



Account/Revue

Synthesis of iminosugars *via* 1,3-dipolar cycloaddition reactions of nitrones to α,β -unsaturated sugar aldonolactones

Sebastian Stecko, Margarita Jurczak, Irma Panfil, Bartłomiej Furman, Barbara Grzeszczyk, Marek Chmielewski*

Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland

ARTICLE INFO

Article history:

Received 23 February 2010

Accepted after revision 27 September 2010

Available online 3 December 2010

Dedicated to Professor Alberto Brandi on the occasion of his 60th birthday.

Keywords:

1,3-dipolar cycloadditions

Nitrones

α,β -unsaturated lactones

Iminosugars

Piperidines

Pyrrrolizidines

Indolizidines

ABSTRACT

1,3-Dipolar cycloaddition reactions of nitrones to α,β -unsaturated γ - and δ -lactones are presented. The special emphasis is placed on cycloadditions involving five-membered nitrones. Contrary to the additions involving δ -lactones, where only the *exo* approach of reactants is observed providing in many cases a single product, γ -lactones can add five-membered ring nitrones in both *exo* and *endo* mode. Moreover, in the case of γ -lactones, upon heating and prolongation of the reaction time, visible reversibility of the reaction is observed and, as the consequence, the formation of more stable, thermodynamic products is noticed. The energies of the 1,3-dipolar cycloaddition of cyclic nitrones with α,β -unsaturated lactones have been investigated through molecular orbital calculations to reproduce well the observed experimental facts. The usefulness of adducts obtained *via* cycloaddition reactions to the iminosugars synthesis is demonstrated by a large number of examples, since both components usually offer good regio- and stereoselectivity with the introduction of convenient functionalities. The strategy involves hydrogenolysis of the N–O bond followed by the construction of the desired iminosugar skeleton *via* intramolecular alkylation of the nitrogen atom.

© 2010 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

The low-molecular weight carbohydrates are convenient substrates for the stereocontrolled synthesis of natural products, owing to the fact that they are inexpensive, enantiomerically pure, and available in many structural and configurational forms [1]. Since they bear many hydroxy groups of similar reactivity, possess too many stereogenic centers and do not have double bonds, they are usually transformed into simpler compounds where the above inconveniences are minimized while the merits of monosaccharides are fully retained. The α,β -unsaturated lactones **1–6**, readily available from monosaccharides, represent particularly attractive compounds

for organic synthesis owing to the presence of the electrophilic en-one fragment and only one or two stereogenic centers that are well defined (Fig. 1) [2,3].

Many structurally diverse polyhydroxylated alkaloids have been isolated from natural sources such as plants or microorganisms. An apparent common structural feature of this group is a nitrogen-containing four- (azetidene), five- (pyrrolidine) or six-membered (piperidine) ring, or a related fused-ring system (pyrrolizidine, indolizidine, and quinolizidine) built up from the above monocycles, substituted with one or more hydroxyl groups (Fig. 2) [4–16]. The structural similarity of these compounds to monosaccharides, is reflected in the fact that they are also called iminosugars, and they have interesting biological activities, typically presented by the selective inhibition of glycosidases. Consequently, the iminosugars show antibacterial, antiviral, antitumor, or antidiabetic activities [4–15]. Therefore, the synthesis of iminosugars and their analogues

* Corresponding author.

E-mail address: chmiel@icho.edu.pl (M. Chmielewski).

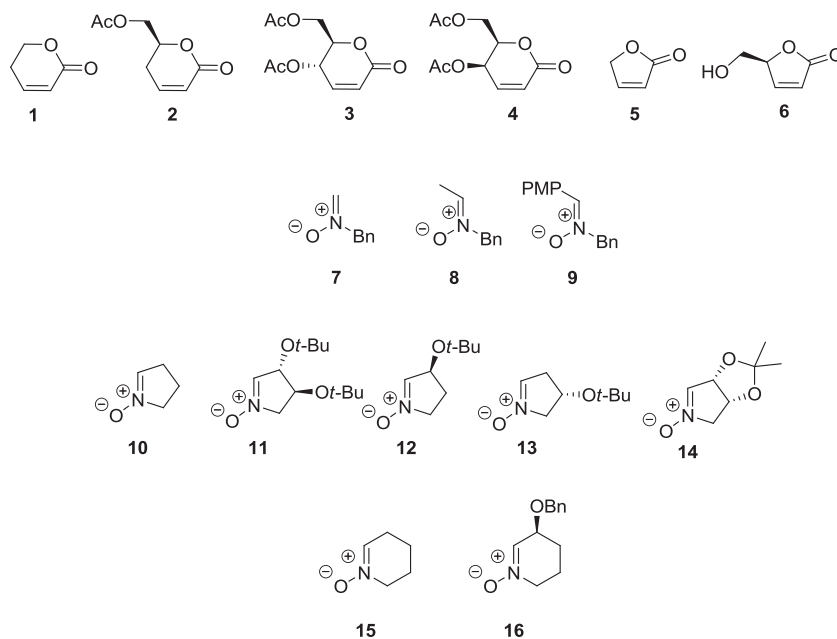


Fig. 1.

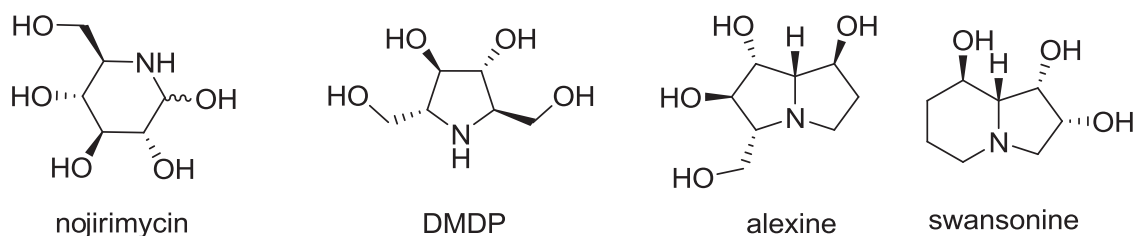


Fig. 2.

has attracted the attention of many academic and pharmaceutical laboratories including our group [4–26].

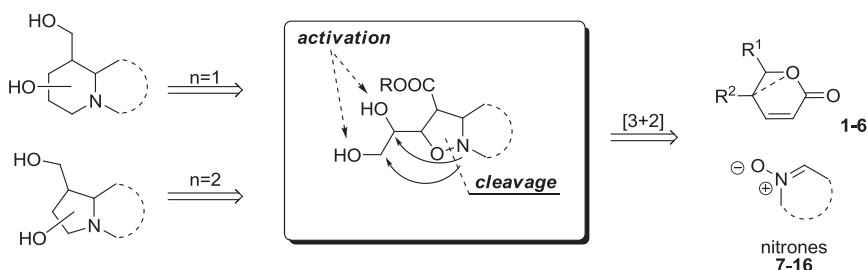
For over 10 years our laboratory has been involved in the elaboration of the methodology of the iminosugar synthesis utilizing the unsaturated lactones **1–6** (Fig. 1) [17–26].

The present account focuses on the stereochemistry of the 1,3-dipolar cycloaddition of open-chain **7–11** [27], five-membered **10–14** [10,28a,29], and six-membered cyclic nitrones **15** [28b] and **16** [30] to both δ - (**1–4**) and γ -lactones (**5**, **6**). Furthermore, we have researched the criteria for the rational selection of cycloaddition components in order to construct the desired structure and exercise full control over the configuration of the formed cycloadduct. Lastly, we wanted to provide a suitable demonstration of an application of this methodology in the synthesis of selected iminosugars. Special emphasis was placed on cycloadditions involving the five-membered ring nitrones **10–13**.

Isoxazolidines, readily available from olefins and nitrones *via* the 1,3-dipolar cycloaddition, represent particularly attractive starting materials for the synthesis of a variety of iminosugars that exhibit biological activity

[27,31,32]. The usefulness of the isoxazolidine approach to the iminosugars has been demonstrated by a large number of reported examples, since nitrones usually offer good regio- and stereoselectivity with the introduction of convenient functionalities [27,31,32]. The strategy usually involves hydrogenolysis of the N–O bond followed by the construction of the iminosugar skeleton *via* intramolecular alkylation or acylation of the nitrogen atom (Scheme 1) [33]. It should be noted, however, that the unsaturated chiral lactones are particularly attractive substrates in the synthesis of iminosugars since, in contrast to their acyclic congeners, they often provide a single adduct and they introduce stereogenic centers bearing the hydroxyl groups that the target molecule requires.

The present approach has an additional advantage, which makes it a powerful method for the iminosugars' synthesis. As is demonstrated in Scheme 1, the intramolecular alkylation step can be easily controlled by a suitable activation of the available hydroxyl function, which eventually leads to the formation of either a pyrrolidine or piperidine ring. Depending on the type of nitrone, acyclic or cyclic, the strategy allows formation of monocyclic or bicyclic iminosugars.



Scheme 1.

2. Synthesis of enantiopure α,β -unsaturated lactones

An unsaturated δ -lactone fragment can be found in many natural products (Fig. 3), both simple such as parasorbic acid (**17**) [34] and osmunda lactone (**18**) [35], and even structurally more complex, such as anamarine (**19**) [36] and boronolide (**20**) [37]. Butenolides (unsaturated γ -lactones) [38] can also be found as fragments of many natural products (Fig. 3) such as isocladospolide (**21**) [39], corrosolin, (**22**) [40] and (–)-incrustoporin (**23**) [41].

In 1977, we proposed [2] a general, two-step methodology for the synthesis of δ -lactones **2–4**. The method consists in the oxidation of the acetal center in 2,3-unsaturated glycosides **24** and **25** with hydrogen peroxide in the presence of molybdenum trioxide leading to the anomeric hydroperoxides **26** and **27**. The subsequent elimination of water, using an acetic anhydride/pyridine mixture (Scheme 2) [2], leads to the final unsaturated lactone **2–4**. Anomeric oxidation of the glycosides **24** and **25** and their other *O*-substituted derivatives can also be performed using hydrogen peroxide in dioxane in the presence of sulphuric acid [42,43].

The racemic compound **rac-2** can be easily obtained from the Diels-Alder adduct of butyl glyoxalate and methoxybutadiene by a reaction sequence which consists of the reduction of the ester group, protection of the hydroxyl group and anomeric oxidation as reported above [2,44].

The *D*-glycero-lactone **2** can be easily obtained from the *D*-erythro-lactone **3** by deoxygenation of the allylic position, followed by the migration of the double bond under the influence of an organic base [45]. It should be noted, as well, that the configuration of the C-5 carbon atom in lactones **3**

and **4** can be reversed by a sequence of reactions which consist of opening of the lactone ring followed by the ring closure under Mitsunobu conditions [46].

In 1982, Lichtenthaler et al. [3] reported the direct oxidation of the glycols **28** with a 3-*O*-acyl substituent to the corresponding α,β -unsaturated δ -lactones **29** using anhydrous *m*-chloroperbenzoic acid in the presence of BF_3 /etherate. It has been shown that the oxidation proceeds *via* anomeric *m*-chloroperbenzoate esters. Lichtenthaler's method [3] appears to have a general value and can be applied to the 2-substituted glycols as well. The one-step oxidation of glycols [3] seems to be superior to the stepwise transformation proposed by us [2]. In the case of lactones bearing different substituents at the O-4 and O-6 oxygen atoms, however, the hydrogen peroxide method, which uses inexpensive reagents, offers certain advantages over the commonly used Lichtenthaler's [3] procedure. Numerous other methods of transformation of simple carbohydrates into the δ -enlactones [47], or formation of such lactones from a non-carbohydrate precursor are known [48].

The unsubstituted butenolide (**5**) and (*S*)-5-hydroxymethyl-(5*H*)-furan-2-one (**6**) and its *O*-substituted derivatives represent also valuable chiral starting materials for the synthesis of a variety of natural products [39,49]. Both compounds **5** and **6** are commercially available and can be easily obtained by several methods [50–52].

3. 1,3-Dipolar cycloaddition of open-chain nitrones to δ and γ -lactones

Earlier we have shown [53] that the cycloaddition of nitrones derived from formaldehyde (**7**) or acetaldehyde

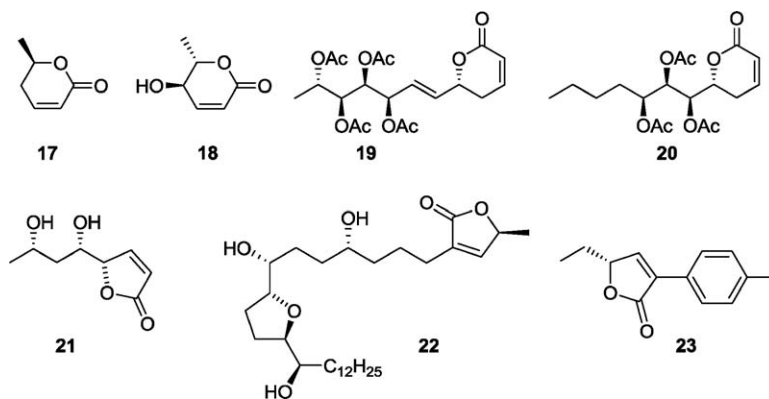
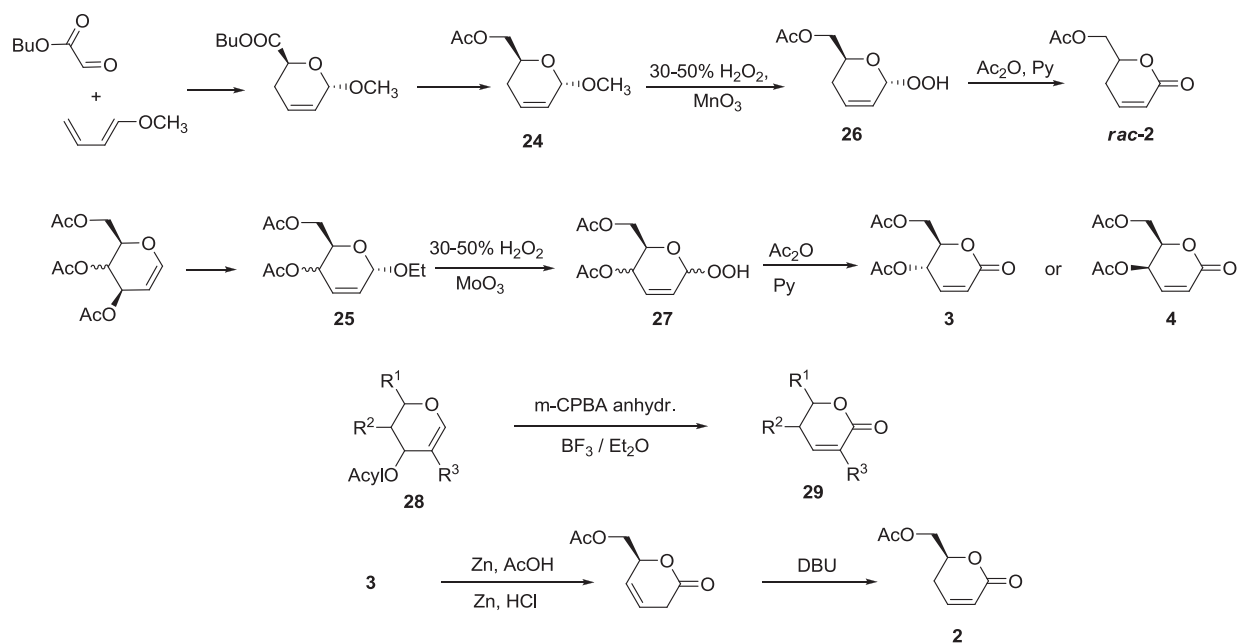


Fig. 3.



Scheme 2.

(**8**) to the sugar enlactones **2** and **4** proceeded with a high regio- and stereoselectivity to yield exclusively *anti*, or *endo-anti* adducts, respectively (Scheme 3) [53]. Such high stereoselectivity is noteworthy, particularly since the less reactive nitrones with aromatic substituents when reacted with the same dipolarophiles gave mixtures of *exo* and *endo* adducts with significant preference for the *exo* one. The *exo* preference can be attributed to the interaction of the aromatic substituent of the nitron with an electrophilic ester carbonyl group. The high preference of the *anti* addition to the terminal substituent of δ -lactone is a result of the axial approach phenomenon [54] of the nitron oxygen atom to the conformationally stabilized dihydropyranone ring. This stereochemical pathway of cycloaddition is probably a consequence of the more advanced formation of the C–O bond of the cycloadduct than the C–C one [53]. In the case of γ -lactones, the *anti* preference can be explained by steric interaction of the terminal substituent of the lactone with the entering nucleophile, while the *exo-endo*-selectivity is controlled by the same factors as for δ -lactones (Scheme 3) [55].

