

Stereocontrolled reactions through heterocyclic intermediates

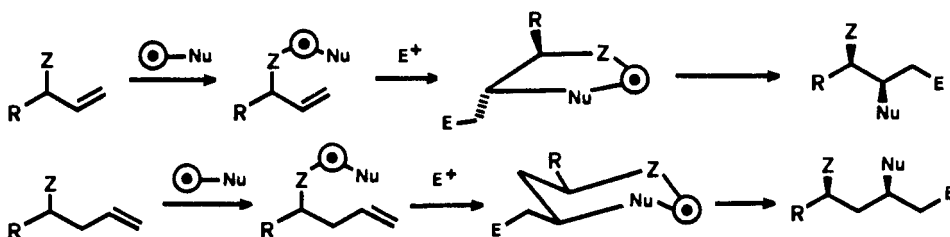
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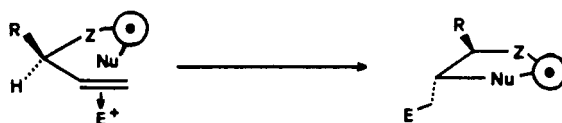
Abstract - New methods of double bonds halofunctionalization of allylic and homoallylic alcohol and amine derivatives have been developed. Carbonates, imidates, urethanes and amides have been cyclized to heterocyclic intermediates whose hydrolysis leads to diols, triols and aminoalcohols. This method has been applied to the synthesis of deoxyaminosugars (ristosamine and daunosamine), sphingamines, sphingosine and 2-amino-2-deoxytetritols. Moreover the use of chiral auxiliaries allows to obtain easily separable diastereomeric mixtures of heterocyclic intermediates, useful for the synthesis of biologically active compounds such as propranolol and GABOB.

INTRODUCTION

The synthesis of biologically active compounds prompted interest in the development of new methods for the construction of a variety of polyfunctionalized compounds. The use of a cyclic system to achieve asymmetric induction in acyclic compounds has become a synthetically useful strategy (ref. 1). In this field we have developed methods for the functionalization of unsaturated alcohol and amine derivatives, simply on addition under kinetic conditions of an electrophile to suitably prepared derivatives containing an internal nucleophile. The electrophile promotes the cyclization, thus allowing a regio- and stereocontrolled synthesis of heterocyclic intermediates. The high stereocontrol seems to rely on the propensity of a cyclic transition state to assume a configuration compatible with the smallest interactions among the substituents. In fact 4,5-trans- and 4,6-cis-relationship for 5- and 6-membered rings respectively, have been preferentially observed. After hydrolysis, polyfunctionalized compounds are obtained, so that the formation of the heterocyclic intermediates is a valuable tool for the transfer of chirality from a preexistent to the newly formed stereocenters.

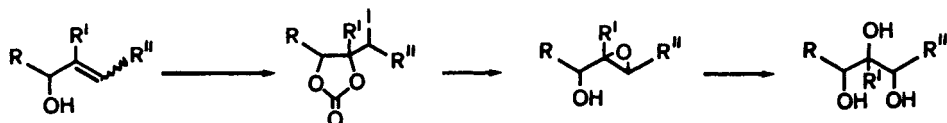


A theoretical approach has been recently envisaged (ref. 2) to explain the high degree of asymmetric induction achieved in 5-membered rings starting from substrates containing an allylic heteroatom. Due to the presence of an internal nucleophile, a concerted mechanism can occur, that proceeds via a more probable intramolecular attack on a π complex, not an onium ion; the electrophilic attack occurs on a preferential conformer with oxygen or nitrogen in plane, giving rise to the major trans product. This agrees with the results reported in the literature.



FUNCTIONALIZATION VIA IODOCARBONATES

Our first work in this area has been the synthesis of five and six membered cyclic iodocarbonates (ref. 3), which are smoothly prepared in good yield by bubbling CO_2 into a THF solution of lithium alkoxides, followed by addition of iodine. This reaction has a wide applicability to a variety of allylic or homoallylic alcohols, and some results are summarized in Table 1.



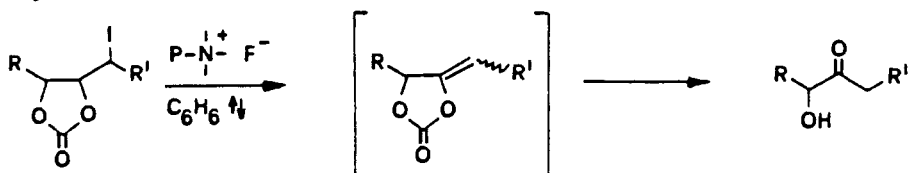
The cyclization exhibits an high regiocontrol, since allylic and homoallylic alcohols give five-membered and six-membered rings, respectively. The cis:trans ratio of diastereomers has been quantified by g.l.c. analysis of the crude reaction mixture. The stereochemistry has been determined by ^1H NMR spectroscopy of the pure diastereomeric compounds or by conversion into epoxyalcohols of known configuration.

