FACOLTA' DI SCIENZE MATEMATICHE, FISICHE E NATURALI.

Scuola di Dottorato in Scienze Chimiche

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*Curriculum Sintesi e Reattività*

# Regio- and stereocontrolled elaborations of 2-substituted epoxides and aziridines: towards the synthesis of differently functionalized fragments.

Tutor: Giuliana Righi

Dottoranda: Ilaria Tirotta

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# Chapter 1. Introduction.

During my three years of PhD I've focused my attention on the reactivity of functionalised epoxides and aziridines (Fig. 1), particularly on epoxy and aziridino esters (type **A**), alcohols (type **B**) and vinyl compounds (type **C**).

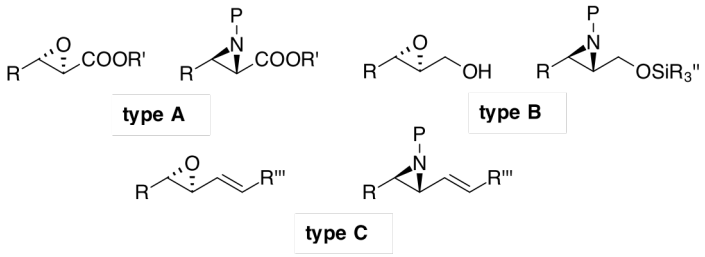


**Fig. 1 Substrates of choice.**

Epoxides and aziridines are strained three-membered heterocycles that can be found in many natural or biologically active compounds and represent useful tools in organic synthesis. Their synthetic utility lies in the broad range of nucleophiles with which they can be ring-opened in a stereo- and regiocontrolled fashion. Moreover 1,2-difunctionalised derivatives represent common motifs in many organic molecules of interest[1].

Their importance in organic synthesis resulted in an increased interest in their preparation and many methods have been developed to date. Particularly interesting is the possibility to obtain these compounds in both their enantiomerically pure forms since their biological activity, and that of their derivatives, is often linked to their optical activity.

In this chapter is reported a brief account of the most widely used methods for the asymmetric synthesis of these compounds and an overview of their reactivity and usefulness in the synthesis of biologically active molecules. With no intention to be fully comprehensive of the enormous literature on the subject, the reader is redirect to the articles and books cited and all references therein reported.

[1] *Aziridines and Epoxides in Organic Synthesis*. Yudin, A. K.; Weinheim 2006 WILEY-VCH Verlag GmbH & Co. KGaA,

# 1. Asymmetric synthesis of epoxides.

Generally epoxides are prepared through olefins oxidation, this is especially true for enantioselective syntheses. Several methodologies have been reported but only few of them are of general value and lead to both enantiomers with good enantiomeric excesses and yields. Two of the most important methodologies are herein presented.

## *1.1. Sharpless asymmetric epoxidation.*

The Sharpless asymmetric epoxidation (AE) procedure, firstly reported in 1980[2], uses *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant, a tartrate as the chiral auxiliary and $Ti(O\text{-}iPr)_4$ as the catalyst (Fig. 2); it requires low temperatures and an inert atmosphere. This methodology requires a pre-coordination of the substrate to the catalyst; hence allylic alcohols are the only suitable substrates. Nevertheless this asymmetric transformation is easily accessible and performable, highly predictable in its outcome, and applicable to a wide range of substrates.

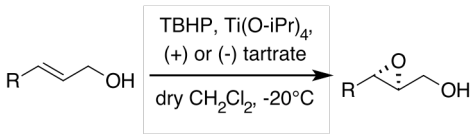


**Fig. 2 Sharpless asymmetric epoxidation.**

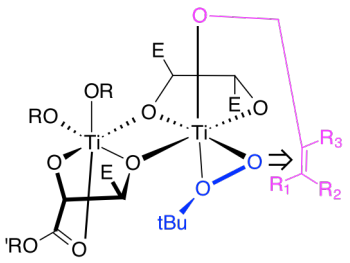


**Fig. 3 Coordination complex between titanium, tartrate, TBHP and olefin.**

The reason for its efficiency lies in the strong associative interactions occurring between the substrate and the catalyst (Fig. 3)[3]. The titanium coordinates the tartrate and the oxidant, prior to the addition of the substrate. This coordination activates the oxidant and facilitates the oxygen transfer. The hydroxyl moiety on the substrate coordinates to the same titanium centre therefore the double bond is activated and close enough for intramolecular oxygen delivery, thus leading to complete regioselectivity in substrates containing several double bonds. As for the enantioselectivity, it is guaranteed by the chiral auxiliary and its coordination to the titanium.

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[2] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*., **1980**, *102*, 5974-5976.

[3] a) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.,* **1991**, *113*, 106-113; b) Finn, M. G.; Sharpless, K. B., *J. Am. Chem. Soc.*, **1991**, *113*, 113-126.

A general rule can predict the result: when (S,S)-(–)-tartrate is employed as chiral ligand the oxygen transfer will take place from "above", whereas using (R,R)-(+)-tartrate the transfer will take place from "below" (Fig. 4).

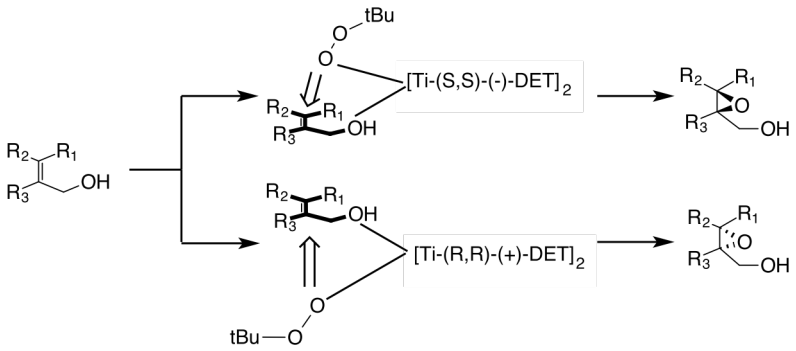


**Fig. 4 Enantioselectivity prediction in the sharpless epoxidation.**

The AE is a fairly reliable system that can be performed on differently functionalised substrates. However, the scope of the reaction is limited to allylic alcohols and it has a lack of efficiency when applied to *cis* disubstituted substrates.

*1.2. Jacobsen-Katsuki asymmetric epoxidation.*

The work of Jacobsen and Katsuki at the beginning of the 1990's[4] came as a breakthrough in the area of asymmetric epoxidation. It was already known that Mn-salen complexes could catalyse olefins epoxidation,[5] so it was a short step from these methodologies to the use of chiral complexes for enantioselective transformations.

The Mn-salen asymmetric epoxidation generally makes use of aq. NaOCl as the stoichiometric oxidant; reactions are run at room temperature in $CH_2Cl_2$ or $CH_3CN$ (Fig. 5). Unlike the Sharpless AE, this reaction does not require pre-coordination of the olefin to the catalyst thus widening the reaction scope to unfunctionalised olefins. Nevertheless the enantioselectivity is sensitive towards the substitution pattern of the substrate: the reaction is

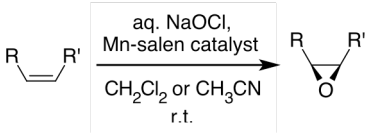


**Fig. 5 Mn-salen asymmetric epoxidation.**

[4] a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc*., **1990**, *112*, 2801; b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.,* **1990**, *31*,7345. c) Linker, T. *Angew. Chem. Int. Ed.* **1997**, 36, *19*, 2060-2062

[5] Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.,* **1986**, *108*, 2309-2320.

particularly efficient towards aryl or alkynyl substituted terminal, *cis* disubstituted, and trisubstituted olefins, whereas *trans* disubstituted olefins were epoxidised with low rates and enantiomeric excesses. As for the catalysts, many have been developed to date, with compounds **1-6** being the most widely used (Fig. 6).

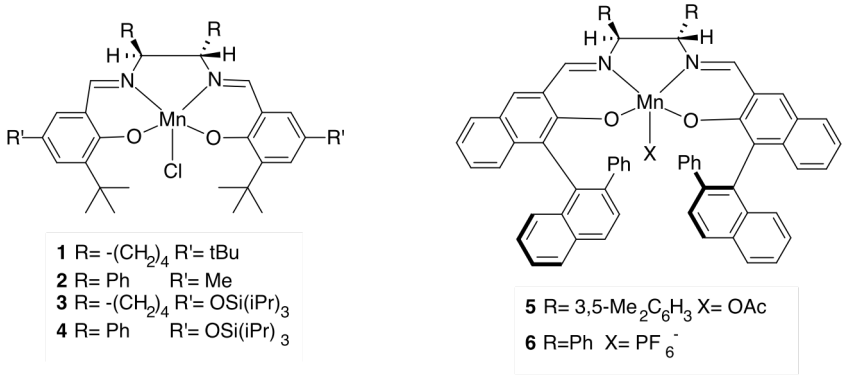


**Fig. 6 Most commonly used Mn-salen catalysts.**

The mechanism of the Mn-salen enantioselective epoxidation is still object of discussion[6]. The most commonly accepted hypothesis depicts a two-step mechanism: in the first step the oxygen is transferred from the terminal oxidant to the Mn(III)-salen catalyst and then, in the second step, from the transition metal to the olefin. However, recent theories suggest that the enantioselectivity is generated by the olefin approach from the side of the aromatic ring (energetically favoured).

Jacobsen epoxidation certainly fills the gap in the reaction scope left by Sharpless method, being able to successfully epoxidise unfunctionalised olefins.

## 2. Asymmetric synthesis of aziridines.

Optically active aziridines can be prepared in numerous ways and these reactions can be grouped into two broad classes: addition and cyclization processes.

Between the addition processes two major subclasses can be named: additions of nitrenes, or equivalents, to alkenes and addition of carbenes, or carbenoids, to imines. As for the cyclization

[6] a) Feichtinger, D.; Plattner, D. A. *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 1718-1719. b) Linde, C.; Koliaï, N.; Norrby, P. O.; Åkermark, B. *Chem. Eur. J.,* **2002**, *8*, 2568-75; c) Abashkin, Y. G.; Burt, S. K. *Org. Lett.,* **2004**, *6*, 59-62; d) Jacobsen, H.; Cavallo, L. *Chem. Eur. J.,* **2001**, *7,* 800-807.

processes, the ring-closure of amino alcohols or equivalents is a widely used and attractive methodology since the aziridine precursors are often available as single stereoisomers.

Some of the most commonly used methodologies are herein presented.

## 2.1. Synthesis from amino acids.

α-amino acids are useful precursors of chiral aziridines[7]; they can be easily reduced to amino alcohols and converted into the corresponding aziridines through a cyclization process using simple basic conditions. An example is offered in Fig. 7.

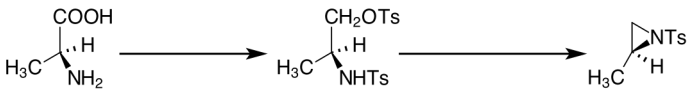


**Fig. 7 Synthesis of aziridines from (+)-alanine.**

A particular case is the synthesis of aziridine-2-carboxylates[8]. These compounds can be afforded by esterification of natural amino acids (serine or threonine), protection of the amine group followed by the conversion of the hydroxyl moiety as mesyl or tosyl derivative, which, at high temperatures, leads to the spontaneous cyclization gaining the corresponding aziridines in generally high yields (Fig. 8).

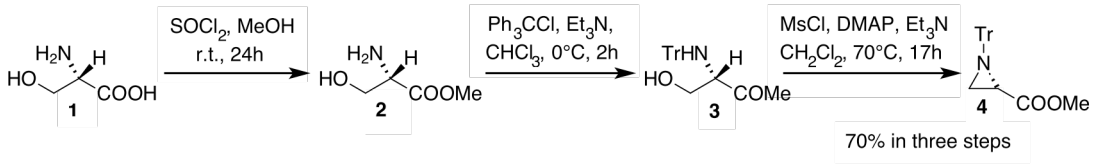


**Fig. 8 Synthesis of aziridine-2-carboxylates from L-serine.**

## 2.2. Synthesis from alkenes.

Addition of nitrogen to alkenes, in analogy to the epoxides syntheses by means of "active" oxygen donors, is not widely used since these compounds are often inert to aziridinating reagents.

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[7] Wipf, P.; Miller, C.P., *Tetrahedon Lett.,* **1992**, *33*, 6267

[8] Doores, K.J.; Davis, B.G.*; Chem. Comm.*, **2005**, 168-170

Some methodologies have been reported but their scope remains limited[9]. Better results have been achieved using diaziridines and oxaziridines as aziridination agents in analogy with epoxidation of alkenes by use of dioxiranes, but also in this case numerous problems related to the reaction scope and reliability still remain unsolved[10]. As a result of the relative inertness of the N-O or N-N bond, compared to the O-O one, enantioselective methodologies for the synthesis of optically active aziridines from alkenes are completely different from those developed for epoxides.

It is an example the asymmetric synthesis of aziridine-2-carboxylates from α,β-unsaturated esters [11]. The reaction makes use of [N-(p-toluenesulfonyl-l)imino]phenyliodinane (PhI=NTs) in the presence of catalytic amounts of Cu(l) salts, such as Cu(OTf) and $CuClO_4$, and a chiral ligand (Fig. 9). Generally dry benzene or acetonitrile are the solvents of choice and the reaction requires an inert atmosphere. Numerous chiral ligands have been developed to date, some examples are reported in Fig. 10.

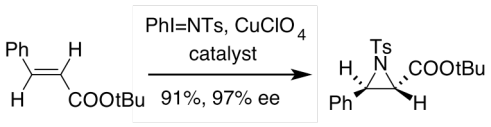


**Fig. 9 Asymmetric synthesis of aziridine-2-carboxylates from alkenes.**

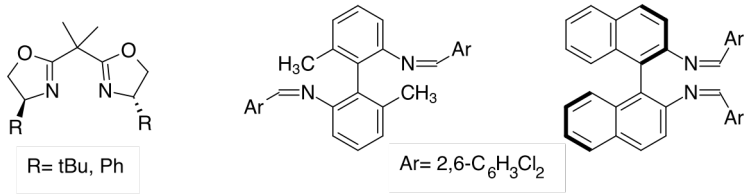


**Fig. 10 Some of the catalysts developed to date.**

Notwithstanding the reliability and complete enantioselectivity of the reaction, the scope is limited to aryl substituted substrates.

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[9] (a) J. E. G. Kemp in *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Ox- ford: Pergamon, 1991; Vol. 7, p. 467; (b) A. Padwa, S. S. Murphree, in *Progress in Heterocyclic Chemistry*, G. W. Gribble, T. L. Gilchrist, Eds.; Oxford: Pergamon Elsevier Science, 2000; Vol. 12, Chapter 4.1, p. 57.

[10] a) Hori, K.; Sugahira, H.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **1999**, *40*, 5207-5210; b) Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327-341.

[11] a) Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; *J. Am. Chem*, **1993**, 115, *12*, 5328-5329; b) Nishikori, H.; Katsuki, T; *Tetrahedon Lett.,* **1996**, *37*, 9245-9248

*2.3. Synthesis from optically active epoxides.*

Probably one of the most reliable, versatile and widely used methodologies for the synthesis of optically active aziridines is from enantiopure epoxides. Given the wide range of asymmetric epoxide syntheses available to date, the multistep preparation of aziridines from these substrates has been extensively investigated.

Numerous stereocontrolled ring-opening reactions of chiral epoxides using different nucleophilic azide sources have been developed to date. These methodologies provide optically active azido alcohols that can be converted into the corresponding enantiopure aziridines through phosphine-mediated ring-closures[12]. The reaction of hydroxyazides with trialkyl- or triarylphosphine gives diastereomeric oxazaphospholidines, which are rapidly formed but slowly converted into the corresponding aziridines upon heating in acetonitrile. The whole procedure is completely stereoselective: both asymmetric centres of the original epoxide are cleanly and predictably inverted. An example is reported in Fig. 11, where the epoxide ring is opened through a non-regioselective procedure using $NaN_3$ as the azide source and the azido alcohol obtained is converted into the corresponding aziridine using $Ph_3P$.

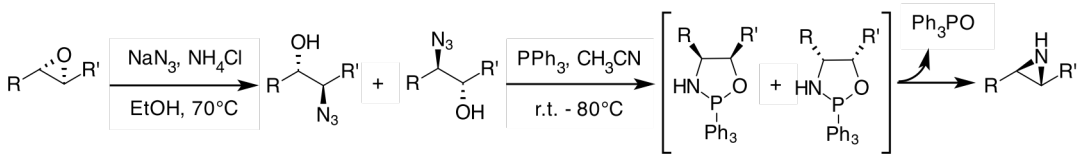



**Fig. 11 Asymmetric synthesis of aziridines from optically active epoxides.**

Probably the most important characteristic of this methodology is its broad scope: a wide range of variously functionalised epoxides can be easily converted into the corresponding enantiopure aziridines, generally in very high yields.

[12] Legters, J.; Thijs, L.; Zwanemburg, B., *Recle. Trav. Chim. Pays-Bas*, **1992**, *111*, 1-15

## 3. Reactivity

The reactivity of these three membered heterocyclic rings is often similar and linked to the ring functionalizations. Probably the most studied reactions are the ring-opening ones: as already noted these compounds can be opened in a regio- and stereocontrolled fashion by a wide range of nucleophiles, giving access to a vast array of naturally occurring fragments. Some examples are reported in Fig. 12.

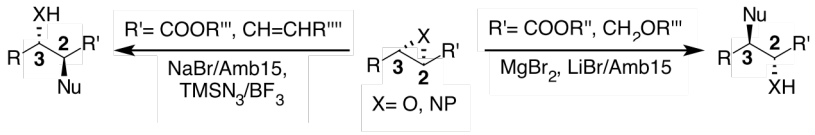



**Fig. 12 Lewis acid mediated ring-opening reactions of epoxides and aziridines.**

When R' is characterised by the presence of an oxygen adjacent to the ring, it is possible to stereo- and regioselectively introduce a bromine in the C-3 position exploiting the chelation ability of metals like Mg or Li. When instead R' is an electron withdrawing group, it is possible to exploit the activation of the C-2 position.

Amongst all variously functionalised epoxides and aziridines, vinyl compounds strike for their peculiar reactivity. Their ambident electrophilic nature makes much of their chemistry revolve around the regio- and stereocontrol of nucleophilic addition reactions.

Nucleophilic addition can take place through SN2' (route a), which is usually favoured using soft nucleophiles, and SN2 attack (route b), usually favoured by hard nucleophiles (Fig. 13). The vinyl moiety functions as a regiochemical-directing element activating the ring, therefore attack at C-4 (route c) is not normally observed.

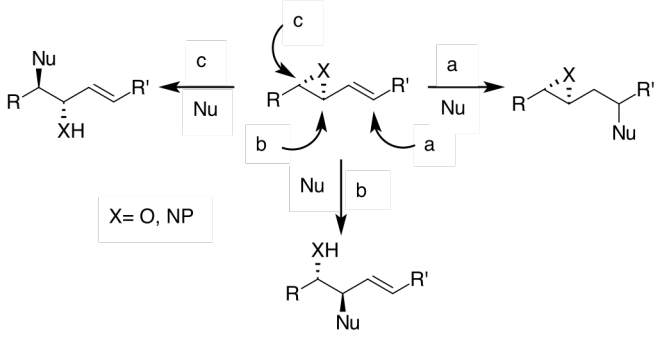
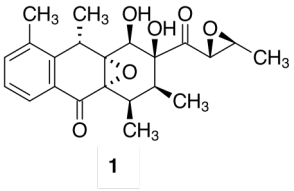



**Fig. 13 Possible routes for the nucleophilic additions to vinyl compounds.**

## 4. Epoxides and aziridines occurrence in natural products.

Epoxides can be found in a wide range of natural products and often exert a key role in the activity of these compounds. Their ring strain can impart rigidity to the molecular structure; their role as alkylating agents can confer cytotoxicity and, thanks to their high reactivity, they can serve as reactive intermediates in complex synthetic cascades. A few examples are herein listed.

- **Mensacarcin**[13] (**1**) (Fig. 14) was isolated in 1998 by Arnold and co-workers from the culture broth of *Streptomyces sp. Gö C4/4*. This anthracene derivative has anticancer potency and represents a rather unique compound containing nine stereogenic centres and two epoxide moieties. The epoxide-containing side chain has been shown to act as the main pharmacophore: a reductive opening of this moiety led to a dramatic decrease of the cytotoxicity.



1

**Fig. 14 Natural product mensacarcin.**

- **Fumagillin**[14] (**2**) (Fig. 15), isolated in 1949 by Elbe and Hanson from the microbial organism *Aspergillus fumigatus*, is a potent, selective inhibitor of angiogenesis[15], the formation of new blood vessels from pre-existing vasculature, which has been implicated in the pathogenesis of several human diseases. Similar activity has been found in **ovalicin**[16] (**3**), isolated from *Sporothrix sp. FO-4649* by Omura, and **RK95113**[17] (**4**), isolated from *Aspergillus fumigatus var. fumigatus sp.* (Fig. 16).

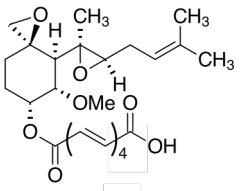


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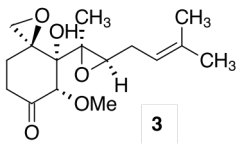
**Fig. 15 Natural product fumagilin.**



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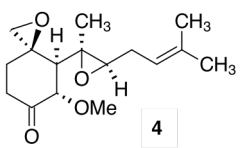

4

**Fig. 16 Natural products ovolacin (3) and RK95113 (4)**

[13] Tietze, L. F.; Gericke, K. M.; Schuberth, I. *Eur. J. Org. Chem.* **2007**, *27*, 4563-4577

[14] a) Hanson, F. R.; Elbe, T. E. *J. Bacteriol.* **1949**, *58*, 527; b) Hanson, F. R.; Elbe, T. E. *Antibiot. Chemother*. **1951**, *1*, 54.

[15] a) Ingber, D.; Fujita, T.; Kishimoto, S.; Sudo, K.; Kanamaru, T.; Brem, H.; Folkman, J. *Nature* **1990**, *348*, 555; b) Kwon, J.; Jeong, H.; Kang, K.; Hang, Y.; Bae, K.; Choi, J.; Lee, U.; Son, K.; Kwon, B. *Antibiotics* **2000**, *53*, 799.

[16] Sigg, H. P.; Weber, H. P. *Helv. Chim. Acta* **1968**, *51*, 1395

[17] Asami, Y.; Kakeya, H.; Okada, G.; Toi, M.; Osada, H. *J. Antibiot.* **2006**, *59*, 724.

- **Urechitol A**[18] **(5)** (Fig. 17) was isolated by Pena-Rodríguez and co-workers from the methanolic root extract *of Pentalinon andrieuxii*, a plant commonly used in Yucatecan traditional medicine for the treatment of cutaneous eruptions derived from leishmaniasis, an infectious disease caused by protozoan parasites of the Leishmania genus.

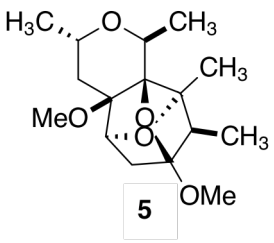


**Fig. 17 Natural product urechitol A.**

Unlike the wide range of epoxide-containing natural product, aziridines can be found only in few molecules known to date. The first to be discovered were the mitomycin antitumor antibiotics, and several others have been isolated since. In those compounds whose mode of action has been extensively studied, the electrophilic nature of the aziridine ring has been shown to play a key role in the molecular mechanism.

- **Mitomycins A**[19] **(6)** and **B**[20] **(7)** (Fig. 18) were isolated by Hata *et al.* from *Streptomyces caespitosus* and were found to have potent antibiotic and antitumor activity[21]. Few years later **mitomycin C**[22] **(8)** was isolated from the same organism and it was found to have antitumor activity. The key aspects of the cytotoxicity of the mitomycins are the interstrand crosslinks that these molecules form in DNA[23].

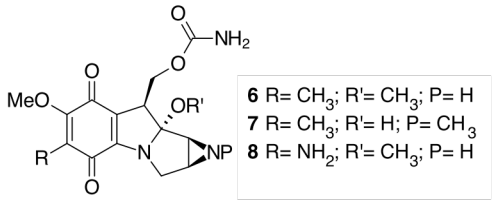


**Fig. 18 Natural products mitomycin A (6), B (7), C (8).**

[18] Yam-Puc, A.; Escalante-Erosa, F.; Pech-López, M.; Chan-Bacab, M. J.; Arunachalampillai, A.; Wendt, O. F.; Sterner, O.; Pena-Rodríguez, L. M. *J. Nat. Prod.* **2009**, *72*, 745–748.

[19] Hata, T.; Sano, Y.; Sugawara, R.; Matsumae, A.; Kanomori, K.; Shima, T.; Hoshi, T. *J. Antibiot.* **1956**, *9*, 141–146.

[20] Hata, T.; Sugawara, R. *J. Antibiot*. **1956**, *9*, 147–151.

[21] Henderson, I.C. *Oncology* **1991**, *1*, 1–83.

[22] Hata, T.; Sugawara, R. *J. Antibiot*. **1956**, *9*, 147–151.

[23] Iyer, V. N.; Szybalski, W. *Proc. Natl. Acad. Sci. U.S.A.* **1963**, *50*, 355–362

- **Azinomycins**[24] **A** and **B** (**9** and **10**; Fig. 19) were isolated from *Streptomyces griseofuscus* and were found to have potent in vitro cytotoxicity and to display significant in vivo antitumor activity, as well as antibiotic activity against both Gram positive and Gram negative bacteria[25].

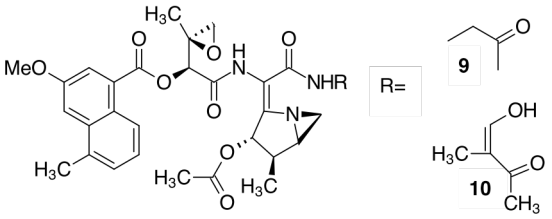


**Fig. 19 Natural products azinomycins A (9) and B (10).**

- **Azicemicins**[26] **A** (**11**) and **B** (**12**) (Fig. 20), were isolated from a species of *Amycolatopsis* related to *Amycolatopsis sulphurea*, and displayed moderate growth inhibition of Gram-positive bacteria and mycobacteria.

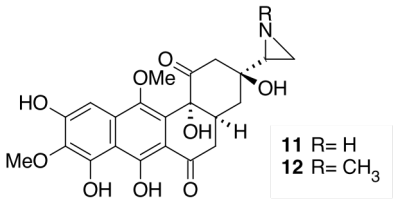


**Fig. 20 Natural products azicemicins A (11) and B (12).**

## 5. Optically active epoxides and aziridines as tools in the asymmetric synthesis of biologically active molecules.

As explained before, epoxides and aziridines are characterised by a broad reactivity that confer to these compounds high versatility and usefulness in organic synthesis. To date, many synthetic strategies that make use of either one of these substrates as key intermediates have been reported. A list of some of these syntheses is herein reported.

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[24] Hodgkinson, T. J.; Shipman, M. *Tetrahedron* **2001**, *57*, 4467–4488.

[25] Nagaoka, K.; Matsumoto, M.; Onoo, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527–1532; b) Ishizeki, S.; Ohtsuka, M.; Irinoda, K.; Kukita, K.I.; Nagaoka, K.; Nakashima, T. *J. Antibiot.* **1987**, *40*, 60–65.

[26] Tsuchida, T.; Iinuma, H. *J. Antibiot.* **1993**, *46*, 1772–1773; b) Tsuchida, T.; Iinuma, H.; Kinoshita, N.; Ikeda, T.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 217–221; c) Tsuchida, T.; Sawa, R.; Takahashi, Y.; Iinuma, H.; Sawa, T.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1148–1152.

- **Piliferolide**[27] **A** and **C** (Fig. 21) were isolated by Ayer and Khan from *Ophiostoma piliferum*, a blue strain fungus known to cause staining of aspen logs and chips.

