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Double asymmetric induction in 1,3-dipolar cycloaddition of five-membered cyclic nitrones to 2-(5*H*)-furanones

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This paper is dedicated to Professor András Lipták on the occasion of his 70th birthday

Abstract—The 1,3-dipolar cycloaddition of nitrones **1**–**4** and their enantiomers **2ent**–**4ent** to α,β-unsaturated γ-lactones, such as achiral **9** and D-*glycero* **10** provides an interesting example of a double asymmetric induction. The reactions are kinetically controlled. Upon heating and prolonged reaction time, however, the reversibility of the cycloaddition was observed and the presence of more stable thermodynamic products detected. Moreover, in the case of lactone **10**, a partial racemization did occur and consequently adducts derived from **10ent** were formed. Contrary to the corresponding additions involving δ-lactones, where only the *exo* approach of the reactants was observed, γ-lactones added nitrones in both *exo* and *endo* modes. The high preference of an *anti* addition to the terminal hydroxymethyl group in lactone **10** and to the 3-*tert*-butoxy group of the nitrone was observed; the 4-*tert*-butoxy substituent plays a secondary role. The *endo* addition of the reactants is energetically more demanding than the *exo* addition and occurs if none of the substituents present in the lactone or nitrone hinders such an approach. Due to the complex steric interactions a single product was formed in two cases only, **2ent/10** and **3/10**. In one case, **3/9**, a high preponderance of a single adduct was observed.

1. Introduction

Recently we have reported that the 1,3-dipolar cycloaddition of nitrones **1**–**3** to the α,β-unsaturated δ-lactones, such as achiral **5**, D-*glycero* **6**, DL-*glycero* **6/6ent**, D-*erythro* **7**, and D-*threo* **8**, constitutes an interesting example of a double asymmetric induction, where the chirality elements of each reactant may influence stereoselectivity either in concert or in opposition.[1–3] The results were interpreted with the assumption that the cycloaddition is kinetically controlled. Such an assumption is reasonable since we have never observed the reversibility of these reactions. In all cases, only the products of an *exo* approach of the reactants had been noticed. A high preference of the *anti* addition to the terminal acetoxymethyl group in lactones **6**–**8** and to the 3-*tert*-butoxy group of the nitrone **2** and **3** was observed. In the case of the mismatched pairs, the configuration of the 4-*O*-acetoxy substituent in the lactone becomes the decisive factor in controlling the outcome of addition.[3] It has also been shown that the obtained cycloadducts offer an entry to iminosugars with an indolizidine skeleton.[4] A synthetic strategy leading to the pyrrolizidines and indolizidines via nitrone cycloaddition has been reported by Tufariello,[5] Brandi,[6] Wightman,[7] and Holmes[8] et al. A similar strategy using nitrone esters has also been developed by Denmark et al.[9]

The results obtained for δ-lactones prompted us to examine similar reactions performed with the five-membered ring lactones [2-(5*H*)-furanones] **9** and **10**. To reach a consistent picture of the reaction, we also decided to expand the number of nitrones; in addition to the nitrones **1**–**3**, we also included nitrone **4** as well as the enantiomeric forms of chiral compounds: **2ent**, **3ent**, and **4ent** (Figs. 1 and 2).

2. Results and discussion

Working with δ-lactones and nitrones **1**–**3**, we have found that the cycloaddition reactions were cleaner

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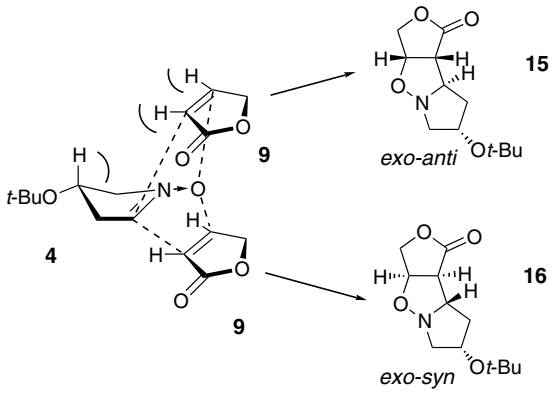
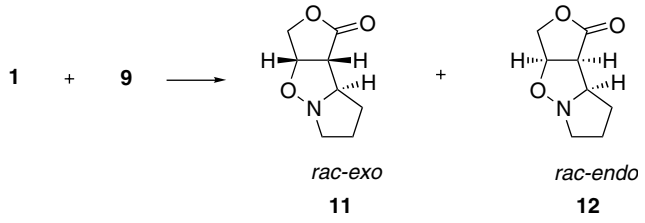


Figure 1. *exo* Approach of the nitrone **4** to the lactone **9**.

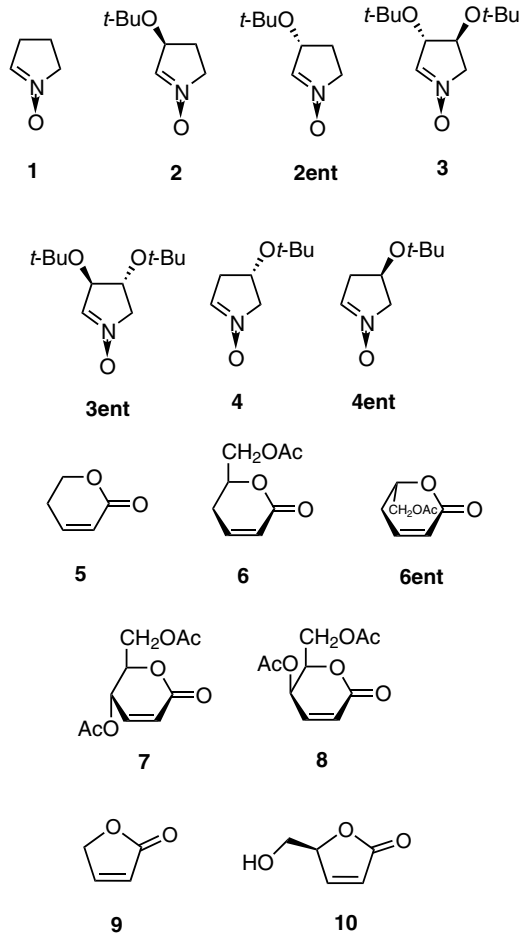
and gave higher yields when both components were allowed to react initially at room temperature and then at reflux at the end of the reaction for only 1 h, to complete the cycloaddition process.[1–3] If reflux was started from the beginning of the reaction, when high concentrations of both components were present, the formation of by-products derived from the nitrone was observed. The cycloadditions were performed in a toluene solution at room temperature followed by 1 h reflux (individual reaction times are given in Table 2).

In 1993 Font et al.[10] reported the 1,3-dipolar cycloaddition between nitrone **1** and lactone **9**. When both components of the reaction were refluxed in a toluene solution, racemic *exo*-**11** and *endo*-**12** adducts were obtained in a ratio of about 3:1, respectively (Scheme 1).



Scheme 1.

The single asymmetric induction in the cycloaddition of chiral nitrone **2** to the non-chiral lactone **9** has been reported by Brandi et al.[11] The authors have noticed



formation of two cycloadducts **13** and **14** in a ratio of 84:16, respectively, as a result of an *exo* approach of the dipole to both sides of the dipolarophile. In light of Font et al.'s report,[10] one would expect *exo* rather than *endo* approach of reactants *anti* in relation to the 3-*tert*-butoxy group in the nitrone. Reinvestigation of the reaction performed by Brandi et al.[11] under our standard conditions showed that indeed the minor product **14** was a consequence of *endo* approach (Scheme 2). The configuration of **14** was easily proven by the NOE's, which showed spin–spin interactions between H-1a, H-4a, and H-4b protons, and by the coupling constant $J_{4a,4b} = 10.2$ Hz, indicating the *syn* orientation of both protons. The configuration of **13** was proven by X-ray crystal structure analysis (Fig. 3). Enantiomers **13ent**

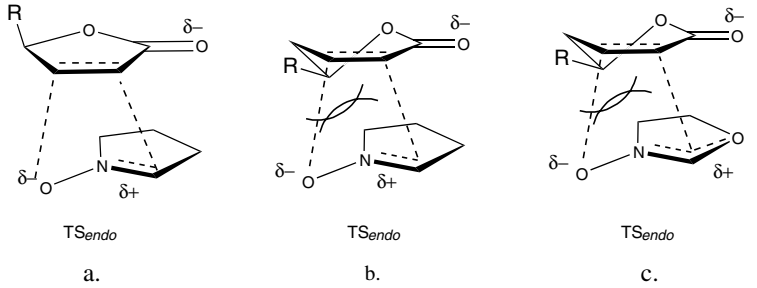
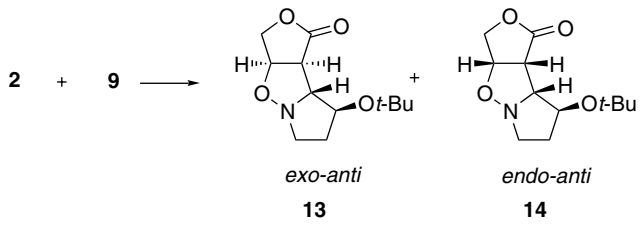


Figure 2. (a) and (b) *endo* transition states of cyclic nitrones to γ- and δ-lactones; (c) *endo* transition state of oxazoline *N*-oxide to δ-lactone.