The cyclization of an allylic carbonate with a terminal double bond shows low diastereoselectivity affording a 40:60 cis:trans ratio of the 2,5-dioxacyclopentanone 1a, whereas the cyclization of a carbonate with a substituted double bond, affords the 2,5-dioxacyclopentanone 1b in a 7:93 cis:trans ratio. In addition, homoallylic carbonates form six-membered cyclic derivatives with a good stereoselectivity towards 4,6-cis-relationship (1d, 1e). Bartlett et al. (ref. 4) exploiting successively the cyclization of homoallylic tert-butyl carbonates under thermodynamic control (I_2 in acetonitrile) observed the same stereoselectivity as we have found in the anionic carbonates cyclization process. They consider key for high stereoselectivity in this and related processes, the thermodynamic conditions employed. Although in our case the diastereomeric ratios for both five and six membered rings could reflect a thermodynamic preference, the data of the literature indicate that neutral conditions provide a kinetic control (ref. 5). It is hypothizable a mechanism which involves a rapid iodonium ion pre-equilibrium, followed by a preferential attack of the internal nucleophile on the iodonium ion, leading to a cyclic transition state that assumes a configuration compatible with the smallest interaction among the substituents.

TABLE 1

| Alcohol | Iodocarbonate (major isomer) | Product distribution (cis:trans) | Epoxyalcohol (major isomer) | Triol (major isomer) |
|---------|------------------------------|----------------------------------|-----------------------------|----------------------|
| | | 40:60 | | |
| | | 7:93 | | |
| | | 60:40 | | |
| | | 95:5 | | |
| | | 94:6 | | |

Iodocarbonates are useful intermediates in organic synthesis; in fact threo-1,2-diols and erythro-1,3-diols are readily obtained from iodocarbonates by Bu_3SnH reduction, followed by basic hydrolysis. Moreover, depending on the hydrolytic conditions, the cyclic iodocarbonates can be converted into the corresponding epoxyalcohols or triols with retention of the configuration. A further application of cyclic iodocarbonates is the regioselective synthesis of α -hydroxyketones through the use of fluoride ion on polymeric support to promote dehydrohalogenation (ref. 6).



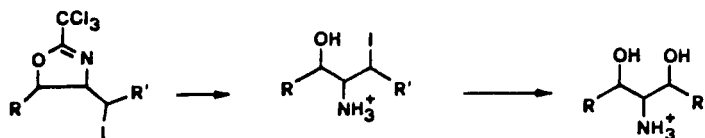
SYNTHESIS OF AMINOALCOHOLS VIA TRICHLOROACETIMIDATES

As a part of a programme aimed at the synthesis of aminosugars, we developed a new method to prepare amino alcohols through the iodocyclization of unsaturated trichloroacetimidates (ref. 7). The reaction has been performed under kinetic conditions by adding iodine in THF to a solution of allylic or homoallylic trichloroacetimidates in the presence of pyridine. Although many factors affect the regiochemistry of this reaction, the cyclization of allylic derivatives with a terminal double bond shows a total regioselectivity and a good stereoselectivity, affording preferentially *trans*-4,5-dihydro-1,3-oxazoles, while homoallylic trichloroacetimidates give 4,5-dihydro-1,3-oxazines exclusively, with 4,6-*cis* stereoselectivity (Table 2).

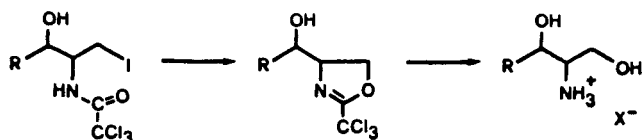
TABLE 2

| | | | |
|---|--------|-------------|--|
| | | | |
| $\text{R} = \text{CH}(\text{CH}_3)_2$ $\text{R} = \text{C}_5\text{H}_{11}$ | yield% | trans : cis | |
| | 70 | 95 : 5 | |
| | 60 | 75 : 25 | |
| | | | |
| $\text{R} = \text{CH}_3$ | yield% | cis : trans | |
| | 65 | 80 : 20 | |

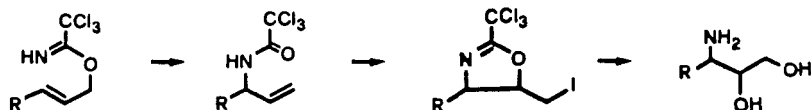
The hydrolysis of these intermediates has been carried out under different conditions. Methanolic HCl at r.t. gives the salts of the corresponding iodoaminoalcohols which by treatment with an excess of acetate ion supported on Amberlyst A 26 in refluxing methanol give rise to the corresponding diols.