4. 1,3-Dipolar cycloaddition reactions of cyclic nitrones to unsaturated lactones

To expand our studies on 1,3-dipolar cycloadditions involving unsaturated lactones, we directed our attention towards the use of cyclic nitrones **10–16** in these reactions [56–62]. The attractiveness of cyclic dipoles as synthons in a target-oriented synthesis has been proven repeatedly [10,27,31,63]. We expected that the combination of both cyclic components should lead to a high stereoselectivity of the cycloaddition and, as depicted in Scheme 1, should also provide an attractive entry to the stereocontrolled

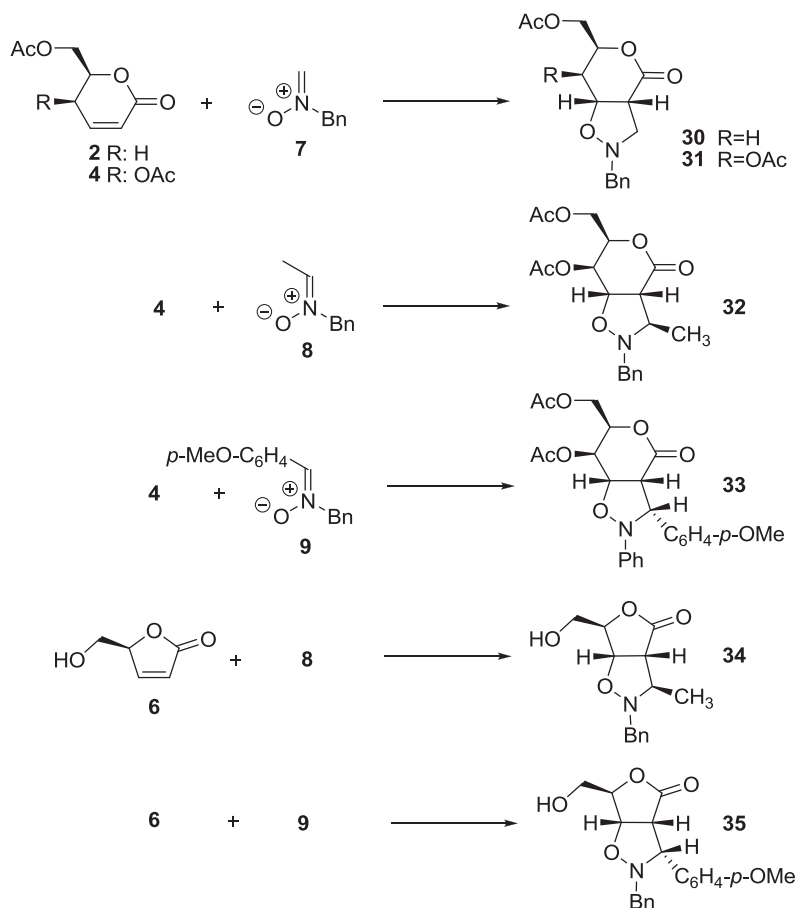
synthesis of polyhydroxylated azabicycloalkanes with a potential bioactivity [17–26].

4.1. Cycloaddition involving δ -lactones

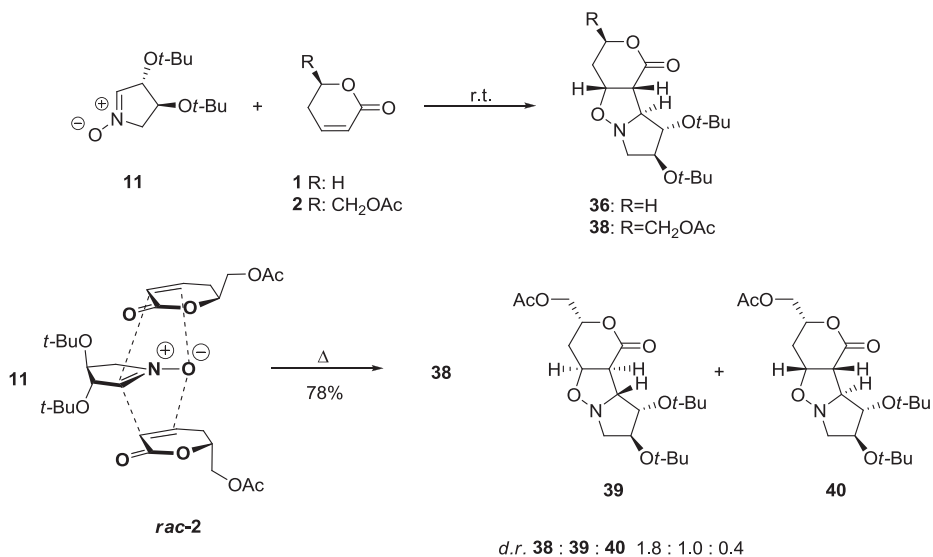
The cycloaddition reactions between chiral five-membered nitrones and γ - and δ -lactones provides an interesting example of single or double asymmetric induction, where the chirality elements of each reactant may influence stereoselectivity either in concert or in opposition. To reach the consistent picture of these reactions, we decided to include both the non-chiral nitron **10**, chiral **11–13**, and racemic **rac-14**, as well as non-chiral lactones **1** and **5**, racemic *D,L*-glycero **rac-2**, *D*-glycero **2**, *D*-erythro **3**, and *D*-threo **4** lactones [56–58].

Due to the significant steric hindrance of the 3-*t*-butoxy substituent, the lactone **1** reacts with nitron **11** to give almost the pure adduct **35** in a high yield as a result of the *exo* approach of the dipole to the *re-re* side of the dipolarophile (Scheme 4) [57]. A similar high stereoselectivity was observed for the cycloaddition of lactone **1** and nitron **12** to afford **37** (Scheme 5). In both cases, the lactone molecule approaches the nitron *anti* to the 3-*t*-butoxy group [58].

Introduction of chirality elements to both reactants influences the stereoselectivity, depending upon whether they constitute a matched or a mismatched pair. The nitron **11** with *D*-glycero lactone **2**, a matched pair, at room temperature produces a single product **38**. On the other hand, the nitron **11** with the racemate **rac-2**, under the reflux leads to a mixture of three adducts **38**, **39**, and **40**. The last two of which are obtained from *L*-glycero lactone **2ent**. The stereochemical relation of **11** and **rac-2** is illustrated by a significant kinetic resolution of the racemate in the reaction of two molar equivalents of the



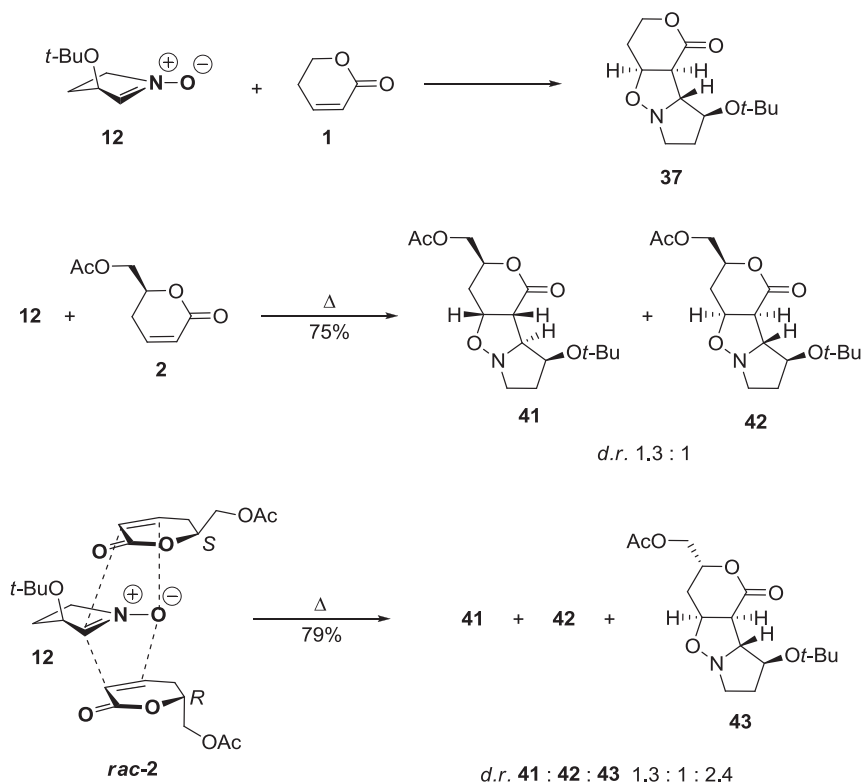
Scheme 3.



Scheme 4.

lactone **rac-2** with the nitrones **11** and **12** at room temperature. Since the *l*-glycero lactone **2ent** (Scheme 4) is less reactive, it can be isolated with 77.4% *e.e.* (86%) [57]. An analogous situation is observed in the case of the

reaction of **12** with *D*-glycero **2** and the *D,L*-glycero lactones **rac-2**. Reactants **12** and **2**, the mismatched pair, under reflux afford two adducts **41** and **42** in a ratio of about 1.3:1. Reaction between **12** and the racemic lactone **rac-2**



Scheme 5.

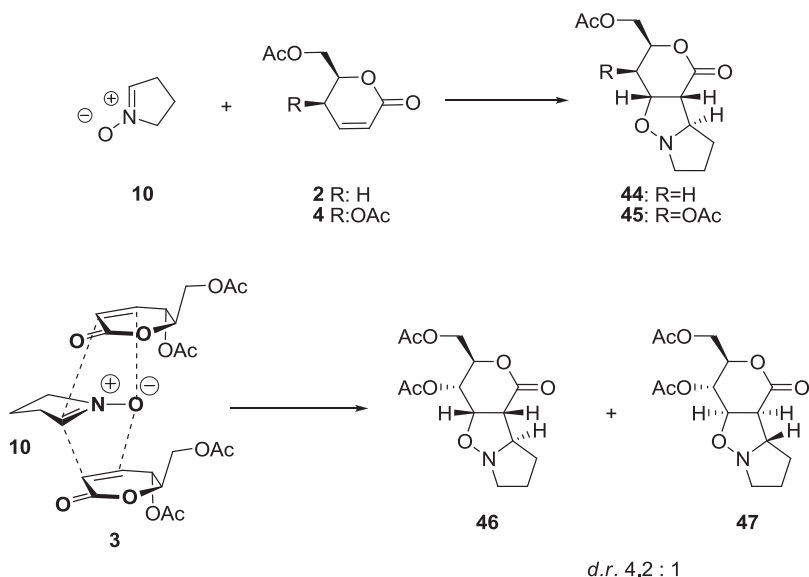
under reflux gives three products **41**, **42**, and **43** in a ratio of about 1.3:1:2.4. At room temperature, a significant kinetic resolution is observed. The *D*-glycero lactone **2** (Scheme 5) is less reactive and could be isolated unreacted in a 93% yield (e.e. 81%) [58]. In the case of cycloaddition involving **11**, the *t*-butoxy substituent at C-4 of the nitron, which introduces a secondary effect in the matched pair **11** and **2**, explains the lower kinetic resolution of the starting enantiomers **rac-2**. The same secondary effect of the 4-*t*-butoxy group in the nitron is quite evident if one compares the proportion of diastereomers in the mismatched pairs **41:42** = 1:1.3 and **39:40** = 2.5:1, obtained in the case of the mismatched pairs **12:2** and **11:2ent** [58]. The optically pure lactones **2** or **2ent** can be obtained if the corresponding discriminating nitrones **11** and **12** are used in excess (at least 20%).

Due to the single asymmetric induction, the cycloaddition of the non-chiral nitron **10** to *D*-glycero **2**, *D*-erythro **3**, and *D*-threo **4** lactones provides the basic information regarding the influence of lactone substituents on the direction of asymmetric induction. The cycloaddition of the nitron **10** to lactones **2** and **4** yields, in each case, a single product, **44** or **45**, respectively. The reaction of nitron **10** with lactone **3** gives cycloadducts **46** and **47** in a ratio of 4.2:1, as a result of the *exo* approach of the dipole to both sides of the dipolarophile (Scheme 6) [56–58].

The high preference for the *anti* addition of the nitron **10** to the terminal acetoxyethyl group in the lactones **2-4** is in accordance with our previous observations [56]. This preference can be explained assuming the axial approach

of the nitron oxygen atom and, as a consequence, the formation of the C–O bond prior to the formation of the C–C bond (Scheme 5). The terminal acetoxyethyl substituent serves as an anchor to stabilize the $^{\circ}\text{H}_5$ conformation [64,65]. The lower stereoselectivity, observed in the case of the addition of **10** to the *D*-erythro lactone **3**, gives an indication of the importance of the steric requirements of the 4-*O*-acetyl substituent in the lactone (Scheme 6) [56].

The significant steric hindrance of the 3-*t*-butoxy substituent in nitrones **11** and **12** and the terminal acetoxyethyl group in lactones **2** and **4** is demonstrated in the cases of a single asymmetric induction (**1** with **11**, or **12**, and **10** with **2**, or **4**) and the cases of double asymmetric induction where the reactants form matched pairs (**2** and **4** with **11**, and **2ent** with **12**) as the exclusive formation of a single cycloadduct. Introduction of additional chirality elements to both reactants influences the stereoselectivity depending on whether the reactants are a matched or a mismatched pair. In the case of a matched pair, the influence of 4-*t*-butoxy in the nitron or 4-acetoxy in the lactone does not significantly change the stereoselectivity. In the case of a mismatched pair, however, the introduction of an additional acetoxy substituent at position 4 of the lactone shifts the direction of the cycloaddition depending on the configuration at C-4 of the lactone. Indeed, the addition of nitron **12** to *D*-erythro lactone **3** proceeds exclusively *syn* to the acetoxyethyl group to form adduct **48**, whereas the addition of nitron **12** to *D*-threo lactone **4** proceeds exclusively *anti* to that group and affords **49** [56] as a sole product (Scheme 7). These results demonstrate



Scheme 6.

that the direction of asymmetric induction and consequently the configuration of newly formed stereogenic centers, could be controlled by the proper selection of substrates [56–58].

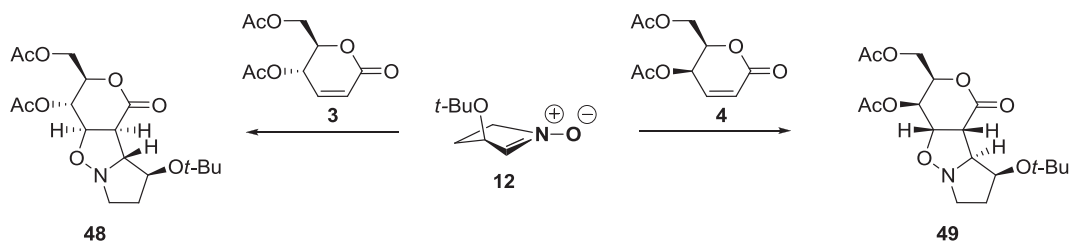
It has been shown that the racemic lactone **rac-2** can be separated into enantiomers using the nitrones **11** [56] and **12** [57]. This prompted us to investigate the opposite case when an enantiomerically pure lactone is applied to the resolution of a racemic nitron. As a model, racemic nitrone **14**, readily available from *D*-arabinose [6,10j], has been chosen [60]. Its enantiomerically pure form can also be obtained; however, its preparation is not trivial, since the synthesis requires an intramolecular alkylation of the corresponding oxime [10l–o,29].

As expected, the nitrone **14** forms a matched pair with lactone **4**, whereas its enantiomer **14ent** forms a mismatched pair. The cycloaddition of the lactone **4** to 2 equiv. of the racemate **rac-14** at room temperature after 6 days results in an apparent kinetic resolution to provide exclusively the adduct **50** in a 82% yield and the unreacted nitrone **14ent** (53% yield) with a 64% *e.e.* (Scheme 8). As shown before, the optically pure nitrone **14ent** can be obtained if an excess of lactone **4** is used. The mismatched pair involving **14ent** and **4** could react *via* both the *exo* and the *endo* modes. In boiling toluene the lactone **4** with 1 equiv. of enantiomerically pure nitrone **14ent** showed the

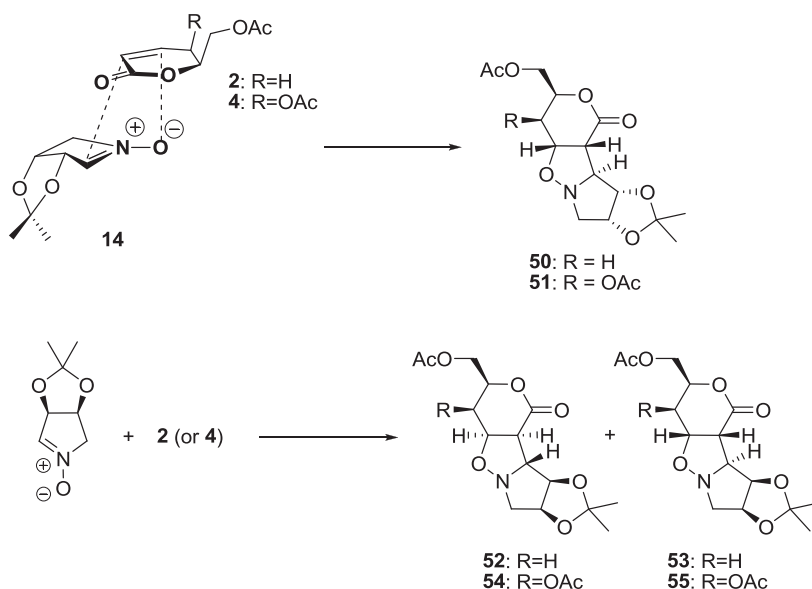
formation of two *exo* products, adducts **53** and **54**, in the ratio of about 2:1, in a 74% yield. Similarly to the previously investigated reactions involving six-membered lactones, the *endo* product is not formed [60].

