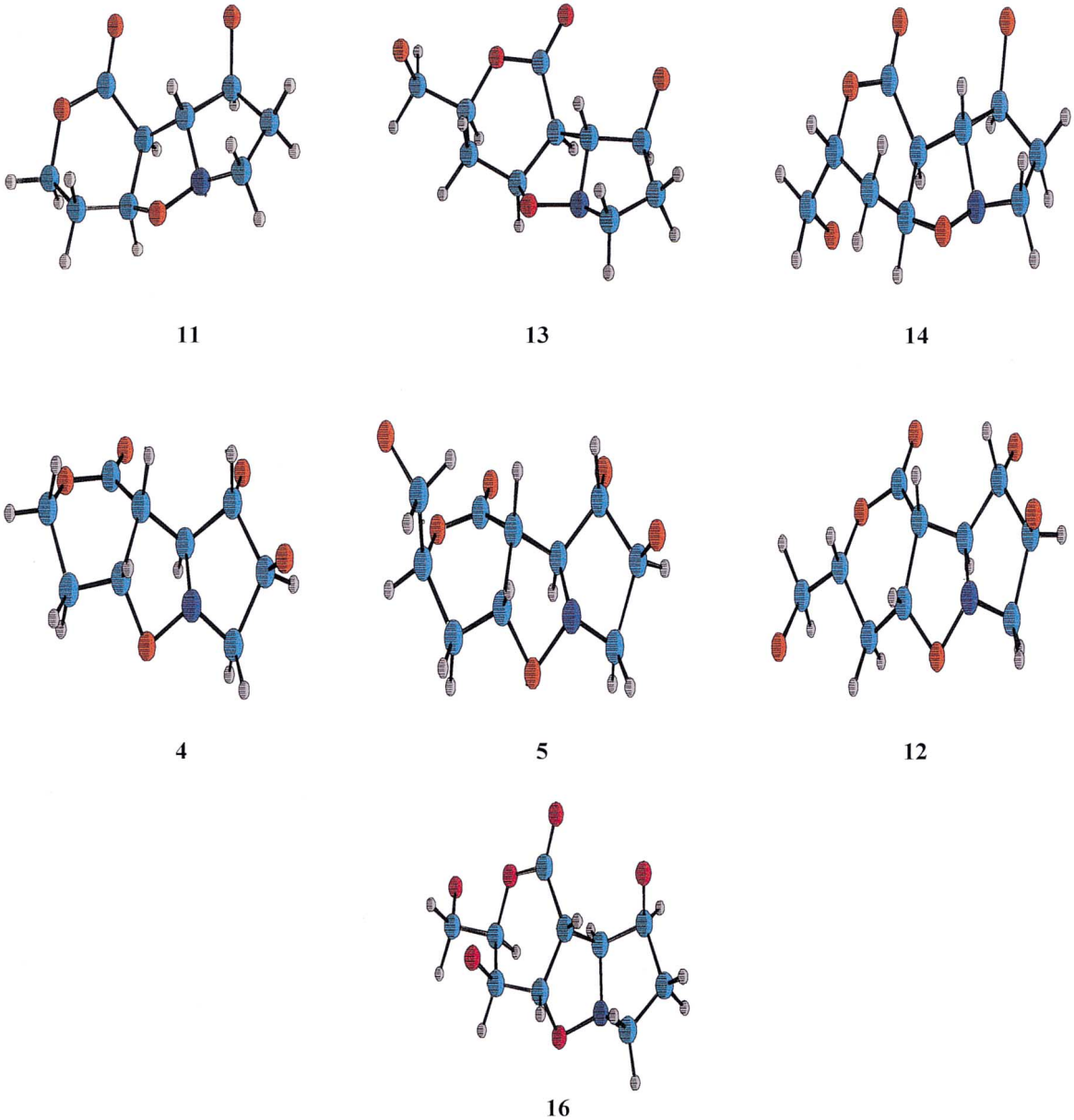
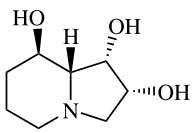
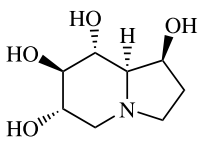


Figure 5. MMX optimized structures of **4**, **5**, **11**–**14** and **16**. For the sake of clarity bulky substituents at C(3), C(6), C(7) and C(2) are partly removed after minimization.



swainsonine



castanospermine

Chart 3.