The hydrolysis in water-methanol quantitatively yields the corresponding trichloroacetamides which in basic media undergo halogen displacement (ref. 8) to give 4,5-dihydro-1,3-oxazoles. The latter compounds may be easily converted into 2-amino-1,3-diols with 2M HCl (ref. 9).



On the basis of the results obtained with amides in basic media, we further extended the approach to other polyfunctionalized sequences, by a thermal rearrangement of trichloroacetimidates to trichloroacetamides (ref. 10). These intermediates undergo the cyclization to 4,5-dihydro-1,3-oxazoles with NIS in chloroform with moderate stereoselectivity (ref. 11). The 4,5-dihydro-1,3-oxazoles so obtained can be converted to 3-amino-1,2-diols.



These reactions allow the regio- and stereoselective introduction of hydroxyamino moieties present in a number of bioactive sugars.

FACTORS AFFECTING THE ALLYLIC IMIDATES IODOCYCLIZATION

One of the interesting aspects of the halofunctionalization of allylic imidates, is the high regioselectivity that can be obtained in the cyclization process. Several factors appear to govern the regioselectivity towards 5-exo or 6-endo closures of allylic imidates under the conditions employed (I_2 /pyridine in THF; NIS in $CHCl_3$; I_2 in $CHCl_3$) (ref. 12). In fact besides electronic factors, the regiochemical outcome of the ring closure, seems to be strongly influenced by the E or Z configuration of the double bond, so that a rationalization of the regioselectivity has been put forward, that could result useful in planning the synthesis of polyfunctionalized natural products. A set of substrates where the regioselectivity is mainly controlled by an incipient cation stabilization, is reported in Table 3. In fact a 4,5-dihydro-1,3-oxazine (typical IR absorption at 1670 cm^{-1}) is exclusively obtained, owing to the stabilization of the benzylic or allylic cation (entries a, b, c). On the other hand the cyclization of 1d proceeds with a total regioselection, leading to a 4,5-dihydro-1,3-oxazole ring (typical IR absorption at $1650\text{--}1660\text{ cm}^{-1}$), owing to an incipient secondary cation; this is in agreement with the cyclization of esters with a terminal double bond (ref. 13), urethanes (ref. 14), imidates (ref. 7), amides (ref. 11, 15), or carbonates (ref. 3), that afford exclusively five-membered heterocyclic rings, with high stereoselectivity. The cyclization of 1e is again controlled by electronic factors: in fact the incipient tertiary cation forces the closure in a 6-endo mode, outweighing the methyl steric hindrance.

A deeper insight on the factors affecting the regioselection of the iodocyclization can be obtained from the results of the cyclization of entries 1f - 1h (Table 4).

In fact by treatment of 2(E)-penten-1-yl imidate 1f with NIS in chloroform the 4,5-dihydro-1,3-oxazine 2f is obtained, while the 2(Z)-isomer 1g affords exclusively the 4,5-dihydro-1,3-oxazole 3g. The subsequent examples reported in the Table 2 confirm that the configuration E or Z of the double bond exerts a strong control on the cyclization, so that only one of the two possible heterocycles is obtained. The preferential formation of a five membered ring, starting from a Z-allylic imidate, can be in fact attributed to the steric hindrance of the substituent on the double bond.

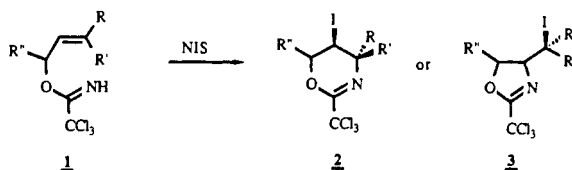


TABLE 3

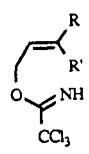
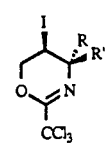
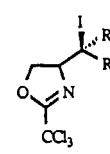
TABLE 4

| | <u>2</u> yield % | <u>3</u> yield % | | <u>2</u> yield % | <u>3</u> yield % |
|---|------------------|------------------|--|------------------|------------------|
| a. R = Ph; R' = H; R'' = H | 80 | - | f. R = C ₂ H ₅ ; R' = H; R'' = H | 90 | - |
| b. R = ; R' = H; R'' = H | 90 | - | g. R = H; R' = C ₂ H ₅ ; R'' = H | - | 88 |
| c. R = ; R' = H; R'' = H | 95 | - | h. R = C ₃ H ₇ ; R' = H; R'' = H | 87 | - |
| d. R = H; R' = H; R'' = C ₁₅ H ₃₁ | - | 90 | i. R = C ₁₅ H ₃₁ ; R' = H; R'' = H | 90 | - |
| e. R = CH ₃ ; R' = CH ₃ ; R'' = H | 85 | - | j. R = H; R' = C ₁₅ H ₃₁ ; R'' = H | - | 90 |
| | | | k. R = H; R' = C ₆ H ₅ ; R'' = H | - | 92 |

To test the role of the bulky substituent **1e** on the regiochemistry of the cyclization with respect to a stabilized carbonium ion, we have cyclized the *Z*-cinnamyl imidate **1k**, where an incipient benzylic carbonium ion can arise during the cyclization. 4,5-Dihydro-1,3-oxazole is exclusively obtained, showing that the bulky phenyl group causes a 5-exo attack to become competitive with a 6-endo closure.

