C-Alkoxycarbonyl Nitrones: Building Blocks for the Synthesis of Butenolides, Lactams and Modified Nucleosides

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Abstract: Elaboration of isoxazolidines derived from the 1,3-dipolar cycloaddition of *C*-alkoxycarbonyl nitrones to suitably substituted alkenes leads to the development of new synthetic methodologies for the preparation of a wide range of natural products and derivatives including lactones, lactams and complex nucleosides. The insertion of a chiral centre in position α, with respect to nitrone functionality, or the presence of a chiral auxiliary at the nitrogen atom have allowed the enantioselective synthesis of the same compounds.

Keywords: Nitrones, butenolides, lactams, modified nucleosides.

1. INTRODUCTION

C-alkoxycarbonyl nitrones find valuable application in synthetic methodologies as key starting material for the construction of a wide range of natural and biologically interesting compounds. A considerable part of synthetic applications is connected with their use as 1,3-dipoles in cycloaddition reactions in stereocontrolled processes. In this context, the spectrum of application of *C*-alkoxycarbonyl nitrones appears to be very broad and the synthetic significance of these compounds could receive a rapid development.

The 1,3-dipolar chemistry of nitrones has been widely reported [1]; thus, the main focus of this review will be limited to recent studies carried out in our laboratories at the Universities of Messina and Catania on the use of *C*-alkoxycarbonyl nitrones for the design of synthetic routes towards butenolides, γ- and δ-lactams, and modified nucleosides.

2. CHIRAL *C*-ALKOXYCARBONYL NITRONES

In particular, optically active *C*-alkoxycarbonyl nitrones have allowed the enantioselective synthesis of various heterocyclic compounds. These active nitrones can be structurally categorized in two different classes: nitrones having the chirality at the *C*-substituent, Fig. (**1**) type I, and those that possess the chirality at the *N*-substituent, Fig. (**1**) type II. The best results have been achieved by the second type of nitrones for which synthetic approaches are easily available.

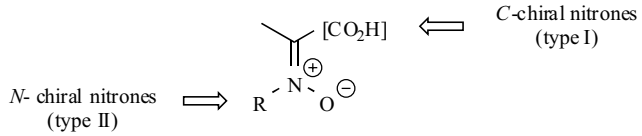
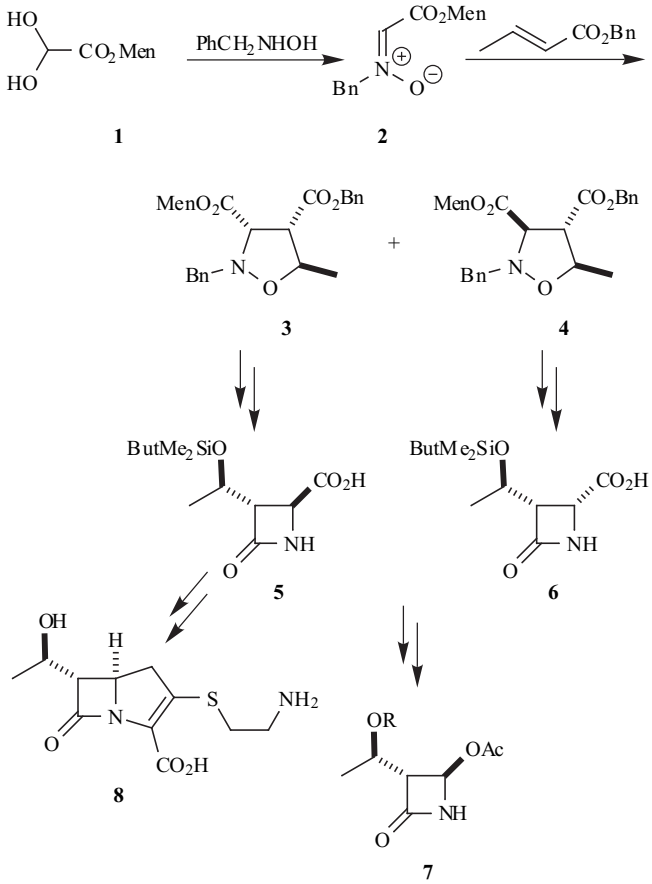


Fig. (1).

Kametani *et al.* applied 1,3-dipolar cycloaddition reactions of nitrones of type I, containing a chiral auxiliary in position α with respect to the nitrone functionality, in the synthesis of (+)- and (–)-thienamycin and penem and carbapenem precursors [2]. Thus, the chiral nitrone **2**, derived from the reaction of (–)-menthyl glyoxylate hydrate **1** with *N*-benzyl hydroxylamine, on reaction with benzyl *trans*-but-2-enoate, afforded isoxazolidines **3** and **4** as major products (1:1 ratio; 60% yield). Ring cleavage and debenzylation reaction of **3** and **4**, performed by catalytic



Scheme 1.

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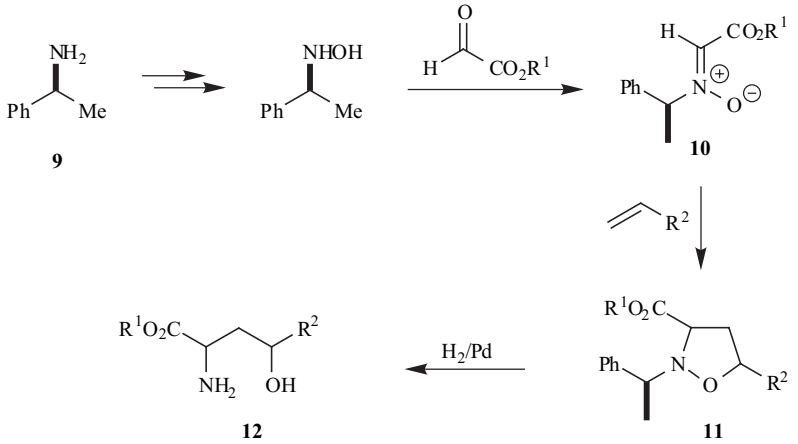
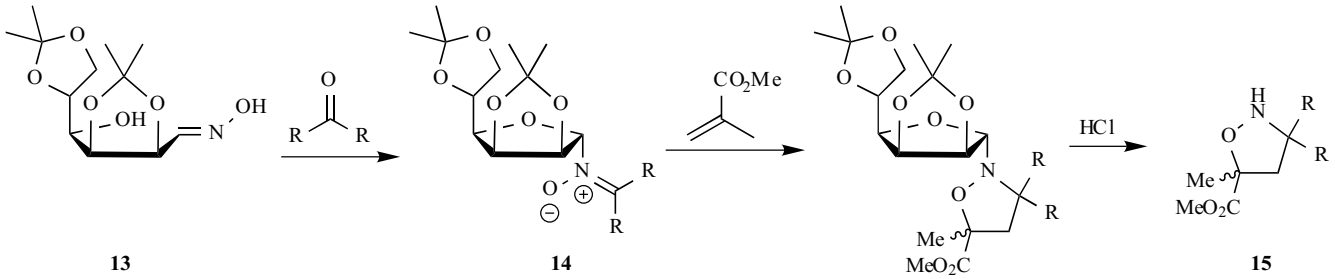


Scheme 2.



Scheme 3.

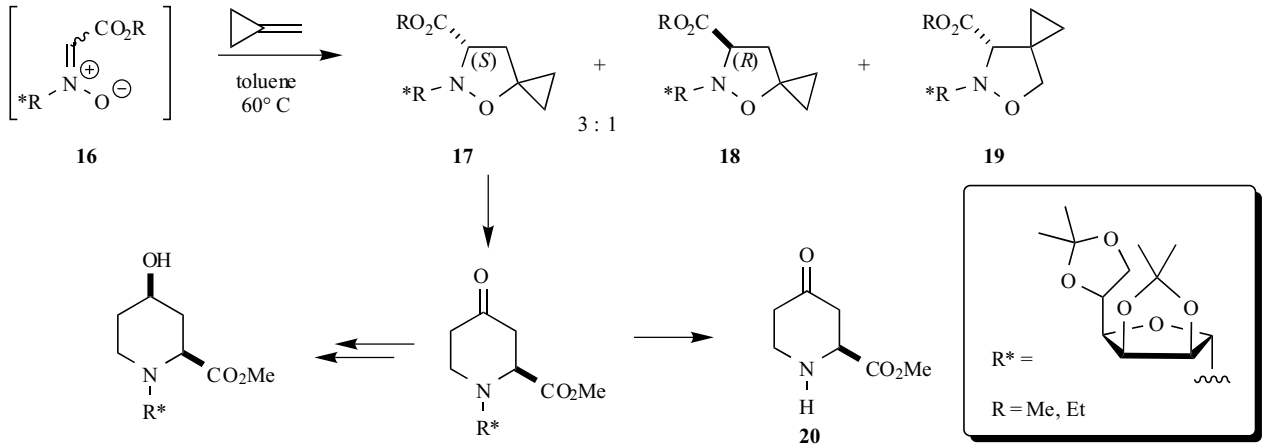
reduction over platinum oxide in methanol, gave the corresponding β-amino acids, which were converted in the corresponding azetidinones **5** and **6**, precursors of (+)- and (–)-thienamycin (**8**), Scheme (**1**).

Finally, the introduction of the acetoxy group at the C_4 position of the azetidinone ring, by oxidative acetoxylation with lead tetraacetate, afforded the desired 3-(1-hydroxymethyl)-2-oxoazetidin-4-yl acetate derivative **7**, precursor of penem and carbapenem.

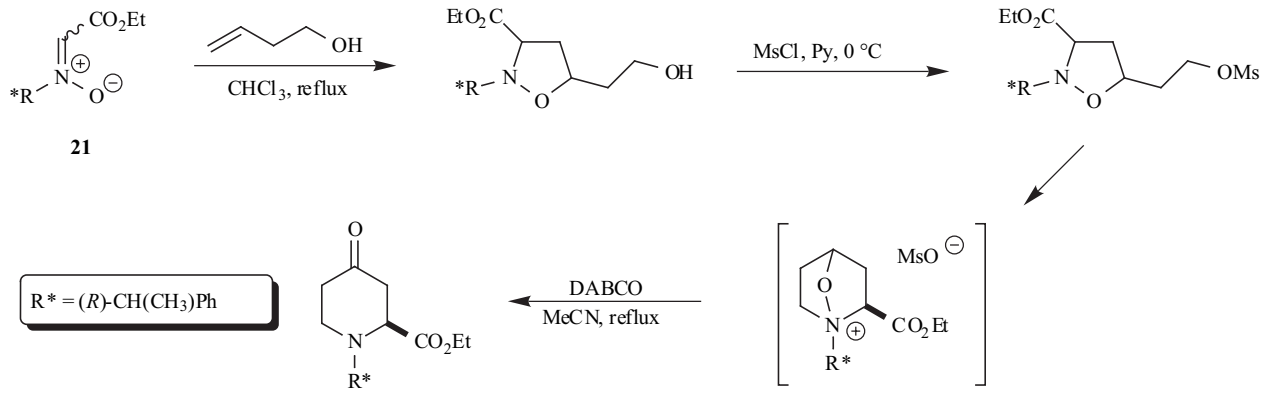
The most commonly used chiral substituent at the *N*-atom in nitrones of type II, is the 1-phenylethyl group [2–8]. These nitrones **10** are available from 1-phenethylamine **9** and the substituent has the advantage that it can be removed from the resulting isoxazolidine product **11**, by hydrogenolysis. In the reduction step the isoxazolidine **11** can be also opened to give the 3-amino alcohol **12** as outlined in Scheme (**2**).

Another type of nitrones bearing the chiral substituent at the nitrogen atom was developed by Vasella *et al.* [9–14]. Optically active nitrones are obtained in an elegant manner from inexpensive glycosides. When partially protected D-mannose oxime **13** reacts with acetone, nitrone **14,** which is formed [9,14], in the presence of methyl methacrylate, gives the isoxazolidines **15** as a mixture of two enantiomers, Scheme (**3**).