On the basis of the discussion presented it can be concluded that circular dichroism spectroscopy is a very useful tool for the assignment of stereochemistry of the adducts of Brandi's nitrones **1** and **7** to unsaturated δ-lactones **2**, **3**, **3ent**, **15**. A simple correlation between the sign of the n–π* Cotton effect and the O–C(=O)–C_α–C_β torsional angle based on the Legrand–Bucourt rule[12] makes possible the direct assignment of stereochemistry at C(5a). Moreover, the extreme sensitivity of CD spectroscopy to the geometry of the investigated compounds is an additional advantage of this method, since it enables the detection of even minute conformational effects, which cannot be studied easily by other spectroscopic methods.

5. 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. Rotations were measured with a JASCO Dip-360 digital polarimeter. UV spectra were measured on a Cary 100

Table 2. 1,3-Dipolar cycloaddition of nitrone **7** to lactones **2**, **3**, **3**/**3ent** and **15**

Entry	Lactone	Lactone:nitrone **7** ratio	Yield (%)	Proportion of stereoisomers (%)	Reaction conditions
1	**2**	1:1 (0.6 mmol:0.6 mmol)	89	**11**(100)	Rt, 48 h
2	**3**	1:1 (0.6 mmol:0.6 mmol)	75	**12**(58):**13**(42)	Reflux, 1 h
3	**3**/**3ent**	1:1 (0.6 mmol:0.6 mmol)	79	**12**(28):**13**(21):**14**(51)	Reflux, 1 h
4[a]	**3**/**3ent**	2:1 (1.0 mmol:0.5 mmol)	87	**14**(100)	Rt, 48 h
5	**15**	1:1 (0.6 mmol:0.6 mmol)	81	**16**(100)	Reflux, 1 h

[a] In this reaction the unreacted D-*glycero* lactone **3** was recovered in 95% yield with 81% e.e.

spectrophotometer in acetonitrile. CD spectra were recorded between 180 and 360 nm at room temperature 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 path length 0.1 or 1 cm. For solid-state CD measurements a crystalline compound (1–3 mg) was ground with Nujol to form a homogenous Nujol mull, which was rotated around the optical axis during the entire measurement using an original JASCO equipment for this purpose. The low-temperature measurement was performed in EPA (5/5/2 mixture by volume of ethyl ether, *iso*-pentane, and ethanol) solution with concentration 1.48×10^{-3} mol dm^{-3} in the range 320–190 nm in the 0.1 cm cell.

Column chromatography was performed using Merck silica gel 230–400 mesh. Racemic lactone **3**/**3ent** was obtained according to Ref. 9. Enantiomerically pure D-*glycero* lactone **3** was obtained according to Roth and Roark protocol.[8a]

5.1. Cycloaddition of nitrone 7 to lactones 2, 3, 3/3ent and 15

General procedure. The respective lactone and nitrone **7** in the ratio reported in Table 2 were dissolved in dry toluene (3 ml) and stirred at room temperature for 48 h (entries 1 and 4) or for 24 h at room temperature followed by reflux for 1 h (entries 2, 3 and 5). The progress of the reaction was monitored by TLC. After removal of the solvent, the residue was purified on a silica gel column to give corresponding cycloadducts.