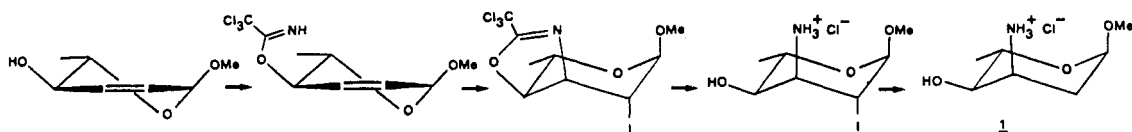
In a further study on the regioselectivity, we have examined the role of an oxygen atom in allylic position to the double bond. It is known that substituents in the allylic positions exert a very pronounced influence on both the stereo and regioselectivity of the electrophilic addition. A polar substituent (ref. 16) such as a methoxy or a hydroxy group, affects the regioselectivity mainly by an inductive effect, directing the attack of the nucleophile on the carbon atom away from the oxygen atom. Thus 5-exo closure is exclusively observed for imidates **1l** - **1n** (Table 5). These compounds, together with a *Z* double bond, have an allylic ethereal group that favours the attack of the nucleophile at C-2, because of combined inductive and steric effects of the alkoxy group. On the contrary, a mixture of six and five-membered rings **2** and **3** has been obtained (**1o** - **1q**), confirming the propensity of the *E* double bond to promote the 5-endo closure in opposition to the oxygen effect.

TABLE 5

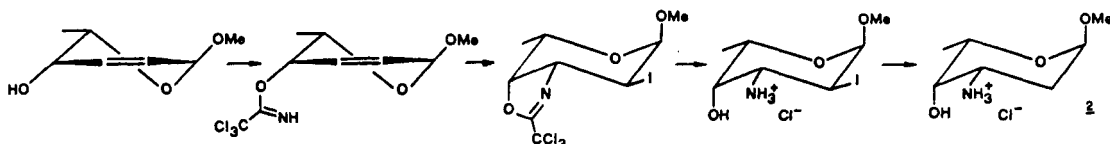
| | | | 2 yield % | 3 yield % | |
|---|----------------------------|---|------------------|---|--|
|  | $\xrightarrow{\text{NIS}}$ |  | and |  | |
| 1 | | 2 | | 3 | |
| l. R = H; R' = CH ₂ OCH ₃ | | | - | 87 | |
| m. R = H; R' = CH ₂ OTHP | | | - | 81 | |
| n. R = H; R' = CH ₂ OBn | | | - | 98 | |
| o. R = CH ₂ OCH ₃ ; R' = H | | | 30 | 61 | |
| p. R = CH ₂ OTHP; R' = H | | | 38 | 55 | |
| q. R = CH ₂ OBn; R' = H | | | 18 | 75 | |

SYNTHESIS OF DEOXYAMINOSUGARS VIA TRICHLOROACETIMIDATES

A number of syntheses of aminosugars have been reported in the last years proving the popularity of this kind of targets. In this field the cyclofunctionalization of imidates shows an interesting applicability, as illustrated by the syntheses of ristosamine (ref. 17) and daunosamine (ref. 18). The methyl α -L-ristosaminide hydrochloride, 3-amino-2,3,6-trideoxy-L-ribohexose, a component of the antibiotic ristomycin, has been obtained starting from the methyl 2,3,6-trideoxyhex-2-en- α -L-erythropranoside, readily accessible from L-rhamnose. After conversion into the trichloroacetimidate, the cyclization with *N*-iodosuccinimide in CHCl₃ (or NBS in *t*-BuOH) afforded the *L*-altro derivative, with total asymmetric induction. The subsequent hydrolysis with HCl in methanol and the cleavage of the carbon-halogen bond with Bu₃SnH allows a simple route to methyl α -L-ristosaminide hydrochloride **1**.