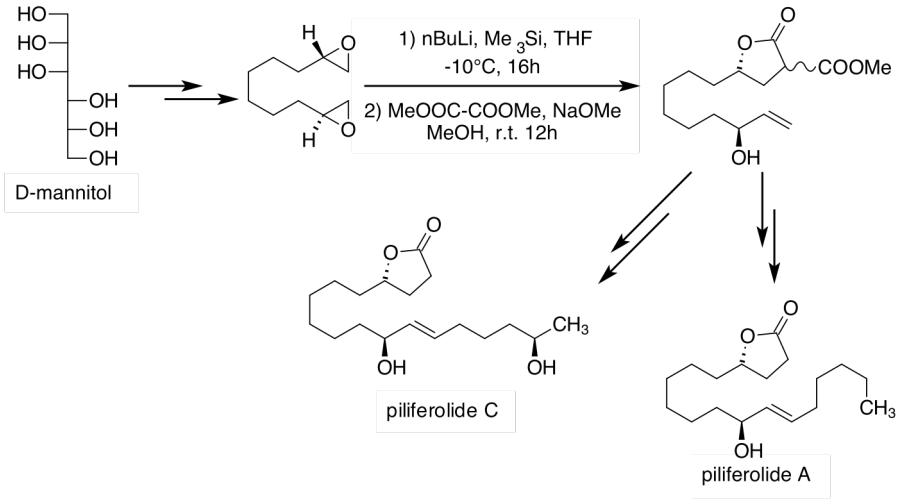



**Fig. 21 Synthesis of piliferolide A and C.**

- **Rapamycin**[28] (Fig. 22) was isolated from fungus *Streptomyces hygroscopicus* by Vozina and co-workers. Initially reported as an antifungal agent, ten years later the discovery of immunosuppressive properties of the related macrolide FK506 led to further studies.

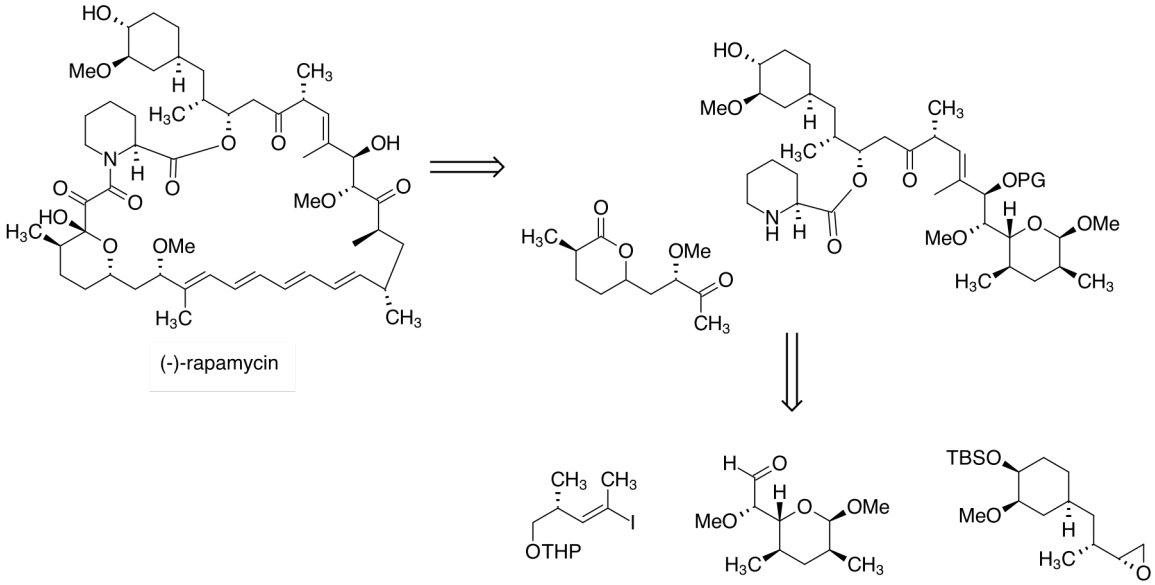



**Fig. 22 Synthesis of rapamycin.**

[27] Guan, K. *et al. Tetrahedron* **2011**, 67, *5*, 860-865

[28] Ley *et al. Chem. Eur. J.* **2009**, 15, *12*, 2874-2914

- **Trichodermamides**[29] **A** and **B** (Fig. 23), isolated as secondary metabolites from marine-derived fungal strains, possess a rare oxazine moiety incorporated into a more complex ring system. Among them, trichodermamide B (**5**) showed significant in vitro cytotoxicity against HCT-116 colon carcinoma ($IC_{50}$ 0.32 μg/mL).

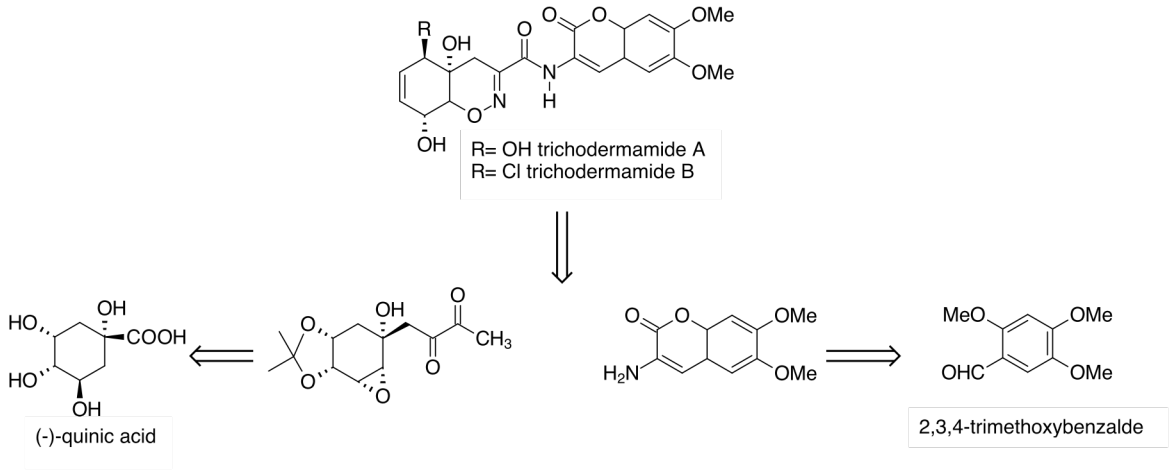



**Fig. 23 Synthesis of trichodermamide A and B.**

- **Chlorodysinosin**[30] **A** (Fig. 24), isolated from the *Dysideidae* family of marine sponges, is characterised by a substituted 2-carboxyperhydroindole core residue and has shown potent inhibitory activity against thrombin, trypsin, and factor VIIa.

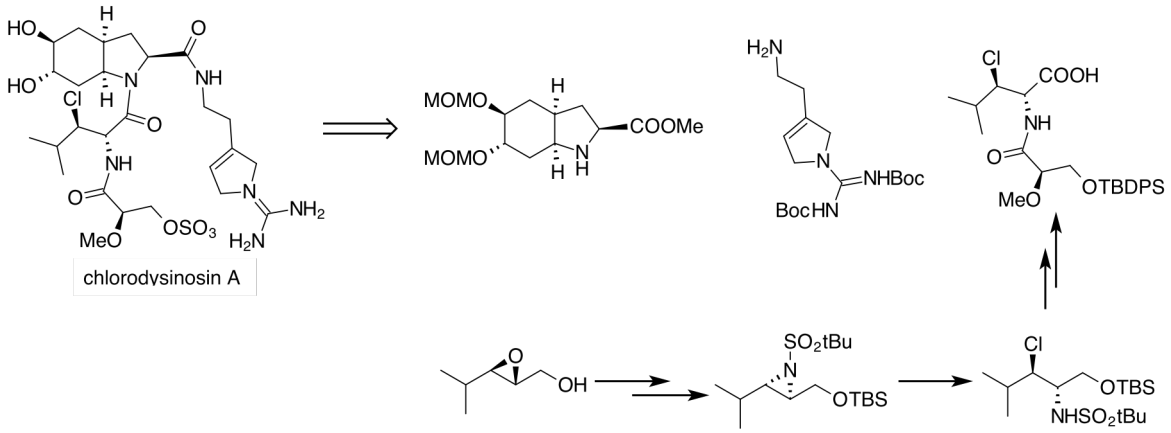



**Fig. 24 Synthesis of chlorodysinosin A.**

[29] Wan, X.; Joullie, M.M. *J. Am. Chem. Soc.* **2008**, 130, *51*, 17236-17237

[30] Hanessian *et al. J. Am. Chem. Soc.* **2006**, 128, *32*, 10491-10495

- **Trunkamide A**[31] (Fig. 25), was isolated from the colonial ascidian *Lissoclinum sp.* and has shown promising antitumor activity. It is characterised by the presence of serine/threonine residues, modified as reverse prenyl ethers.

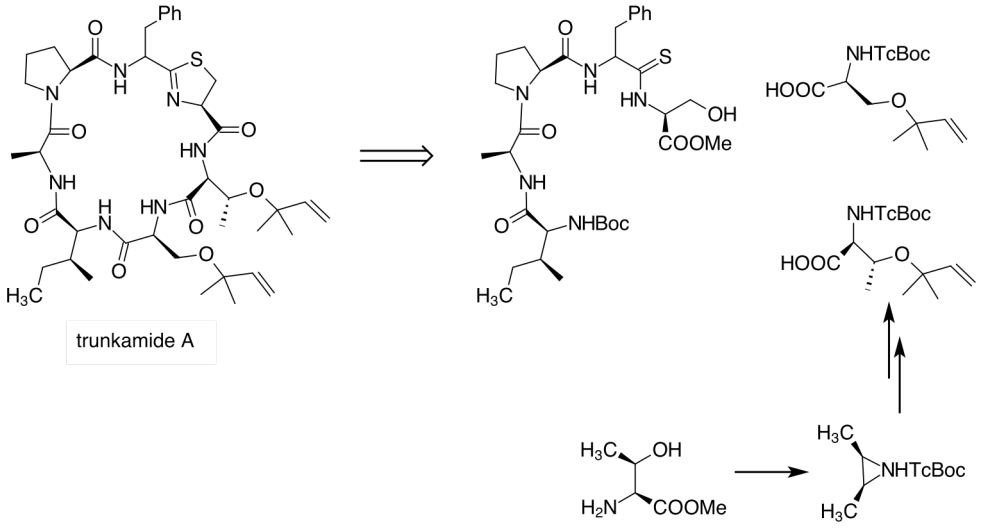



**Fig. 25 Synthesis of trunkamide A.**

- **(S)-Quisqualic acid**[32] (Fig. 26) is the active ingredient of the ancient Chinese drug Shihchuntze, an anthelmintic made from seeds of *Quisqualis indica.* It is the only known compound to act as an agonist at multiple excitatory amino acid receptor subtypes in the central nervous system.

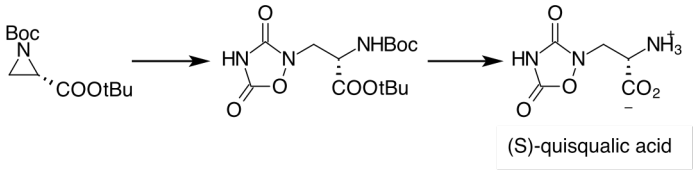



**Fig. 26 Synthesis of (S)-quisquali acid.**

[31] Wipf , P; Uto, Y. *J. Org. Chem.* **2000**, 65, *4*, 1037-1049

[32] Farthing *et al. Tetrahedron Lett.* **1996**, 37, *29*, 5225-5226

# Chapter 2. Preparation of tryptophan derivatives from aziridine-2-carboxylates[1].

## 1. Introduction.

During my second year of PhD I spent six months in Professor Craig Hutton's lab, at the Bio21 Institute, University of Melbourne, Melbourne, Australia. His group has been focused for many years on the total synthesis of peptide-based natural molecules[2], using aminoacids as key intermediates. Modified tryptophan derivatives are interesting molecules since they are found in many natural compounds (Fig. 1).

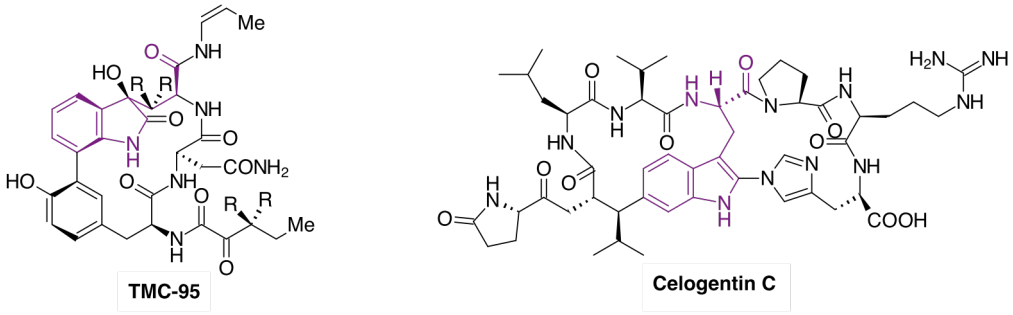



**Fig. 1 Tryptophan derivatives in natural molecules.**

A reasonably efficient method for the preparation of optically pure tryptophan derivatives is through reaction of indoles with optically active aziridines. This coupling, catalysed by Lewis acids, was firstly reported by Kozikowski[3] in 1989 and has since been improved upon[4]. However very low yields and reproducibility still remain unsolved problems of this reaction. As can be gathered from Table 1 and 2 the yield of the tryptophan derivative has been shown to be dependent on the nature of the Lewis acid, though no explanation for this effect has been forthcoming. Also a lack of regioselectivity has been reported in the literature and can be explained by the high reactivity of the

[1] Tirotta, I.; Eakins, J.; Hutton, C.A., *manuscript in preparation*

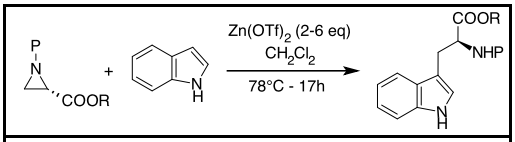
[2] a) Yuen, A. K. L.; Hutton, C. A.; *Nat. Prod. Comm.*, **2006**, *1*, 907–919; b) Li, B. T. Y.; White, J. M.; Hutton, C. A. *Aust. J. Chem.*, **2010**, *63*, 438–444; c) Yuen, A. K. L.; Jolliffe, K. A.; Hutton, C. A. *Aust. J. Chem.*, **2006**, *59*, 819–826

[3] Kozikowski, A.P.; Sato, K., *Tetrahedron Lett.*, **1989**, *30*, 4073-4076

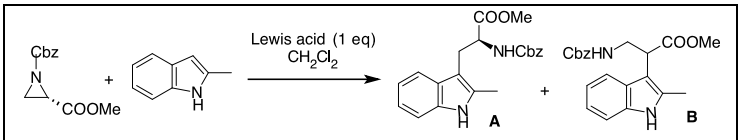
[4] a) Bennani, Y.L. *et al., Synlett,* **1998**, 754-756; b) Nishikawa, T.; *et al., Synthesis*, **2002**, *12*, 1658-1662

C-2 position and the nature of the Lewis acid: when the Lewis acid is not able to efficiently coordinate the N and the carbonyl group the nucleophilic attack at the C-2 position is favoured. As reported by Nishikawa, the optimal conditions seem to be $Sc(OCl_4)_3$ as the Lewis acid, at 0°C.

**Table 1 and 2. Aziridine-indole coupling reactions catalysed by different Lewis acids. (Kozikowski, Nishikawa).**

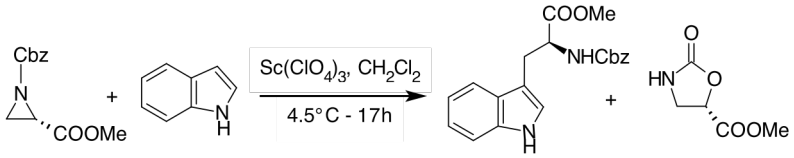



| P | R | Yield (%) |
|---|---|---|
| Cbz | Me | 27 |
| Cbz | Bn | 33 |
| Boc | Me | 30 |




| Lewis acid | T (°C) | Time (h) | Yield (%) | A:B |
|---|---|---|---|---|
| $Sc(OTf)_3$ | 0 | 20 | 68 | 60:40 |
| $Zn(OTf)_2$ | 80 | 19 | 69 | 90:10 |
| $Yb(OTf)_3$ | r.t. | 50 | 57 | 100:0 |
| $Sc(ClO_4)_3$ | 0 | 13 | 70 | 90:10 |

Our first attempt at this reaction led to a rather interesting result (Scheme 1): when a N-benzyloxycarbonyl (N-Cbz) protected aziridine-2-methyl carboxylate was reacted with 1 eq. of $Sc(ClO_4)_3$ and 2 eq. of indole, no lack of regioselectivity was observed and, along with the desired product in very low yield (20%), a large amount of an oxazolidinone was recovered (80%).




**Scheme 1 Cbz protected aziridine-indole coupling, $Sc(ClO_4)_3$ catalysed.**

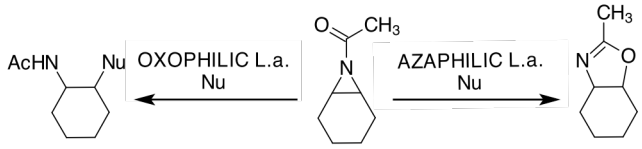



**Fig. 2 "Ring opening" process vs "ring expansion" process in a nucleophilic attack, Lewis acid mediated.**

This could be explained by data already reported in the literature. It is known[5] that N-acyl aziridines can undergo either a '*ring opening*' or a '*ring expansion*' process in the presence of a Lewis acid (Fig. 2). The ratio between the two possible products seems to be dependent on the nature of the Lewis acid: an oxophilic metal would favour the ring opening process whereas an azaphilic one would favour the ring expansion process.

[5] Lectka, T.; *et. al*., *J. Org. Chem*., **1998**, *63*, 4568-4569

Moreover carbamate protected aziridines are known[6] to rearrange into oxazolidinones in the presence of a chelating metal (Fig. 3). For these reasons it seemed particularly interesting to thoroughly study the reaction in order to rationalize the role that the Lewis acid and the aziridine protective group play in it and to identify the best conditions for the synthesis of the tryptophan derivatives.

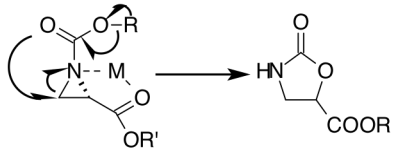
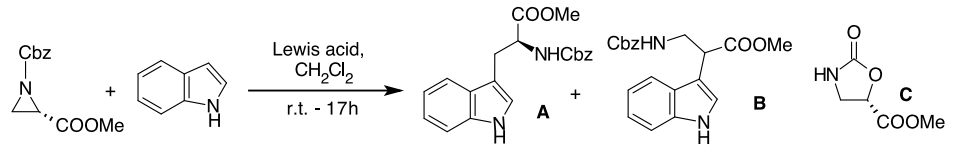



**Fig. 3 From aziridine N-carboxylate to oxazolidinone.**

## 2. Results and discussion.

First of all, a preliminary screening of a vast array of Lewis acids was carried out using the N-Cbz protected aziridine as the substrate. The results are summarized in Table 3.

**Table 3 N-Cbz protected aziridine-indole coupling, catalysed by various Lewis acids.**




| Entry | Lewis acid | Aziridine (%) | A (%) | B (%) | C (%) |
|---|---|---|---|---|---|
| **1** | $Sc(OCl_4)_3$ | - | 20 | - | 80 |
| **2** | $Bi(OTf)_3$ | - | 22 | - | 78 |
| **3** | $Zn(OTf)_3$ | 100 | - | - | - |
| **4** | $Yb(OTf)_3$ | 100 | - | - | - |
| **5** | $Hf(OTf)_3$ | - | - | - | 100 |
| **6** | $Cu(OTf)_2$ | - | 50 | - | 50 |
| **7** | $Sc(OTf)_3$ | - | 66 | 33 | 1 |

Using $Zn(OTf)_3$ and $Yb(OTf)_3$ there was no conversion of the substrate (Entries 3 and 4); using $Bi(OTf)_3$ and $Sc(OCl_4)_3$ the tryptophan was recovered only in a 20% yield (Entries 1 and 2). The behaviour of the last three Lewis acids seemed to be particularly interesting: $Hf(OTf)_3$ proved to be

[6] Tomasini, C.; Vecchione, A., *Org. Letters*, **1999**, *1*, 2153-2156

the more azaphilic Lewis acid in hands, leading only to the oxazolidinone formation (Entry 5); using $Sc(OTf)_3$, the oxazolidinone was recovered only in 1% yield, indicating that this was the most oxophilic Lewis acid between the ones screened, although is important to notice that there was a lack of regioselectivity, obtaining a 33% of the regioisomer (Entry 7); finally $Cu(OTf)_2$ showed an in-between nature, leading to oxazolidinone and tryptophan derivative in a 1:1 ratio (Entry 6). Given these results, the study was carried on using only the last three Lewis acids examined.

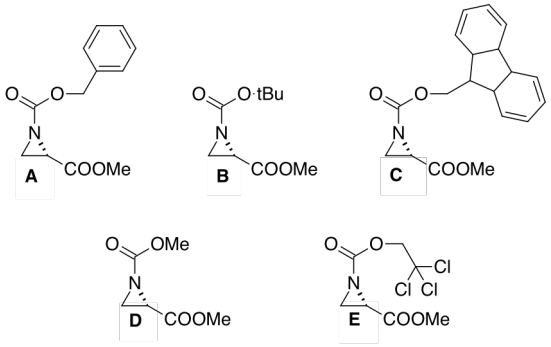
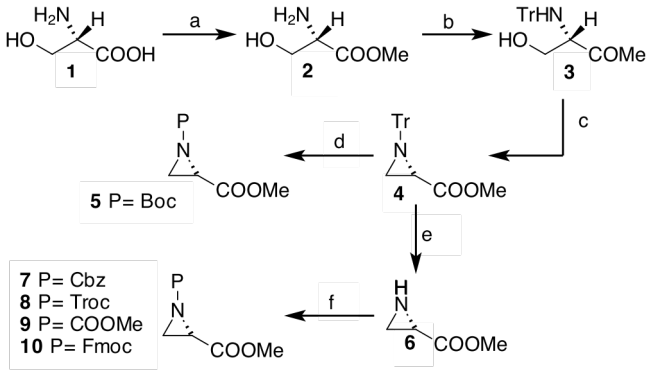



**Fig. 4 Protective groups of choice.**

Another aspect of interest was the role of the aziridine protective group: a group that could easily form a carbocation should favour the formation of the oxazolidinone against the tryptophan. Five different protective groups were chosen (Fig. 4): benzyloxycarbonyl, *tert*-butoxycarbonyl (Boc) and 9-fluorenylmethyloxycarbonyl (Fmoc) groups, which can easily form carbocations, promoting the oxazolidinone formation and methyloxycarbonyl and 2,2,2-trichloroethoxycarbonyl (Troc) groups, which should favour the tryptophan formation.

All the substrates were prepared starting from L-serine in fairly few steps and good yields, following an already reported procedure [7] (Scheme 2). L-serine was methylated, protected as trityl amine and treated with mesyl chloride, $Et_3N$ and 4-(dimethylamino)pyridine (DMAP) at the reflux temperature to give the optically pure trityl protected aziridine-2-methylcarboxylate **4** with a 70% yield after 3 steps. Aziridine **4** was then converted into the differently protected derivatives (compounds **5**, **7**-**10**) in one or two steps, depending on the protective group, generally with good yields (70-85%).

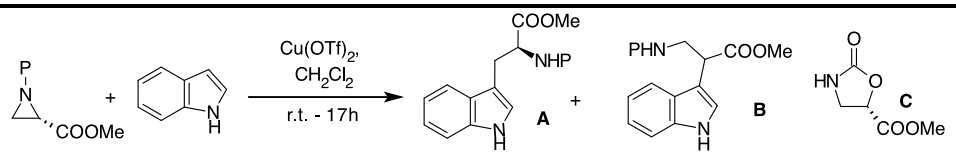



**Scheme 2** *Reagents and conditions*: a) $SOCl_2$, MeOH, r.t., 24h; b) $Ph_3CCl$, $Et_3N$, $CHCl_3$, 0°C, 2h; c) MsCl, DMAP, $Et_3N$, $CHCl_3$, r.t.-70°C, 17h (70% in three steps); d) TFA, $Et_3N$, $Boc_2O$, MeOH, $CH_2Cl_2$ 0°C-r.t., 19h (85%); e) TFA, $CH_2Cl_2$, MeOH, 0°C, 2h; f) chloroformate, $NaHCO_3$, $H_2O$, acetone, r.t., 20h (70-80% in two steps)

[7] a) Doores, K.J.; Davis, B.G.*; Chem. Comm.*, **2005**, 168-170; b) Kato, S.; *et al.*; *J. Chem. Soc. Perk. Trans.*, **1997**, 3219-3225; c) McKeever,B.; Pattenden, G.; *Tetrahedron*, **2003**, *59*, 2701-2712-; d) Lu, Z.; *et al.*; *J. Am. Chem. Soc.*, **2007**, *129*, 7185-7194

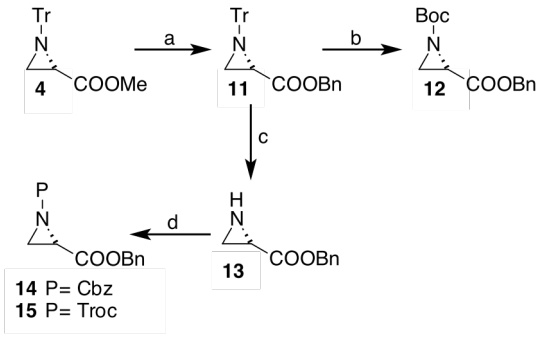
All the substrates were submitted to the coupling reaction using $Cu(OTf)_2$ as the Lewis acid, in order to have a preliminary idea of their behaviour. The results are summarized in table 4.

**Table 4 Screening of the different protective groups in the aziridine-indole coupling reaction, $Cu(OTf)_2$ catalysed.**




| Entry | P | A (%) | B (%) | C (%) |
|---|---|---|---|---|
| **1** | Cbz | 50 | - | 50 |
| **2** | Boc | 60 | - | 40 |
| **3** | Fmoc | | Inconclusive results | |
| **4** | COOMe | | Inconclusive results | |
| **5** | Troc | 100 | - | - |

All the protective groups showed the expected reactivity: Boc and Cbz led to a higher amount of oxazolidinone than that obtained with Troc. However Fmoc and COOMe gave inconclusive results, leading to complex reaction mixtures; for this reason these two groups were ruled out of the study.

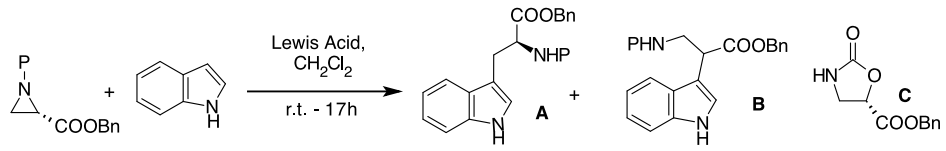



**Scheme 3** *Reagents and conditions*: Otera's catalyst, BnOH, toluene, 110°C, 17h (90%); b) TFA, $Et_3N$, $Boc_2O$, MeOH, $CH_2Cl_2$ 0°C-r.t., 19h (85%); c) TFA, $CH_2Cl_2$, MeOH, 0°C, 2h; d) chloroformate, $NaHCO_3$, $H_2O$, acetone, r.t., 20h (70-80% in two steps)

The products proved to be difficult to purify, therefore, in order to simplify the procedure, all the substrates were converted into the benzyl-ester derivatives so that it was possible to use HPLC. Using Otera's catalyst, aziridine **4** was converted into the benzyl ester derivative **11**, which was then converted into the differently protected aziridines **12**, **14** and **15** as described before (Scheme 3).

The aziridines obtained were then submitted to the coupling reactions and the results are summarised in Table 3. Even if the benzyl ester allowed an easier purification of the crude by HPLC, those substrates tent to be less stable thus leading to complex reaction mixtures in a couple of cases (see Entries 6 and 7). All the while, the expected behaviour for the Lewis acids and for the protective group was again confirmed.

