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STEREOCONTROLLED CYCLOFUNCTIONALIZATIONS OF DOUBLE BONDS THROUGH HETEROCYCLIC INTERMEDIATES

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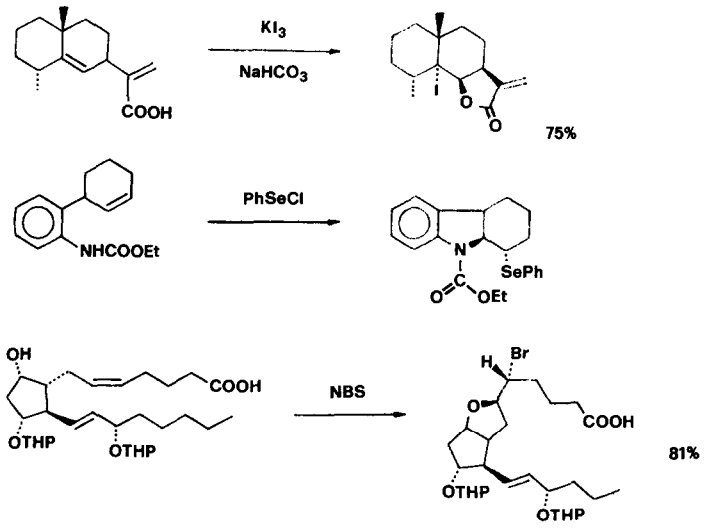
1. INTRODUCTION

The complexity of polyfunctionalized molecules as macrolide antibiotics[1] and polyethers[2] has stimulated more and more synthetic organic chemists in the research of new methods to introduce functionalities. In this context, the control of regio- and stereochemistry in the simultaneous creation of contiguous stereogenic centres is of particular importance in both rigid and flexible systems. Many factors influence the 1,2-control of stereoselectivity in acyclic systems for basic reactions such as aldol condensation, Claisen rearrangement and electrophilic addition to olefins. A rational insight into these factors has allowed improvement in the area of organic synthesis, particularly in planning synthetic strategies.

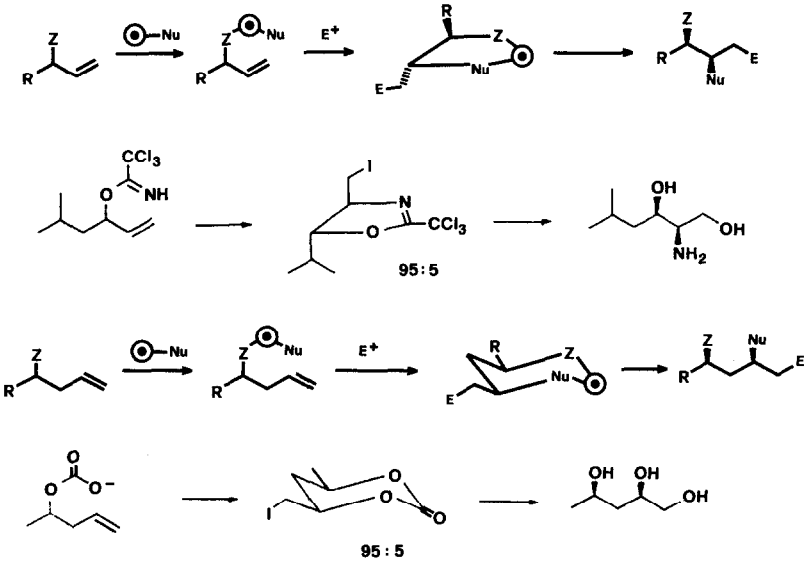
The functionalization of a double bond promoted by an electrophile is one of the most used reactions in organic synthesis. The term "cyclofunctionalization" was introduced by Clive[3] in 1977 indicating a process where the addition of an electrophile to an alkene containing an internal nucleophile, promotes a cyclization where a carbon of the double bond involved in the ring formation becomes attached to a group specifically chosen to allow further modifications.

In addition to the well known halolactonization,[4] a number of interesting methods has been exploited, showing the utility of this new strategy. In fact the ring closure takes place with participation of a number of electron-donating groups, such as OH, NH_2, NHR, SR, COOH, COO^-, $CONR_2$, etc. Some examples are reported in the following scheme.[5-7]



This approach has received growing interest, testified by the number of reports and excellent reviews written on this subject.[8-11]

The development of methods for the stereocontrolled synthesis of biologically interesting compounds containing a number of amino and hydroxy groups, continues to receive significant attention. Among various procedures,[12] the selective heterofunctionalization of acyclic olefins has been widely investigated to yield heterocycles as protected forms of functional groups. Thus the addition of an electrophile to suitable derivatives of unsaturated alcohols or amines promotes a regio- and stereocontrolled synthesis of heterocyclic intermediates.[13,14] As polyfunctionalized compounds are obtained after the hydrolysis, the formation of heterocyclic intermediates is a valuable tool for chirality transfer to a newly formed stereocentre from a pre-existent one.[15,16]

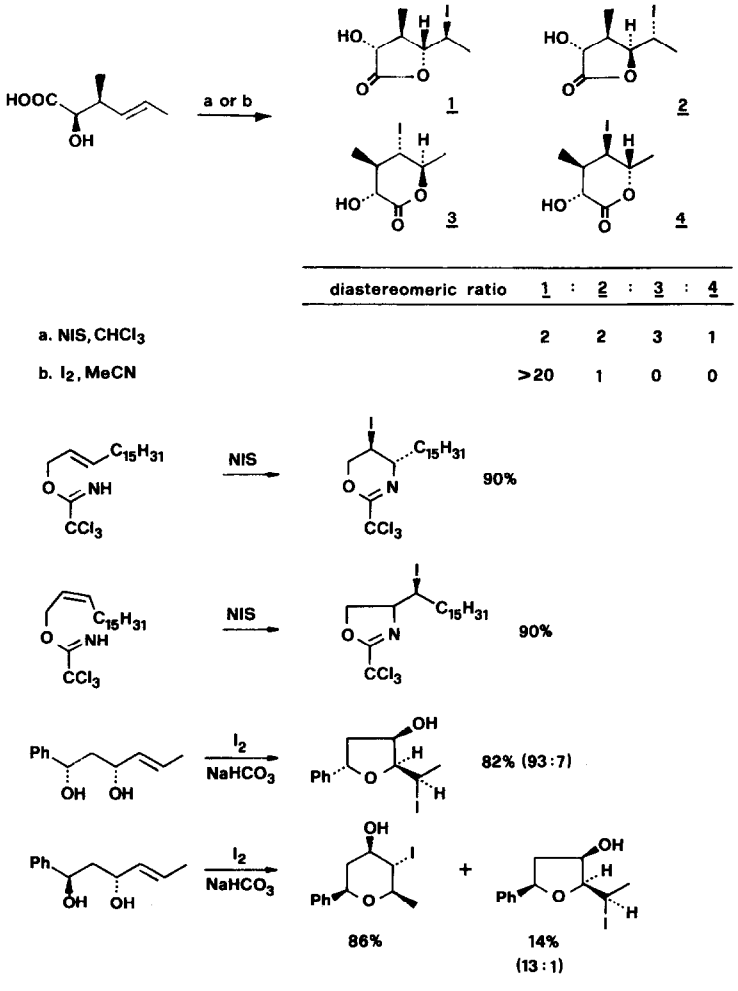


Significant applications to the chemistry of carbohydrates and to the preparation of functionalized pyrans, furans, pyrrolidines and piperidines and other heterocycles have been reported and the factors that affect the cyclization regiochemistry and the diastereofacial selectivity towards an electrophile have been investigated.

Although rings of all sizes are present in naturally occurring compounds, the more common are 5- and 6-membered rings. Baldwin has reported some rules on empirical basis to predict the relative facility of ring-forming reactions.[17] These rules are based on the trajectory of the reagent that attacks the tetrahedral, trigonal or dihedral carbon atom leading to the ring closure reaction.

Several factors appear to direct the regioselectivity towards 5-*exo* or 6-*endo* closures, but both tetrahedral and trigonal ring closures seem to proceed preferentially through the *exo*-modes under kinetic control.

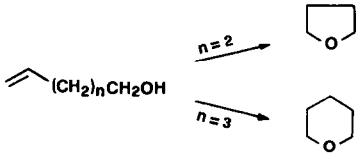
The kinetic or thermodynamic conditions utilized in the reaction are very important to determine the regiochemistry.[11] The structure of the starting material, e.g. the *E* or *Z* configuration of the double bond,[18,19] or the configuration of the stereogenic centre in α- or β-position to the double bond,[20] strongly influence both the stereo- and the regiochemistry, as shown in the following examples.



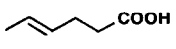
A number of electrophilic agents have been employed in order to obtain ring closure and the nature of the electrophile seems to play an important role. The mechanism of electrophilic attack

has not until now been completely clarified. Thus in the halogen attack both the formation of an onium ion[21] or a concerted mechanism with attack of the nucleophile on a π halogen double bond complex, have been proposed for substrates containing an internal nucleophile.[22,23]

In a study on haloetherification Williams *et al.* have determined the second-order rate coefficients for the haloetherification of a series of unsaturated alcohols and they have found that the neighbouring group rate acceleration is higher for iodination than for bromination.[24]



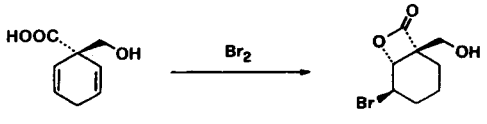
The rate maximum is found for n = 2, corresponding to the formation of tetrahydrofurans, where the neighbouring group rate acceleration is 60 for iodination and 0.7–1.5 for bromination. For n = 3, corresponding to the tetrahydropyran formation, the neighbouring group rate acceleration is 8 for the iodination and 0.2–0.4 for bromination. Moreover Snider and Johnston in a study on the halolactonization of γ,δ-unsaturated acids, have observed that bromolactonization gives a greater percentage of δ-lactones than iodolactonization does.[25]



I_2 – KI – $NaHCO_3$	> 20 : 1	$\gamma:\delta$
Br_2 – MeOH	1 : 1	$\gamma:\delta$

On the basis of these data, different mechanisms have been suggested. In fact the attack of the nucleophile on a bromonium ion is thought to be the rate determining step of the bromocyclization, while in the iodocyclization the rate determining step is the attack of the nucleophile on the iodine double bond complex. The presence of a base in aqueous medium generally results in a kinetic control of the cyclization process,[26] while reversible conditions are favoured by I_2 in MeCN.[27] In addition, NIS in $CHCl_3$, I_2 in $CHCl_3$ and I_2 in pyridine/THF are considered to give cyclizations under kinetic control. On the other hand, the use of NBS or Br_2 affords lower selectivity even where electronic factors seem to induce a preferred closure.[28]

The general preference of β,γ-unsaturated acids to give β-lactones over γ-lactones is well documented.[29] Also γ-lactones are preferentially obtained over δ-lactones under kinetic conditions and in the absence of overwhelming electronic factors.[30]



Under thermodynamic control the preferred ring sizes for lactones are 5 > 4, 5 > 6 and 6 > 7 and in the literature many examples of preference of 5-*exo* over 6-*endo* closure are reported. Thus tetrahydrofurans are preferentially formed in respect to tetrahydropyrans and pyrrolidines in respect to piperidines.

In the formation of cyclic hemiacetals,[31] the thermodynamic preference of 6 > 5-membered rings

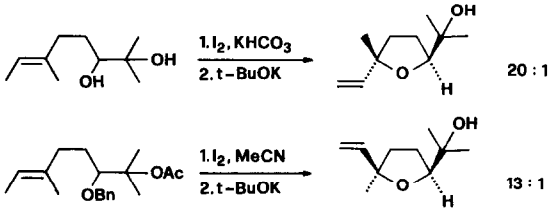
has been reported, in contrast with cyclic thioethers[32] where 5 > 6 thermodynamic stability has been observed.

A deeper insight has been attained during these last years on the factors affecting the stereochemistry of ring formation. The stereochemical relationship between the substituents, thermodynamic or kinetic conditions are of fundamental concern. In fact the cyclofunctionalization strategy is based on the premise that the cyclic nature of the diastereomeric transition states and products in this reaction would differ sufficiently in energy so that one diastereomer is formed preferentially either kinetically or thermodynamically.[33]

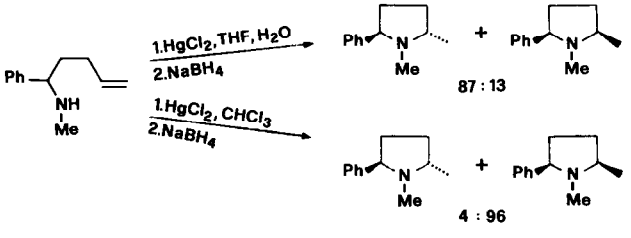
When the reaction is carried out under reversible conditions, the major compound is the more thermodynamically stable one and its amount is determined by the equilibrium constant.[34]

In this context 1,2- or 1,3-high asymmetric induction is usually observed in the formation of 6-membered rings, owing to the preferential chair-like conformation assumed in the transition state, through which a high degree of asymmetry is induced as the largest numbers of substituents take the equatorial position. Simple methods of calculation have been elaborated to determine with accuracy which compound is the more thermodynamically stable.

A good 1,2-control is observed in the formation of 5-membered rings, when bulky substituents are involved and a moderate 1,3-*cis* selectivity seems to be general. Conversely, 1,3-asymmetric induction has been observed in the cyclization of substituted secondary unsaturated amides. In the formation of furans, the structure of the starting material, either alcohol or ether, strongly influences the reaction course,[35] and a reversal of the final compound stereochemistry is observed, owing both to 1,2-strain and the ethereal bond cleavage which allows a slow equilibration through the oxonium ion. So a preferential 2,5-*cis* or 2,5-*trans* relationship is obtained, depending on the starting material.



In addition, the diastereomeric ratio of the products is affected by the electrophile concentration in the reaction medium.[36]

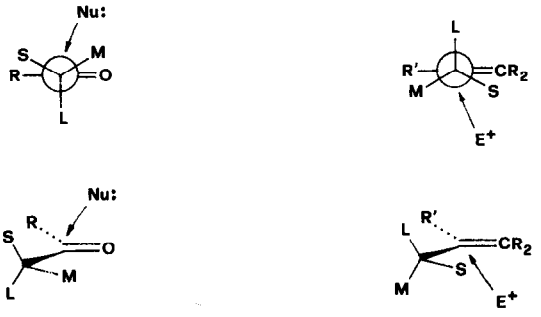


The diastereoselectivity of electrophilic attack in acyclic systems is receiving growing interest. Empirical models have been proposed to rationalize the preferred attack on a trigonal carbon atom adjacent to a stereogenic centre by an electrophile.

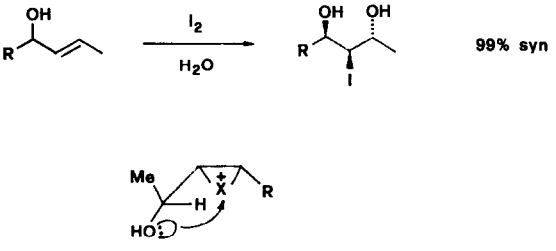
Recently a 'staggered model' for asymmetric induction has been elaborated by Houk *et al.*, based on *ab initio* gradient calculations of transition structures of additions to substituted alkenes.[37]

As already proposed by Felkin[38] and Anh,[39] in this model the nucleophilic attack preferentially occurs from the side *anti* to the large group on the conformer with the medium substituent partially eclipsing the double bond. Conversely the electrophilic attack on a double bond is predictable on the basis of a preferred staggered conformer where the small substituent partially eclipses the double

bond, the electrophile attacking from the side *anti* to the large group.



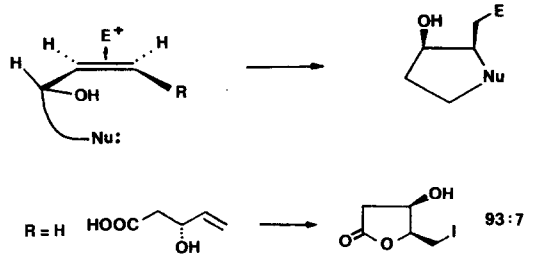
It is known from the literature that the presence of an oxygenated function on the stereogenic centre exerts a strong influence on the 1,2-asymmetric induction,[39] affording high selectivity (>95%). For example, in the iodohydrin formation from acyclic allylic alcohols, Chamberlin *et al.* have found a *syn*-1,2-selectivity of 90–99%.[40]

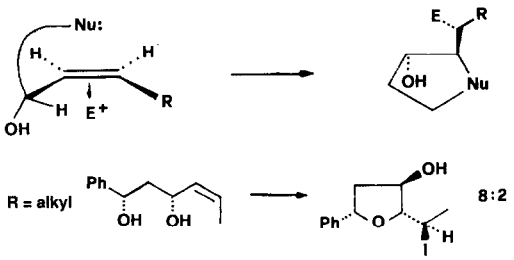


For this reaction, an onium ion like transition state has been modelled theoretically,[41] and a hydrogen-in-plane conformer with the hydroxy group *syn* to the halogen, has been found to be the more stable.

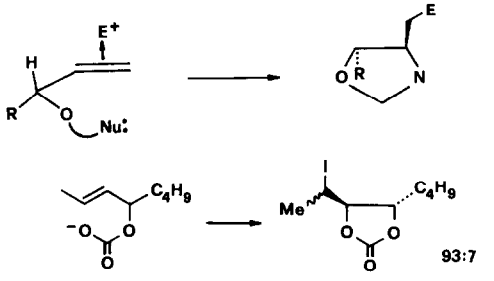
This kind of diastereofacial selectivity is usually opposite to that observed when an internal nucleophile is present.

Chamberlin, Hehre *et al.*[41] have developed a new model for the attack under kinetic control of an electrophile to an olefin containing an internal nucleophile, based on the relative affinity of the diastereotopic face of the double bond towards a proton.[42] In this case the cyclization proceeds via an intramolecular attack on a π complex. Thus, when an OH group is present, the preferential attack of an electrophile on the OH-in-plane conformer occurs from the face of the double bond *syn* to the allylic hydrogen. When R = H, the *cis* diastereomer is formed as the major compound, while substrates with a *cis*-substituent on the double bond (relatively to the stereogenic allylic centre), which destabilizes the OH-in-plane conformer, react on the opposite face.





Substrates with O or N incorporated in the nucleophilic chain preferentially react through an OR or NHR-in-plane conformer affording, although less selectively, *trans*-5-membered heterocyclic compounds as the major product.

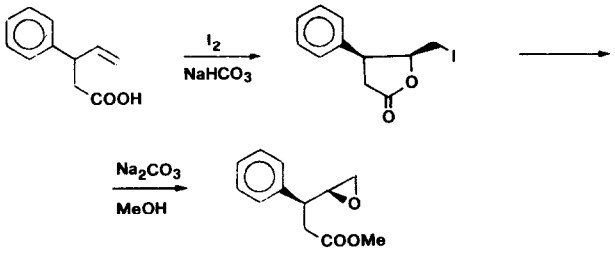


2. ELECTROPHILE INDUCED LACTONIZATION

The lactonization of unsaturated acids and esters, mediated by electrophiles, is a powerful process in synthetic organic chemistry for regio- and stereoselective functionalization of double bonds. This argument has been reviewed by Staninets and Shilov[8] and by Dowle and Davies.[9] Recently excellent reviews on the regio- and stereoselective aspects of this important reaction have been published by Bartlett,[10,11] and a variety of examples of halolactonization controlled by a substituent in acyclic unsaturated precursors has been reported and applied to the synthesis of organic complex molecules. This section is therefore limited to examining a few important examples which have appeared in recent years.

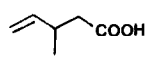
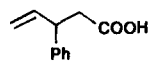
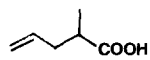
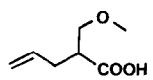
Although it has already been discussed, the high stereoselectivity towards *cis*- or *trans*-iodolactones that may be achieved under either kinetic ($I_2/NaHCO_3/H_2O/CHCl_3$) or thermodynamic (I_2/MeCN) conditions, as reported by Bartlett and Gonzàlez deserves further attention (Table 1).[43]

Iodolactones can easily be converted into the corresponding epoxyesters with anhydrous Na_2CO_3 in MeOH, as shown in the following scheme.

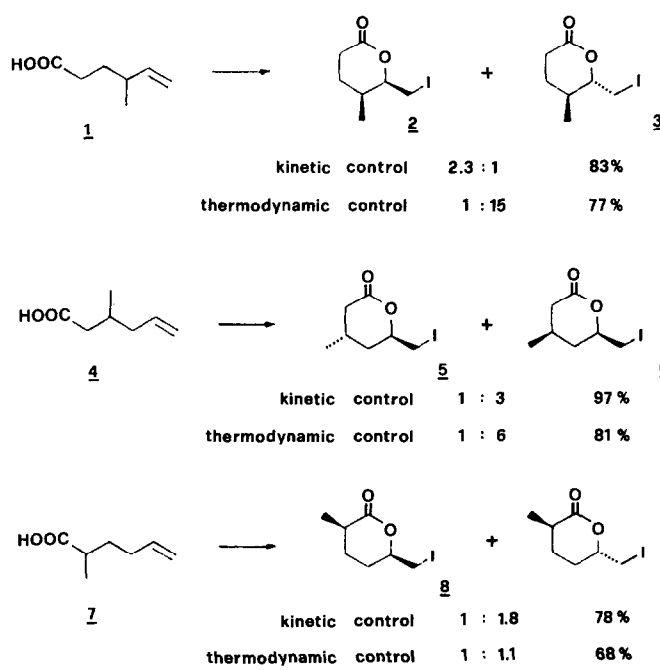


A similar result has been obtained by Jager in the iodolactonization of 4-pentenoic acids, performed under kinetic control: in fact moderate 1,2- (*cis*: *trans* ~3:1) or 1,3- (*cis*: *trans* 2:1) asymmetric induction has been reported.[44]

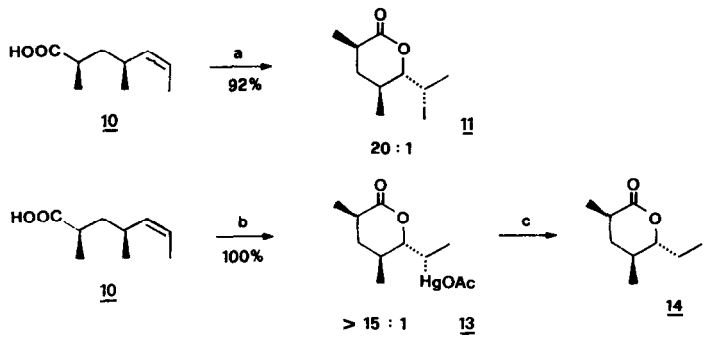
Table 1. Iodolactonization of unsaturated acids[10,44]

Substrate	trans : cis ratio (yield %) thermodynamic control	kinetic control
	10 : 1 (84)	1 : 3 (82)
	20 : 1 (98)	1 : 4 (87)
	–	1 : 3 (99)
	–	1 : 3 (94)

A further study has been conducted by Bartlett, with the aim of clarifying the relative 1,3- and 1,4-asymmetric induction in the cyclization of δ,ε-olefinic acids.[45] The iodolactonization of these compounds under thermodynamic control exhibits a high 1,2- and 1,3-asymmetric induction, the *trans*-isomer being the major component of the diastereomeric mixture. On the other hand, a low 1,4-asymmetric induction is observed.

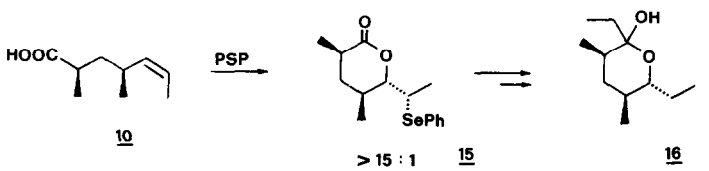


Furthermore both iodo- and mercury-cyclization of **10** proceeds with a good stereocontrol.

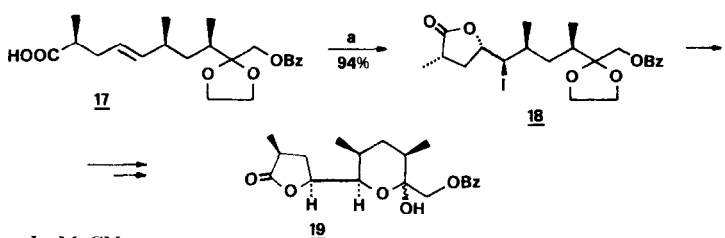


a. I_2, $NaHCO_3$ b. $Hg(OAc)_2$, MeOH c. $NaBH_4$

In order to avoid the difficulties connected with the demercuration reaction, the seleno-lactonization of **10** has been carried out with PSP (phenylselenophthalimide) under kinetic control, the lactone **15** being obtained with a *trans*:*cis* ratio 15:1. This compound has been subsequently converted into serricornin **16**, the pheromone of *Lasioderma serricone*.

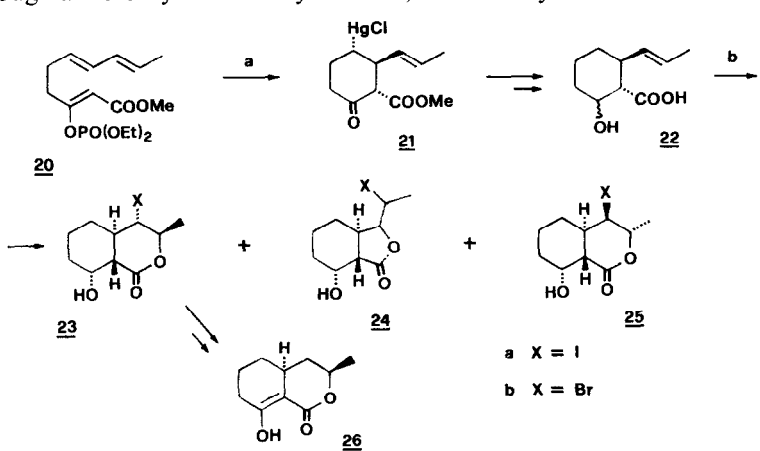


A polyether fragment **19** has been prepared through the iodolactonization of **17**. The *cis*-isomer **18** predominates to the extent of 80%, thus allowing an efficient route to the desired target.[46]



a. I_2, MeCN

A total synthesis of (±)-ramulosin **26**, isolated from the fungus *Pestalotra ramulosa*, has been carried out through a mercury-initiated cyclization, followed by halolactonization.[47]



a. $Hg(OTFA)_2$, then NaCl b. I_2, KI, $NaHCO_3$ or Br_2, MeOH

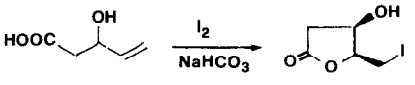
The iodolactonization conducted with I_2 and KI in aqueous $NaHCO_3$ gives in 91% yield a mixture of **23a**, **24a** and **25a** in a 1:4:2 ratio, whereas a 3:2 ratio of **23a** to **24a** in 86% yield is observed when the reaction is performed with I_2 in ether/THF/aqueous $NaHCO_3$. By contrast, the bromolactonization, carried out with Br_2 in MeOH, affords in a 3.5:1 ratio, a mixture of **23b** and **24b** in 88% yield.

Since it has been observed that the regiochemistry of the cyclization depends upon the electrophile employed, a systematic study aimed at reducing the closure bias has been carried out on 4-alkenoic acids with *E*-configuration of the double bond.[25] It has been found that both the substrate structure and the halolactonization method influence the regiochemistry. In all cases bromolactonization affords the δ-lactone more than iodolactonization does (Table 2).

Moreover steric effects play an important role in determining the product mixture: substituents at C-3 hinder attack of the carboxylate at C-4 and favour formation of the δ-lactone, while the substituents at C-6 hinder attack at C-5 and favour formation of the γ-lactone.

A very important investigation into the stereochemistry of the iodolactonization directed by an oxygen substituent in the 3-position of 4-alkenoic acids has been reported by Chamberlin *et al.*[48] These studies have revealed new, interesting aspects of the asymmetric induction directed by an oxygen containing group α to the double bond, so that a new model for the electrophilic attack has been developed.[41] Thus most of the examples reported in the literature for acyclic compounds are covered, and the *cis*-3,4-relationship for γ-lactones has become a topic for organic synthesis.

In fact it has been found that the cyclization reaction, performed under kinetically controlled conditions ($I_2/NaHCO_3$), constitutes a good route to *cis*-3-hydroxy-4-iodomethyl-γ-butyrolactones.



66% (93 : 7)

The stereoselectivity is high and the stereochemical outcome of the reaction is usually predictable. Furthermore it has been found that hydrogen bonds are not involved in the reaction as the same diastereomeric ratio is observed when the hydroxy group is protected as an acetate or a silyl ether (Table 3).

An application of Chamberlin's findings is represented by the efficient synthesis of both the enantiomers of 3,4-dihydroxyprolines starting from 2-amino-3-hydroxypent-4-enoic acids.[49] Thus

Table 2. Iodo- and bromolactonization of unsaturated acids[25]

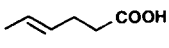
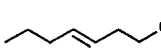
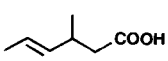
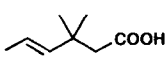
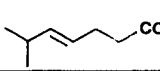
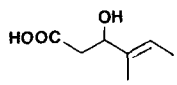
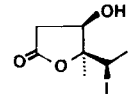
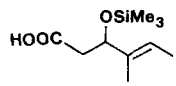
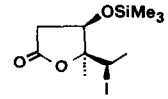
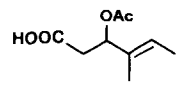
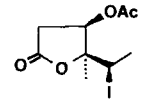
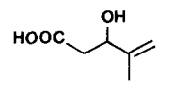
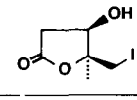
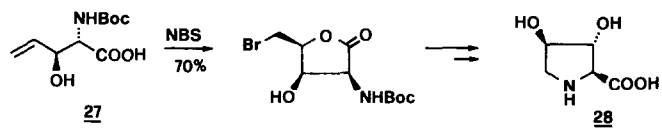
Substrate	I_2–KI $NaHCO_3$	I_2, ether, THF $NaHCO_3$	NBS, THF AcOH	Br_2, MeOH $NaHCO_3$, -78°C
	> 20 : 1 85%	24 : 1 71%	2.7 : 1 91%	1 : 1 46%
	> 15 : 1 91%	–	2.7 : 1 85%	2.7 : 1 50%
	6.5 : 1 88%	1.5 : 1 83%	1 : 1.2 78%	1 : 1.2 66%
	1.1 : 1 86%	1 : 1 81%	1 : 2.4 86%	1 : 2.5 93%
	> 9 : 1 70%	–	9 : 1 76%	> 9 : 1 38%

Table 3. Iodolactonization of 3-hydroxy-4-alkenoic acids[48]

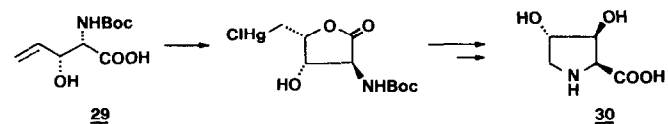
Substrate	Product	yield %	cis:trans ratio
		82	96 : 4
		84	96 : 4
		70	94 : 6
		74	95 : 5

(2*S*, 3*R*, 4*R*)-3,4-dihydroxyproline **28**, an aminoacid constituent of virotoxin, has been obtained with a complete stereocontrol by carrying out a few simple steps, starting from **27** via bromolactonization.



27 **28**

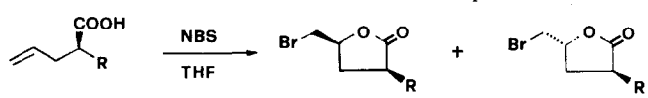
Moreover, starting from **29** the (2*S*, 3*S*, 4*S*)-3,4-dihydroxyproline **30**, isolated from diatom cell walls, has been obtained as a single isomer through mercury-cyclization.[49]



29 **30**

The effect of a nitrogen substituent in the halolactonization reaction of 2-amino-4-pentenoic acid derivatives has been successively examined and the results are summarized in Table 4.[50]

Table 4. Bromolactonization of 2-substituted-4-pentenoic acids[50]

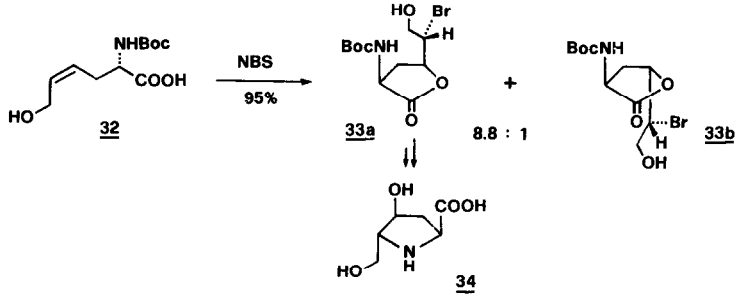


Substrate	yield %	cis:trans ratio
a. R = NHCbz	80	8 : 1
b. R = NHBoc	82	8 : 1
c. R = NHCHO	40	8 : 1
d. R = NPht	81	6 : 1
e. R = NHTs	100	8.8 : 1

The high *cis*-selectivity observed is independent from the properties of the N-substituents, such as steric bulkiness, electronegativity and the absence of the amide hydrogen. To explain this result, a cyclic intermediate **31** has been proposed, in which the bromonium ion is stabilized by the lone pair of the nitrogen.