Scheme 2.

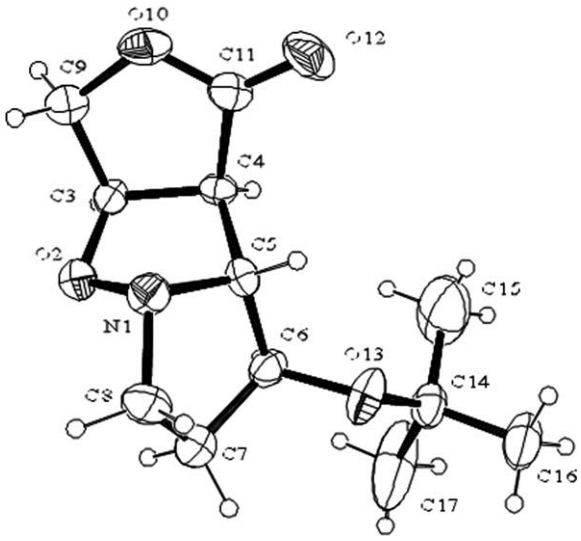
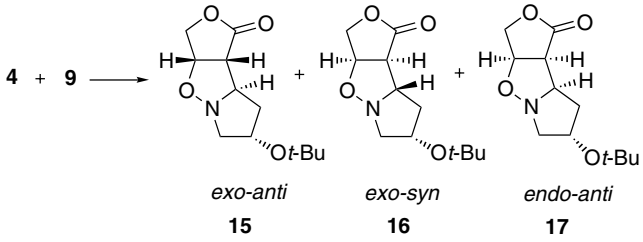


Figure 3. Molecular structure of the compound **13** with the crystallographical numbering scheme.[20]

and **14ent** were obtained by cycloaddition between **9** and **2ent**.

The shift of the *tert*-butoxy substituent in the nitrone from position 3 to 4 (compounds **4/4ent**) changed the preference of the reactants approach. In the reaction with **9**, three products *exo-anti* **15/15ent**, *exo-syn* **16/16ent**, and *endo-anti* **17/17ent** were obtained in a 35:53:12 ratio,[†] respectively (Scheme 3). The configuration of these cycloadducts was determined by the ^{1}H NMR (coupling constants and NOE's) and X-ray diffraction analysis for **15** and **16** isomers (Figs. 4 and 5).



Scheme 3.

The unexpected preference for the *exo-syn* adduct **16** prompted us to check the influence of the solvent on

[†] Average values for reactions of both nitrones **4/4ent**. For details see Table 2, entries 6 and 7.

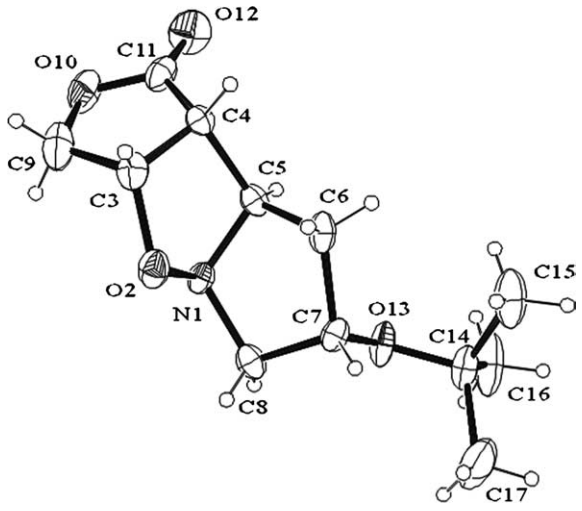


Figure 4. Molecular structure of the compound **15** with the crystallographical numbering scheme.[20]

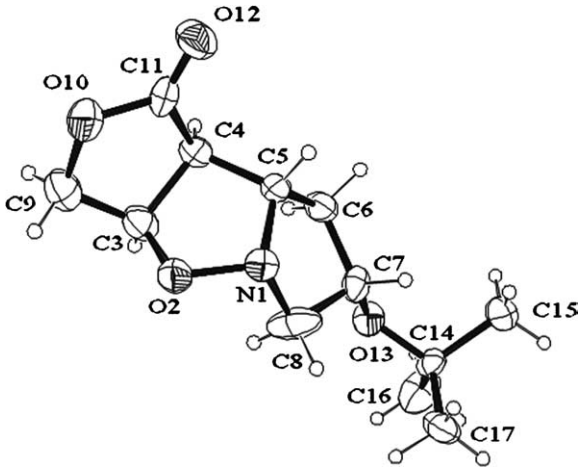


Figure 5. Molecular structure of the compound **16** with the crystallographical numbering scheme.[20]

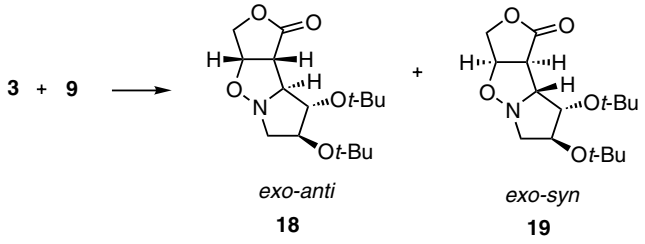
the ratio of the diastereomeric products. It was demonstrated (Table 1) that the increased polarity of the solvent did not significantly affect proportions of adducts, however, it decreased the rate of cycloaddition. The preference for *exo-syn* approach could be explained on the assumption that the conformation of nitrone **4** in the transition state of the cycloaddition resembles the ground-state conformation of **4**. On the basis of the sum of coupling constants of H-4 ($\Sigma J = 22.0$ Hz), the conformation of **4** should be ascribed as ^4E with the nitrone moiety located in the flat part of the ring (such a geometry is reflected to a certain extent in the crystalline state of **16**; Fig. 5). The out of plane C-4 carbon atom but not the equatorially positioned *tert*-butoxy group, decides the preference for the *syn* addition (Fig. 1).

The introduction of two *anti* located *tert*-butoxy substituents to the nitrone molecule (**3/3ent**) eliminated the possibility of *endo* addition to **9** due to the steric interaction of one or the other *tert*-butoxy substituent with the lactone ring. Consequently, two *exo* adducts **18/18ent**

Table 1. Influence of solvent in 1,3-cycloaddition of nitrone **4** to the lactone **9**

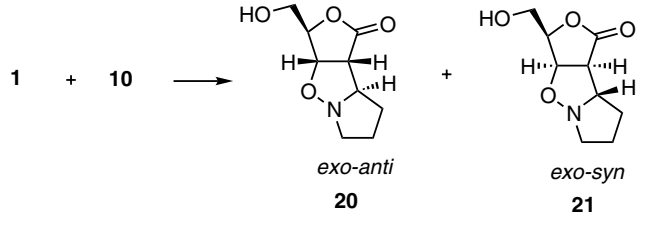
Solvent	Composition of the post-reaction mixture (%)			Time	Yield (%)
	15 (*exo-anti*)	**16** (*exo-syn*)	**17** (*endo-anti*)		
$PhCH_3$	40	50	10	50 h	82
C_6H_6	36.4	49.5	14.1	49 h	76
THF	43	45	12	7 d	85
CH_2Cl_2	41	47	12	7 d	66
n-C_6H_{14}	48	40.5	11.5	14 d	49
CH_3CN	50	38	12	10 d	55
DMF	51	37.5	11.5	10 d	71
CH_3OH	45	44.5	10.5	14 d	64

and **19/19ent** were obtained in a ratio of about 93:7,[‡] respectively (Scheme 4). The high preference for the *anti* addition of the lactone **9** to the 3-*tert*-butoxy group of the nitrone **3** is similar to that observed for addition of **3** to **5**.[1]



Scheme 4.

Cycloaddition of the non-chiral nitrone **1** and the chiral lactone **10** afforded two *exo* adducts **20** and **21** in a ratio of about 70:30 (Scheme 5). Careful examination of the post-reaction mixture did not reveal any traces of the *endo* product, which was expected considering the result of addition of **2** and **9** (Scheme 2). On the other hand, it is worth comparing this result with that found for the corresponding reaction of the same nitrone **1** and the δ-lactone **6** when the *exo-anti* adduct was formed exclusively.[3]



Scheme 5.

The use of a chiral nitrone and a chiral lactone created a double asymmetric induction system, which was different from that observed during addition of nitrones **2** and **3** to lactones **6**–**8**,[3] because both *exo* and *endo* approaches are possible. It should be stressed that the mismatched pairs require a longer reaction time. This may cause partial racemization of lactone **10** via a hydroxyfuran[12] and consequently one can expect a degree of contamination introduced by adducts derived from lactone **10ent**.

The mismatched pair, nitrone **2** and lactone **10** gave three cycloadducts: *exo-syn* **22**, *exo-anti* **23** and *endo-anti* **24** to the 3-*tert*-butoxy group of the nitrone in a ratio of about 21:27:52, respectively (Scheme 6). The configuration of *endo-anti* adduct **24** was determined by X-ray structure analysis (Fig. 6).