**Table 5 Screening of different protective groups and Lewis acids in the aziridine-indole coupling reaction.**




| Entry | Lewis acid | P | A (%) | B (%) | C (%) |
|---|---|---|---|---|---|
| **1** | $Cu(OTf)_2$ | Cbz | 33 | - | 67 |
| **2** | $Hf(OTf)_3$ | Cbz | - | - | 100 |
| **3** | $Sc(OTf)_3$ | Cbz | 48 | 24 | 18 |
| **4** | $Cu(OTf)_2$ | Boc | 20 | - | 80 |
| **5** | $Hf(OTf)_3$ | Boc | - | - | 100 |
| **6** | $Sc(OTf)_3$ | Boc | Inconclusive results | | |
| **7** | $Cu(OTf)_2$ | Troc | Inconclusive results | | |
| **8** | $Hf(OTf)_3$ | Troc | - | - | 100 |
| **9** | $Sc(OTf)_3$ | Troc | 80 | 20 | - |

## 3. Conclusions.

From the data gathered in this work it is possible to conclude that in the coupling reaction between aziridine-2-carboxylates and indoles there are two competitive processes: “ring opening” VS “ring expansion” and both the Lewis acid and the aziridine protective group play a key role in favouring one over the other. Using an oxophilic Lewis acid (such as $Sc(OTf)_3$) the process favoured is the “ring opening” one, leading to the desired tryptophan derivative as the major product; whilst using an azaphilic Lewis acid (such as $Hf(OTf)_3$) it is possible to drive the reaction towards the ring expansion process, obtaining only oxazolidinone. Using a protective group that can easily form a carbocation (such as Boc) the oxazolidinone formation is favoured, whereas using Troc it is possible to eliminate it altogether. Combining these two aspects it is possible to identify the best reaction conditions in order to obtain the tryptophan derivative as the major product: the coupling reaction between N-Troc protected aziridines and indole, catalysed by $Sc(OTf)_3$ led to the desired product with a yield of 80-95%.

# 4. Experimental.

*4.1. General.*

$^{1}$H nmr spectra were recorded using a Varian Unity Inova 500 and spectra were recorded at 298 K unless stated otherwise. Residual solvent peaks were used as internal references for $^{1}$H nmr spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. $^{13}$C spectra were recorded using a Varian Unity Inova 500 and spectra were obtained at 298 K unless stated otherwise. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak; chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

Analytical HPLC was performed using a ChiralPak OD column (Diacel Chemical Industries Ltd), a waters U6K injector and a waters 510 pump; elution was monitored by a Waters 490E Programmable Multiwavelength Detector at λ 220 nm, 254 nm and 270 nm, and by a Waters R10 Differentia Refractometer.

IR spectra on a Perkin Elmer FT-IR spectrometer and were obtained from a thin film of the neat product. Absorption maxima are expressed in wavenumbers ($cm^{-1}$).

Mass spectra were recorded on a Finigan LTQ-FT, FT-ICR mass spectrometer (Bremen, Germany) and all MS are obtained by electrospray ionisation in the positive mode unless otherwise noted. Melting points were determined using a Reichert-Jung hot stage apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-1000 polarimeter at 589 nm with a cell path length of 1 cm; solution concentrations are reported in grams per 100 ml.

Toluene was distilled over sodium benzyl ketyl. Anhydrous THF, $Et_2O$ and $CH_2Cl_2$ were obtained from a solvent dispensing system designed by J. C. Meyer (Glass Contour) where the solvent was dried by passage through two packed columns of neutral alumina. Methanol was distilled from calcium hydride.

Powdered molecular sieves were purchased from Aldrich and activated with a microwave and allowed to cool under vacuum. Deuterated chloroform ($CDCl_3$) was base washed by passage

through a column of basic alumina ($Al_2O_3$). All other reagents and solvents were purified according to the methods of Perrin and Armarego.

Analytical thin layer chromatography was performed with Merck aluminium backed plates precoated with silica gel 60 F254 (0.2 mm), and visualisation was achieved by inspection under short-wave UV light followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)]. Flash chromatography was performed using Scharlau Kieselgel 60 (230-400 mesh) silica gel; eluting solvents reported as % v/v mixtures.

### *4.2. Synthesis of the substrates.*

#### *4.2.1. Synthesis of Methyl (2S)-1-trityl-2-aziridinecarboxylate (**4**):*

To a solution of L-serine (1 mmol, 105 mg) in 2 ml of dry methanol, under argon atmosphere and at 0°C, thionyl chloride (1.5 mmol, 0,1 ml) was added drop-wise and the mixture left stirring at room temperature for 24 hours. The reaction crude was diluted with 0.5 ml of chloroform and washed three times with water (1 ml) and subsequently brine (1 ml). The organic layer was concentrated in vacuo, the residue diluted with 1.25 ml of chloroform and cooled to 0°C. $Et_3N$ (2.4 mmol, 0.3 ml) and trityl chloride (1 mmol, 280 mg) were added portion-wise and the mixture left stirring at 0°C for one hour. The reaction mixture was washed several times with water and brine and the organic layer concentrated in vacuo to reduce the volume. To the solution of N-trityl-L-serine methyl ester in chloroform were subsequently added: $Et_3N$ (2,72 mmol, 0,4 ml), DMAP (0.1 mmol, 12 mg) and methanesulfonyl chloride (1.4, 160 mg) drop-wise, the mixture was left stirring at the reflux temperature for 17 hours and then cooled at room temperature and concentrated in vacuo to leave the crude product as a solid, which was recrystallized from ethanol to give **4** as a white crystal (250 mg, 70% yield in 3 steps): $^1$H NMR (500 MHz $CDCl_3$) δ: 7.54-7.49 (6H, m, $CH_{Ar}$), 7.31-7.27 (6H, m, $CH_{Ar}$), 7.25-7.21 (3H, m, $CH_{Ar}$), 3.77 (3H, s, $CH_3$), 2.27 (1H, dd, *J* 1.6, 2.7 Hz, C$\underline{H}_a$H$_b$-N), 1.91 (1H, dd, *J* 2.7, 6.2 Hz, C$\underline{H}$-N), 1.43 (1H, dd, *J* 1.6, 6.2 Hz, CH$_a\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 172.1, 143.7, 129.5, 127.8, 127.1, 74.5, 52.5, 31.8, 28.8.

All other experimental data were consistent with the ones reported in the literature[8].

#### *4.2.2. Synthesis of Benzyl (2S)-1-trityl-2-aziridinecarboxylate (**11**):*

[8] Kato, S.; et al.*; J. Chem. Soc. Perk. Trans.*, **1997**, 3219-3225

To a solution of Methyl (2S)-1-trityl-2-aziridinecarboxylate (**4**) (1 mmol, 357 mg) in 5 ml of toluene were added benzyl alcohol (10 mmol, 1,03 ml) and Otera's catalyst (0.1 mmol, 110 mg), the mixture was left stirring at the reflux temperature for 24 hours and then the solvent evaporated in vacuo to leave the crude product, which was purified by flash chromatography on silica gel (hexane/AcOEt 9:1) to give **11** as a colourless solid (377 mg, 90% yield): $^{1}$H NMR (500 MHz $CDCl_3$) δ: 7.54-7.49 (6H, m, $CH_{Ar}$), 7.41-7.34 (4H, m, $CH_{Ar}$), 7.25-7.21 (10H, m, $CH_{Ar}$), 5.22 (2H, dd, *J* 12.3, 24.1 Hz, $CH_2Ph$), 2.27 (1H, dd, *J* 1.6, 2.7 Hz, $C\underline{H}_aH_b$-N), 1.91 (1H, dd, *J* 2.7, 6.2 Hz, C<u>H</u>-N), 1.43 (1H, dd, *J* 1.6, 6.2 Hz, $CH_a\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 171.1, 143.7, 135.9, 129.5, 128.7, 128.5, 128.4, 127.8, 127.1, 74.5, 66.8, 31.8, 28.8

All other experimental data were consistent with the ones reported in the literature[9].

### *4.1.3. General procedure for the synthesis of N-Cbz, N-Troc, N-COOMe and N-Fmoc derivatives:*

To a solution of 1 mmol of the appropriate (2S)-1-trityl-2-aziridinecarboxylate (**4** or **10**) in 0.7 ml of methanol and 0.7 ml of chloroform at 0°C, trifluoroacetic acid (6.6 mmol, 0.5 ml) was added drop-wise. The mixture was left stirring at 0°C for two hours and then concentrated in vacuo at 5°C to leave a white precipitate, which was diluted with 1 ml of ice cold water. The suspension was filtrated and extracted with 0.5 ml of diethyl ether and the organic layer neutralized with $NaHCO_3$ at 5°C. To the aqueous solution were added: 0.5 ml of diethyl ether, $NaHCO_3$ (1.5 mmol, 126 mg) and the appropriate chloroformiate (0.9 mmol) drop-wise and the mixture left vigorously stirring for 2 hours. The layers were then separated and the organic one washed several times with brine, dried over $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was then purified by flash chromatography on silica gel (Pet. Spirit/AcOEt 9:1) to give the desired product (70-80% yield).

**Methyl (2S)-1-(N-benzyloxycarbonyl)aziridine-2-carboxylate (7)**: colourless oil (199 mg, 80% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 7.40-7.30 (5H, m, Ph), 5.15 (2H, dd, *J* 12.1, 13.5 Hz, $C\underline{H}_2Ph$), 3.77 (3H, s, $CH_3$), 3.11 (1H, dd, *J* 3.2, 5.4 Hz, $C\underline{H}_aH_b$-N), 2.6 (1H, dd, *J* 1.3, 3.2 Hz, C<u>H</u>-N), 2.48 (1H, dd, *J* 1.3, 5.4 Hz, $CH_a\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 160.9, 135.4, 128.7, 128.6, 127.8, 68.8, 52.9, 35.0, 31.6.

All other experimental data were consistent with the ones reported in the literature (ref. 8)

[9] Schäfer, A. *et al. Tetrahedron: Asymmetry* **2009**, 20, *6-8*, 902-909

**Methyl (2S)-1-(N-2,2,2-trichloroethoxycarbonyl)aziridine-2-carboxylate** (**8**): yellow oil (203 mg, 70% yield); $[\alpha]^{D}_{20}$ -28.96 (c 3.6 in chloroform); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 4.79 (1H, d, *J* 13.3, Hz, C$\underline{H}_a$H$_b$-Cl$_3$), 4.65 (1H, d, *J* 13.3, Hz, CH$_a$$\underline{H}_b$-Cl$_3$), 3.77 (3H, s, CH$_3$), 3.19 (1H, dd, *J* 3.2, 5.4 Hz, C$\underline{H}_a$H$_b$-N), 2.6 (1H, dd, *J* 1.2, 3.2 Hz, C$\underline{H}$-N), 2.56 (1H, dd, *J* 1.2, 5.4 Hz, CH$_a$$\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 159.9, 94.6, 75.9, 52.9, 35.0, 31.6

**Methyl (2S)-1-(N-methoxycarbonyl)aziridine-2-carboxylate** (**9**): pail yellow oil (121 mg, 70% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 3.73 (3H, s, CH$_3$), 3.69 (3H, s, CH$_3$), 3.05 (1H, dd, *J* 3.2, 5.5 Hz, C$\underline{H}_a$H$_b$-N), 2.5 (1H, dd, *J* 1.4, 3.2 Hz, C$\underline{H}$-N), 2.43 (1H, dd, *J* 1.4, 5.5 Hz, CH$_a$$\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 161.4, 53.7, 52.9, 34.0, 31.6

All other experimental data were consistent with the ones reported in the literature[10].

**Methyl (2S)-1-(N-9-fluorenylmethyloxycarbonyl)aziridine-2-carboxylate** (**10)**: yellow oil (238 mg, 70% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 7.79-7.75 (2H, m, Ar$_{Fmoc}$), 7.64-7.59 (2H, m, Ar$_{Fmoc}$), 7.44-7.3 (4H, m, Ar$_{Fmoc}$), 4.49 (1H, dd, *J* 7.2, 10.6 Hz, C$\underline{H}_a$-H$_{bFmoc}$), 4.37 (1H, dd, *J* 7.2, 10.6 Hz, CH$_a$-$\underline{H}_{bFmoc}$), 4.25 (1H, dd, *J* 7.2 Hz, C$\underline{H}_{Fmoc}$), 3.73 (3H, s, CH$_3$), 3.11 (1H, dd, *J* 3.2, 5.4 Hz, C$\underline{H}_a$H$_b$-N), 2.62 (1H, dd, *J* 1.3, 3.2 Hz, C$\underline{H}$-N), 2.43 (1H, dd, *J* 1.3, 5.4 Hz, CH$_a$$\underline{H}_b$-N);

**Benzyl (2S)-1-(N-benzyloxycarbonyl)aziridine-2-carboxylate** (**14**): colourless oil (248 mg, 80% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 7.40-7.30 (10H, m, Ph x2), 5.02-5.08 (4H, m, C$\underline{H}_2$Ph x2), 3.11 (1H, dd, *J* 3.2, 5.4 Hz, C$\underline{H}_a$H$_b$-N), 2.6 (1H, dd, *J* 1.3, 3.2 Hz, C$\underline{H}$-N), 2.48 (1H, dd, *J* 1.3, 5.4 Hz, CH$_a$$\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 160.9, 135.4, 135.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 68.8, 67.6, 35.0, 31.6

All other experimental data were consistent with the ones reported in the literature (ref. 9).

**Benzyl (2S)-1-(N-2,2,2-trichloroethoxy)carbonylaziridine-2-carboxylate** (**15)**: yellow oil (246 mg, 70% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 7.40-7.30 (5H, m, Ph), 5.22 (2H, dd, *J* 12.2, 13.2 Hz, C$\underline{H}_2$Ph), 4.79 (1H, d, *J* 13.3, Hz, C$\underline{H}_a$H$_b$-Cl$_3$), 4.65 (1H, d, *J* 13.3, Hz, CH$_a$$\underline{H}_b$-Cl$_3$), 3.19 (1H, dd, *J* 3.2, 5.4 Hz, C$\underline{H}_a$H$_b$-N), 2.6 (1H, dd, *J* 1.2, 3.2 Hz, C$\underline{H}$-N), 2.56 (1H, dd, *J* 1.2, 5.4 Hz, CH$_a$$\underline{H}_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 159.9, 135.9, 128.7, 128.5, 128.4, 94.6, 75.9, 66.8, 35.0, 31.6

[10] Bernstein, Z.; Ben-Ishai, D. *Tetrahedron*, **1977**, 33, *8*, 881-883

*4.2.4. General procedure for the synthesis of N-Boc derivatives:*

To a solution of 1 mmol of the appropriate (2S)-1-tritylaziridine-2-carboxylate (**4** or **10**) in 0.04 ml of methanol and 5.6 ml of dichloromethane at 0°C, trifluoroacetic acid (2 mmol, 0.15 ml) was added drop-wise at 0°C and the mixture left stirring at room temperature. After 30 minutes $Et_3N$ (5 mmol, 0,7 mml) was added drop-wise; after 10 minutes $Boc_2O$ (1.1 mmol, 239 mg) diluted in 1.2 ml of dichloromethane was added drop-wise and the mixture left stirring for 15 hours. The mixture was washed with a 10% aqueous solution of citric acid (3 ml x3), then with water (3 ml x2). Finally the organic layer was dried over $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was then purified by flash chromatography on silica gel (Pet. Spirit/Ethyl acetate 8:2) to give the desired product (85% yield).

**Methyl (2S)-1-(N-*tert*-butoxycarbonyl)aziridine-2-carboxylate** (**5)**: colourless oil (182 mg, 85% yield); $^1$H NMR (500 MHz $CDCl_3$) δ: 3.77 (3H, s, $CH_3$), 3.02 (1H, dd, *J* 3.2, 5.5 Hz, C$\underline{H}_a$H$_b$-N), 2.51 (1H, dd, *J* 1.4, 3.2 Hz, C$\underline{H}$-N), 2.4 (1H, dd, *J* 1.4, 5.5 Hz, CH$_a\underline{H}_b$-N), 1.44 (9H, s, C$(CH_3)_3$); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 160.9, 82.2, 52.9, 35.0, 31.6, 27.9

All other experimental data were consistent with the ones reported in the literature[11].

**Benzyl (2S)-1-(N-*tert*-butoxycarbonyl)aziridine-2-carboxylate** (**12)**: colourless oil (235 mg, 85% yield); $^1$H NMR (500 MHz $CDCl_3$) δ: 7.38-7.31 (5H, m, Ph), 5.2 (2H, dd, *J* 12.3, 40.1 Hz, $CH_2$Ph), 3.02 (1H, dd, *J* 3.2, 5.5 Hz, C$\underline{H}_a$H$_b$-N), 2.51 (1H, dd, *J* 1.4, 3.2 Hz, C$\underline{H}$-N), 2.4 (1H, dd, *J* 1.4, 5.5 Hz, CH$_a\underline{H}_b$-N), 1.44 (9H, s, C$(CH_3)_3$); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 160.9, 135.4, 128.7, 128.6, 127.8, 68.8, 82.2, 52.9, 35.0, 31.6, 27.9

All other experimental data were consistent with the ones reported in the literature[12].

*4.3. Coupling reactions.*

*4.3.1. General procedure for the coupling reactions:*

At room temperature and under argon atmosphere, 1 mmol of the appropriate aziridine and the indole (2 mmol, 234 mg) were dissolved in 10 ml of anhydrous dichloromethane and 1 mmol of the appropriate Lewis acid was added. After 17 hours the reaction was quenched with $NaHCO_3$, extracted three times with dichloromethane, washed with brine and the organic layer was dried over

[11] Braga, A. et al. *J Org Chem* **2006**, *71*, 4305-4307

[12] Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synlett* **2000**, *9*, 1309-1311

$Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was then purified by flash chromatography on silica gel (Pet. Spirit/AcOEt 9:1) to give the desired products

**5-Oxazolidinecarboxylic acid, 2-oxo-, methyl ester**: colourless oil; $^1$H NMR (500 MHz $CDCl_3$) δ: 5.39 (1H, br s, NH) 4.62 (1H, dd, *J* 9.2 Hz, CHCO), 4.55 (1H, dd, *J* 4.6, 9.2 Hz, $CH_aH_b$-N), 4.4 (1H, dd, *J* 4.6, 9.2 Hz, $CH_aH_b$-N), 3.7 (3H, s, $CH_3$); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 160.9, 135.4, 128.7, 128.6, 127.8, 68.8, 82.2, 52.9, 35.0, 31.6, 27.9

All other experimental data were consistent with the ones reported in the literature[13].

**5-Oxazolidinecarboxylic acid, 2-oxo-, benzyl ester**: colourless oil; $^1$H NMR (500 MHz $CDCl_3$) δ: 7.30 (5H, m, Ph), 6.65 (1H, br s, NH), 6.65 (2H, s, $CH_2$Ph), 5.00 (1H, dd, *J* 9.0, Hz, CHCO), 3.83 (1H, dd, *J* 4.6, 9. Hz, $CH_aH_b$-N), 3.63 (1H, dd, *J* 4.6, 9.0 Hz, $CH_aH_b$-N); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 168.8, 159.1,134.6, 128.7, 128.5, 72.6, 67.7, 43.6

All other experimental data were consistent with the ones reported in the literature[14].

**(S)-methyl-2-(N-benzyloxycarbonyl)amino-3-(1H-indol-3-yl)propanoate**: colourless oil; $^1$H NMR (500 MHz $CDCl_3$) δ: 8.07 (1H, br s, $NH_{INDOLE}$), 7.52 (1H, d, *J* 7.9 Hz, Ar-$H_{INDOLE}$), 7.38-7.28 (6H, M, Ph + Ar-$H_{INDOLE}$), 7.19 (1H, t, *J* 8.1 Hz, Ar-$H_{INDOLE}$), 7.09 (1H, dd, *J* 8.8, 7.9 Hz, Ar-$H_{INDOLE}$), 6.96 (1H, s, Ar-$H_{INDOLE}$), 5.32 (1H, d, *J* 7.9 Hz, NHCbz), 5.16-5.04 (2H, m, $CH_2$Ph), 4.72 (1H, dt, *J* 5.3, 7.9 Hz, CH-NHCbz), 3.58 (3H, s, $CH_3$), 3.31 (2H, d, *J* 5.3 Hz, $CH_2$-CHNH); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 172.5, 156.7, 136.3, 128.6, 128.3, 122.9, 122.4, 119.9, 118.8, 111.3, 110.1, 67.1, 54.7, 52.5, 28.1

All other experimental data were consistent with the ones reported in the literature[15].

**(S)-benzyl-2-(N-benzyloxycarbonyl)amino-3-(1H-indol-3-yl)propanoate**: colourless oil; $^1$H NMR (500 MHz $CDCl_3$) δ: 8.26 (1H, br s, $NH_{INDOLE}$), 7.41-7.33 (11H, m, Ph + Ar-$H_{INDOLE}$), 7.19 (1H, t, *J* 8.1 Hz, Ar-$H_{INDOLE}$), 7.09 (1H, dd, *J* 8.8, 7.9 Hz, Ar-$H_{INDOLE}$), 6.96 (1H, s, Ar-$H_{INDOLE}$), 5.32 (1H, d, *J* 7.9 Hz, NHCbz), 5.16-5.04 (4H, m, $CH_2$Ph x2), 4.72 (1H, dd, *J* 8.0 Hz, CH-NHCbz), 3.31 (2H, d, *J* 5.1 Hz, $CH_2$-CHNH); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 171.8, 155.8, 136.1, 136.0, 135.1, 128.5, 128.4, 128.3, 128.0, 127.5, 127.4, 126.9, 122.9, 122.0, 119.5, 118.5, 111.2, 109.4, 67.1, 66.8, 54.6, 27.8

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[13] Andruszkiewicz, R.; Wyszogrodzka, M. *Synlett*, **2002**, *12*, 2101-2103

[14] Danielmeier,K.; Steckhan,E. *Tetrahedron: Asymmetry* **1995**, 6, *5*, 1181-1190

[15] Nishikawa, T.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Synthesis*, **2002**, *12*, 1658 - 1662

All other experimental data were consistent with the ones reported in the literature[16].

**α-[(N-benzyloxycarbonyl)amino)methyl]indole-3-acetic acid methyl ester:** colourless oil; $^{1}$H NMR (500 MHz $CDCl_3$) δ: 8.19 (1H, br s, N$\underline{H}_{INDOLE}$), 7.68 (1H, d, *J* 7.9 Hz, Ar-$\underline{H}_{INDOLE}$), 7.38-7.28 (6H, M, Ph + Ar-$\underline{H}_{INDOLE}$), 7.19 (1H, t, *J* 7.9 Hz, Ar-$\underline{H}_{INDOLE}$), 7.16-7.09 (2H, m, Ar-$\underline{H}_{INDOLE}$), 5.22-5.05 (3H, m, N$\underline{H}$Cbz + C$\underline{H}_2$Ph), 4.2 (1H, dd, *J* 6.3, 8.3 Hz, C$\underline{H}$-CO), 3.84-3.69 (2H, m, C$\underline{H}_2$-NH), 3.58 (3H, s, $CH_3$); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 172.5, 156.7, 136.3, 128.6, 128.3, 128.9, 122.4, 120.9, 119.4, 111.3, 111.1, 66.1, 52.7, 43.5, 28.1

All other experimental data were consistent with the ones reported in the literature (ref. 15).

**α-[(N-benzyloxycarbonyl)amino)methyl]indole-3-acetic acid benzyl ester:** colourless oil; $^{1}$H NMR (500 MHz $CDCl_3$) δ: 8.21 (1H, br s, N$\underline{H}_{INDOLE}$), 7.65 (1H, d, *J* 7.9 Hz, Ar-$\underline{H}_{INDOLE}$), 7.40-7.25 (11H, M, Ph x2 + Ar-$\underline{H}_{INDOLE}$), 7.20 (1H, t, *J* 7.9 Hz, Ar-$\underline{H}_{INDOLE}$), 7.16-7.09 (2H, m, Ar-$\underline{H}_{INDOLE}$), 5.25-5.0 (5H, m, N$\underline{H}$Cbz + C$\underline{H}_2$Ph x2), 4.2 (1H, dd, *J* 6.3, 8.3 Hz, C$\underline{H}$-CO), 3.84-3.69 (2H, m, C$\underline{H}_2$-NH); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 172.5, 156.7, 136.3, 135.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.9, 122.4, 120.9, 119.4, 111.3, 111.1, 66.1, 66.8, 43.5, 28.1

**(S)-methyl-2-(N-*tert*-butoxycarbonyl)amino-3-(1H-indol-3-yl)propanoate**: pail yellow oil; $^{1}$H NMR (500 MHz $CDCl_3$) δ: 8.05 (1H, br s, N$\underline{H}_{INDOLE}$), 7.55 (1H, d, *J* 8 Hz, Ar-$\underline{H}_{INDOLE}$), 7.33 (1H, d, *J* 8 Hz, Ar-$\underline{H}_{INDOLE}$), 7.19-7.06 (2H, m Ar-$\underline{H}_{INDOLE}$), 5.22-5.05 (1H, d, *J* 7.6 Hz, N$\underline{H}$Cbz), 4.68-4.57 (1H, m, C$\underline{H}$-CO), 3.58 (3H, s, $CH_3$), 3.33-3.22 (2H, m, C$\underline{H}_2$-NH), 1.41 (9H, s, $C(CH_3)_3$), $^{13}$C NMR (125 MHz $CDCl_3$) δ: 173.03, 155.57, 136.38, 127.58, 123.03, 122.35, 119.77, 118.91, 111.46, 110.28, 80.23, 54.44, 52.46, 28.56, 28.21

All other experimental data were consistent with the ones reported in the literature (ref. 16).

**(S)-benzyl-2-(N-*tert*-butoxycarbonyl)amino-3-(1H-indol-3-yl)propanoate**: pail yellow oil (85% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 8.05 (1H, br s, N$\underline{H}_{INDOLE}$), 7.55 (1H, d, *J* 8 Hz, Ar-$\underline{H}_{INDOLE}$), 7.38-7.31 (6H, m, Ph + Ar-$\underline{H}_{INDOLE}$), 7.19-7.06 (2H, m Ar-$\underline{H}_{INDOLE}$), 5.22-5.05 (3H, m, N$\underline{H}$Cbz + C$\underline{H}_2$Ph), 4.68-4.57 (1H, m, C$\underline{H}$-CO), 3.33-3.22 (2H, m, C$\underline{H}_2$-NH), 1.41 (9H, s, $C(CH_3)_3$), $^{13}$C NMR (125 MHz $CDCl_3$) δ: 173.03, 155.57, 136.38, 135.9, 128.7, 128.5, 128.4, 127.58, 123.03, 122.35, 119.77, 118.91, 111.46, 110.28, 80.23, 66.8, 54.44, 28.56, 28.21.

All other experimental data were consistent with the ones reported in the literature[17].

[16] Meyer, F.M. *et al. Organic Letters* **2010**, 12, *17,* 3870-3873

**(S)-methyl-2-(N-methoxycarbonyl)amino-3-(1H-indol-3-yl)propanoate**: yellow oil; $^{1}$H NMR (500 MHz $CDCl_3$) δ: 8.12 (1H, br s, N$\underline{H}_{INDOLE}$), 7.55 (1H, d, *J* 7.9Hz, Ar-$\underline{H}_{INDOLE}$), 7.33 (1H, d, *J* 8.1 Hz, Ar-$\underline{H}_{INDOLE}$), 7.19-7.06 (2H, m Ar-$\underline{H}_{INDOLE}$), 7.0 (1H, m, Ar-$\underline{H}_{INDOLE}$), 5.22-5.05 (1H, d, *J* 7.6 Hz, N$\underline{H}$CO), 4.71 (1H, dt, *J* 5.4, 7.9 Hz C$\underline{H}$-NH), 3.68 (3H, s, $CH_3$), 3.66 (3H, s, $CH_3$), 3.31 (2H, , d, *J* 5.4 Hz, C$\underline{H_2}$-CH), 1.41 (9H, s, $C(CH_3)_3$), $^{13}$C NMR (125 MHz $CDCl_3$) δ: 173.03, 155.57, 136.38, 127.58, 123.03, 122.35, 119.77, 118.91, 112.46, 111.28, 52.46, 41.2, 28.56.