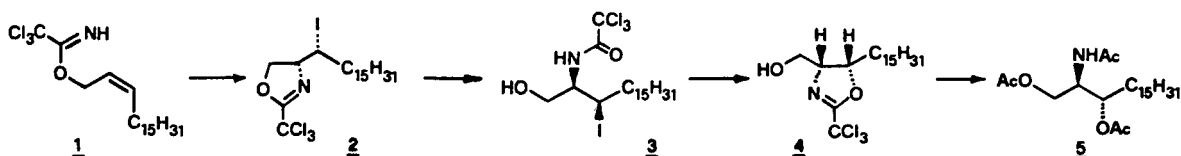
Daunosamine, a 3-amino-2,3,6-trideoxy-L-lyxohexose is important as the carbohydrate constituent of the anthracycline antibiotics with strong antitumor activity such as daunorubicin and adriamycin. Considering the stereochemistry of daunosamine, an appropriate starting material is represented by methyl 2,3,6-trideoxyhex-2-en-L-threopyranoside, which can be obtained through the inversion at C-4 of the *L*-erythropranoside. We have performed the inversion of the configuration by treating the mesyl derivative with an excess of Amberlyst A 26 in the CO₃²⁻ form. Under these conditions, simply by filtering off the resin, the threo derivative **3** has been obtained in 80% yield, without elimination products. The cyclization, hydrolysis and cleavage of the carbon-halogen bond complete the synthesis of methyl α -L-daunosaminide hydrochloride **2**.



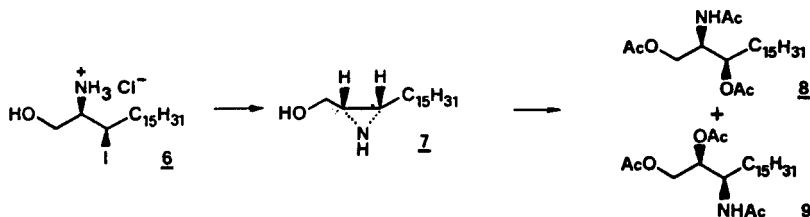
The interest for these syntheses relies on the complete regio- and stereocontrol of the cyclization. The regiochemistry of the cyclization is in total agreement with the above discussed factors affecting the ring closure. In fact in the starting pyranoside the methoxy group in the allylic position of the Z-double bond destabilizes, by an inductive effect, the transition state where a positive charge develops at the adjacent carbon atom, forcing to a 5-exo ring closure.

SYNTHESIS OF (+)-SPHINGANINES AND (+)-SPHINGOSINE

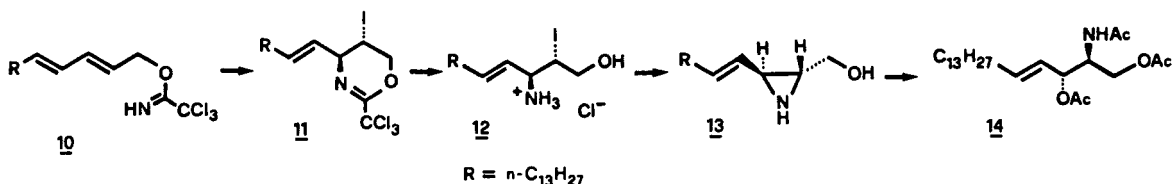
On the basis of the previously discussed regiochemistry, the syntheses of erythro and threo-sphinganine and erythro-sphingosine have been developed. The (+)-erythro-sphinganine triacetate 5 has been obtained in good yield and under complete stereocontrol starting from the easily accessible trichloroacetimidoyloxyoctadec-2(Z)-ene 1 (ref. 19). Due to the presence of the Z double bond, a 4,5-dihydro-1,3-oxazole has been exclusively obtained and subsequently converted with water to the corresponding amide 3. The hydrolysis of the cis-4-hydroxymethyl-4,5-dihydro-1,3-oxazole 4, obtained under basic conditions from the amide, affords the erythro-sphinganine triacetate 5.



Starting from 2, a modified approach has been required to synthesize (+)-threo-sphinganine triacetate 9 (ref. 19). Acidic hydrolysis of 2 gave the corresponding salt that has been converted to the aziridine 7 by treatment with Amberlyst A 26 in the CO_3^{--} form. The salt of the aziridine, dissolved in methanol, on treatment with an excess of Amberlyst A 26 in the AcO^- form affords 9, accompanied by a 30% of its regioisomer 8.



The pathway of the synthesis of the (+)-erythro-sphingosine triacetate 14 is reported in the following scheme (ref. 20). Starting from 2(E),4(E)-octadecadien-1-yl trichloroacetimidate 10, the 4,5-dihydro-1,3-oxazine 11 is obtained as a single compound, for the cooperative effect of the E-double bond and of the allylic stabilization of the incipient carbocation. Owing to the presence of the double bond, the opening of the intermediate trans-aziridine is totally under regio- and stereocontrol, leading exclusively to the (+)-erythro-sphingosine.

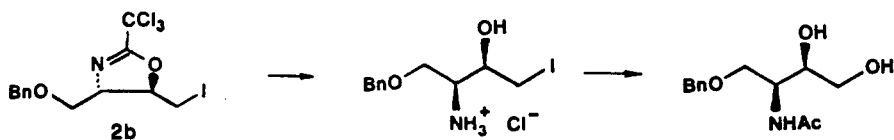


SYNTHESIS OF (+)-2-AMINO-2-DEOXYTETRITOL DERIVATIVES VIA TRICHLOROACETAMIDES

For this approach the starting trichloroacetamides, easily obtained by thermal rearrangement of the corresponding acetimidates, were iodocyclized with NIS in CHCl_3 , leading in quantitative yield to 4,5-dihydro-1,3-oxazoles (ref. 11,21). The ^{13}C diastereomeric ratio reported in the table has been determined by g.l.c. analysis and ^{13}C NMR spectra of the reaction mixtures.