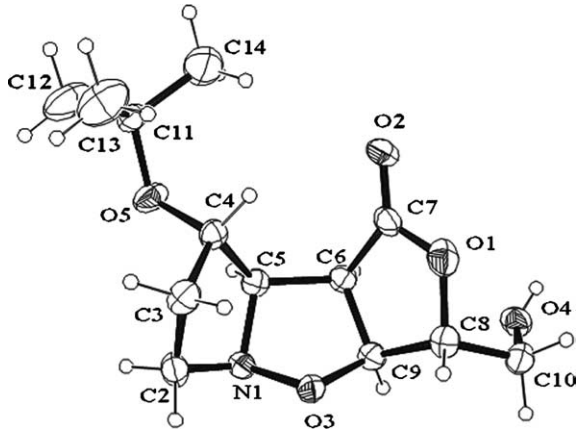
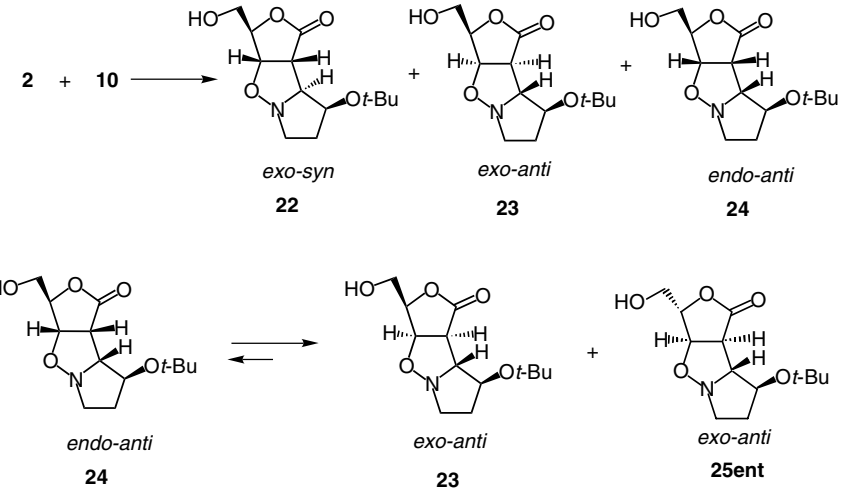


Figure 6. Molecular structure of the compound **24** with the crystallographical numbering scheme.[20]

The main product of the cycloaddition between **2** and **10**, adduct **24**, was refluxed in a toluene solution for 24 h to examine possible reversibility of the reaction (Scheme 6). The post-reaction mixture showed the unreacted *endo* adduct **24** and two new products: the *exo-anti* adduct **23** and a cycloadduct **25ent** (identified as an enantiomer of adduct **25**) in a ratio of about 8:1:3, respectively. Further heating lead to a significant decomposition. Addition of triethylamine accelerated the racemization of lactone **10** and resulted (after 8 d of reflux) in the formation of mixture of **25ent** (derived from the matched pair, **2** and **10ent**) and **24** in a ratio of about 2.7:1, respectively. The reversibility of the investigated cycloaddition can be better demonstrated when the *endo* adduct **14** was heated at reflux to provide only the **13** after 5 d of heating. These observations unequivocally proved the reversibility of cycloaddition investigated.

[‡] Average values for reactions of both nitrones **3/3ent**. For details see, Table 2, entries 4 and 5.



Scheme 6.

Consequently, at a higher temperature and upon prolongation of the reaction time, one can expect that the kinetically controlled mixture of cycloadducts may show the presence of more stable, thermodynamic products. Moreover, as observed by us, racemization of **10**[12] shifts the composition of the reaction mixture toward the formation of products derived from **10ent**. In light of the reversibility of the investigated cycloadditions, the disagreement in the assignment of configuration of **14** can be explained in terms of the isolation by us and by Brandi et al.[11] of different products.

Cycloaddition between matched pairs: the nitrone **2ent** or **3** with lactone **10**, led to the sole *exo-anti* adducts in each case, **25** and **26** (Fig. 7), respectively (Scheme 7). Compare this result with formation of **25ent** upon heating of **24** (Scheme 6).

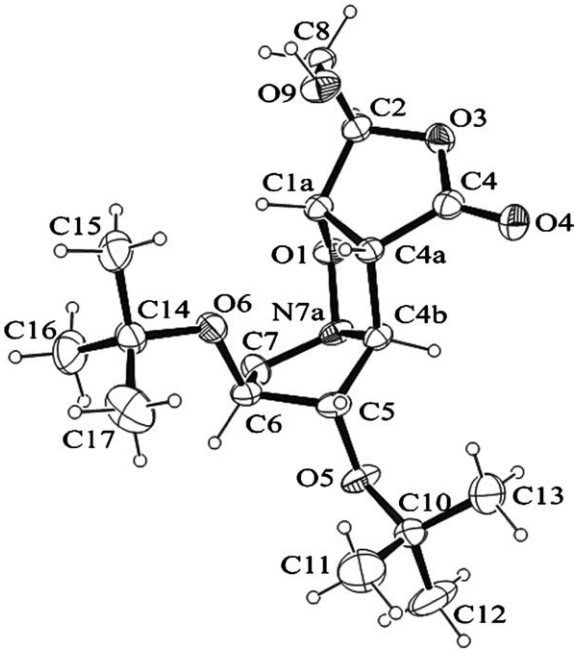
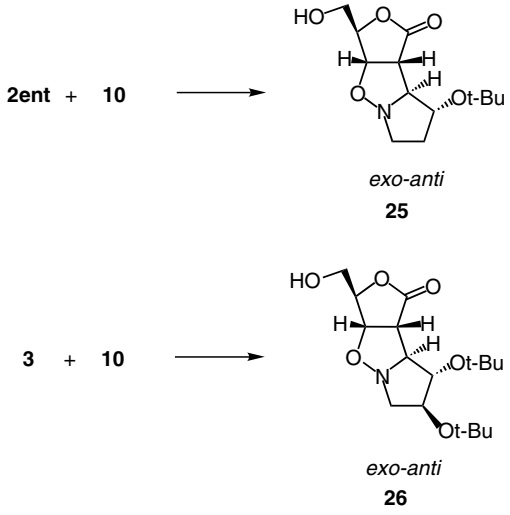


Figure 7. Molecular structure of the compound **26** with the crystallographical numbering scheme.[20]

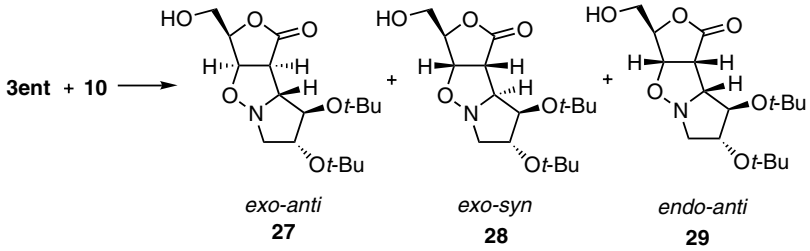
Cycloaddition between **3** and **10** showed that the introduction of an additional, *anti* located *tert*-butoxy substituent to C-4 of the nitrone **2ent** (**3**) did not change the conformational preferences of the reaction (Scheme 7). In both cases, either the presence of hydroxymethyl or 3-*tert*-butoxyl group excluded the possibility of an *endo* approach of reactants.



Scheme 7.

The use of nitrone **3ent** and lactone **10** created a mismatched pair and consequently led to the formation of three products **27**, **28**, and **29** in a ratio of about 45:32:23, respectively (Scheme 8). The direct comparison of these results with those found for the addition of **2** to **10** was noteworthy. It showed the influence of the 4-*tert*-butoxy substituent in the nitrone, which led to a significantly reduced content of *endo* adduct and simultaneous increase of the content of both *exo* adducts.

As could be expected, cycloaddition of the nitrone **4** with the lactone **10** afforded two adducts, *exo-syn* **30** and *exo-anti* **31** (Fig. 8) in a ratio of about 21:79, respectively (Scheme 9). In comparison to cycloaddition of **4**



Scheme 8.