All other experimental data were consistent with the ones reported in the literature [18].

**(S)-methyl-2-(N-2,2,2-trichlorethoxycarbonyl)amino-3-(1H-indol-3-yl)propanoate**: yellow oil (85% yield); $^{1}$H NMR (500 MHz $CDCl_3$) δ: 8.12 (1H, br s, N$\underline{H}_{INDOLE}$), 7.55 (1H, d, *J* 8.0 Hz, Ar-$\underline{H}_{INDOLE}$), 7.33 (1H, d, *J* 8.0 Hz, Ar-$\underline{H}_{INDOLE}$), 7.19-7.06 (2H, m Ar-$\underline{H}_{INDOLE}$), 7.0 (1H, m, Ar-$\underline{H}_{INDOLE}$), 5.56 (1H, d, *J* 7.9 Hz, N$\underline{H}$CO), 4.80 (1H, d, *J* 12.2 Hz C$\underline{H}$-NH), 3.68 (3H, s, $CH_3$), 3.31 (2H, , d, *J* 5.4 Hz, C$\underline{H_2}$-CH); $^{13}$C NMR (125 MHz $CDCl_3$) δ: 171.8, 153.9, 136.1, 127.4, 122.9, 122.3, 119.8, 118.6, 111.2, 109.6, 95.4, 74.6, 54.7, 52.5, 27.9

All other experimental data were consistent with the ones reported in the literature [19].

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[17] Crosignani, S. *et al. J. Org. Chem.* **2004**, 69, *18*, 5897-5905

[18] Nakagava, M.; Kato, S.; Kataoka, S.; Kodato, S.; Watanabe, H.; *et al. Chem. Pharm. Bull.* **1981**, 29, *4*, 1013 - 1026

[19] Snider, B.B.; Zeng,H. *J. Org. Chem*. **2003**, 68, *2*, 545-563

# Chapter 3. Study on the azidolysis reaction of vinyl epoxides and aziridines[1].

## 1. Introduction.

As already mentioned before, vinyl aziridines and epoxides, among all variously functionalized ones, are highly versatile compounds thanks to their particular ability to function as carbon electrophiles and the possibility of further elaborations of the double bond.

Our group has been recently focusing on the study of the azidolysis of vinyl epoxides[2] exploiting the $BF_3$•$OEt_2$/$TMSN_3$ (azidotrimethylsilane) system (Fig. 1), which allowed, in a few hours (0.75-4.1 h), to achieve the corresponding *anti* azido alcohols generally in a satisfactory yield and excellent regioselectivity.

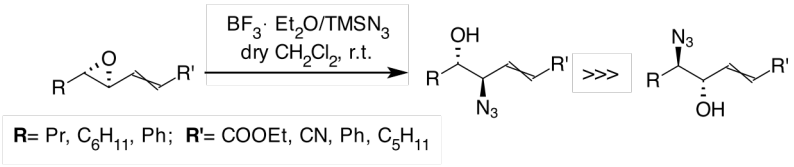


**Fig. 1 Azidolysis of vinyl epoxides.**

This methodology has been recently reported[3] on a particular epoxy ester and makes use of $BF_3$•$OEt_2$ as the chelating agent and $TMSN_3$ as the azide source.

Given the good results obtained and the key role played by the azide moiety as amine precursor, the study was extended to vinyl aziridines, which could give access to diamino sequences. As for vinyl epoxides, despite the rich literature on the chemistry of aziridine opening, there are to the best of our knowledge only few reports[4] concerning a systematic study on the ring-opening reactions of vinyl aziridines by the azide group.

What follows is a full account of the results obtained from the study of the azidolysis on both vinyl epoxides and aziridines.

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[1] Righi, G.; Marucci, C.; Pelagalli, R; Bovicelli, P.; Tirotta, I. *Tetrahedron*, *submitted*

[2] Righi, G.; Salvati Manni, L.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett*., **2011**, *52*, 3895-3896

[3] Rodrigues *et al. Tetrahedron: Asymmetry,* **2005**, 16, *18*, 3099-3106

[4] a) Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5094–5097; b) Marié, J.-C.; Courillon, C.;Malacria, M. *Arkivoc* **2007**, 277–292 (part V).

## 2. Results and discussion.

For a thorough understanding of these substrates reactivity, different compounds were prepared with various R, R' and P (Fig. 2) in order to investigate: the influence of the steric hindrance of R on the heterocycle, the electronic effect of R' on the double bond and the activation given by P to the aziridine ring.

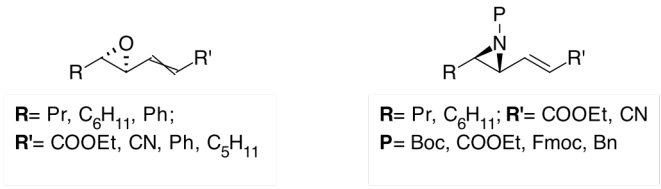
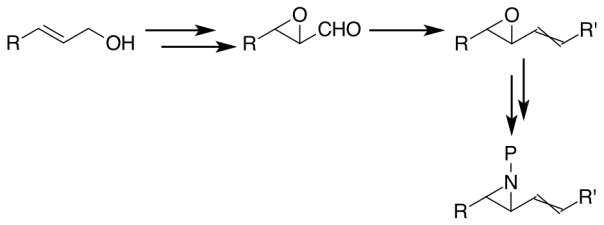



**Fig. 2 Substrates of choice.**

All the substrates of choice can be easily synthesized from the appropriate allylic alcohols[5] (Scheme 1): in only three steps these can give access to the desired vinyl epoxides, which can be converted into the corresponding vinyl aziridines. All compounds can be readily obtained in both their enantiomerically pure forms using the Sharpless protocol for the epoxidation step, however this was not necessary for the purposes of this study[6].



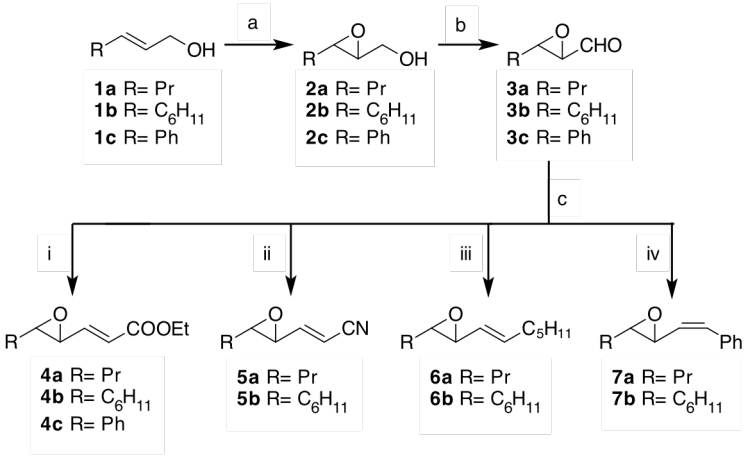

**Scheme 1 Synthetic path from allylic alcohol to vinyl epoxides and aziridines.**

[5] For the substrates with R=cyclohexyl the appropriate alcohol **1b** is not commercially available and it was synthesized from the cyclohexanecarboxaldehyde. A Horner-Emmons reaction, followed by a reduction of the ester using DIBAL, led to alcohol **1b** with an overall yield of 97%. See Chapter 9 for procedures and characterisations.

[6] For the purpose of this work, it is not mandatory to have optically active compounds, all the molecules are intended as racemates and the stereochemistry is only reported as the relative one.

*2.1. Synthesis of vinyl epoxides.*

As shown in Scheme 2, starting from alcohols **1a-c**, an epoxidation reaction followed by an oxydation of the hydroxyl group afforded aldehydes **3a-c**, which were then submitted to the Wittig and Horner-Emmons reactions[7] with the appropriate reagents and conditions in order to afford the desired vinyl epoxides **4a-c**, **5a-b**, **6a-b**, **7a-b** with a yield after three steps of, on average, 50-60%. It is important to notice that for R'=COOEt, CN, $C_5H_{11}$ the major product of the Wittig reaction is the *E* regioisomer, whilst for R'=Ph the *Z* isomer prevails.




**Scheme 2** *Reagents and conditions:* (a) m-CPBA, $CH_2Cl_2$, rt, 3h, (85-95%); (b) TEMPO, IBDA, $CH_2Cl_2$, 2h, r.t. (70-80%); (c) i) for COOEt: TEPA, LiOH, THF, reflux, 2h (85-95%); ii) for CN: $(EtO)_2POCH_2CN$, LiOH, THF, reflux 6h (70-80%). iii) for $C_5H_{11}$: $Ph_3P(CH_2)_5CH_3Br$, BuLi, dry THF, -40°C, o/n (65-75%); iv) for Ph: $Ph_3PCH_2PhBr$, LiOH, PrOH, r.t., 5h (59-70%)

*2.2. $BF_3$•$Et_2O/TMSN_3$ mediated opening reaction on vinyl epoxides.*

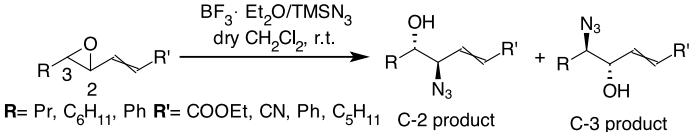
The vinyl epoxides prepared were then submitted to the ring-opening reactions using $BF_3/TMSN_3$ and the results are summarized in Table 1. Performing the reaction using $TMSN_3$ (1 eq.) and $BF_3.OEt_2$ (2 eq.) in dry $CH_2Cl_2$ at room temperature, in a few hours (0.75-4.1) all the substrates were converted into the corresponding azido alcohols in satisfactory to excellent yields. The regiochemistry of the products was established by spin-spin decoupling experiments and, since only one diastereomer was detected, the *anti* configuration was assigned based on a $S_N2$ mechanism.

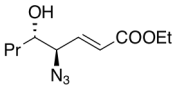
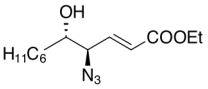
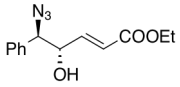
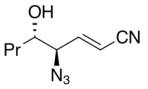
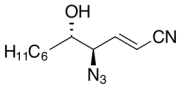
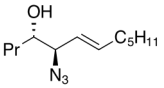
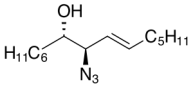
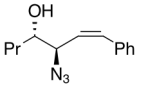
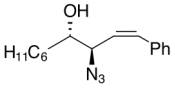
From the data collected for compounds with R= propyl or cyclohexyl, it was clear that the steric hindrance exerted by the R group on the epoxide ring didn't have much of an influence on the regiochemistry of the reaction. Whereas when R was a phenyl group (Entry **3**) the regioselectivity

[7] a) Antonioletti, R.; Bonadies, F.; Ciammaichella, A.; Viglianti, A. *Tetrahedron* **2008**, *64*, 4644–4648; b) Lattanzi, A.; Orelli, L. R.; Barone, P.; Massa, A.; Iannece, C.; Scettri, A. *Tetrahedron Lett*. **2003**, *44*, 1333–1337; c) Bonadies, F.; Scettri, A.; Di Campli, C. *Tetrahedron Lett.* **1996**, *37*, 1899–1900.

of the reaction was dramatically lowered: as already reported for phenyl substituted epoxide rings[8], the benzylic position is strongly activated, therefore it competes with the allylic one for the nucleophilic attack leading to a mixture of regioisomers.

**Table 1 Azidolysis of vinyl epoxides with $TMSN_3$ and $BF_3{\cdot}OEt_2$.**




| Entry | Substrate | C-2:C-3 ratio[a] | Major product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 4a | >95:5 |  **8a** | 1 | 96 |
| 2 | 4b | >95:5 |  **8b** | 1.3 | 96 |
| 3 | 4c | 40:60 |  **8c'** | 3 | 78[b] |
| 4 | 5a | >95:5 |  **9a** | 1.2 | 87 |
| 5 | 5b | >95:5 |  **9b** | 1 | 94 |
| 6 | 6a | 55:45 |  **10a** | 3.5 | 75[b] |
| 7 | 6b | 52:48 |  **10b** | 4.3 | 68[b] |
| 8 | 7a | >95:5 |  **11a** | 4 | 52 |
| 9 | 7b | >95:5 |  **11b** | 4.1 | 48 |

[a] Ratio determined by $^1H$ NMR of the crude product.
[b] Yield of the isomeric mixture.

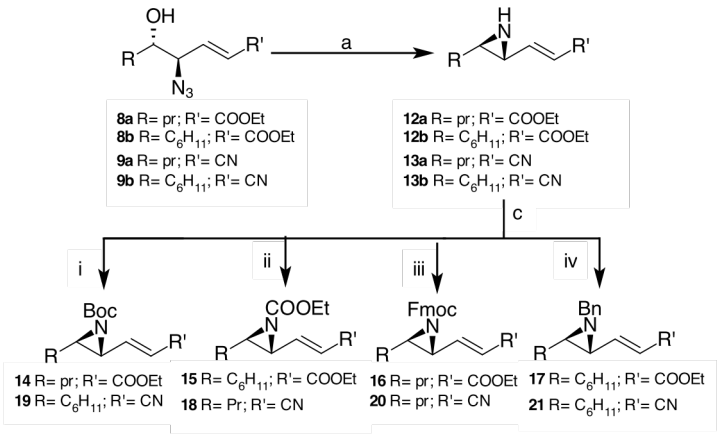
[8] (a) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881-4884; (b) Solladie´-Cavallo, A.; Lupattelli, P.;Bonini, C. *J. Org. Chem.* **2005**, *70*, 1605-1611.

The influence of the R' group is particularly clear from entries **6** and **7**: when R' is an alkyl chain the regioselectivity is almost nullified, whereas for R'= COOEt, CN, and Ph the regioisomeric ratio is always >95:5 in favour of the C-2 product. These results can be justified with the different electronic natures of the R' groups: when R' is not an electron-withdrawing group the allylic position is less activated towards the nucleophilic attack and the reaction cease to be regioselective. It is also relevant that R' groups do affect the overall yield of the reaction. As shown in Table 1 yields are sensibly lower for substrates with R'= $C_5H_{11}$ and even more evidently for R'= Ph, which led to a particularly complex reaction mixture where, along with the azido alcohols, some by-products were detected.

Given these results, from this point on the reactions were carried out only on vinyl aziridines with R= propyl and cyclohexyl and R'= COOEt and CN.

*2.3. Synthesis of vinyl aziridines.*

From the azido alcohols, the pathway to the corresponding aziridines is the same for all the substrates and it is very straightforward (Scheme 3). It only consists of two steps: a ring closing reaction using a well known procedure[9] and a protection reaction with the groups of choice.



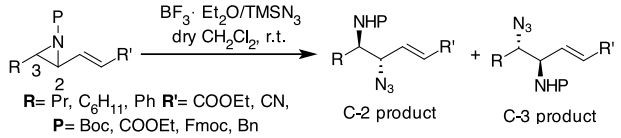

**Scheme 3** *Reagents and conditions*: a) $PPh_3$, acetonitrile, r.t.-70°C, o/n (90%); b): i) $Boc_2O$, DMAP, dry $CH_2Cl_2$, r.t., o/n (97%); ii) $Et_3N$, ClCOOEt, dry $Et_2O$, 0°C-r.t., o/n (98%); iii) FmocOSu, $NaHCO_3$, acetone, r.t., o/n (95%); iv) BnBr, $K_2CO_3$, dry acetonitrile, 80°C, o/n (90%)

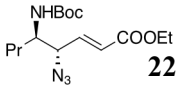
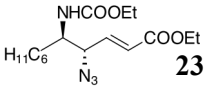
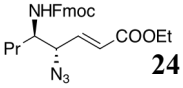
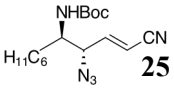
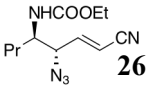
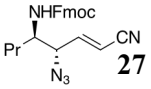
[9] Legters, J.; Thijs, L.; Zwanemburg, B., Recle. Trav. Chim. Pays-Bas, 1992, 111, 1-15

*2.4. $BF_3$•$Et_2O$/$TMSN_3$ mediated opening reaction on vinyl aziridines.*

The aziridines were then submitted to the $BF_3$•$Et_2O$/$TMSN_3$ mediated reaction with the same reaction conditions described before, and the results are summarized in Table 2.

**Table 2 Azidolysis of vinyl aziridines with $TMSN_3$ and $BF_3$·$OEt_2$.**




| Entry | Substrate | C-2:C-3 ratio[a] | Major product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| **1** | **14** | >95:5 |  **22** | 0,5 | >95 |
| **2** | **15** | >95:5 |  **23** | 1 | >95 |
| **3** | **16** | >95:5 |  **24** | 1 | >95 |
| **4** | **17** | - | - | 24 | - |
| **5** | **19** | >95:5 |  **25** | 0,5 | >95 |
| **6** | **18** | >95:5 |  **26** | 1 | >95 |
| **7** | **20** | >95:5 |  **27** | 1 | >95 |
| **8** | **21** | - | - | 72 | - |

[a] Ratio determined by $^1$H NMR of the crude product.

In all cases (except for compounds **17** and **21**) after 0.5-1 hour the substrates were completely converted into the corresponding protected azido amines, with excellent yields. As described before, the regiochemistry of the products was established by spin-spin decoupling experiments and, since only one diastereomer was detected, the $SN_2$ mechanism and the *anti* stereochemistry were confirmed. As for the epoxides, R has no influence on the regiochemistry of the reaction. All carbamate protection proved to activate the aziridine ring to the same extent, whilst the benzyl

group seems to be inadequate for our purposes: even after 72 hours there was no conversion of the substrate. Moreover it is particularly interesting to notice that it was possible to preserve the Boc group by carefully monitoring the reaction time: if the reaction is quenched immediately after the substrate complete consumption no deprotection is observed.

## 3. Conclusions.

The data presented prove the high reproducibility of the $BF_3 \bullet Et_2O/TMSN_3$ mediated azidolysis reaction, which is characterised by a complete stereoselectivity in all cases and an excellent regioselectivity for compounds with R= propyl and cyclohexyl and R'= COOEt, CN and Ph. In all cases, the yields are satisfactory to excellent and the reaction is fast and clean. The study has provided interesting insights into the mechanistic aspects of the reaction: the steric hindrance of R does not affect the stereo- nor the regioselectivity of the reaction whereas the electron-withdrawing nature of R' is extremely important for the activation of the double bond. The aziridine protective group needs to be a carbamate in order to activate the ring towards the nucleophile opening.

The reaction seems to be of general value when applied to vinyl epoxides and aziridine and can give access to amino alcoholic and diamino fragments, which can be useful tools in the synthesis of a wide range of biologically active compounds, especially given the possible further elaborations of the double bond.

## 4. Experimental.

### *4.1. General.*

$^1$H nmr spectra were recorded using a Varian Mercury 300 (300 MHz). Residual solvent peaks were used as internal references for $^1$H nmr spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet;

q, quartet; m, multiplet. $^{13}C$ spectra were recorded using a Varian Mercury 300 (75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak: chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml.

All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 aluminium sheets (Merck Italia) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)].

Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

### *4.2. Synthesis of the substrates.*

For the synthesis of substrates **1a-c**, **2a-c**, **3a-c**, **4a-c** and **12a-b** see Chapter 9: "Experimental"

#### *4.2.1. General procedure for the Horner - Emmons reaction.*

The appropriate compound (1 mmol), LiOH (1,1 mmol, 27 mg) and diethyl (2-cyanoethyl)phosphonate (1,1 mmol, 210 mg, 0.2 ml) were dissolved in 10 ml of THF and then stirred at the reflux temperature for 5h or until consumption of the substrate (TLC monitoring). A saturated solution of $NH_4Cl$ was then added and the reaction mixture concentrated in vacuo. The aqueous solution was then extracted with ethyl acetate and the organic layer washed with $NH_4Cl$ saturated solution and brine until pH=7. The combined organic extracts were dried over $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was then purified by flash chromatography on silica gel (hexane/AcOEt 9:1) to give the desired product (70-80% yield).

**(*E*)-3-(3-propyloxiran-2-yl)acrylonitrile** (**5a)**: pail brown oil (96 mg, 70%) $^1$H NMR (300 MHz $CDCl_3$) δ: 6.53 (1H, dd, *J* 5.9, 16.2 Hz, C<u>H</u>=CHCN), 5.61 (1H, dd, *J* 0.8, 16.2 Hz, C<u>H</u>CN), 3.17 (1H, ddd, *J* 0.8, 1.9, 5.9 Hz, C<u>H</u>-CH=CH), 2.8 (1H, ddd, *J* 1.9, 5.2, 7.1 Hz, $CH_2$-C<u>H</u>), 1.68-1.3 (4H, m, C<u>H$_2$</u>-C<u>H$_2$</u>), 0.89 (3H, t, *J* 7.2 Hz, $CH_2CH_2C$<u>H$_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 151.1, 116.6, 101.2, 62.1, 55.8, 33.7, 19.0, 13.6; HRMS (ES Q-TOF): $[M+H]^+$, found 138.0915. $C_8H_{11}NO$ requires 138.0919

**(*E*)-3-(3-cyclohexyloxiran-2-yl)acrylonitrile** (**5b)**: brown oil (141 mg, 80%) $^1$H NMR (300 MHz $CDCl_3$) δ: 6.56 (1H, dd, *J* 5.8, 16.2 Hz, C<u>H</u>=CHCN), 5.61 (1H, d, *J* 16.2 Hz, C<u>H</u>CN), 3.26 (1H, dd, *J* 1.9, 5.8 Hz, C<u>H</u>-CH=CH), 2.64 (1H, dd, *J* 1.9, 6.6 Hz, cyclohexyl-C<u>H</u>), 1.86-0.9 (11H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 151.3, 116.6, 100.9, 66.5, 54.7, 39.8, 29.4, 29.3, 28.7, 26.0, 25.5; HRMS (ES Q-TOF): [M+H]+, found 178.1235. $C_{11}H_{15}NO$ requires 178.1232

*4.2.2. General procedure for the Wittig reaction*

In a two neck round bottomed flask under nitrogen atmosphere and at -40°C, $Ph_3P(CH_2)_5CH_3Br$ (1 mmol, 427 mg) and a 1,6M solution in hexane of BuLi (1,1 mmol, 0,65 ml) were added to 15 ml of dry THF, the mixture was left stirring for 30 minutes and then 1 mmol of the appropriate aldehyde was added. After completion of the substrate (TLC monitoring) 10 ml of a saturated solution of $NH_4Cl$ were added to the reaction mixture and the solvent evaporated at reduced pressure. The aqueous solution was then extracted with diethyl ether (10 ml x4), the combined organic layers washed with brine, dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product which was purified by chromatography on silica gel (hexane/AcOEt 95:5) to give the desired ester (65-75% yield).

**(E)-4,5-epoxydodec-6-ene** (**6a)**: pail yellow oil (118 mg, 65% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 5.88 (dt, 1H, *J* 7.0, 15.5 Hz, CH=C<u>H</u>-$CH_2$), 5.15 (dd, 1H, *J* 9.0, 15.5 Hz, C<u>H</u>=CH), 3.04 (m, 1H, C<u>H</u>-CH=CH), 2.80 (m, 1H, $CH_2$-C<u>H</u>), 2.04 (dt, 2H, *J* 7.0, 7.0 Hz, CH=CH-C<u>H$_2$</u>), 1.24-1.55 (m, 10H, C<u>H$_2$</u> x5), 0.95 (t, 3H, *J* 7.0 Hz, C<u>H$_3$</u>), 0.87 (t, 3H, *J* 7.5 Hz, C<u>H$_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 136.6, 127.4, 60.2, 58.8, 34.0, 32.3, 31.3, 28.6, 22.5, 19.2, 14.0, 13.9.

All other experimental data were consistent with the ones reported in the literature[10].

**(E)-2-cyclohexyl-3-(hept-1-en-1-yl)oxirane** (**6b)**: colourless oil (166 mg, 75% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 5.63 (1H, ddt, *J* 0.9, 7.7, 11 Hz, CH=C<u>H</u>-$CH_2$), 5.06-4.96 (1H, m, C<u>H</u>=CH),

[10] Kang, B.; Britton, R. *Organic Letters*, **2007**, 9, *24*, 5083 - 5086

3.36 (1H, ddd, *J* 0.9, 2.3, 8.8 Hz, C<u>H</u>-CH=CH), 2.57 (1H, dd, *J* 2.3, 6.7 Hz, cyclohexyl-C<u>H</u>), 2.0-1.56 (7H, m, cyclohexyl + CH=CHC<u>H</u>$_2$), 1.44-0.98 (12H, m, cyclohexyl + C<u>H</u>$_2$ x3), 0.85 (3H, t, *J* 7.3 Hz, C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 136.6, 127.4, 62.2, 59.8, 37.0, 32.3, 31.3, 29.4, 29.3, 28.7, 28.6, 26.0, 25.5, 22.5, 13.9; HRMS (ES Q-TOF): [M+H]+, found 223.2060. $C_{15}H_{26}O$ requires 223.2062

*4.2.3. General procedure for the Wittig reaction.*

LiOH (1.6 mmol, 38 mg) and $Ph_3P^+CH_2PhBr^-$ (1.2 mmol, 520 mg) were added to 4 ml of isopropanol, after 30 minutes 1 mmol of the appropriate aldehyde was added and the mixture left stirring at room temperature until completion of the substrate (TLC monitoring). The reaction mixture was then diluted with AcOEt and washed with a saturated solution of $NH_4Cl$ and brine, the organic layer was dried on $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude product which was purified by chromatography on silica gel (hexane/AcOEt 98:2) to give the desired ester.

**(*Z*)-2-propyl-3-styryloxirane** (**7a)**: colourless oil (112 mg, 60% yield); $^1$H NMR (300 MHz CDCl3) δ: 7.4-7.2 (5H, m, Ph), 6.8 (1H, d, *J* 11.6 Hz, Ph-C<u>H</u>), 5.4 (1H, dd, *J* 8.6, 11.6 Hz, C<u>H</u>-CHPh), 3.5 (1H, dd, *J* 2.2, 8.6 Hz, C<u>H</u>-CH=CH), 2.97 (1H, ddd, *J* 2.2, 4.8, 7.0 Hz, $CH_2$-C<u>H</u>), 1.4-1.7 (4H, m, $CH_2$ x2), 0.9 (3H, t, *J* 7.2, $CH_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 136.5, 135.7, 128.9, 128.2, 126.7, 123.8, 57.6, 55.3, 30.5, 21.6,13.7; HRMS (ES Q-TOF): [M+H]+, found 189.1276. $C_{13}H_{16}O$ requires 189.1279

**(*Z*)-2-cyclohexyl-3-styryloxirane** (**7b)**: colourless oil (159 mg, 70% yield); $^1$H NMR (300 MHz CDCl3) δ: 7.48-7.2 (5H, m, Ph), 6.72 (1H, d, *J* 11.7 Hz, C<u>H</u>Ph), 5.38 (1H, dd, *J* 8.6, 11.7 Hz, C<u>H</u>=CHPh), 3.58 (1H, dd, *J* 3.7, 8.6 Hz, C<u>H</u>-CH=CH), 2.78 (1H, dd, *J* 3.7, 6.5 Hz, cyclohexyl-C<u>H</u>), 1.95-1.59 (5H, m, cyclohexyl), 1.41-1.07 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz CDCl3) δ: 134.4, 129.9, 128.9, 128.5, 127.5, 64.9, 54.0, 40.2, 29.8, 29.2, 26.4, 25.8, 25.7; HRMS (ES Q-TOF): [M+H]+, found 229.1589. $C_{16}H_{20}O$ requires 229.1593

*4.2.4. General procedure for the aziridine ring formation.*

To a stirred solution of 1 mmol of the appropriate substrate in 1 ml of anhydrous acetonitrile, $PPh_3$ (1,2 mmol, 314 mg) was added under nitrogen atmosphere and the flask equipped with a monitoring device for the nitrogen release. After 2h the reaction mixture was heated to the reflux temperature and stirred for 12 h or until consumption of the substrate (TLC monitoring). The

solvent was then removed under reduced pressure, the crude dissolved in cold diethyl ether, filtered, concentrated and purified by flash chromatography on silica gel (hexane/AcOEt 7:3) to give the desired product.