4.2. Cycloaddition reactions involving γ -lactones

The 1,3-dipolar cycloaddition of nitrones **11–13** and their enantiomeric forms **11ent–13ent**, as well as the racemic **14** to the α,β -unsaturated γ -lactones, such as non-chiral **5** and the *D*-glycero **6** proceeds more readily than reported for δ -lactones to provide kinetically controlled products [59,60]. Upon heating and with an extension of the reaction time, however, the reversibility of the cycloaddition can be observed and the presence of more thermodynamically stable products can be detected [60]. Moreover, in the case of lactone **6**, a partial racemization may occur and, consequently, adducts derived from **6ent** are formed. Contrary to the corresponding additions involving δ -lactones [56–58], where only the *exo* approach of reactants is observed, γ -lactones can add nitron in both the *exo* and the *endo* modes. The high preference of *anti* addition to the terminal hydroxymethyl group in lactone **6** and to the 3-*t*-butoxy group of the nitron is observed; the 4-*t*-butoxy substituent plays a secondary role. The *endo* addition of the reactants is energetically more demanding



Scheme 7.



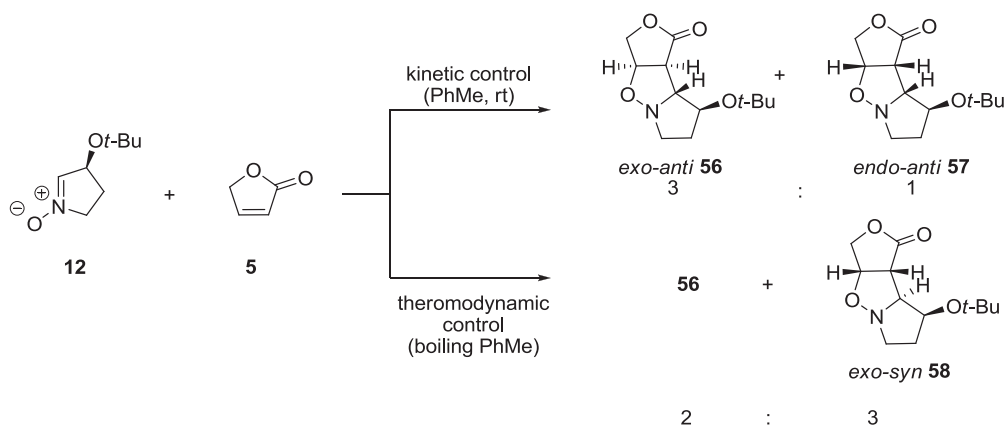
Scheme 8.

than the *exo* addition and occurs if none of the substituents in lactone or nitron hinders such an approach. Due to the presence of complex steric interactions, a single product is formed in two cases only, **11/6** and **12ent/6** [59,60].

The single asymmetric induction in cycloaddition of the chiral nitron **12** to the non-chiral lactone **5** has been reported by Brandi's group in a review article [66]. The reinvestigation of this reaction under our standard conditions in toluene, at room temperature showed the formation of two cycloadducts *exo-anti* **56** and *endo-anti* **57** in a ratio of about 3:1, respectively. The same reaction in boiling toluene revealed the presence of the *exo-syn* adduct **58** after 48 h. Further extension of the reaction time led to the reduction of the concentration of the *endo* compound **57**. After 5 days the proportion of **56:57:58** was found to be 6:1:6 whereas after 7 days it was 9:1:14 (Scheme 9). At the same time, the yield of the reaction decreased to 65 and 56%, respectively. It shows that the adduct *exo-syn* **58**, which was not observed under the kinetic control of the

reaction, is thermodynamically the most stable one [59,60].

Based on common knowledge, the higher stability of **58** compared to **56** and **57** is unexpected since the formation of adducts *syn* to the *t*-BuO group should certainly be less favorable and indeed the calculated activation energy of the transition states supports this conclusion [61,62]. However, the detailed investigation based on NMR and X-ray analysis supported by computational methods revealed that the adduct **58** has an additional stabilizing effect which decreases its energy. The second order perturbation theory analysis of the Fock matrix in a NBO basis [62] shows the stabilizing effect between the lone pair of the oxygen atom of the 3-*t*-butoxy group and the relatively acidic proton H_{4a} located in the α -position to the electron-withdrawing group ($n_{\text{O}} \rightarrow \sigma^*_{\text{C-H}}$, 0.6 kcal/mol, Fig. 4). Such an extra stabilization effect could account for the experimental observation. The interaction between H_{4a} and the oxygen atom of the *t*-BuO group is also observed in



Scheme 9.

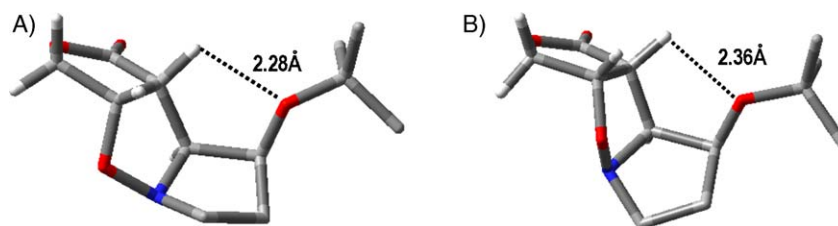


Fig. 4. Extra stabilization interaction in the adduct **58**: A) Calculated lowest energy conformation; B) Solid state conformation by X-ray.

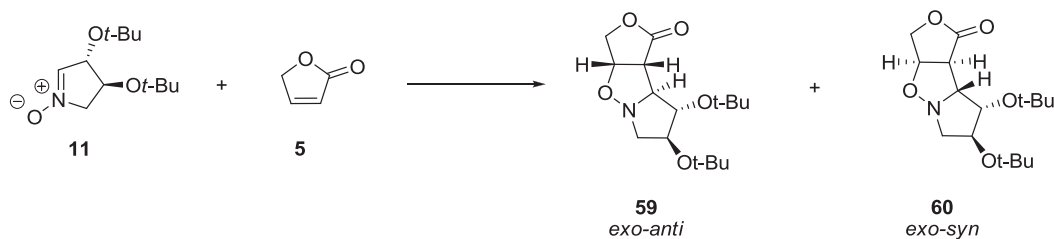
the NMR spectra. The signal of the H_{4a} proton is located downfield for **58** in comparison to its position for both **56** and **57** [62].

Introduction of two *anti* located *t*-butoxy substituents to the nitrono molecule (**11**) eliminates the possibility of *endo* additions to **5** due to a steric interaction of one or the other *t*-butoxy substituent with the lactone ring. Consequently, two *exo* adducts **59** and **60** are obtained in a ratio of about 93:7, respectively (Scheme 10). The high preference for the *anti* addition of the lactone **5** to the 3-*t*-butoxy group of the nitrono **11** is similar to that observed for the addition to six-membered lactones [59,60].

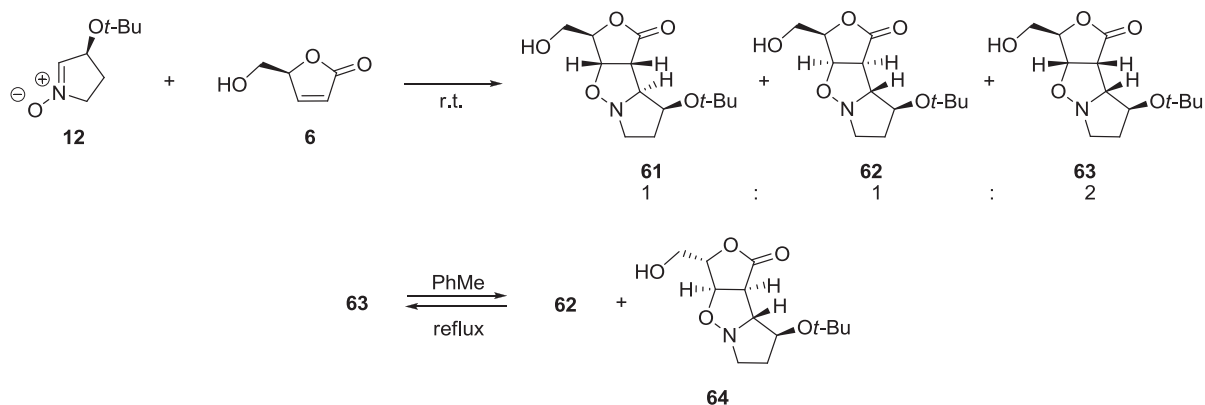
The mismatched pair, the nitrono **12** and the lactone **6** give three cycloadducts: *exo-syn* **61**, *exo-anti* **62**, and *endo-anti* **63** with respect to the 3-*t*-butoxy group of the nitrono in a ratio of about 1:1:2, respectively (Scheme 11). The main product of the cycloaddition between **12** and **6** (*endo*-adduct **63**) when refluxed in a toluene solution for 24 h demonstrated the reversibility of the reaction (Scheme 11). The postreaction mixture shows the unreacted *endo*

adduct **63** and two new products: an *exo-anti* adduct **62** and a cycloadduct **64** in a ratio of about 8:1:3, respectively. We found that further heating leads to a significant decomposition of all of the products. Addition of triethylamine accelerates the racemization of lactone **6** and leads (after 8 days of reflux) to the formation of a mixture of **64** (derived from the matched pair, **12** and **6ent**) and **62** in a ratio of about 2.7:1, respectively, in a low yield [59,60].

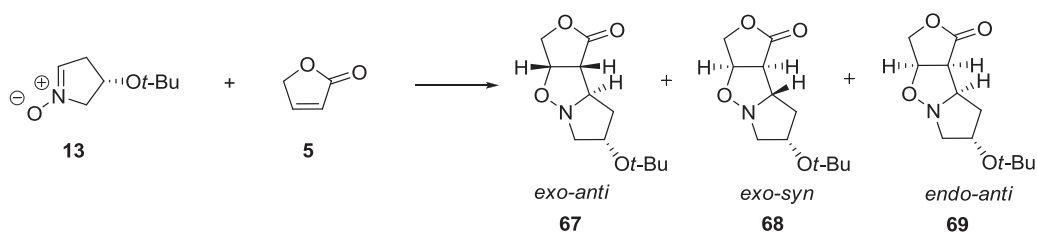
Cycloadditions involving γ -lactones [59,60] proceed with a lower diastereoselectivity, as compared with the cycloaddition to the six-membered congeners [56–58]. A single adduct is formed only in the case of the matching pair when the *endo* approach of the reactants is hindered. Cycloadducts **65** and **66**, readily available from the *D*-glycero lactone **6** and nitronos of L-(+)-tartaric acid **11** and *D*-(+)-malic acid **11ent** respectively, are particularly attractive. The adduct **65**, easily accessible from relatively inexpensive substrates, is a convenient starting material for the synthesis of polyhydroxy pyrrolizidines or indolizidines. The key stereogenic centers (bridgehead carbon atoms) are constructed during the cycloaddition step. The



Scheme 10.



Scheme 11.



Scheme 12.

other stereogenic centers can be easily epimerized or removed (Fig. 5).

The contribution of the nitronium 4-*t*-butoxy substituent to the direction and magnitude of the asymmetric induction is demonstrated by the diastereoselectivity of the cycloaddition of the nitronium **13** to the lactones **5**, and **6**. The shift of the *t*-butoxy substituent in the nitronium from the position 3 to position 4 (compound **13**) changes the preference of the reactants approach. In the reaction with **5**, three products *exo-anti* **67**, *exo-syn* **68**, and *endo-anti* **69** are obtained in a ratio of 35:53:12, respectively (Scheme 12) [59].

The unexpected preference for the *exo-syn* adduct **68** could be explained, based on the assumption that the conformation of nitronium **13** in the transition state of cycloaddition resembles the ground-state conformation of **13** which should be described as an envelope ⁴E with the nitronium part located in the flat part of the ring. Such geometry is reflected in the ¹H NMR spectrum of **13** (Scheme 13) and to a certain extent, in the crystalline state of **68** [59].

As expected, the cycloaddition of nitronium **13** to the lactone **6** affords two adducts, *exo-syn* **70** and *exo-anti* **71** in a ratio of about 21:79, respectively (Scheme 14). In comparison to the cycloaddition of **13** and **5**, the presence of the additional hydroxymethyl group in the lactone molecule causes the disappearance of the *endo* adduct and the *exo-anti* adduct **71** becomes the main product. At the same time, the removal of the 3-*t*-butoxy substituent from the nitronium, in addition to the disappearance of the *endo* adduct, causes a significant increase of the *exo-anti* addition (**71**) [59].

The cycloaddition of the nitronium **13ent** to **6** leads to the formation of the *exo-syn* product **72** as the main component of the postreaction mixture (73%). Since the steric interactions that hinder the *endo* approach are removed, compound **72** is accompanied by the *endo-anti* adduct **73** (27%). The hydroxymethyl group in the lactone influences the direction of the asymmetric induction to a higher degree than the 4-*t*-butoxy substituent in the nitronium (Scheme 15) [59].

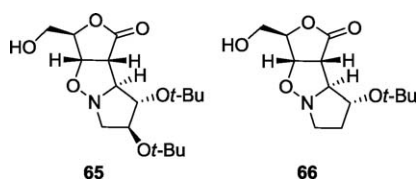
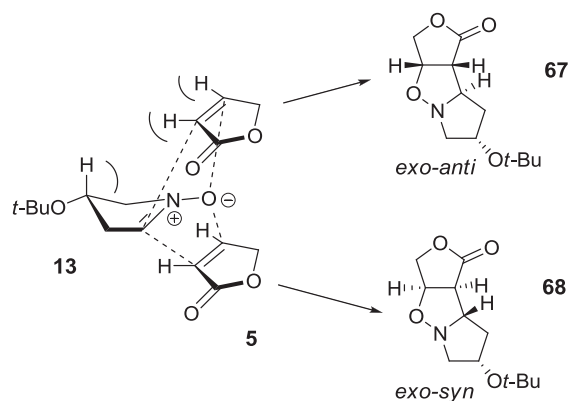


Fig. 5.

Bearing in mind the above results of the cycloaddition of nitronium **10–13** to the γ -lactones **5** and **6**, one could expect that the cycloaddition of lactone **6** to the racemic nitronium **rac-14** under kinetic control should lead to the interesting kinetic resolution providing two adducts: the *exo* adduct with **14** and the *endo* one with its enantiomeric form **14ent** [60]. This reaction has been carried out using the TBDPS protected lactone **74** and **rac-14** to provide at room temperature a mixture of products **75**, **76**, and **77** in a ratio of about 71:23:6, respectively, in 68% overall yield (Fig. 6). For the matched pair (**74** and **14**) only adduct **75** is formed. For the mismatched pair, **6** and **14ent**, however, the *endo* adduct **76** is accompanied by the *exo* one **77** in a ratio of about 4:1, respectively. Under reflux for 7 days, the content of the *endo* adduct **76** raises significantly and only traces of compound **77** are detected. The yield of the reaction, however, drops to 49%. The extension of the reaction time leads to progressive diminishing of the yield while a concurrent racemization of γ -lactones additionally complicates the composition of the postreaction mixtures providing partially racemic products. For this reason, the γ -lactones are not effective for the enantiomer discrimination of racemic nitronium [60].

4.3. Cycloaddition reactions involving cyclic six-membered nitronium

Finally, to provide a better view of the stereochemistry of the cycloaddition of unsaturated lactones to cyclic nitronium, we extended our studies to investigate cases where the cyclic six-membered nitronium **15** and **16** were applied. The reaction of **15** with achiral lactone **1** has been



Scheme 13.

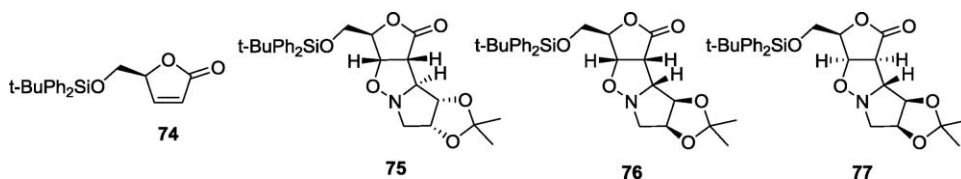
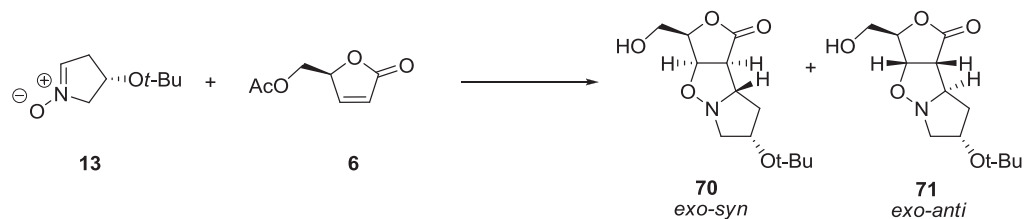
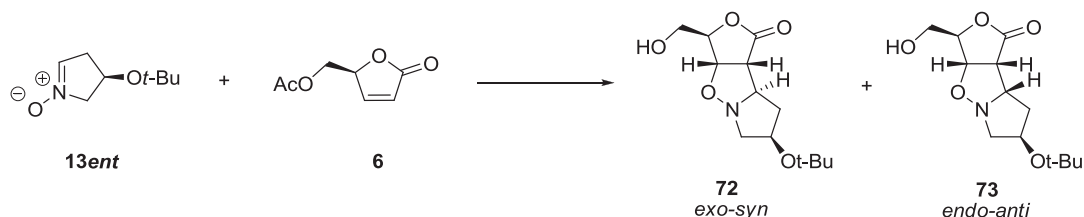


Fig. 6.