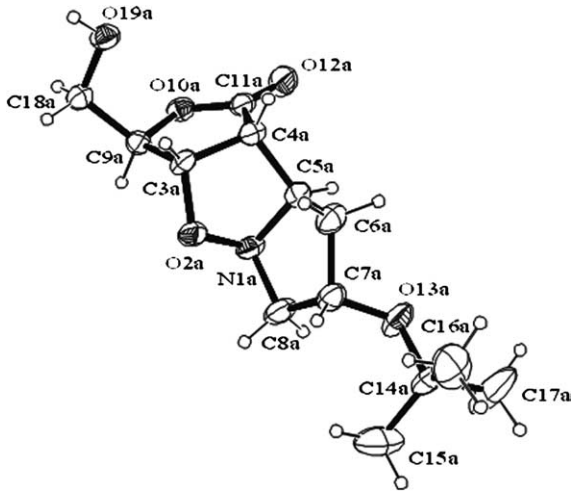
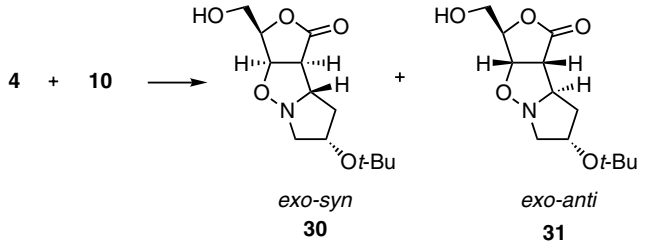


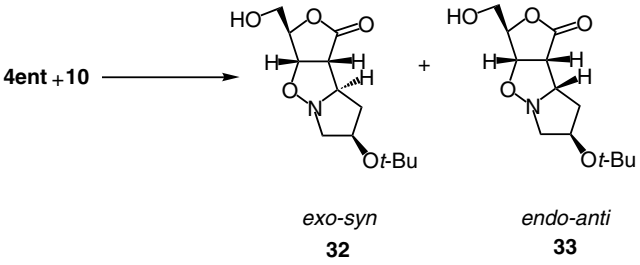
Figure 8. Molecular structure of the compound **31** with the crystallographical numbering scheme.[20]



Scheme 9.

and **9**, the added presence of hydroxymethyl group in the lactone molecule caused disappearance of the *endo* adduct and the *exo-anti* adduct **31** became the main product. At the same time, removal of the 3-*tert*-butoxy substituent from the nitrone, besides the disappearance of *endo* addition, caused a significant increase of *exo-anti* addition (**31**), in comparison to the corresponding adduct formed in reaction of **3ent** with **10**.

The replacement of **4** by its enantiomer **4ent** during the cycloaddition with lactone **10** led to the formation of *exo-syn* product **32** as the main component of the post-reaction mixture (73%). Since the steric interactions that hinder the *endo* approach were removed, compound **32** was accompanied by the *endo-anti* adduct **33** (27%). The hydroxymethyl group in the lactone influenced the direction of asymmetric induction more than the 4-*tert*-butoxy substituent in the nitrone (Scheme 10).



Scheme 10.

The 1,3-dipolar cycloaddition of the five-membered ring nitrones and unsaturated γ-lactones was sterically controlled. The hydroxymethyl group of lactone and the 3-*tert*-butoxy group of nitrone play a decisive role in the stereochemical pathway of the reaction. The bulky 4-*tert*-butoxy group only plays a minor role. Due to the pseudo-rotation arrangement of five-membered ring nitrones, assignment of the ground-state conformation of nitrones **1**–**3** is not straightforward, except for the nitrone **4**/**4ent**, therefore any speculation on the stereochemical models of cycloaddition on this basis is groundless. In contrast to the Diels–Alder cycloadditions, 1,3-dipolar cycloadditions usually do not show a significant preference for *endo* addition since secondary orbital interactions are not strong enough. According to the explanation provided in the paper by Garcia Ruano et al.[13] the *endo*/*exo* selectivity in polar cycloadditions could be elucidated by favorable coulombic interactions between the nitrone positively charged and the furanone, negatively charged, at the corresponding *endo* transition state. This interaction is lower for folded and larger six-membered ring of δ-lactones (Fig. 2b) than for flat γ-lactones (Fig. 2a). Therefore, in the case of the addition of cyclic five-membered nitrones to δ-lactones the *endo* addition has not been observed, though the formation of a minute amount of the *endo* adduct has been reported by Font et al.[10b] during the reaction between **1** and **10**. Recently Langlois et al.[14] repeated the *endo* approach of oxazoline *N*-oxide and unsaturated δ-lactone in the mismatched pair and this has been explained by the interaction between the positively

charged iminoether fragment in the nitrone and the lactone carbonyl group (Fig. 2c).

In order to explain the high preference of the *anti* approach of nitrones to the terminal acetoxymethyl group in **6**, we have postulated an advantage of axial attack of the nitrone oxygen atom.[1–3] This preference and the lack of *endo* addition, together with the steric interactions introduced by substituents in both reactants, cause the cycloadditions involving δ-lactones to usually result in the predominance of one adduct or, in many cases, produce a single product. On the other hand, the γ-lactones can react in *endo* mode, as well. Consequently, the reaction trajectories are more complicated and formation of a single cycloadduct was observed in a few cases only. Moreover, upon prolongation of the reaction time, at higher temperature, the reversibility of the cycloaddition, as well as the racemization of 5-substituted 2-(5*H*)-furanones may additionally complicate the composition of the post-reaction mixture. Therefore, bearing in mind a potential use of adducts in a target-oriented synthesis, cycloadditions involving δ-lactones offer certain advantages over those involving γ-lactones.

3. Experimental

3.1. General

Melting points were determined using a Köfler hot-stage apparatus with microscope and are uncorrected. Proton and carbon NMR spectra were recorded on a Brucker DRX 500 Avance Spectrometer at 500 and 125 MHz, respectively, using deuterated solvents and TMS as a internal standard. Chemical shifts are reported as δ values in parts per million and coupling constants are in hertz. Infrared spectra were obtained on an FT-IR-1600 Perkin–Elmer spectrophotometer. The optical rotations were measured with a JASCO J-1020 digital polarimeter. High resolution mass spectra were recorded on AMD 604 Inectra GmBH spectrometer (EI, 70 eV) and on ESI-TOF Mariner spectrometer (Perspective Biosystem). X-ray analysis was performed on Nonius MACH3 diffractometer.

Thin layer chromatography (TLC) was performed on aluminum sheets silica gel 60 F_{254} ($20 \times 20 \times 0.2$) from Merck. Column chromatography (CC) was carried out using Merck silica gel 230–400 mesh. The TLC spots were visualized by treatment with alcoholic solution of ninhydrine (spray) and heating.

All solvents were dried and purified by standard techniques. Lactone **9** was obtained according to Nasmar and Pensar protocol[15] and lactone **10** was prepared following a known procedure.[16] Nitrones **1**,[17] **2/2ent**,[18] **3/3ent**[19] and **4/4ent**[19] were obtained following the literature procedures.

3.2. Nitrones 4 and 4ent

3.2.1. (4*S*)-4-*tert*-Butoxy-1-pyroline *N*-oxide 4. $[\alpha]_D = +13.1$ (*c* 0.9, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, m, H-2), 4.50 (1H, m, ΣJ 22.0 Hz, H-4), 4.11 (1H, m, H-5), 3.85 (1H, m, H-5′), 3.03 (1H, m, H-3), 2.67 (1H, m, H-3′), 1.20 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 133.87, 74.69, 69.47, 65.41, 39.03, 28.18; IR (film): ν 3402, 2975, 1588 cm^{-1}; HR MS (EI): *m*/*z* [M^+] calcd for $C_8H_{15}NO_2$: 157.11028. Found: 157.11078.

3.2.2. (4*R*)-4-*tert*-Butoxy-1-pyroline *N*-oxide 4ent. $[\alpha]_D = -13.3$ (*c* 0.7, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_8H_{15}NO_2$: 157.11028. Found: 157.11054.

3.3. Cycloaddition of nitrones 1–4 to lactones 9 and 10

3.3.1. General procedure. A lactone (1 equiv) and nitrone (1.4 equiv) were dissolved in dry toluene and stirred at room temperature for 40–50 h and then under reflux for 1 h. The progress of the reaction was monitored by TLC. After removal of solvent, the residue was purified on a silica gel column to afford the corresponding cycloadducts. The reaction times, yields and ratios of cycloadducts are reported in Table 2.

3.3.1.1. (1a*R*,4a*S*,4b*R*,5*S*)-5-*tert*-Butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 13. Colorless needles, mp 150–151 °C (hexane/benzene/diethyl ether 1:1:1); $[\alpha]_D = -3.5$ (*c* 0.5, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.15 (1H, dd, *J* 10.3, 2.0 Hz, H-2′), 4.06 (1H, m, *J* 7.3, 5.9, 2.0 Hz, H-1a), 3.89 (1H, br d, *J* 4.5 Hz, H-4b), 3.76 (1H, m, *J* 7.9, 4.5, 4.0 Hz, H-5), 3.72 (1H, dd, *J* 10.3, 5.9 Hz, H-2), 3.20–3.10 (2H, m, H-7), 2.82 (1H, dd, *J* 7.3, 0.9 Hz, H-4a), 2.04 (1H, m, *J* 13.0, 8.3, 8.0, 7.9 Hz, H-6), 1.55 (1H, m, *J* 13.0, 7.9, 4.2, 4.0 Hz, H-6′), 1.16 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175. 85 (C=O), 78.12 (C-4b), 77.35 (C-5), 76.09 (C-1a), 73.90 (*C*–O*t*-Bu), 72.78 (C-2), 54.60 (C-7), 52.70 (C-4a), 33.93 (C-6), 28.51 (*t*-Bu); IR (film): ν 1758 cm^{-1}; HR MS (ESI): *m*/*z* [M+H^+] calcd for $C_{12}H_{20}NO_4$: 242.1387. Found: 242.1376.