31

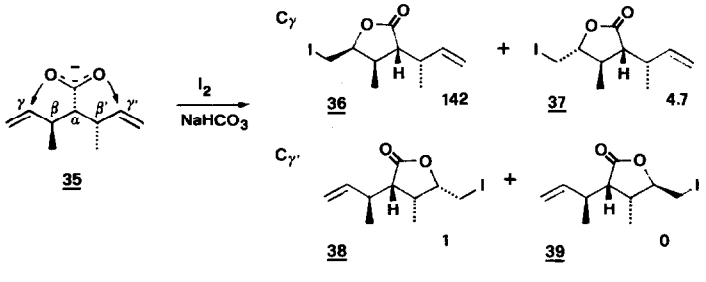
Following this approach, and starting from (2*S*, 4*S*, 5*S*)-γ-butyrolactone **33a**, obtained via a halocyclization from the *Z*-allyl alcohol **32**, a total, stereoselective synthesis of a constituent amino acid of the glycopeptide bulgecin, (−)-bulgecinine **34**, has been devised.



32 33a 33b 34

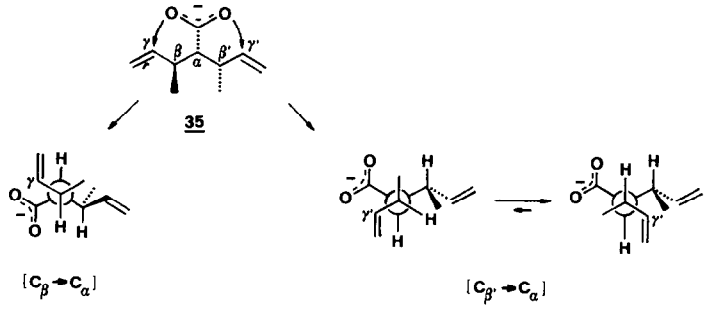
A further study on the stereoselectivity of the iodolactonization reaction describes the efficient, stereoselective functionalization of the heptadienoate **35**, as this transformation proceeds with concomitant group and face selectivity.[51]

In fact the iodolactonization of **35**, carried out under kinetic conditions, results in an excellent olefin selectivity (147 : 1) and high face selectivity (30 : 1), since the iodolactones **36**, **37** and **38** are obtained in a 142 : 4.7 : 1 ratio, respectively.

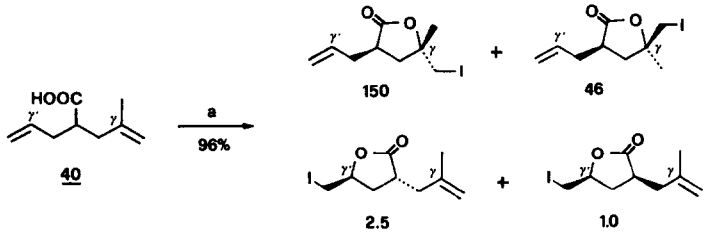


35 36 37 38 39

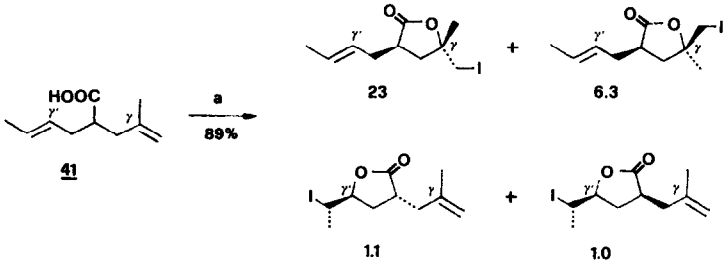
The high kinetic olefin selectivity has been rationalized on the basis of acyclic conformational control. In fact, minimizing gauche interactions, the lowest energy (C_β–C_α)-Newman projection of **35** places the carboxylate and C-olefin in close proximity, whereas the lowest energy ($C_{\beta'}$–C_α)-Newman projection places the carboxylate and C_γ-olefin antiperiplanar. To the extent that a similar bias is experienced in the two transition states (C_γ versus $C_{\gamma'}$ cyclization), the carboxylate of **35** should be predisposed towards C_γ-cyclization. In any case, G* for C_γ-cyclization (**35** → **36**+**37**) is ~3 Kcal mol^{-1} lower in energy than G* for $C_{\gamma'}$-cyclization (**35** → **38**+**39**).



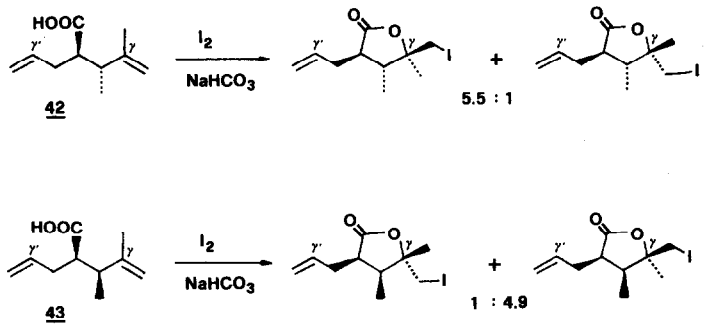
Substituted 1,6-heptadien-4-carboxylic acids have also been cyclized and a comparison of conformational versus electronic control in iodolactonization has been reported. From the cyclization of **40** and **41** the methallyl moiety results as being a powerful director against the allylic moiety, clearly owing to an electronic effect, as can be seen in the following scheme.[52]



a. I_2, $NaHCO_3$



In an attempt to ascertain if electronic control dominates over conformational control, **42** and **43** have been cyclized under kinetic conditions.



Results show that, regardless of the *syn/anti* configuration of the starting acid, kinetic iodolactonization is highly methallyl selective, so that with these substrates, electronic control completely dominates over conformational control. In addition, the stereochemical outcome of the reaction of **42** favours a *trans* ($C_\beta CH_3 \rightarrow C_\gamma CH_2I$)-relationship, while with **43** a *cis*-relationship is observed.

3. ELECTROPHILE INDUCED CYCLIZATION TO TETRAHYDROPYRANS AND TETRAHYDROFURANS

The stereocontrolled construction of substituted ring systems containing oxygen through a cyclization reaction mediated by electrophiles constitutes a useful approach to tetrahydrofurans and tetrahydropyrans. The development of new, stereocontrolled approaches to these compounds is currently of interest, principally because these heterocyclic units are found in a wide range of biologically important natural products, e.g. polyether antibiotics. An interesting route to these heterocycles involves the cyclization between a hydroxy or an alkoxy group and an appropriately placed double bond, mediated by a suitable electrophile.

With regard to the regiochemistry of these compounds, the pyran rings may be constructed either by 6-*exo* cyclization of substrates with δ-position of the double bond or through a favoured 6-*endo* versus 5-*exo* closure, depending on electronic factors, in γ-oxygen substituted olefins.

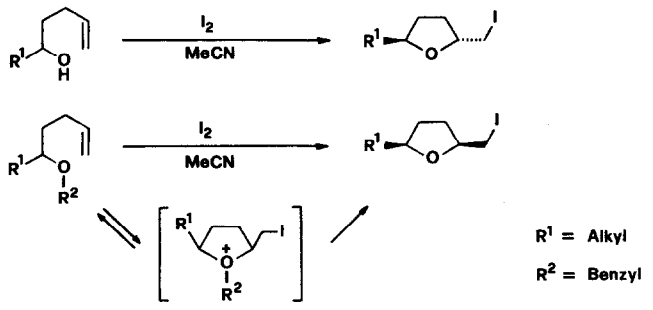
Generally the formation of 6-membered rings proceeds under high 1,2- or 1,3-stereocontrol: in fact the equatorially substituted compounds are preferentially formed.

Although electronic factors generally direct ring closure, some cases have been reported of trisubstituted olefins that afford tetrahydrofurans or tetrahydropyrans, depending on the electrophile (NBS, TBCO) and the solvent used in the reaction.[11]

The ring formation leading to substituted THP-derivatives is a very common procedure. Some observations are worth making concerning the stereochemistry of this reaction. Secondary γ,δ-unsaturated alcohols that afford 2,5-disubstituted tetrahydrofurans preferentially give the *cis*-2,5-relationship under kinetic conditions (I_2/$NaHCO_3$ aq) and the *trans*-2,5-relationship under thermodynamic conditions (I_2/McCN). The opposite results occur when unsaturated ethers are cyclized: in fact under thermodynamic conditions the major product is the *cis*-2,5-disubstituted furan.

This field of study has been developed by Bartlett and rationalized in terms of 1,2- and 1,5-strain, due to the hindrance of the ethereal group.[35]

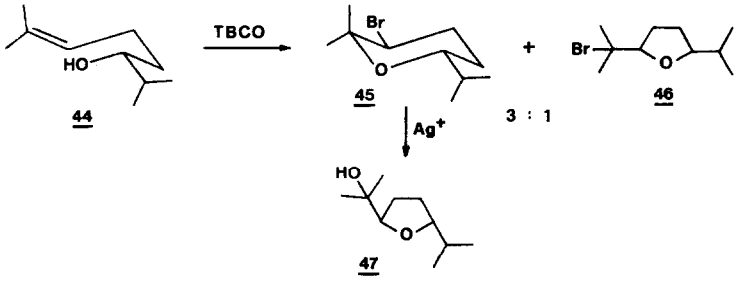
In this context the nature of the alkyl group plays an important role and the most suitable derivatives are the benzyl ones, due to their electrofugal capabilities. The cleavage of the C–O bond takes place on a reasonable time scale so that the equilibration of the reaction mixture can be obtained.



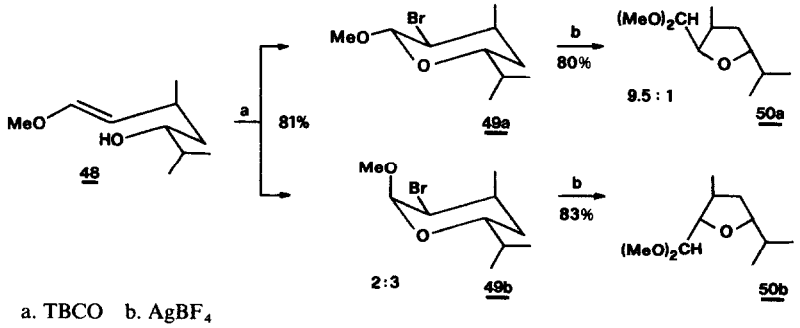
A new, interesting method for achieving a high asymmetric induction in the synthesis of *trans*-2,5-disubstituted tetrahydrofurans has been reported by Bartlett and Ting.[53] Since 1,3-relative asymmetric induction is attained more in 6-membered rings than in 5-membered ones, they have elaborated a sequence allowing *trans*-2,5-disubstituted tetrahydrofurans to be obtained, exclusively through a ring contraction of 6-membered rings, promoted by Ag^+.[54]

Thus alcohol **44**, treated with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO), cyclizes to an easily separable 3 : 1 mixture of 6- and 5-membered rings, **45** and **46**, respectively.

By successive treatment with $AgBF_4$, the tetrahydropyran **45** stereospecifically gives *trans* tetrahydrofuran **47** as the sole compound.

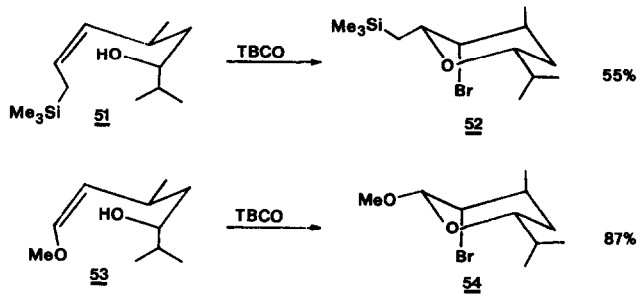


The cyclization of *trans* enol ether **48**, performed with TBCO, affords a 2:3 mixture of 2-equatorial and 2-axial pyrans **49a** and **49b**, that undergo ring contraction to the corresponding tetrahydrofurans **50a** and **50b** with the opposite stereochemistry at C-2. The unexpected formation of **50b** from **49b** can be attributed to severe steric interactions in the transition state, and the reaction must proceed via an intermediate cation in a non-concerted manner.

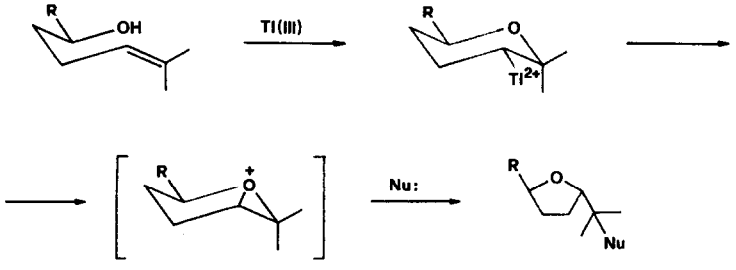


a. TBCO b. $AgBF_4$

By contrast the *cis*-allylsilane **51** and the *cis*-enolether **53** give tetrahydropyrans **52** and **54**, respectively, with bromine in the axial position, that are not suitable for ring contraction.

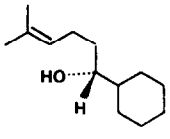
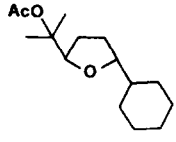
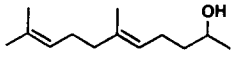
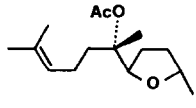
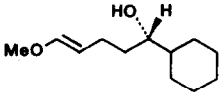
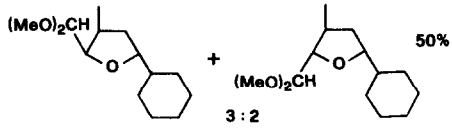
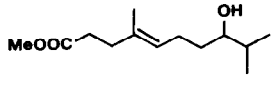
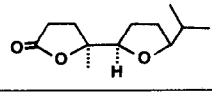


Better results have been obtained by using Tl(III) as the electrophile.[55] In fact Tl(III), owing to its ability as a nucleofuge, causes the formation of a tetrahydropyran which, by means of a bridged oxonium ion, converts into the corresponding *trans*-2,5-disubstituted tetrahydrofuran in a one-step process. Some significant examples are reported in Table 5.

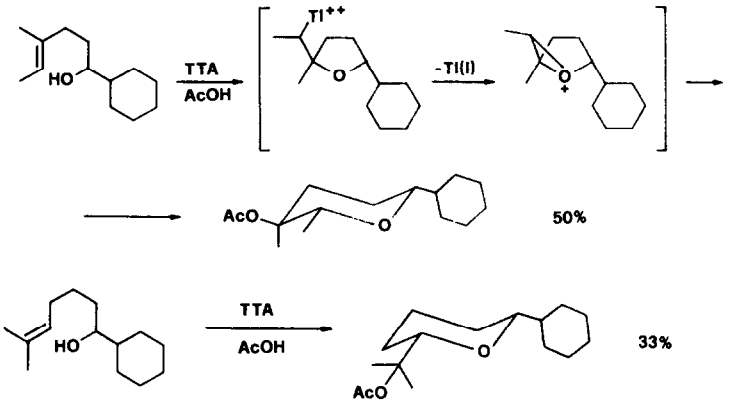


The incorporation of the solvents AcOH or MeOH, acting as nucleophiles, has been observed; conversely, when an internal nucleophile is present, it attacks the cation stereoselectively leading to a single compound in good yield (Table 5).

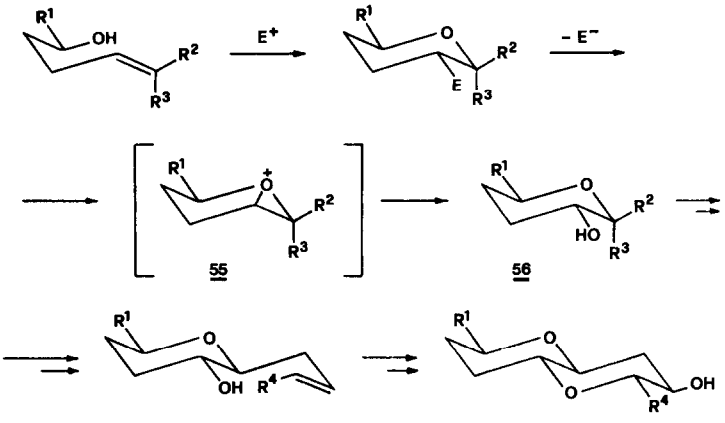
Table 5. Cyclization of γ-unsaturated alcohols to tetrahydrofurans, mediated by Tl(III)[55]

Substrate	Product	yield %
		72%
		61%
		50% (3 : 2)
		49%

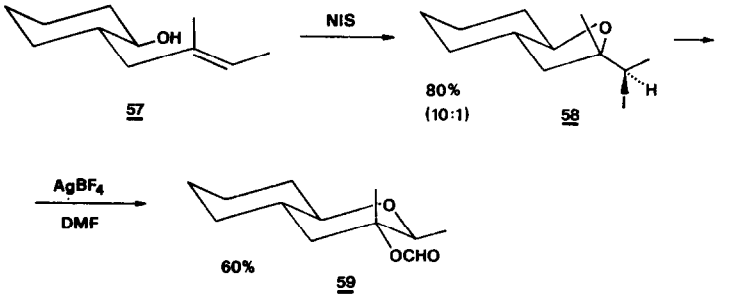
This method is less effective for the formation of tetrahydropyrans by ring-expansion, as shown in the following examples.



The oxiranium intermediate **55** has been thought to be a useful precursor to 3-hydroxytetrahydropyrans **56**, key intermediates to bicyclic systems.[56]

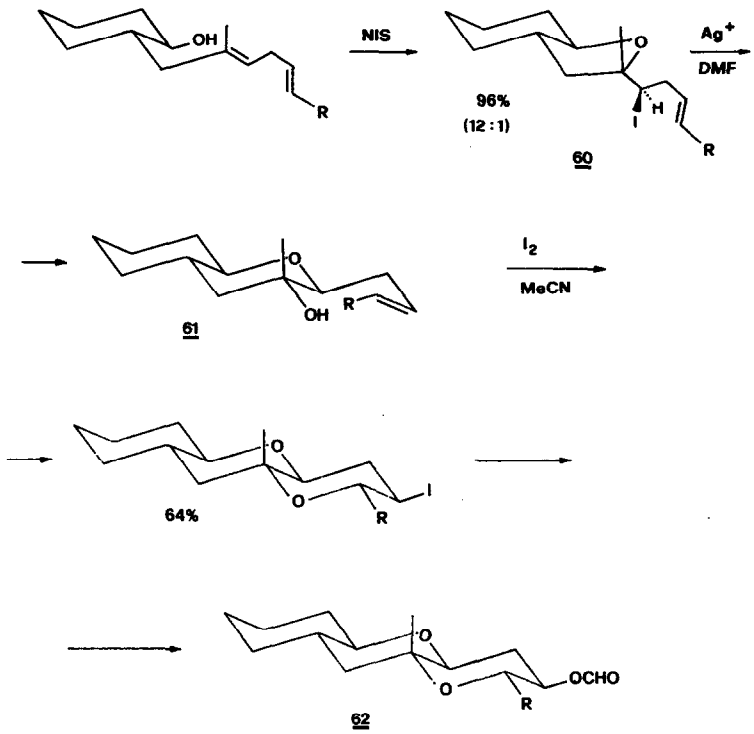


This iterative process of *trans*-fused polycyclic ethers represents a new strategy for the synthesis of compounds that are present in brevetoxins, potent neuro- and cardiotoxins. These compounds have *trans, syn, trans* fused structures. The iodocyclization of alkenol **57** with NIS in CH_2Cl_2 leads to products of both stereoelectronic and Markovnikov control, with the 6,5-isomers **58** in a 10 : 1 ratio and 80% yield. By treatment with $AgBF_4$ in DMF, the 6,6-formate **59** is obtained in 60% yield.

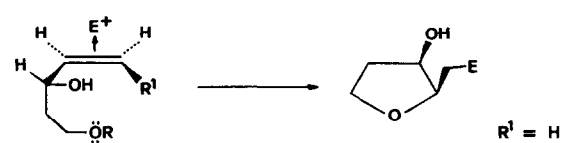


A number of substrates have been cyclized either under kinetic or thermodynamic conditions, in order to obtain 5,6- or 6,6-polycyclic compounds, depending on the properties of the starting

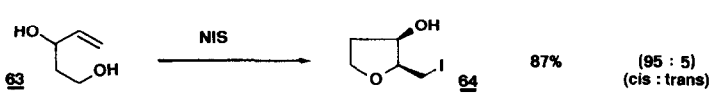
material. In addition, the formation of tricyclic compound **62** has been reported, starting from tertiary alcohol **61**, which is readily obtained from the furan **60**. All the steps of this sequence are highly stereoselective.



The pronounced stereochemical *cis* preference in cyclizations directed by an allylic OH group in the synthesis of 5-membered rings under kinetic conditions is in agreement with the proposed reactivity model. In fact the electrophilic attack is preferred on the OH-in-plane conformer from the face of the π bond *syn* to allylic hydrogen, when R′ = H. If R′ ≠ H, a reversed facial stereoselectivity is observed.[41]



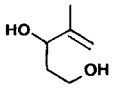
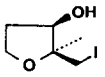
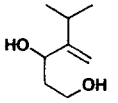
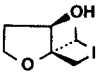
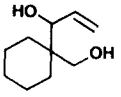
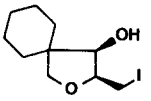
A systematic investigation into the iodoetherification of 4-pentene-1,3-diol **63** and its monosubstituted derivatives has been reported by Yoshida *et al.*[57]



Thus intramolecular iodoetherification of 4-pentene-1,3-diol under kinetic control proceeds with a diastereoselectivity 95% in a predictable way, providing *cis*-2-iodomethyl-3-hydroxytetrahydrofuran **64** (Table 6).

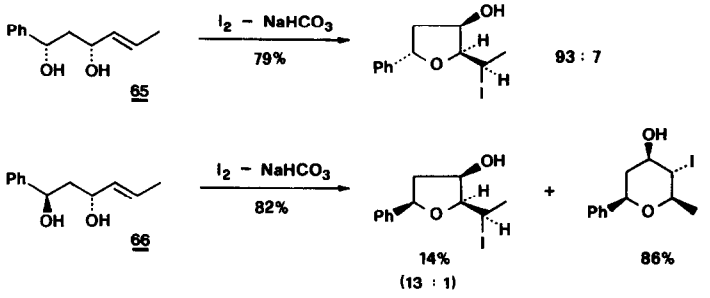
Stereoselectivity in the formation of *cis*-2,3-disubstituted tetrahydrofurans is high under all the conditions employed and this method constitutes a general route to *cis*-3-hydroxy-2-iodomethyl

Table 6. Iodocyclization of 4-Penten-1,3-diols[57]

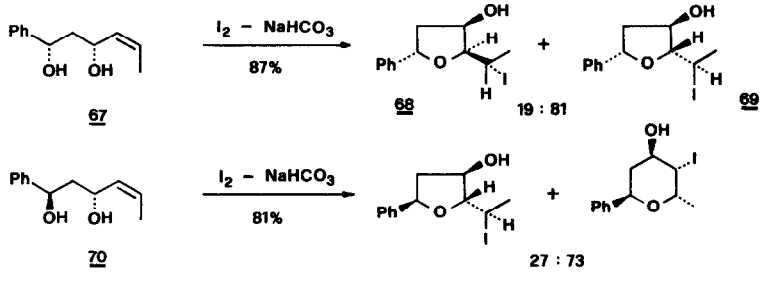
Substrate	Product	yield%	cis:trans
		94	91 : 9
		73	95 : 5
		98	98 : 2

tetrahydrofurans. The interest in this approach depends on the possibility of introducing a 2,3-*cis*-relationship as this is frequently observed in naturally occurring polyether antibiotics.

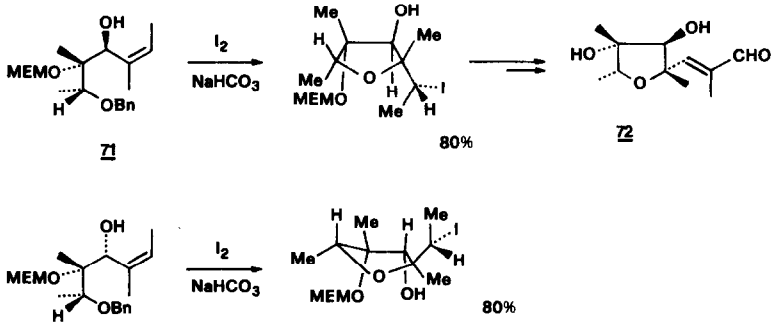
From the data reported in Table 6 it appears that *cis*-selectivity generally exceeds 95% in monosubstituted derivatives. Moreover, the 1,3-*syn* or *anti* relationship of the hydroxy groups, **65** and **66**, strongly influences regio- and stereochemistry. In fact it is worth mentioning that the *anti* configuration of **66** favours a 6-*endo* closure.[58]



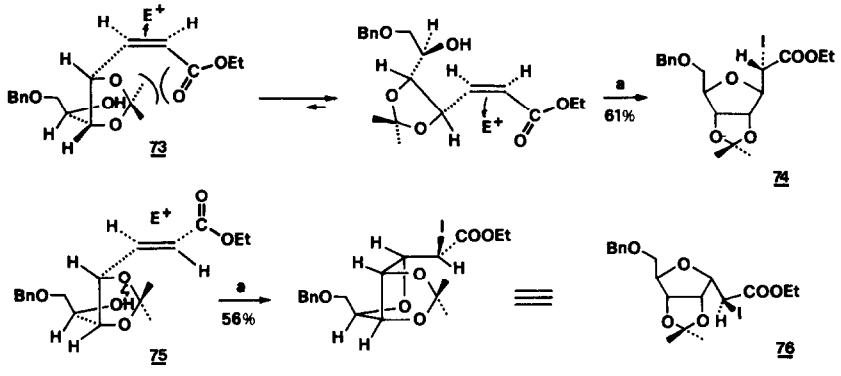
Furthermore, the configuration of the double bond also dramatically alters stereoselectivity. In fact, starting from the (*Z*)-*syn*-diol **67**, the *trans*-2-iodoethyl-3-hydroxytetrahydrofuran **69** becomes the main product. This reversed stereochemistry has been rationalized on the basis of the fact that the *cis*-substituent destabilizes the OH-in-plane conformer, making the conformer with the hydrogen in plane energetically more accessible.



The same relationship between the configuration of the starting diol and stereoselectivity in the formation of a furan ring has been observed in the cyclization of *Z*-alkenes in the synthesis of (+)-citreoviral **72**.[59,60]

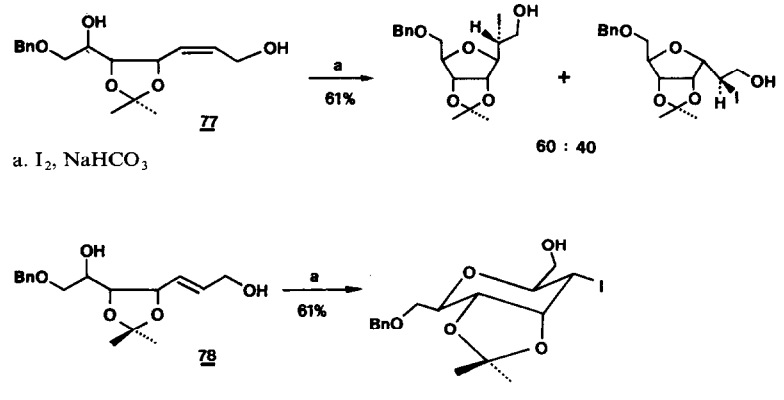


Further examples of the influence of the *E*- or *Z*-configuration of the double bond on the stereochemical outcome of the cyclization have been reported.[61] In fact (*Z*)-2-heptenoate **73** gives the β-ribofuranose **74**, while the cyclization of the (*E*)-isomer **75** exclusively affords the α-ribofuranose **76**.



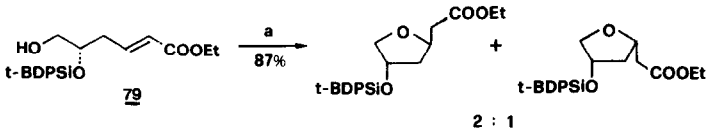
a. I_2, $NaHCO_3$

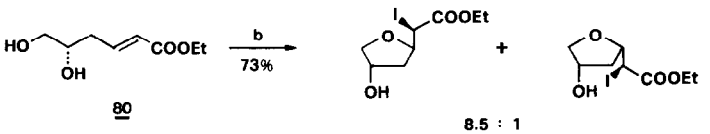
Double bond geometry plays a significant role also on the regiochemistry of cyclization, since the (*Z*)-olefin **77** gives a 5-*exo* closure with low β:α selectivity, while starting from the (*E*)-olefin **78** the 6-*endo* closure is exclusively observed.



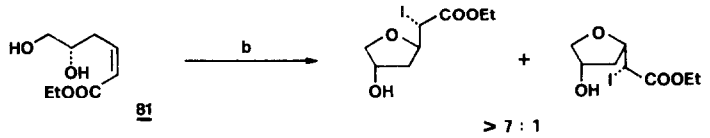
a. I_2, $NaHCO_3$

An interesting strategy based on iodoetherification, followed by ring opening promoted by dimethylboron bromide, has been developed with the aim of preparing highly functionalized 1,3-*syn* diols, useful for the synthesis of mevinolin and compactin derivatives.[62,63] Thus the chiral 5-protected ethyl (*E*)-5,6-dihydroxyhex-2-enoate **79** has been easily prepared starting from (*S*)-malic acid. The intramolecular Michael addition of the primary hydroxy group to the double bond under thermodynamic conditions (EtONa in refluxing EtOH) proceeds in high yield and moderate stereoselectivity, affording a 2 : 1 *cis* : *trans* mixture. On the contrary, the iodoetherification reaction, performed on **80** under kinetic conditions, results in the formation of 2,4-disubstituted tetrahydrofurans with higher stereoselectivity (8.5 : 1 *trans* : *cis*). The (*Z*)-isomer **81** has also been cyclized and a >7 : 1 *trans* : *cis* mixture has been obtained.





a. EtONa, EtOH b. I_2, $NaHCO_3$



Furthermore it has been observed that the stereoselectivity of this process depends on the solvent as reported in Table 7.[64]

As it appears from Table 7, low polar solvents favour the selectivity, but slower reaction rates are observed, because high iodine concentrations are not available.

The cleavage of 2-substituted tetrahydrofuran **82** with Me_2BBr proceeds smoothly with complete regioselectivity thus affording the corresponding bromoalcohol **83** in high yield.

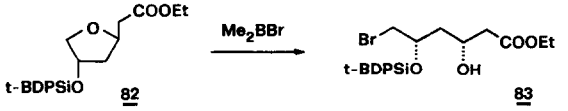
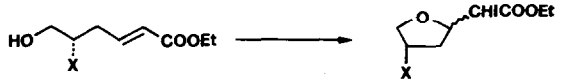


Table 7. Factors affecting the stereoselectivity of iodoetherification[64]

Solvent	trans:cis ratio	ε	I_2 (M)
THF	4.5 : 1	7.58	4.87
DME	5.2 : 1	7.20	2.05
t-Butyl methyl ether	7 : 1		1.15
Diethyl ether	8.6 : 1	4.34	0.88
Diisopropyl ether	12 : 1	3.88	0.27

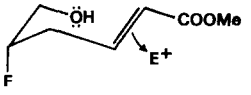
Table 8. Effect of an homoallylic substituent on the stereoselectivity of the iodoetherification[64]



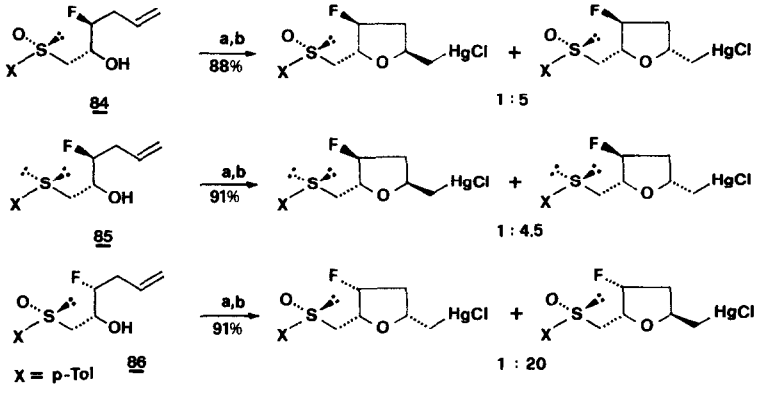
X	cis:trans ratio
OH	1 : 4
OMe	1 : 4.6
F	1 : 6.3
Me	3.6 : 1

Iodocyclization directed by a number of substituents in the homoallylic position has been studied and the results are reported in Table 8.