(1a*S*,5a*S*,5b*R*,6*S*)-6-*tert*-Butoxy-5-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran 11: colorless oil; $[\alpha]_D$ −23.5 (*c* 1.0, CH_2Cl_2); IR (film): 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.59 (m, 1H, H-1a), 4.56 (ddd, 1H, *J* 2.9, 9.9, 11.4 Hz, H-3), 4.25 (dddd, 1H, *J* 1.1, 3.9, 4.9, 11.4 Hz, H-3′), 4.19 (ddd, 1H, *J* 2.4, 2.5, 9.5 Hz, H-6), 3.73 (dd, 1H, *J* 2.4, 5.2 Hz, H-5b), 3.38 (m, 1H, H-8), 3.26 (dd, 1H, *J* 5.2, 8.1 Hz, H-5a), 3.04 (m, 1H, H-8′), 2.28 (m, 1H, H-7), 2.06 (m, 1H, H-2), 1.99 (m, 1H, H-2′), 1.76 (m, 1H, H-7′), 1.20 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ: 170.12, 77.76, 75.71, 74.30, 72.63, 64.83, 54.04, 51.85, 33.00, 28.30, 27.75; MS (EI/HR) *m*/*z* M$^{+\bullet}$, calcd for $C_{13}H_{21}NO_4$: 255.1471. Found: 255.1492. Anal. calcd for $C_{13}H_{21}NO_4$ (255.31): C, 61.16; H, 8.29; N, 5.49. Found: C, 61.0; H, 8.6; N, 5.4%.

(1a*R*,3*S*,5a*R*,5b*S*,6*S*)-3-Acetoxymethyl-6-*tert*-butoxy-5-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran 12: colorless oil; $[\alpha]_D$ +43.2 (*c* 0.6, CH_2Cl_2); IR (film): 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.97 (dddd, 1H, *J* 2.4, 3.3, 5.3, 11.6 Hz, H-3), 4.51 (m, 1H, H-1a), 4.28 (dd, 1H, *J* 3.3, 12.2 Hz, C**H**$_A$H$_B$OAc), 4.23 (m, 1H, H-6), 4.19 (dd, 1H, *J* 5.2, 12.2 Hz, CH$_A$**H**$_B$OAc), 3.95 (dd, 1H, *J* 1.9, 6.9 Hz, H-5b), 3.71 (dd, 1H, *J* 1.9, 6.7 Hz, H-5a), 3.23 (m, 1H, H-8), 3.02 (m, 1H, H-8′), 2.10 (s, 3H, Ac), 1.84–2.07 (m, 4H, H-2,2′,7,7′), 1.23 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ: 171.51, 170.60, 74.59, 73.14, 72.73, 71.09, 65.29, 53.52, 48.44, 33.70, 28.47, 28.31, 20.70; MS (EI/HR) *m*/*z* M$^{+\bullet}$, calcd for $C_{16}H_{25}NO_6$: 327.1682. Found: 327.1677. Anal. calcd for $C_{16}H_{25}NO_6$ (327.37): C, 58.70; H, 7.70; N, 4.28. Found: C, 58.9; H, 7.8; N, 4.1%.

(1a*S*,3*S*,5a*S*,5b*R*,6*S*)-3-Acetoxymethyl-6-*tert*-butoxy-5-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran 13: colorless crystals; mp 94–96°C; $[\alpha]_D$ −17.2 (*c* 1.0, CH_2Cl_2); IR (film): 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.56 (ddd, 1H, *J* 6.7, 8.4, 9.7 Hz, H-1a), 4.39 (dddd, 1H, *J* 1.9, 3.5, 5.9, 12.0 Hz, H-3), 4.27 (dd, 1H, *J* 3.5, 12.1 Hz, C**H**$_A$H$_B$OAc), 4.22 (dd, 1H, *J* 5.9, 12.1 Hz, CH$_A$**H**$_B$OAc), 4.14 (m, 1H, H-6), 3.91 (dd, 1H, *J* 3.2, 4.2 Hz, H-5b), 3.36 (m, 1H, H-8), 3.20 (dd, 1H, *J* 4.2, 8.4 Hz, H-5a), 3.18 (m, 1H, H-8′), 2.22 (m, 1H, H-7), 2.17 (m, 1H, H-2), 2.10 (s, 3H, Ac), 1.91 (m, 1H, H-7′), 1.73 (m, 1H, H-2′), 1.21 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ: 170.61, 169.74, 76.86, 76.24, 74.10, 73.51, 72.44, 65.11, 54.73, 51.68, 33.00, 29.58, 28.42, 20.69; MS (EI/HR) *m*/*z* M$^{+\bullet}$, calcd for $C_{16}H_{25}NO_6$: 327.1682. Found: 327.1693. Anal. calcd for $C_{16}H_{25}NO_6$ (327.37): C, 58.70; H, 7.70; N, 4.28. Found: C, 58.8; H, 7.9; N, 4.1%.