3.3.1.2. (1a*S*,4a*R*,4b*R*,5*S*)-5-*tert*-Butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 14. Colorless crystals, mp 83–85 °C (benzene/diethyl ether 1:1); $[\alpha]_D = -31.9$ (*c* 1.3, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.83 (1H, br d, *J* 5.8 Hz, H-5), 3.99 (1H, dd, *J* 5.6, 4.3 Hz, H-1a), 3.81 (1H, br d, *J* 10.5 Hz, H-4b), 3.77 (1H, d, *J* 10.9 Hz, H-2′), 3.29 (1H, dd, *J* 10.9, 4.3 Hz, H-2), 3.25 (1H, ddd, *J* 13.3, 6.8, 1.7 Hz, H-7′), 3.14 (1H, ddd, *J* 13.3, 11.5, 5.6 Hz, H-7), 2.75 (1H, dd, *J* 10.4, 5.7 Hz, H-4a), 2.00 (1H, m, *J* 13.0, 6.8, 6.8, 5.9 Hz, H-6), 1.54 (1H, ddd, *J* 13.0, 5.6, 1.7 Hz, H-6′), 1.19 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 174.96 (C=O), 78.42 (C-1a), 77.68 (C-4b), 74.20 (*C*–O*t*-Bu), 71.78 (C-5), 68.60 (C-2), 55.10 (C-7), 51.03 (C-4a), 33.43 (C-6), 28.49 (*t*-Bu); IR (film): ν 1755 cm^{-1}; HR MS (ESI): *m*/*z* [M+H^+] calcd for $C_{12}H_{20}NO_4$: 242.1387. Found: 242.1393.

3.3.1.3. (1a*S*,4a*R*,4b*S*,5*R*)-5-*tert*-Butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 13ent. Colorless crystals, mp 149–151 °C (benzene/hexane 1:1); $[\alpha]_D = +5.6$ (*c* 0.7, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{19}NO_4$ 241.13141. Found 241.13158.

Table 2. 1,3-Dipolar cycloaddition of nitrones **1**–**4** to lactones **9**–**10**

Entry	Lactone	Nitrone	Time (h)[a]	Yield (%)	Cycloadducts ratio	Column chromatography (v/v)
1	**9**	**1**	2	84	75(**11**), 25(**12**)[b]	[b]
2	**9**	**2**	48	75	84(**13**), 16(**14**)	EA:H 2:1
3	**9**	**2ent**	72	85	78(**13ent**), 22(**14ent**)	EA:H 2:1
4	**9**	**3**	46	72	91(**18**), 9(**19**)	EA:H 1:2
5	**9**	**3ent**	55	62	94(**18ent**), 6(**19ent**)	EA:H 1:2
6	**9**	**4**	50	82	38(**15**), 52(**16**), 10(**17**)	EA:H 1:1
7	**9**	**4ent**	56	61	32(**15ent**), 54(**16ent**), 14(**17ent**)	EA:H 1:1
8	**10**	**1**	50	69	70(**20**), 30(**21**)	EA:H 4:1
9	**10**	**2**	48	89	21(**22**), 27(**23**), 52(**24**)	(a) E:H 4:1 (b) EA:H 4:1[c]
10	**10**	**2ent**	47	86	100(**25**)	EA:H 2:1
11	**10**	**3**	48	81	100(**26**)	EA:H 1:1
12	**10**	**3ent**	49	77	45(**27**), 32(**28**), 23(**29**)	EA:H 2:1
13	**10**	**4**	40	82	79(**31**), 21(**30**)	EA:H 1:1
14	**10**	**4ent**	52	83	73(**32**), 27(**33**)	EA:H 2:1

EA: ethyl acetate; H: hexane; E: methyl-*tert*-butyl ether.

[a] Including 1 h heating.

[b] Ref. 10b.

[c] Compounds **22**, **23**, and **24** were separated by a two stage column chromatography. The first stage separated cycloadduct **23** from the mixtures **22** and **24** using ethyl acetate/hexane 4:1 v/v as an eluent. Subsequently the mixtures **22** and **24** was separated using methyl-*tert*-butyl ether/hexane 4:1 v/v as an eluent.

3.3.1.4. (1a*R*,4a*S*,4b*S*,5*R*)-5-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 14ent. Colorless crystals, mp 83–86 °C (benzene/hexane 1:2); $[\alpha]_D = +33.3$ (*c* 0.5, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{19}NO_4$: 241.13141. Found: 241.13176.

3.3.1.5. (1a*S*,4a*R*,4b*R*,6*S*)-6-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 15. Colorless crystals, mp 129–130 °C (toluene/diethyl ether 2:1); $[\alpha]_D = +52.9$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.18 (1H, m, *J* 7.9, 6.6, 5.8, 3.2 Hz, H-6), 4.06 (1H, dd, *J* 10.3, 2.2 Hz, H-2′), 3.96 (1H, m, *J* 7.6, 6.2, 2.2 Hz, H-1a), 3.91 (1H, dd, *J* 8.7, 8.0 Hz, H-4b), 3.62 (1H, dd, *J* 10.3, 6.2 Hz, H-2), 3.53 (1H, dd, *J* 14.5, 6.6 Hz, H-7), 2.88 (1H, dd, *J* = 14.5, 5.8 Hz, H-7′), 2.57 (1H, d, *J* 7.6 Hz, H-4a), 1.61 (1H, ddd, *J* 13.3, 8.0, 3.2 Hz, H-5′), 1.45 (1H, ddd, *J* = 13.3, 8.7, 7.9 Hz, H-5), 0.95 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175.49 (C=O), 75.99 (C-1a), 73.63 (C-2), 72.99 (*C*–O*t*-Bu), 72.66 (C-6), 69.76 (C-4b), 64.24 (C-7), 53.39 (C-4a), 39.33 (C-5), 28.29 (*t*-Bu); IR (film): ν 1764 cm^{-1}; HR MS (ESI): *m*/*z* [M+Na^+] calcd for $C_{12}H_{19}NO_4Na$: 264.1206. Found: 264.1217.

3.3.1.6. (1a*R*,4a*S*,4b*S*,6*S*)-6-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 16. Colorless crystals, mp 104–105 °C (toluene/diethyl ether 4:1); $[\alpha]_D = -13.4$ (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.28 (1H, m, *J* 6.6, 5.0 Hz, H-1a), 4.00 (1H, d, *J* 10.6 Hz, H-2′), 3.79 (1H, m, *J* 7.5, 6.4, 1.7 Hz, H-4b), 3.58 (1H, m, *J* 6.5, 6.3, 5.1, 3.8 Hz, H-6), 3.55 (1H, dd, *J* 10.6, 5.0 Hz, H-2), 3.12 (1H, dd, *J* 13.7, 6.3 Hz, H-7), 3.00 (1H, dd, *J* 13.7, 3.7 Hz, H-7′), 2.74 (1H, dd, *J* 6.6, 1.7 Hz, H-4a), 1.68 (1H, m, *J* 13.2, 7.5, 6.5 Hz, H-5), 1.50 (1H, m, *J* 13.2, 6.4, 5.1 Hz, H-5′), 0.92 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 176.33 (C=O), 76.70 (C-1a), 73.31 (*C*–O*t*-Bu), 71.71 (C-6), 71.47 (C-2), 69.48 (C-4b), 63.77 (C-7), 54.81 (C-4a), 39.34 (C-5), 28.16 (*t*-Bu); IR (film): ν 1773 cm^{-1}; HR MS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{12}H_{20}NO_4$: 242.1387. Found: 242.1398.

3.3.1.7. (1a*R*,4a*S*,4b*R*,6*S*)-6-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 17. Colorless crystals, mp 128–130 °C (benzene/hexane 1:1); $[\alpha]_D = +76.0$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.18 (1H, m, *J* 7.0, 6.3, 4.9, 3.7 Hz, H-6), 4.04 (1H, dd, *J* 6.6, 4.9 Hz, H-1a), 3.83 (1H, ddd, *J* 9.3, 8.4, 7.7 Hz, H-4b), 3.77 (1H, d, *J* 11.0 Hz, H-2′), 3.50 (1H, dd, *J* 14.5, 6.3 Hz, H-7), 3.30 (1H, dd, *J* 11.0, 4.9 Hz, H-2), 2.96 (1H, dd, *J* 14.5, 4.9 Hz, H-7′), 2.80 (1H, dd, *J* 9.3, 6.6 Hz, H-4a), 2.20 (1H, m, *J* = 13.6, 8.3, 7.0 Hz, H-5), 1.88 (1H, ddd, *J* 13.6, 7.7, 3.7 Hz, H-5′), 0.94 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 174.56 (C=O), 78.63 (C-1a), 73.26 (*C*–O*t*-Bu), 72.56 (C-6), 69.06 (C-2), 67.24 (C-4b), 63.72 (C-7), 52.32 (C-4a), 36.65 (C-5), 28.24 (*t*-Bu); IR (film): ν 1782 cm^{-1}; HR MS (ESI): *m*/*z* [M+Na^+] calcd $C_{12}H_{19}NO_4Na$: 264.1206. Found: 264.1219.

3.3.1.8. (1a*R*,4a*S*,4b*S*,6*R*)-6-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 15ent. Colorless crystals, mp 124–126 °C (benzene–hexane 1:1); $[\alpha]_D$ −48.3 (*c* 0.3, CH_2Cl_2); HR MS (EI): *m*/*z* calcd [M^+] $C_{12}H_{19}NO_4$: 241.13141. Found: 241.13106.