One of the advantages of this method developed by Vasella is that the chiral auxiliary is easily removed upon acidic hydrolysis. The *N*-unsubstituted isoxazolidines **15** are formed with optical purity of 90% ee.



Scheme 4.



Scheme 5.

Analogous nitrones have been recently applied in the synthesis of (2*S*)-4-oxo-pipecolic acid (**20**) [15]. The reaction route develops through a domino process having as a key step the diastereoselective cycloaddition of the *C*-alkoxycarbonyl nitrone **16** to methylene cyclopropane, followed by the thermal rearrangement of the adduct **17,** Scheme (**4**).

An alternative synthesis of both enantiomers of 4-oxopipecolic acid has been reported *via* the 1,3-dipolar cycloaddition of *C*-ethoxycarbonyl-*N*-(1*R*)-phenylethyl nitrone (**21**) to but-3-en-1-ol [16], Scheme (**5**).

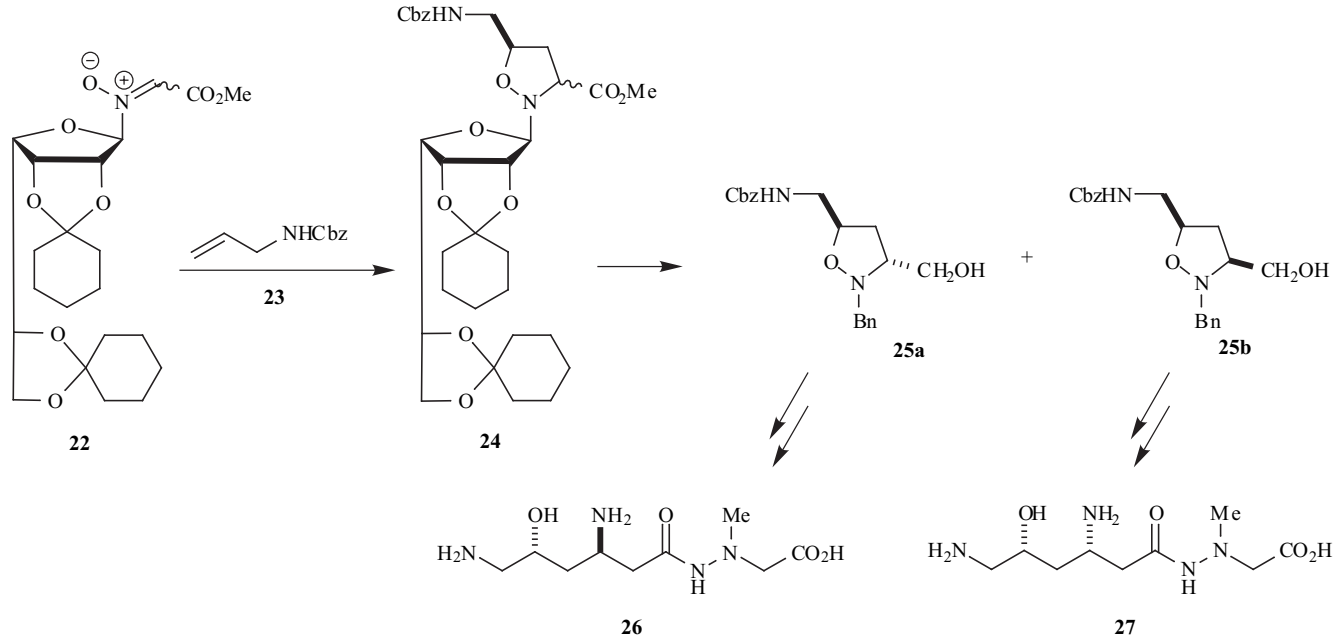
Kibayashi *et al.* have exploited the use of glycosyl nitrones in the synthesis of (+)-negamycin and (–)-epinegamycin [17,18]. The 1,3-dipolar cycloaddition reaction of nitrone **22**, formed from the protected D-gulose oxime and methyl glyoxylate, with allylamine **23** gives **24** in a 2:3 ratio of the *trans* and *cis* isomers. Contrary to the poor *cis*/*trans* selectivity, the diastereofacial selectivity of **22** and **23** is high. After hydrolysis, benzylation and reduction of the ester group, compounds **25 a**,**b** were obtained in high optical purities. By further reactions of **25a** and **25b**, respectively, (+)-negamycin (**26**) and (–)-epinegamycin (**27**) were formed, Scheme (**6**).

The opposite enantiomeric chiral induction was obtained starting from the L-gulosyl nitrone.

3. BUTENOLIDES

The ring system of butenolides constitutes the central skeleton of a series of natural oxygenated heterocycles [19] and is widely present in secondary metabolites [20], which show interesting physiological activities [21]. Besides their biological features, butenolides are useful intermediates in organic synthesis; starting with such compounds, peptide analogues or HIV-1 protease inhibitors have, for example, been prepared [22].

By exploiting the synthetic possibilities offered by the presence of the alkoxycarbonyl group on the *N*,*O*-heterocyclic nucleus, originated in the initial cycloaddition process, the synthesis of a series of α,γ-disubstituted butenolides, Fig. (**2**), has been performed, based on the hydrogenolytic ring cleavage of 3-alkoxycarbonyl substituted isoxazolidines [23].



Scheme 6.

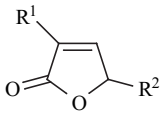


Fig. (2).

With respect to methodologies so far reported in literature [24], this approach provides a novel and flexible reaction pathway leading to a variety of 3,5-dialkyl substituted (5*H*)furanones, according to the substitution pattern present on dipole and dipolarophile.

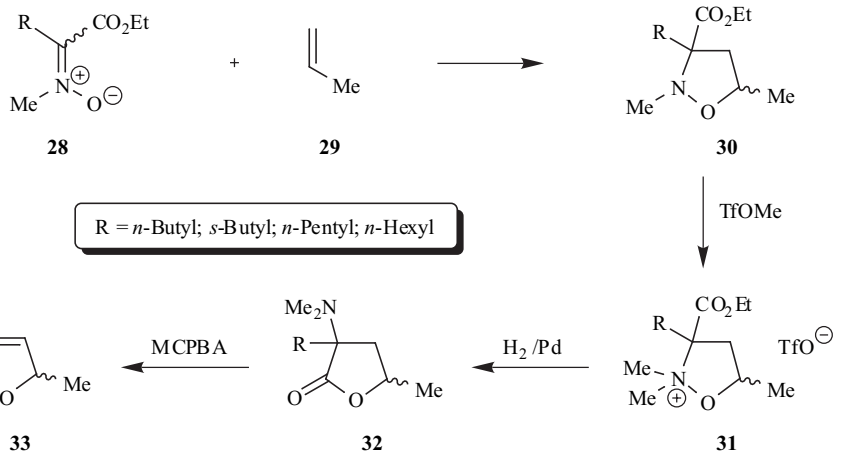
The reaction route towards the formation of volatile Streptomyces lactones [23] has been designed according to a four-step sequence starting from *C*-alkoxycarbonyl-*C*-alkyl-*N*-methyl nitrones **28**, which have been prepared from the corresponding α-ketoester and *N*-methyl hydroxylamine.

The reaction of **28** with propene **29** in decalin at 150 °C for 60 h affords a non-separated, epimeric mixture of isoxazolidines **30** (55–68% yield) which turn, by treatment with methyl trifluoromethansulfonate in dry CCl_4 at 0 °C for 3 h, into the corresponding isoxazolidinium salts **31**, in a nearly quantitative yield. Subsequent hydrogenolysis with 10% Pd on activated carbon in dry MeOH led to lactones **32** (90–95% yields), which were converted by Cope elimination into α,γ-disubstituted butenolides **33** (82–90% overall yields) [25], Scheme (**7**).

Following a similar procedure, a series of naturally occurring butenolides, as the peach lactone **35**, Scheme (**8**) and the 2-methylmuconolactone **37**, Scheme (**9**), have been synthesised [26].

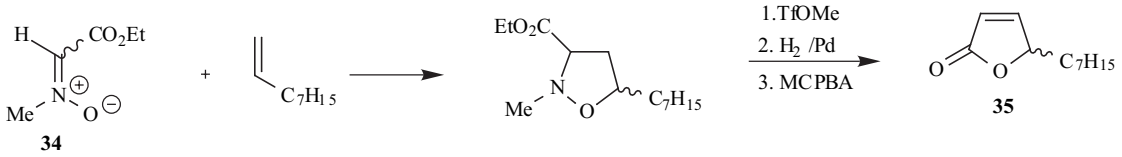
The approach to butenolide **39**, possessing the typical mushroom flavour, was, instead, troublesome. The final target was attained by the synthesis of butenolide **38**, prepared by 1,3-dipolar cycloaddition of nitrone **36** and allylic alcohol, which was tosylated and then converted in **39**, with $NaCNBH_3$ in 50% yield, Scheme (**10**).

Methyl isoacarenoate (**44**), a long-chain butenolide present in lichens, was prepared following a slight modification of the above reported procedure. Nitrone **40** was reacted with 1-tridecene **41**, and the mixture of epimeric



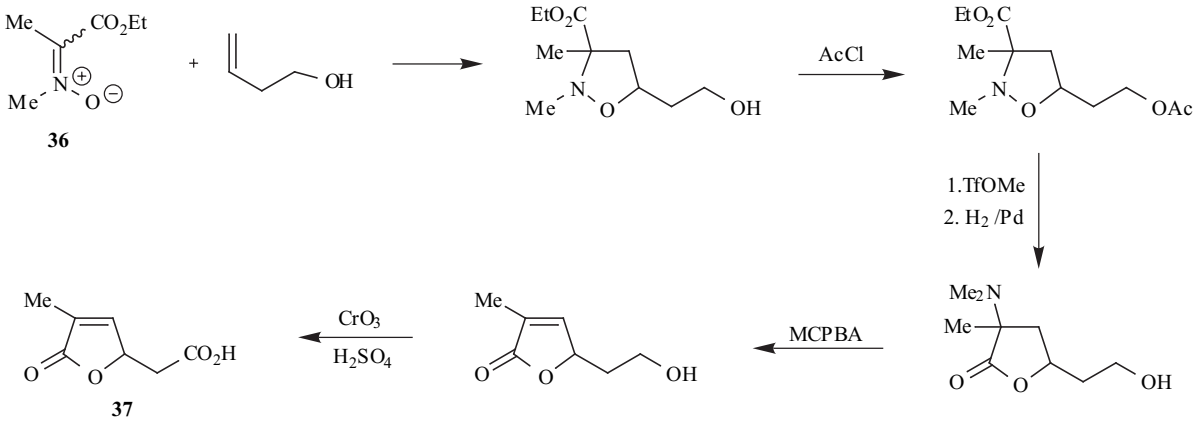
28 **29** **30** **31** **32** **33**

Scheme 7.



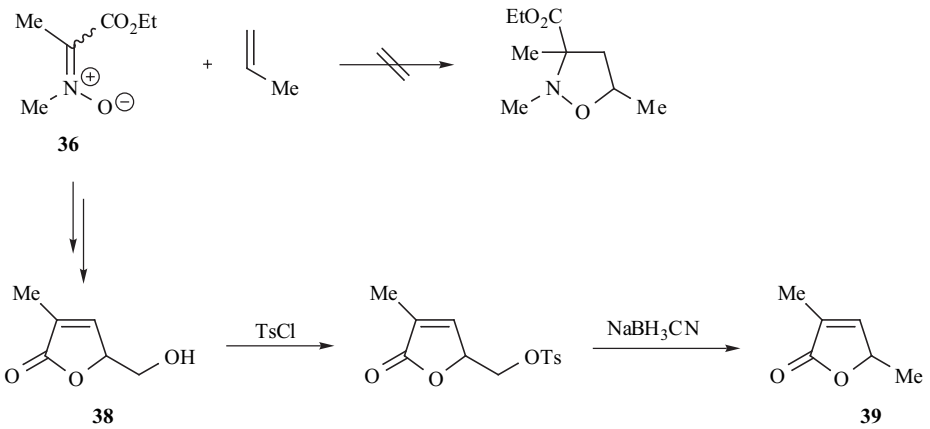
34 **35**

Scheme 8.