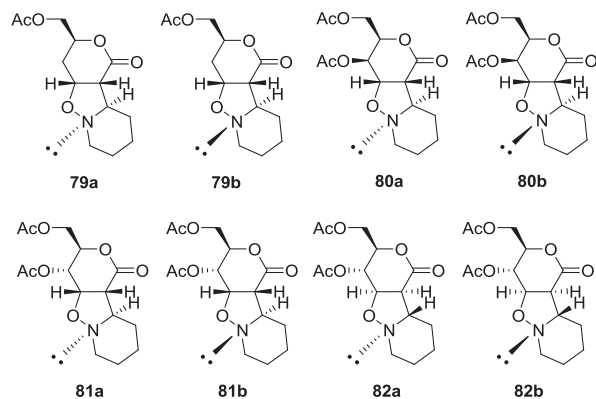
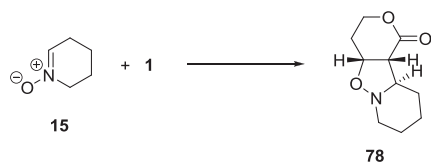
Scheme 14.



Scheme 15.

conducted by Cid and de March [67] to show the exclusive formation of *exo* adduct **78** (Scheme 16).

In our studies, we subjected the nitronium **15** to the 1,3-dipolar cycloaddition reaction with lactones **2–4** [22]. The reaction between **15** and **2** provides a single adduct **79** as a result of the *exo-anti* approach of reactants [22]. The ^1H NMR spectrum of **79** at room temperature displays lines



Scheme 16.

characteristic of definite single nitrogen invertomers **79a** and **79b** in a ratio of about 2:1. In toluene- d_8 at 100 °C, owing to the fast inversion process the ^1H NMR spectrum of adduct **79** shows the presence of averaged signals only, but with substantial line broadening [22]. The same phenomena have been observed by Cid and de March for compound **78** [67].

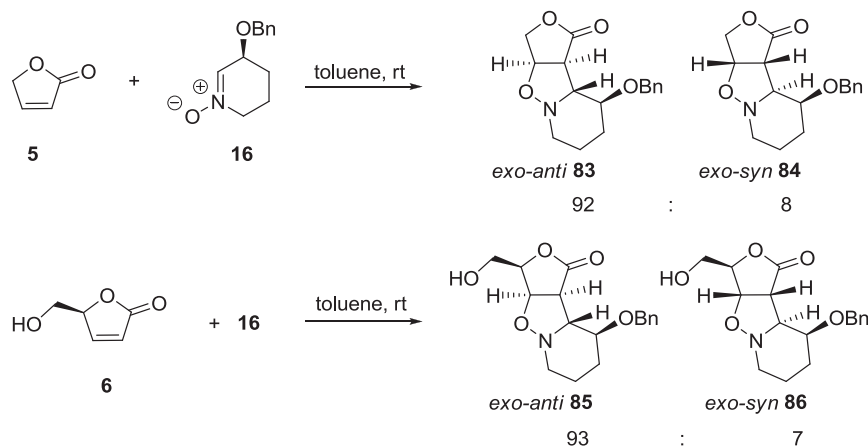
A single product was also isolated from the reaction of nitronium **15** with the *D-galacto* lactone **4**. As observed for the other adducts, compound **80**, at ambient temperature, displays the presence of two invertomers **80a/80b** in a ratio of about 1.25:1 [22].

As could be expected, a lower diastereoselectivity is observed for the reaction of nitronium **15** with the lactone **3** due to the reverse effect of both substituents in the dipolarophile on the asymmetric induction. In this case, two adducts are obtained (**81** and **82**) in the ratio of about 3:2; the *exo-anti* approach to the terminal acetoxyethyl group dominates. As in previous cases, both adducts exist as two nitrogen invertomers [22].

An additional substituent in the nitronium ring (compound **16**) decreases the conformational lability of the six-membered ring and therefore all of the adducts do not show the presence of definite invertomers [68].

The reaction of nitronium **16** with butenolide **5** affords a mixture of two *exo* products **83** and **84** in a ratio 92:8 (Scheme 17); the *anti*-approach product, with respect to the BnO group, dominates [68].

As was already demonstrated [59,60], the cycloaddition reactions between γ -lactones and five-membered nitrones are reversible and their stereochemical outcome depends on the reaction conditions. Such behavior has never been



Scheme 17.

observed for reactions involving δ -lactones regardless of the nitrones' type [56–58]. A reversibility of the cycloaddition has been, however, observed for the 1,3-DC of γ -lactones (**5,6**) with the six-membered nitrone **16** [68]. For example, the *exo-anti* adduct **83** under reflux in toluene solution gives a mixture of both compounds **83** and **84** in a ratio 2:1 after 4 days. This phenomenon can be explained by a similar interaction that was found for the adduct **58** [68], albeit, for **84** an extra stabilization is weaker due to a larger conformational lability of the six-membered ring.

These [68] as well as previous studies [59–62], lend us to conclude that the reversibility of cycloaddition is determined by the ring size of the lactone component. It seems to be reasonable to conclude that this phenomenon is related to the reactivity of both types of lactones but it is the domain of the more reactive five-membered ones. Obviously, it is not out of the question that the cycloadditions involving δ -lactones are also reversible but an equilibrium state has not been experimentally recorded. Such a possibility, however, cannot be categorically excluded.

Replacement of the achiral lactone **5** by its chiral analogue **6** does not change significantly the outcome of the reaction and again two products **85** and **86** are obtained (Scheme 17) [68]. As in the case of **5** and **16**, the major product is assigned to be an *exo-anti* adduct **85** and the minor one an *exo-syn* **86**; formation of an *endo* adduct is not observed.

4.4. 1,3-Dipolar cycloaddition of five-membered nitrones to δ - and γ -lactones: theoretical studies

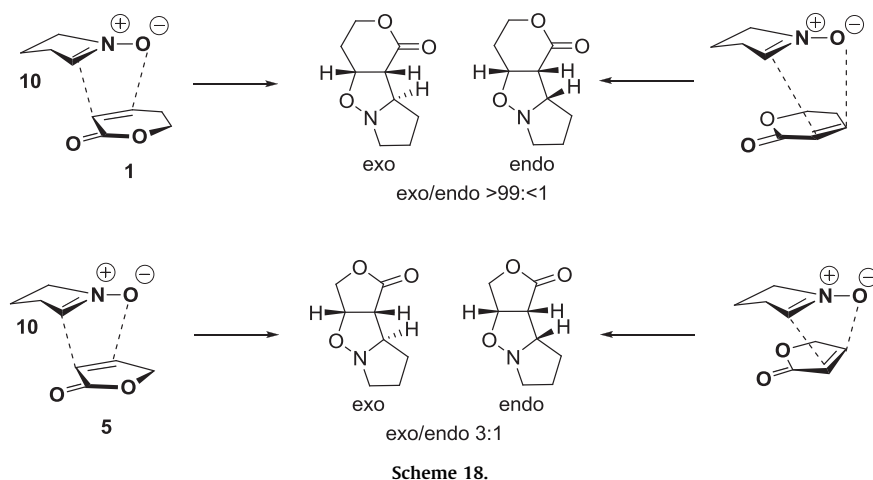
As was highlighted in section 4.1, the reactions involving six-membered lactones proceed with a high diastereoselectivity which is manifested in the exclusive formation of *exo*-adducts [56–58]. In contrary, five-membered ones react with a lower diastereoselectivity affording a mixture of products; in this case we have observed the formation of *endo* adducts, as well [59,60]. Similar observations have been noticed by Cid et al. [67]. Moreover, it was found that the stereochemical pathway of cycloadditions involving γ -lactones is more complicated

due to the reversibility of the reaction, which has never been observed for the δ -lactones.

Observed differences in reactivity and stereocontrol of both types of lactones encouraged us to perform a deeper analysis of the studied reactions from the theoretical point of view, applying computational methods.

As the simplest models, the reactions displayed in Scheme 18 were chosen [61,62,67]. Calculations carried out using DFT methods at the B3LYP/6-31+G(d) level theory show that the overlap of the oxygen atom orbital of the nitron with the C- β orbital of the lactone and the carbon atom orbital of the nitron and the C- α of the lactone should be preferred for both five- and six-membered ring lactones [61]. These theoretical predictions are in agreement with the experimental observation; the formation of only one type of regioisomer is observed for the reactions shown in Scheme 18.

As shown in Fig. 7, the low energy difference of ~ 0.4 kcal/mol between the *exo* and *endo* adducts for δ -lactones might suggest that under thermodynamic control the formation of an equimolar mixture of both adducts should be taken into consideration. This is, however, not the case since the significant energy difference between the transition states (*endo* versus *exo* 3.0 kcal/mol) causes the reaction to be kinetically controlled providing *exo* adducts only. The reversibility of the reaction has never been observed experimentally. In the case of γ -lactones the situation is the opposite, the relatively small energy difference between the transition states (*endo* versus *exo* 0.7 kcal/mol) compared to a 2.0 kcal/mol energy difference between the *endo* and *exo* adducts causes the reaction to be under thermodynamic control and an asymmetric transformation might occur and a more stable adduct should be formed [61]. This effect can be experimentally observed since upon extension of the reaction time under reflux, the reversibility of the cycloaddition is observed [60]. The low stability of the nitron causes, however, a dramatic decrease of the reaction yield, practically excluding such an asymmetric transformation. Hence, the progress of the reaction is usually stopped after the disappearance of substrates leading to the mixture of adducts.



To explain the experimentally observed different reactivity of γ - and δ -lactones, especially the ability to form *endo*-adducts by the former and lack of that ability exhibited by the latter, we have analyzed more carefully the geometries of both of the *endo* transition states [61]. We have found unfavorable interactions between the hydrogen atoms of the nitron and the δ -lactone in the transition state (Fig. 8). The distance between the indicated hydrogen atoms is 1.96 Å, and this value is close to that at which a bond is formed. A similar interaction can also be observed for a transition state involving the γ -lactone. However, in this case, such an interaction is less strong since the corresponding distance amounts to 2.60 Å (Fig. 8) [61]. The unfavorable interaction in the *endo* approach is larger for the transition state involving a six-membered lactone which causes an increase of the *endo* transition state energy and thus, consequently, increases the diastereoselectivity of the reaction (strong preference for the formation of the *exo* product). However, during the

reaction involving a five-membered lactone the steric interaction in the *endo* approach is smaller and thus the *exo/endo* diastereoselectivity is lower.

The explanation of the *endo/exo* selectivity in 1,3-dipolar cycloadditions, based on experimental observations, has been provided by Garcia Ruano et al. [69]. It was attributed to the favorable coulombic interactions between the nitron, positively charged and the lactone, negatively charged, at the corresponding *endo* transition state. This interaction has a lower energy for the folded and larger six-membered ring lactones than for the flat γ -ones. Therefore, in the case of the addition of cyclic five-membered nitrones to δ -lactones the *endo* addition has not been observed. This explanation corresponds well with our calculations carried out using DFT methods. Recently reported by Langlois' group [70], the *endo* approach of oxazoline *N*-oxide **87** to unsaturated δ -lactone **88** and to other α,β -unsaturated esters in the mismatched pair is explained by the interaction between the positively

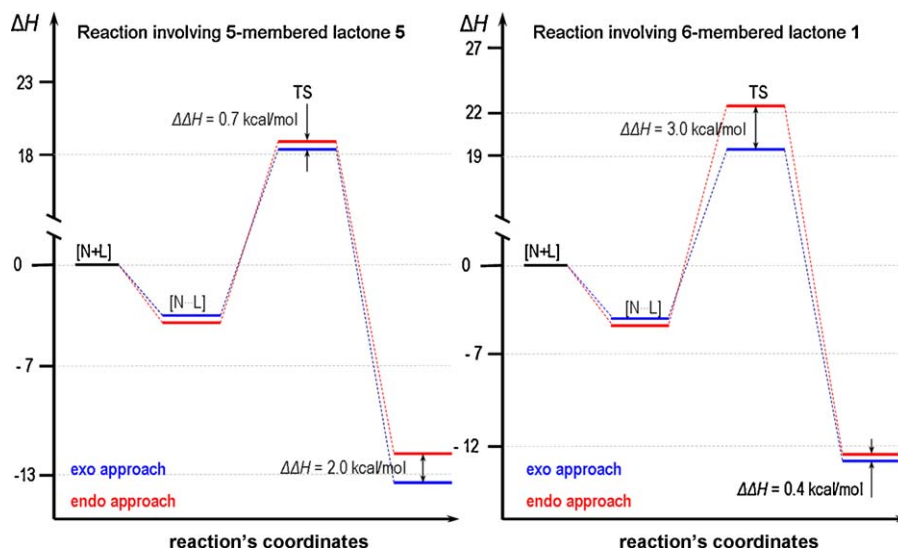


Fig. 7. Energy diagrams of the cycloaddition reactions involving five-membered nitrones and δ - and γ -lactones.

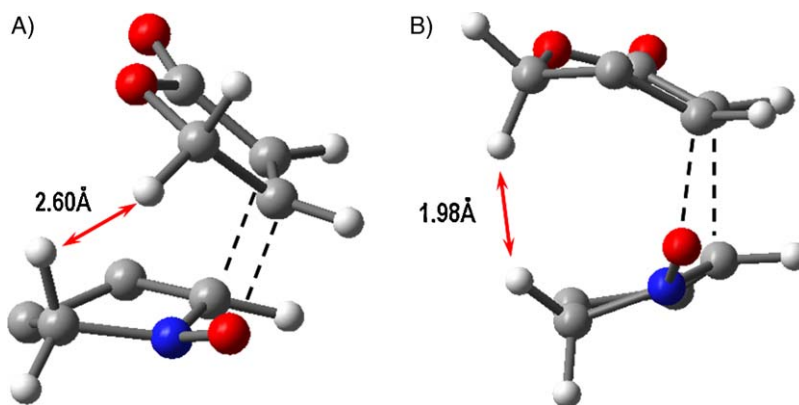


Fig. 8. Unfavorable interaction in the *endo* transition states of cycloaddition involving five-membered nitrones and: A) γ -lactone; B) δ -lactone.

charged iminoether fragment in the nitron and the negatively charged lactone carbonyl group (Fig. 9).

In the transition state of cycloaddition reactions to both the γ - and the δ -lactone, the C–O distance is shorter than the C–C distance. Such a situation is in agreement with the previously studied 1,3-dipolar cycloadditions to open-chain nitrones [71]. If we take into consideration that C–O bonds are more advanced than C–C bonds, it means that the first step can be envisioned to some extent as a Michael addition (oxygen of nitron acts as a nucleophile). In one of our previous papers [56], we have postulated more advanced C–O bond formation, bearing in mind a high preference of the *anti* approach of a nitron to the terminal substituent of the δ -lactone. Such a stereochemical preference has been noticed as a general trend for all conjugated additions to δ -lactones [54].

Our theoretical studies on 1,3-dipolar cycloadditions of nitrones and unsaturated lactones [61,62] reproduce very well the experimental observations such as the regioselectivity, the *endo/exo* selectivity and the reversibility of reactions involving γ -lactones. This allows us to explain not only the observed phenomena, but also to plan and predict the result of a more complicated reaction involving a single or double asymmetric induction, where the chirality elements of each reactant may influence stereoselectivity either in concert or in opposition, as in matched and mismatched pairs. Consequently, this permits us to plan the target-oriented synthesis of iminosugars *via* a proper selection of cycloaddition components, lactone and nitron.

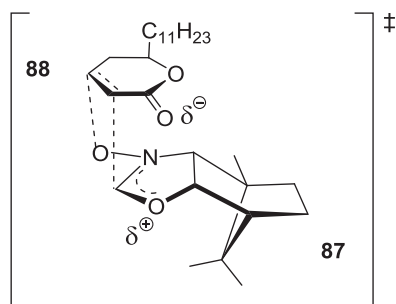


Fig. 9. *Endo* transition state of cycloaddition involving six-membered lactone **88** and oxazoline *N*-oxide **87**.

5. Synthesis of selected iminosugars

Brandi's 1,3-dipolar cycloaddition methodology [10] has been expanded by us to pyrrolidine and piperidine related iminosugars. For a detailed study leading to piperidine and pyrrolidine related iminosugars the lactones **74**, **89**, **90** and the nitron **7** have been selected. The cycloaddition reactions using lactones **74** and **89**, performed under standard procedures, yield only the single cycloadducts *D*-ribo **91** and *D*-gulo **92**, respectively. In the case of lactone **90** two products are formed, *L*-allo **93** and *L*-manno **94** in a ratio of about 2.5:1 (Fig. 10) [18].

Cycloadducts **91–94** were subjected to a sequence of reactions consisting of the reduction of the lactone fragment to the diol, suitable protection (double acetylation or isopropylidene formation), hydrogenolysis of the *N*–*O* bond, desilylation, mesylation and intramolecular nucleophilic substitution to provide, depending on the site of mesylation, pyrrolidine **95** or piperidine **96** closely related to isofagomine **97** (Scheme 19) [72]. A similar transformation sequence applied to the adduct **92** affords the iminosugar having the *L*-gluco configuration **97** (Scheme 19) [18].