**(E)-(*2R*,3R**)-3-(3-propylaziridin-2-yl)acrylonitrile (13a):** yellow oil (135 mg, 90% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.34 (1H, dd, *J* 8.3, 16.1 Hz, C<u>H</u>=CHCN), 5.53 (1H, d, *J* 16.1 Hz, C<u>H</u>CN), 2.29 (1H, dd, *J* 2.1, 8.3 Hz, C<u>H</u>-CH=CH), 2.04-1.92 (2H, m, $CH_2$-C<u>H</u> + N<u>H</u>), 1.65-1.29 (4H, m, $CH_2$ x2), 0.9 (3H, t, *J* 7.1, $CH_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 155.9, 117.6, 99.4, 46.2, 42.5, 35.4, 20.4, 13.3; HRMS (ES Q-TOF): [M+H]+, found 137.1075. $C_8H_{12}N_2$ requires 137.1079.

**(E)-(*2R*,3R**)-3-(3-cyclohexylaziridin-2-yl)acrylonitrile (13b):** pail yellow oil (171 mg, 90% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.24 (1H, dd, *J* 8.2, 16.1 Hz, C<u>H</u>=CHCN), 5.49 (1H, d, *J* 16.1 Hz, C<u>H</u>CN), 2.29 (1H, dd, *J* 2.5, 8.2 Hz, C<u>H</u>-CH=CH), 2.04-1.92 (2H, m, cyclohexyl-C<u>H</u> + N<u>H</u>), 1.82-1.5 (5H, m, cyclohexyl), 1.23-0.96 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 155.1, 117.2, 99.1, 46.9, 42.0, 30.8, 30.5, 26.2, 25.7, 25.6; HRMS (ES Q-TOF): [M+H]+, found 177.1395. $C_{11}H_{16}N_2$ requires 177.1392

*4.2.5. General procedure for the Boc protection.*

Under nitrogen atmosphere, 1 mmol of the appropriate substrate was dissolved in 10 ml of anhydrous dichloromethane. 1,1 mmol (248 mg) of $Boc_2O$ and a catalytic amount of DMAP were then added and the reaction mixture stirred at room temperature for 12h or until consumption of the substrate (TLC monitoring). The solvent was then evaporated under reduced pressure to give the desired product, which was used without any purification.

**(*2R*,3R**) N-*tert*-butoxycarbonyl-(E)-ethyl-3-(3-propylaziridin-2-yl)acrylate (14)**: yellow oil (275 mg, 97% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.40 (1H, dd, *J* 9.3, 15.9 Hz, C<u>H</u>=CHCO), 6.12 (1H, d, *J* 15.9 Hz, C<u>H</u>CO), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.81 (1H, dd, *J* 2.7, 9.3 Hz, C<u>H</u>-CH=CH), 2.50 (1H, m, $CH_2$C<u>H</u>), 1.80-1.45 (13H, m, C<u>H</u>$_2$ x2 + C(C<u>H</u>$_3$)$_3$), 1.30 (3H, t, *J* 7.2 Hz, $COCH_2C\underline{H}_3$), 0.98 (3H, t, *J* 7.3 Hz, $CH_2CH_2C\underline{H}_3$ ); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.2, 159.2, 143.4, 124.0, 81.0, 60.5, 45.8, 43.1, 33.1, 31.2, 27.9, 14.4, 14.0; HRMS (ES Q-TOF): [M+H]+, found 284.1860. $C_{15}H_{25}NO_4$ requires 284.1862

**(*2R*,3R**) N-*tert*-butoxycarbonyl-(*E*)-3-(3-cyclohexylaziridin-2-yl)acrylonitrile (19)**: pail yellow oil (281 mg, 98% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 5.76 (1H, dd, *J* 9.6, 10.5 Hz, C<u>H</u>=CHCN), 5.36 (1H, d, *J* 10.5 Hz, C<u>H</u>CN), 3.08 (1H, dd, *J* 2.3, 9.6 Hz, C<u>H</u>-CH=CH), 2.21-2.15

(1H, m, cyclohexyl-C<u>H</u>), 1.82-1.43 (5H, m, cyclohexyl), 1.28 (9H, s, Boc), 1.11-0.9 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 159.1, 149.9, 114.9, 101.1, 80.6, 50.1, 41.0, 39.8, 30.0, 29.6, 27.5, 25.6, 25.5, 25.2; HRMS (ES Q-TOF): [M+H]+, found 277.1919. $C_{16}H_{24}N_2O_2$ requires 277.1916

*4.2.6. General procedure for the COOEt protection.*

Under nitrogen atmosphere 1 mmol of the appropriate substrate was dissolved in 3 ml of anhydrous diethyl ether. 1,2 mmol (121 mg; 0,2 ml) of $Et_3N$ and 1,2 mmol (130 mg; 0,1 ml) of ethyl chloroformate were then added and the reaction mixture stirred at room temperature for 3 hours or until consumption of the substrate (TLC monitoring). The mixture was then filtered through a celite pad and the solvent evaporated under reduced pressure to give the desired product, which was used without any purification.

**(*2R*,3R**) N-ethoxycarbonyl-(*E*)-ethyl-3-(3-cyclohexylaziridin-2-yl)acrylate (15)**: pail yellow oil (289 mg, 98% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.29 (1H, dd, *J* 9.4, 15.4 Hz, C<u>H</u>=CHCO), 6.08 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.22-4.00 (4H, m, COC<u>H$_2$</u>CH$_3$ + NCOC<u>H$_2$</u>CH$_3$), 2.89 (1H, dd, *J* 2.8, 9.4 Hz, C<u>H</u>-CH=CH), 2.38-2.29 (1H, m, cyclohexyl-C<u>H</u>), 1.99-0.96 (17H, m, cyclohexyl + COCH$_2$C<u>H$_3$</u> + NCOCH$_2$C<u>H$_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.2, 161.0, 143.6, 124.2, 62.3, 60.3, 50.3, 42.3, 39.5, 30.2, 29.6, 26.0, 25.5, 25.3, 14.1, 14.0; HRMS (ES Q-TOF): [M+H]+, found 296.1865. $C_{16}H_{25}NO_4$ requires 296.1862

**(*2R*,3R**) N-ethoxycarbonyl-(*E*)-3-(3-propylaziridin-2-yl)acrylonitrile (18)**: yellow oil (218 mg, 98% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.33 (1H, dd, *J* 7.6, 16.0 Hz, C<u>H</u>=CHCN), 5.65 (1H, d, *J* 16.0 Hz, C<u>H</u>CN), 4.2 (2H, q, *J* 7.2, COC<u>H$_2$</u>CH$_3$), 2.85 (1H, dd, *J* 2.8, 7.6 Hz, C<u>H</u>-CH=CH), 2.5 (1H, ddd, *J* 2.8, 5.8, 8.6, CH$_2$-C<u>H</u>), 1.8-1.4 (4H, m, CH$_2$ x2), 1.13 (3H, t, *J* 7.2, COCH$_2$C<u>H$_3$</u>); 0.9 (3H, t, *J* 7.1, C<u>H$_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 161.0, 155.9, 117.6, 99.4, 62.3, 46.2, 42.5, 35.4, 20.4, 14.2, 13.3; HRMS (ES Q-TOF): [M+H]+, found 209.1294. $C_{11}H_{16}N_2O_2$ requires 209.1290

*4.2.7. General procedure for the Fmoc protection.*

1 mmol of the appropriate substrate was dissolved in 10 ml of acetone. $NaHCO_3$ (3.2 mmol, 268 mg) and Fmoc-Osu (1.2 mmol, 404 mg) were then added and the reaction mixture stirred at room temperature for 12h or until completion of the substrate (TLC monitoring). The reaction mixture

was then filtered and the solvent evaporated in vacuo to leave the crude product, which was used without any purification.

**(*2R*,3R**) N-fluorenylmethyloxycarbonyl-(*E*)-ethyl-3-(3-propylaziridin-2-yl)acrylate (16)**: yellow oil (389 mg, 95% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.76-7.30 (8H, m, $\underline{H}_{Ar\ Fmoc}$), 6.40 (1H, dd, *J* 8.7, 15.5 Hz, C$\underline{H}$=CHCO), 6.12 (1H, d, *J* 15.5 Hz, C$\underline{H}$CO), 4.76 (1H, dd, *J* 6.5, 10.8 Hz, C$\underline{H}_a$H$_{bFmoc}$), 4.54 (1H, dd, *J* 6.5, 10.8 Hz, CH$_a\underline{H}_{bFmoc}$), 4.2 (1H, dd, *J* 6.5, Hz, C$\underline{H}_{Fmoc}$), 4.12 (2H, q, *J* 7.2 Hz, COC$\underline{H}_2$CH$_3$), 2.81 (1H, dd, *J* 2.9, 8.7 Hz, C$\underline{H}$-CH=CH), 2.44 (1H, ddd, *J* 2.9, 5.7, 9.6 Hz, CH$_2$C$\underline{H}$), 1.80-1.45 (4H, m, C$\underline{H}_2$ x2), 1.30 (3H, t, *J* 7.2 Hz, COCH$_2$C$\underline{H}_3$), 0.98 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C$\underline{H}_3$ ); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.4, 160.8, 143.6, 141.4, 127.8, 127.2, 125.1, 124.9, 124.0, 119.9, 67.9, 60.5, 47.1, 45.9, 43.7, 32.9, 20.1, 14.4, 14.0; HRMS (ES Q-TOF): [M+H]+, found 406.2013. $C_{25}H_{27}NO_4$ requires 406.2017

**(*2R*,3R**) N-fluorenylmethyloxycarbonyl-(*E*)-3-(3-propylaziridin-2-yl)acrylonitrile (20)**: orange oil (357 mg, 95% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.76-7.30 (8H, m, $\underline{H}_{Ar\ Fmoc}$), 5.97 (1H, dd, *J* 7.7, 16.1 Hz, C$\underline{H}$=CHCN), 5.65 (1H, d, *J* 16.1 Hz, C$\underline{H}$CN), 4.76 (1H, dd, *J* 5.4, 10.8 Hz, C$\underline{H}_a$H$_{bFmoc}$), 4.54 (1H, dd, *J* 5.4, 10.8 Hz, CH$_a\underline{H}_{bFmoc}$), 4.2 (1H, dd, *J* 5.4, Hz, C$\underline{H}_{Fmoc}$), 2.65 (1H, dd, *J* 2.5, 7.7 Hz, C$\underline{H}$-CH=CH), 2.2-2.16 (1H, m, CH$_2$-C$\underline{H}$), 1.5-1.2 (4H, m, CH$_2$ x2), 0.9 (3H, t, *J* 7.1, C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.7, 150.9, 141,6; 127.8, 127.2, 125.1, 124.9, 121,0; 116.6, 105.4, 67.2, 47.2, 46.5, 43.2, 32.4, 20.4, 13.3; HRMS (ES Q-TOF): [M+H]+, found 359.1753. $C_{23}H_{22}N_2O_2$ requires 359.1759

*4.2.8. General procedure for the Bn protection.*

Under nitrogen atmosphere, 1 mmol of the appropriate substrate was dissolved in 10 ml of anhydrous acetonitrile. $K_2CO_3$ (3 mmol, 414 mg) and benzyl bromide (1 mmol, 171 mg, 0,1 ml) were then added and the reaction mixture stirred at 80°C for 12h or until completion of the substrate (TLC monitoring). The reaction mixture was then diluted with water and the aqueous layer extracted with AcOEt three times. The combined organic layers were dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was used without any purification.

**(*2R*,3R**) N-benzyl-(*E*)-ethyl-3-(3-cyclohexylaziridin-2-yl)acrylate (17)**: colourless (282 mg, 90% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.36-7.2 (5H, m, Ph), 6.81 (1H, dd, *J* 7.9, 15.6 Hz, C$\underline{H}$=CHCO), 6.05 (1H, d, *J* 15.6 Hz, C$\underline{H}$CO), 4.22 (2H, q, *J* 7.2 Hz, COC$\underline{H}_2$CH$_3$), 3.5 (2H, dd, *J* 13.1, 34.1 Hz, C$\underline{H}_2$Ph), 2.16 (1H, dd, *J* 7.9 Hz, C$\underline{H}$-CH=CH), 1.8-0.96 (15H, m, cyclohexyl-C$\underline{H}$ + cyclohexyl + COCH$_2$C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 166.2, 146.1, 138.7, 128.4, 127.2, 123.2,

65.3, 60.3, 53.3, 44.3, 37.5, 31.2, 30.0, 26.0, 25.5, 14.0; HRMS (ES Q-TOF): [M+H]+, found 314.2124 $C_{20}H_{27}NO_2$ requires 314.212

**(*2R*,3R**) N-benzyl-(*E*)-3-(3-cyclohexylaziridin-2-yl)acrylonitrile (21)**: colourless oil (239 mg, 90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.4-7.23 (5H, m, Ph), 5.97 (1H, dd, *J* 7.7, 16.1 Hz, CH=CHCN), 5.65 (1H, d, *J* 16.1 Hz, CHCN), 3.86-3.47 (2H, m, $CH_2$Ph), 2.53 (1H, dd, *J* 2.5, 7.7 Hz, CH-CH=CH), 2.0-0.8 (12H, m, cyclohexyl-CH + cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 151.1, 128.7, 128.4, 128.2, 127.5, 117.1, 101.6, 58.3, 55.3, 43.3, 41.5, 30.8, 30.0, 26.0, 25.5, 25.7; HRMS (ES Q-TOF): [M+H]+, found 267.1860. $C_{18}H_{22}N_2$ requires 267.1862

*4.3. $BF_3$/$TMSN_3$ mediated ring-opening reaction, general procedure.*

To a stirred solution of the appropriate substrate (1 mmol) in 3,3 ml dichloromethane were added drop-wise, under argon atmosphere at 0°C, $TMSN_3$ (1 mmol, 115 mg; 0,13 ml) and $BF_3 \cdot OEt$ (2 mmol, 28 mg; 0,25 ml) and the mixture left stirring at room temperature. After complete consumption of the substrate (TLC monitoring) the reaction mixture was diluted with dichloromethane and washed with aqueous solutions of $NaHCO_3$ and NaCl till pH7. The combined organic layers were dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was used without any purification. (The data are given only for the major compound)

**(4*R**,5*S**) (*E*)-ethyl-4-azido-5-hydroxyoct-2-enoate (8a)**: pale orange oil (218 mg, 96% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.89 (1H, dd, *J* 7.2, 15.4 Hz, CH=CHCO), 6.08 (1H, d, *J* 15.4 Hz, CHCO), 4,20 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 4.08 (1H, dd, *J* 3.9, 7.2 Hz, CH-$N_3$), 3.79-3.70 (1H, m, CH-OH), 2.17 (1H, br s, OH), 1.61-1.34 (4H, m, $CH_2$ x2), 1.30 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 0.92 (3H, t, *J* 7.3 Hz, $CH_2CH_2CH_3$); $^{13}$C NMR (75 MHz$CDCl_3$) δ: 165.2, 140.4, 124.7, 72.2, 66.9, 60.3, 34.2, 18.3, 13.6, 13.3

All other experimental data were consistent with the ones reported in the literature[11].

**(4*R**,5*S**) (*E*)-ethyl-4-azido-5-cyclohexyl-5-hydroxypent-2-enoate (8b)**: pail yellow oil (256 mg, 96% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.92 (1H, dd, *J* 7.8, 15.7 Hz, CH=CHCO), 6.05 (1H, d, *J* 15.7 Hz, CHCO), 4.18 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 4.12 (1H, dd, *J* 4.5, 7.8 Hz, CH-$N_3$), 3.41 (1H, dd, *J* 4.5, 7.1 Hz, CH-OH), 2.48 (1H, br s, OH), 1.96-0.85 (14H, m, cyclohexyl +

[11] Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem. Int. Ed.*, **2005**, 44, *32*, 5094 - 5097

$COCH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 165.6, 140.7, 125.6, 76.9, 64.7, 60.9, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 268.1665. $C_{13}H_{21}N_3O_3$ requires 268.1661.

**(4*R*,5S**) (*E*)-ethyl-5-azido-4-hydroxy-5-phenylpent-2-enoate (8c')**: yellow oil (122 mg, 47% yield); $^1H$ NMR (300 MHz $CDCl_3$) δ: 7.44-7.3 (5H, m, Ph), 6.92 (1H, dd, *J* 4.8, 15.7 Hz, C<u>H</u>=CHCO), 6.05 (1H, d, *J* 1.7, 5.7 Hz, C<u>H</u>CO), 4.63 (1H, d, *J* 6.0 Hz, C<u>H</u>-$N_3$), 4.44 (1H, ddd, *J* 1.7, 4.8, 6.0 Hz, C<u>H</u>-OH), 4.18 (2H, q, *J* 7.2 Hz, $COC\underline{H}_2CH_3$), 2.45 (1H, br s, O<u>H</u>), 1.27 (3H, t, *J* 7.2 Hz, $COCH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 169.9, 143.2, 136.1, 128.7, 128.5, 126.7, 123.1, 70.6, 60.5, 43.9, 13.9; HRMS (ES Q-TOF): [M+H]+, found 262.1190. $C_{13}H_{15}N_3O_3$ requires 262.1192

**(4*R*,5S**) (*E*)-4-azido-5-hydroxyoct-2-enenitrile (9a)**: pail yellow oil (157 mg, 87% yield); $^1H$ NMR (300 MHz $CDCl_3$) δ: 6.7 (1H, dd, *J* 6.0, 16.3 Hz, C<u>H</u>=CHCN), 5.67 (1H, dd, *J* 1.5, 16.3 Hz, C<u>H</u>CN), 4.08 (1H, ddd, *J* 1.5, 4.1, 6.0 Hz, C<u>H</u>$N_3$), 3.77 (1H, dt, *J* 4.1, 8.3 Hz, C<u>H</u>-OH), 2.29 (1H, br s, O<u>H</u>), 1.61-1.25 (4H, m, $C\underline{H}_2$ x2), 0.93 (3H, t, *J* 7.2, $C\underline{H}_3$); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 148.3, 116.6, 103.5, 72.8, 67.4, 34.9, 18.8, 13.9; HRMS (ES Q-TOF): [M+H]+, found 181.1083. $C_8H_{12}N_4O$ requires 181.1089

**(4*R*,5S**) (*E*)-4-azido-5-cyclohexyl-5-hydroxypent-2-enenitrile (9b)**: yellow oil (207 mg, 94% yield); $^1H$ NMR (300 MHz $CDCl_3$) δ: 6.78 (1H, dd, *J* 6.8, 16.4 Hz, C<u>H</u>=CHCN), 5.67 (1H, dd, *J* 1.3, 16.4 Hz, C<u>H</u>CN), 4.14 (1H, ddd, *J* 1.3, 4.7, 6.8 Hz, C<u>H</u>$N_3$), 3.45 (1H, dd, *J* 4.7, 7.0 Hz, C<u>H</u>-OH), 2.29 (1H, br s, O<u>H</u>), 1.96-0.9 (11H, m, cyclohexyl); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 148.3, 116.6, 103.5, 76.8, 64.7, 39.9, 29.9, 27.9, 26.2, 25.9, 25.7; HRMS (ES Q-TOF): [M+H]+, found 221.1406. $C_{11}H_{16}N_4O$ requires 221.1403

**(4*S*,5R**) (*E*)-ethyl-4-azido-5-(*tert*-butoxycarbonyl)amino-oct-2-enoate (22)**: pail yellow oil (310 mg, 95% yield); $^1H$ NMR (300 MHz $CDCl_3$) δ: 6.79 (1H, dd, *J* 6.3, 15.6 Hz, C<u>H</u>=CHCO), 6.07 (1H, dd, *J* 15.6 Hz, C<u>H</u>CO), 4.59 (1H, d, *J* 9.01 Hz, N<u>H</u>Boc), 4.31 (1H, dd, *J* 6.3 Hz, C<u>H</u>$N_3$), 4.2 (2H, q, *J* 7.2 Hz, $COC\underline{H}_2CH_3$), 3.77-3.67 (1H, m, C<u>H</u>-NHBoc), 1.48-1.34 (13H, m, $C\underline{H}_2$ x2 + Boc), 1.28 (3H, t, *J* 7.2, $COCH_2C\underline{H}_3$), 0.93 (3H, t, *J* 7.2, $C\underline{H}_3$); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 165.6, 155.5, 141.7, 124.7, 79.9, 66.4, 60.5, 53.5, 31.7, 22.3, 19.5, 14.0, 13.9; HRMS (ES Q-TOF): [M+H]+, found 327.2036 $C_{15}H_{26}N_4O_4$ requires 327.2032.

**(4*S*,5R**) (*E*)-ethyl 4-azido-5-cyclohexyl-5-(ethoxycarbonyl)amino-pent-2-enoate (23)**: yellow oil (321 mg, 95% yield); $^1H$ NMR (300 MHz $CDCl_3$) δ: 6.80 (1H, dd, *J* 6.7, 15.8 Hz,

C<u>H</u>=CHCO), 6.07 (1H, dd, *J* 15.8 Hz, C<u>H</u>CO), 4.59 (1H, d, *J* 10.2 Hz, N<u>H</u>), 4.31 (1H, dd, *J* 2.7, 6.7 Hz, C<u>H</u>$N_3$), 4.2 (4H, q, *J* 7.2 Hz, COC<u>$H_2$</u>$CH_3$ x2), 3.53 (1H, ddd, *J* 2.7, 10.2, 10.7Hz, C<u>H</u>-NH), 1.83-1.55 (5H, m, cyclohexyl), 1.3-0.9 (12H, m, cyclohexyl+ C<u>$H_3$</u> x2); $^{13}$C NMR (75 MHz $CDCl_3$) δ:171.2, 165.4, 142.1, 124.5, 63.4, 61.1, 6.8, 57.8, 39.9, 30.1, 29.0, 26.1, 25.9, 25.8, 14.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 339.2030 $C_{16}H_{26}N_4O_4$ requires 339.2032

**(4*S**,5*R**) (*E*)-ethyl 5-(9-fluorenylmethyloxycarbonyl)amino-4-azidooct-2-enoate** (**24**): pail yellow oil (428 mg, 95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.76-7.30 (8H, m, <u>H</u>$_{Ar\ Fmoc}$), 6.82 (1H, dd, *J* 6.1, 15.5 Hz, C<u>H</u>=CHCO), 6.07 (1H, dd, *J* 15.5 Hz, C<u>H</u>CO), 4.78 (1H, d, *J* 9.01 Hz, N<u>H</u>Fmoc), 4.65 (1H, dd, *J* 6.5, 10.8 Hz, C<u>H</u>$_a$H$_{bFmoc}$), 4.40 (1H, dd, *J* 6.5, 10.8 Hz, CH$_a$<u>H</u>$_{bFmoc}$), 4.3-4.1 (4H, m, C<u>H</u>$N_3$ + C<u>H</u>$_{Fmoc}$ + COC<u>$H_2$</u>$CH_3$), 3.77-3.67 (1H, m, C<u>H</u>-NHFmoc), 1.48-1.2 (7H, m, C<u>$H_2$</u> x2 + $COCH_2$C<u>$H_3$</u>), 0.93 (3H, t, *J* 7.2, C<u>$H_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 156.5, 143.9, 143.8, 141.5, 127.9, 127.2, 125.1, 120.7, 66.9, 66.4, 60.5, 53.5, 47.5, 31.7, 19.5, 14.0, 13.9; HRMS (ES Q-TOF): [M+H]+, found 449.2185. $C_{25}H_{28}N_4O_4$ requires 449.2188

**(4*S**,5*R**) (*E*)-5-(tert-butoxycarbonyl)amino-4-azido-5-cyclohexylpent-2-enenitrile** (**25**): yellow oil (mg, 95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.49 (1H, dd, *J* 10.2, 15.8 Hz, C<u>H</u>=CHCN), 5.57 (1H, d, *J* 15.8 Hz, C<u>H</u>CN), 4.49 (1H, d, *J* 10.1 Hz, N<u>H</u>), 4.33 (1H, dd, *J* 10.2, 9.5 Hz, C<u>H</u>$N_3$), 3.59 (1H, ddd, *J* 10.6, 10.1, 9.5 Hz, C<u>H</u>-NHBoc), 1.87-1.54 (6H, m, cyclohexyl), 1.4 (9H, s, $C(CH_3)_3$), 1.35-1.07 (5H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 155.8, 149.1, 115.0, 103.4, 80.1, 62.9, 57.0, 37.9, 30.6, 28.4, 26.3, 26.1; HRMS (ES Q-TOF): [M+H]+, found 320.2083 $C_{16}H_{25}N_5O_2$ requires 320.2087

**(4*S**,5*R**) (*E*)-5-(ethoxycarbonyl)amino-4-azidooct-2-enenitrile** (**26**): pail yellow oil (238 mg, 95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.61 (1H, dd, *J* 5.5, 16.2 Hz, C<u>H</u>=CHCN), 5.68 (1H, dd, *J* 16.2 Hz, C<u>H</u>CN), 4.7 (1H, d, *J* 9.01 Hz, N<u>H</u>), 4.4-4.3 (1H, m, C<u>H</u>$N_3$), 4.15 (2H, q, *J* 7.2 Hz, COC<u>$H_2$</u>$CH_3$), 3.8-3.7 (1H, m, C<u>H</u>-NH), 1.48-1.28 (4H, m, C<u>$H_2$</u> x2), 1.28 (3H, t, *J* 7.2, $COCH_2$C<u>$H_3$</u>), 0.93 (3H, t, *J* 7.2, C<u>$H_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 156.5, 148.7, 116.7, 103.9, 66.4, 61.5, 53.5, 31.7, 19.5, 14.0, 13.9; HRMS (ES Q-TOF): [M+H]+, found 252.1466 $C_{11}H_{17}N_5O_2$ requires 252.1461

**(4*S**,5*R**) (*E*)-5-(9-fluorenylmethyloxycarbonyl)amino-4-azidooct-2-enenitrile** (**27**): pail yellow oil (383 mg, 95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.76-7.30 (8H, m, <u>H</u>$_{Ar\ Fmoc}$), 6.58 (1H, dd, *J* 5.3, 16.2 Hz, C<u>H</u>=CHCN), 5.65 (1H, dd, *J* 16.2 Hz, C<u>H</u>CN), 4.78 (1H, d, *J* 8.9 Hz, N<u>H</u>Fmoc), 4.56-4.29 (3H, m, C<u>$H_2$</u>C<u>H</u>$_{Fmoc}$), 4.21 (1H, dd, *J* 5.3 Hz, C<u>H</u>$N_3$), 3.8-3.7 (1H, m, C<u>H</u>-NHFmoc), 1.48-1.2 (4H, m, C<u>$H_2$</u> x2), 0.93 (3H, t, *J* 7.2, C<u>$H_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 156.5,

148.9, 143.8, 141.5, 127.9, 127.2, 125.1, 120.7, 116.5, 103.5, 66.9, 66.4, 60.5, 53.5, 47.5, 31.7, 19.5, 13.9; HRMS (ES Q-TOF): [M+H]+, found 402.1929. $C_{23}H_{23}N_5O_2$ requires 402.1929

# Chapter 4. Regio- and stereocontrolled opening of three-membered heterocyclic rings: a greener approach[1].

## 1. Introduction.

The concept of 'green chemistry', firstly used in 1991 by P.T. Anastas, incorporates a new approach to the synthesis, processing and application of chemical substances aiming at reducing threats to health and the environment. It can be described by 12 principles[2]:

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible

[1] Righi, G.; Barontini, M.; Bovicelli, P.; Tirotta, I. *Green Chem., submitted*

[2] Anastas, Paul, T.; Warner, J. C. Green Chemistry Theory and Practice (Oxford University Press, New York) 1998.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

In this work, focusing particularly on some of these twelve principles (see from **2** to **6**), we were intrigued by the possibility of replacing harmful or carcinogenic solvents (such as dichloromethane, acetone, etc.) with the non-harmful dimethyl carbonate (DMC), a green reagent that has been gaining prominence in the past two decades for its versatility.