Reversed selectivity can be observed where an electron withdrawing group (OCH_3, F) changes with an electron releasing one (Me). The authors propose a chair-like conformation, with fluorine in the axial position, as a model for the electrophilic attack.



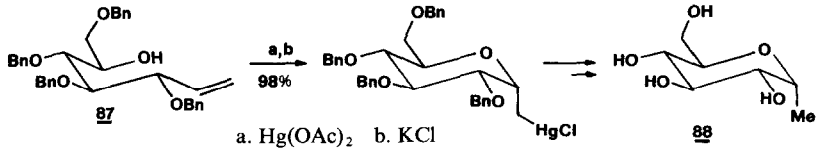
The same diastereofacial selectivity in the presence of fluorine as substituent has been reported by Bravo *et al.*[65,66] In fact the cyclization of the alcohols (2*S*, 3*S*, R_S) **84**, (2*S*, 3*S*) **85** and (2*S*, 3*R*, R_S) **86**, carried out by using $Hg(OTFA)_2$ in THF, followed by treatment with KCl affords the corresponding tetrahydrofurans with high stereoselectivity and a preferential *trans*-relationship.



a. $Hg(OTFA)_2$ b. KCl

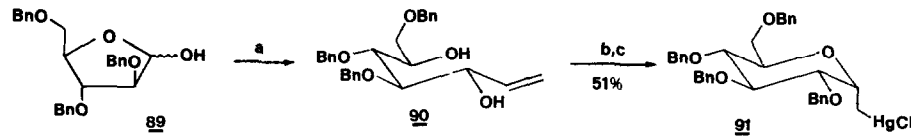
The synthesis of C-glycosyl compounds has become an area of increasing interest since they are useful synthons and potential inhibitors of metabolic processes.[67]

As was demonstrated by Sinay, when 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose is subjected to a Wittig reaction with methylenetriphenylphosphorane, the unsaturated derivative **87** ensues which in turn, by means of a mercury-cyclization, provides the α-D-C-glucopyranosyl derivative **88**.[68,69]



a. $Hg(OAc)_2$ b. KCl

Russo and Nicotra have utilized commercially available D-pentoses **89** to synthesize C-glycosides **91** through a reaction with a vinyl metal reagent, followed by mercury-cyclization.[70]



a. Divinylzinc b. $Hg(OAc)_2$ c. KCl

While the use of vinyl magnesium bromide in THF leads to a reaction showing a moderate stereoselectivity, divinylzinc gives better results, affording in each case predominantly or solely one diastereomer.

As shown in Table 9, a preferential *cis*-relationship, ascribable to *cis*-directing bias of the hydroxy group, can be observed between the hydroxy group at C-2 of the starting sugar and the newly introduced stereogenic centre. On the other hand D-manno-1-heptenitol **92** gives the β-C-manno-pyranoside **93** where the anomeric substituent is *trans* with respect to the substituent at C-2.

As an extention of this reaction, 2-amino-2-deoxy-α-C-glucopyranoside **101** has been synthesized by means of a mercury-cyclization starting from **100**.[71]

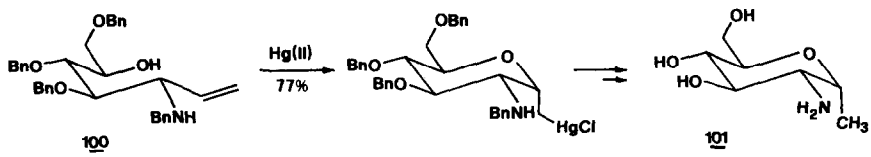
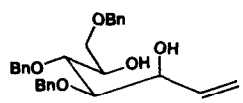
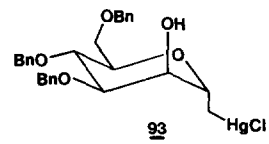
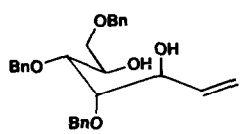
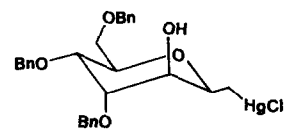
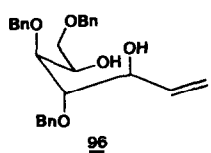
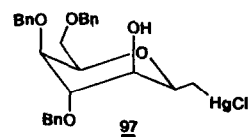
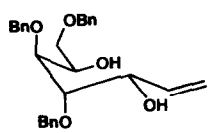
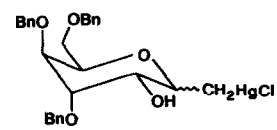
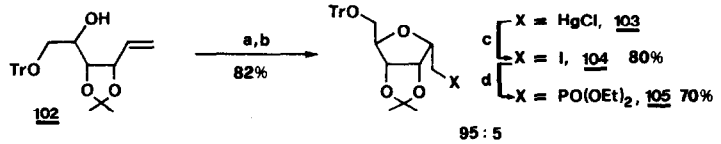


Table 9. Synthesis of C-glycosides via mercury-cyclization[70]

Substrate	Product	yield%
 92	 93	20
 94	 95	71
 96	 97	73
 98	 99 60 : 40	73

Cyclization gives a 78:22 $\alpha:\beta$ anomeric ratio, thus confirming also in this case the propensity of the C-3 substituent (O or N) to induce a *cis*-1,2-relationship.

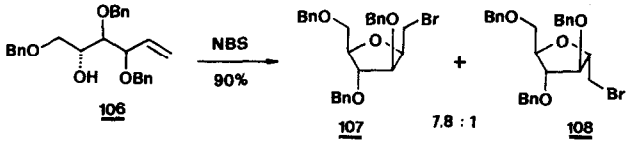
An interesting phosphono analog of α-D-ribose-1-phosphate **105** has been synthesized as a potential inhibitor of biological processes. The vinyl derivative **102**, obtained from 2,3-isopropylidene-5-trityl α-D-ribose, has been treated with $Hg(OAc)_2/KCl$.[72]



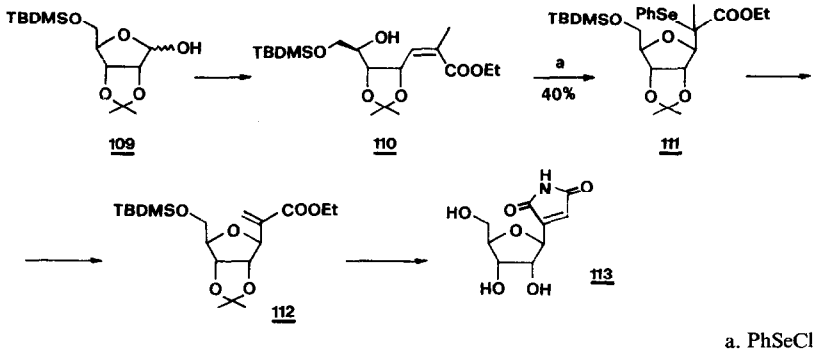
a. $Hg(OAc)_2$ b. KCl c. I_2, CCl_4 d. $P(OEt)_3$

Mercury-cyclization provides the predominant α-compound **103** (95:5) which in turn, when treated with iodine in CCl_4, gives the iododerivative **104**. The successive Arbuzov reaction affords the corresponding methanephosphonate **105**.

Reitz *et al.* have observed that the C-arabinofuranoside structure **107** is obtained predominantly as the β-anomer by treating hydroxyalkene **106** with NBS in THF. In fact a strongly stereoselective preference leads to C-arabinofuranoside structures in which a *cis*-relationship occurs between the substituents at C-2 and C-3.[73]

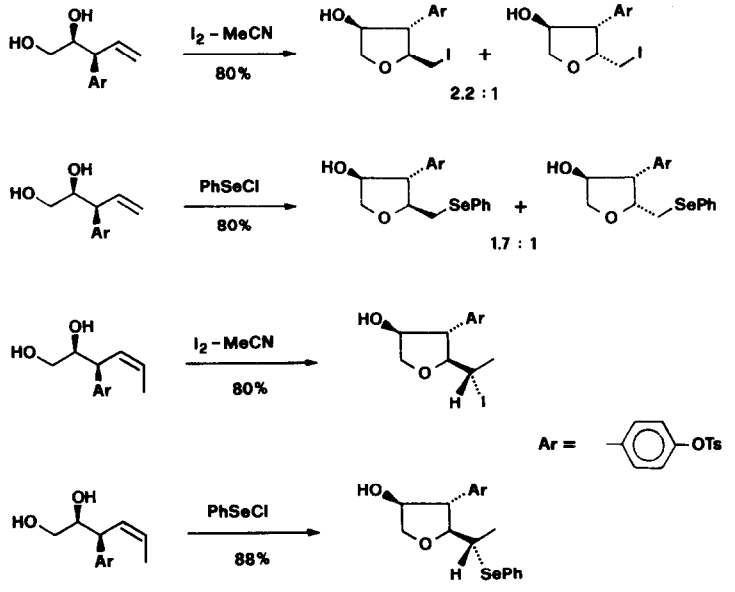


On the contrary a reversed stereoselectivity, due to the presence of the acetonide moiety, results in cyclization promoted by phenylselenyl chloride. Protected D-(−)-ribose **109** is firstly converted into unsaturated ester **110** and the subsequent cyclization produces β-anomeric derivative **111** in 40% yield. This compound has been employed as an intermediate in the synthesis of showdowmycin **113**.[74]

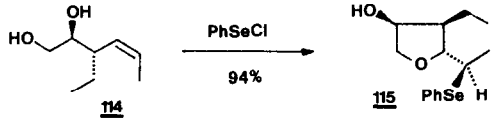


a. PhSeCl

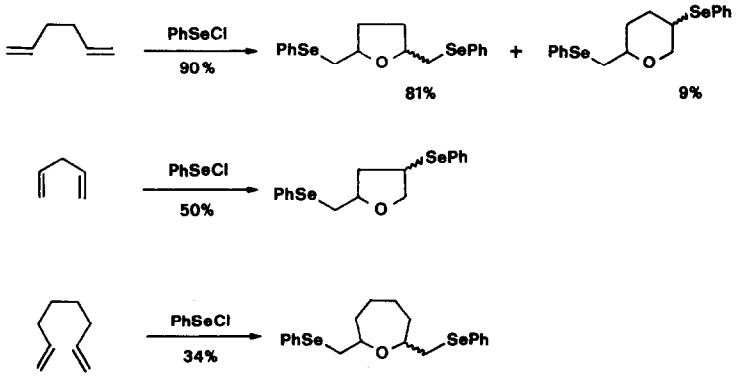
A preferred 1,3-*cis*-relationship between the C-2 hydroxyl group and the newly formed stereogenic centre has been observed in the formation of 2,3,4-trisubstituted tetrahydrofurans starting from 1,2-diols. The cyclization has been performed using I_2 in MeCN or PhSeCl in CH_2Cl_2 at −78°C.[75]



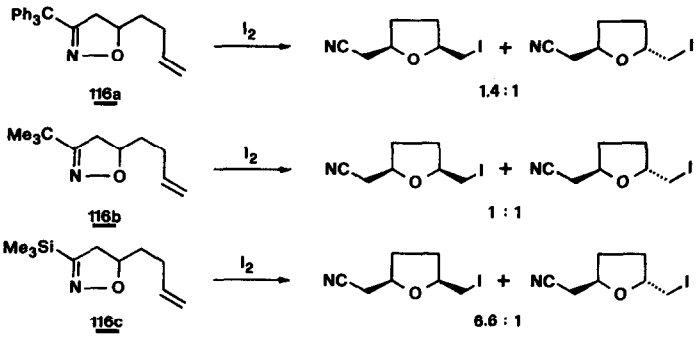
However, the opposite facial selectivity is reported in the cyclization of **114**. In this case, minimizing unfavorable steric repulsions between the substituents at C-2 and C-3, the configuration at C-3 and the *Z*-configuration of the double bond lead exclusively to the 1,3-*trans*-compound **115**.



Cyclic ethers containing two phenylseleno-groups have been obtained in 90% yield and high regioselectivity following the reaction of non-conjugated dienes with two equivalents of PhSeCl in $MeCN/H_2O$ 5 : 1 at reflux.[76]

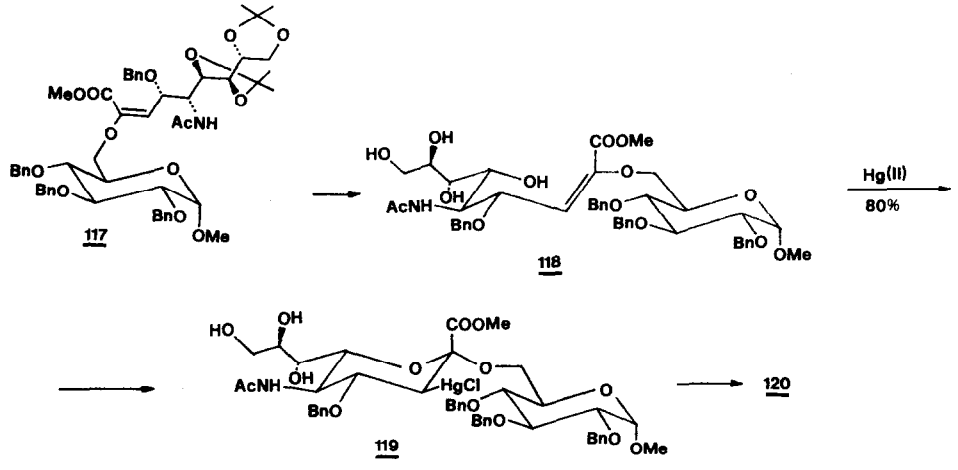


An interesting tandem 1,5-hexadiene-1,3-dipolar cycloaddition/electrophilic cyclization sequence has been devised to give 2,5-disubstituted tetrahydrofurans via the intermediate isooxazolines. In fact the cycloaddition of 1,5-hexadiene and the nitriloxide furnishes the corresponding isooxazolines **116 a–c** in quantitative yield. By treating these heterocycles with iodine, mixtures of *cis*- and *trans*-2,5-disubstituted tetrahydrofurans have been obtained.[77]

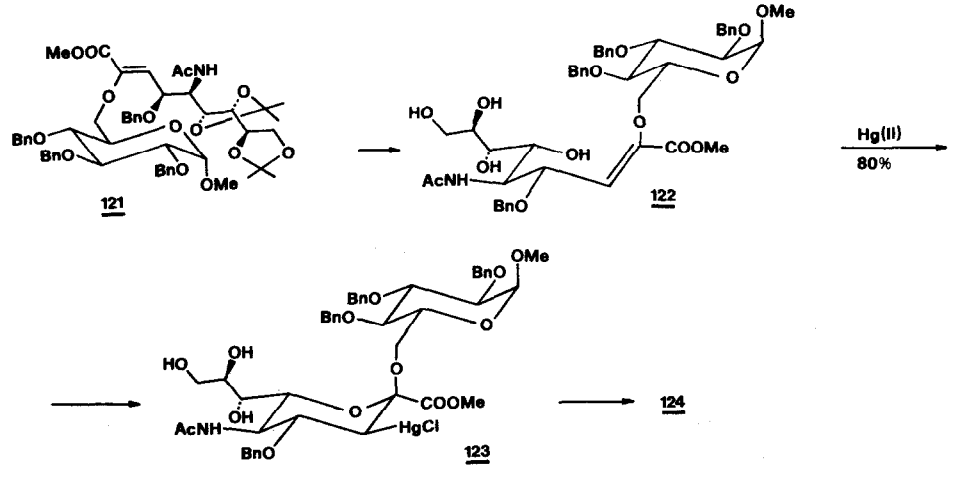


These results show a kinetic versus a thermodynamic control that can be attributed to the electrofugal properties of the leaving group, as observed by Bartlett in the cyclization of benzyl ethers.[35]

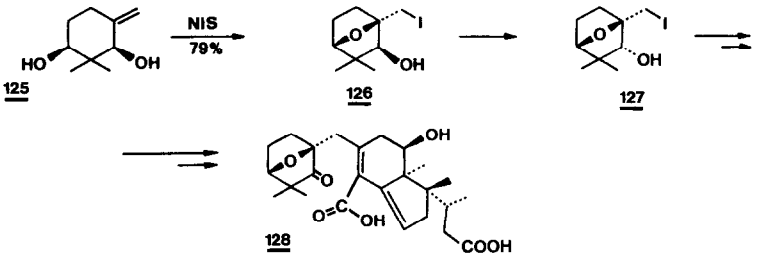
The N-acetylneuraminic acid (Neu5Ac) is a member of the sialic acid family present as glucosides in cellular organelles, body fluids and microorganisms. Sinay, by using an oxymercuration–demercuration sequence, has obtained Neu5Ac-α(2,6)Glu **120** and Neu5Ac-β(2,6)Glu **124** derivatives.[78]



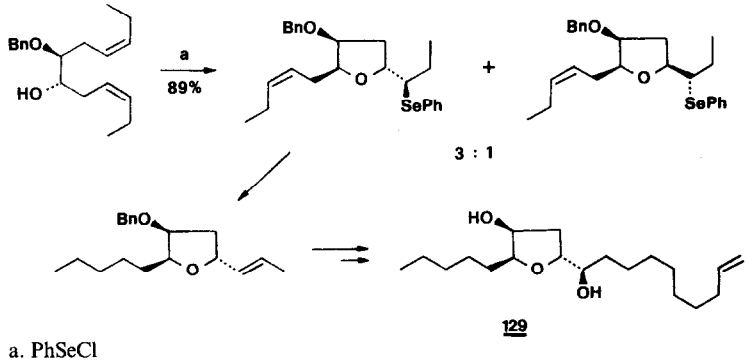
In fact both the (*Z*)-**117** and the (*E*)-isomer **121**, subjected to an Hg(II) induced cyclization in THF, afford only a single mercury-derivative.



Glycinoeclepin A **128**, revealing stimulative activity for the soybean cyst nematode, has been isolated and its structure elucidated.[79] The total synthesis of this compound has been reported, and in particular the A ring is obtained with total stereoselectivity starting from the *cis*-diol **125**, which in turn can be easily obtained in a few steps from 2,2-dimethylcyclohexane-1,3-dione by enzymatic methods.[80]

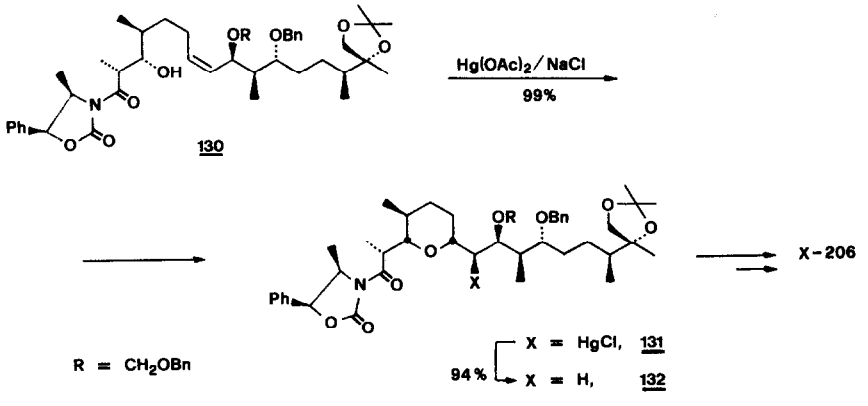


The enantioselective preparation of the marine natural product **129** has been reported starting from L-tartrate, by using a selenoetherification as the key step of the synthesis.[81]

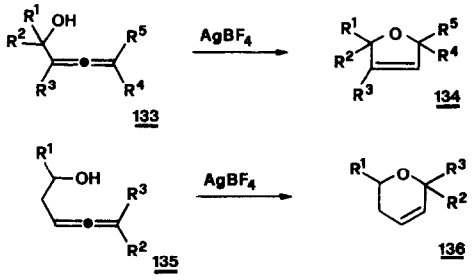


a. PhSeCl

A convergent asymmetric total synthesis of the polyether antibiotic X-206 has been reported by Evans *et al.*[82] In order to develop the synthesis of this stereochemically complex target, a plane has been elaborated relying exclusively on the asymmetric synthesis to resolve the absolute stereochemical issues. The acyclic stereoselective functionalization of the double bond allows the problem of the A ring synthesis to be resolved. The analysis of the steric and conformational aspects of the pyran ring in **132** suggests that *Z*-olefin **130** can be an appropriate material for a mercury-promoted cyclization to this target.



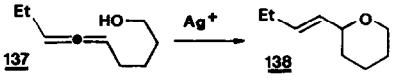
Analogous pathways have been devised using an allenic substrate, to give an alkenyl substituted product. In fact α-**133** and β-allenic alcohols **135** have been converted into 2,5-dihydrofurans **134** and 5,6-dihydro-2H-pyrans **136**, respectively, by treating them with a catalytic amount of Ag^+, but the stereochemical outcome of the reaction has not been studied.[83]



133 134 135 136

R^1, R^2, R^3, R^4, R^5 = H, Alkyl

Also δ-allenic alcohols **137** have been treated with both Ag^+ or Hg^{2+}, in order to obtain 2-alkenyltetrahydropyrans **138**, and the results are reported in Table 10.[84,85]

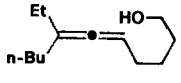
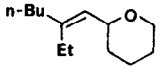
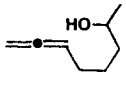
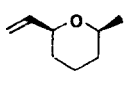
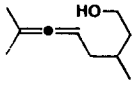
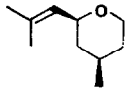
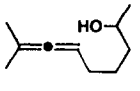
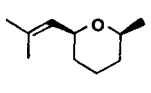


137 138 90% (92 : 8 E:Z)

Cyclization takes place at room temperature and proceeds with total regioselectivity since only 6-membered rings are observed. The stereoselectivity is good both for ring formation and for double bond. In fact *cis*-tetrahydropyran is the major component of the reaction mixture and the substituted double bond has the prevalent *E*-configuration.

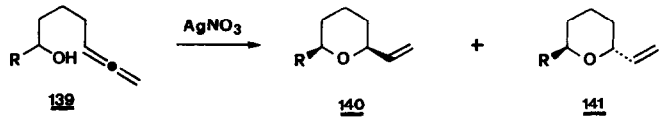
An analogous stereoselection has been reported for the cyclization of some δ-allenic alcohols **139** with $AgNO_3$ in acetone, in which the stereoselectivity increases by increasing the hindrance of the R group, as reported in Table 11.[86]

Table 10. Cyclization of δ-allenic alcohols mediated by metal cations[84]

Substrate	Product	yield%	cis:trans	E : Z
		40[a] 80[b]		55 : 45
		78[a] 78[b]	92 : 8 83 : 17	
		75[a] 90[b]	91 : 9 94 : 6	
		87[a] 83[b]	81 : 19 95 : 5	

a. Ag^+ b. Hg^{2+}

Table 11. Cyclization of δ-allenic alcohols mediated by Ag^{+}[86]



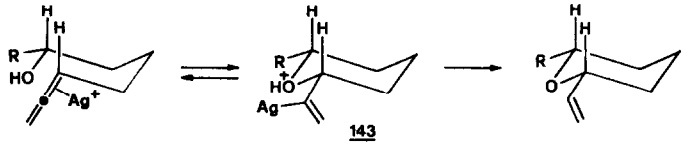
139 140 141

Substrate	yield %	cis : trans ratio
a. R = Me	75	96 : 4
b. R = t-Bu	50	99 : 1
c. R = c-C_5H_{11}	97	93 : 7
d. R = Ph	93	97 : 3
e. R = CH=CH_2	50	99 : 1

This method has been applied to the synthesis of **142**, a component of the glandular secretion of *Viverra civetta*.

140a 142

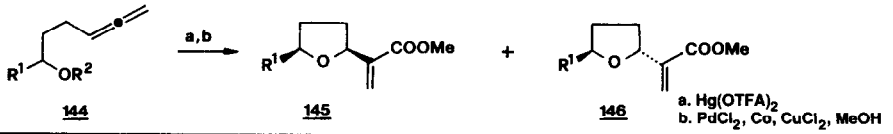
Although the formation of the *cis*-isomer can be rationalized in terms of an intermediate chair conformation, it is not clear whether the high selectivity observed is a function of kinetic control. *cis*-Isomer formation could be the result of a reversible cyclization step, followed by an irreversible protonation of the resulting complex **143**, regenerating Ag^{+}.



143

A further development in the cyclization of trialkylsilyl ethers of allenic alcohols **144**, where the allenic moiety lies at the γ-position with respect to the oxygenated function, has been obtained by treating these compounds with $Hg(OTFA)_2$ and then with a catalytic amount of $PdCl_2$ under a CO atmosphere.[87] The reaction proceeds with total regioselectivity to give 2-(2-tetrahydrofuranyl)acrylates **145** and **146**, exclusively. In some cases cyclization proceeds with high stereoselectivity, the *cis*-isomer being the preferred compound isolated from the reaction (Table 12).

Table 12. Cyclization of γ-allenic silyl ethers to 2-(2-tetrahydrofuranyl) acrylates[87]



144 145 146

Substrate	yield %	cis : trans ratio
a. R^1 = CH_3; R^2 = $SiMe_2{}^tBu$	53	94 : 6
b. R^1 = $CH_2COC(CH_3)_3$; R^2 = $SiMe_2{}^tBu$	80	92 : 8
c. R^1 = CH_2COCH_3; R^2 = $SiMe_2{}^tBu$	70	50 : 50
d. R^1 = $CH_2CH(OH)CH_3$; R^2 = $SiMe_2{}^tBu$	67	92 : 8

4. N-FUNCTIONALIZATION OF DOUBLE BONDS STARTING FROM AN O-FUNCTION

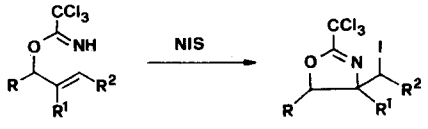
4.1. *Cyclization via imidates*

The preparation of aminoalcohols starting from unsaturated alcohols is an interesting process set up by us through the intramolecular halocyclization of unsaturated imidates. Hydrolysis of heterocyclic intermediates affords the polyfunctionalized sequence of 2-amino-1,3-diols.

The unsaturated imidates are easily obtained by treating a solution of the appropriate allylic alcohol with trichloroacetonitrile in the presence of a catalytic amount of NaH.[88] Cyclization can be carried out under kinetic conditions by adding either iodine in THF in the presence of pyridine, or NIS in chloroform to a solution of the allylic **147** or homoallylic trichloroacetimidate **149**.[14]

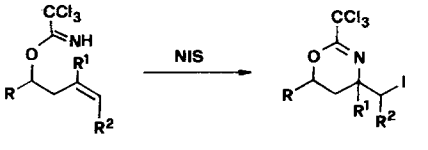
Cyclization of allylic derivatives with terminal double bonds shows total regioselectivity affording 4,5-dihydro-1,3-oxazoles **148**, while homoallylic derivatives give 4,5-dihydro-1,3-oxazines **150**, exclusively. A moderate to high stereoselectivity has been observed, depending on the increased hindrance of the substituent R; in fact, when R = C_5H_{11} (**148c**) only a 75:25 *trans*:*cis* ratio is observed; but when R = $CH(CH_3)_2$ (**148b**), a 95:5 *trans*:*cis* ratio is obtained. In addition homoallylic trichloroacetimidates give 4,5-dihydro-1,3-oxazines with moderate selectivity, since 80:20 *cis*:*trans* ratio is obtained when R is a methyl group (**150c**) (Table 13).

Table 13. Iodocyclization of allylic and homoallylic trichloroacetimidates[14]



147 148

Substrate	yield %	cis : trans
a. R = R^2 = H; R^1 = CH_3	85	–
b. R = $CH(CH_3)_2$; R^1 = R^2 = H	70	5 : 95
c. R = C_5H_{11}; R^1 = R^2 = H	60	25 : 75
d. R, R^2 = $-(CH_2)_3-$; R^1 = H	55	99 : 1

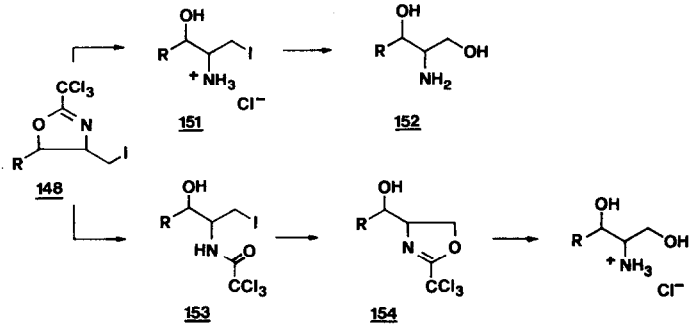


149 150

Substrate	yield %	cis : trans
a. R = R^2 = H; R^1 = CH_3	90	–
b. R = R^1 = H; R^2 = CH_2CH_3	80	–
c. R = CH_3; R^1 = R^2 = H	65	80 : 20

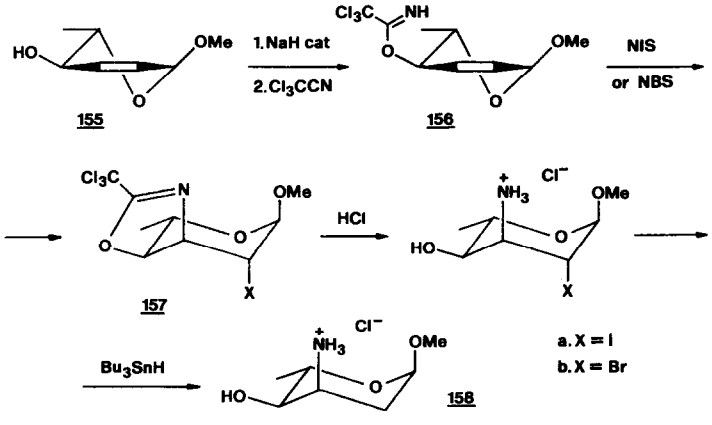
Hydrolysis of heterocyclic intermediates has been carried out under different conditions.[89] Under acidic conditions the salt **151** is obtained in quantitative yield, and the subsequent displacement of iodine is performed in refluxing methanol with an excess of acetate ion on polymeric support. The use of polymer supported reagents avoids the difficulties connected with an aqueous work-up, owing to the high water solubility of the products.

On the other hand, the hydrolysis in water/methanol affords the corresponding amide. As reported in the literature, the α-haloamides **153** undergo iodine displacement in basic media,[90,91] to give hydroxyalkyl-4,5-dihydro-1,3-oxazoles **154** and the subsequent hydrolysis with HCl allows salts of the corresponding 2-amino-1,3-diols **152** to be obtained.



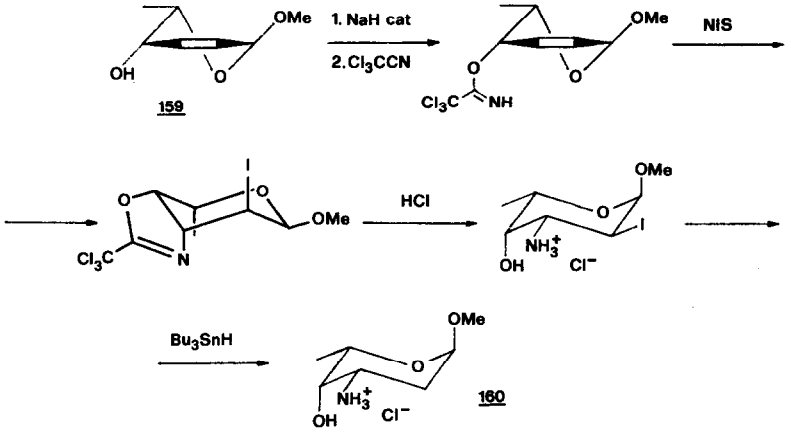
When this method is employed in cyclic systems, the *cis*-1-amino-2-hydroxy moiety can be introduced, starting from an unsaturated alcohol.