The same transformation of adducts **93** and **94** gives the corresponding *D*-galacto **99** and *D*-ido **100** iminosugars (Scheme 20) [18].

With the exception of transformations leading to **96**, the reaction sequence involves the inversion of the configuration at the carbon atom that is assigned the *D*- or the *L*-conformation series of the starting sugar lactone. In all cases, exchange of substituents at the C-2 carbon atom occurs, thus from adduct *D*-ribo **91**–*L*-xylo **95**, or *D*-arabino **96**, from *D*-gulo **92**–*L*-gluco **98** (Scheme 19), from *L*-allo **93**–*D*-galacto **99** and from *L*-manno **94**–*D*-ido compound **100** (Scheme 20) are obtained (Scheme 21) [18].

Cycloadduct **101** obtained by the 1,3-dipolar cycloaddition of *N*-benzyl nitron **7** to the *D*-threo lactone **4** was subjected to a rearrangement to the γ -lactone and then to a sequence of reactions displayed in Scheme 21, to provide the (–)-isofagomine (**97ent**) [21], the enantiomer of (+)-isofagomine (**97**) which has been found to be one of the most potent β -glucosidase inhibitors synthesized by a Danish group [72].

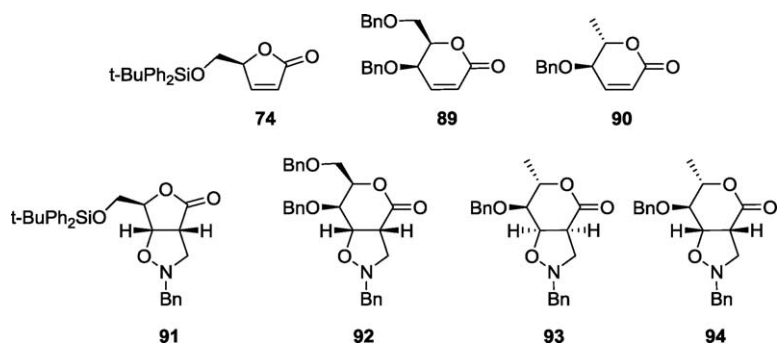
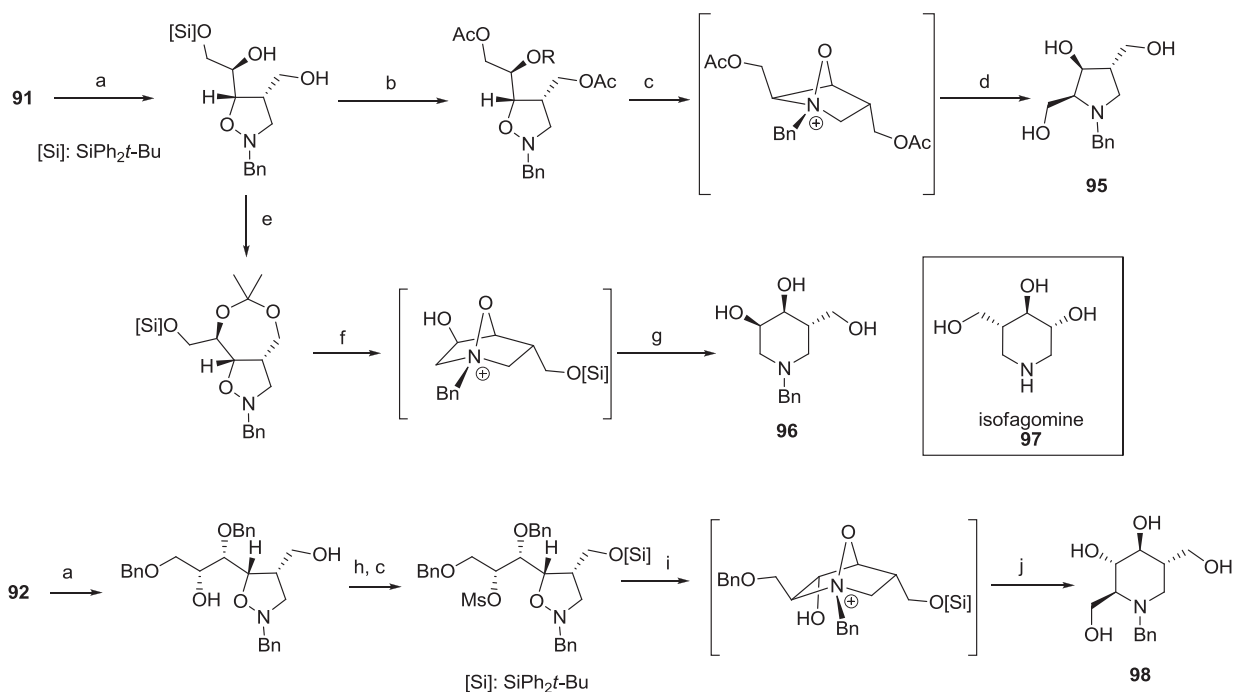


Fig. 10.



Reagents: a) LiAlH₄, THF; b) i. Ac₂O, Py; ii. TBAF, THF; c) MsCl, Et₃N, CH₂Cl₂; d) i. H₂, Pd/C, MeOH; ii. NH₃, MeOH; e) 2,2-dimethoxypropane, PTSA; f) i. TBAF, THF; ii. MsCl, Et₃N, CH₂Cl₂; g) i. AcOH; ii. H₂, Pd/C, MeOH; h) TBDPSCI, DMAP, CH₂Cl₂; i) TBAF, THF; j) H₂, Pd/C, MeOH;

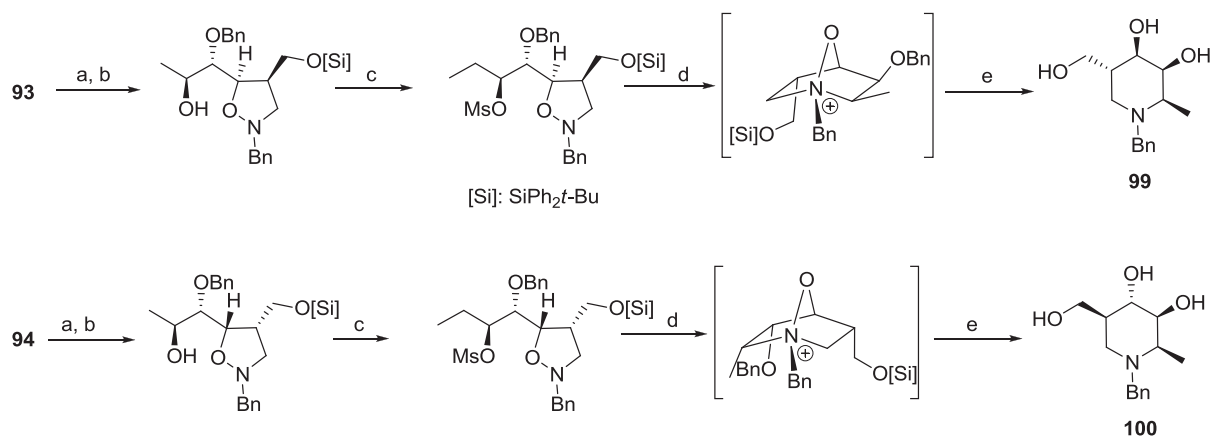
Scheme 19.

Application of a 1,3-dipolar cycloaddition of Brandi's nitrones **11** and **12** [10a,73] and the lactones **1-6** demonstrates the usefulness of the above methodology for the preparation of polyhydroxylated pyrrolizidines and indolizidines. The adduct **36**, available preparatively with an excellent stereoselectivity, was transformed into lentiginosine **102** and 7-hydroxylentiginosine **103** (Scheme 22) [17].

Barton's decarboxylation procedure [74] applied in the presence of oxygen provided an oxidative decarboxylation leading to the regioisomer of castanospermine **104** with the retention of configuration (Scheme 22) [17].

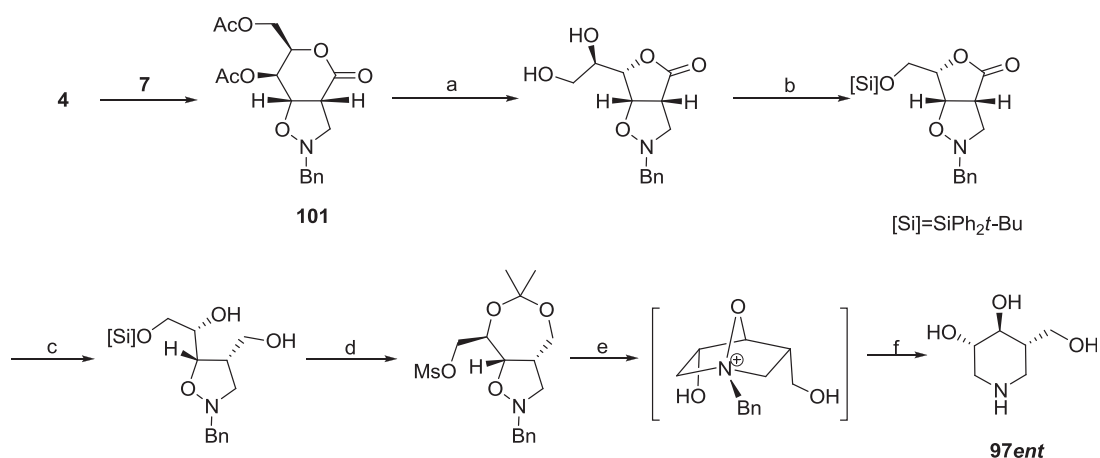
The same reaction scheme applied to adduct **49** opens an easy access route to analogs of castanospermine **105** and australine **106** (Scheme 23) [19,20]. The configuration of the stereogenic centers at C-1, C-6, C-7, C-8 and C-8a of

castanospermine **105** is the same as the configuration at C-6, C-2, C-1a, C-5a and C-5b of the adduct **49**. Therefore, the removal of the terminal CH₂OAc, followed by the hydrogenolysis of the N-O bond and intramolecular alkylation of the nitrogen atom should provide the 8-homoindolizidine **107** [20]. However, the configuration of the stereogenic centers at C-1, C-5, C-6, C-7 and C-7a of australine **106** is different from the configuration at C-6, C-2, C-1a, C-5a and C-5b of the adduct **49** only at the stereogenic center of the C-2 carbon atom. However, bearing in mind that alkylation of the nitrogen atom, in order to form the pyrrolizidine skeleton, should proceed with an inversion of configuration, the adduct **49** represents an excellent substrate for the synthesis of 7-homoaustraline **108** [19]. Both syntheses were completed



Reagents: a) LiAlH₄, THF; b) TBDPSCI, DMAP, CH₂Cl₂; c) MsCl, Et₃N, CH₂Cl₂; d) TBAF, THF; e) H₂, Pd/C, MeOH.

Scheme 20.



Reagents: a) NH₃, MeOH; b) i. NaIO₄, MeOH/H₂O (2:1); ii. NaBH(OAc)₃, CH₂Cl₂; iii. TBDPSCI, DMAP, CH₂Cl₂; c) LiAlH₄, THF; d) i. 2,2-dimethoxypropane, PTSA; ii. TBAF, THF; iii. MsCl, Et₃N, CH₂Cl₂; e) i. AcOH; ii. H₂, Pd/C, MeOH; f) i. Ac₂O, Py; ii. NH₃, MeOH

Scheme 21.

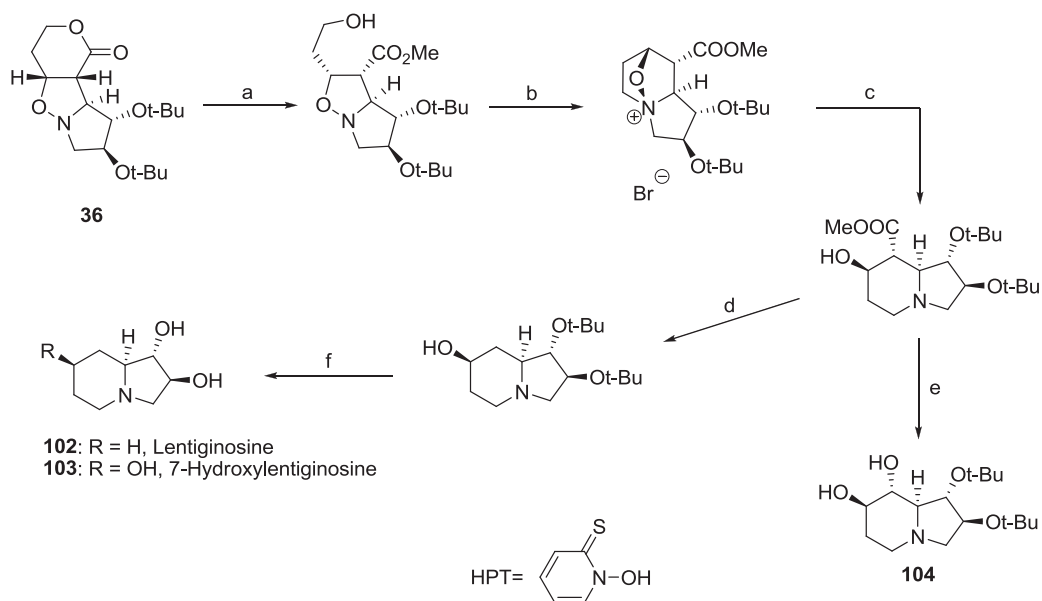
to provide the expected indolizidine **107** and pyrrolizidine **108** [19,20].

The high stereoselectivity of formation of the cycloadduct **49**, which creates a proper substrate for the synthesis of castanospermine **105** and australine **106**, is worthy of note since the 1,3-dipolar cycloaddition of an olefin *syn* to the protected oxygen atom at C-3 of the five-membered ring nitron can be undertaken generally as an intramolecular process (Scheme 24) [75]. The competition between both substituents in the lactone **4** and 3-*tert*-butoxy in the nitron **12** in 1,3-dipolar cycloaddition creates a unique situation which results in the formation of a sole product **49** as a result of the *syn* approach to the C-3 substituent in the nitron.

Synthesis of a potential mannosidase inhibitor **109** which can be indolizidine with a *D*-manno configuration around the piperidine ring, is not straightforward,

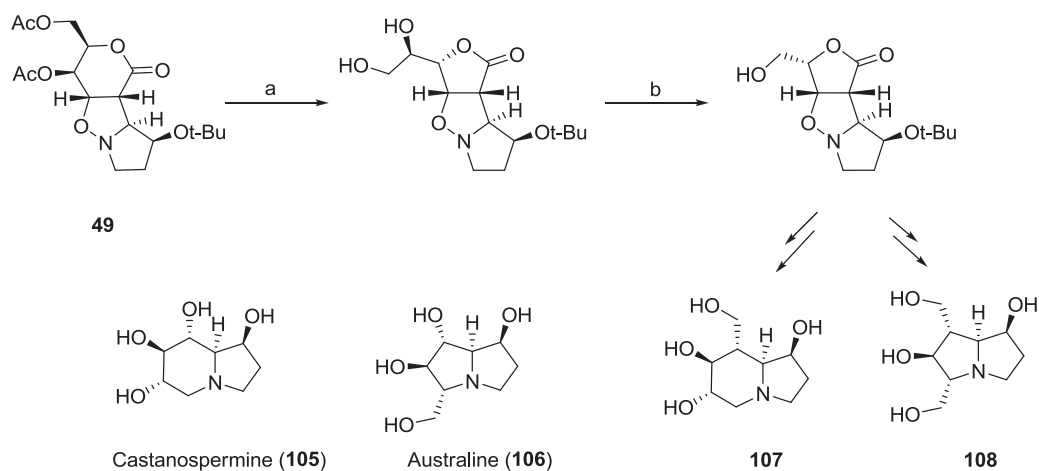
according to a previous report [25]. The opposite configuration at C-4 of the *D*-erythro lactone **3**, causes the preferential addition *anti* to the *t*-butoxy group of the nitron to give, in the case of **3** and **12**, the adduct **48**. Therefore, the configuration of all stereogenic centers of the piperidine fragment of the indolizidine **110** would be reversed to that of **49** providing the *L*-gluco configuration [58]. The desired *D*-manno configuration of that fragment may be produced only if the *D*-erythro lactone **3** and nitron **11** are used. However, the adduct **111**, derived from the lactone **3** and nitron **11** is accompanied by 10% of the alternative *exo* isomer **112** (Fig. 11) [58].

Although analogous cycloadditions involving γ -lactones proceed with a lower diastereoselectivity, compared to that of δ -lactones, due to the possible formation of *endo* adducts, in the case of **6** and **11** a single product **65** is formed [59]. Compound **65**, subjected to the same



Reagents: a) K_2CO_3 , MeOH; b) CBr_4 , PPh_3 ; c) H_2 , $Pd(OH)_2/C$, MeOH; d) i. $LiOH-H_2O$; ii. HPT, DCC, DMAP, *t*-BuSH; argon; e) i. $LiOH-H_2O$; ii. HPT, DCC, DMAP, *t*-BuSH; oxygen; f) TFA or $Im_2C=S$, Bu_3SnH , TFA

Scheme 22.