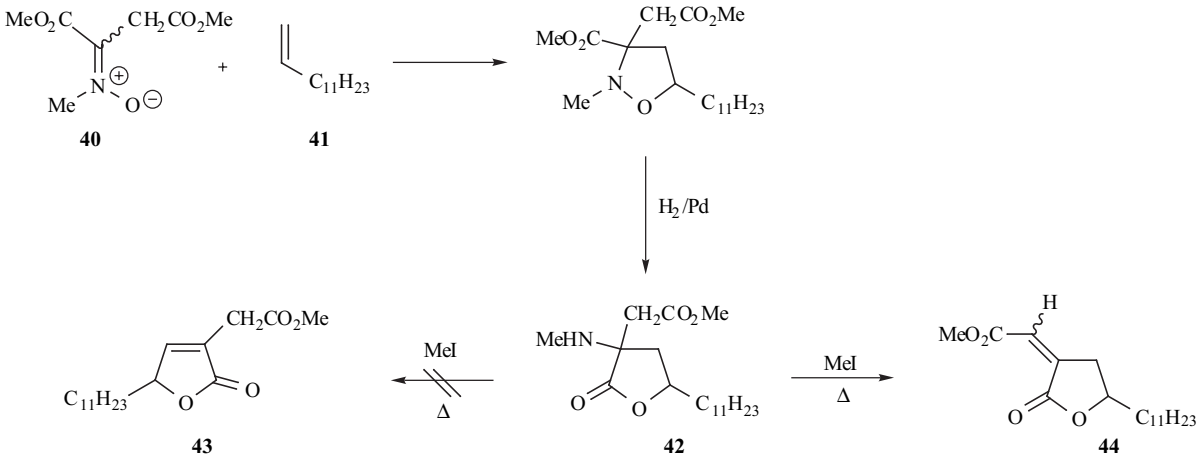


36 **37**

Scheme 9.



Scheme 10.



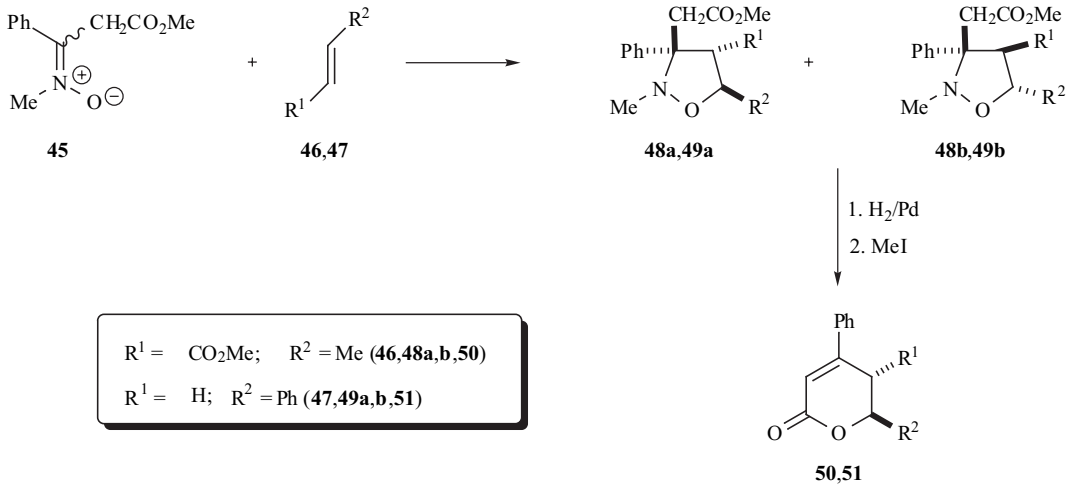
Scheme 11.

isoxazolidines so obtained was converted by ring opening reaction to amino lactones **42**, which by iodomethane treatment and Hofmann elimination, led to the termodynamically more stable lactone **44**, instead of methyl acarenoate (**43**), Scheme (**11**).

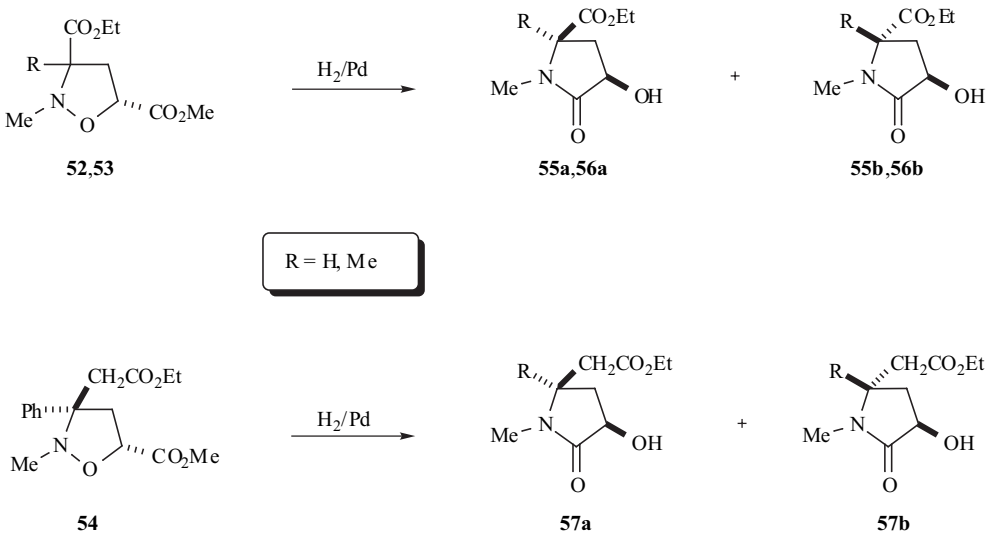
The synthetic route has been extended as an easy entry to homologous 2-pyranones, useful as intermediates in organic synthesis and in the biochemical and pharmaceutical sector [27].

Thus, the reaction of nitrone **45** with methyl crotonate (**46**) or styrene (**47**) leads to isoxazolidines **48** and **49,** which were converted by hydrogenolysis and iodomethane treatment into the corresponding δ-lactones **50** and **51**, Scheme (**12**).

The influence of an additional alkoxycarbonyl group, inserted at the 5 position of the heterocyclic nucleus, on the hydrogenolytic cleavage of the five-membered ring was also investigated [27]. Thus, the isoxazolidines **52**–**54**, obtained



Scheme 12.



Scheme 13.

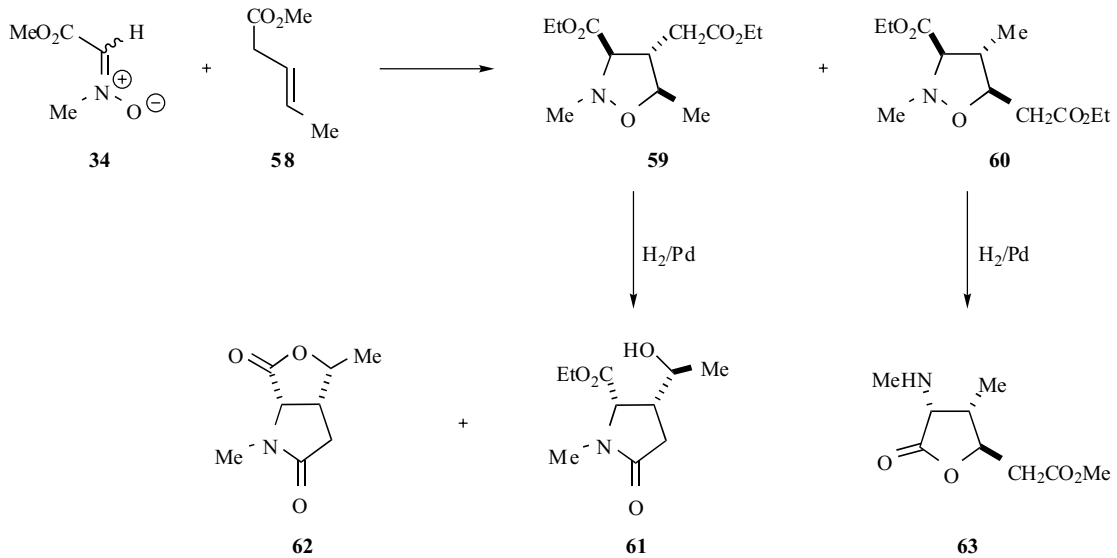
by 1,3-dipolar cycloaddition of the corresponding nitrones **34**, **36** and **45**, with methyl propenoate, upon treatment with H_2, in the presence of 10% Pd/C, gave rise to the epimeric hydroxypyrrolidones **55**–**57**. The reaction route leading to α-hydroxy-γ-lactams was exclusive with respect to the alternative five- or six-membered lactone formation showing a complete chemoselective intramolecular nucleophilic substitution, Scheme (**13**).

Analogously, the reaction of nitrone **34** with methyl *trans* 3-pentenoate (**58**), gave rise to the isoxazolidines **59** and **60,** which by hydrogenolytic ring cleavage, afforded derivatives **61**–**63**, Scheme (**14**). The formation of **61** and **62** from **59** is easily explainable on the basis of intramolecular lactamisation involving the *N*-methylamino group and the methoxycarbonyl substituent and leading to **61**, which undergoes spontaneous intramolecular esterification to the bicyclo derivatives **62**. On the contrary, the hydrogenolytic ring cleavage of **60** produces the five-membered lactone **63**, arising from a straightforward intramolecular esterification process, Scheme (**14**).

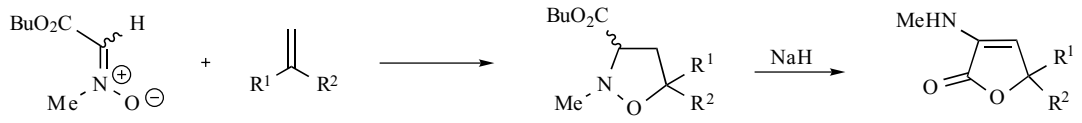
Treatment of 3-alkoxycarbonyl-substitued isoxazolidines with NaH affords a new reaction pathway towards 3-amino-2(5*H*)furanones, versatile synthons of β-lactams [28].

The reaction route develops in only two steps, starting from a 1,3-dipolar cycloaddition between nitrone **64** and the corresponding alkenes **65**–**71**, followed by NaH treatment [29], Scheme (**15**).

The chemical conversion of isoxazolidines **72**–**78** into furanones **79**–**85** has been rationalised as follows: the electron-withdrawing group CO_2Bu improves the acidity of the hydrogen atom at C_3, so promoting its abstraction by basic attack of NaH. The obtained enolate ion **86** evolves, *via* ring-opening, towards the formation of the anion **87**, which affords by a straightforward intramolecular nucleophilic acyl substitution the intermediate **88**, and then after double bond migration the 3-methylamino-2-(5*H*)furanones **79**–**85**, Scheme (**16**).



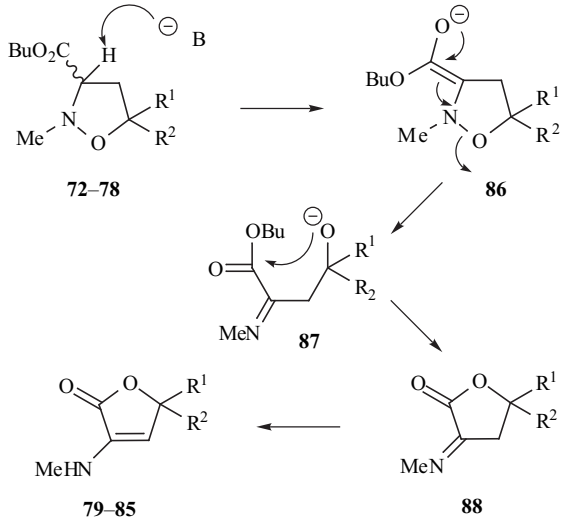
Scheme 14.