The cyclofunctionalization of imidates shows an interesting application in the synthesis of aminosugars ristosamine and daunosamine. Methyl α-L-ristosaminide hydrochloride **158**, a component of the antibiotic ristomycin, has been obtained starting from methyl 2,3,6-trideoxyhex-2-en-α-L-*erythro* pyranoside **155**, readily available from L-rhamnose. After conversion into the trichloroacetimidate **156**, cyclization with NIS in $CHCl_3$ or NBS in *t*-BuOH affords the altro-derivative **157**, with total asymmetric induction. Subsequent hydrolysis with HCl in methanol and cleavage of the C–halogen bond with Bu_3SnH opens a simple route to methyl α-L-ristosaminide hydrochloride **158**.[92]



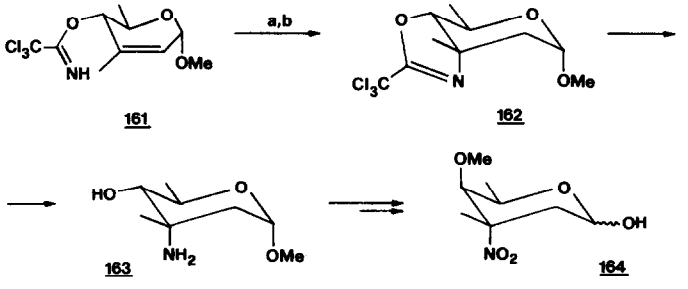
Daunosamine is an important carbohydrate constituent of the anthracycline antibiotics with strong antitumor activity such as daunorubicin and adryamicin.[93] Considering the stereochemistry of daunosamine, an appropriate starting material is represented by methyl 2,3,6-trideoxyhex-2-en-α-L-threopyranoside **159** which can be obtained through the inversion at C-4 of L-erythropyranoside

155 either by the Mitsunobo method or by treating the mesyl derivative with an excess of Amberlyst A 26 in the CO_3^{2-} form. Cyclization, hydrolysis and cleavage of the C–halogen bond complete the synthesis of methyl α-L-daunosaminide hydrochloride **160**.[94]



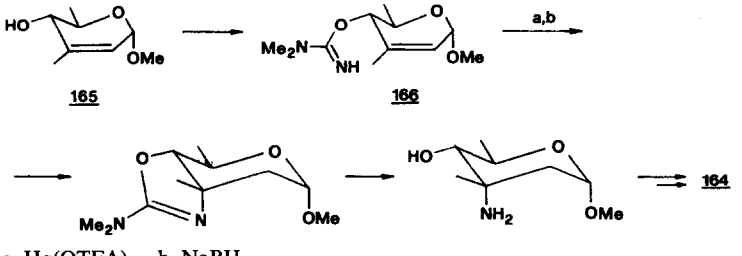
The main interest for these syntheses depends on the complete regio- and stereocontrol of the reaction sequence.

The cyclization of allylic trichloroacetimido derivatives has also been exploited for the synthesis of a key intermediate to nitrosugars such as D-rubranitrose **164**.[95] Treatment with $Hg(OTFA)_2$ of the imidate **161**, followed by $NaBH_4$ reduction, gives a bicyclic 4,5-dihydro-1,3-oxazole **162**. Successive hydrolysis with $Ba(OH)_2$ affords aminoalcohol **163**, a known precursor to D-rubranitrose **164**.



a. $Hg(OTFA)_2$ b. $NaBH_4$

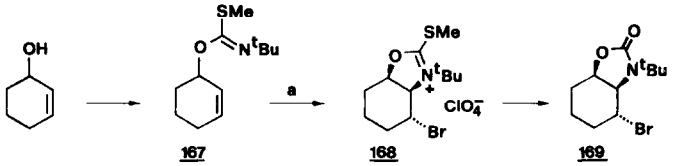
Better yields have been achieved starting from the imidate **166**, obtained by adding dimethylcyanamide to the pyranoside **165**.[95]



a. $Hg(OTFA)_2$ b. $NaBH_4$

Vicinal *cis*-aminoalcohol functionality is the main structural characteristic of aminocyclitols.[96] In many of these compounds another hydroxy group flanks the aminoalcohol moiety.

In connection with the synthesis of aminocyclitols from non-carbohydrate precursors, Knapp has prepared some *cis*-1,2-N-methylaminoalcohols by cyclization of thiocarbimidates **167**, as illustrated for cyclohexenol.[97]



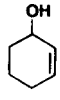
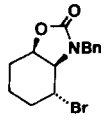
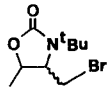
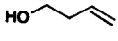
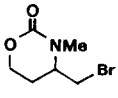
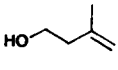
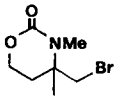
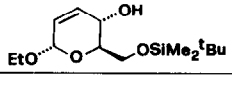
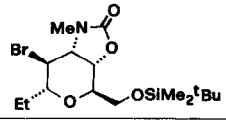
167 168 169

a. $Br(coll)_2ClO_4$

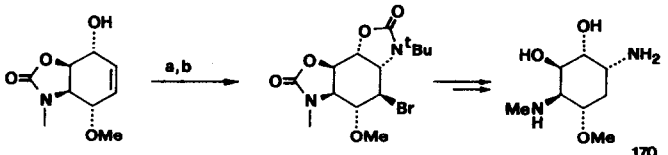
Treatment of the sodium alkoxide with an alkyl isothiocyanate gives an ambident anion that reacts with iodomethane at sulphur, to produce the thiocarbimidate **167**. Successive bromocyclization with bis(collidinebromonium) perchlorate affords 1,3-oxazolidin-2-one **169** in good yield. The intermediates of this bromocyclization reaction are the 4,5-dihydro-1,3-oxazoles **168**. In fact quenching with aqueous sodium bicarbonate allows the isolation of the iminium salt. Subsequent hydrolysis using aqueous sodium carbonate gives the corresponding oxazolidin-2-one. Table 14 shows the application of this procedure to several cyclic and acyclic unsaturated alcohols using benzyl, *t*-butyl and methyl isothiocyanate.

As shown in Table 14, the regiochemistry of this reaction is in perfect agreement with the results discussed above for the trichloroacetimidates. Moreover, starting from cyclic compounds, *cis*-1,2-aminoalcohols are exclusively obtained. In fact the conversion of a bromocarbamate into (±)-

Table 14. Bromocyclization of allylic and homoallylic thiocarbimidates[97]

Substrate	Isocyanate	Product	yield %
	BnNCS		83
	^{t}BuNCS		68 (1.4:1 cis : trans)
	MeNCS		69
	MeNCS		83
	MeNCS		82

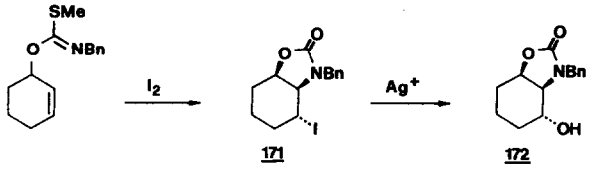
sporamine **170** has been realized in 90% overall yield. The sporamine is an aminocyclitol portion of the broad-spectrum antibiotic sporaricin A.



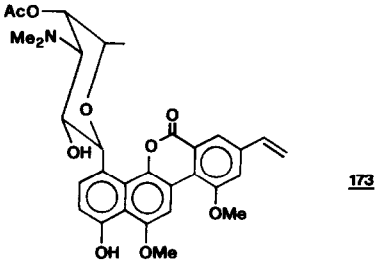
a. *t*-BuCNS b. $Br(coll)_2ClO_4$

The N-*t*-butyl group is easily removed by conversion into *t*-butyl trifluoroacetate on treatment with trifluoroacetic acid.

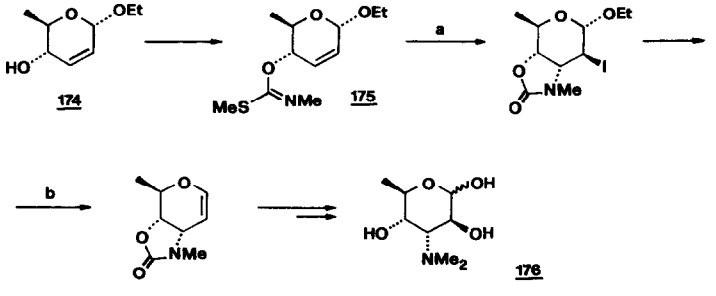
It is worth mentioning that the use of iodine in THF as the electrophile is a procedure superior to the use of bis(collidinebromonium) perchlorate in terms of yield and ease of operation. Displacement of iodine with silver trifluoroacetate in nitromethane gives hydroxycarbamate **172** with retained configuration.[98]



Following this approach, the (−)-methyl ravidosaminide **176** (3,6-dideoxy-3-(N,N-dimethylamino)altropyranose), a component of the antibiotic ravidomycin **173**, has been synthesized.[99]

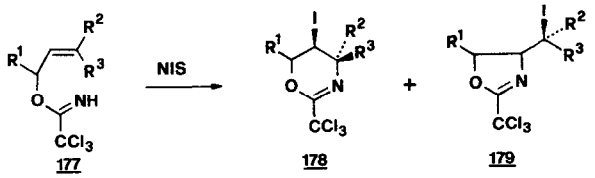


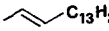
The unsaturated alcohol **174**, obtained in four steps from the commercially available tri-O-acetyl-D-glucal, has been converted into the corresponding N-methylcarbonimidothioate **175** which is cyclized to the altropyranose derivative.



a. I_2, Na_2CO_3, THF b. Zn, EtOH

Table 15. Electronic factors affecting the regiochemistry of allylic imidates cyclization[100]



Substrate	178 yield%	179 yield%
a. R^1 = H; R^2 = Ph; R^3 = H	80	–
b. R^1 = H; R^2 =  ; R^3 = H	90	–
c. R^1 = H; R^2 =  $C_{13}H_{27}$; R^3 = H	95	–
d. R^1 = $C_{15}H_{31}$; R^2 = H; R^3 = H	–	90
e. R^1 = H; R^2 = Me; R^3 = Me	85	–

Several factors appear to govern regioselectivity towards 5-*exo* or 6-*endo* closures of acyclic allylic imidates under the conditions employed, and that is I_2/pyridine in THF, NIS in $CHCl_3$ or I_2 in $CHCl_3$. Moreover the regiochemical outcome of the ring closure seems to be influenced by the *E* or *Z* configuration of the double bond. The formation of 6-membered rings can be easily established by i.r. spectroscopy, whereby the absorption at 1670 cm^{-1} is consistent with a C=N stretching in a 6-membered ring of 2-trichloromethyl-4,5-dihydro-1,3-oxazines **178**. The absorption at 1650 cm^{-1} however, can be used as the diagnostic feature for 2-trichloromethyl-4,5-dihydro-1,3-oxazoles **179**.[100]

A set of substrates where regioselectivity is controlled by electronic factors is reported in Table 15. Due to the stabilization of a benzylic or allylic incipient cation, compounds **177a, b** and **c** give the corresponding iodooxazines **178** exclusively. On the other hand, the cyclization of **177d** proceeds with a total regioselection, leading to iodo-1,3-dihydrooxazole **179d**. The cyclization of compound **177e** is again controlled by electronic factors, the incipient tertiary cation in 6-*endo* transition state outweighting the steric hindrance of the methyl group, so that **178e** is exclusively obtained.

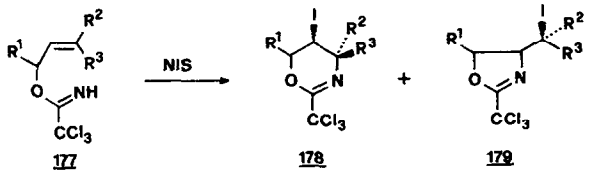
In Table 16 we have considered the influence of *E* or *Z* double bond configuration on the regioselectivity.

Treatment of the 2(*E*)-pentenyl trichloroacetimidate **177f** affords exclusively iodooxazine **178f**, while its 2(*Z*)-isomer **177g** affords only the corresponding iododihydro-1,3-oxazole **179g**. The remaining examples reported in Table 16 confirm that the configuration *E* or *Z* of the double bond exerts a total control on cyclization, so that only one of the two possible rings is obtained.

In a further study on regioselectivity, we have examined the role of an oxygen atom in a position allylic to the double bond. It is known that substituents in the allylic positions exert a very pronounced influence on both the stereo- and regioselectivity of the electrophilic addition. A polar substituent such as a methoxy or a hydroxy group, affects the regioselectivity mainly through an inductive effect, directing the attack of the nucleophile on the carbon atom away from the oxygen atom. Thus 5-*exo* closures are exclusively observed for imidates **177l–n** (Table 17).

These compounds possess an allylic ethereal group which favours the attack of the nucleophile at C-2, because of the combined inductive and steric effects of the alkoxy group. By contrast, a mixture of 6- and 5-membered rings **178** and **179** is obtained with the imidates **177o–q**, thus confirming the propensity of the *E* double bond to promote the 5-*endo* closure in opposition to the oxygen effect.

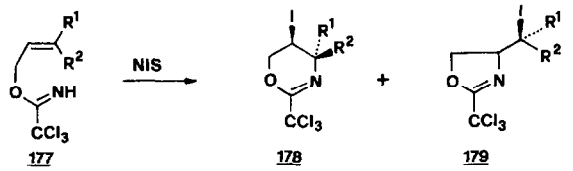
Table 16. Geometric factors affecting the regiochemistry of allylic imidates cyclization[100]



177 178 179

Substrate	178 yield%	179 yield%
f. R^1 = H; R^2 = Et; R^3 = H	90	–
g. R^1 = H; R^2 = H; R^3 = Et	–	88
h. R^1 = H; R^2 = Pr; R^3 = H	87	–
i. R^1 = H; R^2 = $C_{15}H_{31}$; R^3 = H	90	–
j. R^1 = H; R^2 = H; R^3 = $C_{15}H_{31}$	–	90
k. R^1 = H; R^2 = H; R^3 = Ph	–	92

Table 17. Effect of an O-substituent on the regiochemistry of allylic imidates cyclization[100]



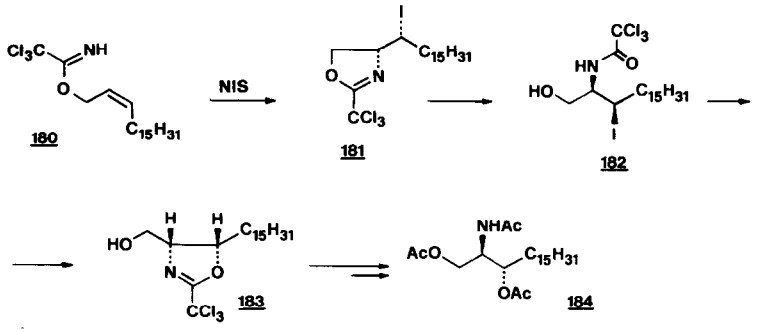
177 178 179

Substrate	178 yield%	179 yield%
l. R^1 = H; R^2 = CH_2OMe	–	87
m. R^1 = H; R^2 = CH_2OTHP	–	81
n. R^1 = H; R^2 = CH_2OBn	–	98
o. R^1 = CH_2OMe; R^2 = H	30	61
p. R^1 = CH_2OTHP; R^2 = H	38	55
q. R^1 = CH_2OBn; R^2 = H	18	75

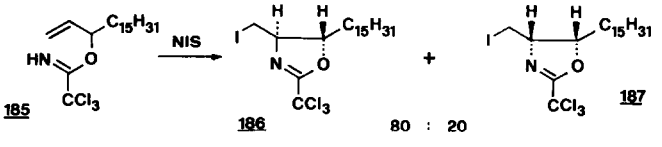
On the basis of the previously discussed regiochemistry, the synthesis of *erythro*- **184** and *threo*-sphinganine **192** and *erythro*-sphingosine **196**, important components of cerebrosides, gangliosides and sphingomyelins, has been developed.

Racemic *erythro*-sphinganine **184** has been obtained in good yield and under complete stereocontrol starting from the easily accessible 2(*Z*)-octadecenol. Due to the presence of a *Z* double bond, the 4,5-dihydro-1,3-oxazole **181** is obtained exclusively in high yield and then opened in water to the corresponding amide **182**; this compound, under basic conditions, affords as the major product the *cis*-dihydroxazole **183**. The hydrolysis of the *cis*-4,5-dihydro-1,3-oxazole **183** and direct

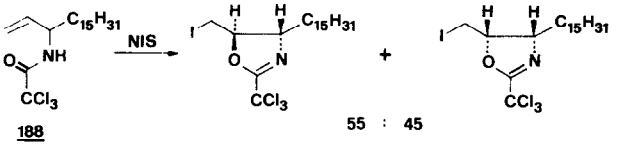
acetylation of the salt allows the (±)-*erythro* sphinganine triacetate **184** to be obtained in good yield.[18]



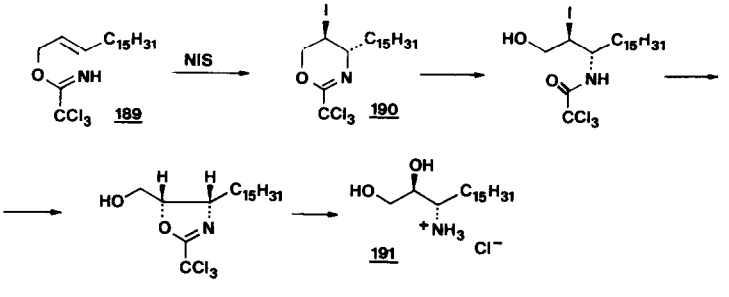
The exclusive 5-*exo* closure obtained starting from a double bond in the *Z* configuration constitutes an interesting approach to the synthesis of 2-amino-1,3-diols in *anti* configuration. A further application of the imidate pathway to the synthesis of sphinganines starts from octadec-1-en-3-ol. The corresponding trichloroacetimidate **185** is cyclized to give a diastereomeric mixture of 4,5-dihydro-1,3-oxazoles **186** and **187** in a *trans*:*cis* ratio of 80:20, a selectivity which has to be considered good in comparison with other results obtained in the ring closure of terminal double bonds of allylic imidates. The *trans*-isomer **186** is easily converted into *threo*-sphinganine **192**.[18]



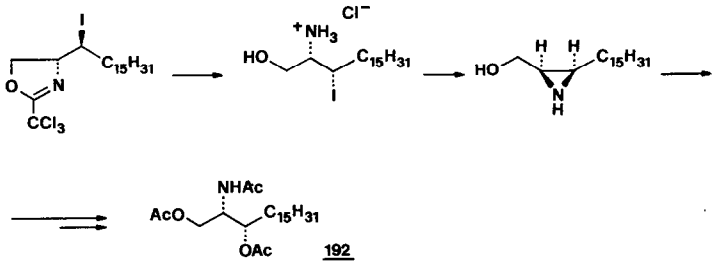
However, the iodocylization of the corresponding amide **188** is less selective, affording a 55:45 *trans*:*cis* ratio. All these heterocycles have been employed for the synthesis of the regioisomers of sphinganines.[19]



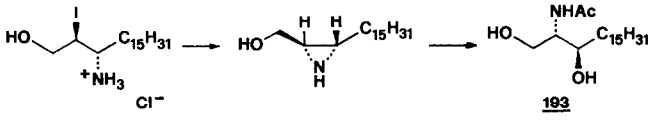
Cyclization of 2(*E*)-octadecenyl trichloroacetimidate **189** gives in 80% yield 4,5-dihydro-1,3-oxazine **190** as the only product. The strong dependence of the regioselectivity on the *E*-configuration of the double bond can be a valuable tool for the synthesis of *anti* 3-amino-1,2-diols under high stereocontrol, as reported for the synthesis of the regioisomer of *erythro*-sphinganine **191**.[19]



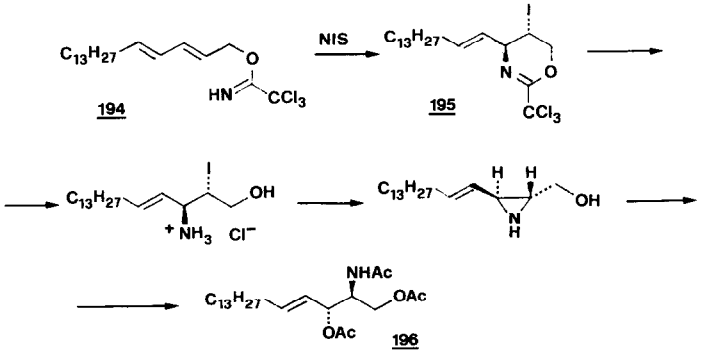
We have also envisaged an alternative route to *threo*- and *erythro*-sphinganine starting from 2(*Z*)-octadecen-1-ol through the opening of the corresponding aziridine. The opening of the aziridinium salt is performed with Amberlyst A 26 in the AcO^- form to give a regioisomeric mixture 70 : 30, where *threo*-sphinganine **192** is the major component.[18]



The preferential attack of the nucleophile at C-3 can be attributed to the effect of the neighbouring hydroxyl group.[19]



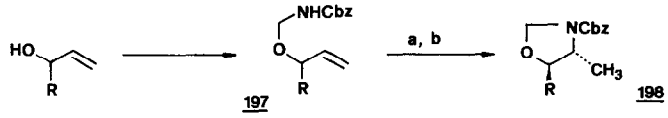
On the basis of the previously reported studies on the regioselectivity of this reaction, we have developed an efficient synthesis of (±)-*erythro* sphingosine **196**, the most widely occurring of the sphingolipid bases. In this case electronic factors play a dominant role so that the attack is directed towards the more stabilized carbocation and the sphingosine is obtained under complete regio- and stereocontrol.[101] The cyclization of the trichloroacetimidate **194**, due to the stabilization of the allylic carbocation, affords the corresponding 4,5-dihydro-1,3-oxazine **195** in 95% yield as the sole product. The acidic cleavage affords the ammonium salt. This is then treated with Amberlyst A 26 in the AcO^- form to give the corresponding amide. The reaction proceeds via the intermediate aziridine, which can be easily isolated under mild basic conditions. The opening of the aziridine occurs exclusively at the carbon atom in the allylic position.



4.2. *Cyclization via N-acylaminomethyl ethers*

The mercury initiated cyclization of N-acylaminomethyl ether derivatives **197**, developed by Harding *et al.*, proceeds stereoselectively to form 4,5-disubstituted oxazolidines **198** preferen-

tially.[102] The stereoselectivity is in agreement with the results observed by us in the cyclization of trichloroacetimidates.



		trans : cis ratio
a.	R = Me	75 : 25
b.	R = ^{i}Pr	95 : 5
c.	R = Ph	95 : 5

a. $Hg(OAc)_2$ b. $NaBH_4$

The starting material is prepared by the reaction of allylic alcohols with N-hydroxymethyl benzyl carbamates using *p*-TsOH as a catalyst. The cyclization is performed with $Hg(OAc)_2$ in MeCN, and subsequent reduction with $NABH_4$, gives the disubstituted oxazolidines **198** in good yield.

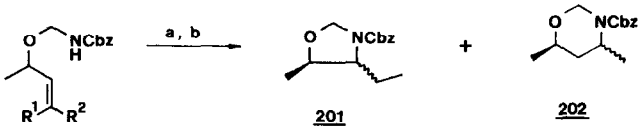
This cyclization gives interesting, different results depending on whether control is kinetic or thermodynamic. Thus the cyclization of (*E*)- or (*Z*)-3-penten-2-ol derivatives **199** and **200** has been carried out in CD_3CN and examined by ^{1}H NMR.[103]

As shown in Table 18, the reaction proceeds through a 5-*exo* and 6-*endo* closure. The ratio of 5-membered ring to 6-membered ring products varies little with time, but significant change in the stereochemistry is observed. The double bond configuration affects the ratio of oxazolidines **201** to tetrahydro-1,3-oxazines **202**. In fact, while the cyclization of the (*E*)-isomer gives a 1 : 2 ratio of **201** : **202**, the (*Z*)-isomer gives a 2 : 1 ratio.

The greater thermodynamic stability of *trans* N-acyl-4,6-dialkyltetrahydro-1,3-oxazines **202** is predicted by MM2 calculations. In fact the energy of the diequatorial conformation of the *cis*-isomer is increased by the A(1,3)-type interaction between the equatorial methyl and the planar carbamate functionality.

In contrast to our results in the cyclization of allylic imidates,[100] the configuration of the double bond of the acylaminomethyl derivatives prepared from (*Z*)- and (*E*)-2-buten-1,4-diol, respectively,

Table 18. Kinetic/thermodynamic control in the cyclization of N-acylaminomethyl ethers[103]



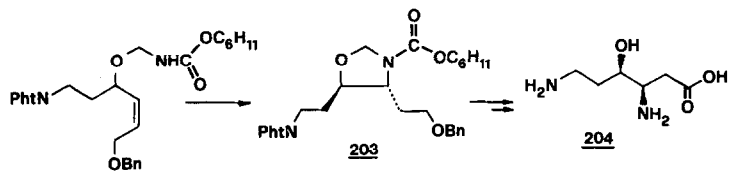
199 R^1 = H; R^2 = Me

200 R^1 = Me; R^2 = H

Substrate	Reaction time	trans-201 : cis-201	trans-202 : cis-202	201:202
199	15 min	2 : 1	1 : 17	1 : 2
	20 hr	2 : 1	4 : 1	1 : 2
	11 days	2 : 1	29 : 1	1 : 1.5
200	19 min	10 : 1	1 : 2	2 : 1
	44.5 hr	9 : 1	20 : 1	2 : 1

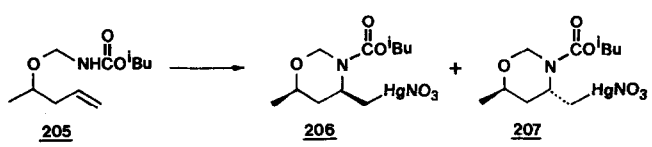
has no effect on the regioselectivity, since the exclusive formation of 5-membered or 6-membered ring products is not observed.

Intramolecular cyclization mediated by Hg(II) has been applied to the synthesis of non-proteinogenic β-aminoacids and γ-hydroxy-β-aminoacids.[104] Racemic *threo*-γ-hydroxy-β-lysine **204** is a basic aminoacid isolated from the antitubercular peptides tuberactinomycin A and N. The synthesis is reported in the following scheme. The *trans* 5-*exo* compound **203** is obtained as a single stereoisomer in 65% yield, contamined by 17% of its regioisomer.



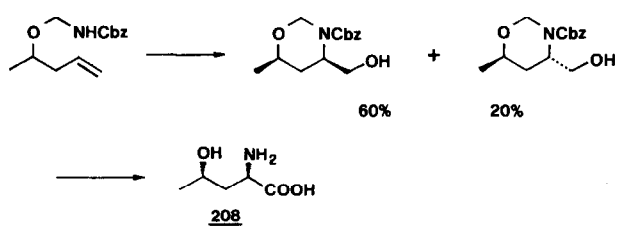
This intramolecular cyclization has been used as the key step in the stereoselective synthesis of either the *erythro*- or *threo*-1,3-aminoalcohol moiety from a single precursor, by simply carrying out the reaction under kinetic or thermodynamic control.

In fact the examination by ^{1}H NMR of the cyclization of the carbamate **205**, carried out with $Hg(NO_3)_2$ in acetone-d_6, after 30 min indicates that the *cis* organomercurial predominates by a ratio of 4 : 1. After a period of 1 h the *cis* : *trans* ratio is 1 : 1 and after 46 h the ratio changes to 5 : 95. Thus, a short reaction time gives predominantly the *cis*-isomer **206**, while longer reaction times lead to the more stable *trans*-isomer **207** with very high stereoselectivity.[105]

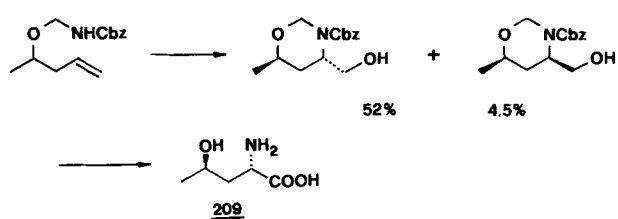


30 min	4 : 1
14 hr	1 : 1
46 hr	< 5 : 95

These results have been utilized for the synthesis of *erythro*-γ-hydroxynorvaline **208**, where the cyclization is carried out under kinetic control.



On the contrary, the synthesis of *threo*-γ-hydroxynorvaline **209** requires the cyclization under thermodynamic control.



4.3. *Cyclization via N-sulphonyl carbamates*

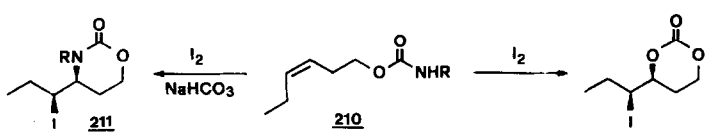
Functionalization of double bonds via iodocarbonates is a well known reaction that can be carried out with high stereocontrol under kinetic[16,106] or thermodynamic conditions.[107] This goal can be achieved easily through the iodocyclization of unsaturated O-carbamates.[108]

Because of the ambident nature of these compounds, an appropriate substitution on the nitrogen atom, such as a sulphonyl group, favours the nitrogen attack. Thus N-substituted carbamates **210**, prepared by mixing the corresponding alcohol with the requisite N-substituted isocyanate, give rise to an iodine-induced cyclization, affording the corresponding cyclic carbamates **211** in good yield (Table 19).[109]

The presence of the base suggests that the reaction proceeds under kinetically controlled conditions. This is confirmed by the fact that the *cis*:*trans* diastereomeric ratio is independent of reaction time. Starting from N-sulphonylated allylic carbamates **212**, the oxazolidin-2-ones **213** have been prepared in good yield. A preferential diastereoselectivity in favour of the *cis*-4,5-compounds is observed, in agreement with a transition state model where H is in plane. These results provide an interesting stereoselective route to 1,2-*anti* aminoalcohols (Table 20).

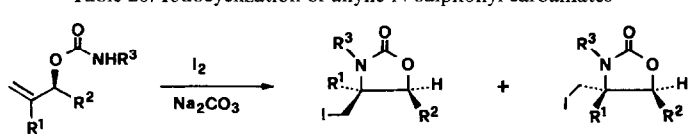
In the same way, N-substituted homoallylic carbamates **215** cyclize with high stereoselectivity to give *cis*-1,3-cyclic carbamates **216**, useful intermediates for the preparation of 1,3-*syn* aminoalcohols (Table 21).

Table 19. Regioselectivity of the iodocyclization of primary N-sulphonyl carbamates[109]



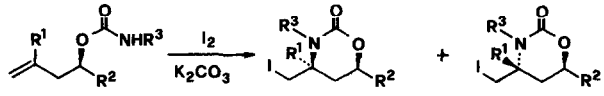
	Substrate	yield %	yield %
a.	R = H	0	64
b.	R = SO_3Me	22	16
c.	R = $SO_3CH_2CCl_3$	67	10
d.	R = Ts	75	7
d.	R = Ts	64 (Na_2CO_3)	0

Table 20. Iodocyclization of allylic N-sulphonyl carbamates[109]



	Substrate	yield %	diastereomeric ratio
a.	R^1 = Me; R^2 = H; R^3 = Ts	67	–
b.	R^1 = Me; R^2 = H; R^3 = SO_2Ph	74	–
c.	R^1 = H; R^2 = Me; R^3 = Ts	78	2.7:1
c.	R^1 = H; R^2 = Me; R^3 = Ts	52 (-25°C)	3.4:1

Table 21. Iodocyclization of homoallylic N-sulphonyl carbamates[109]



215 216 217

Substrate	yield %	diastereomeric ratio
a. R^1 = Me; R^2 = H; R^3 = Ts	71	–
b. R^1 = H; R^2 = Me; R^3 = Ts	59	5.2 : 1
c. R^1 = H; R^2 = Me; R^3 = SO_2Ph	68	6.2 : 1
d. R^1 = H; R^2 = Me; R^3 = SO_2– 	52	5.5 : 1

4.4. *Cyclization via intramolecular Michael reactions*

Intramolecular cyclizations that take place via Michael addition have been utilized in the synthesis of complex molecules, since the reaction shows a high regio- and stereocontrol.

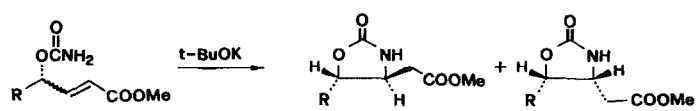
Hirama and Ito have developed a carbamate-mediated functionalization useful for the diastereoselective introduction of the nitrogen functionality in the α-position of γ- and δ-hydroxy-α,β-unsaturated esters and in the α-position of a vinyl sulfoxide.[110]

O-Carbamates **218** are easily synthesized from the corresponding alcohols and $ClSO_2NCO$ or CCl_3CONCO, followed by partial hydrolysis. By treatment of these carbamate esters with *t*-BuOK in THF under argon atmosphere, a rapid cyclization via nitrogen occurs, producing mainly the *trans*-oxazolidin-2-ones **219**, useful intermediates to 1,2-*syn* aminoalcohols (Table 22).