(1a*S*,3*R*,5a*S*,5b*R*,6*S*)-3-Acetoxymethyl-6-*tert*-butoxy-5-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran 14: colorless oil; $[\alpha]_D$ −34.3 (*c* 1.0, CH_2Cl_2); IR (film): 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.92 (dddd, 1H, *J* 2.2, 3.5, 5.4, 11.8 Hz, H-3), 4.63 (ddd, 1H, *J* 2.2, 3.7, 7.9 Hz, H-1a), 4.26 (dd, 1H, *J* 3.5, 12.1 Hz, C**H**$_A$H$_B$OAc), 4.19 (dd, 1H, *J* 5.4, 12.1 Hz, CH$_A$**H**$_B$OAc), 4.19 (m, 1H, H-6), 3.68 (dd, 1H, *J* 2.7, 4.7 Hz, H-5b), 3.36 (m, 1H, H-8), 3.33 (dd, 1H, *J* 4.7, 7.9 Hz, H-5a), 3.06 (m, 1H, H-8′), 2.30 (m, 1H, H-7), 2.09 (s, 3H, Ac), 2.03 (dt, 1H, *J* 2.2, 2.2, 14.9 Hz, H-2), 1.88 (ddd, 1H, *J* 3.6, 11.7, 14.9 Hz, H-2′), 1.76 (m, 1H, H-7′); ^{13}C NMR ($CDCl_3$) δ: 170.49, 169.73, 78.61,

75.82, 74.36, 73.32, 72.08, 64.99, 54.09, 51.39, 33.12, 29.80, 28.30, 20.65; MS (ESI/HR) m/z $(M+Na)^+$, calcd for $C_{16}H_{25}NO_6Na$: 350.1574. Found: 350.1551. Anal. calcd for $C_{16}H_{25}NO_6$ (327.37): C, 58.70; H, 7.70; N, 4.28. Found: C, 58.7; H, 7.8; N, 4.0%.

(1a*S*,2*R*,3*R*,5a*R*,5b*S*,6*S*)-2-Acetoxy-3-acetoxymethyl-6-*tert*-butoxy-5-oxo-pyrrolidino[1,2-*b*] isoxazolidino[4,5-*c*]-tetrahydropyran 16: colorless crystals; mp 80–82°C; $[\alpha]_D$ +58.5 (c 0.7, CH_2Cl_2); IR (film): 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.17 (dd, 1H, J 1.5, 3.5 Hz, H-32), 5.12 (ddd, 1H, J 1.5, 5.6, 6.9 Hz, H-3), 4.32 (dd, 1H, J 3.5, 7.1 Hz, H-1a), 4.26 (dd, 1H, J 5.6, 11.7 Hz, C**H**$_A$H$_B$OAc), 4.24 (m, 1H, H-6), 4.21 (dd, 1H, J 6.9, 11.7 Hz, CH$_A$**H**$_B$OAc), 3.81 (m, 2H, H-5a,5b), 3.35 (ddd, 1H, J 3.9, 7.6, 13.3 Hz, H-8), 2.91 (ddd, 1H, J 7.2, 9.7, 13.3 Hz, H-8′), 2.12, 2.08 (2s, 6H, 2Ac), 2.05 (m, 1H, H-7), 1.91 (m, 1H, H-7′); ^{13}C NMR ($CDCl_3$) δ: 170.33, 169.39, 77.20, 74.892, 74.58, 74.56, 74.02, 71.45, 65.83, 62.10, 53.59, 47.31, 33.92, 28.29, 20.67, 20.62; MS (ESI/HR) m/z $(M+Na)^+$, calcd for $C_{18}H_{27}NO_8Na$: 408.1629. Found: 408.1639. Anal. calcd for $C_{18}H_{27}NO_8$ (385.41): C, 56.10; H, 7.06; N, 3.63. Found: C, 56.3; H, 7.3; N, 3.6%.