64 **65–71** **72–78** **79–85**

Alkene	R^1	R^2	Isoxazolidine	Furanone	Overall yield (%)
65	C_4H_9	H	**72**	**79**	53
66	C_5H_{11}	H	**73**	**80**	56
67	C_6H_{13}	H	**74**	**81**	61
68	C_3H_7	CH_3	**75**	**82**	58
69	C_6H_{11}	H	**76**	**83**	73
70	$-(CH_2)_5-$		**77**	**84**	48
71	CH_2OH	H	**78**	**85**	48

Scheme 15.



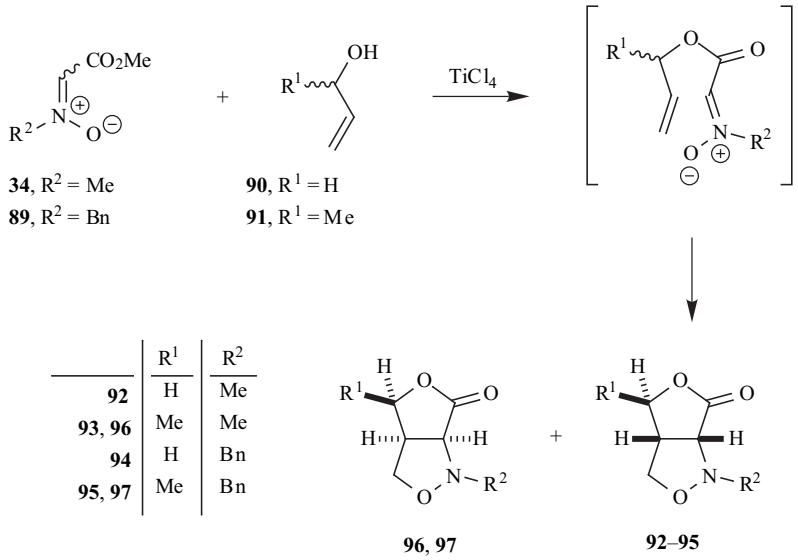
72–78 **86** **87** **88** **79–85**

Scheme 16.

With bicyclic furoisoxazolidines, a different reaction route is revealed, which leads to 3-amino-2(5*H*)furanones through a new rearrangement process of isoxazolidines nucleus [30].

The furoisoxazolidines have been synthesised by an intramolecular 1,3-dipolar cycloaddition of α-allyloxycarbonylnitrones, according to Tamura procedure [31], Scheme (**17**).

Treatment of isoxazolidines **92**–**97** with NaH leads to compounds **101**–**104** with very satisfactory yields. With reference to the synthesis reported in the Scheme (**18**), the lactone ring created in the intramolecular cycloaddition process is maintained and its functionalisation is controlled by the fragmentation of the isoxazolidine nucleus. The formation of lactone ring has been rationalised according to the Scheme (**18**), in which the driving force of the reaction is the retroaldol condensation reaction of the intermediate anion **99**. No evidence of the formation of compounds **105a**,**b** *via* path a has been found.

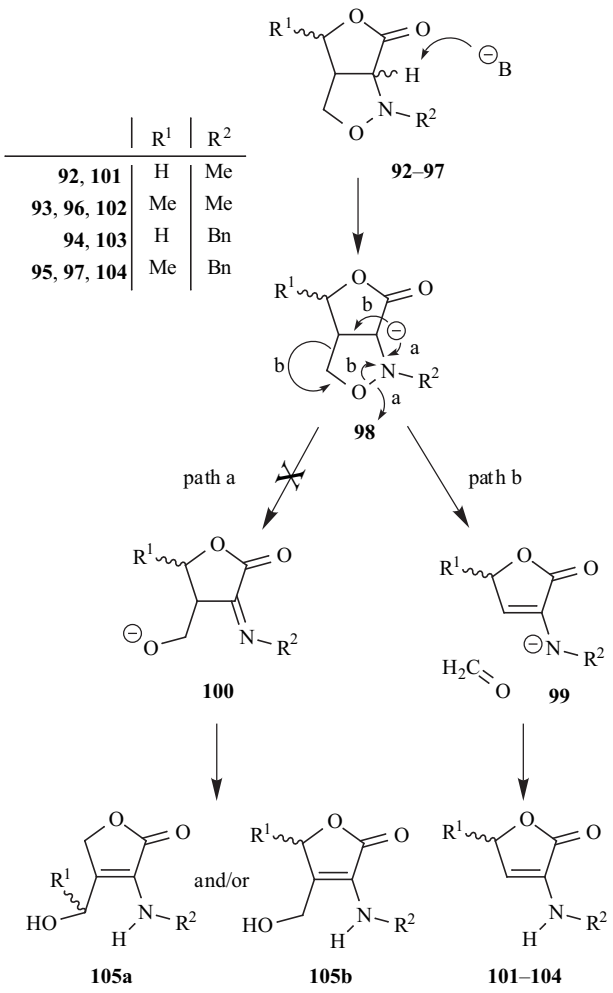


34, R^2 = Me
89, R^2 = Bn
90, R^1 = H
91, R^1 = Me

	R^1	R^2
92	H	Me
93, **96**	Me	Me
94	H	Bn
95, **97**	Me	Bn

96, **97** **92–95**

Scheme 17.



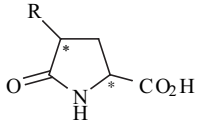
	R1	R2
92, **101**	H	Me
93, **96**, **102**	Me	Me
94, **103**	H	Bn
95, **97**, **104**	Me	Bn

Scheme 18.

The overall process has been addressed towards a versatile entry to enantiomerically pure 2-(5*H*)-furanones. According to path b, the synthesis of enantiomerically pure (5*R*)- and (5*S*)-3-methylamino-5-methyl-2-(5*H*)-furanone (**102**) has been carried out through the use of (2*R*)- and (2*S*)-3-buten-2-ol as dipolarophiles.

4. AMINO ACIDS AND LACTAMS

Pyroglutamic acid **106a** (the cyclic form of glutamic acid) and its derivatives have a wide range of synthetic applications [32], Fig. (**3**). Protected derivatives of **106a** have been used as versatile building blocks for the asymmetric synthesis of a number of natural and pharmacologically interesting products [33]. Pyroglutamic acid derivatives can also be considered as conformationally constrained glutamate analogues of biological interest [34].

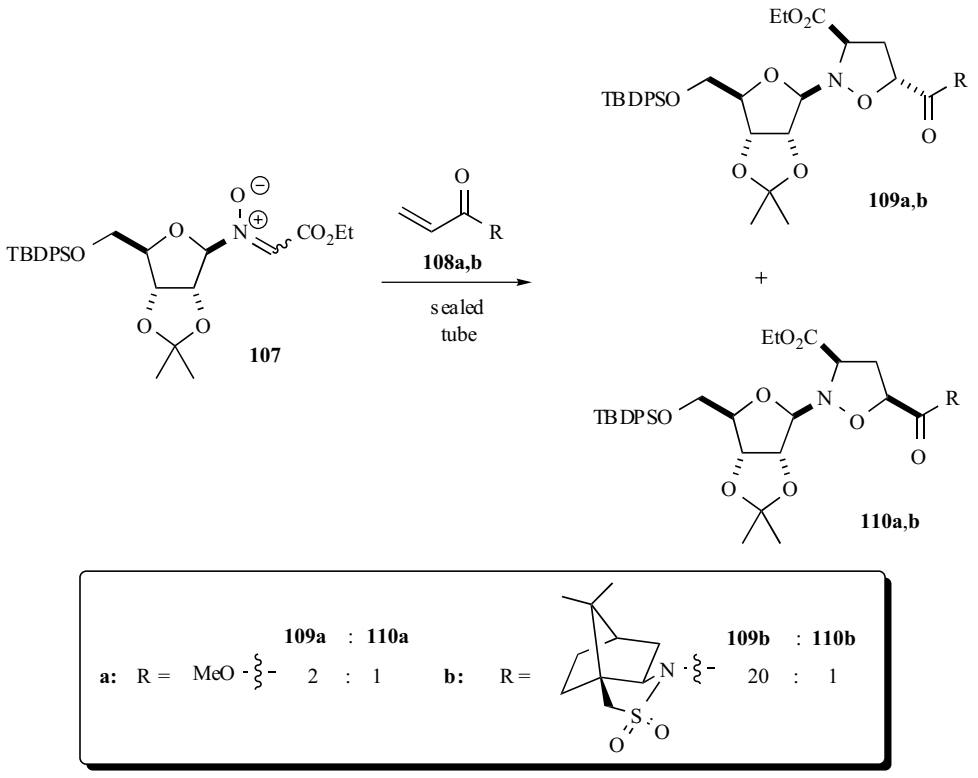


106a; R = H
106b; R = OH

Fig. (3).

However, in spite of the growing interest in highly functionalised pyrrolidines related to pyroglutamic acids [35], the synthesis of 4-hydroxypyroglutamic acids **106b** has received little attention. These compounds, in addition to their potential as synthetic intermediates, constitute an entry to important 4-substituted glutamic acid analogues [36].

The reaction of *N*-chiral *C*-alkoxycarbonyl nitrones, derived from ethyl glyoxylic ester and protected D-ribosyl



Scheme 19.

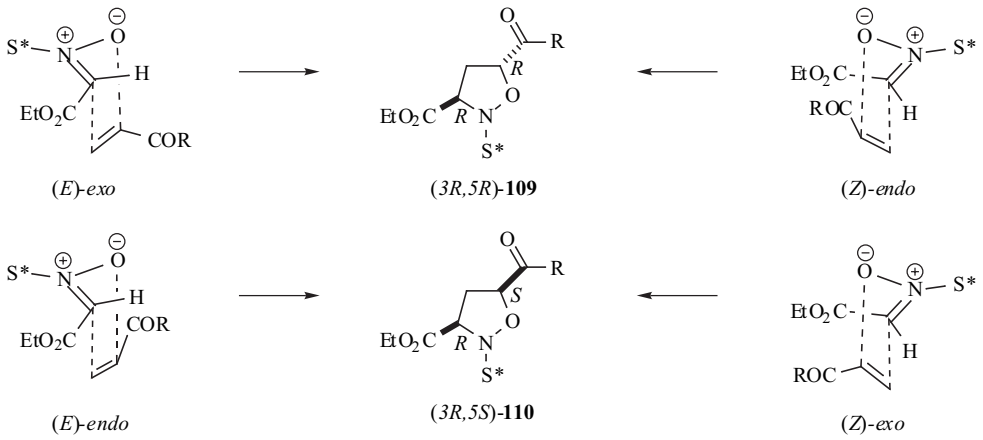


Fig. (4).

hydroxylamine, with methyl acrylate or the acrylamide of Oppolzer's sultam offers an efficient synthetic route towards (2*R*,4*R*)-, and (2*S*,4*R*)-4-hydroxypyroglutamic acids [37].

In particular, the reaction of nitrone **107** with methyl acrylate **108a** or the acrylamide **108b** in a sealed tube for 18 h led to the formation of two adducts **109a**,**b** and **110a**,**b** in a 2:1 or 20:1 ratio, respectively, Scheme (**19**).

The observed diastereoselectivity has been rationalised as shown in Fig. (**4**); the formation of (3*R*,5*R*)-**109** as the predominant adduct comes from a *Re-Re* attack either by an *E-exo* or a *Z-endo* approach [38].