The *trans* : *cis* ratio is not affected by changing the reaction time; moreover a high 1,2-asymmetric induction is observed, especially in the compounds where R is a sterically demanding group. As shown in Table 22, the configuration of the double bond strongly influences the stereochemistry, since, by using the (*Z*)-olefin, the *trans* oxazolidin-2-one is exclusively obtained. All these results suggest that the reaction occurs under kinetic control.

Also the homoallylic carbamates **221** afford the corresponding 1,3-oxazin-2-ones **222** and **223** with a high asymmetric induction (Table 23).

Table 22. Stereoselectivity in Michael reaction of allylic O-carbamates[110]



218 219 220

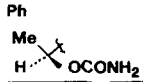
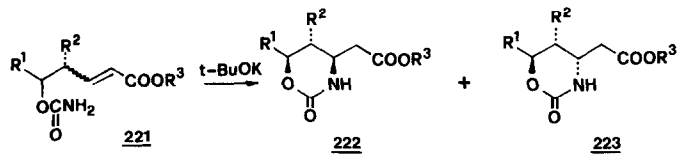
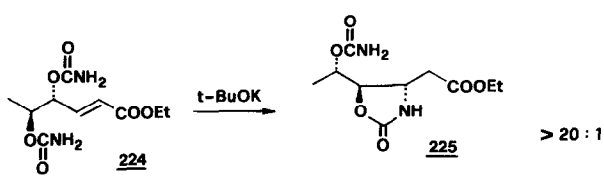
Substrate	2,3-double bond	74 : 75	yield %
a. R = Me	E	5 : 1	66
b. R = Ph	E	12 : 1	85
b. R = Ph	E	7 : 1	68
c. R = Ph	Z	>100 : 1	75
d. R = 	E	>20 : 1	79

Table 23. Stereoselectivity in Michael reaction of homoallylic O-carbamates[110]

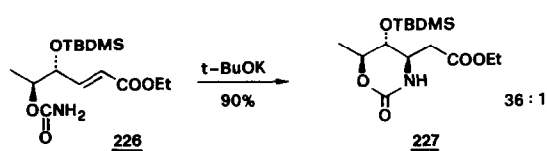


Substrate	2,3-double bond	77 : 78	yield %
a. R^1 = Me; R^2 = H; R^3 = Me	E	10 : 1	53
b. R^1 = Me; R^2 = H; R^3 = Me	Z	20 : 1	70
c. R^1 = Me; R^2 = O^{t}Bu; R^3 = Et	E	7 : 1	91
d. R^1 = Me; R^2 = OAc; R^3 = Et	E	19 : 1	52
e. R^1 = Me; R^2 = OTBDMS; R^3 = Et	E	36 : 1	90

When both (*E*)- and (*Z*)-isomers **221a** and **221b** are cyclized, it has been observed that the *Z*-configuration of the double bond improves the stereoselectivity; moreover the presence of an *anti* substituent in the α-position increases the 1,3-*syn* diastereoselectivity, as expected. It is worth mentioning that a complementary diastereofacial selection can be accomplished by changing the site of the carbamoyloxy group between the α- and β-position. In fact because of the competitive cyclization between allylic and homoallylic carbamate groups of the biscarbamate **224**, the former adds with greater selectivity to afford the 1,3-*anti* derivative **225**.

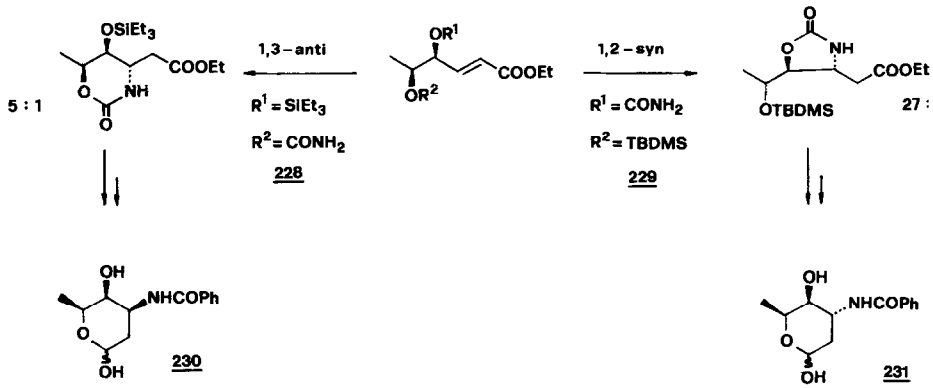


On the other hand, from the homoallylic carbamate **226**, where the OH at C-4 is protected as a silyl ether, the oxazin-2-one **227** is obtained with a high 1,3-asymmetric induction.

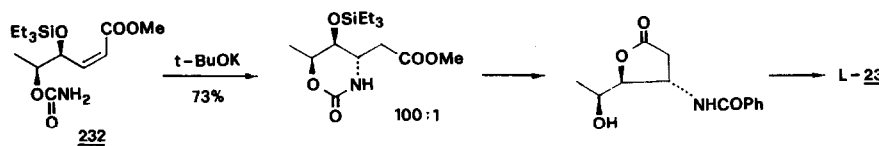


The synthetic utility of this strategy has been demonstrated by the stereoselective synthesis of all four possible diastereomers of 2,3,6-trideoxyhexose.

Thus the synthesis of both N-benzoyl-D,L-daunosamine **230** and N-benzoyl-D,L-3-*epi*-daunosamine **231** has been accomplished starting from an appropriate (*E*)-carbamate. As reported in the following scheme, a 1,3-*anti* stereoselection (5 : 1 *anti* : *syn* ratio) is achieved through the cyclization of the homoallylic carbamate **228** to the corresponding oxazin-2-one. This route has been utilized for the racemic synthesis of N-benzoyl-D,L-daunosamine **230**. On the contrary, the allylic carbamate **229** cyclizes smoothly to the corresponding oxazolidin-2-one in 98% yield and 27 : 1 *trans* : *cis* diastereomeric ratio, useful for the synthesis of N-benzoyl-D,L-3-*epi*-daunosamine **231**.[111]

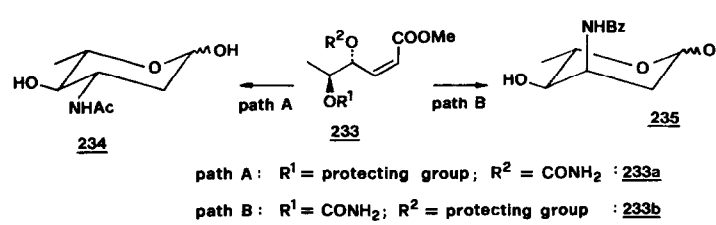


Furthermore, the (*Z*)-carbamate **232**, easily prepared from O-*t*-butyldimethylsilyl lactaldehyde, cyclizes under standard conditions with complete stereocontrol (> 100 : 1). This result allows a facile synthesis of N-benzoyl-L-daunosamine **230**.[112]

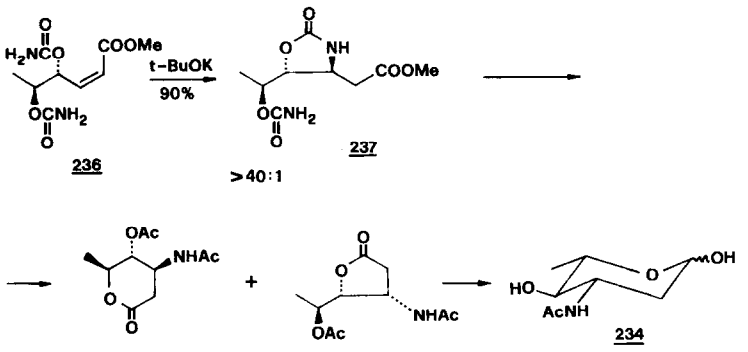


The higher asymmetric induction observed in the cyclization of the *Z*-olefin can be explained by considering the transition state constrained by severe repulsive interactions of the ester group with the allylic hydrogen and ethereal group (A(1,3) strain).[113] The allylic conformation of the *E*-olefin is much more flexible so that the antiperpiplanar effect acts to a lesser extent.

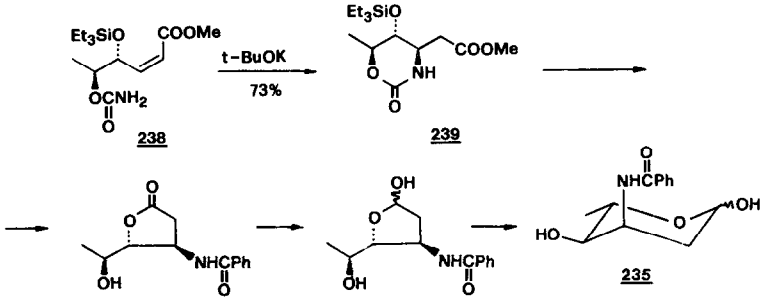
A further development of this divergent route to synthesize both N-acetyl-L-acosamine **234** and N-benzoyl-L-ristosamine **235** starting from L-lactaldehyde via a *Z*-olefin has been reported.[114,115] By coupling O-(*t*-butyldimethylsilyl)lactaldehyde and methyl propiolate, the corresponding unsaturated ester **233** is the common intermediate to both N-acetyl-L-acosamine **234** and N-benzoyl-L-ristosamine **235**.



Thus the (*Z*)-biscarbamate **236** is cyclized smoothly under the reported conditions to give a *trans*-oxazolidin-2-one **237** (3,4-*syn* aminoalcohol derivative) in 90% yield, with high selectivity (> 40 : 1). The alkaline hydrolysis and successive lactonization with acetic anhydride afford a mixture of γ- and δ-lactones; after reduction with DIBAL, N-acetyl-L-acosamine **234** is easily obtained.

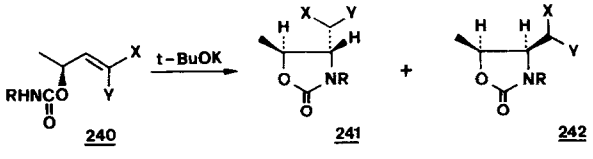


The synthesis of N-benzoyl-L-ristosamine **235** requires the regiocontrolled protection of the diol. The cyclization of **238** with *t*-BuOK gives, as expected, the 1,3-*syn* cyclic carbamate **239**, the crucial intermediate for the synthesis of **235**.



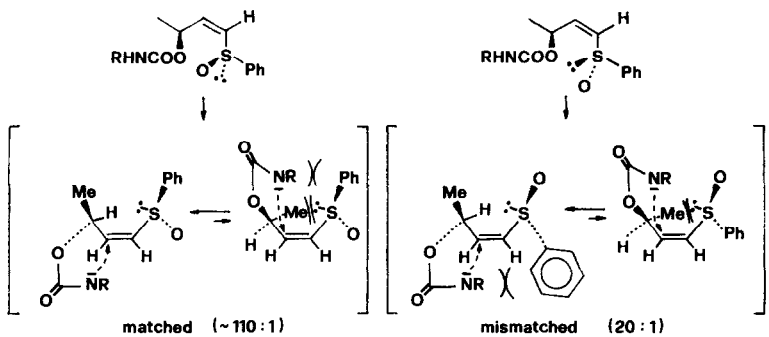
In a further development of the Michael reaction, the conjugate addition of an internal nucleophile to vinyl sulphones and sulphoxides bearing a stereogenic centre at the allylic carbon atom, has been carried out under basic conditions. The results are listed in Table 24.[116]

Table 24. Stereoselectivity in Michael addition to vinyl sulphones and sulphoxides[116]

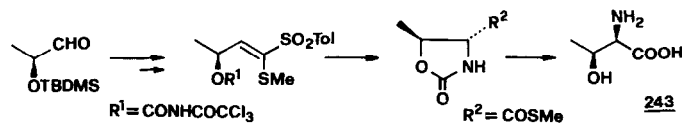


Substrate	241 : 242 ratio	yield %
a. X = H; Y = SO_2Ph	130 : 1	83
b. X = $SiMe_3$; Y = SO_2Ph	120 : 1	71
c. X = SO_2Tol; Y = SMe	100 : 1	86
d. X = SO_2Tol; Y = STol	100 : 1	86
e. X = SOPh (S); Y = H	3.3 : 1	81
f. X = SOPh (R); Y = H	23 : 1	93
g. X = H; Y = SOPh (S)	110 : 1	98
h. X = H; Y = SOPh (R)	20 : 1	100

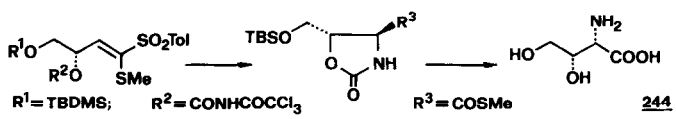
The excellent 2,3-*syn* diastereoselectivity of sulphones **240a–d** has been rationalized in terms of A(1,3) strain in the transition state. Moreover, as it appears from the data reported in Table 24, both the double bond and the sulphoxide group configurations influence the diastereomeric ratio. In fact, while the stereogenic centre induces 1,2-asymmetric induction by the A(1,3) strain in the transition state, the additional sulphoxide chirality also effects 1,3-asymmetric induction by steric interaction between the incoming nucleophile and the phenyl group on the sulphur, or by electronic interaction between the nucleophile and the lone pair.



This procedure can be applied to the synthesis of D-threonine **243**.[117]



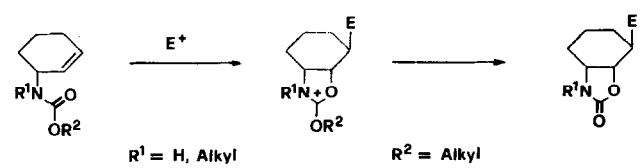
By a similar reaction sequence, L-γ-hydroxythreonine **244** has been obtained.



5. O-FUNCTIONALIZATION OF DOUBLE BONDS STARTING FROM AN N-FUNCTION

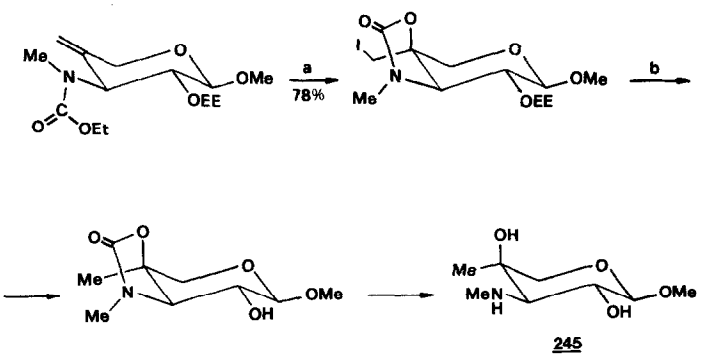
5.1. *Halocyclization via N-carbamates*

Halocyclocarbamation is an interesting reaction which efficiently introduces functional groups such as aminoalcohols. Fraser-Reid *et al.* have made a significant advance towards the synthesis of aminosugars by using this reaction for cyclic systems.[118] In fact the halocyclofunctionalization of double bonds in a cyclic system is a simple strategy that proceeds under high regio- and stereocontrol, as shown in the following scheme.



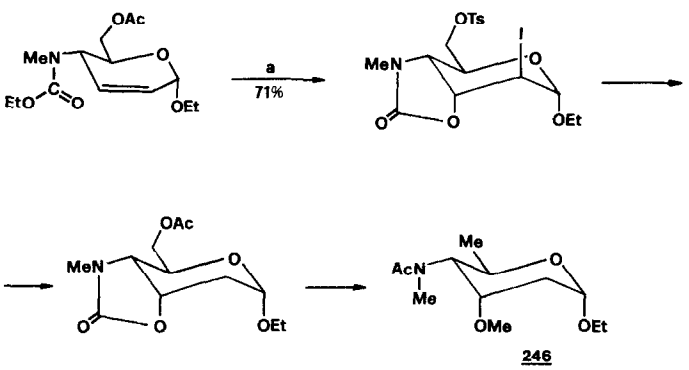
With the aim of introducing an hydroxy group *cis* to a pre-existing amino group, this strategy has been applied to the synthesis of deoxyaminosugars as the methyl α-L-garosaminide **245**, a key

component of a number of important aminocyclitol antibiotics, including the gentamycins and sisomycin. The most interesting steps of this synthesis are herewith reported.[118]



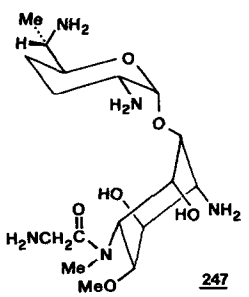
a. $I(coll)_2ClO_4$ b. Bu_3SnH

Holacosamine **246** is a component of the glycosteroids holantiosine, holacurtine, holarosine and mitiphylline, all of which are cardiotonic agents. The starting material for the synthesis is D-glucal triacetate. The crucial C-4 configuration in **246**, useful for the correct introduction of the amino group, has been obtained by applying the Mitsunobo reaction. Moreover the desired configuration at C-3 is obtained through halocyclization.[119]

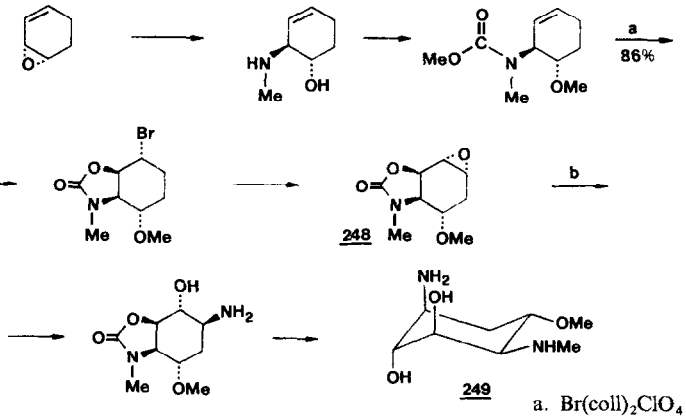


a. $I(coll)_2ClO_4$

A new group of broad spectrum antibiotics of the aminocyclitol class, the fortimicins, has been isolated and characterized as pseudo-disaccharides. Fortimicin A **247** is one of the representative components of this new class of compounds, consisting of 6-*epi*-D-purpurosamine B **256** and fortamine **251**, a novel 1,4-diaminocyclitol.

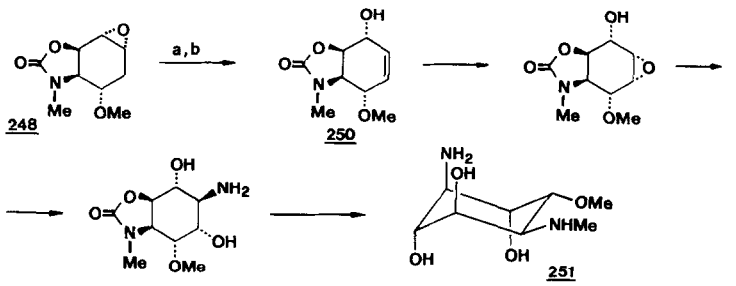


A highly stereocontrolled synthesis of racemic deoxyfortamine **249** and fortamine **251**, starting from non carbohydrate precursors, has been reported by Knapp. Thus the efficient conversion of 1,3-cyclohexadiene to cyclitols occurs through highly regio- and stereospecific steps.[120]



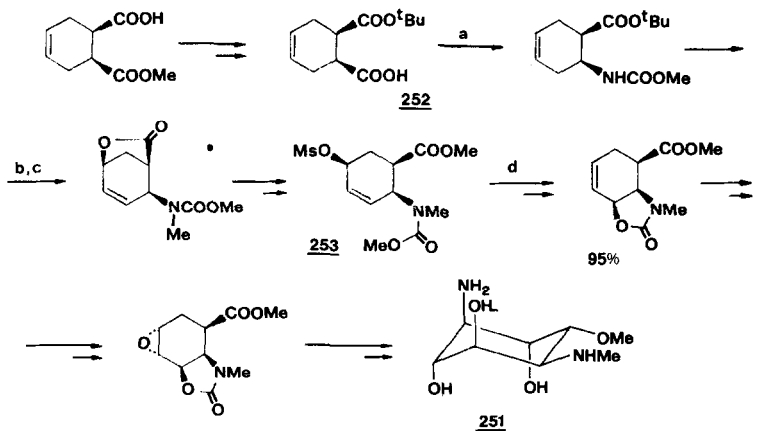
a. $Br(coll)_2ClO_4$ b. NaN_3, MeOH; H_2, Pd-C

The conversion of epoxide **248** into allylic alcohol **250**, accomplished by the selenophenolate addition–selenoxide elimination process, allows a convenient synthesis of fortamine **251**.



a. PhSeNa b. MCPBA

The enantioselective synthesis of (−)-fortamine **251** under complete regio- and stereocontrol has been described by Ohno *et al.*[121] The key feature of this approach is the use of a chiral cyclohexene derivative obtained from methyl *cis*-1,2-cyclohex-4-ene dicarboxylate. The meso diester, treated with pig liver esterase, affords the chiral monoester **252** in 98% chemical and 96% optical yields.

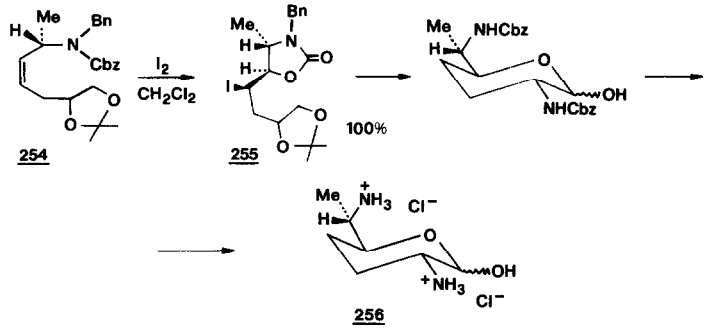


a. ClCOOEt, Et_3N, NaN_3; MeOH, *p*-TsOH b. I_2, KI, $NaHCO_3$ c. DBU d. Δ

Moreover, iodolactonization and the successive cyclocarbamation, performed on the mesyl derivative **253**, allow the functionalities to be introduced in the stereochemical relationship present in the fortamine **251**.

The synthesis of 6-*epi*-D-purpurosamine B **256** completes the total synthesis of fortimycin A **247**. The carbon skeleton is constructed by L-alanine and L-malic acid coupling; the 5(*S*) absolute configuration is introduced by 1,2-asymmetric induction through an iodocyclocarbamation reaction.[122]

The crucial step of the synthesis is the cyclization reaction. It is worth mentioning that, when the *Z*-olefin **254** is subjected to iodocyclocarbamation, the desired *trans*-oxazolidin-2-one **255** is obtained in quantitative yield as the sole product. While the stereoselectivity observed starting from the *Z*-olefin is excellent, only a moderate stereoselectivity, affording *trans*- and *cis*-oxazolidin-2-ones in a ratio of 71 : 29, is observed in the case of the *E*-isomer.

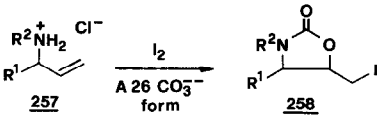


Oxazolidin-2-ones are useful starting materials for the synthesis of 3-amino-1,2-diols and are easily prepared by treating an allylic amine with benzyl chloroformate and then cyclizing the product with iodine in CH_2Cl_2.

An alternative one-step route, leading to cyclic carbamates **258**, has been carried out by us by treating the salts of acyclic allylic amines **257** under kinetic conditions with a reagent obtained by adsorbing iodine on Amberlyst A 26 in the CO_3^{2-} form. Following this route, cyclic carbamates have been obtained in high yield and with total regioselection. The diastereomeric ratios of the products are reported in Table 25.[123]

As is evident from Table 25, the stereoselectivity of the reaction is highly dependent upon the nature of the substituents R^1 and R^2. For $R^1 = C_3H_7$ the selectivity *cis* : *trans* is very low, increasing

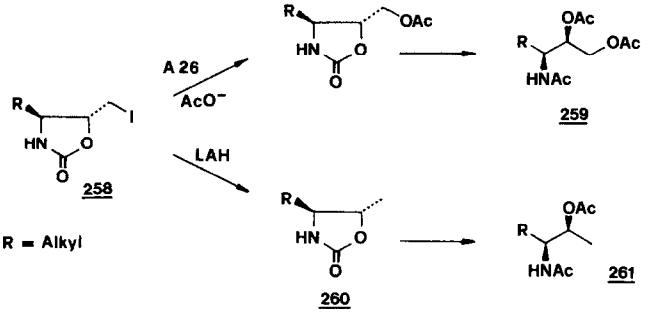
Table 25. Cyclization of allylic amines to iodomethyl oxazolidin-2-ones[123]



Substrate	yield %	cis : trans ratio
a. R^1 = Pr; R^2 = H	95	45 : 55
b. R^1 = Pr; R^2 = Bn	95	30 : 70
c. R^1 = CH_2OBn; R^2 = H	94	30 : 70
d. R^1 = CH_2OBn; R^2 = Bn	90	1 : 99
e. R^1 = CH_2OH; R^2 = H	80	7 : 93

if R^1 becomes a benzyloxy group (30 : 70) or an hydroxymethyl group (7 : 93). An important role is also played by the nitrogen substituent R^2. In fact an N-benzyl substituent increases the diastereoselectivity of the reaction, as demonstrated by **258b** (30 : 70) and **258c** (1 : 99) in Table 25.

The cyclic carbamates **258** thus obtained can be easily converted into 3-amino-1,2-diol derivatives **259** via iodine displacement performed with Amberlyst A 26 in the AcO^- form. In addition, the cleavage of the C–I bond, by means of LAH or Bu_3SnH, leads to the *trans*-oxazolidin-2-ones **260** which are useful intermediates for the synthesis of a 1,2-*syn* aminoalcohol system **261**.



Oxazolidin-2-ones and 1,3-oxazin-2-ones have also been prepared by a reaction of allylamines and homoallylamines, respectively, with carbon dioxide and iodine via an intramolecular cyclization in MeOH.[124]

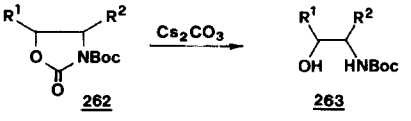
A versatile ring opening of 5- and 6-membered cyclic carbamates **262** into acyclic N-protected 1,2- and 1,3-aminoalcohols **263** consists of the N-*t*-butoxycarbonyl protection, followed by treatment with bases. The N-protection of cyclic carbamates has been achieved with di-*t*-butyldicarbonate and Et_3N, in the presence of a catalytic amount of DMAP. N-Boc cyclic carbamates undergo an extremely smooth ring opening to give acyclic N-Boc aminoalcohols on treatment with catalytic amounts of Cs_2CO_3 in methanol. Some significant results are reported in Table 26.[125]

A similar hydrolysis of secondary amides and lactams with a large excess of LiOH has also been reported.[126]

As the key step in the synthesis of functionalized alkaloids, the stereo- and regiospecific addition to the olefinic bond of an allylic amine has been reported by Parker *et al.*[127]

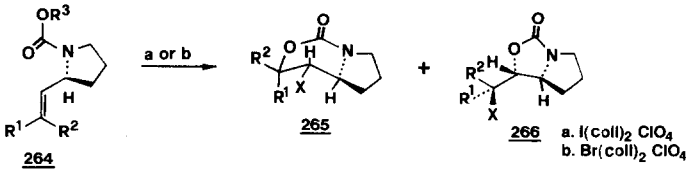
As it appears from Table 27, both the processes **264** → **265** and **264** → **266** are stereospecific. Furthermore regioselectivity of cyclization depends on the electronic properties of the olefinic

Table 26. Cleavage of N-Boc oxazolidin-2-ones[125]



Substrate	yield %
a. R^1 = COOMe; R^2 = H	72
b. R^1 = Ph; R^2 = H	94
c. R^1 = H; R^2 = COOMe	56
d. R^1 = Me; R^2 = COOMe (trans)	70
e. R^1 = Me; R^2 = COOMe (cis)	76

Table 27. Halocyclization of allylic carbamates[127]



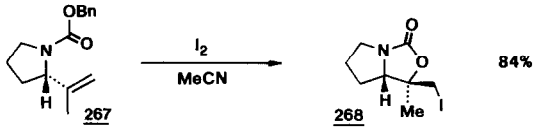
Substrate	265 yield %	266 yield %
a. $R^1 = H$; $R^2 = H$; $R^3 = Me$; X = I	–	82
b. $R^1 = H$; $R^2 = Ph$; $R^3 = {}^tBu$; X = I	73	–
c. $R^1 = Ph$; $R^2 = H$; $R^3 = {}^tBu$; X = I	60	–
d. $R^1 = H$; $R^2 = o\text{-}C_6H_4CN$; $R^3 = {}^tBu$; X = Br	62	–
e. $R^1 = o\text{-}C_6H_4CN$; $R^2 = H$; $R^3 = {}^tBu$; X = Br	13	26
f. $R^1 = H$; $R^2 = p\text{-}C_6H_4NO_2$; $R^3 = {}^tBu$; X = Br	60	–
g. $R^1 = p\text{-}C_6H_4NO_2$; $R^2 = H$; $R^3 = {}^tBu$; X = Br	11	58

substituents R^1 and R^2. In fact the carbamate **264a** affords exclusively a 5-membered ring, due to the stabilization of the incipient secondary carbocation. In contrast, the cyclization of **264b** and **264c** affords oxazin-2-ones as the unique compound.

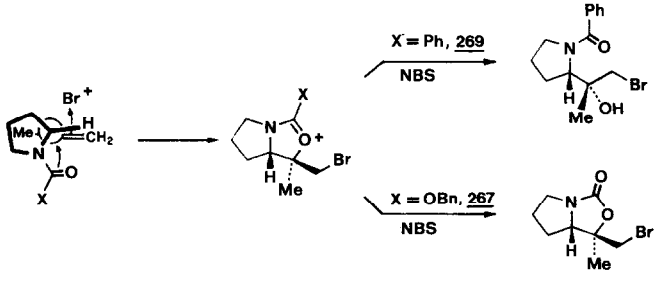
When the substituent is an electron withdrawing group such as $o\text{-}C_6H_4CN$ and $p\text{-}C_6H_4NO_2$, a mixture of 5- and 6-membered rings is obtained.

Moreover the configuration of the double bond influences the regioselectivity of cyclization. In fact the *E*-configuration of the double bond seems to favour the formation of 6-membered rings more than the *Z*-configuration does (see **264d**, **264e** and **264f**, **264g**).

Similarly a total selectivity has been observed by Overman in the cyclization of the allylic carbamate **267**, which is a useful intermediate in the synthesis of the pumiliotoxin A alkaloid class.[128]



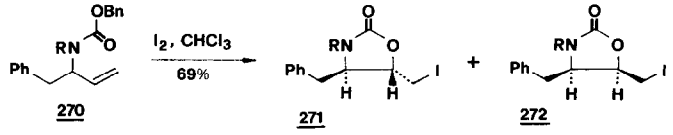
Using NBS in $DMSO/H_2O$, or I_2 in MeCN as the electrophile, a single bicyclic carbamate **268** is obtained. The high stereoselectivity observed in this reaction can be rationalized in terms of preferential reaction of the conformer with the hydrogen in the plane of the double bond.



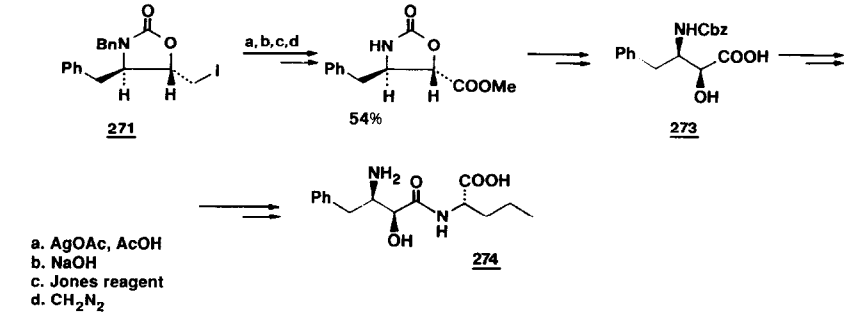
A similar selectivity has been observed in the bromohydrin formation starting from the benzamide **269** with NBS in THF/H_2O.

The stereochemical course of the cyclization of acyclic substrates has been studied by Ohno, with the aim of synthesizing biologically active compounds. It has been found that, starting from chiral allylic and homoallylic amines, iodocyclocarbamation occurs with high stereocontrol only if bulky groups are involved.[129]

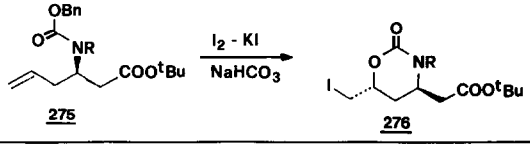
Thus the carbamate **270**, readily obtained from D-phenylalanine ethyl ester, cyclizes by treatment with iodine to afford a mixture of *trans*- **271** and *cis*-5-iodomethyloxazolidin-2-one **272** in a ratio of 1.5 : 1.