Until recently DMC has been used mainly as a non-toxic reagent, particularly as a methylating agent instead of the carcinogenic methyl iodide or dimethyl sulphate, or as a carbonylating agent in place of the very toxic phosgene. It is characterized by three reactive electrophilic centers: two methyl groups and a carbonyl.

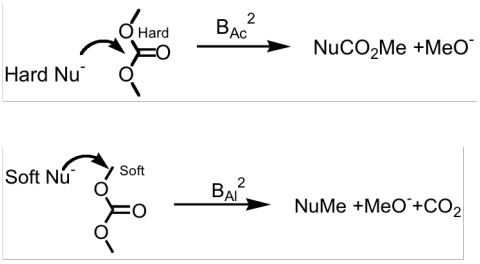



**Fig. 1 Reactivity of DMC in the presence of a nucleophile.**

P. Tundo *et al.* [1,2] have published a large number of works on the use of DMC as methylating and methoxycarbonylating agent: selecting the appropriate nucleophile and reaction conditions it is possible to discriminate between its two different reactivities (Fig. 1). For both the reactions the only by-products are $CO_2$ (non toxic) and methanol (easily removable and recoverable)[3]. All the while, due to its properties and low toxicity, DMC is a good, environmentally friendly reaction media (Table 1)[4]. It is almost completely insoluble in water, but miscible in a vast array of organic solvents (e.g.. methanol, diethyl ether, etc.) and it is able to dissolve a wide range of organic molecules.

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[1] a) Tundo, P. *Pure Appl. Chem.* **2001**, *73*, 1117-1124. b) Memoli, S.; Selva, M.; Tundo, P. *Chemosphere* **2001**, *43*, 115-121. c) Tundo, P.; Perosa, A. Chem. Rec. **2002**, 2, 1343-1346.

[2] a) Tundo, P.; Selva, M. *Acc. Chem. Res*. **2002**, *35*, 706-716. b) Tundo, P.; Memoli, S.; Herault, D.; Hill, K. *Green Chem*. **2004**, *6*, 609-616. c) Tundo, P.; Rossi, L.; Loris, A. *J. Org. Chem.* **2005**, *70*, 2219-2224. d) Bonino, F.; Damin, A.; Bordiga, S.; Selva, M.; Tundo, P.; Zecchina, A. *Angew. Chem. Int. Ed.* **2005**, 44, 4774-4777.

[3] Delledonne, D.; Rivetti, F. *J. Organomet. Chem.* **1995**, *448*, 15-18.

[4] a) Serad G.A. Fibers, Carbonic esters. In Encyclopedia of chemical technology Kirk- Uthmer [electronic version] (2007); b) Sigma-Aldrich MSDS

Moreover it can be extremely easily removed from the reaction mixture exploiting the fairly volatile azeotrope with methanol (MeOH/DMC= 4/1, bp 60°C).

**Table 1 DMC, chemical and physical properties.**

| **Properties** | | |
|---|---|---|
| **Solubility parameters** | $(cal/cm^3)^{1/2}$ | 9.9 |
| **Miscibility in water** | Solvent $H_2O_2$ , %w | 12.8 |
| **Boiling point** | °C | 90 |
| **LD50** | Oral, mice, g/Kg | 13.8 |
| **LC50** | Oral, mice, ppm | 35000/4h |
| **Biodegradability** | 28 days in a closed bottle | 89 |
| **Irritability** | Non irritant | |
| **VOC** | Class V | |

Despite its characteristics and its low toxicity there still is a limited number of works[1] in the literature that make use of DMC as a solvent in synthetic reactions.

The knowledge gathered through the past years by our group on the ring-opening of three membered heterocycles and the wide range of synthetic applications of these methodologies prompted us to investigate the possibility of performing the already reported reactions in a more eco-friendly media such as DMC.

## 2. Results and discussion.

Six classes of substrates have been chosen for this study (Fig. 2): epoxy alcohols (type **A**), silylated aziridino alcohols (type **B**), epoxy- and aziridino esters (type **C** and **D**), vinyl epoxides (type **E)** and vinyl aziridines (type **F**).

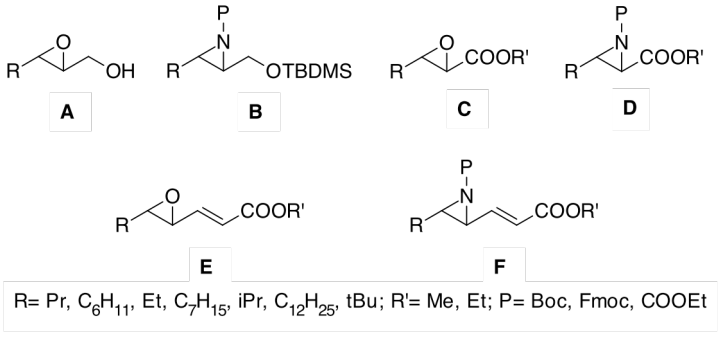
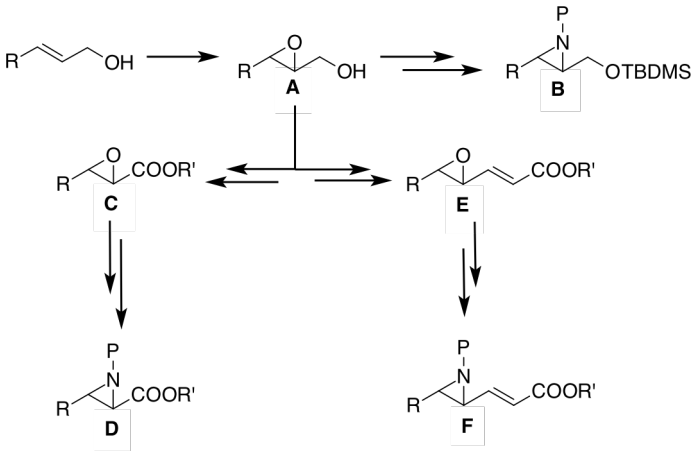



**Fig. 2 Classes of substrates of choice.**

[1] a) Yoshio, O. *Catalysis Today* **1997**, *35*, 15-25; b) Bernini, R.; Mincione, E.; Barontini, M.; Crisante, F.; Fabrizi, G. *Tetrahedron*, 2007, *63*, 6895-6900.

As shown in Scheme 1, all the substrates can be easily prepared from the same allylic alcohol in fairly few steps[1]. Moreover they can be readily obtained in both their enantiomerically pure forms performing the epoxidation reaction using the Sharpless protocol; since all the reactions are stereoselective these pathways can easily gain access to optically active fragments. However for this study all the reactions were performed on the racemic compounds[2].




**Scheme 1 Synthetic path**

As reported in our precedent works, these substrates, when submitted to the reactions reported below, afforded the corresponding derivatives with complete stereoselectivity and good to excellent regioselectivity. Moreover changes in the functionalizations (R, R‘ and P groups) have none to little influence on the regiochemistry of the reactions: the steric hindrance exerted by the R group on the ring can only slightly influence the regioselectivity and the aziridine ring activation due to the protective group is the same for all the carbamates.

The nucleophilic ring-opening methodologies examined are:

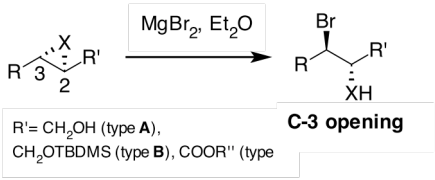
1. $MgBr_2$
2. LiBr/Amberlyst15
3. NaBr/Amberlyst15
4. $BF_3 \cdot Et_2O/TMSN_3$

[1] All the substrates of this study were synthesised using the procedures reported in the works previously published by our group cited in the following paragraphs and also reported in the following articles and other works therein cited: a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc*. **1973,** 95, *18*, 6136-6137; b) Gao, Y.; Klunder, J.M.; Hanson, R.M.; Masamune, H.; Ko, S.Y.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, 109, *19*, 5765-5780; c) Tanner, D.; He, H.M.; Somfai, P. *Tetrahedron* **1992**, 48, *29*, 6069-6078; d) Legters, J.; Thijs, L.; Zwanemburg, B., *Recle. Trav. Chim. Pays-Bas*, **1992**, *111*, 1-15; e) Dai-Fei,H.; Liang, H. *Tetrahedron* **1990**, 46, *9*, 3135-3142

[2] For the purpose of this work it is not mandatory to have optically active compounds, all the molecules are intended as racemates and the stereochemistry is only reported as the relative one.

## *2.1. $MgBr_2$ mediated ring-opening reactions.*[3]

In this methodology $MgBr_2$ acts both as the nucleophile source and as the Lewis acid required to activate the ring towards the bromine attack. The reaction, firstly reported on epoxy alcohols[4] (type **A**) to give 1-bromodiols, was extended to silylated aziridino alcohols[5] (type **B**), epoxy esters[6] (type **C)** and aziridino esters[7] (type **D),** leading to the corresponding C-3 halo derivatives (Scheme 2).




**Scheme 2 $MgBr_2$ mediated ring-opening reaction on substrates types A, B, C, D.**

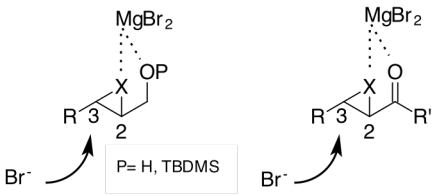
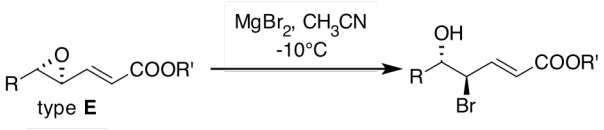



**Fig. 3 Five membered chelate.**

The regioselectivity of $MgBr_2$ towards the C-3 position seems to be due to the chelating properties of Mg[8]: the formation of a five membered chelate between the ring heteroatom, the oxygen on the adjacent carbon and the metal leaves the carbon in 3 more easily attacked by the nucleophile (Fig. 3).

More recently this methodology has been reported also on vinyl epoxides[9] (type **E**) (Scheme 3): in this case the nucleophilic attack occurs preferentially at the allylic position and the regioselectivity is solely due to the peculiar reactivity of this position.




**Scheme 3 $MgBr_2$ mediated ring-opening reaction on substrates type E.**

As reported, the reaction is generally performed in $Et_2O$ at room temperature and the work-up requires of a filtration, washings with aqueous solutions and multiple extractions. It makes a slight exception the case of vinyl epoxides which are reported to react best in $CH_3CN$ at -10°C and therefore require a previous removal of the solvent during the work-up.

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[3] Federici, C.; Righi, G.; Rossi, L.; Bonini, C.; Chiummento, L; Funicello, M. *Tetrahedron Lett.*, **1994**, 35, *5*, 797-800

[4] Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.,* **1991**, *56*, 6206-6209

[5] Righi, G.; Franchini, T.; Bonini, C. *Tetrahedron Lett*., **1998**, *39*, 2385-2388

[6] Righi, G.; Rumboldt, G. *J. Org. Chem,* **1996**, *61*, 3557-3560

[7] Righi, G.; D'Achille, R. *Tetrahedron Lett*., **1996**, 37, 38, 6893-6896

[8] Righi, G.; Chionne,A.; Bonini, C. *Eur. J. Org. Chem.* **2000**, *18*, 3127-3131

[9] Ha, Kim, S.Y.; Lee, S.J.; Kang, S.K.; Ahn, J.H.; Kim, S.S; Choi, J.K. *Tetrahedron Lett.*, **2004**, *45*, 5969-5972

Table 2 summarizes our results against literature data (when present) for the reactions performed in harmful solvents.

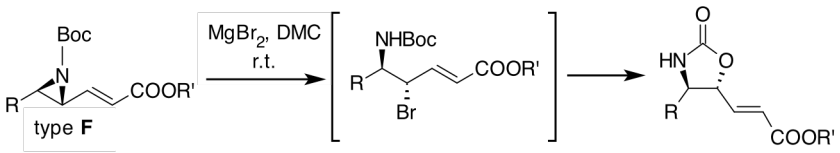
**Table 2 General trends of the $MgBr_2$ mediated ring-opening reactions in DMC vs harmful solvents.**

| Entry | Substrate type | Solvent | $MgBr_2$ (eq.) | T (C°) | Time (h) | Yield[a] (%) | Regioselectivity[b] (%) |
|---|---|---|---|---|---|---|---|
| **1** | **A** | dry $Et_2O$ | 1 | -60 | 2-4 | 85-90 | ≥95 |
| **2** | **A** | DMC | 1 | r.t. | 5-10 | ≥95 | ≥95 |
| **3** | **B** | $Et_2O$ | 2 | r.t. | 2-4 | ≥95 | ≥95 |
| **4** | **B** | DMC | 2 | r.t. | 5-10 | ≥95 | ≥95 |
| **5** | **C** | $Et_2O$ | 1.5 | r.t. | 2-4 | ≥95 | ≥95 |
| **6** | **C** | DMC | 1.5 | r.t. | 5-10 | ≥95 | ≥95 |
| **7** | **D** | $Et_2O$ | 1.5 | r.t. | 2-4 | ≥95 | ≥95 |
| **8** | **D** | DMC | 1.5 | r.t. | 5-10 | ≥95 | ≥95 |
| **9** | **E** | $CH_3CN$ | 1 | -10 | 5-10 | ≥90 | 85-95 |
| **10** | **E** | DMC | 1 | r.t. | 1-2 | ≥95 | ≥95 |
| **11** | **F** | Never reported in harmful solvents | | | | | |
| **12** | **F** | DMC | 1 | r.t. | 1-2 | ≥95 | ≥95 |

[a] yields of the regioisomeric mixture
[b] regioselectivity towards the C-3 position for entries 1-8, and towards the allylic position for entries 9-12

In all cases $Et_2O$ and $CH_3CN$ were successfully replaced with DMC and no substantial loss of regioselectivity nor yield decrease was observed. All the reactions were performed at room temperature, even the ones previously reported at low temperatures, and the only noticeable difference is in the reaction times (see Table 2: 5-10h DMC vs. 2-4h $Et_2O$ Entries **1-8**; 1-2h DMC vs. 5h $CH_3CN$ Entries **9-10**). Moreover, the work-up was simplified to a filtration and subsequent removal of the DMC in vacuo, upon addition of 3 volumes of methanol.

Regarding the $MgBr_2$ mediated opening of N-Boc protected vinyl aziridines (type **F**), to the best of our knowledge never reported in the literature, the reaction in DMC led to a *trans* oxazolidinone, characterized by the presence of the oxygen in the allylic position, as the major product (Scheme 4). This can be explained by an intramolecular nucleophilic substitution of the bromine, regioselectively introduced in the allylic position, by the

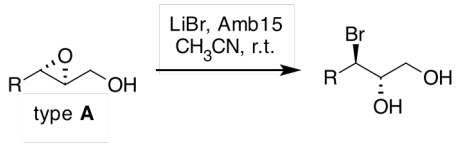



**Scheme 4 Spontaneous oxazolidinone formation in the $MgBr_2$ mediated ring-opening reaction of N-Boc protected vinyl aziridines.**

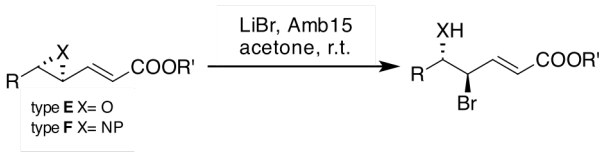
Boc carbonyl group driven by the peculiar reactivity of the allylic position and already reported for nucleophile mediated ring-opening reactions of N-Boc protected vinyl aziridines[10].

*2.2. LiBr/Amb15 mediated ring-opening reactions.*

Similar considerations as for the $MgBr_2$ mediated opening reactions can be made for this methodology. It was firstly reported on 2,3-epoxy alcohols[11] (Scheme 5) leading to the same compounds as the $MgBr_2$ method. In this case the regioselectivity is due to the chelating effect of the lithium, while the Amberlyst15 (an acidic resin) activates the heterocyclic ring: without it the reaction does not start.




**Scheme 5 LiBr/Amb15 mediated ring-opening reaction on 2,3-epoxyalcohols type A.**




**Scheme 6 LiBr/Amb15 mediated ring-opening reaction on substrates types E and F.**

The methodology was then extensively reported on vinyl compounds[12] (type **E** and **F**, Scheme 6) as a method of general value, with low to zero influence of the compounds functionalizations on the regiochemistry of the reaction, which is due exclusively to the peculiar reactivity of the allylic position.

The reaction is reported in either acetone or $CH_3CN$ at room temperature (except for vinyl aziridines that require a temperature of -20°C) and the work-up is the same as for the reaction with $MgBr_2$. Table 3 summarizes our results against literature data (when present) for the reactions performed in harmful solvents. As shown, it was possible to replace acetone and $CH_3CN$ with DMC, performing all the reactions at room temperature and avoiding the work-ups by filtering the reaction mixture and removing the solvent in vacuo upon addition of four volumes of methanol. Performing these reactions in DMC it is not only possible to obtain the same yields as reported for the reactions in acetone in a consistent amount of time, but also to enhance the regioselectivity (see

[10] see ref. 19 b

[11] Bonini, C.; Giuliana, C.; Righi, G.; Rossi, L. *Synth. Comm.* **1992**, 22, *13*, 1863-1870

[12] a) Antonioletti, R.; Bovicelli, P.; Fazzolari, E.; Righi, G. *Tetrahedron Lett*. **2000**, *41*, 9315–9318. b) Righi,G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett*. **2002**, *43*, 5867–5869

Entries **2** and **12**). Moreover this methodology is reported, to the best of our knowledge, for the first time on compounds type **B**, **C** and **D**.

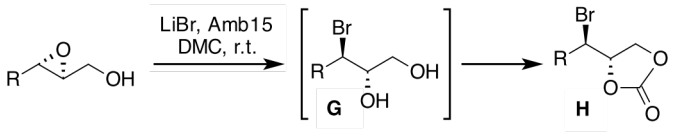
**Table 3 General trends of the LiBr/Amb15 mediated ring-opening reactions in DMC vs harmful solvents.**

| Entry | Substrate type | Solvent | LiBr (eq.) | Amb15 (eq.) | T (C°) | Time (h) | Yield[a] (%) | Regioselectivity[b] (%) |
|---|---|---|---|---|---|---|---|---|
| **1** | **A** | $CH_3CN$ | 1 | 1 | r.t. | 2-4 | ≥95 | ≥90 |
| **2** | **A** | DMC | 2 | 2 | r.t. | 5 | ≥90 | ≥95 |
| **3** | **B** | Never reported in harmful solvents | | | | | | |
| **4** | **B** | DMC | 4 | 2 | r.t. | 5 | ≥90 | ≥95 |
| **5** | **C** | Never reported in harmful solvents | | | | | | |
| **6** | **C** | DMC | 4 | 2 | r.t. | 5 | ≥95 | ≥95 |
| **7** | **D** | Never reported in harmful solvents | | | | | | |
| **8** | **D** | DMC | 4 | 2 | r.t. | 5 | ≥95 | ≥90 |
| **9** | **E** | acetone | 4 | 1 | r.t. | 2 | ≥95 | ≥95 |
| **10** | **E** | DMC | 4 | 1 | r.t. | 2 | ≥95 | ≥95 |
| **11** | **F** | acetone | 4 | 1 | -20 | 2 | ≥90 | ≥90 |
| **12** | **F** | DMC | 4 | 1 | r.t. | 2 | ≥95 | ≥95 |

[a] yields of the regioisomeric mixture

[a] regioselectivity towards the C-2 position for entries 1-8, and towards the allylic position for entries 9-12

Particularly interesting is the case of 2,3-epoxy alcohols (type **A**): after five hours and the substrate consumption, NMR on crude revealed a mixture of the desired product and a small amount of a cyclic carbonate **H** (Scheme 7) presumably derived from the partial trans-esterification of the bromodiol **G**. Prolonging the reaction time to 12 hours, compound **H** was recovered as the major product. This reaction allows the one-pot formation of a protected 1,2-diol from an epoxide. This seems particularly interesting since cyclic carbonates are common 1,2-diol protecting groups in the carbohydrate chemistry: they are very stable to acidic conditions, more stable to basic ones than esters and can also be easily cleaved to give mono-protected diols.

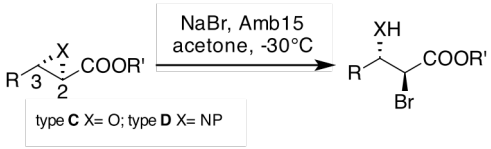



**Scheme 7 LiBr/Amb15 mediated opening of substrate type A: cyclic carbonate formation.**

As already reported for the reaction in acetone, when N-Boc protected vinyl aziridines were reacted with the LiBr/Amb15 methodology the only product recovered was a *trans* oxazolidinone.

*2.3. NaBr/Amb15 mediated ring-opening reactions.*

This methodology (Scheme 8) was firstly reported on epoxy esters[13] and is complementary to the previous one (LiBr/Amb15): in this case Amberlyst 15 works again as an activating agent of the heterocyclic ring but the sodium is unable to form a chelate, therefore the nucleophilic attack preferentially occurs at the C-2 position, the most reactive one, leading to α-bromoderivatives. The methodology works as well on aziridino esters[14] and is particularly interesting because can lead to 2,3-bromo amines which, after further elaborations, can give access to β-aminoacids.




**Scheme 8 NaBr/Amb 15 mediated ring-opening reaction on substrates type C and D**

In acetone a temperature of at least -30°C is required in order to favor the formation of the kinetic product. In the case of DMC, the melting point of the solvent is 5°C so the reaction had to be performed at room temperature. Surprisingly a satisfying regioselectivity was observed: after approximately five hours the reaction was complete and a mixture of the two regioisomers with a ratio of, on average, 80:20 in favor of the α-bromoderivative was observed (Table 4).

**Table 4 General trends of the NaBr/Amb15 mediated ring-opening reactions in DMC vs harmful solvents.**

| Entry | Substrate type | Solvent | NaBr (eq.) | Amb15 (eq.) | T (C°) | Time (h) | Yield[a] (%) | Regioselectivity[b] (%) |
|---|---|---|---|---|---|---|---|---|
| **1** | **C** | acetone | 2 | 1 | -30 | 6 | ≥95 | ≥95 |
| **2** | **C** | DMC | 2 | 1 | r.t. | 5-10 | ≥95 | ≥85 |
| **3** | **D** | $Et_2O$ | 2 | 1 | -40 | 6 | ≥95 | 75-95 |
| **4** | **D** | DMC | 2 | 1 | r.t. | 5-10 | ≥95 | 70-80 |

[a] yields of the regioisomeric mixture

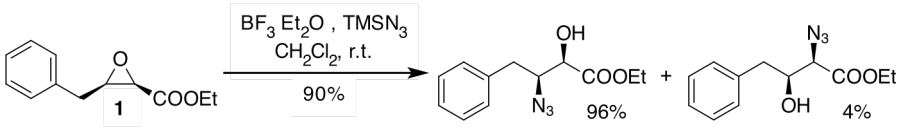
[b] regioselectivity towards the C-2 position

[13] Righi, G. Rumboldt, G. *Tetrahedron* **1995**, 51, *48*, 13401-13408

[14] Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, 8, *6*, 903-907

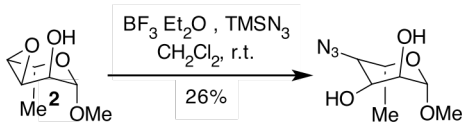
*2.4. $BF_3$•$Et_2O$/$TMSN_3$ mediated ring-opening reactions.*

As explained in Chapter 3, this methodology was recently reported by Rodrigues[15] on epoxy ester **1** (Scheme 9) and it makes use of $TMSN_3$ as the nucleophile source and $BF_3{\cdot}Et_2O$ as the Lewis acid. The regioselectivity of the reaction seems to be due to the chelating ability of $BF_3{\cdot}Et_2O$ that can direct the $N_3$ attack towards the C-3 position. However, as the author himself reports, this methodology seems not to be of general value.

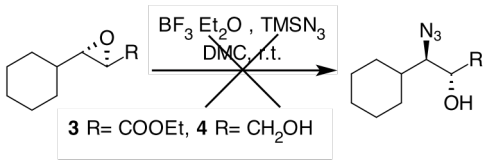



**Scheme 9 $BF_3{\cdot}Et_2O$/$TMSN_3$ mediated ring-opening reaction on an epoxy ester (Rodrigues).**

More recently Kiefel M. J.[16] reported that epoxy alcohol **2** reacts with $BF_3{\cdot}Et_2O$ and $TMSN_3$ to give the desired azido alcohol with an excellent regioselectivity but in very poor yield (Scheme 10).




**Scheme 10 $BF_3{\cdot}Et_2O$/$TMSN_3$ mediated ring-opening reaction on an epoxyalcohol (Kiefel).**




**Scheme 11 $BF_3{\cdot}Et_2O$/$TMSN_3$ mediated ring-opening reaction on substrates type A and C.**

Performing the reaction in $CH_2Cl_2$ (Scheme 11) on compounds **3**, even after 12 hours, only the starting material was recovered, whilst compound **4** led to a complex mixture.

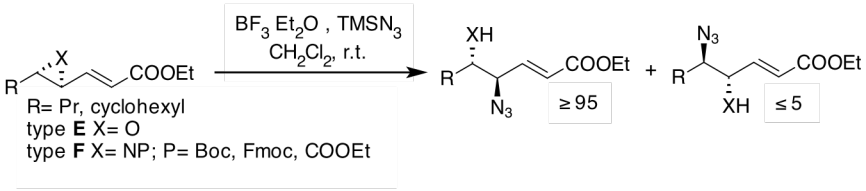
All the same this methodology has been found to be of general value when applied on vinyl compounds[17] (type **E** and **F**), although to the best of our knowledge it was never reported in the literature. As described in Chapter 4, a study on these reactions has been recently carried out by our group (Scheme 12): the methodology has been found to be highly reproducible, with really high yields (≥95%) and regioselectivity (≥98%) which is solely due to the reactivity of the allylic

[15] Augusto, J.; Rodrigues, R.; Milagre, H.M.S.; Milagre, C.D.F.; Moran, P.J.S. *Tetrahedron: Asymmetry* **2005**, *16*, 3099–3106

[16] Zunk, M.; Kiefel, M.J. *Tetrahedron Lett.* **2011**, *52*, 1296–1299

[17] a) Righi, G.; Salvati Manni, L.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett.* **2011**, *52*, 3895–3896. b) Righi, G.; Marucci, C.; Bovicelli, P.; Tirotta, I. submitted

position; none to very little influence on the regiochemistry of the reaction was exerted by the steric hindrance of the R group or the aziridine protective group.




**Scheme 12 $BF_3$·$Et_2O$/$TMSN_3$ mediated opening reaction on substrates type E and F**

Exactly the same results were obtained replacing $CH_2Cl_2$ with DMC: neither the yields nor the regioselectivity were affected at all (see Table 5). Also in this case the work-up was simplified from a quench with ice cold water followed by a washing with a basic solution and several extractions, to a simple removal in vacuo of the solvent.