A recent DFT study on the 1,3-dipolar cycloaddition reaction of *C*-methoxycarbonyl-*N*-methyl nitrone with methyl acrylate [39] shows a substantial preference for an *endo* approach that can be inferred to a higher reactivity of the *Z* isomer. The Mulliken population analysis provides some evidence for secondary orbital interaction between the dipole and the dipolarophile. In fact the **TS1A** shows a positive overlap density of 0.015, 0.005 and 0.005 for O_3H_{21}, C_4O_7 and $O_{13}H_{20}$, respectively Fig. (**5**); similar interaction can be seen in **TS2B** (C_4O_7=0.002 and O_3H_{22}=0.010). On the other hand, these interactions are not observed for the *exo* approach with the exception of **TS1B**, which are less intensive (O_3H_{21}= 0.011, C_4O_7= 0.002, and $O_{13}H_{20}$= 0.003).

Compounds **109** and **110** were, then, converted to the target 4-hydroxypyroglutamic acid derivatives in a one-flask procedure consisting of four sequential steps, Scheme (**20**). Elimination of the sugar moiety by acidic hydrolysis and subsequent *N-O* cleavage by hydrogenolysis gave unprotected ethyl 4-hydroxy-D-pyroglutamates **111** and **112**.

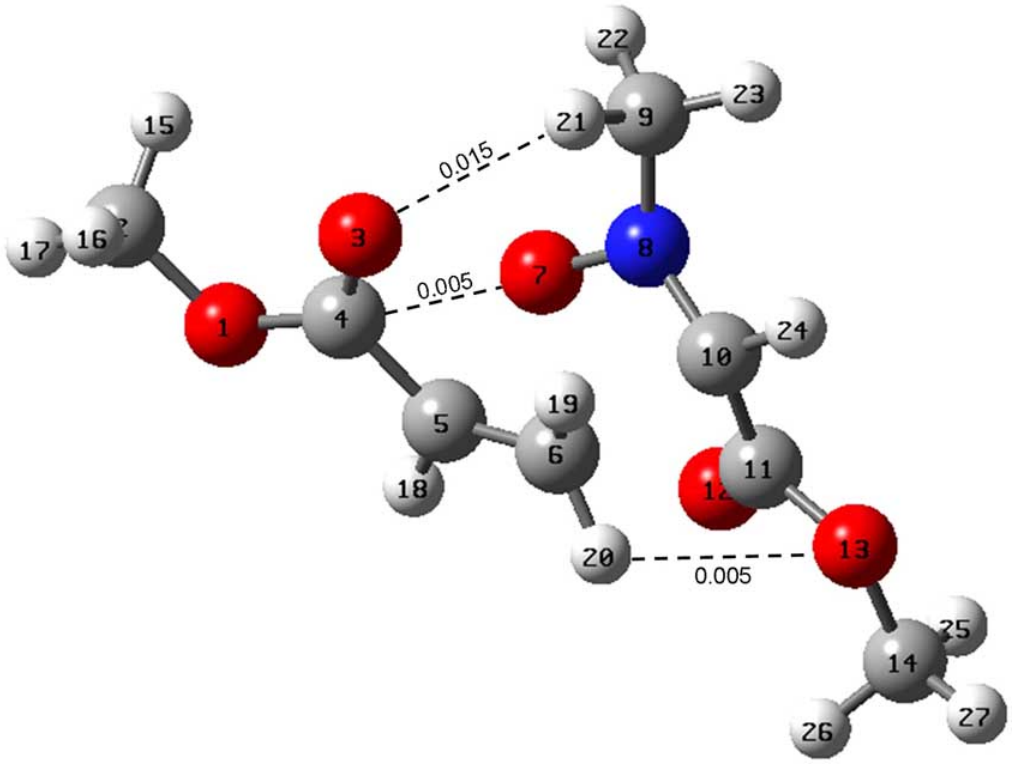
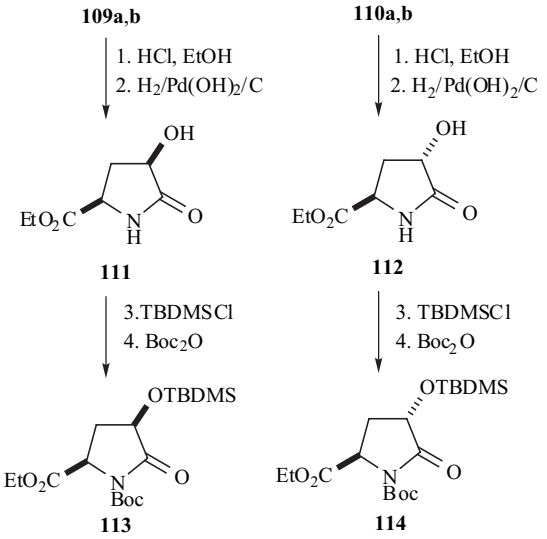


Fig. (5).

In situ protection of these compounds with *tert*-butyldimethylsilyl and *tert*-butoxycarbonyl groups afforded the protected compounds **113** and **114**.



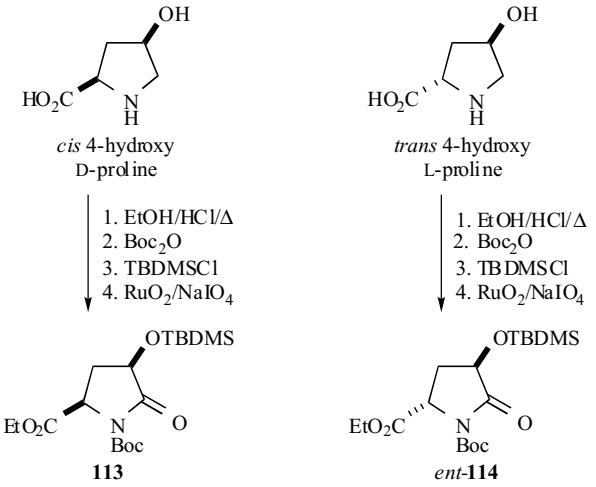
Scheme 20.

The absolute configuration of **113** and **114** was unambiguously assigned by a comparison of the physical and spectroscopic properties of compound independently obtained from *cis* 4-hydroxy-D-proline and *trans* 4-hydroxy-L-proline [40], respectively, Scheme (**21**).

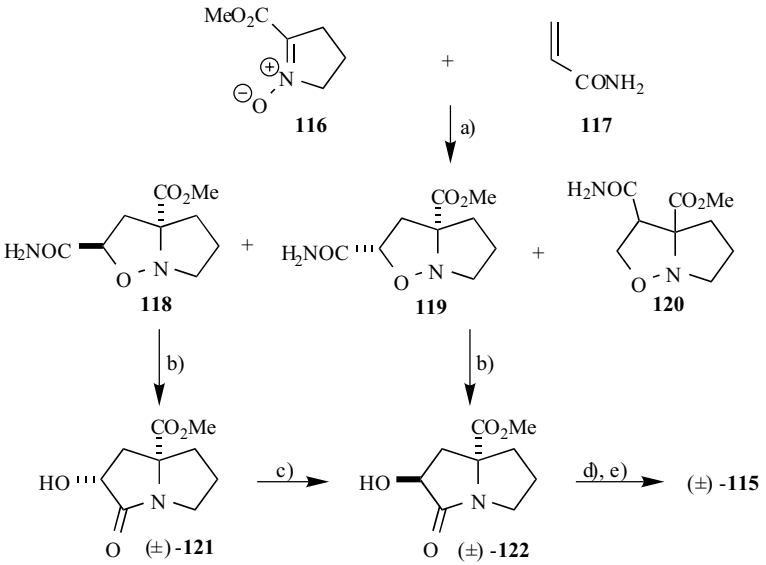
A previously reported enantioselective synthesis of the *cis* isomer **113**, formally derived from D-pyroglutamic acid, utilises the Oppolzer's sultam as a chiral auxiliary and the furane ring as effective carboxyl group equivalent. Thus, subsequent ruthenium-mediated oxidation was needed to deliver the desired pyroglutamates [41].

The approach starting from *C*-alkoxycarbonyl nitrones appears as a useful synthetic improvement: the method obviates the need for metal-assisted oxidation.

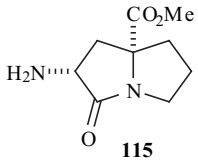
Bicyclic lactams have been prepared by the use of a cyclic *C*-alkoxycarbonyl nitrone: the process has been addressed towards the construction of the bicyclic dipeptide **115**, Fig. (**6**), which can be regarded as a β-turn mimetic of dipeptide *cis* Gly-Pro (GPTM) [42].



Scheme 21.



Scheme 22. a) H_2O, 60 °C, 14h (**118**: 37%, **119**: 42%, **120**: 19%); b) $Pd(OH)_2$ (cat), MeOH, AcOH, H_2, 12h (98%); c) (i) NaOH, MeOH, 70 °C, 2h, (ii) Dowex 50, (iii) CH_2N_2 (60%); d) (i) MsCl, Py, (ii) NaN_3, DMF (87%); e) Ni-Raney (80%).



115

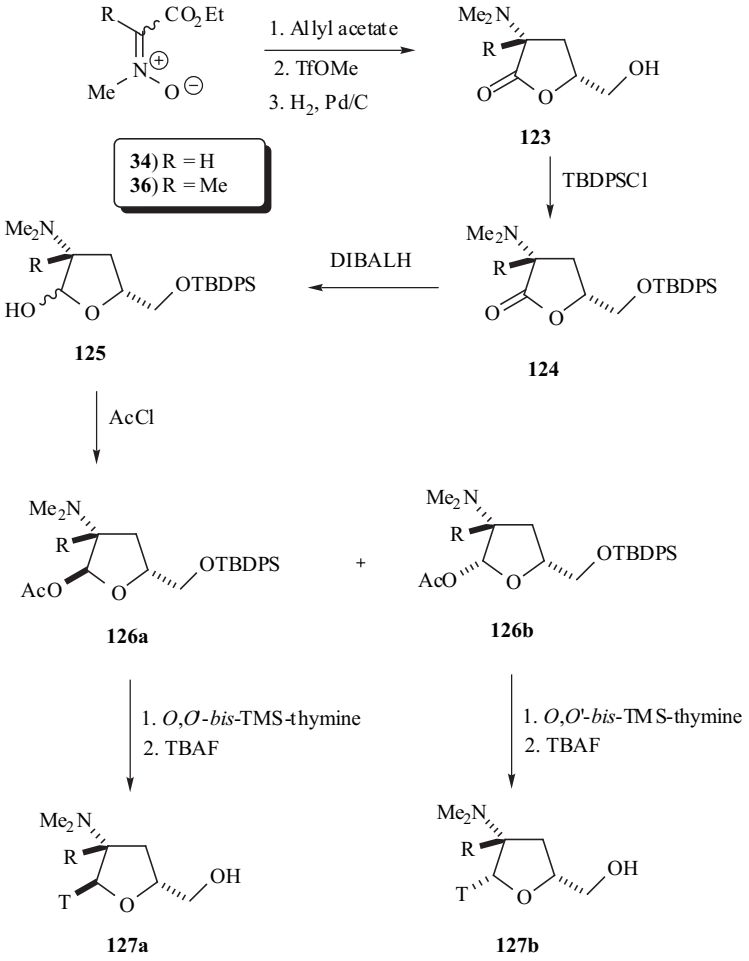
Fig. (6).

Thus, the synthesis of GPTM either in racemic or enantiomerically pure form starts from the 1,3-dipolar cycloaddition of nitrone **116** and an acrylic acid derivative **117**, followed by reductive ring opening of the isoxazolidine **119** and intramolecular cyclisation, to give pyrrolizidines **122**, possessing the bicyclic skeleton of GPTM **115**. Moreover, the *cis*-substituted pyrrolizidine **121**, analogously derived from **118**, could be quantitatively isomerised to the corresponding *trans* hydroxy ester **122** by the treatment with NaOH/MeOH at 70 °C followed by methylation with CH_2N_2. The *trans* alcohol **122** was easily converted into the corresponding *cis* amine **115** by mesylation followed by a nucleophilic displacement with NaN_3 and reduction of the azido group with Ni-Raney, Scheme (**22**).