The N-benzyl group in **270b** improves the stereoselectivity to a 6.7 : 1 mixture of *trans* : *cis* oxazolidin-2-ones **271b** and **272b**. The high degree of stereocontrol reached under these conditions has been utilized for the synthesis of (2*S*, 3*R*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenyl butanoic acid, **273** the key part of bestatin **274**, an important immunopotentiator.



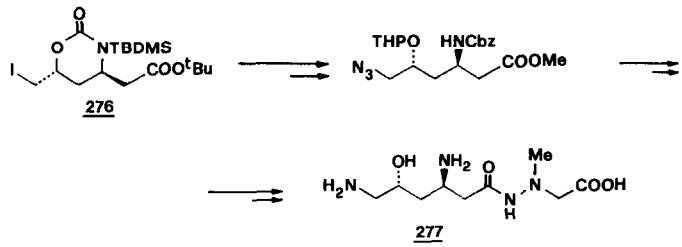
Similar results have been achieved by using the homoallylic carbamate **275** prepared from monomethyl (*S*)-3-aminoglutarate, which can be obtained by enzymatic hydrolysis of the prochiral diester.[130]



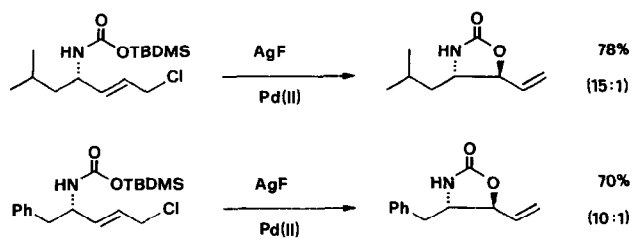
Substrate	yield %	trans : cis ratio
a. R = H	>90	3 : 7
b. R = Bn	83	23 : 1
c. R = Si^{t}BuMe$_2$	69	14 : 1

The treatment of the carbamate **275** with iodine affords the corresponding oxazolidin-2-one in excellent yield, the *trans*-isomer **276** being the major product of the reaction. When the amino group is protected with a bulkier substituent as in **275b**, the *trans* : *cis* ratio rises to 23 : 1. Good results have also been observed when the protecting group is *t*-butyldimethylsilyl (TBDMS) as in **275c**.

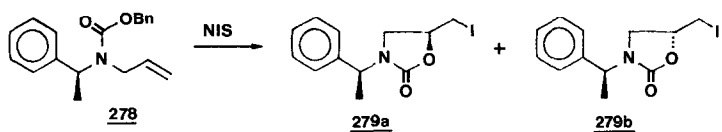
This high asymmetric induction has been utilized in the synthesis of (+)-negamycin **277**, that shows a strong inhibitory activity against Gram-negative bacteria.



Finally, stereoselective construction of 1,2-*syn* aminoalcohols has been carried out using an S_N2' reaction initiated by AgF/Pd(II). Oxazolidin-2-ones are obtained in high yield starting from unsaturated TBDMS-carbamates, and the *trans*-selectivity of the cyclization ranges from 8 : 1 to 15 : 1.[131,132]

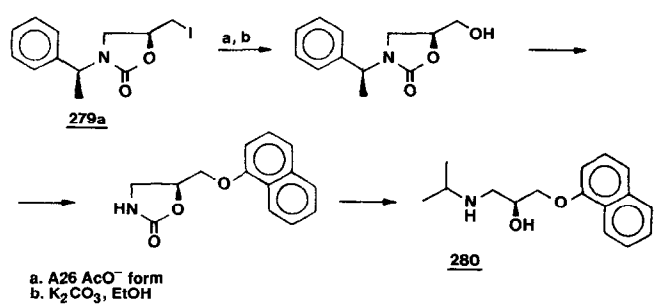


With the aim of obtaining chiral synthons, we have developed an efficient method of resolution of diastereomeric mixtures of oxazolidin-2-ones utilizing the commercially available (*S*)-1-phenylethylamine as the optically active portion of the molecule.[133] The N-benzyloxycarbonyl derivative **278** is then cyclized with NIS and the 1 : 1 mixture of diastereomeric iodomethyl oxazolidin-2-ones **279a** and **279b** can be separated by chromatography.

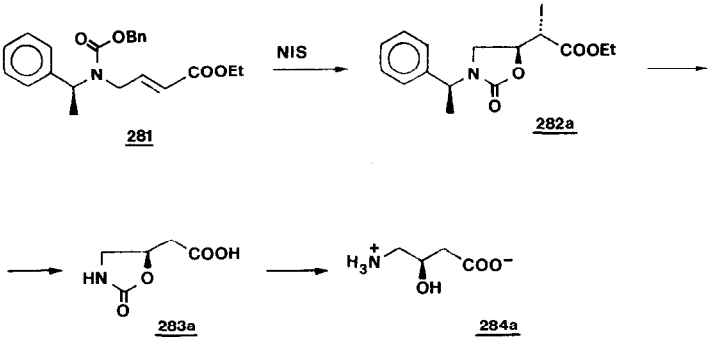


By comparison of ^{1}H-NMR spectra of each pure diastereomer, we have observed that the chemical shift of the hydrogen at C-4 of the heterocycle strongly depends on the shielding of the phenyl group bonded to the stereogenic centre and the conformational energies, calculated by molecular mechanics methods, confirm the ^{1}H-NMR data, thus allowing the absolute configuration to be assigned.

Following this strategy, the synthesis of (*S*)-(−)-propranolol **280** has been realized starting from (1*S*, 5*S*)-oxazolidin-2-one **279a**.

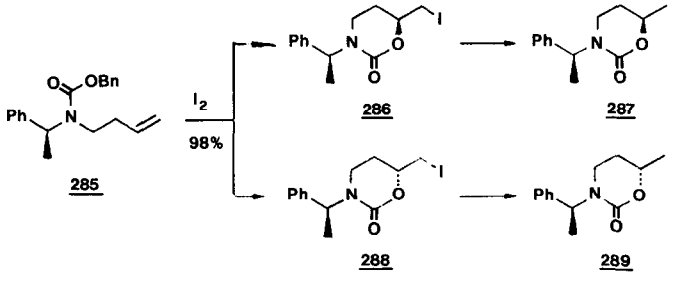


A facile synthesis of the biologically active (*R*)-**284a** and (*S*)-4-amino-3-hydroxybutanoic acid (GABOB) **284b**, a neuromodulator present in the mammalian central nervous system, has been developed. Cyclization of the allylic carbamate **281** gives a 1 : 1 diastereomeric ratio of the corresponding oxazolidin-2-ones **282a** and **282b**, which can be easily separated.[134]

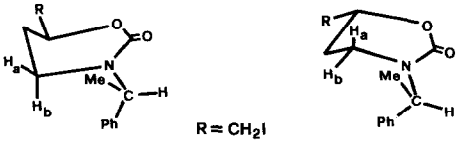


Cleavage of the C–I bond of the pure (1*S*, 5*S*)-isomer **282a** affords the (1*S*, 5*R*)-oxazolidin-2-one. Reductive cleavage with Li in NH_3 and hydrolysis in HCl give the (*R*)-compound **284a**.

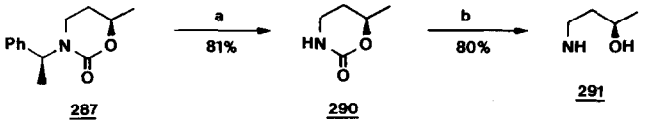
By halocyclization of homallylic carbamate **285**, diastereomeric mixtures of 1,3-oxazin-2-ones **286** and **288** are obtained, which can be easily resolved by chromatography and identified by ^1H NMR spectroscopy.[135]



On the basis of the chemical shifts and the values of the coupling constants of H_a and H_b, it is possible to establish the absolute configuration of the molecule, through a preferential conformation, successively confirmed by MM2 calculations.



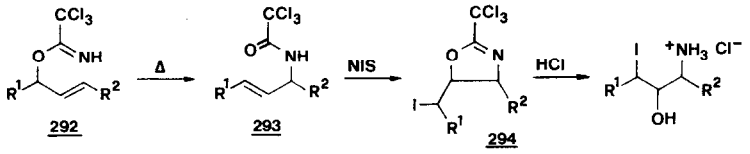
Treatment of **287** with Li/NH_3 gives **290**, and on successive basic hydrolysis, the (*R*)-1-amino-3-hydroxybutane **291** is obtained.



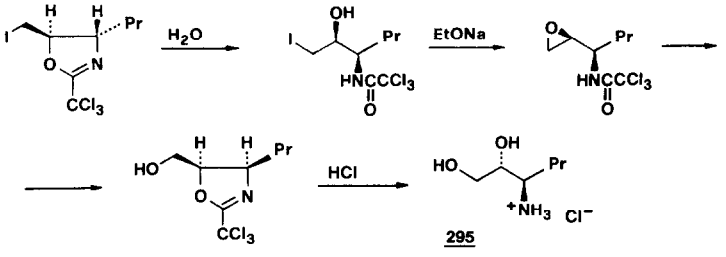
a. Li, NH_3 b. LiOH

5.2. *Halocyclization of amides*

The thermal rearrangement of trichloroacetimidates **292**[88] to the corresponding amides **293** has been utilized with the aim of obtaining a different regiofunctionalized sequence of aminodiols or aminoalcohols with respect to the one discussed above.[15] In fact the cyclization of these substrates is a complementary reaction to the previously reported iodoamination, since treatment of unsaturated trichloroacetamides **293** with NIS in $CHCl_3$ affords the corresponding iodo-4,5-dihydro-1,3-oxazoles **294** in high yield.[136]



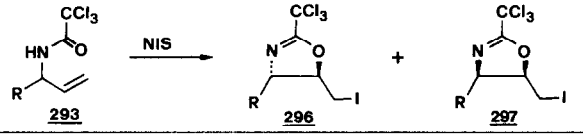
These compounds are versatile intermediates which are useful for further transformations. Following this approach a synthesis of 1,2-*anti* aminoalcohols **295** has been devised.



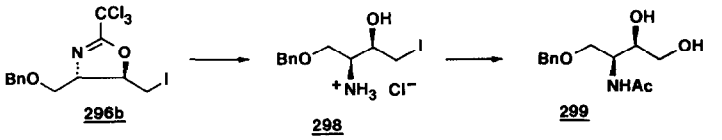
As reported in Table 28, low selectivity is observed if the substituent *R* is an alkyl group. On the contrary, when a free or a protected hydroxy group is present, the cyclization process gives rise to a high stereoselectivity that is useful in the synthesis of aminosugars.[137]

The *trans*-4-benzyloxymethyl-4,5-dihydro-1,3-oxazole **296b** has been used as the starting material for both *threo*- and *erythro*-(±)-2-amino-2-deoxytetritol derivatives **299** and **303**. *Threo* ammonium salt **298** has been obtained in a quantitative yield by treatment of **296b** with HCl in methanol. The salt has then been converted into the corresponding *threo* acetamide **299** by using Amberlyst A 26 in the AcO^- form.

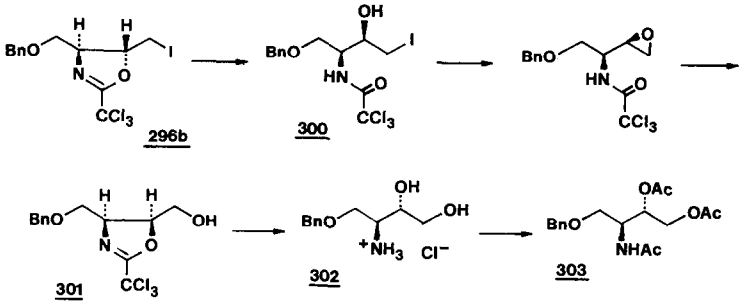
Table 28. Iodocyclization of allylic trichloroacetamides



Substrate	trans : cis ratio
a. R = n-Pr	66 : 34
b. R = CH_2OBn	80 : 20
c. R = CH_2OH	95 : 5
d. R = $CH_2OSi^tBuPh_2$	90 : 10
e. R = Ph	24 : 76



On the other hand *trans*-4,5-dihydro-1,3-oxazole **296b** undergoes hydrolytic cleavage in refluxing aqueous methanol, leading to the corresponding *threo*-amide **300**. Subsequent reaction with EtONa in CH_2Cl_2 affords the corresponding *cis*-4,5-dihydro-1,3-oxazole **301**. Hydrolytic cleavage yields the salt of the protected erytritol **302**, then converted into the *erythro*-triacetate **303**.[138]



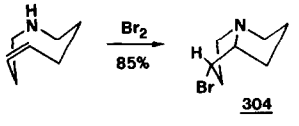
6. SYNTHESIS OF HETEROCYCLES CONTAINING NITROGEN

6.1. *Cyclization mediated by halonium and selenonium ions*

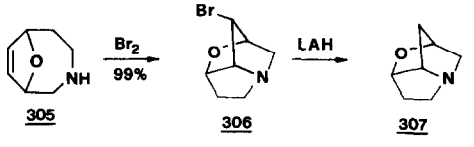
The direct cyclization of amines to heterocycles containing nitrogen has rarely been employed owing to the difficulties connected with this kind of reaction.

In fact only a few examples of direct haloamination reactions are reported and all of these refer to intramolecular cyclization used to obtain bicyclic compounds.

An approach to the bicyclic ring system of the pyrrolizidine alkaloids results in the stereospecific formation of C-1 substituted pyrrolizine **304** via a *trans*-annular cyclization. The reaction gives good yields of the cyclized products with various electrophiles, such as Br_2, $HgCl_2$ and PhSBr.[139]

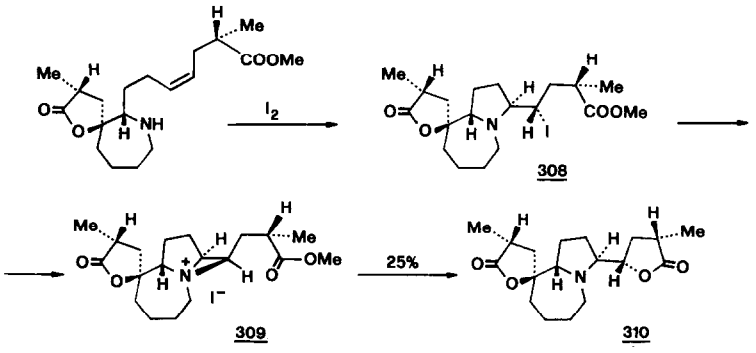


An application of this method to an intermediate useful for the synthesis of bridged pyrrolizidine alkaloids such as loline has been reported. The halogenation of 3-aza-9-oxa-bicyclo[4.2.1] non-7-ene **305** with Br_2 or I_2 leads to the corresponding haloderivative **306** in good yield. Unfortunately this compound is unreactive towards the nucelophilic substitution of the halide with methylamine to give the loline, whereas the reduction with LAH affords emiloline **307**.[140]

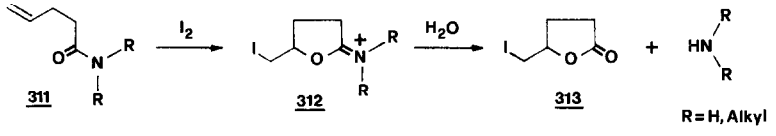


A direct iodoamination reaction also constitutes the key step of a total synthesis of (+)-croomine **310**, an alkaloid extracted from *Stemonaceae*. In fact the double cyclization occurring in a single

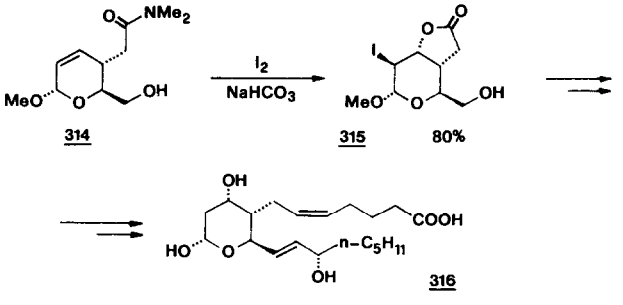
step involves first the formation of the initial iodoamination product **308**, followed by nucleophilic anchimeric assistance by the vicinal tertiary amine. Intramolecular capture of the intermediate aziridinium salt **309** following on the participation of the proximate ester results in a net retention of C-14 configuration and the formation of the vicinal pyrrolidino butyrolactone.[141,142]



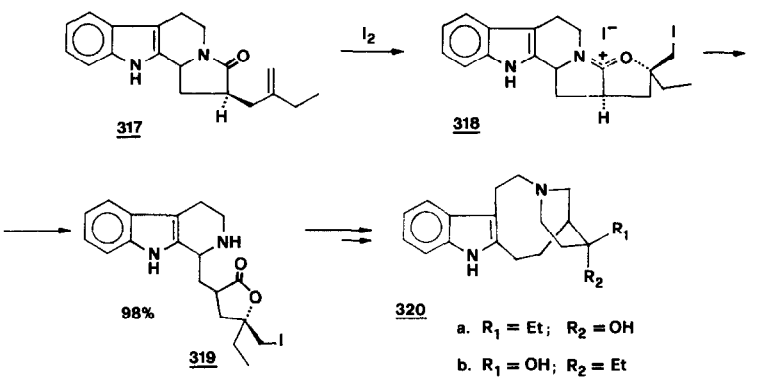
Upon treatment with halonium sources, the olefinic amides **311** form halolactones **313**, exclusively, through the corresponding cyclic imidates **312**; the key step of the reaction is the attack on the halonium ion by the more nucleophilic oxygen of the bidentate functional group. The successive hydrolysis in the aqueous reaction medium gives the corresponding lactone.



A useful application of this reaction constitutes the key step in the total synthesis of Thromboxane B_2 **316**, the corresponding iodolactone **315** being easily obtained by treating the amide **314** with I_2 in THF/H_2O.[143]

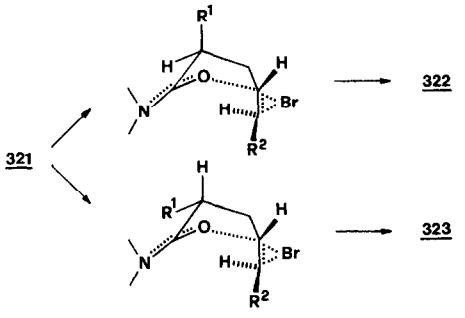


A similar reaction has been employed in a total synthesis of (±)-velbanamine **320a** and (±)-isovelbanamine **320b**, indole alkaloids related to the cleavamine-type alkaloids, which are potentially important for the preparation of oncolytic agents such as vinblastine, vincristine and pandoline. The reaction proceeds with I_2 in aqueous THF and, through the participation of the carbonyl group of the lactam **317**, which forms the rigid onium intermediate **318**, the iodolactone **319** is thus selectively obtained.[144]



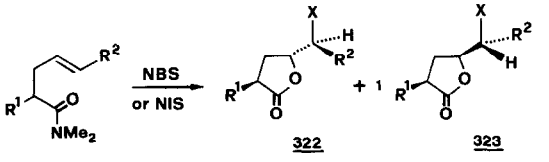
The 1,3-*trans* asymmetric induction in the halocyclization of N,N-dimethyl 2-substituted-4-penteneamides **321** has been studied by Tamaru *et al.* By using NBS in DME/H_2O as the source of the electrophile, the *trans*-isomer **322** is obtained almost exclusively (Table 29).[145]

This high 1,3-*trans* stereoselection is in sharp contrast to a moderate 1,3-*cis* selection in the iodolactonization of 2-substituted-4,5-unsaturated carboxylic acids, and is explained in terms of interaction between the C-2 substituent and the N,N-dimethylamido group.



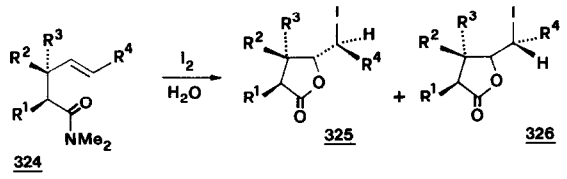
In addition, a high stereoselection has been observed when 2,3-disubstituted N,N-dimethyl-4-penteneamides **324** are cyclized with I_2 in DME/H_2O. The 1,3-*trans* selectivity is lost in the *threo*

Table 29. Bromocyclization of N,N-dimethyl-2-substituted-4-penteneamides[145]



Substrate	X	yield%	trans:cis ratio
a. R^1 = Me; R^2 = H	I	85	90 : 10
b. R^1 = Me; R^2 = H	Br	75	>99 : 1
c. R^1 = Bn; R^2 = H	I	84	>99 : 1
d. R^1 = Me; R^2 = Me	Br	74	94 : 6
e. R^1 = Bn; R^2 = Me	I	82	>99 : 1

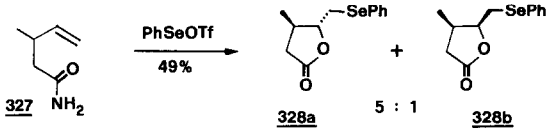
Table 30. Iodocyclization of N,N-dimethyl-2,3-disubsituted-4-penteneamides[145]



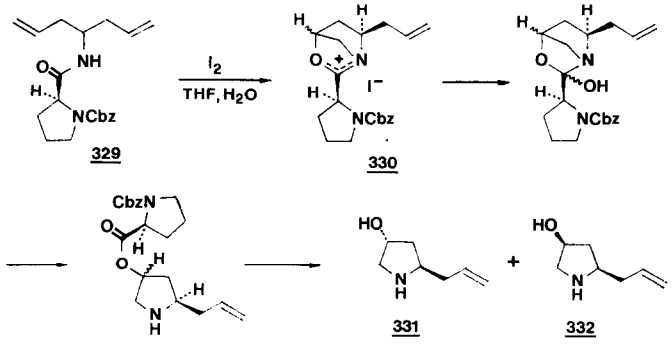
Substrate	yield %	325 : 326 ratio
a. $R^1 = R^2 = Me$; $R^3 = R^4 = H$	63	97 : 3
b. $R^1 = R^3 = Me$; $R^2 = R^4 = H$	63	97 : 3
c. $R^1 = Me$; $R^2 = OH$; $R^3 = R^4 = H$	88	20 : 80
d. $R^1 = Me$; $R^3 = OH$; $R^2 = R^4 = H$	84	99 : 1
e. $R^1 = Me$; $R^2 = OAc$; $R^3 = R^4 = H$	68	45 : 55
f. $R^1 = Me$; $R^3 = OAc$; $R^2 = R^4 = H$	95	99 : 1
g. $R^1 = R^4 = Me$; $R^3 = OAc$; $R^2 = H$	75	99 : 1

diastereomers of amides with 3-OH or 3-OAc substituents, in agreement with the results reported by Chamberlin (Table 30).

Furthermore, a high 1,2-asymmetric induction has been observed in the cyclization of a 3-methyl-4-penteneamide with PhSeOTf. In fact, by reacting the amide **327**, the lactones **328a** and **328b** have been obtained in a 5 : 1 *trans* : *cis* diastereomeric ratio.[146]



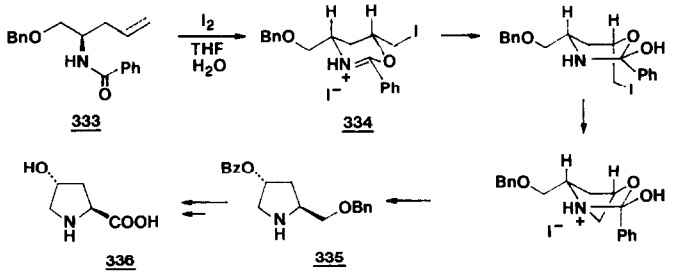
Treatment of the homoallylic amide **329** with I_2 in MeCN/H_2O 1 : 1 gives a mixture of pyrrolidine derivatives where the *trans*-isomer **331** is predominating over the *cis*-one.[147]



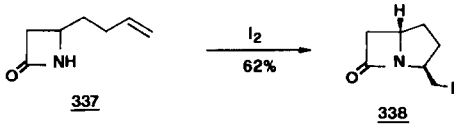
The formation of these compounds can be explained by the sequential formation of a highly strained bicyclic quaternary iodide **330** that successively undergoes hydrolysis, thus allowing a convenient synthesis of 2-allyl-4-hydroxyproline **331**.

Following the same approach, an efficient route to (2*R*, 4*S*)-4-hydroxyproline **336** starting from

(*R*)-O-benzylglycidol has been developed. The cyclization of the amide **333**, carried out with I_2 in THF/H_2O, is believed to proceed through the initial formation of an iododihydrooxazinium salt **334**, which is sequentially converted into **335** via the corresponding iodotetrahydrooxazine and the oxazinium salt.[148]



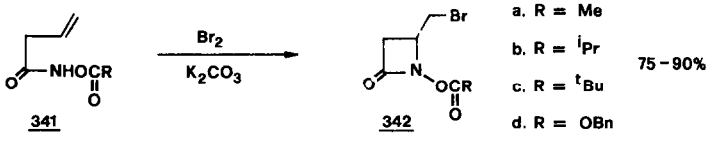
When the nucleophilic attack by the amidic oxygen is forbidden by geometric causes, the attack by the nitrogen atom is then observed. In fact the cyclization of 4-(3′-butenyl)azetidin-2-one **337**, initiated by various electrophilic reagents such as I_2, PhSBr and $Hg(OAc)_2$, gives a bicyclic β-lactam ring **338** having the carbapenam skeleton.[149]



By contrast, with unsaturated amides, nitrogen atom attack on the halonium ion can be obtained by substituting an amidic proton with an electron-withdrawing group. It has been found that in this case the lowered pK of the carboxamido group leads to the imide anion under basic conditions, so that the nitrogen atom becomes the most nucelophilic centre of the amido moiety.

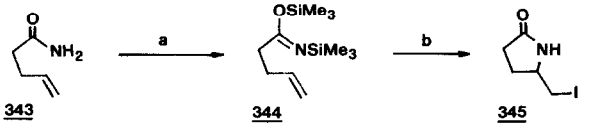
In order to obtain suitable halo-β-lactams, capable of affording structural analogues of the monobactams, the halocyclization of appropriate amide derivatives has been carried out, followed by dehalogenation with Bu_3SnH. Thus a variety of N-sulphonylated β,γ-unsaturated amides **339** has been cyclized with Br_2 or I_2 in aqueous $NaHCO_3$, and this methodology constitutes a convenient approach to N-tosyl-β-lactams **340** (Table 31).[150]

Analogously, O-acylhydroxamates **341** have been cyclized: the corresponding β-lactams **342** have been obtained in high yield upon treatment with Br_2/K_2CO_3 in aqueous MeCN.[151]



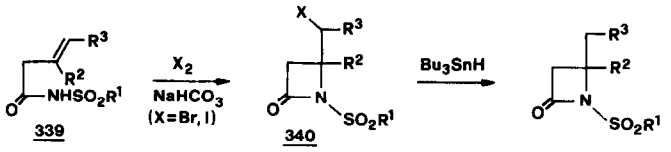
Five- and six-membered iodolactams **345** have been prepared by cyclization of unsaturated amides **343**, after conversion into their N,O-bis-trimethylsilyl derivatives **344**. The treatment of these derivatives with I_2 in THF allows the corresponding iodolactams to be obtained in good yield.[152a]

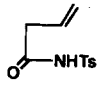
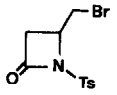
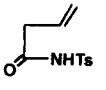
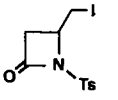
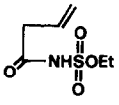
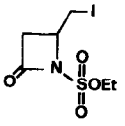
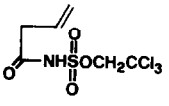
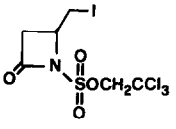
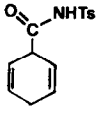
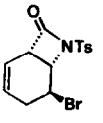
The first example of halocyclization of an iminoester group has been reported by Eschenmoser in a stereoselective synthesis of an aziridine, intermediate to the corrin system.[153]



a. Me_3SiOTf, Et_3N b. I_2, THF

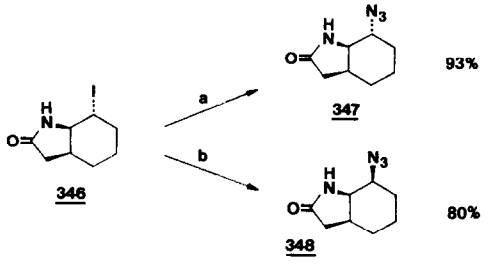
Table 31. Halocyclization of N-sulphonylated-β,γ-unsaturated amides[150]



	Substrate	Product	yield%
a.			67
b.			83
c.			77
d.			95
e.			67

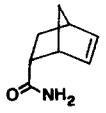
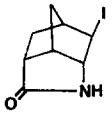
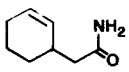
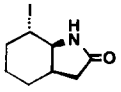
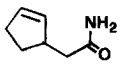
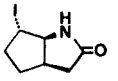
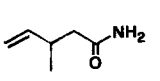
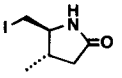
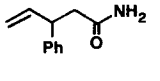
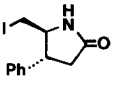
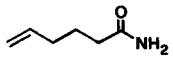
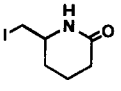
It is worth mentioning that the stereoselection of this reaction closely matches that of the corresponding lactones under thermodynamic conditions (I_2/MeCN),[10] showing a high preference for the *trans*-diastereomer (Table 32).

An extention of this method leads to a stereocontrolled synthesis of diamines, which are components of biologically active compounds. In fact the reaction of the iodolactam **346**, obtained through the method previously described, with NaN_3 in THF affords the azidolactams **347** or **348** depending on the presence of NaH as reagent.[152b]

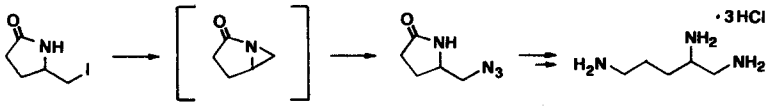


a. NaN_3, NaH, DMF, 23°C b. NaN_3, DMF, 110°C

Table 32. Synthesis of γ-iodolactams from unsaturated amides[152a]

Substrate	Product	yield%	diastereomeric ratio
		63	
		68	
		63	
		58	11:1
		52	22:1
		35	

It has been observed that, by proper choice of the reaction conditions, either the *trans*-**347** or the *cis*-azidolactam **348** can be obtained, depending upon whether N-acylaziridine **349** intervenes as the intermediate of the reaction.



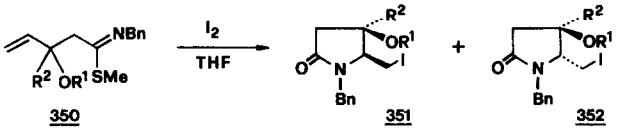
349

An interesting method leading to functionalized γ-lactams **351** and **352** relies on the iodine induced cyclization of 3-substituted-4,5-unsaturated thioimidates **350**. The reaction proceeds with high regio- and stereoselectivity and the configuration of the major diastereomer is 4,5-*cis*, owing to the well known 1,2-*cis* directing ability of the hydroxy or alkoxy groups in the transition state of cyclization (Table 33).[154,155]

It has been observed that the iodolactamization of 2-alkyl-4,5-unsaturated thioimidates **353** occurs with a high 1,3-*trans* selectivity, rationalizable in terms of transition state (Table 34).

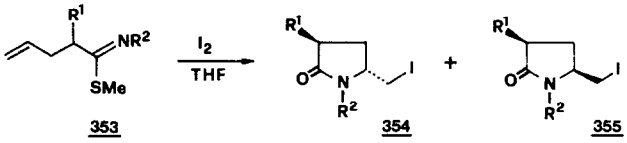
In fact, among the possible cyclic transition states, the most likely one, the 1,3-di-quasi-equatorial state **357**, may be discarded owing to an A(1,2) strain between the α-substituent R^1 and the methylthio group. This strain forces the substituent to take on a quasi-axial orientation, pushing the iodomethyl group into a quasi-equatorial orientation, as in the transition state **356**.