The data of the Table 6 show that the cyclization of a substrate with an alkyl group in the place of the free or protected CH_2OH results in a greatly diminished selectivity (compare entry 1a with 1b,c,d). In contrast, high stereoselectivity obtained when R is an hydroxy or an alkoxy group is useful in the synthesis of aminosugars. In fact the *trans*-4,5-dihydro-1,3-oxazole 2b has been utilized as the starting material for both threo and erythro 2-amino-2-deoxytetritols (ref. 22).

After hydrolysis of 2b with 6M HCl in methanol, the corresponding threo salt has been obtained in a quantitative yield. By treatment with Amberlyst A 26 in the AcO^- form in refluxing methanol, the salt has been converted into the corresponding acetamide in quantitative yield.



On the other hand 2b undergoes hydrolytic cleavage in refluxing aqueous methanol leading to the corresponding threo amide in 83% yield. Subsequent treatment of the amide with MeONa in CH_2Cl_2 , affords the corresponding *cis*-4,5-dihydro-1,3-oxazole. The reaction proceeds through the intermediate epoxide that can be isolated when the reaction is carried out with *t*-BuOK. Hydrolytic cleavage with 6M HCl in methanol gives quantitatively the salt of the protected erythritol.

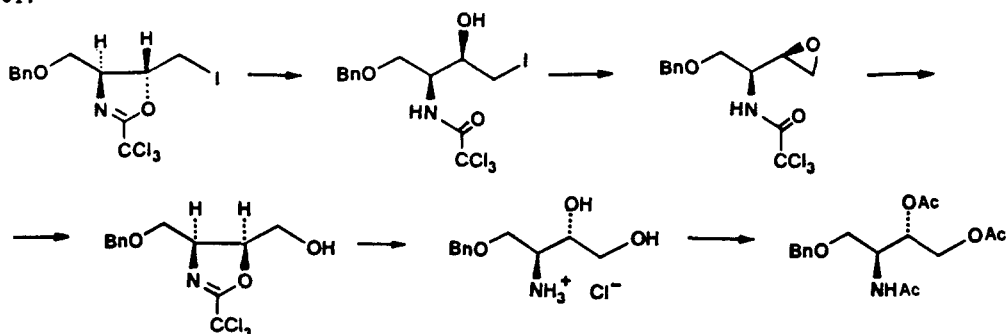


TABLE 6

TABLE 7

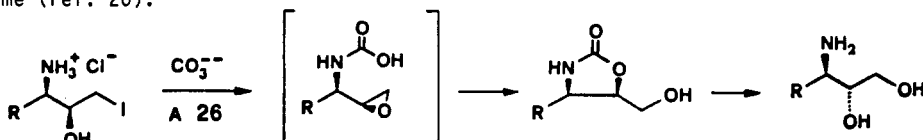
| | <i>trans</i> : <i>cis</i> ratio | Entry | yield% | <i>cis</i> : <i>trans</i> ratio |
|--|---------------------------------|---|--------|---------------------------------|
| a. R = $n\text{-C}_3\text{H}_7$ | 66 : 34 | a. R = C_3H_7 ; R' = H | 95 | 45 : 55 |
| b. R = BnOCH_2 | 80 : 20 | b. R = C_3H_7 ; R' = CH_2Ph | 95 | 30 : 70 |
| c. R = HOCH_2 | 95 : 5 | c. R = $\text{CH}_2\text{OCH}_2\text{Ph}$; R' = H | 94 | 30 : 70 |
| d. R = $t\text{-BuPh}_2\text{SiOCH}_2$ | 90 : 10 | d. R = $\text{CH}_2\text{OCH}_2\text{Ph}$; R' = CH_2Ph | 90 | 1 : 99 |
| | | e. R = CH_2OH ; R' = H | 80 | 7 : 93 |

SYNTHESIS OF 3-AMINO-1,2-DIOLS AND AMINOALCOHOLS FROM OXAZOLIDIN-2-ONES

A one-step procedure leading to 5-(iodomethyl)oxazolidin-2-ones has been accomplished by treating allylic amine hydrochlorides or the free amines with a reagent obtained by adsorbing iodine on the resin Amberlyst A 26 in the CO_3^{--} form (ref. 23). The oxazolidin-2-ones have been obtained in very high yield and in the diastereomeric ratios reported in the Table 7.