5. NUCLEOSIDE ANALOGUES

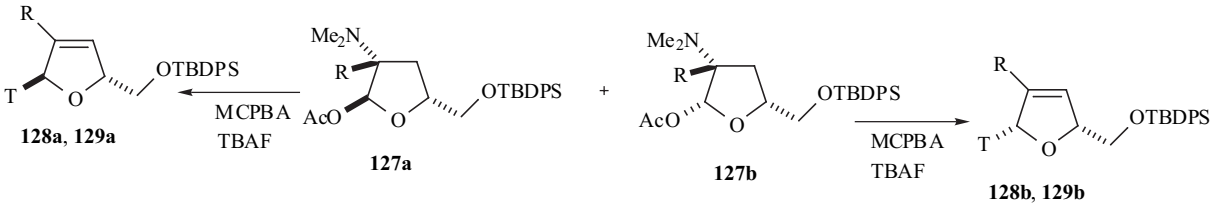
In the treatment of human viral diseases, nucleoside analogues have recently emerged as important therapeutic agents [43]. The majority of nucleoside analogues consists of modifications of the natural substrates in the heterocyclic base and/or the sugar moiety. Any variation on the base moiety should preserve the possibility of hydrogen bond interactions between heterocyclic bases, which are fundamental for the biological activity; as a consequence, only minor modifications of bases are present in biologically active modified nucleosides [44]. The most notable structural variations are found in the furanose ring with its replacement by an acyclic chain [45] or alternative carbo- [46] or heterocyclic systems [47] to give a series of biologically interesting compounds.

The synthetic strategy based on the 1,3 dipolar cycloaddition of *C*-ethoxycarbonyl nitrone **34** has been usefully exploited in order to provide a new and direct entry towards nucleosides analogues containing an amino function at 2 position [48]. The synthetic design, reported in Scheme (**23**), involves the formation of the 3-(dimethylamino)-5-(hydroxymethyl)dihydro-2(3*H*)-furanone (**123**), as key intermediate, which has been protected with TBDPSCl at C_5 hydroxyl group, reduced with DIBALH to lactols **125**, acetylated with acetyl chloride to compounds **126**, coupled with silylated thymine and then TBAF deprotected to give the 2'-dimethylamino-2',3'-dideoxynucleosides **127**. The generality of the synthetic scheme has also been tested by the preparation of the methyl analogue, starting from *C*-methyl-*C*-ethoxycarbonyl nitrone (**36**).

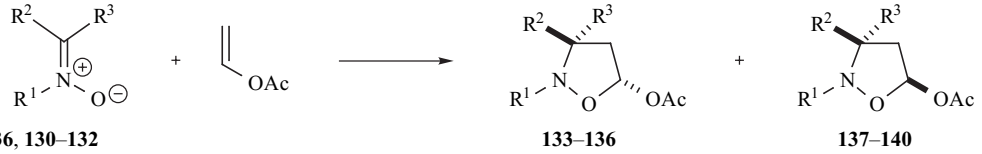


Scheme 23.

The reported methodology has been further directed to the synthesis of d4T and its methyl analogues. The interest for this synthetic way is widely demonstrated by the known and clinically tested anti-HIV activity of d4T. Thus d4T **128b** (R = H) and its methyl analogue **129b** (R = Me) have been synthesised after the removal of the dimethylamino group in **127b**, performed, according to a Cope elimination, by the treatment with MCPBA, followed by TBAF treatment, Scheme (**24**). Similar reaction performed with **127a** leads to the *trans* derivatives **128a** and **129a**.

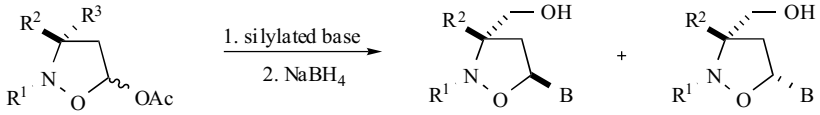


Scheme 24.



Nitrone	R^1	R^2	R^3	Yield %[a]	Epimeric ratio *cis*/*trans*
36[b]	Me	Me	CO_2Et	90	**133:137** (1:1)
130[b]	$PhCH_2$	CH_3-$(CH_2)_4$-	CO_2Et	81	**134:138** (1:1)
131[b]	$PhCH_2$	H	CO_2Et	87	**135:139** (1:4)[d]
132[c]	$PhCH_2$	H	PhCO	92	**136:140** (1:3)

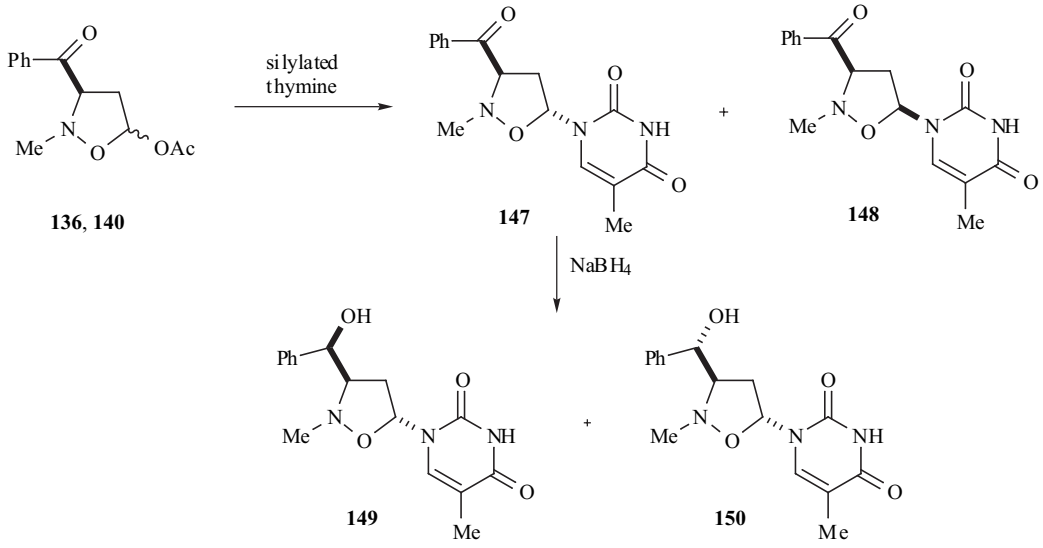
[a]Total yield. [b]Reaction at 70 °C in sealed tube. [c]Reaction at room temperature. [d]Unseparable mixture.



Isoxazolidine	R^1	R^2	R^3	B	Yield %[a]	Nucleoside
133, **137**	Me	Me	CO_2Et	Thymine	72	**141**, **144**[b]
134, **138**	$PhCH_2$	CH_3-$CH_2)_4$-	CO_2Et	5-Fluorouracil	70	**142**, **145**[b]
135, **139**	$PhCH_2$	H	CO_2Et	5-Fluorouracil	74	**143**, **146**[b]

[a]Yield of α + β mixture. [b]Separated by silica gel flash-chromatography.

Scheme 25.



Scheme 26.

Following the discovery of AZT, DDC, DDI, and 3TC as potent antiviral agents, acting as competitive inhibitors of the viral reverse transcriptase, the preparation of modified nucleosides with structural modifications in the heterocyclic ring [49] has become a very active research area and new synthetic methods have been designed and developed. In this context, the design of novel "ribose" rings has resulted in the discovery of effective biological agents, and promising results have been obtained from a new generation of nucleoside where the furanose ring has been replaced by an alternative isoxazolidine ring [50].

In this context, a deep study on modified nucleosides containing, as alternative ribose unit, an isoxazolidine ring, has been performed.

Scheme (**25**) shows a facile entry to *N*,*O*-nucleosides in only three steps with high overall yields, according to the pericyclic reaction of substituted nitrones **36**, **130**–**132** with vinyl acetate, followed by Vörbruggen nucleosidation [51], and $NaBH_4$ reduction of alkoxycarbonyl group present at position C_3 of the isoxazolidine ring [52].

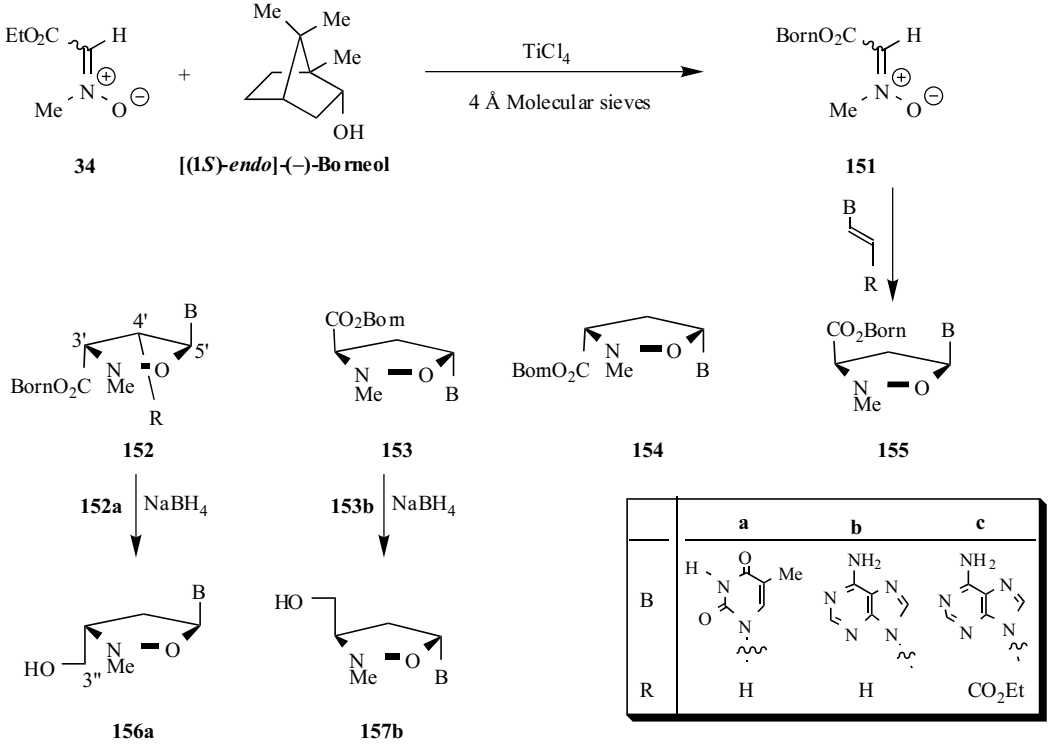
The Vörbruggen nucleosidation proceeded in all cases with a moderate stereoselectivity, to give **141**–**143** (α) and **144**–**146** (β) in 60:40 ratio, respectively.

A similar reaction performed with isoxazolidines **136** and **140** and silylated thymine lead to a mixture of compounds **147** and **148** in a 54% and 36% yield, respectively. The relative reduction of nucleoside **147** afforded, after chromatographic separation, the expected pair of diastereoisomers **149** and **150** (81% yield; 2:1 ratio), Scheme (**26**).