Table 33. Iodocyclization of 3-O-substituted-4,5-unsaturated thioimidates[155]

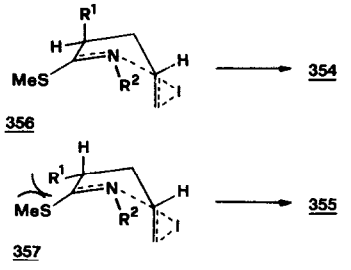


Substrate	yield %	cis:trans ratio
a. R^1 = H; R^2 = H	61	12 : 1
b. R^1 = $^tBuMe_2Si$; R^2 = H	56	7 : 1
c. R^1 = H; R^2 = Me	40	10 : 1

Table 34. Iodocyclization of 3-alkyl-4,5-unsaturated thioimidates[155]



Substrate	yield %	trans:cis ratio
a. R^1 = Me; R^2 = Ph	69	6 : 1
b. R^1 = Me; R^2 = Bn	48	12 : 1
c. R^1 = cyclohexyl; R^2 = Bn	42	13 : 1
d. R^1 = Ph; R^2 = Bn	48	14 : 1



An intramolecular haloamidation of 3-hydroxy-4-pentenylamine derivatives allows the stereoselective formation of *cis*-2-halomethyl-3-hydroxypyrrolidines to be obtained in good yield. The product of the reaction not only shares the partial structure with many types of interesting alkaloids (e.g. anisomycin), but, through the halomethyl functionality, constitutes the basis for the total synthesis of these alkaloids.

By treatment of the unsaturated carbamate **358** with I_2/Na_2CO_3 in DME/H_2O, the cyclization product **359a, b** is obtained in 83% yield and 93 : 7 *cis* : *trans* ratio.[41,156]

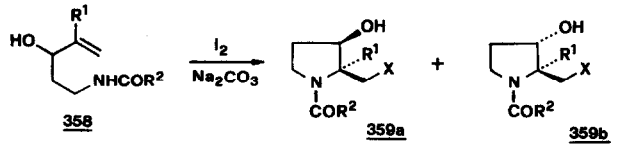
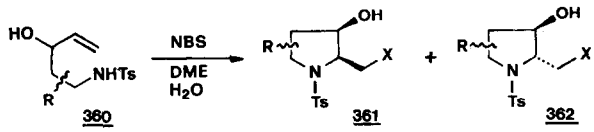
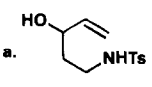
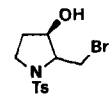
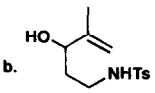
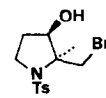
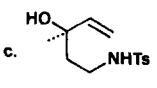
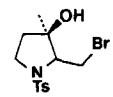
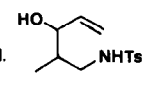
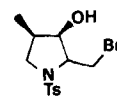


Table 35. Bromocyclization of 3-hydroxy-4,5-unsaturated tosylamides[157]



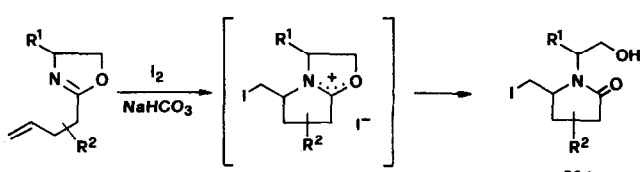
360 361 362

Substrate	Product	yield%	diastereomeric ratio
a. 		88	95 : 5
b. 		95	95 : 5
c. 		77	97 : 3
d. 		80	97 : 3

Since with more hindered carbamates or substituted double bonds no reaction is observed, the haloamidation of *p*-toluenesulphonamides **360** has been examined, using NBS in DME/H_2O. The reaction is fast and goes to completion with high yields and good stereoselectivity, as reported in Table 35.[157]

Furthermore the diastereomeric ratio remains unaffected when the reaction conditions (I_2/MeCN; I_2/$NaHCO_3$/H_2O; NIS/CH_2Cl_2) are changed.

An investigation of the iodolactamization of γ,δ-unsaturated oxazolines **363** has also been reported, the aim being to study stereocontrol in this transformation, as well as the substituent effects on the stereochemical outcome of cyclization.[158]

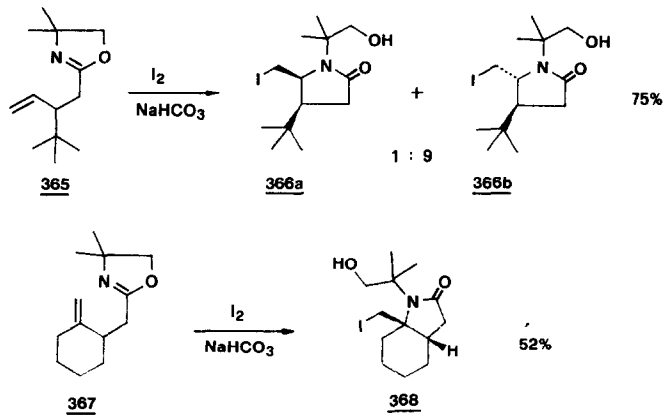


363 364

R^1, R^2 = Alkyl

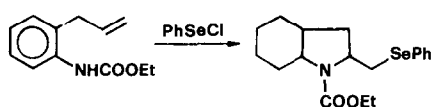
The treatment of the oxazoline **363** with I_2/THF/$NaHCO_3$ affords the corresponding γ-lactam **364** in good yield. Moderate 1,2-asymmetric induction (2 : 1 *cis* : *trans*) is observed when a methyl substituent is in the allylic position. The cyclization has also been performed under 'thermodynamic' conditions (I_2/MeCN) which would result in the reversible formation of the *trans* diastereomer. Since under all conditions cyclization of the intermediate oxazolinium salt is apparently not reversible, the hydroxylactam is formed under kinetic control. This behaviour has been exploited to increase olefinic facial selectivity during cyclization. A bulky substituent such as the *t*-butyl group allows in

fact a selective lactamization of **365** and a *cis* : *trans* ratio 1 : 9 of **366a** and **366b** is obtained. Moreover the cyclization of oxazoline **367** proceeds with high stereoselectivity and the *cis*-fused lactam **368** is the only product of the reaction.



Unsaturated carbamates have been cyclized with PhSeCl (Table 36). Following this methodology pyrrolidines and piperidines can be obtained starting from olefinic amines. The reaction is efficient when it is carried out in the presence of silica gel, and the yields are generally above 80%. The

Table 36. Cyclization of unsaturated carbamates with PhSeCl[159]



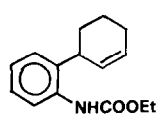
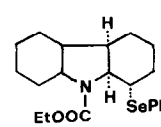
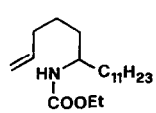
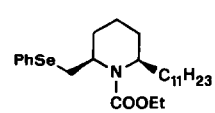
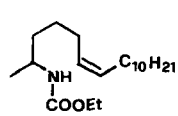
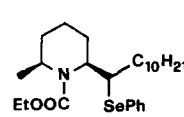
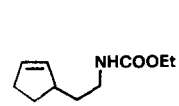
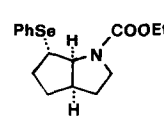
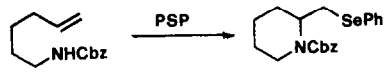
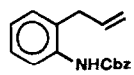
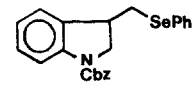
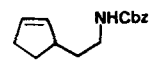
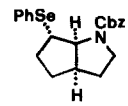
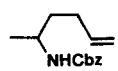
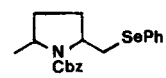
Substrate	Product	yield %
		82
		84
		35
		94

Table 37. Cyclization of unsaturated carbamates with PSP[160]

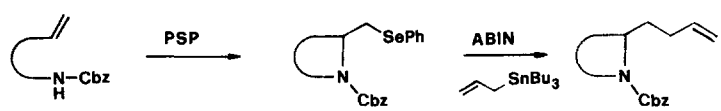


Substrate	Product	
		
		
		1:1

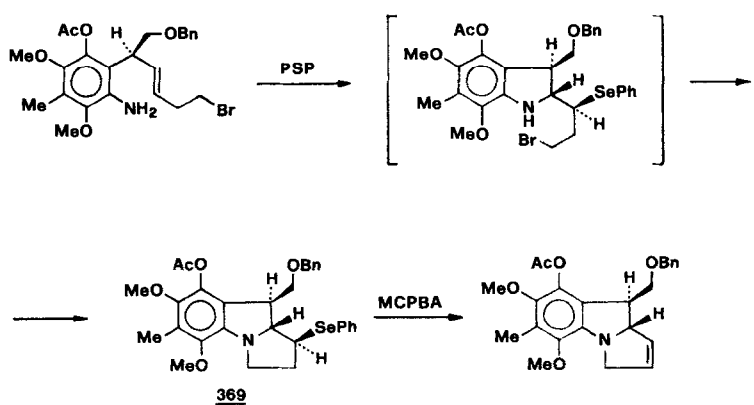
stereochemical outcome of the reaction is worth mentioning: a 2,6-*cis* relationship is indeed observed and has been rationalized on the basis of mechanistic considerations.[159]

An analogous cyclization has been carried out by using N-phenylselenophthalimide (PSP) to activate the double bond. The reaction is performed in CH_2Cl_2 and the heterocyclic products are obtained in high yield (Table 37). Stereoselection is good only when the starting material is a cyclic olefin: otherwise a 1 : 1 diastereomeric mixture is observed.[160]

Subsequent treatment of the selenophenyl derivatives with an allyltin reagent, in the presence of ABIN, leads to the coupling products being obtained in good yield. These are useful intermediates for the synthesis of alkaloids.

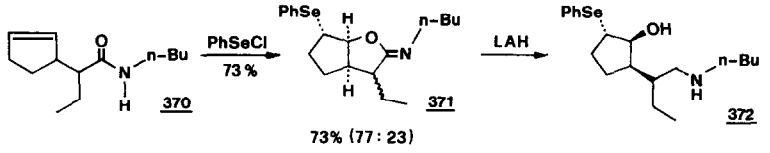


This methodology has found an interesting application for devising a stereospecific route to aziridinomitosanes via a stereospecific selenoamination which affords **369**, the key intermediate for the synthesis of aziridinomitosanes.[161]

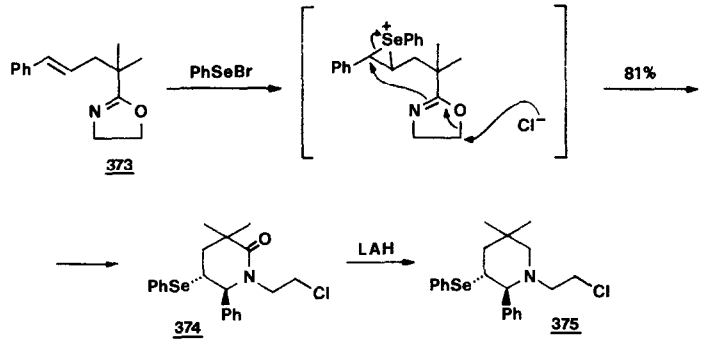


369

The olefinic amide **370**, upon treatment with PhSeCl or PhSeBr in MeCN, affords the iminolactone **371** in good yield and moderate stereoselectivity. Further reduction with LAH gives the corresponding aminoalcohol **372**.[162]

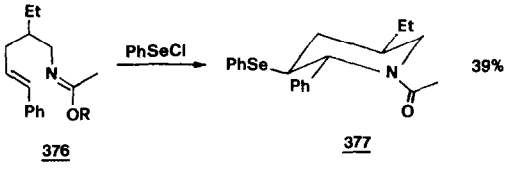


By the reaction of a 2-alkenyl-1,3-oxazoline with PhSeBr in MeCN, the corresponding lactam is obtained through the intramolecular attack of the nitrogen atom of the oxazoline on the episelenonium ion, with ring opening of the oxazoline. In fact, when the oxazoline **373**, having a 4-phenylbut-3-enyl substituent, is used as a starting material, endocyclization occurs to give the δ-lactam **374** that consists of a single diastereomer.[163–165]



This intermediate can be successively converted into the piperidine derivative **375** by treatment with LAH.

In the case where a linear imidate **376** possessing a cinnamyl moiety, is used as the starting material, a piperidine derivative **377** is produced in very high selectivity, albeit in low yield. In all the other cases no stereoselection has been observed.[166]



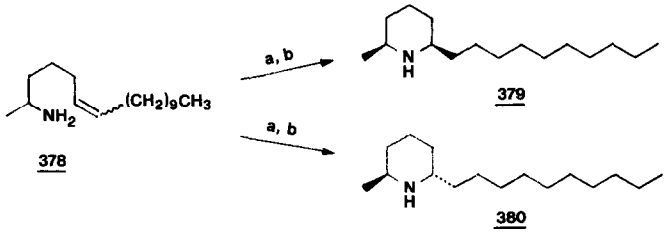
6.2. *Cyclization mediated by metal cations*

The mercury-cyclization reaction constitutes a useful approach to many heterocyclic compounds since the direct cyclization of an amine without a previous protection of the nitrogen atom is compatible with the reaction conditions. The stereochemical outcome has been further studied and a *trans*-addition mechanism has been established.[167,168]

The reaction has been applied to the preparation of disubstituted pyrrolidines and piperidines. The intramolecular cyclization of a diastereomeric mixture of unsaturated amines leads to 5- or 6-membered saturated nitrogen containing heterocycles through an aminomercuration–demercuration sequence.

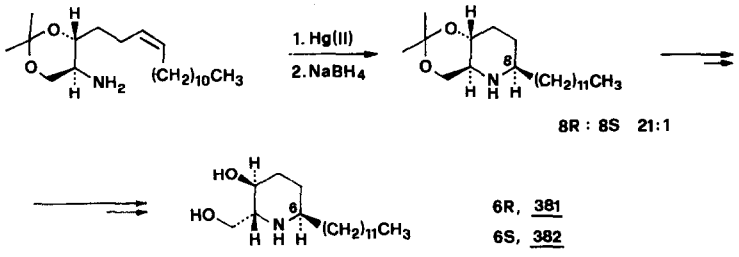
The regioselectivity is very high, since γ-unsaturated amines afford a pyrrolidine derivative, while δ-unsaturated amines give a piperidine derivative, exclusively. By applying this approach the

piperidine alkaloids isosolenopsine **379** and solenopsine **380** have been prepared in moderate yield, but the stereoselectivity cannot be established, since the starting amine **378** is a *Z*,*E*-diastereomeric mixture.[169]

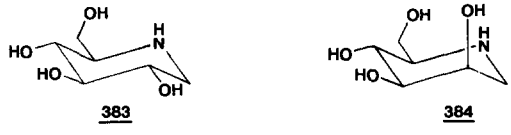


a. Hg(II) b. $NaBH_4$

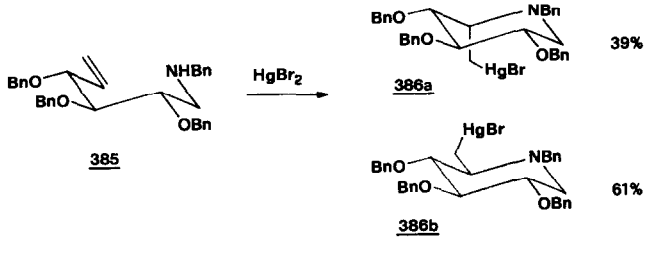
Moreover the stereoselective, total syntheses of (−)-deoxoprosopinine **381** and (−)-deoxoprosophylline **382**, starting from L-serine, proceed through the aminomercuration–demercuration sequence of a *δ*,*ε*-unsaturated amine: in this case cyclization gives rise to a diastereomeric mixture of piperidine acetonides in 21 : 1 *cis* : *trans* ratio.[170]



The intramolecular aminomercuration reaction has found interesting applications to the synthesis of enantiomerically pure cyclic aminoalditols. Following this approach, 1-deoxynojirimicin **383** and 1-deoxymannojirimicin **384**, potent glucosidase inhibitors, have been synthesized. This method allows the direct conversion of a natural sugar into an aza-alditol having the same relative and absolute configuration.[171]

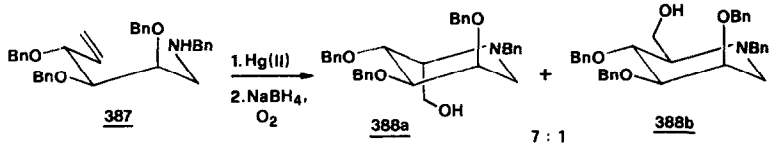


Thus the intramolecular aminomercuration reaction, performed on the aminoalkene **385**, obtained from methyl α-D-glucopyranoside, affords **386a** and **386b** as an epimeric mixture in a 1 : 1.6 epimeric ratio.

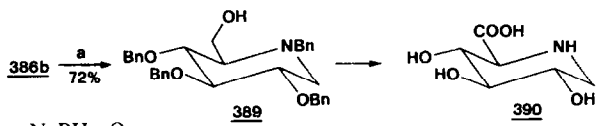


The aminoalkene **387**, obtained from methyl α-D-mannopyranoside, after reaction with $HgBr_2$, affords the corresponding bromomercurial derivatives in quantitative yield and 7 : 1 ratio.

These intermediates are reductively oxidized to the corresponding alcohols **338a** and **388b** by using $NaBH_4/DMF/O_2$.

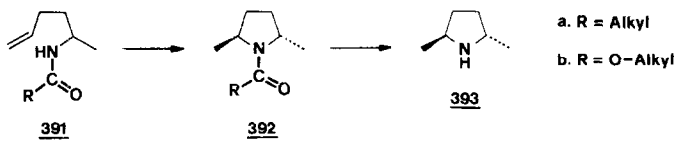


Thus **389**, a key intermediate for the glucuronic acid analogue of 1-deoxynojirimicin **390**, an inhibitor of liver α-D-glucuronidase, has been obtained from alcohol **386b**.[172]

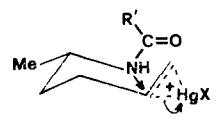


a. $NaBH_4$, O_2

Harding *et al.* have reported that treatment with $Hg(OAc)_2$ in THF of the amide **391a** or the carbamate **391b** of 2-amino-5-hexene, followed by $NaBH_4$ reduction, gives the *trans*-cyclization product **393**, and only a trace of the *cis*-isomer is revealed by analytical methods.[173]

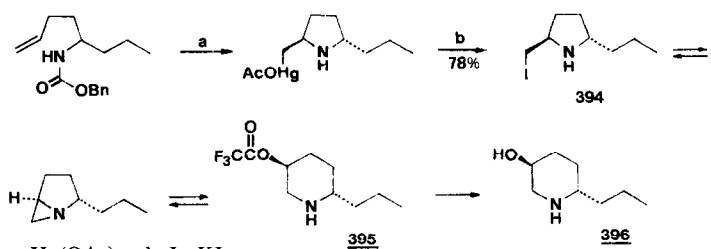


The stereochemistry of this cyclization has been rationalized in terms of a preference for a chair-like transition state with an equatorial methyl group.[173]



Since *trans*-2,5-dialkylpyrrolidines are characteristic components of the poison gland products of a variety of ant species, a highly stereoselective synthesis of *trans*-2,5-dimethylpyrrolidine **393** derivatives constitutes an efficient route to these compounds.

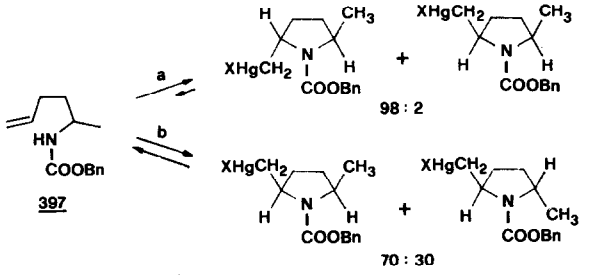
Utilizing intramolecular mercury-cyclization, γ-alkenyl carbamates have been converted into *trans*-2-alkyl-5-substituted piperidines and this approach has been employed for a stereoselective synthesis of racemic pseudoconhydrine **396**. This method is based on the finding that Hg(II)-initiated cyclization of δ-alkenyl carbamates leads to the formation of a *trans*-pyrrolidine derivative with high stereoselectivity. The conversion of the halomethylpyrrolidine **394** into a 3-substituted piperidine **395** takes place through a bicyclic aziridine intermediate.[174]



a. $Hg(OAc)_2$ b. I_2, KI

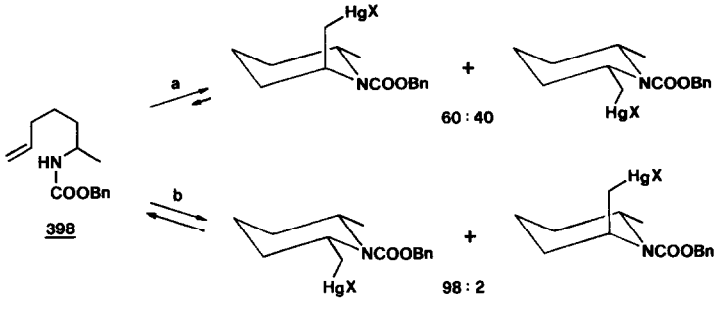
A deeper insight of the stereoselectivity of Hg(II)-mediated cyclization shows that the intramolecular cyclization of carbamates **397** and **398** critically depends upon whether the reaction conditions result in kinetic or thermodynamic control of the products.[35,175]

In fact **397** gives a 98 : 2 *trans* : *cis* diastereomeric mixture on treatment with $Hg(OAc)_2$ in THF (kinetic conditions), while a 70 : 30 *cis* : *trans* mixture is obtained by cyclization with $Hg(OTFA)_2$ in CH_3NO_2 (thermodynamic conditions).



a. $Hg(OAc)_2$, THF b. $Hg(OTFA)_2$, CH_3NO_2

Treatment with $Hg(OAc)_2$ in THF, **398** affords a 40 : 60 *cis* : *trans* diastereomeric mixture (under kinetic conditions), while with $Hg(OTFA)_2$ in CH_3NO_2 (under thermodynamic conditions) a 98 : 2 *cis* : *trans* diastereomeric mixture is obtained.



a. $Hg(OAc)_2$, THF b. $Hg(OTFA)_2$, CH_3NO_2

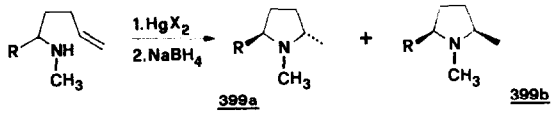
In the formation of 5-membered rings it is reasonable to assume that the main factor controlling the relative stability of the *cis*- and *trans*-isomers is an A(1,3)-type strain involving carbamate functionality and the C-2 and C-5 substituents. Thus a clear divergence of behaviour between the δ-alkenylcarbamate **397** (kinetic stereoselectivity and thermodynamic non-stereoselectivity) and the ε-alkenylcarbamate **398** (kinetic non-selectivity and thermodynamic selectivity) has been observed.

Also N-methyl-2,5-dialkylpyrrolidines **399a, b** have been synthesized by a cyclization–reduction sequence. Hg(II) initiated cyclization has been studied and the effect of the solvent employed has been determined (Table 38).[36,176]

In fact, when the cyclization is performed in THF : H_2O, *trans*-2,5-disubstituted pyrrolidines **399a** are obtained stereoselectively, while *cis*-2,5-disubstituted pyrrolidines **399b** are the main product when THF or $CHCl_3$ is the solvent. The results reported in Table 38 can be ascribed to a thermodynamic control of the reaction, favoured by the heterogeneous medium (organic solvent), while a kinetic control is reached in homogeneous conditions (H_2O/THF).

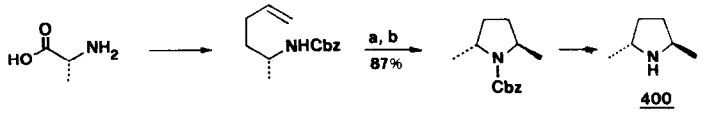
As a consequence of these findings, (*R,R*)- and (*S,S*)-*trans*-2,5-dimethylpyrrolidine have been stereoselectively synthesized, since these compounds, employed as chiral auxiliaries, give excellent enantiomeric excesses. An EPC synthesis of both the enantiomers has been devised starting from

Table 38. Mercury-cyclization of N-methyl-4-pentenylamines under kinetic or thermodynamic control[36]



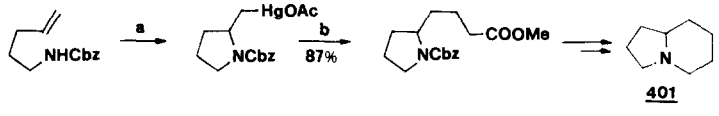
Substrate	HgX_2	Solvent	yield%	trans : cis ratio
R = Ph	$HgCl_2$	H_2O – THF	64	87 : 13
R = Ph	$HgCl_2$	THF	36	10 : 90
R = Ph	$HgCl_2$	$CHCl_3$	50	4 : 96
R = Ph	$Hg(OAc)_2$	THF	56	88 : 12
R = p-MeC_6H_4	$HgCl_2$	H_2O – THF	82	84 : 16
R = p-MeC_6H_4	$HgCl_2$	THF	53	2 : 98
R = p-$MeOC_6H_4$	$HgCl_2$	H_2O – THF	86	93 : 7
R = p-$MeOC_6H_4$	$HgCl_2$	THF	40	25 : 75
R = Me	$HgCl_2$	H_2O – THF	28	93 : 7
R = Me	$HgCl_2$	THF	43	36 : 64
R = Et	$HgCl_2$	H_2O – THF	55	90 : 10
R = Et	$HgCl_2$	THF	50	20 : 80

(*R*)- or (*S*)-alanine. The key step is the mercury-cyclization–reduction sequence following the Harding method, and **400** is obtained in high yield.[177]



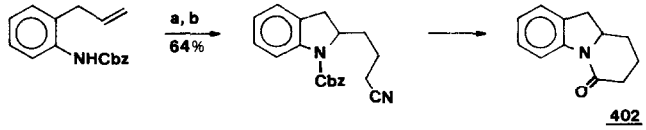
a. $Hg(OAc)_2$ b. $NaBH_4$

A four-step synthesis of δ-coniceine **401**, developed by Danishefsky, involves the cyclization of N-Cbz-5-amino-1-pentene with $Hg(OAc)_2$ and reduction with sodium trimethoxyborhydride in CH_2Cl_2 containing a 2-fold excess of methyl acrylate as Michael acceptor.[178]



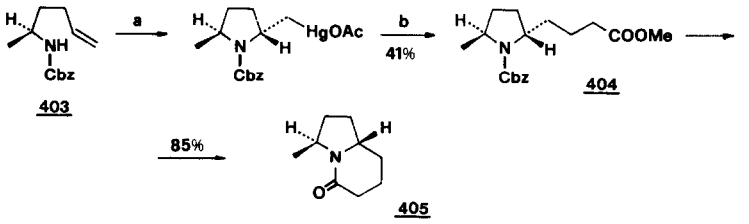
a. $Hg(OAc)_2$ b. $(MeO)_3NaBH$

In a similar way a benzo[*b*]indolizidinone **402** has been obtained, and this kind of transformation can be useful for preparing a variety of indolic alkaloids.[178]



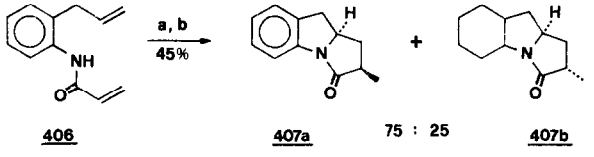
a. $Hg(OAc)_2$ b. $NaBH_3CN$, $CH_2{=}CHCN$

The stereochemistry of this reaction is in agreement with the one discussed above. In fact N-Cbz-5-amino-1-hexene **403** has been cyclized with Hg(II) and the organomercurial derivative undergoes a reductive coupling to give the *trans*-ester **404** which is further cyclized into the bicyclic *trans*-lactam **405**, exclusively.[178]



a. $Hg(OAc)_2$ b. $NaBH_4$, CH_2=CHCOOMe

Intramolecular reductive coupling constitutes the key step in the synthesis of a bicyclic system. The acrylanilide **406** is treated with Hg(II) and the addition compound is successively reduced so that a diastereomeric mixture of the lactams **407a** and **407b** is obtained.[179]

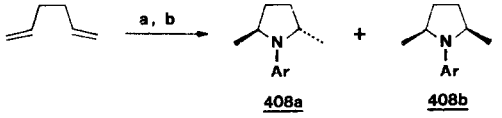


a. $Hg(OAc)_2$ b. $NaBH_4$

As an extension of the aminomercuration–demercuration sequence, N-arylpyrrolidines have been obtained via a one-pot process, starting from 1,4- or 1,5-hexadiene and an aromatic amine. After reduction with $NaBH_4$, 2,5-dimethyl-N-arylpyrrolidines **408** are obtained in good yield and high stereoselection, the *trans*-isomer being the major component of the diastereomeric mixture (Table 39).[180,181]

The reaction of *p*-toluenesulphonamide or alkyl carbamates with both 1,4- or 1,5-dienes and diallyl ethers has been studied, in order to obtain pyrrolidine and morpholine derivatives under mercuration–demercuration conditions. Since it has been found that *p*-toluenesulphonamide adds to olefins in the presence of anhydrous $Hg(NO_3)_2$ and subsequent reduction with $NaBH_4$ leads to

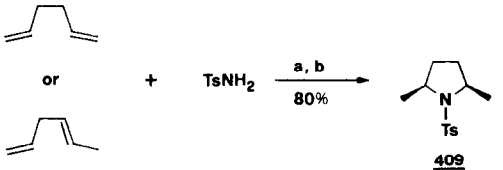
Table 39. Cyclization of 1,5-hexadiene to N-aryl-2,5-disubstituted pyrrolidines[181]



a. $Hg(OAc)_2$, $ArNH_2$ b. $NaBH_4$

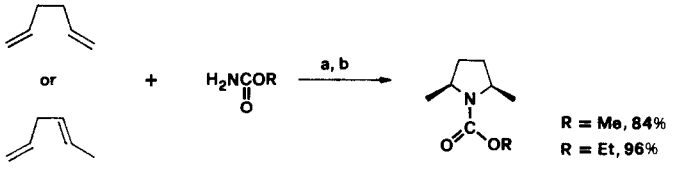
Substrate	yield%	trans:cis ratio
Ar = p-Tol	93	92 : 8
Ar = Ph	99	98 : 2
Ar = p-Cl-C_6H_4	83	99 : 1
Ar = o-Cl-C_6H_4	75	94 : 6

the corresponding N-alkylsulphonamides, the addition to 1,4- or 1,5-dienes has been carried out. A stereoselective synthesis of *cis*-2,5-dimethyl-N-tosylpyrrolidines **409** has been realized and the prevalent formation of the *cis*-isomer can be ascribed to a thermodynamic control, due to the reaction conditions.[182–184]



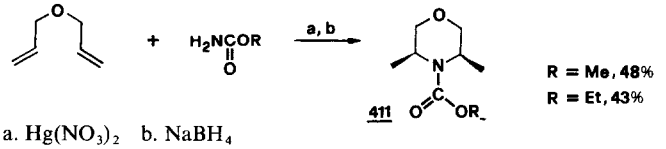
a. $Hg(NO_3)_2$ b. $NaBH_4$

The same results have been observed by treating both the 1,4- and 1,5-dienes with alkyl carbamates in the presence of $Hg(NO_3)_2$. In fact the *cis*-isomer **410** is the sole compound isolated from the reaction and the mechanism could be analogous to that proposed in the case of sulphonamidomercuration.[185]



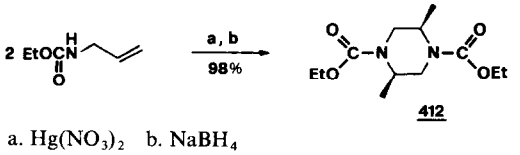
a. $Hg(NO_3)_2$ b. $NaBH_4$

The reaction of diallyl ether with alkyl carbamates in the presence of $Hg(NO_3)_2$ in CH_2Cl_2, followed by reduction with $NaBH_4$, allows only *trans*-N-alkoxycarbonyl-3,5-dimethylmorpholine **411**, to be obtained while the aminomercuration of the same ether, carried out with $Hg(OAc)_2$ in THF, gives a *cis*: *trans* diastereomeric mixture.[185]



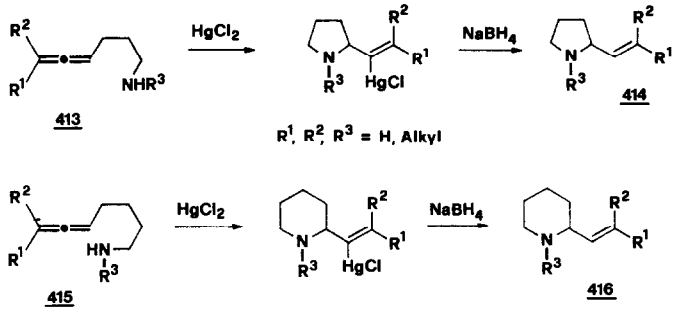
a. $Hg(NO_3)_2$ b. $NaBH_4$

Finally, the same cyclization process, performed on the N-allylcarbamate, affords the N,N′-carbalkoxy-*cis*-2,5-dimethylpiperazine **412**.[185]

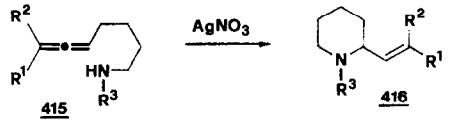


a. $Hg(NO_3)_2$ b. $NaBH_4$

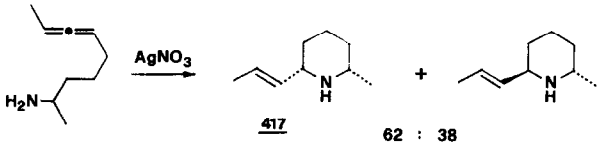
In analogy with the mercury-cyclization of unsaturated amines, allenic amines **413** and **415** have been treated with $HgCl_2$ in THF. The successive reduction of the organomercurial intermediates with $NaBH_4$ under phase-transfer conditions, affords the corresponding alkenyl pyrrolidines **414** or piperidines **416** in good yields.[186]



Piperidines **416** are obtained with better yields by treating the allenic amine **415** with $AgNO_3$ in H_2O/acetone. The reaction proceeds with high stereoselectivity, since a 95 : 5 diastereomeric ratio is obtained, with the major component having the *E*-configuration.[186]



The synthetic usefulness of this method has been confirmed by the preparation of (±)-pinidine **417**, an alkaloid isolated from *Pinus sabiniana* Dougl.[187]

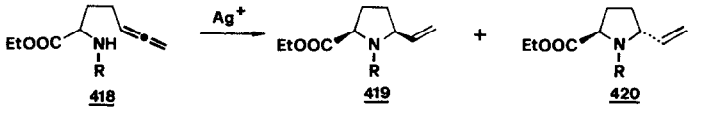


Cyclization affords a mixture of two isomers (62 : 38), where the *cis*-isomer is the major component and the *E*-configuration of the double bond is exclusively observed.