3.3.1.9. (1a*S*,4a*R*,4b*R*,6*R*)-6-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 16ent. Colorless crystals, mp 99–101 °C (benzene/hexane 1:1); $[\alpha]_D = +18.2$ (*c* 0.6, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{19}NO_4$: 241.13141. Found: 241.13094.

3.3.1.10. (1a*S*,4a*R*,4b*S*,6*R*)-6-*tert*-Butoxy-hexahydro-furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 17ent. Colorless crystals, mp 127–129 °C (benzene–hexane 1:1); $[\alpha]_D$ −74.5 (*c* 0.5, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{19}NO_4$: 241.13141. Found: 241.13177.

3.3.1.11. (1a*S*,4a*R*,4b*S*,5*S*,6*S*)-5,6-Di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 18. Colorless crystals, mp 103–105 °C (toluene/diethyl ether 1:1); $[\alpha]_D = +28.1$ (*c* 0.5, CH_2Cl_2); ^1H NMR: (500 MHz, C_6D_6): δ 4.35 (1H, dd, *J* 6.2, 4.3 Hz, H-1a), 3.98–3.93 (2H, m, H-4b, H-2′), 3.79 (1H, dd, *J* 3.9, 3.1 Hz, H-5), 3.71 (1H, m, *J* 5.7, 5.3, 3.9 Hz, H-6), 3.61 (1H, dd, *J* 10.7, 4.3 Hz, H-2), 3.45 (1H, dd, *J* 12.0, 5.7 Hz, H-7), 2.88 (1H, dd, *J* 6.2, 2.7 Hz, H-4a), 2.79 (1H, dd, *J* 12.0, 5.3 Hz, H-7′), 1.16 (9H, s, *t*-Bu), 0.97 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 176.09 (C═O), 82.34 (C-5), 77.21 (C-1a), 76.65 (C-6), 75.84 (C-4b), 74.22 (C–O, *t*-Bu), 73.74 (*C*–O*t*-Bu), 69.87 (C-2), 61.03 (C-7), 54.21 (C-4a), 28.74 (*t*-Bu), 28.30 (*t*-Bu); IR (film): *v* 1777 cm^{-1}; HR MS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{27}NO_5$: 313.18892. Found: 313.18789.

3.3.1.12. (1a*R*,4a*S*,4b*R*,5*S*,6*S*)-5,6-Di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 19. Colorless crystals, mp 123–125 °C (toluene/diethyl ether 2:1); $[\alpha]_D = +12.2$ (*c* 0.3, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.00 (1H, ddd, *J* 6.9, 5.1, 1.3 Hz, H-1a), 3.98–3.93 (2H, m, H-4b, H-2′), 3.90 (1H, m, *J* 8.9, 7.2, 6.3 Hz, H-6), 3.77 (1H, dd, *J* 7.5, 6.3 Hz, H-5), 3.52 (1H, dd, *J* 10.4, 5.1 Hz, H-2), 3.36 (1H, dd, *J* 6.9, 1.7 Hz, H-4a), 3.28 (1H, dd, *J* 14.0, 7.2 Hz, H-7′), 2.84 (1H, dd, *J* 14.0, 8.9 Hz, H-7), 1.08 (9H, s, *t*-Bu), 1.00 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175.80 (C═O), 77.69 (C-1a), 77.47 (C-5), 76.71 (C-6), 74.55 (*C*–O*t*-Bu), 73.15 (C–O, *t*-Bu), 71.57 (C4b) 71.37 (C-2), 60.47 (C-7), 50.20 (C-4a), 28.59 (*t*-Bu), 28.57 (*t*-Bu); IR (film): *v* 1777 cm^{-1}; HR MS (ESI): *m*/*z* [M+H^+] calcd for $C_{16}H_{28}NO_5$: 313.1962. Found: 314.1976.

3.3.1.13. (1a*R*,4a*S*,4b*R*,5*R*,6*R*)-5,6-Di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 18ent. Colorless crystals, mp 105–107 °C (toluene/diethyl ether 2:1); $[\alpha]_D$ −28.5 (*c* 0.7, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{27}NO_5$: 313.18892. Found: 313.18809.

3.3.1.14. (1a*S*,4a*R*,4b*S*,5*R*,6*R*)-5,6-Di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 19ent. Colorless crystals, mp 123–124 °C (toluene/diethyl ether 2:1); $[\alpha]_D$ −11.2 (*c* 0.2, CH_2Cl_2); HR MS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{27}NO_5$: 313.18892. Found: 313.18822.

3.3.1.15. (1a*S*,2*R*,4a*R*,4b*R*)-2-Hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 20. Colorless crystals, mp 77–80 °C (hexane/benzene 1:1); $[\alpha]_D = +10.5$ (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.50 (1H, d, *J* 7.1 Hz, H-1a), 4.41 (1H, m, H-2), 3.6 (1H, m, H-4b), 3.45 (1H, dd, *J* 12.3, 2.7 Hz, C*H*HOH), 3.22 (1H, dd, *J* 12.3, 2.5 Hz, CH*H*OH), 3.16 (1H, d, *J* 7.1 Hz, H-4a), 3.12 (1H, ddd, *J* 13.3, 7.7, 3.8 Hz, H-7), 2.68 (1H, m, H-7′), 1.69–1.58 (1H, m, H-6), 1.52–1.42 (1H, m, H-5), 1.27–1.10 (2H, m, H-5′, H-6′); ^{13}C NMR (125 MHz, C_6D_6): δ 176.96 (C═O), 85.81 (C-2), 78.87 (C-1a), 70.47 (C-4b), 62.42 (*C*H_2OH), 56.03 (C-7), 55.89 (C-4a), 29.88 (C-5), 24.23 (C-6); IR (film, CH_2Cl_2): *v* 3364, 1766 cm^{-1}; HR MS (EI): *m*/*z* [M^+] calcd for $C_9H_{13}NO_4$: 199.08446. Found: 199.08491.

3.3.1.16. (1a*R*,2*R*,4a*S*,4b*S*)-2-Hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 21. Colorless oil; $[\alpha]_D = -1.8$ (*c* 0.3, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 3.96 (1H, dd, *J* 7.9, 5.8 Hz, H-1a), 3.92–3.84 (3H, m, H-2, CH_2OH), 3.43 (1H, m, H-4b), 2.99 (1H, ddd, *J* 14.1, 7.9, 3.3 Hz, H-7′), 2.55 (1H, d, *J* 7.9 Hz, H-4a), 2.33 (1H, dt, *J* 14.1, 8.7, 8.7 Hz, H-7), 1.57–1.50 (1H, m, H-6), 1.33–1.23 (1H, m, H-5′), 1.08–1.00 (1H, m, H-6), 0.95–0.88 (1H, m, H-5); ^{13}C NMR (125 MHz, C_6D_6): δ 174.48 (C═O), 82.63 (C-2), 76.89 (C-1a), 70.50 (C-4b), 60.37 (*C*H_2OH), 55.76 (C-7), 54.72 (C-4a), 29.57 (C-5), 24.01 (C-6); IR (film): *v* 3379, 1770 cm^{-1}; HR MS (EI): *m*/*z* [M^+] calcd for $C_9H_{13}NO_4$: 199.08446. Found: 199.08463.

3.3.1.17. (1a*S*,2*R*,4a*R*,4b*S*,5*S*)-5-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 22. Colorless oil; $[\alpha]_D = +19.0$ (*c* 0.9, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.58 (1H, dd, *J* 7.0, 1.1 Hz, H-1a), 4.33 (1H, m, *J* 2.9, 2.5, 1.3 Hz, H-2), 3.86 (1H, dd, *J* 7.0, 1.5 Hz, H-4a), 3.81 (1H, dd, *J* 7.3, 1.3 Hz, H-4b), 3.64 (1H, m, *J* 7.3, 7.1, 5.9 Hz, H-5), 3.22 (1H, dd, *J* 12.2, 2.9 Hz, C*H*HOH), 3.19 (1H, ddd, *J* 13.1, 7.7, 3.5 Hz, H-7′), 3.00 (1H, dd, *J* 12.2, 2.5 Hz, CH*H*OH), 2.63 (1H, ddd, *J* 13.2, 10.0, 7.1 Hz, H-7), 1.73 (1H, dddd, *J* 12.7, 10.0, 7.7, 5.9 Hz, H-6′), 1.50 (1H, m, *J* 12.7, 7.1, 7.1, 3.5 Hz, H-6), 0.96 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 177.89 (C═O), 85.02 (C-2), 80.28 (C-1a), 73.93 (*C*–O*t*-Bu), 73.74 (C-4b), 71.58 (C-5), 62.50 (*C*H_2OH), 53.30 (C-7), 51.74 (C-4a), 34.12 (C-6), 28.15 (*t*-Bu); IR (film): *v* 3452, 1770 cm^{-1}; HR MS (ESI): *m*/*z* [M+H^+] calcd for $C_{13}H_{22}NO_5$: 272.1492. Found: 272.1499.