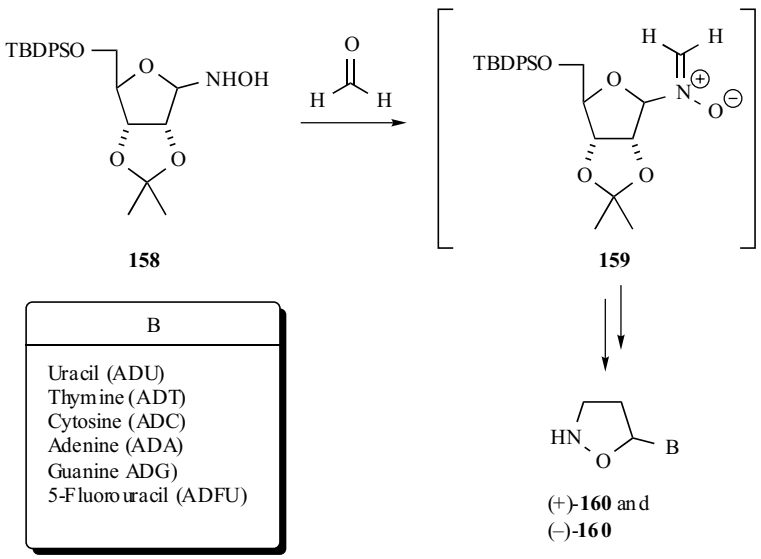
The presence of a chiral auxiliary on the *C*-carbon of the nitrone offers a variable degree of stereochemical control over the cycloaddition process, thus providing a good mean of access to *N*,*O*-nucleosides, in enantiomerically pure form. In fact, the stereoselective construction of the isoxazolidine ring [53] has been achieved through the cycloaddition of the chiral nitrone **151,** containing the [(1*S*)-*endo*]-(–)-borneol as chiral auxiliary, and vinyl nucleobases [54], followed by $NaBH_4$ reduction, Scheme (**27**).

Nitrone **151** has been prepared, as a mixture of *E* and *Z* isomers in a 3:1 ratio, from **34** through a transesterification reaction with [(1*S*)-*endo*]-(–)-borneol (1:1.5 ratio) in the presence of $TiCl_4$ as catalyst and molecular sieves. The subsequent reaction with vinylthymine in dry benzene at reflux for 48 h, afforded a mixture of three stereoisomeric compounds, two *trans* **152a** and **153a** (relative ratio 9.7:1) and one *cis* **154a** (*trans/cis* ratio 6.1:1). The cycloaddition reaction shows a complete regioselectivity, a satisfactory control over *cis*/*trans* diastereoselectivity with a preference for the *exo* approach (producing *trans* adducts, a good level of asymmetric induction. The absolute configuration of the major cycloadduct **152a** (3'*S*,5'*S*) has been tentatively assigned by PM3 calculations, assuming the nitrone *E* as the more reactive. In this case, the *E*-*Exo* TS (addition of vinylthymine to the *Si* face of nitrone) results 1.37 kcal/mol more stable than *E*-*exo* attack which, instead, leads to other stereoisomer **153a** (3'*R*,5'*R*).

The generality of this synthetic approach was also tested with vinyladenine. In this case only two adducts **153b** and **155b** were formed with a relative ratio of 10:1. The compound **153b** shows a C_3,C_5 *trans* relationship, while **155b** a *cis* one. Although the cycloaddition process shows a good control of *cis*/*trans* diastereoselectivity, and a nearly complete level of asymmetric induction, the absolute configuration of the obtained compounds cannot confidently be assigned on the basis of semiempirical support. In fact,



Scheme 27.



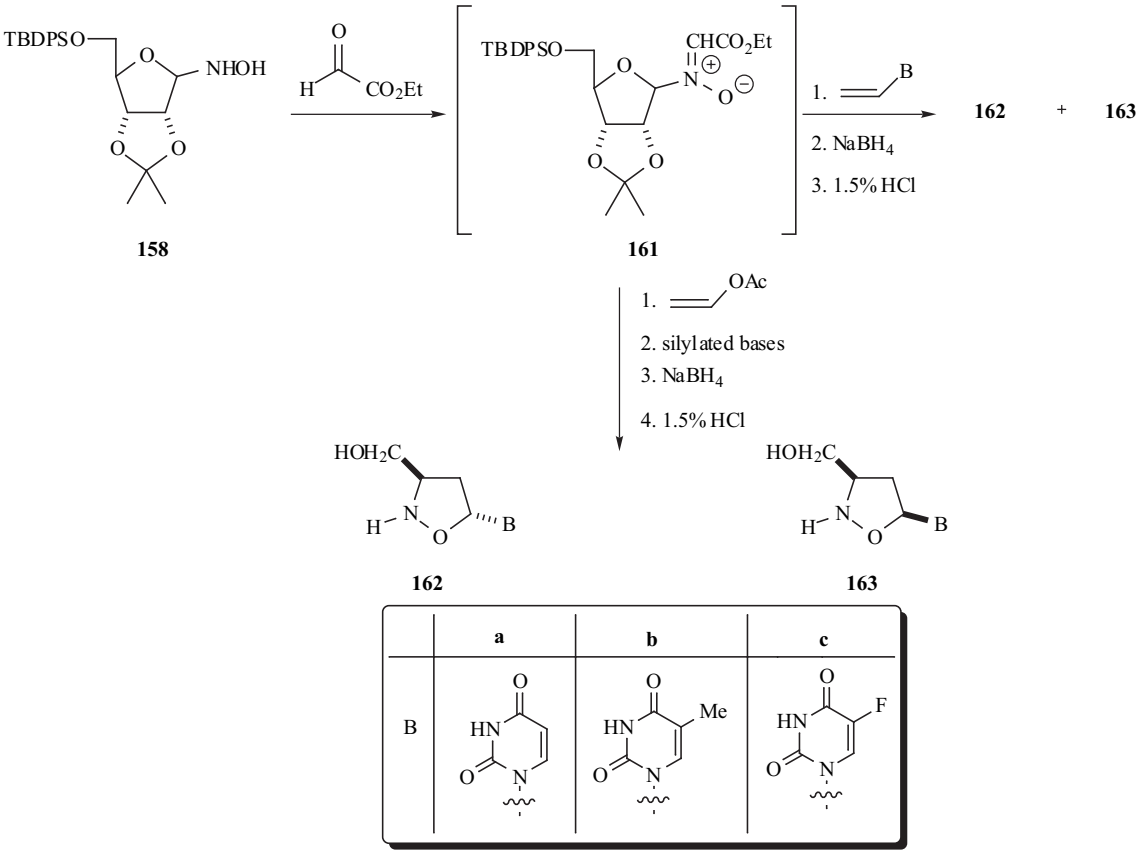
Scheme 28.

PM3 data do not provide theoretical support for the experimental results, indicating the formation of three adducts, two *trans* and one *cis*, in a relative ratio 62.2:25.5:8.5. It is worthy to mention that the most selective entry of the above reported scheme was obtained with disubstituted olefine which yielded **152c** as the only product isolated.

The C_3-hydroxymethyl nucleosides **156a** and **157b** were prepared by reductive manipulation of the major stereoisomers **152a** and **153b** respectively.

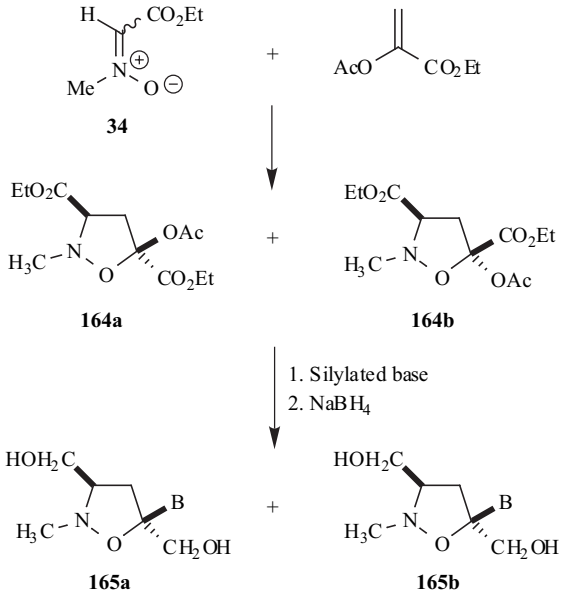
The chirality on the nitrone functionality can also be introduced at the nitrogen atom, using the sugar moiety as inductor of chirality. As mentioned before, Vasella-like nitrones are versatile building blocks in the preparation of *N,O*-nucleosides: the chiral auxiliary is easily introduced before the cycloaddition process and easily removed to give *N,O*-nucleosides unsubstituted at the nitrogen atom.

In this way, isoxazolidinyl nucleosides **160**, unsubstituted at the nitrogen atom, in enantiomerically pure form, have been recently synthesised [55] by the use of



Scheme 29.

nitrone intermediate **159** obtained by the reaction of (4*S*,5*R*)-5-[(1*R*)-2[[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy]1-hydroxy-ethyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde oxime **158** with formaldehyde, Scheme (**28**).



34 **164a** **164b** **165a** **165b**

Scheme 30.

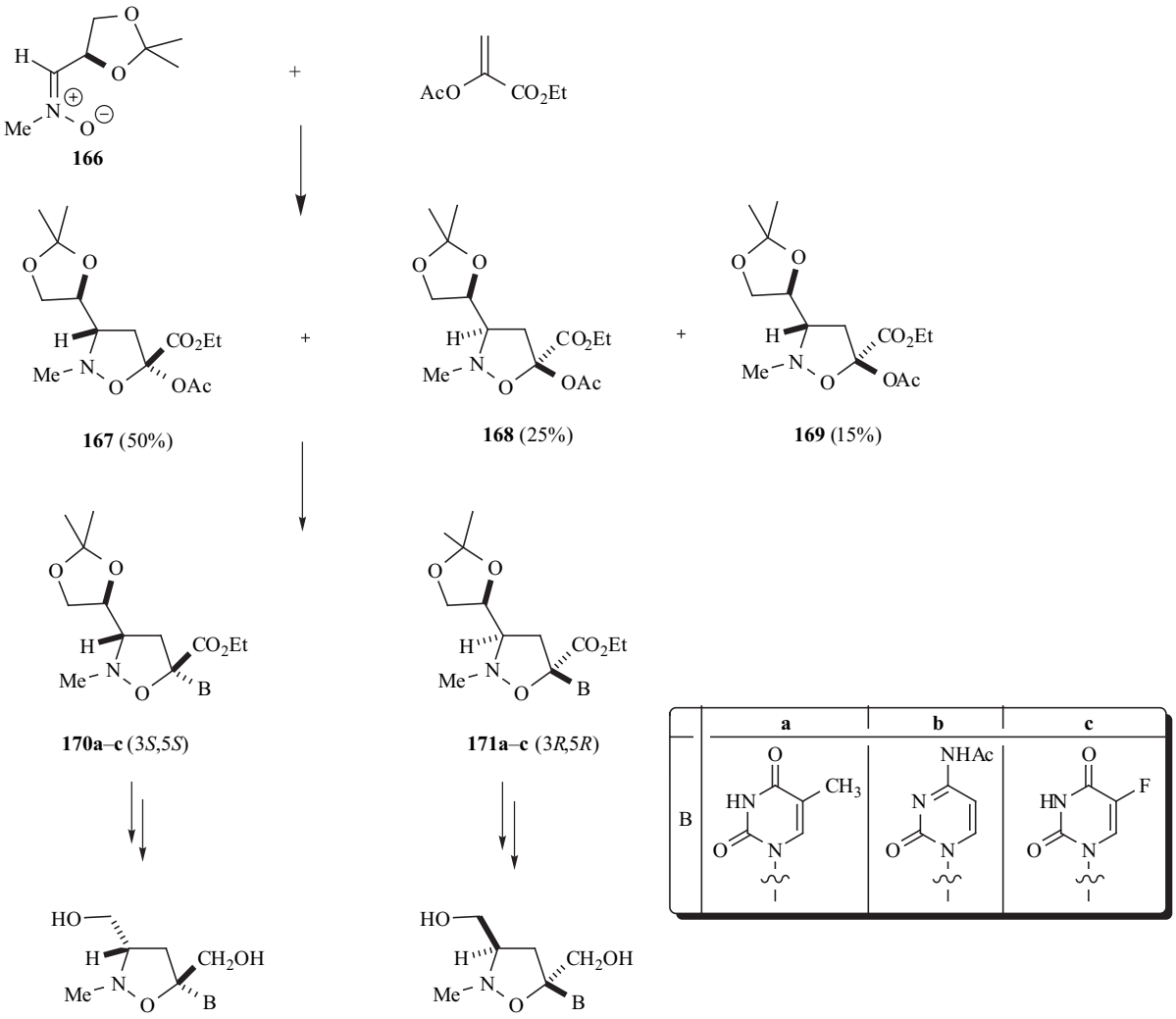
In particular, (–)-ADFU has revealed important biological properties. It is a good inductor of apoptosis on lymphoid and monocytoid cells, acting as a strong potentiator of Fas-induced cell death [56]. It is important to note that this compound represents the first evidence of the biological activity of isoxazolidinyl nucleosides.