**Table 5 General trends of the $BF_3$·$Et_2O$/$TMSN_3$ mediated ring-opening reactions in DMC vs $CH_2Cl_2$**

| Entry | Substrate type | Solvent | $BF_3$·$Et_2O$ (eq.) | $TMSN_3$ (eq.) | T (C°) | Time (h) | Yield[a] (%) | Regioselectivity[a] (%) |
|---|---|---|---|---|---|---|---|---|
| **1** | **C** | $CH_2Cl_2$ | 2 | 1 | r.t. | 1-2 | ≥95 | ≥95 |
| **2** | **C** | DMC | 2 | 1 | r.t. | 1-2 | ≥95 | ≥95 |
| **3** | **D** | $CH_2Cl_2$ | 2 | 1 | r.t. | 0.5-1 | ≥95 | ≥95 |
| **4** | **D** | DMC | 2 | 1 | r.t. | 0.5-1 | ≥95 | ≥95 |

[a] yields of the regioisomeric mixture

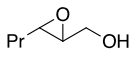
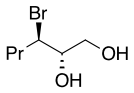
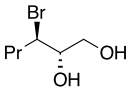
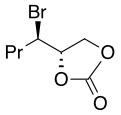
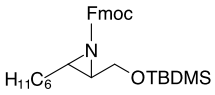
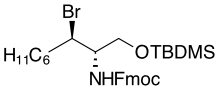
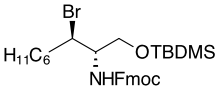
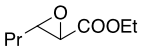
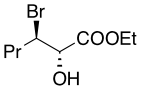
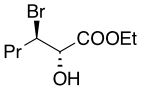
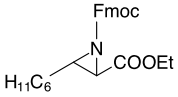
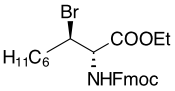
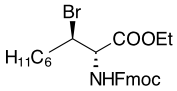
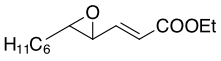
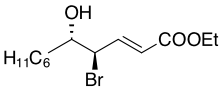
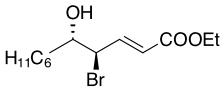
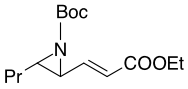
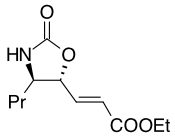
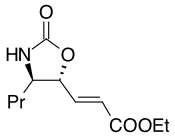
[b] regioselectivity towards the allylic position

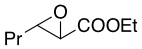
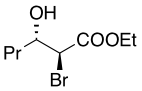
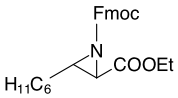
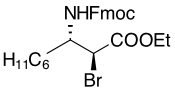
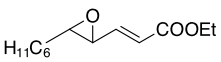
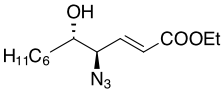
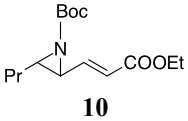
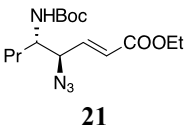
## 3. Conclusions.

These data show how easily dichloromethane, $Et_2O$ and acetone can be replaced with DMC in the four nucleophile mediated ring-opening reactions of choice. It was also possible to reduce the need of work-ups and therefore the amount of solvents used during the whole procedure, and to perform all the reactions at room temperature. The reactions proved to be completely stereo and regioselective in the new, greener conditions.

An overall summary of the results of this study is reported in Table 6. Selected compounds for each class are reported.

**Table 6 Results for selected compounds.**

| | | | Products | | | |
|---|---|---|---|---|---|---|
| **Entry** | **Class** | **Substrate** | **$MgBr_2$** | **Yield (%)** | **LiBr/ Amb15** | **Yield (%)** |
| **1** | **A** |  **5** |  **11** | 95 |  **11** | 90[a] |
| **2** | | | | |  **17** | 70[b] |
| **3** | **B** |  **6** |  **12** | 96 |  **12** | 92 |
| **4** | **C** |  **7** |  **13** | 97 |  **13** | 95 |
| **5** | **D** |  **8** |  **14** | 95 |  **14** | 95 |
| **6** | **E** |  **9** |  **15** | 98 |  **15** | 96 |
| **7** | **F** |  **10** |  **16** | 97 |  **16** | 96 |

| | | | Products | | | |
|---|---|---|---|---|---|---|
| **Entry** | **Class** | **Substrate** | **NaBr/ Amb15** | **Yield (%)** | **$BF_3$•$Et_2O$/ $TMSN_3$** | **Yield (%)** |
| **8** | **C** |  **7** |  **18** | 80 | - | - |
| **9** | **D** |  **8** |  **19** | 70 | - | - |
| **10** | **E** |  **9** | - | - |  **20** | 99 |
| **11** | **F** |  **10** | - | - |  **21** | 99 |

[a] after 4 hours

[b] after 12 hours

# 4. Experimental.

## *4.1. General.*

$^{1}$H nmr spectra were recorded using a Varian Mercury 300 (300 MHz). Residual solvent peaks were used as internal references for $^{1}$H nmr spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. $^{13}$C spectra were recorded using a Varian Mercury 300 (75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak: chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml.

All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 aluminium sheets (Merck Italia) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)].

Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

## *4.2. General procedures.*

### *4.2.1. General procedure for the $MgBr_2$ mediated ring-opening reactions.*

$MgBr_2$ (2 mmol, 516 mg) was added to 1 mmol of the appropriate substrate dissolved in 10 ml of DMC and the mixture left stirring at room temperature. After complete consumption of the substrate (TLC monitoring) the mixture was filtered and the solvent evaporated in vacuo to give the desired product.

### *4.2.2 General procedure for the LiBr/Amb15 mediated ring-opening reactions.*

LiBr (4 mmol, 260 mg) and Amberlyst15 (1 mmol, 212 mg) were added to 1 mmol of the appropriate substrate dissolved in 10 ml of DMC and the mixture left stirring at room temperature until completion of the reaction (TLC monitoring). After filtration of the mixture, the solvent was removed in vacuo to give the desired product.

### *4.2.3 General procedure for the NaBr/Amb15 mediated ring-opening reactions.*

NaBr (4 mmol, 260 mg) and Amberlyst15 (2 mmol, 424 mg) were added to 1 mmol of the appropriate substrate dissolved in 10 ml of DMC and the mixture left stirring at room temperature until completion of the reaction (TLC monitoring). After filtration of the mixture, the solvent was evaporated in vacuo to give the desired product.

### *4.2.4 General procedure for the $BF_3/TMSN_3$ mediated ring-opening reaction.*

To a stirred solution of the appropriate substrate (1 mmol) in DMC (10 ml), $TMSN_3$ (1 mmol, 115 mg; 0,13 ml) and $BF_3 \cdot OEt$ (2 mmol, 28 mg; 0,25 ml) were added drop-wise and the mixture left stirring at room temperature. After complete consumption of the substrate (TLC monitoring) the reaction mixture was diluted with DMC and washed with saturated solutions of $NaHCO_3$ and NaCl until pH7. The organic layer was dried on $Na_2SO_4$ and the solvent evaporated in vacuo to leave the desired product.

*4.3. Experimental data for representative compounds.*

**(*2S*,3R**)-3-bromo-hexan-1,2-diol** (**11**): colorless oil (90-95% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 4.12-4.06 (1H, m, C<u>H</u>Br), 3.88-3.73 (3H, m, C<u>H</u>$_2$OH + C<u>H</u>OH), 2.8 (1H, br s, O<u>H</u>), 2.32 (1H, br s, O<u>H</u>), 1.96-1.75 (2H, m, C<u>H</u>$_2$CH$_2$CH$_3$), 1.72-1.36 (2H, m, CH$_2$C<u>H</u>$_2$CH$_3$), 0.95 (3H, t, *J* 7.4, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 74.8, 64.4, 58.3, 36.2, 20.9, 13.5; HRMS (ES Q-TOF): [M+H]+, found 197.0179. $C_6H_{13}BrO_2$ requires 197.0177.

**(*2S*,3R**)-2-(N-9-fluorenylmethyloxycarbonyl)amino-3-bromo-3-cyclohexyl-(O-tert-butyl dimethylsilyl)propanol** (**12**): pail yellow oil (92-96% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.78 (2H, d, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.61 (2H, d, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.42 (2H, dd, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.33 (2H, dd, *J* 7.4 Hz, Ar$_{Fmoc}$), 5.19 (1H, d, *J* 8.4 Hz, N<u>H</u>), 4.47-4.36 (2H, m, C<u>H</u>$_{2Fmoc}$), 4.26 (1H, dd, *J* 6.9 Hz, C<u>H</u>$_{Fmoc}$), 4.17-4.02 (3H, m, C<u>H</u>$_2$OTBDMS + C<u>H</u>Br), 3.83-3.74 (1H, m, C<u>H</u>-NHFmoc), 2.04-1.60 (5H, m, cyclohexyl), 1.46-1.11 (6H, m, cyclohexyl), 0.9 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.11 (6H, s, Si(C<u>H</u>$_3$)$_2$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 155.7, 144.2, 141.5, 127.8, 12.1, 125.1, 120.1, 67.0, 64.4, 63.9, 59.8, 47.3, 40.3, 32.2, 29.3, 26.3, 26.0, 25.9, 18.4, -5.2; HRMS (ES Q-TOF): [M+H]+, found. 572.2190. $C_{30}H_{42}BrNO_3Si$ requires 572.2194.

(***2S*,3R****) ethyl 3-bromo-2-hydroxyhexanoate** (**13**): pail yellow oil (95-97% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 4.38 (1H, d, *J* 3.1 Hz, C<u>H</u>OH), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.18-4.1 (1H, m, C<u>H</u>Br), 3.48 (1H, br s, O<u>H</u>), 1.96-1.75 (2H, m, C<u>H</u>$_2$CH$_2$CH$_3$), 1.72-1.36 (2H, m, CH$_2$C<u>H</u>$_2$CH$_3$), 1.31 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.95 (3H, t, *J* 7.4, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 74.5, 62.4, 57.3, 32.2, 25.9, 13.2, 14.3; HRMS (ES Q-TOF): [M+H]+, found. 239.0280 $C_8H_{15}BrO_3$ requires 239.0283.

**(*2S*, 3R**)-ethyl 2-(N-9-fluorenylmethyloxycarbonyl)amino-3-bromo-3-cyclohexyl propanoate (14)**: pail yellow oil (95% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.78 (2H, d, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.61 (2H, d, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.42 (2H, dd, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.33 (2H, dd, *J* 7.4 Hz, Ar$_{Fmoc}$), 5.19 (1H, d, *J* 8.4 Hz, N<u>H</u>), 4.47-4.36 (2H, m, C<u>H</u>$_{2Fmoc}$), 4.26 (1H, dd, *J* 6.9 Hz, C<u>H</u>$_{Fmoc}$), 4.32-4.16 (3H, m, C<u>H</u>-NHFmoc + COC<u>H</u>$_2$CH$_3$), 3.96 (1H, dd, *J* 6.6, 8.4, C<u>H</u>Br), 2.04-1.60 (5H, m, cyclohexyl), 1.46-1.11 (6H, m, cyclohexyl), 1.31 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 168.8; 155.3; 143.7; 143.6; 141.3; 127.7; 127.0; 125.0; 119.9; 67.2; 64.0; 61.9; 55.8; 47.2; 41.4; 31.7; 30.9; 26.1; 25.8; 14.1; HRMS (ES Q-TOF): [M+H]+, found. 500.1439. $C_{26}H_{30}BrNO_4$ requires 500.1435.

***(E)*-(4*R*,5S**)-ethyl 4-bromo-5-cyclohexyl-5-hydroxypent-2-enoate** (**15**): pail yellow oil (96-98% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.15 (1H, dd, *J* 10.2, 15.6 Hz, C<u>H</u>=CHCO), 6.02 (1H, d, *J* 15.6 Hz, CH=C<u>H</u>CO), 4.79 (1H, dd, *J* 3.8, 10.2 Hz, C<u>H</u>Br), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.64 (1H, dd, *J* 3.8, 7.7 Hz, C<u>H</u>-OH), 2.8 (1H, br s, O<u>H</u>), 1.8-0.93 (14H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 140.7, 125.6, 76.9, 64.7, 60.9, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2. HRMS (ES Q-TOF): [M+H]+, found 305.0720. $C_{13}H_{21}BrO_3$ requires 305.0725

**(*E*)-ethyl 3-((4*R*,5S**)-2-oxo-4-propyloxazolidin-5-yl)acrylate** (**16**): pail yellow oil (96-97% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.96 (1H, dd, *J* 5.1, 15.4 Hz, C<u>H</u>=CHCO), 6.42 (1H, br s, N<u>H</u>), 6.06 (1H, dd, *J* 1.5, 15.4 Hz, CH=C<u>H</u>CO), 4.74 (1H, ddd, *J* 1.5, 6.6 Hz, C<u>H</u>CH=CH), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.54 (1H, dd, *J* 6.6 Hz, C<u>H</u>NH), 1.90-1.42 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.31 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.95 (3H, t, *J* 7.4, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.5, 158.4, 141.8, 123.2, 80.2, 60.9, 57.7, 37.0, 18.6, 14.1, 13.7; HRMS (ES Q-TOF): [M+H]+, found. 228.1239 $C_{11}H_{17}NO_4$ requires 228.1236

**(*S**)-4-((*R**)-1-bromobutyl)-1,3-dioxolan-2-one** (**17**): colorless oil (70% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 4.74 (1H, ddd, *J* 6.7, 8.2 Hz, C<u>H</u>OCO), 4.6 (1H, dd, *J* 6.7, 8.9 Hz, C<u>H$_a$</u>-<u>H$_b$</u>-OCO), 4.35 (1H, dd, *J* 6.7, 8.9 Hz, CH$_a$-<u>H$_b$</u>-OCO), 4.03 (1H, ddd, *J* 3.2, 8.2, 9.7 Hz, C<u>H</u>Br), 2.07-1.38 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.95 (3H, t, *J* 7.4, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 159.4, 77.7, 68.3, 54.4, 36.2, 20.0, 13.3; HRMS (ES Q-TOF): [M+H]+, found 222.9973. $C_7H_{11}BrO_3$ requires 222.997.

**(*2S*,3S**) ethyl 2-bromo-3-hydroxyhexanoate** (**18**): colorless oil (80% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 4.32-4.19 (3H, m, COC<u>H</u>$_2$CH$_3$ + C<u>H</u>Br), 3.85-3.77 (1H, m, C<u>H</u>$_2$OH), 2.68 (1H, d, *J* 6.8 Hz, O<u>H</u>), 1.96-1.75 (2H, m, C<u>H</u>$_2$CH$_2$CH$_3$), 1.72-1.36 (2H, m, CH$_2$C<u>H</u>$_2$CH$_3$), 1.31 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.95 (3H, t, *J* 7.4, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 162.3, 76.2, 62.3, 45.4, 36.0, 20.8, 13.9, 13.3 ; HRMS (ES Q-TOF): [M+H]+, found. 239.0280 $C_8H_{15}BrO_3$ requires 239.0283

**(2*S**,3*S**)-ethyl 3-(N-9-fluorenylmethyloxycarbonyl)amino-2-bromo-3-cyclohexyl propanoate** (**19**): yellow oil (70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.78 (2H, d, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.61 (2H, d, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.42 (2H, dd, *J* 7.4 Hz, Ar$_{Fmoc}$), 7.33 (2H, dd, *J* 7.4 Hz, Ar$_{Fmoc}$), 5.19 (1H, d, *J* 8.4 Hz, N<u>H</u>), 4.47-4.36 (2H, m, C<u>H</u>$_{2Fmoc}$), 4.26 (1H, dd, *J* 6.9 Hz, C<u>H</u>$_{Fmoc}$), 4.2-4.05 (3H, m, C<u>H</u>Br + COC<u>H</u>$_2$CH$_3$), 4.45 (1H, m, C<u>H</u>NH), 2.04-1.60 (5H, m, cyclohexyl), 1.46-1.11 (6H, m, cyclohexyl), 1.31 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 169.3; 156.5;

144.1; 143.8; 141.3; 127.6; 127.0; 125.1; 119.9; 66.8; 62.2; 58.5; 47.4; 45.2; 41.1; 29.2; 25.9; 25.8; 13.8; HRMS (ES Q-TOF): [M+H]+, found. 500.1431. $C_{26}H_{30}BrNO_4$ requires 500.1435.

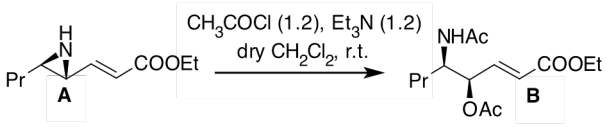
**(*E*) (4*R**,5*S**)-ethyl 4-azido-5-cyclohexyl-5-hydroxypent-2-enoate (20)**: pail yellow oil (99% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.92 (1H, dd, *J* 7.8, 15.7 Hz, C<u>H</u>=CHCO), 6.05 (1H, d, *J* 15.7 Hz, CH=C<u>H</u>CO), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.12 (1H, dd, *J* 4.5, 7.8 Hz, C<u>H</u>-N$_3$), 4.12 (1H, dd, *J* 4.5, 7.1 Hz, C<u>H</u>-OH), 2.48 (1H, br s, O<u>H</u>), 1.96-0.85 (14H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 140.7, 125.6, 76.9, 64.7, 60.9, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 268.1664. $C_{13}H_{21}N_3O_3$ requires 268.1661.

**(*E*) (4*R**,5*S**)-ethyl-4-azido-5-(*tert*-butoxycarbonyl)amino-oct-2-enoate** (**21**): pail yellow oil (98% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.79 (1H, dd, *J* 6.3, 15.6 Hz, C<u>H</u>=CHCO), 6.07 (1H, dd, *J* 15.6 Hz, C<u>H</u>CO), 4.59 (1H, d, *J* 9.01 Hz, N<u>H</u>Boc), 4.31 (1H, dd, *J* 6.3 Hz, C<u>H</u>N$_3$), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.77-3.67 (1H, m, C<u>H</u>-NHBoc), 1.48-1.34 (13H, m, C<u>H</u>$_2$ x2 + Boc), 1.28 (3H, t, *J* 7.2, COCH$_2$C<u>H</u>$_3$), 0.93 (3H, t, *J* 7.2, C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 155.5, 141.7, 124.7, 79.9, 66.4, 60.5, 53.5, 31.7, 22.3, 19.5, 14.0, 13.9; HRMS (ES Q-TOF): [M+H]+, found 327.2034. $C_{15}H_{26}N_4O_4$ requires 327.2032.

# Chapter 5. One-pot procedure for the synthesis of diprotected amino alcohols from unprotected vinyl aziridines[1].

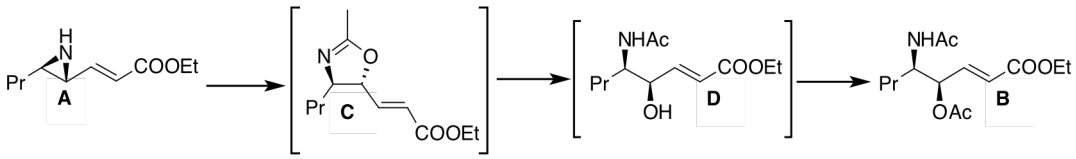
## 1. Introduction.

The functionalization of the aziridine nitrogen with electron-withdrawing groups is a broadly used strategy for the activation of the heterocyclic ring towards nucleophilic attack. During an attempt in this direction, an unexpected reactivity was observed when particular aziridines were submitted to the usual acylation conditions[2] (Scheme 1): when vinyl aziridine **A** was reacted with 1.2 mmol of $Et_3N$ and 1.2 mmol of $CH_3COCl$, the expected N-protected aziridine wasn't detected in the reaction crude, instead the main product recovered was diprotected amino-alcohol **B**.




**Scheme 1 Unexpected opening reaction.**

NMR studies revealed the complete regio- and stereoselectivity of the reaction, detecting in the crude only one diastereomer with the oxygen in the allylic position. This result could be explained by the formation of oxazoline **C** that can open to give monoprotected *syn*-amino alcohol **D**, which then reacts with acetyl chloride to give **B** (Scheme 2).




**Scheme 2 Proposed mechanism.**

[1] Righi, G.; Patanè, M.; Bovicelli, P.; Tirotta, I. *manuscript in preparation*.

[2] Toshimitsu,A.; *et al.*, *J. Org. Chem.*, **1981**, 46, 4727

N-acyl or N-carboxyl vinyl aziridines are known to undergo rearrangements when reacted with catalysts: aza-[3,3]-claisen enolate[3] rearrangements are known to take place in the presence of a strong base, leading to lactams (Fig. 1).

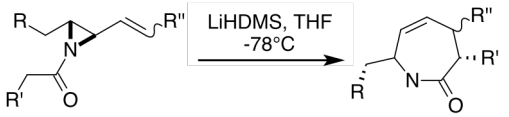



**Fig. 1 Aza-[3,3]-claisen enolate rearrangement: from aziridines to lactams.**

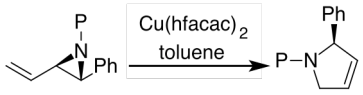



**Fig. 2 Cu catalysed rearrangement: from aziridines to pyrrolidines.**

More recently[4] Cu catalysed ring expansions have been reported, leading to pyrrolidines (fig. 2).

There are also few cases reported in the literature that show an instable behaviour from certain N-acyl aziridines: they have been reported to rearrange to oxazoline either during flash chromatography[5], or via Lewis acid catalysis. In particular Cardillo et al.[6] reported a three steps strategy that leads to *syn* monoprotected amino-alcohols (Fig. 3).

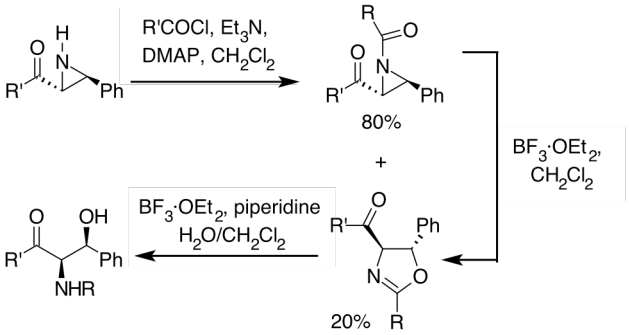



**Fig. 3 $BF_3 \bullet Et_2O$ catalysed rearrangement: from aziridines to oxazolines.**

To the best of our knowledge there doesn't seem to be in the literature a thorough study on these substrates or a one-pot procedure for the formation of diprotected *syn*-amino alcohols from vinyl aziridines. For these reasons the reaction was investigated in order to verify its reproducibility and scope, to understand its mechanism and the influence that the aziridine functionalizations have on its stereo- and regioselectivity.

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[3] Lindstrom,U.M.; Somfai,P. *Chem. Eur. J.,* **2001**, 7, *1*, 94-98

[4] Brichacek, M.; NavarroVillalobos, M.; Plichta, A.; Njardarson, J.T. *Organic Letters* **2011,** 13, *5*, 1110-1113

[5] Lindström, U.M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, 119, *35*, 8385-8386

[6] a) Cardillo,G.; Gentilucci,L. ; Tolomelli,A. *Tetrahedron Lett*., **1999,** *40*, 8261-8264; b) Cardillo,G.; Gentilucci,L.; Gianotti,M.; Tolomelli,A. *Eur. J. Org. Chem*. **2000**, 2489-2494

## 2. Results and discussion.

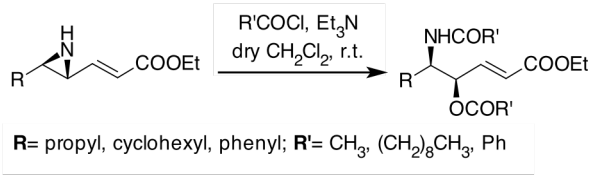
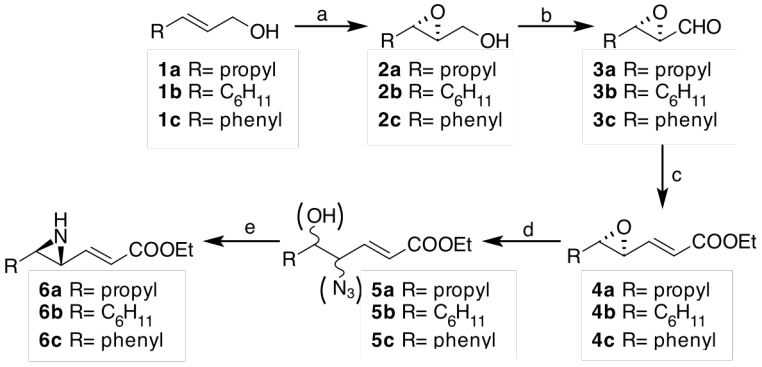



**Fig. 4 Substrates and acyl chlorides of choice.**

In order to fully investigate the influence of the aziridine functionalizations on the reaction, three different vinyl aziridines were prepared (Fig. 4): the R group was changed in order to evaluate the influence that its steric hindrance and electronic effects have on the reaction. In addition, to investigate the possibility of a broader scope, different acyl chlorides were chosen: $CH_3COCl$, $CH_3(CH_2)_8COCl$ (interesting for its long alkyl chain, which is found in many natural products), and PhCOCl (interesting for the possible effects of the phenyl group on the reaction).

*2.1. Synthesis of the substrates.*

All the substrates can be easily and in fairly good yield prepared starting from the corresponding allylic alcohols[7] **1a-c** (Scheme 3). A non-asymmetric epoxidation reaction[8], followed by an oxidation of the hydroxyl moiety and a subsequent Horner-Emmons reaction led to *trans* α,β-unsaturated esters **4a-c**, which were then converted into the corresponding aziridines via a well known two steps procedure[9] to give compounds **6a-c**, substrates of choice for this study.




**Scheme 3** ***Reagents and conditons*****:** a) *m*-CPBA, $CH_2Cl_2$, 0°C, 3h (85-90%); b) TEMPO, IBDA, $CH_2Cl_2$, r.t., 2h (70-80%); c) LiOH, TEPA, THF, 70°C, 2h (85-95%); d) $NaN_3$, $NH_4Cl$, EtOH, 70°C, o/n (80-90%); e) $PPh_3$, acetonitrile, r.t.-70°C, o/n (90%);

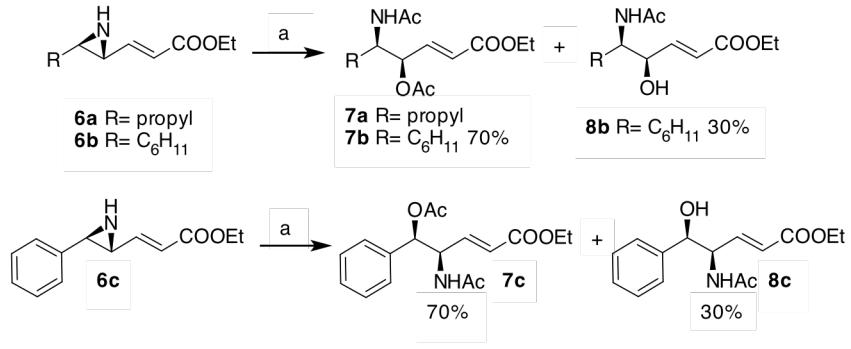
[7] For the substrates with R=cyclohexyl the appropriate alcohol **1b** is not commercially available and it was synthesized from the cyclohexanecarboxaldehyde. A Horner-Emmons reaction, followed by a reduction of the ester using DIBAL, led to alcohol **1b** with an overall yield of 97%. See Chapter 9 for procedures and characterizations.

[8] For this work it is not mandatory to have optically active compounds, all the molecules are intended as racemates and the stereochemistry is only reported as the relative one.

[9] Legters, J.; Thijs, L.; Zwanemburg, B., Recle. Trav. Chim. Pays-Bas, 1992, 111, 1-15

*2.2. Acyl chloride mediated ring-opening reactions.*

In order to verify the reproducibility of the reaction, all substrates were reacted with 1.2 eq. of $Et_3N$ and 1.2 eq. of acetyl chloride in dry dichloromethane at room temperature. After on average 10 hours all substrates were converted into the products, but, surprisingly, for compounds **6b** and **6c** the crudes showed the presence of two products: the expected diprotected amino alcohol and the monoprotected derivative in a 70:30 ratio (Scheme 3). Moreover, compound **6c** led to derivatives **7c** and **8c** both characterised by the presence of the oxygen in the benzylic position instead of the allylic one.

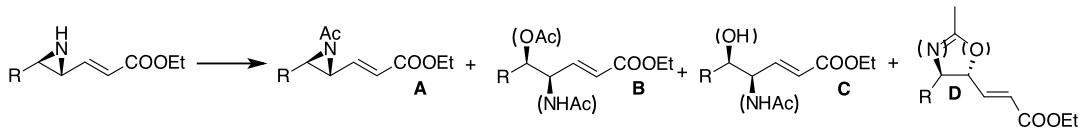



**Scheme 3** *Reagents and coditions*: $Et_3N$ (1.2 eq.), $CH_3COCl$(1.2 eq.), dry $CH_2Cl_2$, r.t. 3-5h (50% overall).

The reaction proved to be regioselective nonetheless, and the regioselectivity seems to be driven by the peculiar reactivity of the allylic position for compounds **6a** and **6b**, whereas for compound **6c** the benzylic position proved to be more reactive than the allylic one. The recovery of monoprotected derivatives **8b** and **8c** could be explained by the insufficient amount of acetyl chloride in the reaction media. Another possible explanation is that not all the oxazoline was opened during the reaction, but a small part opened during the work-up, hence leading to the monoprotected derivative.