5.2. Hydrogenolysis of cycloadducts 11–14

General procedure. Cycloadduct (**11**–**14**, 0.18 mmol) was dissolved in a mixture of AcOH/Ac_2O 4:1 v/v (4 ml) and hydrogenated over 10% Pd/C (20 mg) at room temperature under atmospheric pressure for 24 h. Subsequently, the catalyst was filtered off, the solvent evaporated and the product purified on a silica gel to afford diastereomerically pure compound **17**–**20**, respectively.

(2′*R*,3′*S*)-*N*-Acetyl-3′-*tert*-butoxy-2,4-dideoxy-2-*C*-pyrrolidin-2′-yl-L-*erythro*-pentaldono-1,5-lactone 17: colorless oil; $[\alpha]_D$ −4.4 (c 0.9, CH_2Cl_2); IR (film): 1743, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.76 (d, 1H, J 2.5 Hz, OH), 4.55 (ddd, 1H, J 6.0, 7.1, 11.4 Hz, H-5a), 4.51 (m, 1H, H-3′), 4.40 (d, 1H, J 10.4 Hz, H-2′), 4.20 (m, 1H, H-5b), 4.11 (m, 1H, H-3), 3.69 (m, 1H, H-5′a), 3.45 (m, 1H, H-5′b), 2.15 (s, 3H, Ac), 1.98–2.16 (m, 4H, H-4′a,4′b,4a), 1.89 (m, 1H, H-4b), 1.25 (s, 9H, t-Bu); MS (ESI/HR) m/z $(M+Na)^+$, calcd for $C_{15}H_{25}NO_5Na$: 322.1625. Found: 322.1625.

(2′*S*,3′*S*)-*N*-Acetyl-6-*O*-acetyl-3′-*tert*-butoxy-2,4-dideoxy-2-*C*-pyrrolidin-2′-yl-D-*ribo*-hexaldono-1,5-lactone 18: colorless oil; $[\alpha]_D$ +30.8 (c 0.45, CH_2Cl_2); IR (film): 1743, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.41 (bs, 1H, OH), 4.95 (m, 1H, H-5), 4.61 (d, 1H, J 6.7, 7.3 Hz, H-2′), 4.47 (q, 1H, H-3′), 4.29 (dd, 1H, J 3.4, 12.0 Hz, C**H**$_A$H$_B$OAc), 4.18 (dd, 1H, J 5.2, 12.0 Hz, CH$_A$**H**$_B$OAc), 4.15 (m, 1H, H-3), 3.61 (m, 1H, H-5′a), 3.49 (m, 1H, H-5′b), 3.10 (dd, 1H, J 2.1, 6.7 Hz, H-2), 2.11, 2.10 (2s, 6H, 2Ac), 2.05–2.15 (m, 2H, H-4a,4′a), 2.02 (m, 1H, H-4′b), 1.86 (m, 1H, H-4b), 1.22 (s, 9H, t-Bu); MS (ESI/HR) m/z $(M+H)^+$, calcd for $C_{18}H_{30}NO_7$: 372.2011. Found: 372.2003.