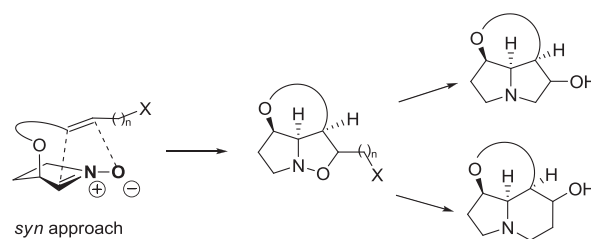


Reagents: a) Na_2CO_3 , MeOH; b) i. $NaIO_4$, MeOH ii. $NaBH(OAc)_3$, MeOH.

Scheme 23.

transformations as applied for the synthesis of 8-homocastanospermine **107** and 7-homoaustraline **108**, gives the indolizidine **113** [25] with a *D-manno* configuration around the piperidine ring, or the pyrrolizidine **114** [24] related to casuarine (**115**) [76] and its 3-epimer (**116**) (Scheme 25).

There are numerous polyhydroxylated alkaloids containing methyl group attached to the iminosugar skeleton [4,7,12–15,77]. Interesting biological properties of methyl-iminosugars encouraged us to propose a synthetic route to the methyl substituted pyrrolidines related to casuarine



Scheme 24.

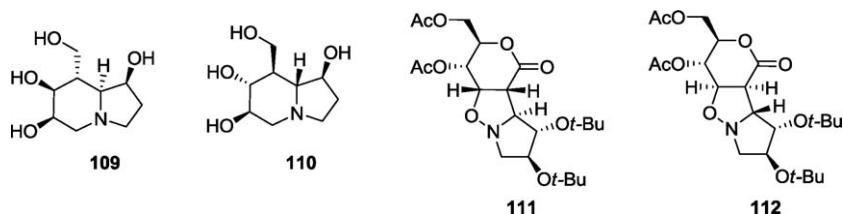


Fig. 11.

[24]. For this purpose, we reported a synthetic route to transform adduct **65** into the 1-methyl- or 3-methyl analogues of 3-*epi*-casuarine (**117** and **118**) (Scheme 26). The key step of that strategy was deoxygenation of the corresponding hydroxymethyl groups. It was performed by treatment of a proper mesylate with LiBHET_3 . Depending on the position of the methyl group, the deoxygenation step can be done either at an earlier, or at a later stage of our standard transformation sequence [24]. In the case of **117**, the deoxygenation was performed at the late synthesis step after formation of the pyrrolizidine skeleton, whereas for **118**, we were forced to perform the reduction at an earlier step (isoxazolidine step) otherwise numerous side reactions, including ring rearrangement leading to **119**, occurred (Scheme 26) [24].

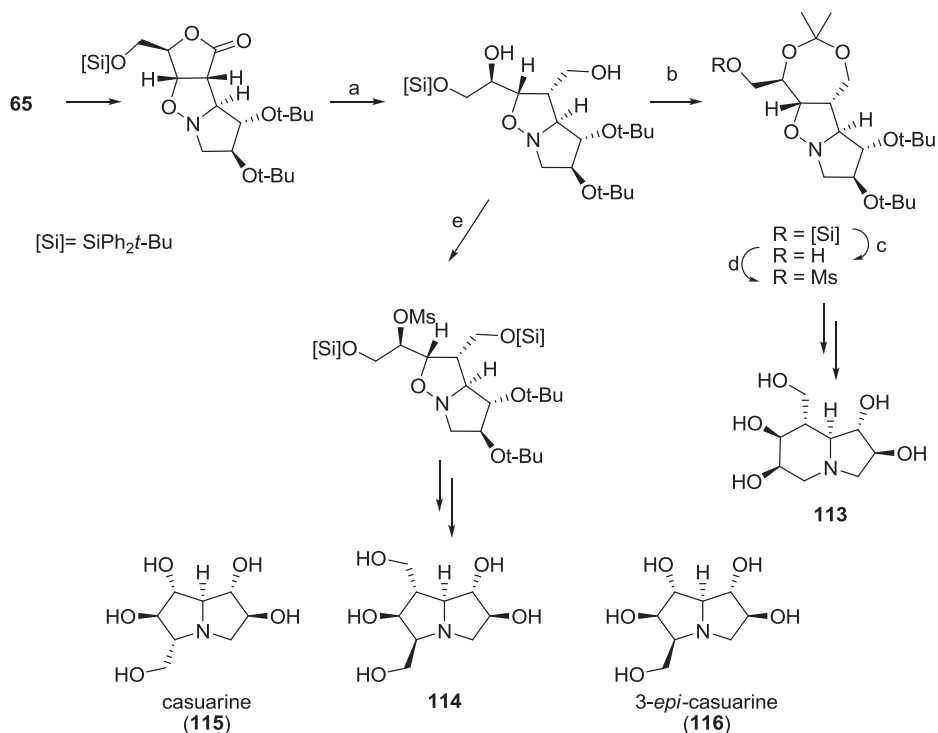
The same adduct **65** can be used for the synthesis of 2,6-dihydroxy-hastanecine **120** [23]. Transformations leading to the necine **120** are the same as used for the synthesis of pyrrolizidine **114** except for the removal of a terminal

atom of the side chain diol (Scheme 27). In this case, cycloaddition provides two crucial stereogenic centers at the bridgehead carbon atoms C-7 and C-7a (Scheme 27).

Alkaloids containing the amino-pyrrolizidine and the amino-indolizidine motifs are widespread in nature (Fig. 12) [5,8,12–15,78]. Their potential bioactivity as antidepressant, analgesic, antiviral, antibacterial, or anti-tumor agents should make them particularly attractive synthetic targets for academic and industrial research laboratories.

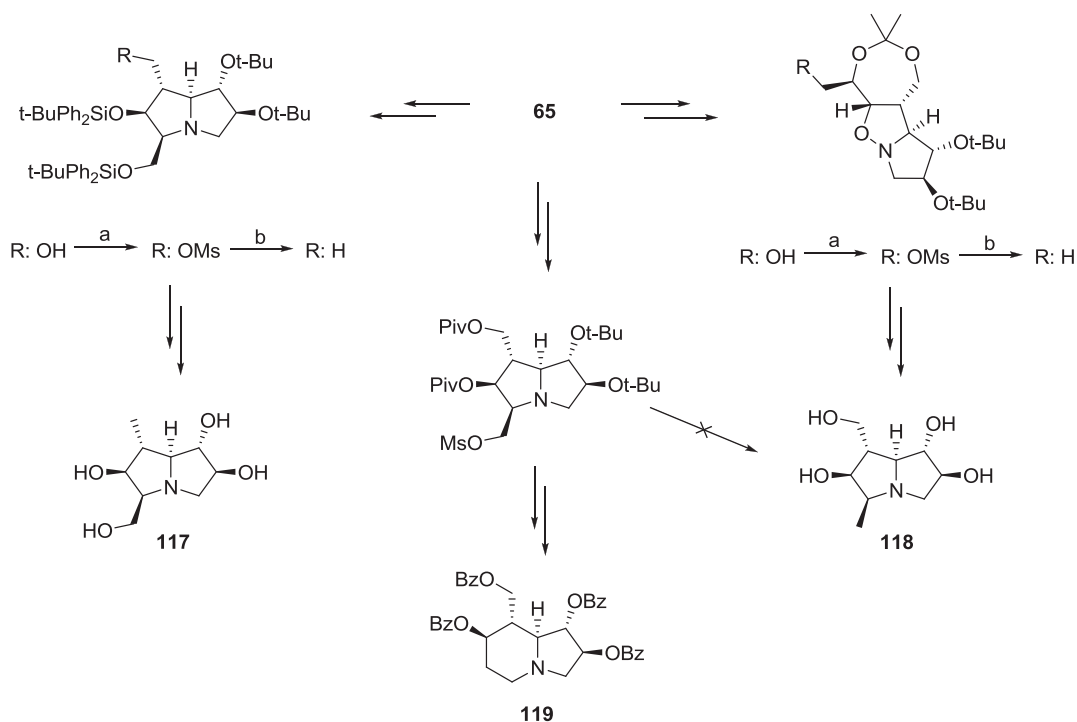
However, there are only a few reports about the synthesis and biological activity of their polyhydroxylated analogues—amino-iminosugars [4,79]. This prompted us to check whether our strategy can be also applied to the synthesis of molecules containing the amino function attached to either a polyhydroxylated pyrrolizidine or indolizidine skeleton (Scheme 28).

The ammonolysis of a lactone moiety in the tricyclic cycloadducts **59** and **65** (derived from non-racemic five-



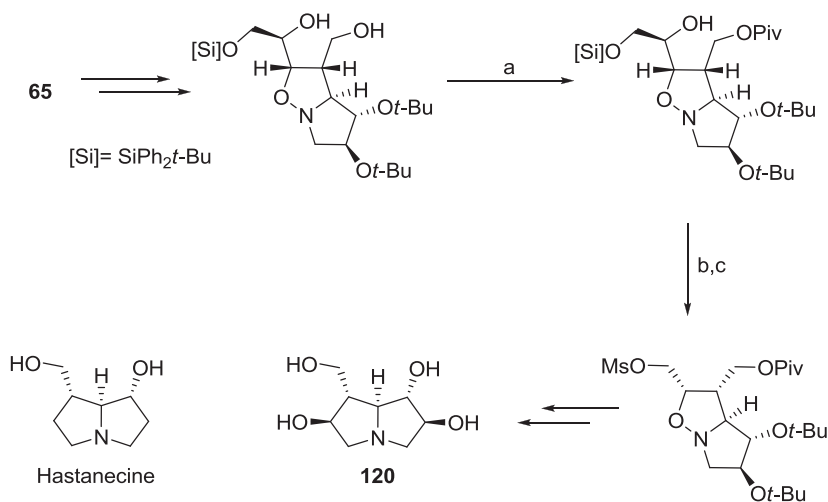
Reagents: a) $\text{BH}_3\text{-Me}_2\text{S}$, THF b) 2,2-dimethoxypropane, PTSA; c) TBAF, THF; d) MsCl , Et_3N , CH_2Cl_2 ; e) i. TBDPSCl, imidazole, CH_2Cl_2 , ii. MsCl , Et_3N , CH_2Cl_2

Scheme 25.



Reagents: a) MsCl, Et₃N, CH₂Cl₂; b) LiBHET₃, THF

Scheme 26.



Reagents: a) PivCl, DMAP, CH₂Cl₂; b) i. TBAF, THF, ii. NaIO₄, MeOH, iii. NaBH₄, MeOH; c) MsCl, Et₃N, CH₂Cl₂

Scheme 27.

membered cyclic nitrone **11** and unsaturated lactones **5** and **6**) furnishes an amido function, which after a subsequent Hoffmann rearrangement, leads to a protected amino group directly attached to the bicyclic isoxazolidine skeleton [26]. The subsequent standard transformation as

shown above, involving the cleavage of the *N*-*O* bond followed by the intramolecular *N*-alkylation, provides an access to the polyhydroxylated 7-aminopyrrolizidines **121**, **122** and 8-aminoindolizidine **123**, which are potential glycosidase inhibitors (Scheme 28) [26].

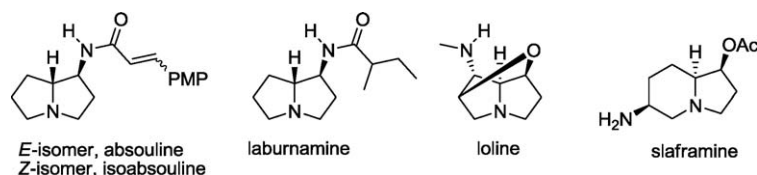
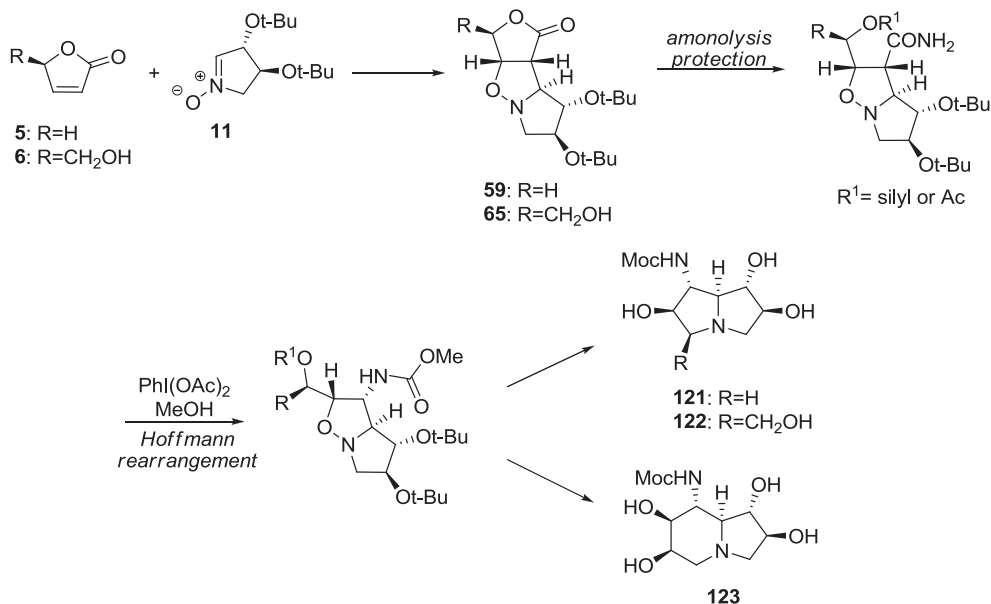
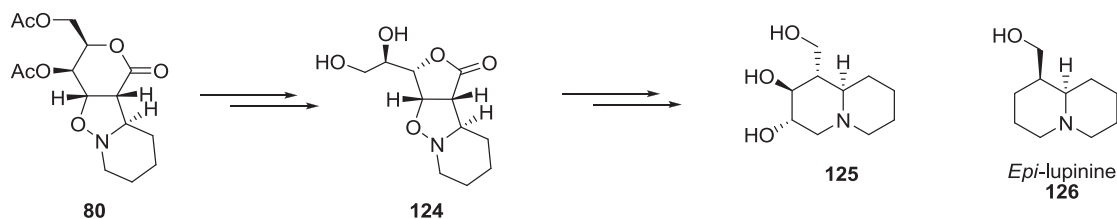


Fig. 12.



Scheme 28.



Scheme 29.

As stated previously, the 1,3-dipolar cycloaddition of the unsaturated *D*-*threo*-hexaldonolactone **3** and a six-membered cyclic nitron **15** leads to a single adduct **80**, which after rearrangement of the six-membered lactone ring to the five-membered lactone ring to the five-membered lactone **124**, can be transformed into the 1-hydroxymethyl-2,3-dihydroxyquinolizidine **125** related to lupinine **126** via a standard reaction sequence (Scheme 29). It should be pointed out, however, that the conformational lability of a nitrogen atom bearing an oxygen makes it difficult to follow the configuration of the adduct by NMR spectra [22] due to the broadening of the spectral lines.

6. Biological activity of synthesized compounds

Studies on the structure-bioactivity relationship of synthesized compounds become an integral part of our

ongoing research program leading to iminosugars obtained via transformation of adducts of 1,3-dipolar cycloaddition reactions. The glycosidases' inhibition tests were conducted against six commercially available enzymes: α -*D*-glucosidase from rice; β -*D*-glucosidase from almonds, α -*D*-mannosidase from jeak bean, α -*L*-fucosidase from bovine kidney, β -*D*-galactosidase and β -*D*-glucuronidase both from bovine liver. Some selected results are summarized in Table 1.

(-)-Isomagomine **97ent** and its *N*-substituted derivatives show a weak activity against tested enzymes. Amongst them, the *N*-benzylated derivative of **97ent** is the most selective and interacts only with α -*D*-mannosidase [21]. In comparison, the natural (+)-isomagomine **97** is a potent inhibitor of β -*D*-glucosidase [4].

A weak inhibition was also noticed for bicyclic iminosugars. Both 8-homocastanospermine **107** [20] and

Table 1
Selected results of bioactivity tests of selected iminosugars.

Compound	IC ₅₀ values [mM] ^a						References
	EN1	EN2	EN3	EN4	EN5	EN6	
97ent	<i>n.a.</i>	9.0	<i>n.a.</i>	8.3	15.0	12.0	[21]
N-Ac-97ent	<i>n.a.</i>	8.5	21.5	6.6	9.1	3.5	[21]
N-Bn-97ent	<i>n.a.</i>	<i>n.a.</i>	5.1	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[21]
107	<i>n.a.</i>	<i>n.a.</i>	26.8	1.6	<i>n.a.</i>	<i>n.a.</i>	[20]
108	20.0	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	24.0	[19]
113	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	1.0	0.9	0.6	[25]
114	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[24]
117	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[24]
118	<i>n.a.</i>	13.0	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[24]
120	9.9	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[23]
121	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[26]
122	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	0.9	<i>n.a.</i>	<i>n.a.</i>	[26]
123	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[26]
126	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	[22]
127	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	8.0	[80]
128	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>	7.0	[80]

EN1: α -D-glucosidase from rice; EN2: β -D-glucosidase from almond; EN3: α -D-mannosidase from jeak bean; EN4: β -D-galactosidase from bovine liver; EN5: β -D-glucuronidase from bovine liver; EN6: α -L-fucosidase from bovine kidney; *n.a.* = no bioactivity.