Following a similar approach, the synthesis of 3-hydroxymethyl derivatives of ADT, ADU and ADFU has been developed using the *C*-alkoxycarbonyl-*N*-ribosylnitrone **161** obtained from **158** and ethyl glyoxylate [57,58], Scheme (**29**). The presence in the molecule of the hydroxymethyl group represents an improvement of the above synthetic procedure, because this group should promote the biological phosphorylation of the compounds and hence enhance their biological activity.

The *N*,*O*-nucleosides have been prepared according to two different procedures:

1) three step synthesis, based on the cycloaddition reaction of nitrone **161** with vinyl nucleobases, $NaBH_4$ reduction of alkoxycarbonyl group and easy removal of sugar moiety by dilute aqueous HCl treatment;

2) four step procedure based on the 1,3-dipolar cycloaddition of **161** with vinyl acetate, followed by



166 **167** (50%) **168** (25%) **169** (15%) **170a–c** (3*S*,5*S*) **171a–c** (3*R*,5*R*)

Scheme 31.

Vörbruggen nucleosidation, and then reduction and HCl treatment.

The three-step procedure showed a better stereoselectivity towards β-nucleosides, but proceeds with a lower yield.

The cycloaddition approach for constructing the isoxazolidine ring has been employed for the synthesis of a new class of *N,O*-nucleosides, the so called *N*,*O*-psiconucleosides, which carry an hydroxymethyl group at the anomeric carbon atom [59–61].

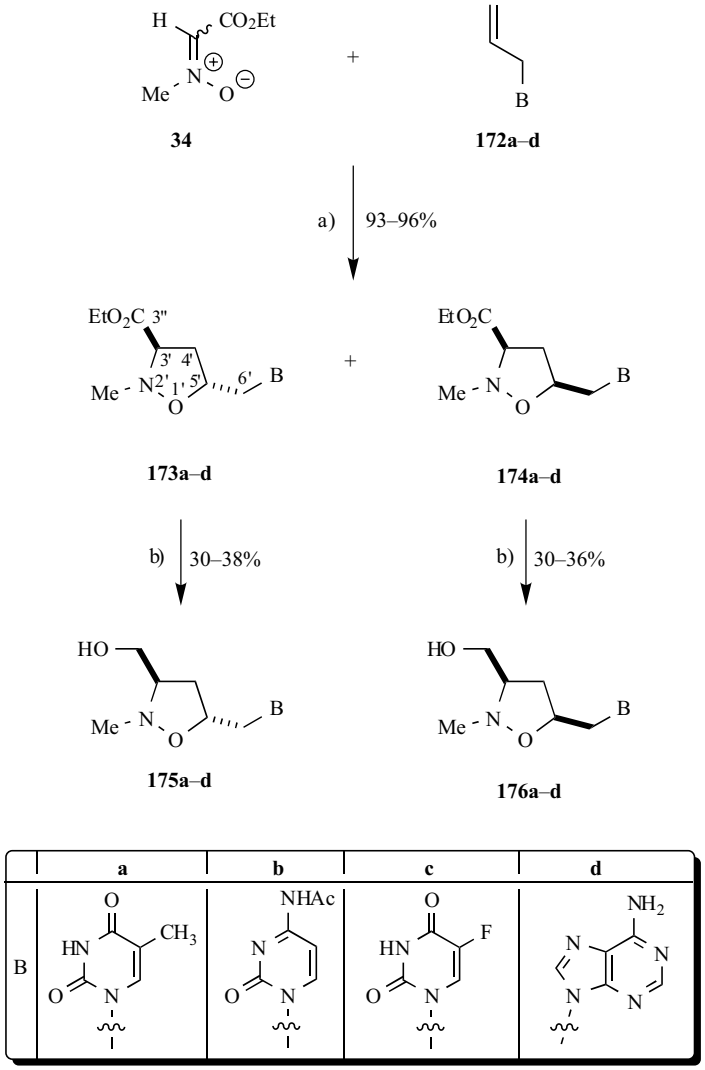
Thus, starting from nitrone **34** the acetoxy derivatives **164** were obtained. This mixture was used for preparing racemic nucleosides **165** by Vörbruggen nucleosidation and subsequent reduction of CO_2Et group, Scheme (**30**).

The asymmetric version of this reaction route has been developed through the use of nitrone **166** derived from D-glyceraldehyde [62]. The target nucleosides were achieved through the conversion of the dioxolane ring into hydroxymethyl group, by subsequent treatment with catalytic *p*-TsOH acid, sodium periodate, and sodium borohydride, Scheme (**31**).

The physiological properties of nucleosides can change dramatically if the anomeric aminal function is removed from the nucleoside [63]. Thus, the insertion of a carbon bridge between the base and the carbohydrate leads to homo-*N*-nucleosides, which show an increased resistance to hydrolytic or enzymatic cleavage, and increased conformational flexibility and rotational freedom [64]. In particular, homo-*N*-nucleosides with a guanine or adenine base moiety exhibit a good antiviral activity, while the 1'*C*-azanucleosides have shown to be very valuable as sequence-specific glycosidase inhibitors [65]. In this context, we have recently reported the synthesis [66] of the new class of homo-*N*,*O*-nucleosides containing pyrimidine and purine nucleobases in an effort to develop new specific glycosidase inhibitors.

Two different routes have been designed, involving the *C*-alkoxycarbonyl nitrone **34**, or the *C*-α-silyloxymethyl-*N*-methyl nitrone **177**. In particular, the reaction of **34** with allyl nucleobases **172a–d** give a mixture of epimeric isoxazolidines **173a–d** and **174a–d** (*ca*. 2:1 ratio), which following $LiAlH_4$ reduction leads to homo-*N*,*O*-nucleosides **175a–d**, and **176a–d** in moderate yields, Scheme (**32**).

This reaction route, even though versatile, is limited by the low yields of the obtained adducts.



Scheme 32. a) Toluene, sealed tube, 80 °C, 1h; b) $LiAlH_4$, THF, 0 °C, 1h.

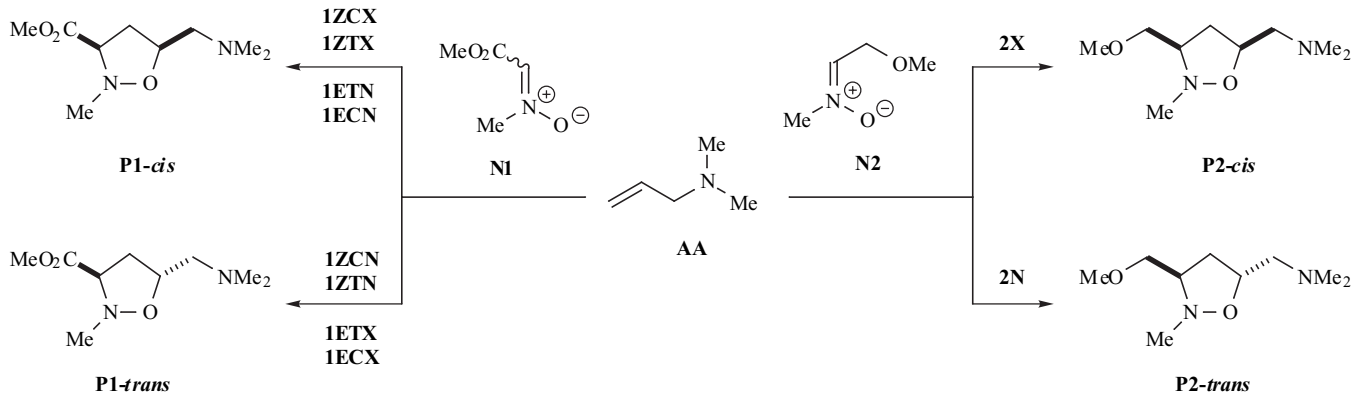
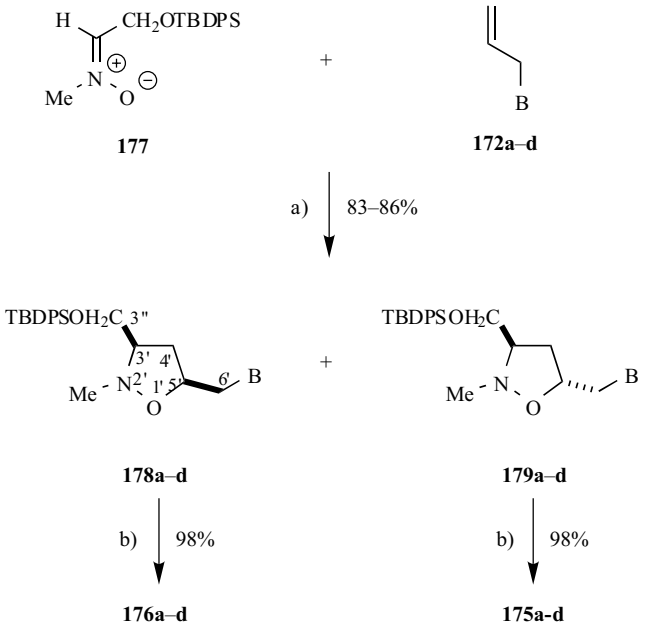


Fig. (7).

On the contrary, the cycloaddition of nitrone **177**, followed by TBAF treatment, has allowed a successful implementation of the synthetic strategy giving the β-derivatives **176a–d** as the major compounds, in high yields, Scheme (**33**).



Scheme 33. a) Toluene (THF for **172d**), sealed tube, 80 °C, 24h; b) TBAF, THF, r.t., 1h.

The reversal of *endo*/*exo* selectivity for nitrone **177** with respect to nitrone **34**, was rationalised by a DFT calculations. Accordingly, the *cis/trans* selectivity observed for the reaction of *N*,*N*-dimethyl allyl amine **AA**, chosen as model compounds for nucleobases **172a–d**, with nitrone **34** (**N1)** was due to the equilibrium between *E* and *Z* isomers, since in all cases the *exo* approach was favoured with respect to the *endo* one. The preferential formation of the *trans* isomer is promoted by the higher reactivity of the *E*-isomer as inferred from the energy differences between optimised transition structures 1ECX *vs*. 1ECN (ΔG_{ECX} 28.73; ΔG_{ECN} 32.71 kcal/mol). With the *C*-hydroxymethyl-*N*-methyl nitrone **N2**, chosen as a model compound for nitrone **177**, which exists only as the *Z*-isomer, the *exo* approach is still favoured and, in consequence, the reaction is more selective giving rise preferentially to the *cis* isomer, (ΔG_{2X} 31.56; ΔG_{2N} 33.93 kcal/mol) as depicted in Fig. (**7**).

6. CONCLUDING REMARKS

From the previous discussion, it becomes evident that our methodology based on *C*-alkoxycarbonyl nitrones is appropriate for the development of highly efficient stereoselective synthetic routes to a variety of interesting nitrogen-incorporating compounds. For further applications of *C*-alkoxycarbonyl nitrones our attention is now focused in their use with different nucleophiles, which allow access to more elaborated compounds. Thus, there is still great room for development of effective synthetic methodologies based on the nucleophilic addition to *C*-alkoxycarbonyl nitrones.

ACKNOWLEDGEMENT

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