(2′*R*,3′*S*)-*N*-Acetyl-6-*O*-acetyl-3′-*tert*-butoxy-2,4-dideoxy-2-*C*-pyrrolidin-2′-yl-D-*lyxo*-hexaldono-1,5-lactone 19: colorless oil; $[\alpha]_D$ +2.3 (c 0.6, CH_2Cl_2); IR (film): 1746, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.70 (d, 1H, J 3.2 Hz, OH), 4.46 (d, 1H, J 10.6 Hz, H-2′), 4.40 (m, 1H, H-5), 4.32 (bd, 1H, J 3.2 Hz, H-3), 4.27 (dd, 1H, J 3.1, 12.1 Hz, C**H**$_A$H$_B$OAc), 4.17 (dd, 1H, J 7.1, 12.1 Hz, CH$_A$**H**$_B$OAc), 4.16 (m, 1H, H-3′), 3.70 (m, 1H, H-5′a), 3.45 (m, 1H, H-5′b), 2.30 (m, 1H, H-4a), 2.15, 2.08 (2s, 6H, 2Ac), 2.10 (m, 1H, H-2), 2.06–1.80 (m, 2H, H-4′a,4′b), 1.83 (m, 1H, H-4b); MS (ESI/HR) m/z $(M+Na)^+$, calcd for $C_{18}H_{29}NO_7Na$: 394.1836. Found: 394.1846.

(2′*R*,3′*S*)-*N*-Acetyl-6-*O*-acetyl-3′-*tert*-butoxy-2,4-dideoxy-2-*C*-pyrrolidin-2′-yl-L-*ribo*-hexaldono-1,5-lactone 20: colorless oil; $[\alpha]_D$ −19.1 (c 0.7, CH_2Cl_2); IR (film): 1740, 1619 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.90 (t, 1H, OH), 4.99 (m, 1H, H-5), 4.69 (bd, 1H, H-3′), 4.31 (d, 1H, J 10.1 Hz, H-2′), 4.26 (dd, 1H, J 3.3, 12.1 Hz, C**H**$_A$H$_B$OAc), 4.19 (dd, 1H, J 5.2, 12.1 Hz, CH$_A$**H**$_B$OAc), 4.08 (m, 1H, H-3), 3.70 (m, 1H, H-5′a), 3.45 (m, 1H, H-5′b), 2.16, 2.09 (2s, 6H, 2Ac), 2.13 (dd, 1H, J 1.9, 10.1 Hz, H-2), 2.00–2.13 (m, 2H, H-4a,4′a), 1.90 (m, 1H, H-4′b), 1.79 (m, 1H, H-4b), 1.25 (s, 9H, t-Bu); MS (ESI/HR) m/z $(M+Na)^+$, calcd for $C_{18}H_{29}NO_7Na$: 394.1836. Found: 394.1824.

(2′*S*)-3,6-*O*-Acetyl-4′-*N*-acetamino-23′-*tert*-butoxy-2-butyl-2,4-dideoxy-L-*ribo*-hexaldono-1,5-lactone 21: colorless oil; $[\alpha]_D$ −35.9 (c 0.7, CH_2Cl_2); IR (film): 1742, 1663, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.68 (dd, 1H, J 4.6, 7.2 Hz, NH), 5.29 (ddd, 1H, J 2.1, 3.4, 10.2 Hz, H-3), 5.16 (m, 1H, H-5), 4.33 (dd, 1H, J 3.1, 12.1 Hz, C**H**$_A$H$_B$OAc), 4.11 (dd, 1H, J 6.5, 12.1 Hz, CH$_A$**H**$_B$OAc), 4.01 (m, 1H, H-2′), 3.69 (m, 1H, H-4′a), 3.41 (dd, 1H, J 3.4, 11.1 Hz, H-2), 2.84 (m, 1H, H-4′b), 2.35 (ddd, 1H, J 2.1, 7.6, 14.4 Hz, H-4a), 2.08, 2.06, 2.05 (3s, 3H, 3Ac), 1.88 (m, 1H, H-1′a), 1.80 (ddd, 1H, J 5.3, 10.1 Hz, H-4b), 1.70 (m, 1H, H-3′a), 1.70–1.50 (m, 2H, H-1′b, 3′b), 1.17 (s, 9H, t-Bu); MS (ESI/HR) m/z $(M+Na)^+$, calcd for $C_{20}H_{33}NO_8Na$: 438.2098. Found: 438.2072.

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