Once again, when R = C_3H_7 , a low diastereoselectivity has been observed; a benzyl substituent on the nitrogen increases to 30:70 the *cis*:*trans* ratio (entry 1b). The presence of a benzyloxy group induces a 30:70 *cis*:*trans* ratio that becomes 1:99 in the corresponding N-benzyloxyamine (entry 1d). An high stereoselectivity is observed when the OH is unprotected (entry 1e).

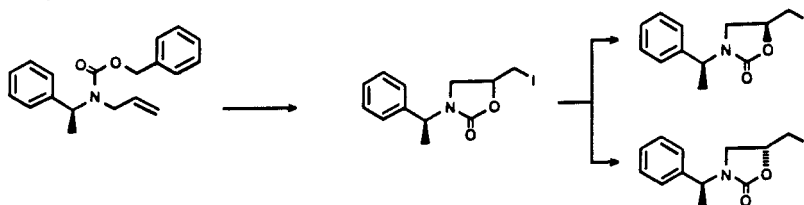
Since the capability of an amino group to bind a CO_2 molecule, the resin Amberlyst A 26 in the CO_3^{--} form has been further utilized in a new approach to aminodiols, as reported in the scheme (ref. 20).



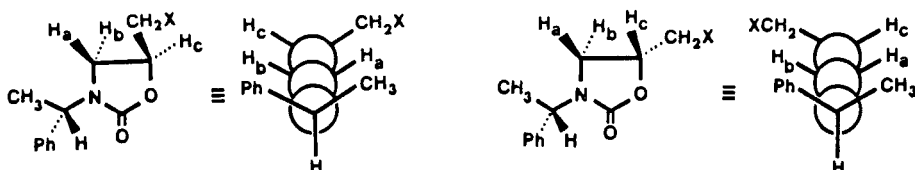
It is worth mentioning that in this process the intermediate formation of an oxazolidin-2-one causes the inversion of the starting stereogenic center bearing the OH group.

SYNTHESIS OF ENANTIOMERICALLY PURE AMINOALCOHOLS FROM THE RESOLVED 5-IODOMETHYLOXAZOLIDIN-2-ONES

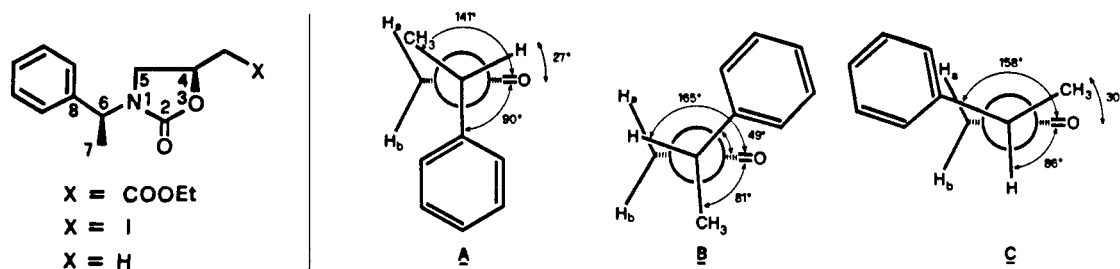
The iodocyclofunctionalization of allylic carbamates containing as chiral moiety the commercially available (S)-1-phenylethylamine allows to prepare in a 1:1 ratio diastereomeric mixtures of iodomethyloxazolidin-2-ones 1a and 1b, which can be easily separated by flash chromatography (ref. 24).



We have observed that the ^1H NMR chemical shifts of the hydrogens at C-4 of the heterocycle, strongly depend on the shielding of the phenyl group and on the substituent at C-5. On the basis of the ^1H NMR chemical shifts, we have proposed a conformational model for each diastereomer via an extended Newman projection, so that it is possible to attribute the configuration of the newly introduced stereogenic centers in this class of compounds by considering the shielding effect on H_a and H_b of the phenyl group and the CH_2X .

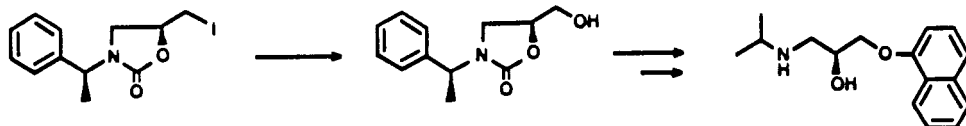


The conformational energies calculated by a molecular mechanics method for 5-substituted oxazolidin-2-ones confirm the ^1H NMR results (ref. 25). In fact the relative equilibrium abundance of available conformers is the main factor which needs to be considered to account the ^1H NMR spectra.