3.3.1.18. (1a*R*,2*R*,4a*S*,4b*R*,5*S*)-5-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 23. Colorless crystals, mp 112–113 °C (benzene/diethyl ether 3:1); $[\alpha]_D = -4.7$ (*c* 0.7, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 4.99 (1H, dd, *J* 8.1, 6.4 Hz, H-1a), 4.64 (1H, ddd, *J* 6.4, 4.9, 3.3 Hz, H-2), 4.03–4.00 (2H, m, C*H*HOH, H-5), 3.95 (1H, dd, *J* 12.5, 4.9 Hz, CH*H*OH), 3.79 (1H, br d, *J* 5.0 Hz, H-4b), 3.62 (1H, br d, *J* 8.1 Hz, H-4a), 3.42 (1H, ddd, *J* 14.3, 8.0, 3.1 Hz, H-7), 3.35 (1H, m, *J* 14.3, 9.5, 8.0 Hz, H-7′), 2.34 (1H, m, *J* 13.3, 9.5, 8.0, 7.7 Hz, H-6), 1.74 (1H, m, *J* 13.3, 8.0, 3.3, 3.1 Hz, H-6′), 1.21 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 174.50, 82.55, 77.71, 74.03, 60.38, 60.03, 54.86, 53.49, 33.47, 29.70, 28.51; IR (film): *v* 3401, 1771 cm^{-1}; HR MS (ESI): *m*/*z* [M+H^+] calcd for $C_{13}H_{22}NO_5$: 272.1492. Found: 272.1479.

3.3.1.19. (1a*S*,2*R*,4a*R*,4b*R*,5*S*)-5-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 24. Colorless crystals, mp 109–111 °C (toluene); $[\alpha]_D = -25.6$ (*c* 0.9, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.85 (1H, br d, *J* 5.8 Hz, H-5), 4.36 (1H, d, *J* 5.7 Hz, H-1a), 4.07 (1H, dd, *J* 2.7, 2.3 Hz, H-2), 3.89 (1H, br d, *J* 10.6 Hz, H-4b), 3.52 (1H, dd, *J* 10.6, 5.7 Hz, H-4a), 3.31 (1H, ddd, *J* 13.3, 6.8, 1.7 Hz, H-7′), 3.22–3.15 (2H, m, H-7, C*H*HOH), 2.94 (1H, dd, *J* 12.0, 2.3 Hz, CH*H*OH), 2.07 (1H, m, *J* 13.0, 11.7, 6.8, 5.9 Hz, H-6), 1.57 (1H, ddd, *J* 13.0, 5.6, 2.0 Hz, H-6′),

1.19 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175.6 (C=O), 81.31 (C-1a), 81.03 (C-2), 77.72 (C-4b), 74.3 (*C*–O*t*-Bu), 72.00 (C-5), 62.34 (*C*H_2OH), 55.18 (C-7), 52.51 (C-4a), 33.4 (C-6), 28.4 (*t*-Bu); IR (film): ν 3616, 1766 cm^{-1}; HR MS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{13}H_{22}NO_5$: 272.1492. Found: 272.1482.

3.3.1.20. (1a*S*,2*R*,4a*R*,4b*S*,5*R*)-5-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 25. Colorless crystals; mp 68–70 °C (benzene); $[\alpha]_D = +39.0$ (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.82 (1H, dd, *J* 7.0, 1.0 Hz, H-1a); 4.58 (1H, m, *J* 2.6, 2.4, 1.0 Hz, H-2), 4.09 (1H, ddd, *J* 7.5, 4.4, 3.9 Hz, H-5), 3.95 (1H, dd, *J* 12.4, 2.6 Hz, C*H*HOH), 3.78 (1H, dd, *J* 12.4, 2.4 Hz, CH*H*OH), 3.75 (1H, br d, *J* 4.4 Hz, H-4b), 3.61 (1H, d, *J* 7.0 Hz, H-4a), 3.45–3.30 (2H, m, H-7, H-7′), 2.57 (1H, br s, OH), 2.31 (1H, m, H-6), 1.75 (1H, m, H-6′), 1.21 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 176.19 (C=O), 85.04 (C-2), 78.77 (C-1a), 78.36 (C-4b), 77.38 (C-5), 73.51 (*C*–O*t*-Bu), 62.40 (*C*H_2OH), 54.72 (C-7), 54.67 (C-4a), 33.88 (C-6), 28.49 (*t*-Bu); IR (film): ν 3426, 1769 cm^{-1}; HR MS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{21}NO_5$: 271.1497. Found: 271.14191.

3.3.1.21. (1a*R*,2*S*,4a*S*,4b*R*,5*S*)-5-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 25ent. A solution of **24** (0.014 g, 0.052 mmol) in toluene (5 mL) was refluxed for 24 h. After this time, the solvent was evaporated and residue was purified by column chromatography using ethyl acetate/hexane 2:1 v/v as an eluent giving 1 mg of **23**, 3 mg of **25ent**, and 8 mg of the substrate **24**; $[\alpha]_D = -31.6$ (*c* 0.1, CH_2Cl_2); HR MS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{21}NO_5$ 271.1497. Found 271.14076.

3.3.1.22. (1a*S*,2*R*,4a*R*,4b*S*,5*S*,6*S*)-2-Hydroxymethyl-5,6-di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-2(3*H*)-one 26. Colorless crystals, mp 148–150 °C (benzene/hexane 1:1); $[\alpha]_D = +22.7$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.86 (1H, d, *J* 6.0 Hz, H-1a), 4.37 (1H, m, *J* 2.5, 2.2 Hz, H-2), 4.04 (1H, dd, *J* 2.9, 2.5 Hz, H-4b), 3.91 (1H, dd, *J* 3.8, 2.5 Hz, H-5), 3.78 (1H, ddd, *J* 5.5, 5.2, 3.7 Hz, H-6), 3.69 (1H, dd, *J* 6.0, 2.9 Hz, H-4a), 3.64 (1H, br dd, *J* 12.0, 2.5 Hz, C*H*HOH), 3.58 (1H, dd, *J* 12.1, 5.5 Hz, H-7), 3.34 (1H, br d, *J* 12.0 Hz, CH*H*OH), 1.54 (1H, dd, *J* 12.1, 5.2 Hz, H-7′), 1.18 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu); ^{13}C NMR: (125 MHz, C_6D_6): δ 177. 60 (C=O), 82.75 (C-2), 82.27 (C-5), 80.73 (C-1a), 76.49 (C-6), 76.04 (C-4b), 62.35 (*C*H_2OH), 61.28 (C-7), 60.12 (*C*–O*t*-Bu), 55.82 (C-4a), 28.68 (*t*-Bu), 28.26 (*t*-Bu); IR (film): ν 3430, 1774 cm^{-1}; HR MS (ESI): *m*/*z* [M$^+$] calcd for $C_{17}H_{29}NO_6$: 343.19949. Found: 343.198595.

3.3.1.23. (1a*R*,2*R*,4a*S*,4b*R*,5*R*,6*R*)-2-Hydroxymethyl-5,6-di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 27. Colorless oil; $[\alpha]_D = -38.6$ (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.34 (1H, dd, *J* 6.8, 5.0 Hz, H-1a), 4.06 (1H, ddd, *J* 5.5, 5.0, 4.9 Hz, H-2), 3.91 (1H, dd, *J* 4.2, 2.2 Hz, H-4b), 3.83 (1H, dd, *J* 12.2, 5.5 Hz, C*H*HOH), 3.78 (2H, m, H-5, CH*H*OH), 3.68 (1H, ddd, *J* 6.0, 4.7, 4.0 Hz, H-6), 3.26 (1H, dd, *J* 13.0, 6.0, H-7), 2.98 (1H, dd, *J* 6.8, 2.2 Hz, H-4a), 2.84 (1H, dd, *J* 13.0, 4.7 Hz, H-7′), 2.45 (1H, br s, OH), 1.14 (9H, s, *t*-Bu), 0.93 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175.03 (C=O), 82.5 (C-5), 81.34 (C-2), 77.70 (C-6), 77.32 (C-1a), 72.23 (C-4b), 74.16 (*C*–O*t*-Bu), 73.32 (C–O, *t*-Bu), 61.25 (C-7), 60.57 (*C*H_2OH), 55.00 (C-4a), 28.87 (*t*-Bu), 28.30 (*t*-Bu); IR (film): ν 3421, 1775 cm^{-1}; HR MS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{29}NO_6$: 343.19949. Found: 343.20003.