^a The half maximal inhibitor concentration in mM.

the 7-homolog of australine (**108**) [19] have lower activity in comparison to the native molecules. Although compound **113** has a *manno*-configuration on the piperidine ring, it does not exhibit any significant activity against α -D-mannosidase, but is weakly active against other enzymes [25]. Interesting results were obtained for dihydroxy-hastanecine **120** [23] and its 3-methyl derivative **118** [24]. The former one showed activity against α -D-glucosidase, whereas the addition of a methyl group at position C-3 changed the selectivity and **118** became active against β -D-glucosidase. Some weak activity was also found for several intermediate compounds used in the synthesis of the iminosugars **107** and **108**. The isoxazolidine **127**, as well as the *N*-acetylated pyrrolidine **128**, both derived from adduct **65**, possess activity against α -L-fucosidase [80]. These compounds are intermediates in the synthesis of the iminosugars **113** and **114** (Fig. 13).

A lack of activity was observed for 3-*epi*-1-homocapsuarine **114** [24], its 1-methyl derivative **117** [24], quinolizidine **126** [22] and the also amino-iminosugars **121** and **123** [26]. However, the amino-pyrrolidine **122** displays a weak inhibition of β -D-galactosidase [26]. It is worthwhile to point out that there is not much known about the bioactivity of this relatively new subclass of iminosugars (amino-iminosugars). According to some biological data provided in the literature for monocyclic amino-iminosugars [4], one could expect that these compounds might possess glycoaminidases' inhibition activity.

Although the tested compounds display only a weak inhibition of the tested glycosidases, the results obtained

might provide an interesting basis for further structure-activity relationship studies.

7. Conclusions

In this account, we present the characteristic features of 1,3-dipolar cycloaddition of nitrones to readily available γ - and δ -lactones such as stereoselectivity, kinetic and thermodynamic control of reactions. The influence of structure and configuration of both components on the stereoselectivity of the cycloaddition was investigated and discussed. A special emphasis was placed on the cycloadditions involving five-membered ring nitrones since owing to their rigid conformation, the interpretation of experimental facts is straightforward and the obtained adducts offer a broad application for the synthesis of iminosugars having pyrrolizidine or indolizidine structures. For these reactions, the results of calculations carried out using DFT methods at the B3LYP/6-31+G(d) level showed a very good agreement with the experimental facts.

Broad investigations show the influence of the substituents in the lactone and nitron on the stereoselectivity of cycloaddition. It has been shown that the 3-*t*-butoxyl in the nitron and the terminal oxymethyl group in the lactone play a decisive role in stereo selection. Other substituents may influence the stereoselectivity only in the mismatched pair situation of the primary groups. We have shown that cycloadditions involving δ -lactones are not reversible and proceed in the *exo* mode exclusively. In many cases, a single product is formed, therefore δ -lactones are particularly attractive in the target-oriented synthesis. The corresponding transformations involving γ -lactones are more complicated. As we have shown, the cycloadditions to γ -lactones proceed with a lower diastereoselectivity, as compared to the cycloaddition to six-membered ones because of the possible formation of *endo* adducts. Moreover, the reversibility of the cycloaddition, as well as racemization of the 5-substituted 2-(5*H*)-furanones,

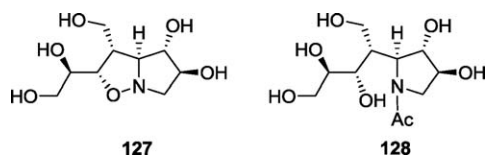


Fig. 13.

additionally complicates the composition of the post-reaction mixtures and may lead to the formation of partially racemic products. Because of this, γ -lactones are less attractive in synthetic applications.

A proper selection of the readily available components of the 1,3-dipolar cycloaddition controls the absolute stereochemistry of the newly created stereogenic centers of the adduct. It allows us to design the desired configuration of the adduct and the synthesis of the core part of the target molecule. It is demonstrated that a standard reaction sequence involving hydrogenolysis of the *N*–*O* bond followed by alkylation of the nitrogen atom works well in many configurational arrangements.

Acknowledgements

This publication was financed by the European Union within the European Regional Development Fund, Project POIG.01.01.02.–14–102/09.

References

- (a) F.W. Lichtenthaler, in: Z. Yoshida, T. Shiba, Y. Oshiro (Eds.), *New Aspects of Organic Chemistry*, vol. 1, VCH Publishers, New York, 1989, 351 p;
- (b) F.W. Lichtenthaler, *Pure Appl. Chem.* 50 (1978) 1343;
- (c) S. Hanessian, *Acc. Chem. Res.* 12 (1979) 159;
- (d) B. Fraser-Reid, *Acc. Chem. Res.* 8 (1975) 192;
- (e) B. Fraser-Reid, R.C. Anderson, *Progr. Chem. Org. Nat. Prod.* 39 (1980) 1;
- (f) A. Vasella, in: R. Scheffold (Ed.), *Modern Synthetic Methods*, 2, Verlag Sauerländer, O. Salle, Frankfurt, 1980, 173 p.;
- (g) S. Hanessian, *Total Synthesis of Natural Products: the "Chiron" Approach*, Pergamon Press, Montreal, 1983 ;
- (h) T.D. Inch, *Tetrahedron* 40 (1984) 3161;
- (i) Z. Kaluza, W. Abramski, M. Chmielewski, *Indian J. Chem.* 33B (1994) 913;
- (j) B. Furman, Z. Kaluza, A. Stencel, B. Grzeszczuk, M. Chmielewski, in: S. El Ashry (Ed.), *Topics in Heterocyclic Chemistry*, vol. 7, Springer Verlag, 2007, 101 p.
- (a) J. Mieczkowski, J. Jurczak, M. Chmielewski, A. Zamojski, *Carbohydr. Res.* 56 (1977) 180;
- (b) M. Chmielewski, J. Jurczak, S. Maciejewski, *Carbohydr. Res.* 165 (1987) 111.
- (a) P. Jarglis, F.W. Lichtenthaler, *Tetrahedron Lett.* 23 (1982) 3781;
- (b) F.W. Lichtenthaler, S. Rönninger, P. Jarglis, *Liebigs Ann. Chem.* (1989) 1153.
- (a) A. Stütz, *Iminosugars as glycosidase inhibitors*, Wiley-VCH, Weinheim, 1999;
- (b) P. Compain, O.R. Martin, *Iminosugars: from synthesis to therapeutic applications*, John Wiley and Sons, Chichester UK, 2007;
- (c) A.A. Watson, G.W.J. Fleet, N. Asano, R.J. Molyneux, R.J. Nash, *Phytochemistry* 56 (2001) 265.
- E.S.H. El Ashry, A. El Nemr, *Synthesis of naturally occurring nitrogen heterocycles from carbohydrates*, Blackwell Publishing, Oxford, 2005.
- A.E. McCaig, K.P. Meldrum, R.H. Wightman, *Tetrahedron* 54 (1998) 9429.
- A. El Nemr, *Tetrahedron* 56 (2000) 8579.
- P. Herczegh, I. Kovács, F. Sztaricskai, in: G. Lukacs (Ed.), *Recent progress in chemical synthesis of antibiotics and related microbial products*, Springer-Verlag, Berlin, 1993, 751 p.
- J.J. Tufariello, J.M. Puglis, *Tetrahedron Lett.* 27 (1986) 1489.
- (a) S. Cicchi, A. Goti, A. Brandi, *J. Org. Chem.* 60 (1995) 4743;
- (b) A. Brandi, S. Cicchi, F.M. Cordero, R. Frignoli, A. Goti, S. Picasso, P. Vogel, *J. Org. Chem.* 60 (1995) 6806;
- (c) A. Goti, F. Cardona, A. Brandi, S. Picasso, P. Vogel, *Tetrahedron: Asymmetry* 7 (1996) 1659;
- (d) F. Cardona, S. Valenza, A. Goti, A. Brandi, *Tetrahedron Lett.* 38 (1997) 8097;
- (e) F. Cardona, S. Valenza, S. Picasso, A. Goti, A. Brandi, *J. Org. Chem.* 63 (1998) 7311;
- (f) F. Cardona, P. Salański, M. Chmielewski, S. Valenza, A. Goti, A. Brandi, *Synlett* (1998) 1444;
- (g) S. Cicchi, J.J. Nunes, A. Goti, A. Brandi, *Eur. J. Org. Chem.* (1998) 419;
- (h) A. Goti, F. Cardona, A. Brandi, *Synlett* (1996) 761;
- (i) F.M. Cordero, M. Gensini, A. Goti, A. Brandi, *Org. Lett.* 2 (2000) 2475;
- (j) A. Goti, S. Cicchi, M. Cacciarini, F. Cardona, V. Fedi, A. Brandi, *Eur. J. Org. Chem.* (2000) 3633;
- (k) F. Machetti, F.M. Cordero, F. De Sarlo, A. Brandi, *Tetrahedron* 57 (2001) 4995;
- (l) F. Cardona, A. Goti, S. Picasso, P. Vogel, A. Brandi, *J. Carbohydr. Chem.* 19 (2000) 585;
- (m) S. Cicchi, M. Corsi, A. Brandi, A. Goti, *J. Org. Chem.* 67 (2002) 1678;
- (n) S. Cicchi, M. Marradi, P. Vogel, A. Goti, *J. Org. Chem.* 71 (2006) 1614;
- (o) J. Revuelta, S. Cicchi, A. Goti, A. Brandi, *Synthesis* (2007) 485.
- (a) S. Mzengeza, R.A. Whitney, *J. Org. Chem.* 53 (1988) 4074;
- (b) W. Carruthers, M.J. Williams, *J. Chem. Soc., Chem. Commun.* 38 (1986) 1287;
- (c) R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata, M. Kawanishi, *Bull. Chem. Soc. Jpn* 60 (1987) 215;
- (d) P. Merino, E.M. del Alamo, M. Bona, S. Franco, F.L. Merchan, T. Tejero, O. Vieceli, *Tetrahedron Lett.* 41 (2000) 9239.
- (a) J.R. Liddell, *Nat. Prod. Rep.* 14 (1997) 653;
- (b) J.R. Liddell, *Nat. Prod. Rep.* 15 (1998) 363;
- (c) J.R. Liddell, *Nat. Prod. Rep.* 16 (1999) 499;
- (d) J.R. Liddell, *Nat. Prod. Rep.* 17 (2000) 455;
- (e) J.R. Liddell, *Nat. Prod. Rep.* 18 (2001) 441;
- (f) J.R. Liddell, *Nat. Prod. Rep.* 19 (2002) 773.
- (a) J.P. Michael, *Nat. Prod. Rep.* 14 (1997) 619;
- (b) J.P. Michael, *Nat. Prod. Rep.* 15 (1998) 571;
- (c) J.P. Michael, *Nat. Prod. Rep.* 16 (1999) 675;
- (d) J.P. Michael, *Nat. Prod. Rep.* 17 (2000) 579;
- (e) J.P. Michael, *Nat. Prod. Rep.* 18 (2001) 520;
- (f) J.P. Michael, *Nat. Prod. Rep.* 19 (2002) 719;
- (g) J.P. Michael, *Nat. Prod. Rep.* 20 (2003) 458;
- (h) J.P. Michael, *Nat. Prod. Rep.* 21 (2004) 625;
- (i) J.P. Michael, *Nat. Prod. Rep.* 22 (2005) 603;
- (j) J.P. Michael, *Nat. Prod. Rep.* 24 (2007) 191.
- F. Cardona, A. Goti, A. Brandi, *Eur. J. Org. Chem.* (2007) 1551–1565.
- H. Yoda, *Curr. Org. Chem.* 6 (2002) 223–243.
- (a) J. Rabczko, M. Chmielewski, *J. Org. Chem.* 64 (1999) 1347;
- (b) J. Rabczko, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Tetrahedron* 58 (2002) 1433.
- D. Socha, M. Jurczak, M. Chmielewski, *Carbohydr. Res.* 336 (2001) 315.
- I. Panfil, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Polish J. Chem.* 79 (2005) 239.
- D. Socha, K. Paśniczek, M. Jurczak, J. Solecka, M. Chmielewski, *Carbohydr. Res.* 341 (2006) 2005.
- K. Paśniczek, D. Socha, J. Solecka, M. Jurczak, M. Chmielewski, *Can. J. Chem.* 84 (2006) 534–539.
- I. Panfil, J. Solecka, M. Chmielewski, *J. Carbohydr. Chem.* 25 (2006) 673.
- K. Paśniczek, M. Jurczak, J. Solecka, Z. Urbańczyk-Lipkowska, M. Chmielewski, *J. Carbohydr. Chem.* 26 (2007) 195.
- S. Stecko, M. Jurczak, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Carbohydr. Res.* 343 (2008) 2215.
- S. Stecko, J. Solecka, M. Chmielewski, *Carbohydr. Res.* 344 (2009) 167.
- S. Stecko, K. Paśniczek, M. Jurczak, J. Solecka, M. Chmielewski, *Polish J. Chem.* 83 (2009) 237.
- S. Stecko, M. Jurczak, O. Staszewska-Krajewska, J. Solecka, M. Chmielewski, *Tetrahedron* 65 (2009) 7056.
- (a) K.B.G. Torrsell, *Nitrile oxides, nitrones and nitronates in organic synthesis*, Vch Publishers, Inc, New York, 1988;
- (b) E. Breuer, H.G. Aurich, A. Nielsen, *Nitrones, nitronates and nitroxides*, Wiley, New York, 1989;
- (c) H. Feuer (Ed.), *Nitrile oxides, nitrones and nitronates in organic synthesis*, Wiley, New York, 2008.
- (a) S. Cicchi, I. Hold, A. Brandi, *J. Org. Chem.* 58 (1993) 5274;
- (b) F. Cordero, F. Machetti, F. De Sarlo, A. Brandi, *Gazz. Chim. Ital.* 127 (1997) 25.
- (a) M. Closa, R. Wightman, *Synth. Commun.* 28 (1998) 3443;
- (b) O. Tamura, A. Toyao, H. Ishibashi, *Synlett* 8 (2002) 1344.
- A. Ashoorzadeh, V. Caprio, *Synlett* (2005) 346.
- (a) A. Padwa, *1,3-dipolar cycloaddition chemistry*, Wiley, New York, 1984
- (b) K.V. Gothelf, K.A. Jørgensen, *Chem. Rev.* 98 (1998) 863–909;
- (c) S. Karlsson, H.E. Högborg, *Org. Prep. Prod. Int.* 33 (2001) 103;
- (d) S. Kobayashi, K.A. Jørgensen, *Cycloaddition reactions in organic synthesis*, Wiley-VCH, Weinheim, 2002;
- (e) H. Pellissier, *Tetrahedron* 63 (2007) 3235;
- (f) A. Padwa, in: A. Padwa, W.H. Pearson (Eds.), *Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*, Wiley & Sons, Hoboken, NJ, 2003;
- (g) P. Merino, in: A. Padwa (Ed.), *Science of Synthesis*, Vol. 27, George Thieme, New York, NY, 2004, 511 p.;
- (h) P.N. Confalone, E.M. Hule, *Org. React.* 36 (1988) 1;