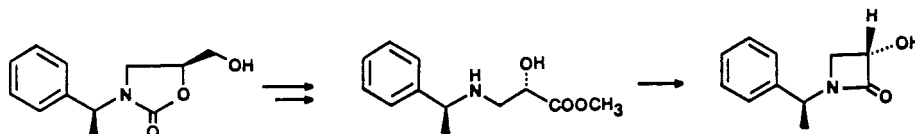


The calculated energies show that of the possible conformers A, B and C, A is the most stable, whereas B is scarcely populated. From the geometry of A, it results that H_b experiences the phenyl shielding more than H_a . By analysis of the contributions to the total energy we can mainly attribute the difference on energy to the increased long-range interaction between oxygen and hydrogen, phenyl or methyl, respectively. A further destabilizing interaction between the phenyl and the H_a is present in the conformation C, so this structure gets the top of the energetic profile.

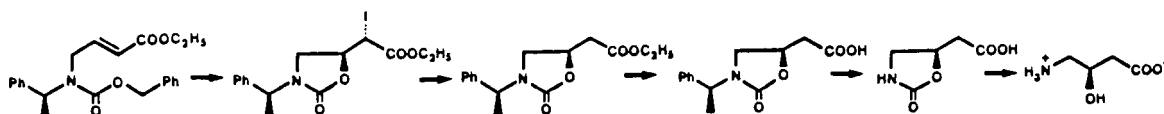
Through simple steps, the synthesis of (S)-(-)-propranolol and (R)-(+)-propranolol has been accomplished. In the Scheme are reported the main steps of the synthesis of (S)-(-)-propranolol starting from the 1*S*,5*S*-oxazolidin-2-one (ref. 24).



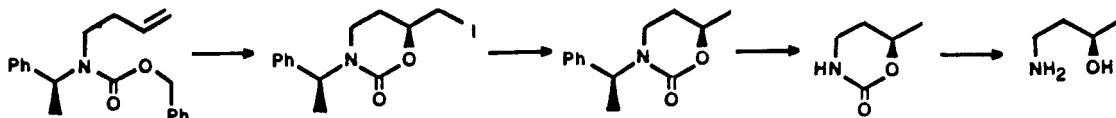
A *N*-substituted 5-hydroxymethyloxazolidin-2-one has been further utilized as the key intermediate for the synthesis of a β -lactam ring (ref. 26).



A facile preparation of the biologically active (R)- and (S)-4-amino-3-hydroxybutanoic acid (GABOB) is reported in the following scheme (ref. 25).

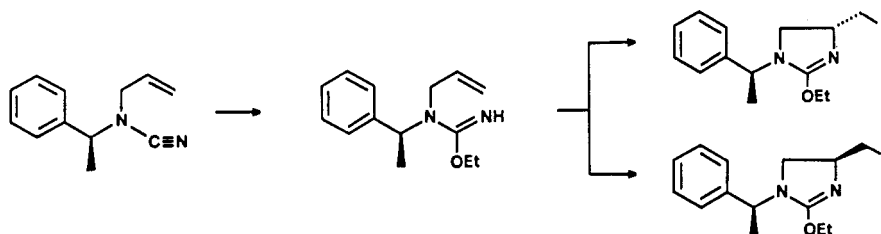


The cleavage of (1*S*,5*S*,*R*)-3-(1'-phenyleth-1'-yl)iodooxazolidin-2-ones represents a simple route to the synthesis of enantiomerically pure 1-amino-2-alcohols, while 1-amino-3-alcohols have been obtained via perihydro-1,3-oxazin-2-ones (ref. 27).

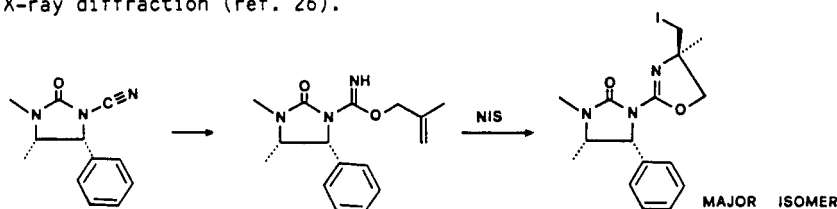


On comparison of ^1H NMR and ^{13}C NMR spectra of the diastereomers, we have elaborated a method to assign the absolute configuration of the newly introduced stereogenic center. Another useful application of (S)-1-phenylethylamine is the preparation of imidazolines starting materials for vicinal diamines.

The imidates obtained by addition of ethanol to the chiral cyanamide is cyclized to an easily separable diastereomeric mixture of heterocycles (ref. 26).



In our approach to the enantiomerically pure 2- or 3-aminoalcohols, we have exploited the possibility to promote the cyclization of imidates bonded to a sterically crowded chiral auxiliary, in order to improve the diastereomeric ratio of the final products. Starting from the anion of (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one (ref. 28), the corresponding nitrile is obtained by treating with BrCN in THF at low temperature. Following the standard procedure (ref. 10), the imidates are obtained in very good yield and successively cyclized with NIS in CHCl_3 . The diastereomeric mixtures, determined by ^{13}C NMR, can be easily separated by flash chromatography and the absolute configuration assigned in few cases by X-ray diffraction (ref. 26).



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