When allenic, α-substituted amine derivatives **418** are cyclized by using $AgBF_4$ in CH_2Cl_2, *cis*-2,5-disubstituted pyrrolidines **419** have been isolated, as expected, owing to an A(1,3) allylic strain. The primary amine in fact undergoes non-stereoselective cyclization under these conditions (Table 40).[188]

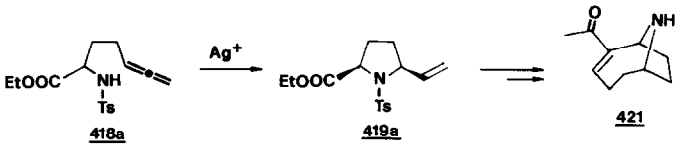
The synthetic potential of this conversion can be easily appreciated since the stereoselective cyclization of the allenic aminoester **418a**, which gives the *cis*-2,5-disubstituted pyrrolidine **419a**,

Table 40. Cyclization of N-substituted allenic amines to vinyl pyrrolidines[188]



Substrate	yield %	cis:trans ratio
a. R = Ts	100	> 50 : 1
b. R = Bn	93	> 50 : 1
c. R = Boc	70	> 50 : 1
d. R = H	60	1 : 1

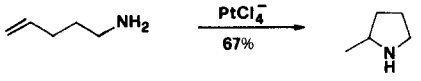
constitutes the key step of a total synthesis of (±)-anatoxin-a **421**, the most potent antagonist known for the nicotinic acetylcholine receptor (nAChR).[189]



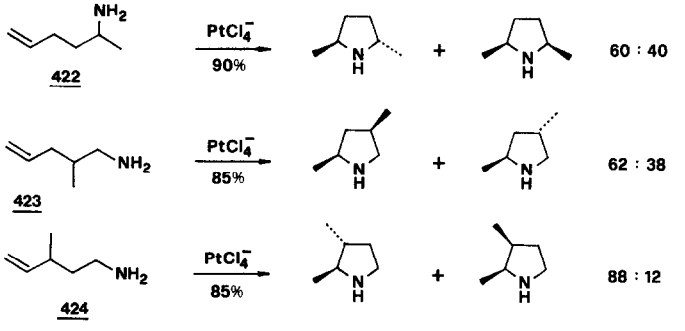
7. CYCLIZATION MEDIATED BY TRANSITION METALS

The reaction between olefins coordinated with transition metals and nucleophiles which give species containing metal carbon σ bonds has been reported and a wide variety of olefin complexes have been made to react with a large number of nucleophiles and their products characterized.

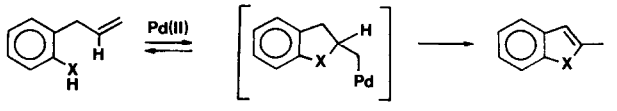
It has been observed that olefinic amines undergo cyclization in acidic aqueous solution in the presence of $PtCl_4^-$, which is regenerated at the end of the reaction, so that the reaction can be considered as catalytic, even though very long reaction times are required.[190]



The reaction of 1-, 2-, and 3-methylpent-4-enylamines **422**, **423** and **424** has been studied and diastereoselectivity decreases as the distance between the stereogenic centre and the double bond increases. The high 1,2-asymmetric induction that gives rise to a 88:12 *trans*:*cis* diastereomeric ratio in the cyclization of 3-methylpent-4-enylamine **424** is worth mentioning.



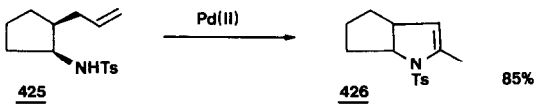
Hegedus has reported the synthesis of indoles and isocoumarins by the palladium-assisted cyclization of *o*-allylanilines and *o*-allylbenzoic acids, respectively. In this case cyclization is thought to proceed through a σ-alkylpalladium intermediate, followed by the elimination of a β-hydride.[191]



X = NH, NMe, NAc, COO

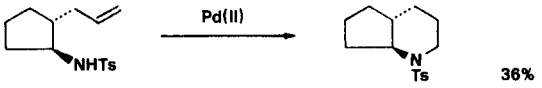
While the reaction of aromatic amines proceeds smoothly under mild conditions, any attempt to cyclize non-aromatic amino-olefins under similar conditions has been unsuccessful, owing to the increased basicity and nucleophilicity of the aliphatic amino group. To overcome this problem, a compatible protecting group has been introduced and a number of olefinic tosylamides **425** have

been synthesized and cyclized with the system Pd(II)/Na_2CO_3/benzoquinone. *cis*-Fused 5,5-ring systems **426** have been obtained in good to moderate yield.[192]

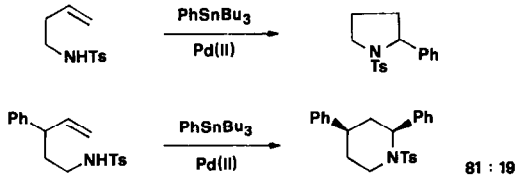


425 426

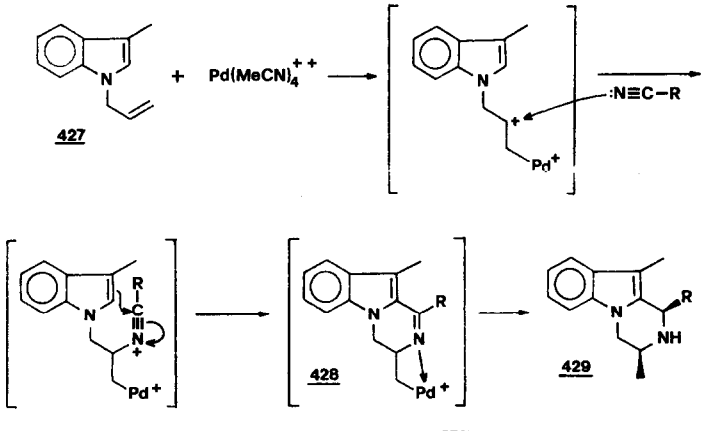
Furthermore, when a *trans*-relationship occurs between the unsaturated chain and the tosylamido group, a *trans*-fused 5,6-ring system is formed in low yield through a 6-*exo* closure.



Pd(II)-Catalyzed regiospecific 1,1-arylamination of unsaturated tosyl amides provides 2-arylated 5- and 6-membered nitrogen heterocycles which share the partial structure with many interesting alkaloids. The reaction is performed by treating the amide with $ArSn(n\text{-}Bu)_3$ in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ under oxidative conditions due to the presence of $CuCl_2$. Five- and six-membered rings can be obtained in 65–77% yield.[193]



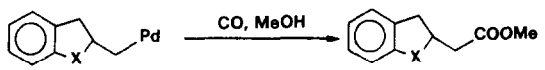
The highly electrophilic $Pd(MeCN)_4(BF_4)_2$ strongly interacts with the olefins and activates them to undergo nucleophilic attack by nitriles. N-allylskatole **427** has been made to react with a stoichiometric amount of $Pd(MeCN)_4(BF4)_2$ in the nitrile solution. A relatively stable palladium complex, presumed to be **428**, is thus formed. The successive reduction of **428** with $NaBH_4$ gives *syn* 1,2,3,4-tetrahydropyrazino[1,2*a*]indoles **429** in fair yield. A possible mechanism, similar to the Ritter reaction, has been envisaged for the nitrile insertion.[194]



427 428 429

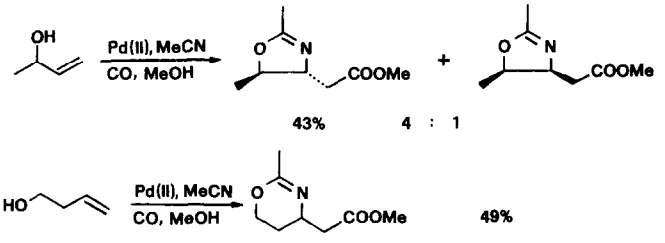
R = Me, 58%; R = Et, 48%; R = Ph, 37%

A typical reaction of σ-alkylpalladium(II) complexes is the insertion of unsaturated molecules into the metal–carbon σ-bond. Carbon monoxide inserts most readily, generally under mild conditions.[195]



X = NMe, NAc, COO

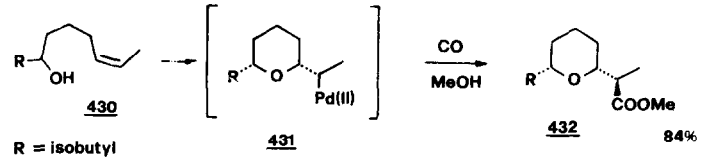
With allylic and homoallylic alcohols as substrates, intramolecular trapping of the nitrilium ion by the hydroxy group is observed, to give oxazolines or oxazines, respectively, albeit in low yield and moderate stereoselectivity.[194]

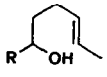
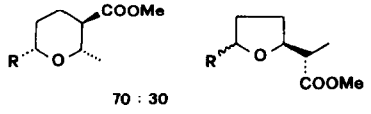
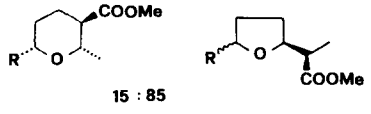
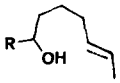
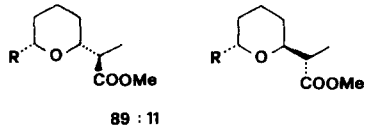


Hydroxyalkenes of appropriate length can be activated by Pd(II) favouring the addition of the hydroxy group to the double bond. The cyclization product is an alkylpalladium(II) complex, which can be cleaved by CO to give an ester. Some hydroxyalkenes have been cyclized to study the effect of the alkene geometry on the selectivity and the preferences for ring-size. The results are reported in Table 41.[196]

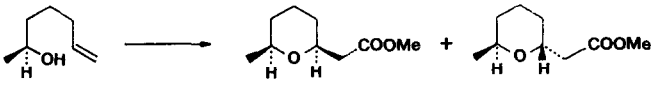
As it appears from Table 41, the alkene geometry plays a dominant role in the formation of 5- versus 6-membered rings. While a total stereoselectivity is observed in the formation of 6-membered rings, mixtures of 5-membered rings are generally obtained.

Table 41. Alkoxycarbonylation of hydroxyalkenes[196]



Substrate	yield %	Products
	84	 70 : 30
	65	 15 : 85
	88	 89 : 11

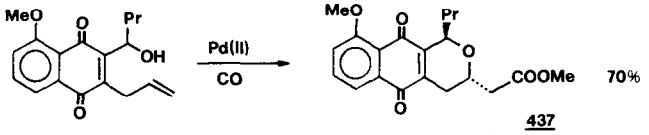
This reaction has been employed for a short, stereoselective synthesis of **434**, a component of the glandular secretion of *Viverra civetta*, starting from (*S*)-5-hepten-2-ol **433**.



433 **434** 20 : 1 **435**

The key compound is obtained in 74% yield and 20 : 1 *cis* : *trans* diastereomeric ratio.

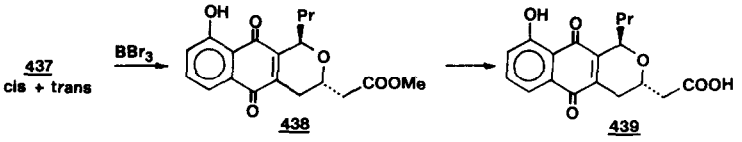
Deoxyfrenolicin **439** is a member of a group of naphthoquinone antibiotics based on the isochroman skeleton. The efficient pyran ring formation process, termed alkoxycarbonylation, has been obtained by treating the hydroquinone **436** with a catalytic amount of Pd(II) in methanol under CO atmosphere. The reaction gives the ester **437** in 70% yield and 3 : 1 *trans* : *cis* ratio.[197]



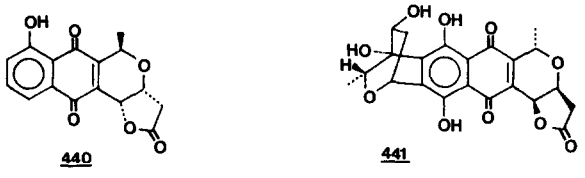
436 **437**

3 : 1 trans : cis

Further treatment of the diastereomeric mixture with BBr_3 causes demethylation to phenol **438** and complete isomerization to the *trans* natural series, constituting, moreover, a convenient approach to the racemic deoxyfrenolicin **439**, which has significant antibiotic and potential antitumor activity.



A simple approach to pyran lactones **443** has then been envisaged, since the fused pyran γ-lactone is the structural feature characterizing a number of interesting natural compounds such as kalafugin **440** and granaticin **441**.[198]



The desired cyclization has been performed by using a stoichiometric amount of Pd(II) under a CO atmosphere (Table 42).

The results obtained with the free hydroxy compounds suggest a strong directing effect of the allylic hydroxyl group, favouring the formation of a *cis*-lactone, irrespective of the configuration of the methyl group at C-1. On the contrary the corresponding methyl ether affords a 1 : 1 diastereomeric *cis* : *trans* mixture.

The directing effect observed here can arise through the coordination of the hydroxyl group with Pd (as in **444**), of the alkoxide (as in **445**) or of the alkoxyacyl (as in **446**).

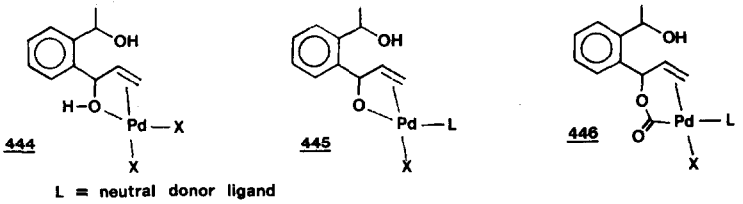
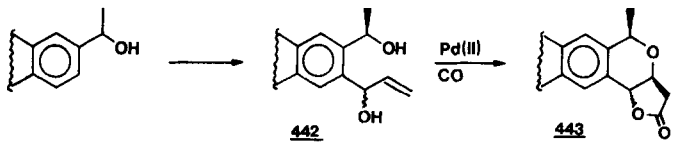
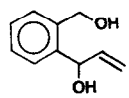
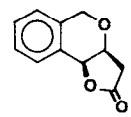
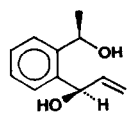
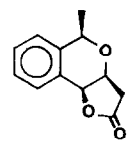
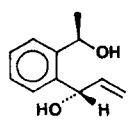
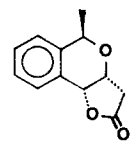
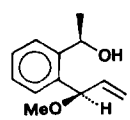
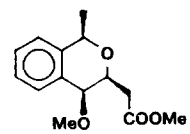


Table 42. Alkoxycarbonylation of unsaturated 1,4-diols[198]

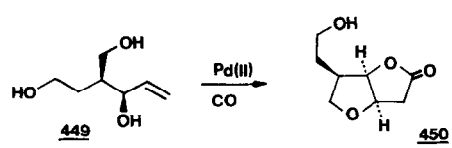


Substrate	Product	yield %	cis:trans ratio
		68	99 : 1
		77	83 : 17
		84	83 : 17
		94	51 : 49

A convenient, stereoselective synthesis of *cis*-3-hydroxy tetrahydrofuran-2-acetic acid lactones **448** has been achieved by intramolecular oxycarbonylation of 4-penten-1,3-diols **447**.[199]

The reaction, developed by Yoshida and Tamaru, proceeds with high yields and total regio- and stereoselectivity, as shown in Table 43. In fact, owing to the –OH directing effect, only *cis*-lactones are isolated; in addition, when a substituent is present on the furanic ring, a single isomer is isolated from the reaction mixture (Table 43).

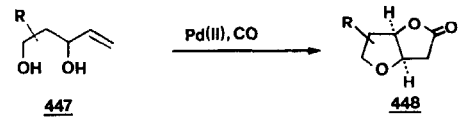
The only limitation is due to the substitution on the double bond: in fact in this case lower yields are observed. *Syn* 3-hydroxymethyl-4-hydroxy-5-hexenol **449** nicely demonstrates the high regio- and stereoselectivity of this reaction, since **450** is obtained as the sole product.



An extension of this method relies on a stereoselective, Pd(II)-catalyzed intramolecular double cyclization of 3-hydroxy-4-pentenoic acids **451** to bis-lactones **452**, carried out under a CO atmosphere (Table 44).[200]

It has been further observed that the substituents on the double bond do not significantly affect the yield, while the substitution at C-2 increases reactivity. The most important feature of the reaction is the high *cis*-stereoselection, in agreement with Chamberlin's results.

Table 43. Alkoxycarbonylation of unsaturated 1,3-diols[199]



447 448

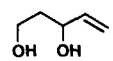
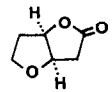
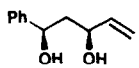
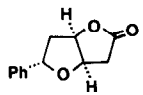
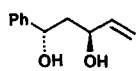
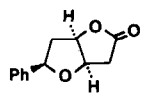
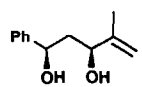
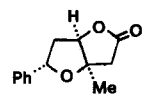
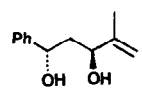
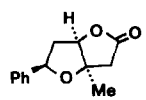
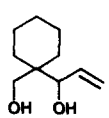
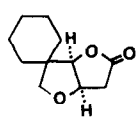
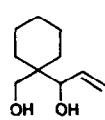
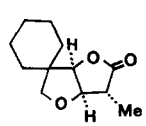
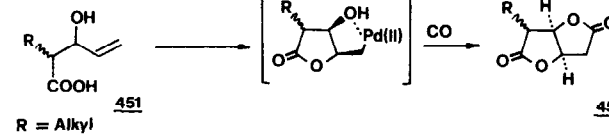
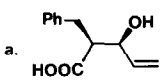
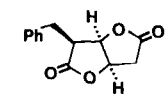
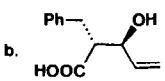
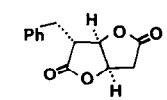
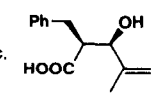
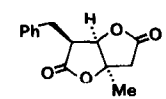
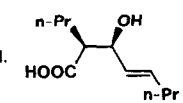
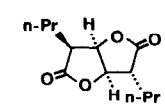
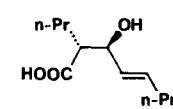
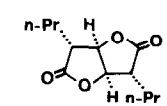
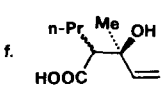
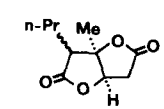
Substrate	Product	yield%
		60
		80
		70
		80
		29
		86
		24

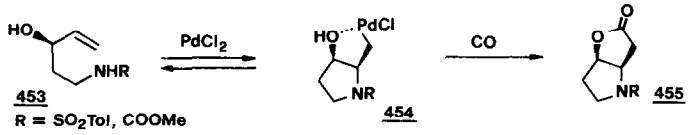
Table 44. Cyclization of 3-hydroxy-2-pentenoic acids to bis-lactones[200]



451 452

	Substrate	Product	yield%
a.			60
b.			60
c.			84
d.			83
e.			88
f.			78

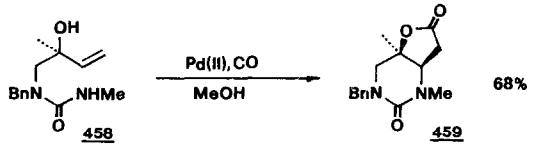
With the aim of preparing multifunctionalized nitrogen heterocycles, which are useful intermediates for many syntheses of pyrrolizidine alkaloids, urethanes and tosylamides of substituted 3-hydroxypent-4-enylamines **453** have been employed, giving substituted *cis*-3-hydroxypyrrolidine-2-acetic acid lactones **455** in good yield. In analogy with a cyclization of 3-hydroxy-4-pentenylamides with various electrophiles, the use of Pd(II) allows the *cis*-2-(palladiomethyl)-3-hydroxypyrrolidines **454** to be obtained as intermediates. These then undergo carbonylation and intramolecular esterification to give *cis*-3-hydroxypyrrolidine-2-acetic acid lactones **455**. The key step of this conversion is the Pd(II)catalyzed aminocarbonylation, performed in AcOH under Co atmosphere.[201]



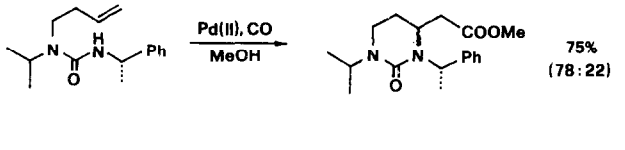
The total stereoselectivity of this reaction depends on the electrophilic addition of Pd(II) to the double bond and may be attributed to the equilibrium between **453** and **454**, owing to a coordination of the hydroxyl group to Pd(II) (Table 45).[202]

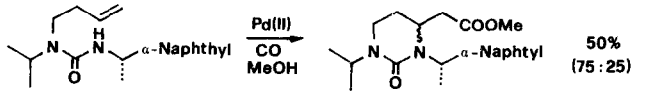
Also N-protected 4-hydroxy-5-hexenylamines **456** have been cyclized under the same conditions: in this case *cis*-3-hydroxypiperidineacetic acid derivatives **457** are formed (Table 46).

As an extension of this reaction, the urea **458** undergoes a smooth aminocarbonylation under the reported conditions and *cis*-lactone **459** is produced in moderate yield.



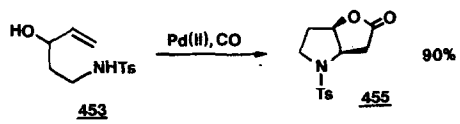
Following this result, many unsaturated ureas have been studied in an attempt to find a convenient and general method for the synthesis of physiologically important β,γ- and β,δ-diamino and aminohydroxyacids. The ureidocarbonylation of some N,N′-2-propenyl or N,N′-3-butenyldialkyl ureas affords the corresponding imidazolidin-2-ones or pyrimidin-2-ones in good yield and with high regioselectivity. The reaction is performed in methanol with a catalytic amount of Pd(II) under CO atmosphere. Some examples have been examined to clarify the possibility of asymmetric induction using chiral ureas. In these cases only a moderate diastereoselection has been observed.[203]





The factors affecting the chemoselection of the reaction have been studied by reacting N-unsubstituted, N′-substituted 4-pentenyl or 5-hexenylamine derivatives. It has been observed that cyclization, performed in protic solvents (MeOH or AcOH) on the ureas, affords bicyclic systems only, whereas with tosylamides, monocyclic carbonylation products are exclusively obtained.

Table 45. Cyclization of 3-hydroxy-4-pentenylamides[202]



453 455

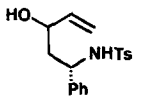
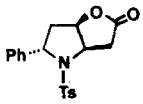
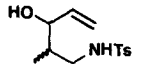
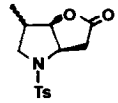
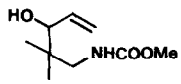
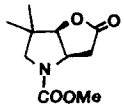
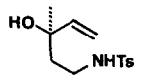
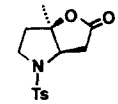
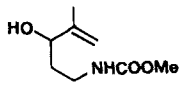
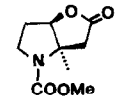
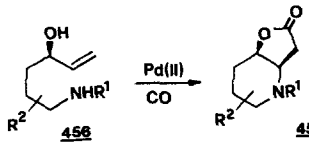
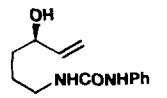
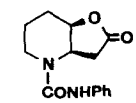
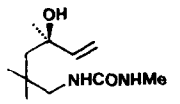
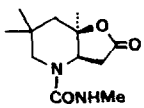
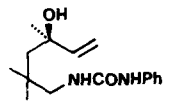
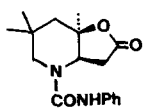
Substrate	Product	yield %
		74
		70
		70
		66
		28

Table 46. Cyclization of 4-hydroxy-5-hexenylureas[202]

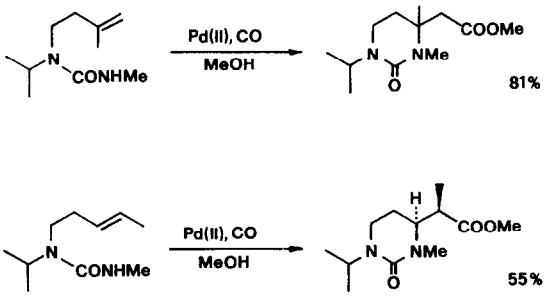


456 457

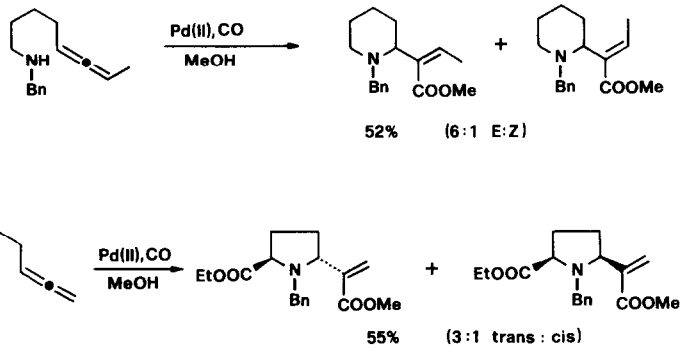
R^1 = CONHMe, CONHPh; R^2 = H, Alkyl

Substrate	Product	yield%
		35
		34
		33

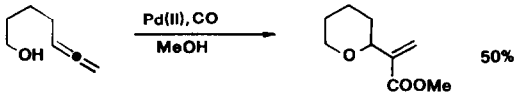
Furthermore, when substituted double bonds are present, only one isomer is detected, owing to the *trans*-addition of the aminocarbonylation reaction.[203]



The intramolecular amino or ureidocarbonylation reaction catalyzed by Pd(II), which constitutes a useful approach to functionalized heterocyclic compounds, has also been exploited to prepare 2-piperidino or 2-pyrrolidino acrylates. Allenic amines or their derivatives (tosylamides or carbamates) undergo intramolecular cyclization under the aminocarbonylation conditions, in MeOH, and the reaction proceeds with moderate yields and isomerization of the double bond.[204]

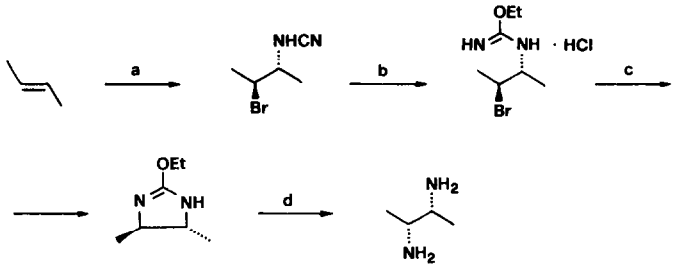


When a 2,5-disubstituted pyrrolidine is the reaction product, a 3 : 1 *trans* : *cis* mixture is obtained. This reaction differs from the cyclizations reported previously as it tolerates a relatively basic nitrogen function such as N-benzyl, although the free primary amino group remains uneffective under the reaction conditions. It is also worth mentioning that this reaction can be extended to the synthesis of 2-tetrahydropyranyl acrylates.[204]



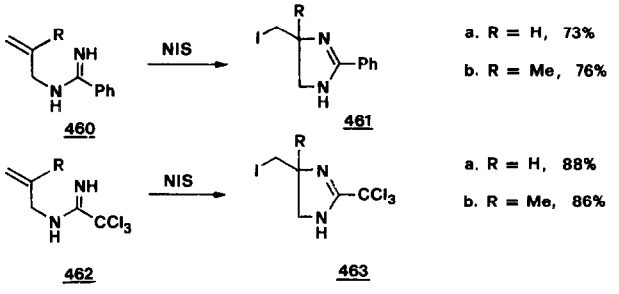
8. HALOCYCLIZATION OF AMIDINES

The palladium-promoted cyclization of allylic and homoallylic ureas constitutes a good method for synthesizing imidazolidin-2-ones or pyrimidin-2-ones, which are useful intermediates for the preparation of diamines, multipurpose compounds.[205] In fact the diamino moiety is present in some naturally occurring compounds and medicinal agents and plays an important role in chelating agents. A synthetic approach to these compounds via an *anti* addition of Br_2 and cyanamide to an alkene has been recently reported by Cohn and Jung.[206]



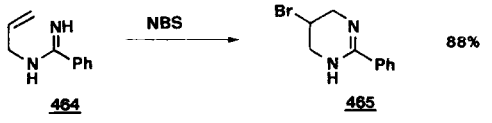
a. NH_2CN, NBS b. EtOH, HCl c. $NaHCO_3$ d. $Ba(OH)_2$

Benzo- **460** and trichloro-acetamidines **462**, which are easily prepared starting from the corresponding allylic amines and benzonitrile or trichloro-acetonitrile, readily cyclize on treatment with NIS or I_2 in THF, to give imidazolines **461** and **463** that could be converted into the corresponding diamines.[207]



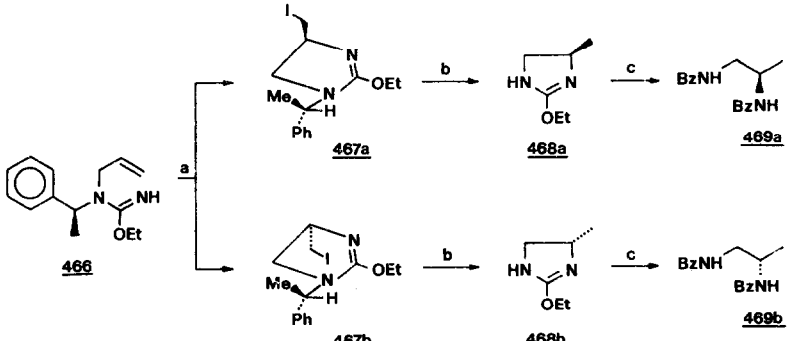
a. R = H, 73%
b. R = Me, 76%
a. R = H, 88%
b. R = Me, 86%

When NBS is used as the electrophile in the cyclization of the allylic benzamidine **464**, a 6-*endo* closure is observed with the formation of the corresponding bromotetrahydropyrimidine **465**, probably owing to a change in the reaction mechanism.



88%

The iodocyclization of unsaturated amidines, containing (*S*)-1-phenylethylamine as the chiral moeity, leads to synthons in which diamino groups are present and the stereogenic centre has a defined configuration. In fact, starting from (*S*)-1-phenylethylamine, the corresponding cyanamide is easily derived and then converted, after allylation, into the isourea **466**. The cyclization of **466**, performed with NIS in $CHCl_3$, affords a 1 : 1 diastereomeric mixture of imidazolines **467a** and **467b** in 90% yield, that can be easily separated by chromatography.[208]



a. NIS b. LAH

From the analysis of the ^{1}H-NMR spectrum of each diastereomer the absolute configuration is assigned on the basis of both chemical shifts and coupling constants.

The Birch reaction of diastereomerically pure imidazolines **467a** and **467b**, respectively, gives the corresponding imidazolines **468a** and **468b**; the successive hydrolysis of the heterocyclic ring, carried out with 6M HCl, affords the enantiomerically pure 1,2-diamines, isolated as dibenzoyl derivatives **469a** and **469b**.

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