- (i) P. DeShong, S. Lander, J.M. Leginus, C.M. Dicken, in: D.P. Curran (Ed.), *Advances in Cycloaddition*, Vol.1, JAI Press Inc, 1988, 87 p.;
- (j) D. Black, R.F. Crozier, V.C. Davies, *Synthesis* (1975) 205.
- [32] M. Frederickson, *Tetrahedron* 53 (1997) 403.
- [33] (a) J.J. Tufariello, J.P. Tette, *J. Org. Chem.* 40 (1975) 3866;
(b) J.J. Tufariello, *Acc. Chem. Res.* 12 (1979) 396.
- [34] (a) J.A. Findlay, J.M. Matsoukas, J. Krepinsky, *Can. J. Chem.* 54 (1976) 3419;
(b) S. Yamagiva, N. Hoshi, H. Sato, H. Kosugi, H. Uda, *J. Chem. Soc., Perkin Trans. 1* (1978) 214.
- [35] K.H. Hollenbeak, M.E. Kuehne, *Tetrahedron* 30 (1974) 2307.
- [36] A. Alemany, C. Marquez, C. Pascual, S. Valverde, M. Martinez-Ripoll, J. Fayos, A. Perales, *Tetrahedron Lett.* 20 (1979) 3583.
- [37] A. Kjaer, R. Norrestam, J. Polonsky, *Acta Chem. Scand. B* 39 (1985) 745.
- [38] (a) K. Mori, in: J. ApSimon (Ed.), *The total synthesis of natural products*, Wiley, New York, 1992, , 216 p.;
- (b) D.W. Knight, *Contemp. Org. Synth.* 1 (1994) 287;
(c) T. Laduwahetty, *Contemp. Org. Synth.* 2 (1995) 133;
(d) I. Collins, *Contemp. Org. Synth.* 3 (1996) 295;
(e) I. Collins, *Contemp. Org. Synth.* 4 (1997) 281;
(f) I. Collins, *J. Chem. Soc., Perkin Trans. 1* (1999) 1377;
(g) T.M. Ugurchieva, V.V. Veselovsky, *Russian Chem. Rev.* 78 (2009) 337;
(h) I. Panfil, W. Abramski, M. Chmielewski, *J. Carbohydr. Chem.* 17 (1998) 1395.
- [39] (a) H.Q. Dai, Q.J. Kang, G.H. Li, Y.M. Shen, *Helv. Chim. Acta* 89 (2006) 527;
(b) L. Ferrie, S. Reymond, P. Capdevielle, J. Cossy, *Synlett* (2007) 2891.
- [40] D. Kim, E. Ma, K. Suk, J.K. Son, J.S. Lee, M. Woo, *J. Nat. Prod.* 64 (2001) 502.
- [41] (a) R. Rossi, F. Bellina, M. Biagetti, L. Mannica, *Tetrahedron: Asymmetry* 10 (1999) 1163;
(b) Q. Yu, J.F. Liu, Y.L. Wu, *J. Asian Nat. Prod. Res.* 1 (1999) 183.
- [42] H.W. Fehlhaber, G. Sznatzke, I. Vlahov, *Liebigs Ann. Chem.* (1987) 637.
- [43] (a) C.L. Dwyer, C.D. Gill, O. Ichihawa, R.J.K. Taylor, *Synlett* (2000) 704;
(b) A. Bundu, N.G. Berry, C.D. Gill, C.L. Dwyer, A.V. Stachulski, R.J.K. Taylor, *J. Whittall, Tetrahedron Asymmetry* 16 (2005) 283.
- [44] A. Zamojski, A. Banaszek, G. Grynkiewicz, *Adv. Carbohydr. Chem. Biochem.* 40 (1982) 1.
- [45] (a) F.W. Lichtenthaler, F.D. Klinger, P. Jarglis, *Carbohydr. Res.* 132 (1984) 1;
(b) B.D. Roth, W.H. Roark, *Tetrahedron Lett.* 29 (1988) 1255.
- [46] S. Valverde, S. Garcia-Ochoa, M. Martin-Lomas, *J. Chem. Soc., Chem. Commun.* (1987) 1714.
- [47] (a) P. Rollin, P. Sinay, *Carbohydr. Res.* 98 (1981) 1392;
(b) M. Gouedard, F. Gademer, *Bull. Soc. Chim. Fr.* (1973) 577;
(c) D.M. Mackie, A.S. Perlin, *Carbohydr. Res.* 24 (1972) 67;
(d) S. Lesage, A.S. Perlin, *Can. J. Chem.* 56 (1978) 2889;
(e) J.R. Parikh, W. Doering, *J. Am. Chem. Soc.* 89 (1967) 5505;
(f) J.P. Gesson, J.C. Jacquesy, M. Mondon, *Tetrahedron* 45 (1989) 2627;
(g) M. Bessodes, R. Benamghar, K. Antonakis, *Carbohydr. Res.* 200 (1990) 493;
(h) M. Inanaga, J. Katsuki, M. Yamaguchi, *Chem. Lett.* (1991) 1025;
(i) J.T. Link, S. Raghavan, M. Gallant, S.J. Danishefsky, T.C. Chou, L.M. Ballas, *J. Am. Chem. Soc.* 118 (1996) 2825;
(j) J.C. Lopez, A.M. Gomez, S. Valverde, *J. Chem. Soc., Chem. Commun.* (1992) 613;
(k) A.M. Gomez, S. Mantecon, S. Valverde, J.C. Lopez, *J. Org. Chem.* 62 (1997) 6612.
- [48] (a) S. Takano, Y. Shimazaki, Y. Sekiguchi, K. Ogasawara, *Synthesis* (1989) 539;
(b) S. Valverde, B. Herradon, M. Martin-Lomas, *Tetrahedron Lett.* 26 (1985) 3731;
(c) F. Sanchez-Sancho, S. Valverde, B. Herradon, *Tetrahedron Asymmetry* 7 (1996) 3209;
(d) A.S. Gopalan, H.K. Jacobs, *Tetrahedron Lett.* 31 (1990) 5575;
(e) W.R. Roush, A.P. Spada, *Tetrahedron Lett.* 23 (1982) 3773;
(f) S. Schabbert, R. Tiedemann, E. Schaumann, *Liebigs Ann. Recl.* (1997) 879;
(g) T. Bauer, *Tetrahedron* 53 (1997) 4763;
(h) M. Oizumi, M. Takahashi, K. Ogasawara, *Synlett* (1997) 1111;
(i) F. Marion, R. Le Fol, Ch. Courillon, M. Malacria, *Synlett* (2001) 138;
(j) I. Collins, *J. Chem. Soc., Perkin Trans. 1* (1999) 1377;
(k) J.M. Harris, G.A. O'Doherty, *Tetrahedron* 57 (2001) 5161.
- [49] (a) J.P. Vigneron, R. Meric, M. Larcheveque, R. Debal, G. Kunesch, P. Zagetti, M. Gallois, *Tetrahedron Lett.* 23 (1982) 5051;
(b) J.P. Vigneron, R. Meric, M. Larcheveque, R. Debal, J.Y. Lallemand, G. Kunesch, P. Zagetti, M. Gallois, *Tetrahedron* 40 (1984) 3521;
(c) K. Tomioka, T. Ishiguro, K. Koga, *J. Chem. Soc. Chem. Commun.* (1979) 652;
(d) K. Tomioka, T. Ishiguro, K. Koga, *Tetrahedron Lett.* 21 (1980) 2973;
(e) K. Tomioka, F. Sato, K. Koga, *Heterocycles* 17 (1982) 311;
(f) J. Mann, A. Thomas, *J. Chem. Soc., Chem. Commun.* (1985) 737;
(g) J. Mann, A. Thomas, *J. Chem. Soc., Perkin Trans I* (1986) 2287;
(h) F. Tabusa, T. Yamada, K. Suzuki, T. Mukaiyama, *Chem. Lett.* (1984) 405.
- [50] (a) P. Camps, J. Cardellach, J. Font, R.M. Ortuno, O. Ponsati, *Tetrahedron* 38 (1982) 2395;
(b) G.A. Danilova, V.I. Melnikova, K.K. Pivnitsky, *Tetrahedron Lett.* 27 (1986) 2489;
(c) J.A.J.M. Vekemans, G.A.M. Franken, G.J.F. Chittenden, E.F. Godefroi, *Tetrahedron Lett.* (1987) 2299;
(d) S. Takano, A. Kurotaki, M. Takahashi, K. Ogasawara, *Synthesis* (1986) 403;
(e) J.A.J.M. Vekemans, G.A.M. Franken, C.W.M. Dapperens, E.F. Godefroi, *J. Org. Chem.* 53 (1988) 627;
(f) F. Sanchez-Sancho, S. Valverde, B. Herradon, *Tetrahedron Asymmetry* 7 (1996) 3209;
(g) J. Ishihara, J. Miyakawa, T. Tsujimoto, A. Murai, *Synlett* (1997) 1417;
(h) F. Fazio, M.P. Schneider, *Tetrahedron Asymmetry* 11 (2000) 1869;
(i) A.K. Ghosh, S. Leshchenko, M. Noetzel, *J. Org. Chem.* 69 (2004) 7822.
- [51] (a) C. Schmidt, J. Bryant, *Org. Synth.* 72 (1995) 6;
(b) J. Mann, A. Weymouth-Wilson, *Org. Synth.* 75 (1998) 139.
- [52] J. Nasman, *Org. Synth.* 68 (1990) 162.
- [53] (a) I. Panfil, M. Chmielewski, *Tetrahedron* 41 (1985) 4713;
(b) I. Panfil, C. Bełzecki, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Tetrahedron* 47 (1991) 10087.
- [54] (a) W. Streicher, H. Reinshagen, F. Turnowsky, *J. Antibiot.* 31 (1978) 725;
(b) M. Chmielewski, J. Jurczak, A. Zamojski, *Tetrahedron* 34 (1978) 2977;
(c) K. Torsel, M.P. Tyagi, *Acta Chem. Scand B* 31 (1977) 237;
(d) S. Takano, Y. Shimazaki, M. Moriya, K. Ogasawara, *Chem. Lett.* (1990) 1177;
(e) S. Maciejewski, I. Panfil, C. Bełzecki, M. Chmielewski, *Tetrahedron* 48 (1992) 10363;
(f) I. Panfil, J. Krajewski, P. Gluziński, L. Stefaniak, M. Chmielewski, *Tetrahedron* 50 (1994) 7219.
- [55] I. Panfil, M. Śnieżek, B. Furman, M. Chmielewski (to be published).
- [56] K. Pańniczek, D. Socha, M. Jurczak, J. Frelek, A. Suszczyńska, Z. Urbańczyk-Lipkowska, M. Chmielewski, *J. Carbohydr. Chem.* 22 (2003) 612.
- [57] D. Socha, M. Jurczak, J. Frelek, A. Klimek, J. Rabczko, Z. Urbańczyk-Lipkowska, K. Suwińska, M. Chmielewski, F. Cardona, A. Goti, A. Brandi, *Tetrahedron Asymmetry* 12 (2001) 3163.
- [58] M. Jurczak, J. Rabczko, D. Socha, M. Chmielewski, F. Cardona, A. Goti, A. Brandi, *Tetrahedron Asymmetry* 11 (2000) 2015.
- [59] S. Stecko, K. Pańniczek, M. Jurczak, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Tetrahedron Asymmetry* 17 (2006) 68.
- [60] S. Stecko, K. Pańniczek, M. Jurczak, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Tetrahedron Asymmetry* 18 (2007) 1085.
- [61] S. Stecko, K. Pańniczek, C. Michel, A. Millet, S. Perez, M. Chmielewski, *Tetrahedron Asymmetry* 19 (2008) 1660.
- [62] S. Stecko, K. Pańniczek, C. Michel, A. Millet, S. Perez, M. Chmielewski, *Tetrahedron: Asymmetry* 19 (2008) 2140.
- [63] (a) A. Brandi, F. Cardona, S. Cicchi, F.M. Cordero, A. Goti, *Chem. Eur. J.* 15 (2009) 7808;
(b) P. Merino, P. Tejero, *Synlett* (2000) 442;
(c) M. Lombardo, C. Trombini, *Synthesis* (2000) 759;
(d) A. Goti, F. Cardona, *Angew. Chem. Int. Ed.* 44 (2005) 7832;
(e) A.E. Koumbis, J.K. Gallos, *Curr. Org. Chem.* 7 (2003) 585;
(f) S. Stecko, A. Mames, B. Furman, M. Chmielewski, *J. Org. Chem.* 73 (2008) 7402;
(g) S. Stecko, A. Mames, B. Furman, M. Chmielewski, *J. Org. Chem.* 74 (2009) 3094;
(h) E.L. Tsou, S.Y. Chen, M.H. Yang, S.C. Wang, T.R.R. Cheng, W.C. Cheng, *Biorg. Med. Chem.* 16 (2008) 10198;
(i) P. Merino, I. Delso, T. Tejero, F. Cardona, M. Marrani, E. Gaggi, C. Parmeggiani, A. Goti, *Eur. J. Org. Chem.* (2008) 2929;
(j) A. Toyao, O. Tamura, H. Talagi, H. Ishibashi, *Synlett* (2003) 35;
(k) F. Cardona, G. Moreno, F. Guarna, P. Vogel, C. Schuetz, P. Merino, A. Goti, *J. Org. Chem.* 70 (2005) 6552;
(l) C.Y. Yu, M.H. Huang, *Org. Lett.* 8 (2006) 3021;
(m) P. Merino, S. Franco, F.L. Merchant, T. Tejero, *Synlett* (2000) 442;
(n) E. Racine, C. Bello, S. Gerber-Lemaire, P. Vogel, S. Py, *J. Org. Chem.* 74 (2009) 1766;
(o) V. Jäger, L. Bierer, H.Q. Dong, A.M. Palmer, D. Shaw, W. Frey, *J. Heterocyclic Chem.* 37 (2000) 455;
- [64] M. Jurczak, D. Mostowicz, I. Panfil, J. Rabczko, D. Socha, M. Chmielewski, *Targets Heterocycl. Syst.* 5 (2001) 59.
- [65] M. Chmielewski, S. Stecko, W. Kośnik, *Curr. Org. Chem.* 12 (2008) 973.
- [66] A. Goti, S. Cicchi, F.M. Cordero, V. Fedi, A. Brandi, *Molecules* 4 (1999) 1.

- [67] (a) P. Cid, P. de March, M. Figueredo, J. Font, S. Milan, *Tetrahedron Lett.* 33 (1992) 667;
(b) D. Alonso-Perarnau, P. de March, M. Figueredo, J. Font, A. Soria, *Tetrahedron* 49 (1993) 4267;
(c) P. Cid, P. de March, M. Figueredo, J. Font, S. Milan, A. Soria, A. Virgili, *Tetrahedron* 49 (1993) 3857.
- [68] S. Stecko, J. Frelek, M. Chmielewski, *Tetrahedron Asymmetry* 20 (2009) 1778.
- [69] J.L. Garcia Ruano, A. Fraile, A.M. Martin Castro, M. Rosario Martin, *J. Org. Chem.* 70 (2005) 8825.
- [70] (a) O. Dirat, C. Kouklovsky, Y. Lanlglois, P. Lesot, J. Courtieu, *Tetrahedron Asymmetry* 10 (1999) 3197;
(b) C. Kouklovsky, O. Dirat, Th. Berranger, Y. Lanlglois, M.E. Tran-Huu-Dau, C. Riche, *J. Org. Chem.* 63 (1998) 5123.
- [71] (a) P. Merino, T. Tejero, U. Chiacchio, G. Romeo, A. Rescifina, *Tetrahedron* 63 (2007) 1448;
(b) P. Merino, S. Anoro, F.L. Merchan, T. Tejero, *Heterocycles* 53 (2000) 861;
(c) P. Merino, J.A. Mates, J. Revuelta, T. Tejero, U. Chiacchio, G. Romeo, D. Iannazze, R. Romeo, *Tetrahedron Asymmetry* 13 (2002) 173;
(d) P. Merino, J. Revuelta, T. Tejero, U. Chiacchio, A. Rescifina, G. Romeo, *Tetrahedron* 59 (2003) 3581;
(e) L.R. Domingo, *Eur. J. Org. Chem.* (2000) 2273;
(f) M. Carda, P. Portoles, J. Murga, S. Uriel, J.A. Marco, L.R. Domingo, R. Zaragoza, H. Röper, *J. Org. Chem.* 65 (2000) 7000;
(g) M. Aurell, L.R. Domingo, P. Perez, R. Conreras, *Tetrahedron* 60 (2004) 11503.
- [72] (a) T.M. Jaspersen, W. Dong, M.R. Sierks, T. Skrydstrup, I. Lundt, M. Bols, *Angew. Chem. Int. Ed. Engl.* 33 (1994) 1778;
(b) T.M. Jaspersen, M. Bols, M.R. Sierks, T. Skrydstrup, *Tetrahedron* 50 (1994) 13449.
- [73] S. Cicchi, I. Höld, A. Brandi, *J. Org. Chem.* 58 (1993) 5274.
- [74] D.H.R. Barton, D. Crich, W.B. Motherwell, *Tetrahedron* 41 (1985) 3901.
- [75] (a) F.M. Cordero, M. Gensini, A. Goti, A. Brandi, *Org. Lett.* 2 (2000) 2475;
(b) F.M. Cordero, F. Pisaneschi, M. Gensini, A. Goti, A. Brandi, *Eur. J. Org. Chem.* (2002) 1941;
(c) F. Pisaneschi, F.M. Cordero, A. Brandi, *Synlett* (2003) 1889.
- [76] (a) R. Nash, P. Thomas, R. Waigh, G. Fleet, M. Wormald, P. Lilley, D. de Watkin, *Tetrahedron Lett.* 35 (1994) 7849;
(b) M. Wormald, R. Nash, A. Watson, B. Bhadoria, R. Langford, M. Sims, G. Fleet, *Carbohydr. Lett.* 2 (1996) 16.
- [77] (a) G. Pandey, D. Chakrabarti, *Tetrahedron Lett.* 37 (1996) 2885;
(b) A. Hakansson, J. Ameijde, G. Horne, R. Nash, M. Wormald, A. Kato, G. Besra, S. Gurcha, G. Fleet, *Tetrahedron Lett.* 49 (2008) 179.
- [78] (a) J. Royer (Ed.), *Asymmetric synthesis of nitrogen heterocycles*, Wiley-VCH, Weinheim, 2009;
(b) T. Hudlicky, J.W. Reed, *The way of synthesis*, Wiley-VCH, Weinheim, 2007.
- [79] (a) R.H. Furneaux, G.J. Gainsford, J.M. Mason, P. Tyler, *Tetrahedron* 51 (1995) 12611;
(b) G. Pandey, S. Dumbre, S. Pal, M. Khan, M. Shabab, *Tetrahedron* 63 (2007) 4756;
(c) B. Alcaide, P. Almendros, J.M. Alonso, M.F. Aly, *Chem. Eur. J.* 9 (2003) 3415;
(d) B. Alcaide, P. Almendros, M.C. Redondo, M.P. Ruiz, *J. Org. Chem.* 70 (2005) 8890 ;
(e) S. Hashimoto, H. Setoi, S. Takeno, Y. Ito, *Patent JP 61,277,685* (1986); *Chem. Abstr.* 106 (1987) 138253y;
(f) M. Ramana Rao, E. Pinyol, W.D. Lubell, *J. Org. Chem.* 72 (2007) 736;
(g) X. Li, Z. Zhu, K. Duan, H. Chen, Z. Li, Z. Li, P. Zhang, *Tetrahedron* 65 (2009) 2322.
- [80] S. Stecko, J. Solecka, M. Chmielewski, unpublished results.