3.3.1.24. (1a*S*,2*R*,4a*R*,4b*S*,5*R*,6*R*)-2-Hydroxymethyl-5,6-di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 28. Colorless crystals, mp 140–142 °C (benzene/hexane 1:2); $[\alpha]_D = -8.8$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.57 (1H, dd, *J* 7.0, 1.1 Hz, H-1a), 4.29 (1H, m, *J* 2.9, 2.4, 1.3 Hz, H-2), 4.09–4.00 (2H, m, H-6, H-4b), 3.91 (1H, dd, *J* 7.0, 1.8 Hz, H-4a), 3.85 (1H, dd, *J* 7.2, 6.4 Hz, H-5), 3.39 (1H, dd, *J* 13.8, 7.0 Hz, H-7′), 3.23 (1H, dd, *J* 12.2, 2.9 Hz, C*H*HOH), 3.03 (1H, dd, *J* 12.2, 2.4 Hz, CH*H*OH), 2.89 (1H, dd, *J* 13.8, 8.6 Hz, H-7), 1.09 (9H, s, *t*-Bu), 0.99 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 177.00 (C=O), 83.84 (C-2), 80.59 (C-1a), 77.48 (*C*–O*t*-Bu), 77.51 (C-5), 76.83 (C-4b), 71.63 (C-6), 62.38 (*C*H_2OH), 60.50 (C-7), 51.62 (C-4a), 28.55 (*t*-Bu), 28.53 (*t*-Bu); IR (film): ν 3426, 1774 cm^{-1}; HR MS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{29}NO_6$: 343.19949. Found: 343.20062.

3.3.1.25. (1a*S*,2*R*,4a*R*,4b*R*,5*R*,6*R*)-2-Hydroxymethyl-5,6-di-*tert*-butoxy-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 29. Colorless oil; $[\alpha]_D = -32.5$ (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 5.00 (1H, dd, *J* 3.0, 1.1 Hz, H-5), 4.19 (1H, dd, *J* 2.8, 2.3 Hz, H-2), 4.00 (1H, ddd, *J* 4.7, 4.5, 3.0 Hz, H-6), 3.84 (1H, dd, *J* 10.3, 1.0 Hz, H-4b), 3.40 (1H, dd, *J* 12.0, 4.7 Hz, H-7), 3.36 (1H, dd, *J* 10.3, 6.1 Hz, H-4a), 3.22 (1H, dd, *J* 12.0, 4.5 Hz, H-7′), 3.12 (1H, dd, *J* 12.0, 2.8 Hz, C*H*HOH), 2.88 (1H, dd, *J* 12.0, 2.3 Hz, CH*H*OH), 1.25 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu); IR (film): ν 3413, 1764 cm^{-1}; HR MS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{29}NO_6$: 343.19949. Found: 343.20039.

3.3.1.26. (1a*R*,2*R*,4a*S*,4b*S*,6*S*)-6-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-2-(3*H*)one 30. Colorless oil; $[\alpha]_D = -22.0$ (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.18 (1H, dd, *J* 7.6, 5.8 Hz, H-1a), 3.98 (1H, ddd, *J* 5.7, 4.9, 4.2 Hz, H-2), 3.92 (1H, dd, *J* 12.2, 4.2 Hz, C*H*HOH), 3.87 (1H, dd, *J* 12.2, 4.9 Hz, CH*H*OH), 3.62 (1H, m, H-4b), 3.59 (1H, dddd, *J* 9.7, 7.2, 7.1, 3.7 Hz, H-6), 3.13 (1H, br s, OH), 3.05 (1H, dd, *J* 14.6, 3.7 Hz, H-7′), 2.89 (1H, dd, *J* 14.6, 7.1 Hz, H-7), 2.73 (1H, d, *J* 7.6 Hz, H-4a), 1.65 (1H, dt, *J* 13.0, 7.2, 7.2 Hz, H-5), 1.42 (1H, ddd, *J* 13.0, 9.4, 6.3 Hz, H-5′), 0.93 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175.04 (C=O), 82.41 (C-2), 76.93 (C-1a), 73.28 (*C*–O*t*-Bu), 72.68 (C-5), 69.35 (C-4b), 63.42 (C-7), 60.44 (*C*H_2OH), 54.74 (C-4a), 39.06 (C-5), 28.30 (*t*-Bu); IR (film): ν 3379, 1772 cm^{-1}; HR MS (ESI): *m*/*z* [M+Na$^+$] calcd for $C_{13}H_{21}NO_5Na$: 294.1312. Found: 294.1325.

3.3.1.27. (1a*S*,2*R*,4a*R*,4b*R*,6*S*)-6-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-4(3*H*)-one 31. Colorless plates, mp 114–116 °C (benzene/diethyl ether 4:1); $[\alpha]_D = +77.3$ (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 4.80 (1H, br d, *J* 7.3 Hz, H-1a), 4.59 (1H, m, *J* 2.6, 2.4, 1.2 Hz, H-2), 4.47 (1H, m, *J* 7.1, 6.7, 6.1, 4.5 Hz, H-6), 4.02 (1H, t, *J* 8.1, 8.0 Hz, H-4b), 3.91 (1H, dd, *J* 12.5, 2.6 Hz, C*H*HOH), 3.72 (1H, dd, *J* 12.5, 2.4 Hz, CH*H*OH), 3.58 (1H, dd, *J* 14.6, 6.7 Hz, H-7), 3.45 (1H, d, *J* 7.3 Hz, H-4a), 2.94 (1H, dd, *J* 14.6, 6.1 Hz, H-7′), 2.04–1.92 (2H, m, H-5, H-5′), 1.16 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 176.84 (C=O), 86.36 (C-2), 78.76 (C-1a), 73.13 (*C*–O*t*-Bu), 72.58 (C-6), 69.74 (C-4b), 64.27 (C-7), 62.43 (*C*H_2OH), 55.37 (C-4a), 394.22 (C-5), 28.30 (*t*-Bu); IR (film): *v* 3402, 1768 cm^{-1}; HR MS (ESI): *m*/*z* calcd $[M+H^+]$ $C_{13}H_{22}NO_5$: 272.1492. Found: 272.1497.

3.3.1.28. (1a*R*,2*R*,4a*R*,4b*R*,6*R*)-6-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-2(3*H*)-one 32. Colorless crystals, mp 147–149 °C (benzene/hexane 1:1); $[\alpha]_D = +21.3$ (*c* 0.2, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.60 (1H, d, *J* 6.6 Hz, H-1a), 4.27 (1H, br t, *J* 3.0, 2.3 Hz, H-2), 3.83 (1H, dt, *J* 7.2, 6.5, 1.8 Hz, H-4b), 3.59 (1H, m, *J* 12.2, 6.0, 3.8, H-6), 3.25 (1H, dd, *J* 6.7, 1.8 Hz, H-4a), 3.19 (1H, br d, *J* 12.2 Hz, C*H*HOH), 3.14 (1H, dd, *J* 13.9, 6.4 Hz, H-7), 3.08 (1H, dd, *J* 13.9, 3.7 Hz, H-7′), 2.97 (1H, br d, *J* 12.2, CH*H*OH), 1.67 (1H, m, H-5), 1.54 (1H, m, H-5′), 0.94 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.42 (C=O), 83.00 (C-2), 81.00 (*C*–O*t*-Bu), 74.44 (C-1a), 70.69 (C-6), 69.46 (C-4b), 64.15 (C-7), 62.51 (*C*H_2OH), 56.22 (C-4a), 39.47 (C-5), 28.22 (*t*-Bu); IR (film): *v* 3419, 1769 cm^{-1}; HR MS (EI): *m*/*z* $[M^+]$ calcd for $C_{13}H_{21}NO_5$: 271.14197. Found: 271.14077.

3.3.1.29. (1a*S*,2*R*,4a*R*,4b*S*,6*R*)-6-*tert*-Butoxy-2-hydroxymethyl-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-2(3*H*)-one 33. Colorless crystals, mp 113–115 °C (benzene/hexane 1:1); $[\alpha]_D = -84.4$ (*c* 0.1, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 4.47 (d, 1H, *J* 6.5 Hz, H-1a), 4.22 (ddt, 1H, *J* 3.8, 4.8, 6.3, 6.8 Hz, H-6), 4.13 (t, 1H, *J* 2.4, 2.8 Hz, H-2), 3.91 (br q, 1H *J* 8.3, 8.4, 9.4 Hz, H-4b), 3.55 (dd, 1H, *J* 6.3, 14.5 Hz, H-7), 3.46 (dd, 1H, *J* 6.5, 9.4 Hz, H-4a), 3.20 (dd, 1H, *J* 2.8, 12.1 Hz, C*H*HOH), 3.02 (dd, 1H, *J* 4.9, 14.5 Hz, H-7′), 2.96 (dd, 1H, *J* 2.4, 12.1 Hz, CH*H*OH), 2.26 (ddd, 1H, *J* 6.8, 8.3, 13.6 Hz, H-5), 1.92 (ddd, 1H, *J* 3.8, 7.8, 13.6 Hz, H-5′), 0.96 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 175.33 (C=O), 81.58 (C-1a), 81.31 (C-2), 73.29 (*C*–O*t*-Bu), 72.61 (C-6), 67.26 (C-4b), 63.75 (C-7), 62.61 (*C*H_2OH), 53.84 (C-4a), 36.75 (C-5), 28.25 (*t*-Bu); IR (film): *v* 3210, 1763 cm^{-1}; HR MS (ESI): *m*/*z* $[M+H^+]$ calcd for $C_{13}H_{22}NO_5$: 272.14925. Found: 272.15000.

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20. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center, Cambridge, UK, as a supplementary publications: **13** (CCDC 282892), **15** (CCDC 282893), **16** (CCDC 282896), **24** (CCDC 282895), **26** (CCDC 282897), **31** (CCDC 282894).