The results obtained from the first three reactions enlightened the need for a more reproducible procedure; moreover the overall yield was definitely unsatisfactory (50%). The reaction conditions were varied in order to identify the best suitable ones for the synthesis of diprotected derivatives and the results are summarised in Table 1.

**Table 1 Different reaction conditions for the acetyl chloride mediated ring-opening: results.**




| Entry | $CH_3COCl$ (eq.) | $Et_3N$ (eq.) | Solvent | Overall yield (%) | A (%) | B (%) | C (%) | D (%) |
|---|---|---|---|---|---|---|---|---|
| **1** | 1.2 | 1.2 | Dry $CH_2Cl_2$ | 50 | - | 70-100 | 0-30 | Traces |
| **2** | 2.4 | 2.4 | Dry $CH_2Cl_2$ | 50 | - | 70-100 | 0-30 | Traces |
| **3** | 1.6 | 2 | Dry $CH_2Cl_2$ | Variable results | | | | |
| **4** | 3 | 1 | Dry $CH_2Cl_2$ | 70 | - | >95 | - | Traces |

As described before when the aziridines were reacted with 1.2 eq. of $CH_3COCl$ and $Et_3N$ (Entry 1), no protected aziridine was recovered and the amount of diprotected amino alcohol and monoprotected derivative were, on average, 70-100% for the former and 0-30% for the latter, with an overall yield of 50%. It is also important to notice that in some cases it was possible to identify the oxazoline in the reaction crude and to isolate it in very small amount after purification; this corroborates our mechanism hypothesis.

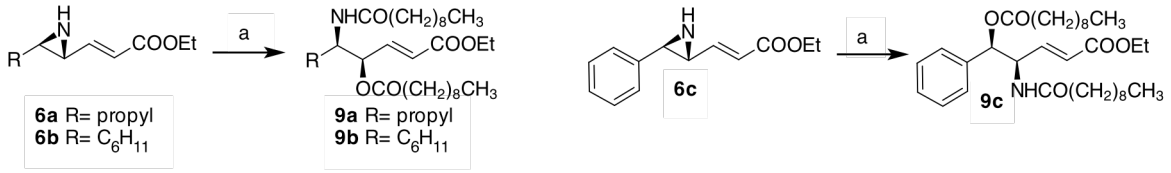
When the equivalents of both $CH_3COCl$ and $Et_3N$ were doubled (Entry 2), in an effort to drive the reaction towards the diprotected derivative, the exact same results were obtained.

Interestingly, when aziridines **6a** and **6c** (R= propyl, phenyl) were reacted with an excess of $Et_3N$ (Entry 3) it was possible to recover the protected aziridine even after purification of the reaction crude, even though only in small amounts (40% yield). However, these data are not reproducible: performing the reaction on compound **6b** (R= cyclohexyl) only the correspondent oxazoline was detected in the reaction crude. This led to the conclusion that the reaction evolves through very labile equilibria that are difficult to control so much to obtain only one of the intermediates. What seemed more plausible was the possibility to drive the reaction towards the last product, the diprotected amino alcohol.

Finally, when the all three aziridines were reacted with 3 eq. of $CH_3COCl$ and only 1 eq. of $Et_3N$ (Entry 4), the only product recovered was the diprotected derivative in a satisfactory yield (70%).

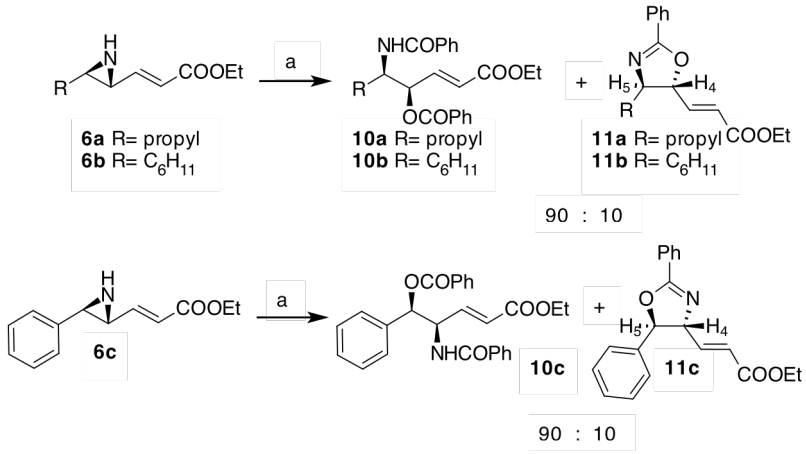
Once the best suitable conditions were identified the reactions were carried out with other acyl chlorides in order to broaden the scope of the reaction.

Performing the reactions on all three substrates, using 3 eq. of decanoyl chloride and 1 eq. of $Et_3N$, the expected diprotected derivatives were recovered, on average, in 70% yield (Scheme 4). Also in this case the corresponding oxazolines were isolated in traces.




**Scheme 4** *Reagents and conditions*: decanoyl chloride (3 eq.), $Et_3N$ (1 eq.), dry $CH_2Cl_2$, r.t., 2-5 h (70%)

Similar results were obtained reacting aziridines **6a-c** with 3 eq. of benzoyl chloride and 1 eq. of $Et_3N$: the major compounds recovered were diprotected derivative **10a-c** alongside with small amounts of the corresponding oxazolines in a 90:10 ratio (Scheme 5). In these cases the amount of oxazoline recovered was higher than what previously observed.

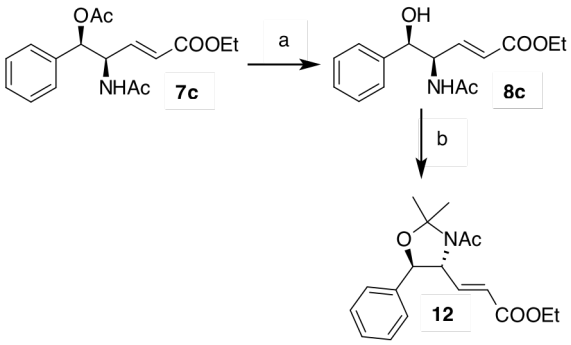



**Scheme 5** *Reagents and conditions*: decanoyl chloride (3 eq.), $Et_3N$ (1 eq.), dry $CH_2Cl_2$, r.t., 2-5 h (60-70%)

The *trans* configuration for oxazolines **11a-11c** was assigned by comparison with literature data:[10] as reported in the experimental section, vicinal coupling constants for protons H4 and H5 were always 6-7 Hz as in accordance with the literature, whilst coupling constants for *cis* isomers reported are 9-10Hz. Moreover these data allow a first confirmation of the proposed mechanism.

[10] Matsushima, Y.; Kino, J. *Tetrahedron Lett.* **2006**, 47, *49*, 8777-8780 and references therein cited.

Currently compound **7c** is being converted into the corresponding oxazolidine **12** (Scheme 6), in order to confirm the *syn* correlation between the hydroxyl and the amine moiety in both the mono and the diprotected derivatives, hence confirming our mechanistic hypothesis.




**Scheme 6** *Reagents and conditions*: a) $Na_2CO_3$, MeOH, r.t., o/n (70%); b) CSA, DMP, $CH_2Cl_2$, r.t., o/n (50%)

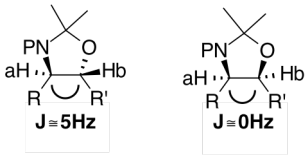



**Fig. 5 Oxazolidines coupling constants.**

Oxazolidines are characterised[11] by peculiar coupling constants for protons $H_a$ and $H_b$ (Fig. 5): the approximate value is 5 Hz for *trans* oxazolidines and 0 Hz for *cis* ones. A *trans* configuration for compound 12 would definitely confirm the *syn* configuration for the amino-alcohols obtained.

Only recently compound **7c** was successfully converted into oxazolidine **12**, via a selective deprotection[12] of the hydroxyl moiety, followed by an intramolecular cyclization. Compound **12** proved to be a *trans* oxazolidine, thus confirming the hypothesized syn configuration for both the mono and the diprotected derivatives and ultimately our proposed mechanism.

## 3. Conclusions.

The data collected showed the complete regio- and stereoselectivity of the reaction: in all cases only one diastereomer was recovered, characterised by the oxygen in the allylic position for compounds with R= propyl and cyclohexyl, and in the benzylic position for the compound with R= phenyl.

The steric hindrance of the R group does not influence the reaction at all, obtaining the exact same results for compounds with R= propyl or cyclohexyl; the influence exerted by the phenyl group can be ascribed to the particular reactivity of the benzylic position, which proved to be sensibly more reactive than the allylic one.

[11] Cui, P.; *et al. Bioorg. Med. Chem.,* **2008**, 16, *5*, 2212-2225

[12] Devijver, C. *et al. J. Nat. Prod.* **2000**, 63, *7*, 978-980

The reaction performed with 3 eq. of acyl chloride and 1 eq. of triethylamine proved to be reproducible and applicable to different substrates and acyl chlorides. It is fast (2-4 h), fairly clean and leads to the desired diprotected *syn* amino alcohol with good yield (60-70%).

To the best of our knowledge this is the first one-pot procedure reported for the synthesis of diprotected *syn* amino alcohols from vinyl aziridines.

## 4. Experimental.

### *4.1. General*

$^{1}$H NMR spectra were recorded using a Varian Mercury 300 (300 MHz). Residual solvent peaks were used as internal references for $^{1}$H NMR spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. $^{13}$C spectra were recorded using a Varian Mercury 300 (75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak: chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml.

All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 aluminium sheets (Merck Italia) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)].

Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

*4.2. Synthesis of substrates*

For the synthesis of compounds **2a-c/6a-c** see Chapter 9 "Experimental"

*4.3. General procedure for the acyl chloride mediated ring-opening reactions.*

1 mmol of the appropriate substrate was dissolved in 1 ml of dry dichloromethane and the solution cooled to 0°C. $Et_3N$ (1.2 mmol, 0.2 ml) and the appropriate acyl chloride (1.2 mmol) were added drop-wise and the mixture left stirring at room temperature until complete consumption of the substrate (TLC monitoring). The reaction mixture was diluted with dichloromethane, washed with ice cold water and neutralised with a saturated solution of $NaHCO_3$, the organic layer was dried over $Na_2SO_4$ and the solvent removed in vacuo to leave the crude, which was purified by flash chromatography.

The procedure remains the same for all reactions, with different equivalents for $Et_3N$ and acyl chloride.

*4.4. General procedure for the selective deprotection.*

1 mmol of the appropriate substrate was dissolved in 10 ml of methanol and $Na_2CO_3$ (1 mmol, 105 mg) and the mixture left stirring at room temperature until completion of the substrate (TLC monitoring). The reaction mixture was then filtered and the solvent removed under reduced pressure. The crude residue was utilised without any purification.

*4.5. General procedure for the oxazolidine formation.*

The appropriate substrate (1 mmol) was dissolved in 10 ml of dichloromethane, DMP (5 mmol, 1.4 ml) and a catalytic amount of *p*-toluensulphonic acid were added and the mixture left stirring at room temperature until completion of the substrate (TLC monitoring). The reaction mixture was then filtered and the solvent removed under reduced pressure to leave the crude, which was purified by flash chromatography.

*4.6. Compounds characterization.*

**(4*R*,5R*,E*)-ethyl 5-(N-acetyl)amino-4-(O-acetyl)hydroxyoct-2-enoate (7a)**: pail yellow oil (200 mg, 70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.81 (1H, dd, *J* 5.1, 15.8 Hz, C<u>H</u>=CHCO), 5.91 (1H, dd, *J* 1.6, 15.8 Hz, C<u>H</u>CO), 5.49 (1H, ddd, *J* 1.6, 5.1, 5.3 Hz, C<u>H</u>-OAc), 5.4 (1H, d, *J* 9.9, Hz, N<u>H</u>), 4.31-4.08 (3H, m, COC<u>H</u>$_2$CH$_3$ + C<u>H</u>NAc), 2.14 (3H, s, COC<u>H</u>$_3$), 1.99 (3H, s, COC<u>H</u>$_3$), 1.53-1.15 (7H, m, COCH$_2$C<u>H</u>$_3$ + C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.89 (3H, t, *J* 7.1 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 170.1, 169.9, 165.7, 142.5, 123.3, 73.7, 60.8, 51.1, 33.9, 23.3, 20.9, 19.2, 14.3, 13.9; HRMS (ES Q-TOF): [M+H]+, found 286.1659. $C_{14}H_{23}NO_5$ requires 286.1654

**(4*R*,5R*,E*)-ethyl 5-(N-acetyl)amino-5-cyclohexyl-4-(O-acetyl)hydroxypent-2-enoate (7b)**: pail yellow oil (228 mg, 70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.77 (1H, dd, *J* 4.9, 15.7 Hz, C<u>H</u>=CHCO), 5.83 (1H, dd, *J* 1.4, 15.7 Hz, C<u>H</u>CO), 5.63 (1H, ddd, *J* 1.4, 3.5, 4.9 Hz, C<u>H</u>-OAc), 5.57 (1H, d, *J* 10.2, Hz, N<u>H</u>), 4.14 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.02 (1H, ddd, *J* 3.5, 8.6, 10.2 Hz, C<u>H</u>-NHAc), 2.14 (3H, s, COC<u>H</u>$_3$), 1.99 (3H, s, COC<u>H</u>$_3$), 1.9-1.56 (5H, m, cyclohexyl), 1.24 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 1.2-0.9 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ:173.2, 172.4, 165.2, 143.6, 122.7, 71.4, 60.9, 55.7, 20.8, 19.3, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 326.1968. $C_{17}H_{27}NO_5$ requires 326.1968

**(4*R*,5R*,E*)-ethyl 4-(N-acetyl)amino-5-(O-acetyl)hydroxy-5-phenylpent-2-enoate (7c)**: yellow oil (223 mg, 70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.34-7.22 (5H, m, Ph); 6.74 (1H, dd, *J* 5.2, 15.7 Hz, C<u>H</u>=CHCO), 6.3 (1H, d, *J* 9.1 Hz, N<u>H</u>), 5.91 (1H, dd, *J* 1.6, 15.7 Hz, C<u>H</u>CO), 5.81 (1H, d, *J* 6.3 Hz, C<u>H</u>-OAc), 5.15-5.06 (1H, m, C<u>H</u>NHAc), 4.11 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.04 (3H, s, COC<u>H</u>$_3$), 1.99 (3H, s, COC<u>H</u>$_3$), 1.2 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz

$CDCl_3$) δ: 169.9; 169.6; 165.6; 143,2; 136.1, 128.7; 128.5; 126.7, 123.1; 75.6; 60.5, 53.9; 22.8; 22.7; 13.9 ; HRMS (ES Q-TOF): [M+H]+, found 320.1494. $C_{17}H_{21}NO_5$ requires 320.1498

**(4*R*,5R*,E*)-ethyl 5-(N-acetyl)amino-4-hydroxyoct-2-enoate**: yellow oil (24 mg, 10%); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.86 (1H, dd, *J* 7.0, 15.4 Hz, C<u>H</u>=CHCO), 6.07 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 5.48 (1H, d, *J* 9.7, Hz, N<u>H</u>), 4.64 (1H, dd, *J* 1.6, 7.0 Hz, C<u>H</u>-OH), 4.4-4.29 (1H, m, C<u>H</u>NAc), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.84 (1H, br s, O<u>H</u>), 2.01 (3H, s, COC<u>H</u>$_3$), 1.74-1.43 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.29 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$); 0.94 (3H, t, *J* 7.1 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 170.1, 165.7, 142.5, 123.3, 70.7, 60.8, 51.1, 33.9, 23.3, 20.9, 14.3, 13.9; HRMS (ES Q-TOF): [M+H]+, found 244.1542. $C_{12}H_{21}NO_4$ requires 244.1549

**(4*R*,5R*,E*)-ethyl 5-(N-acetyl)amino-5-cyclohexyl-4-hydroxypent-2-enoate (8b)**: pail yellow oil (42 mg, 15%); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.88 (1H, dd, *J* 4.0, 15.5 Hz, C<u>H</u>=CHCO), 6.11-6.01 (2H, m, C<u>H</u>CO + N<u>H</u>), 4.54 (1H, ddd, *J* 1.7, 4.2, 5.6 Hz, C<u>H</u>-OH), 4.14 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.54 (1H, ddd, *J* 5.6, 8.1, 9.5 Hz, C<u>H</u>-NHAc), 3.1 (1H, br s, O<u>H</u>), 2.14 (3H, s, COC<u>H</u>$_3$), 1.9-1.56 (5H, m, cyclohexyl), 1.24 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 1.2-0.9 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ:173.2, 165.2, 143.6, 122.7, 68.4, 60.9, 55.7, 20.8, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 284.1865. $C_{15}H_{25}NO_4$ requires 284.1862

**(4*R*,5R*,E*)-ethyl 4-(N-acetyl)amino-5-hydroxy-5-phenylpent-2-enoate (8c)**: yellow oil (30 mg, 10%); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.62-7.22 (5H, m, Ph); 6.94 (1H, dd, *J* 8.4, 17.6 Hz, C<u>H</u>=CHCO), 5.95 (1H, dd, *J* 1.7, 17.6 Hz, C<u>H</u>CO), 5.87 (1H, d, *J* 8.8 Hz, N<u>H</u>), 5.22 (1H, dddd, *J* 1.7, 4.6, 8.4, 8.8 Hz, C<u>H</u>-NHAc), 5.11 (1H, d, *J* 4.6 Hz, C<u>H</u>OH), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.5 (1H, br s, O<u>H</u>), 1.99 (3H, s, COC<u>H</u>$_3$), 1.2 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 169.9; 165.6; 143,2; 136.1, 128.7; 128.5; 126.7, 123.1; 70.6; 60.5, 53.9; 22.7; 13.9; HRMS (ES Q-TOF): [M+H]+, found 278.1396. $C_{15}H_{19}NO_4$ requires 278.1392

**(4*R*,5R*,E*)-ethyl 5-(N-decanoyl)amino-4-(O-decanoyl)hydroxyoct-2-enoate (9a)**: yellow oil (305 mg, 70%); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.79 (1H, dd, *J* 4.9, 15.7 Hz, C<u>H</u>=CHCO), 5.88 (1H, dd, *J* 1.6, 15.7 Hz, C<u>H</u>CO), 5.52-5.4 (2H, m, C<u>H</u>-OCO + N<u>H</u>), 4.32-4.16 (3H, m, C<u>H</u>NH + COC<u>H</u>$_2$CH$_3$), 2.46-2.06 (4H, m, COC<u>H</u>$_2$ x2), 1.77-1.13 (35H, m, COCH$_2$C<u>H</u>$_3$ + C<u>H</u>$_2$ x16), 0.9-0.74 (9H, m, CH$_3$ x3); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 173.0, 172.6, 165.7, 142.8, 123.2, 73.4, 60.8, 50.8, 36.9, 34.3, 34.1, 31.9, 29.5, 29.4, 29.3, 25.2, 25.1, 22.8, 19.2, 14.3, 14.2, 14.1, 13.9; HRMS (ES Q-TOF): [M+H]+, found 510.4154. $C_{30}H_{55}NO_5$ requires 510.4159

**(4*R*,5R*,E*)-ethyl 5-(N-decanoyl)amino-5-cyclohexyl-4-(O-decanoyl)hydroxypent-2-enoate (9b):** pail yellow oil (368 mg, 70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.77 (1H, dd, *J* 4.7, 15.7 Hz, C<u>H</u>=CHCO), 5.83 (1H, d, *J* 15.7 Hz, C<u>H</u>CO), 5.66-5.61 (1H, m, C<u>H</u>-OCO), 5.72 (1H, d, *J* 10.0 Hz, N<u>H</u>), 4.16 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.04 (1H, ddd, *J* 3.3, 8.5, 10.0 Hz, C<u>H</u>-NHCO), 2.40-2.03 (4H, m, COC<u>H</u>$_2$ x2), 1.82-1.09 (42H, m, COCH$_2$C<u>H</u>$_3$ + C<u>H</u>$_2$ x14 + cyclohexyl), 0.9-0.74 (6H, m, CH$_3$ x2); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 173.0, 172.5, 165.6, 143.3, 122.9, 71.6, 60.7, 55.4, 39.6, 36.9, 34.3, 31.9, 30.0, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 26.2, 26.1, 26.0, 25.1, 22.8, 14.3, 14.2; HRMS (ES Q-TOF): [M+H]+, found 550.4474. $C_{33}H_{59}NO_5$ requires 550.4471

**(4*R*,5R*,E*)-ethyl 4-(N-decanoyl)amino-5-(O-decanoyl)hydroxy-5-phenylpent-2-enoate (9c)**: orange oil (382 mg, 70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.34-7.22 (5H, m, Ph); 6.77 (1H, dd, *J* 5.0, 15.7 Hz, C<u>H</u>=CHCO), 5.91-5.82 (2H, m, C<u>H</u>CO + C<u>H</u>-OCO), 5.72 (1H, d, *J* 9.2 Hz, N<u>H</u>), 5.2-5.11 (1H, m, C<u>H</u>-NH), 4.17 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.41-2.28 (2H, m, COC<u>H</u>$_2$), 2.2-2.09 (2H, m, COC<u>H</u>$_2$), 1.67-1.47 (4H, m, C<u>H</u>$_2$ x2), 1.35-1.16 (27H, m, C<u>H</u>$_2$ x12 + COCH$_2$C<u>H</u>$_3$), 0.91-0.83 (6H, m, C<u>H</u>$_3$ x2); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.9, 172.8, 165.7, 143.5, 136.3, 128.8, 126.9, 123.2, 75.5, 60.6, 54.0, 36.6, 34.5, 34.0, 31.9, 29.5, 29.4, 29.3, 29.1, 29.0, 26.6, 24.9, 24.8, 22.7, 14.1, 14.0; HRMS (ES Q-TOF): [M+H]+, found 544.4004. $C_{33}H_{53}NO_5$ requires 544.4002

**(4*R*,5R*,E*)-ethyl 5-(N-benzoyl)amino-5-cyclohexyl-4-(O-benzoyl)hydroxypent-2-enoate (10b):** yellow oil (300 mg, 67%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.55-7.35 (10H, m, Ph), 7.01 (1H, dd, *J* 5.2, 15.4 Hz, C<u>H</u>=CHCO), 6.23 (1H, d, *J* 10.1 Hz, N<u>H</u>), 6.07-5.97 (2H, m, C<u>H</u>CO + C<u>H</u>-OCO), 4.45 (1H, ddd, *J* 4.2, 7.5, 10.1 Hz, C<u>H</u>-NHCO), 4.16 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 1.92-1.52 (6H, m, cyclohexyl), 1.31-1.07 (8H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 175.6, 174.5, 165.6, 142.9, 133.7, 131.7, 129.9, 128.8, 126.9, 123.5, 72.6, 60.7, 56.4, 39.6, 30.0, 29.5, 26.2, 26.1, 26.0, 14.2; HRMS (ES Q-TOF): [M+H]+, found 450.2277. $C_{27}H_{31}NO_5$ requires 450.2279.

**(4*R*,5R*,E*)-ethyl 4-(N-benzoyl)amino-5-(O-benzoyl)hydroxy-5-phenylpent-2-enoate (10c)**: orange oil (310 mg, 70%); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 8.11-7.13 (15H, m, Ph), 6.82 (1H, dd, *J* 5.0, 15.5 Hz, C<u>H</u>=CHCO), 6.66 (1H, d, *J* 8.7 Hz, N<u>H</u>), 6.11 (1H, d, *J* 7.6 Hz, C<u>H</u>-OCO), 5.92 (1H, d, *J* 15.5 Hz, C<u>H</u>CO), 5.45 (1H, ddd, *J* 5.0, 7.7, 8.7 Hz, C<u>H</u>-NHCO), 4.06 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 1.16 (1H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 142.9, 133.7, 133.6, 131.9, 130.3, 129.9, 129.3, 129.1, 128.8, 128.7, 128.6, 128.5, 127.4, 127.1, 123.9, 76.8, 60.8, 55.1, 14.3; HRMS (ES Q-TOF): [M+H]+, found 444.1805. $C_{27}H_{25}NO_5$ requires 444.1809

**(*E*)-ethyl 3-((4*R**,5*R**)-4-cyclohexyl-2-phenyl-4,5-dihydrooxazol-5-yl)acrylate (11b)**[11]**:** pail orange (9 mg, 3%); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.55-7.35 (5H, m, Ph), 6.94 (1H, dd, *J* 5.2, 15.6 Hz, C<u>H</u>=CHCO), 6.08 (1H, dd, *J* 1.4, 15.6 Hz, C<u>H</u>CO), 5.0 (1H, ddd, *J* 1.4, 5.2, 6.7 Hz, C<u>H</u>-O), 4.16 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.96 (1H, dd, *J* 6.7 Hz, C<u>H</u>-N), 1.92-1.52 (6H, m, cyclohexyl), 1.31-1.07 (8H, m, cyclohexyl + $COCH_2C\underline{H}_3$);

**(*E*)-ethyl 3-((4*R**,5*R**)-2,5-diphenyl-4,5-dihydrooxazol-4-yl)acrylate (11c)**[11]**:** orange oil (16 mg, 5%); $^1$H NMR (300 MHz $CDCl_3$) δ: 8.11-7.24 (10H, m, Ph), 7.02 (1H, dd, *J* 6.4, 15.6 Hz, C<u>H</u>=CHCO), 6.06 (1H, d, *J* 15.6 Hz, C<u>H</u>CO), 5.26 (1H, d, *J* 7.8 Hz, C<u>H</u>-O), 4.72 (1H, dd, *J* 6.4, 7.8 Hz, C<u>H</u>-N), 4.06 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 1.16 (1H, t, *J* 7.2 Hz, $COCH_2C\underline{H}_3$).

# Chapter 6. Study on the stereochemical control of the dihydroxylation reaction of optically active vinyl epoxides and derivatives[1].

## 5. Introduction.

As already explained, the extensive knowledge of the stereo and regioselective ring-opening methodologies, particularly applied to vinyl compounds, can give us access to different amino-alcoholic fragments in a stereo- and regiocontrolled fashion. A subsequent osmilation reaction of the double bond could lead to four adjacent stereogenic centers in a controlled fashion, thus providing useful precursors of aminopolyalcoholic structures (Fig. 1).

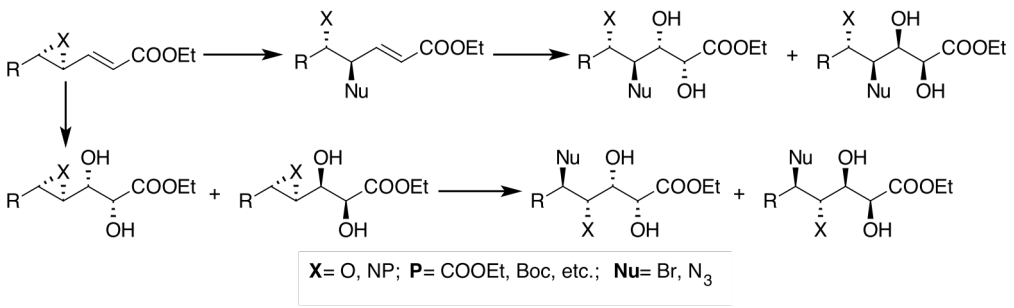



**Fig. 1 Formation of 4 adjacent stereocenters.**

The osmilation reaction is characterized by a *syn* stereospecificity. A pre-existing stereocenter adjacent to the double bond can direct the osmium tetroxide approach preferentially on one of the two faces of the olefin leading to different extents of diastereoselectivity[2]. A large number of studies have appeared in the literature on this matter but only few of them[3] regarded vinyl epoxides, vinyl aziridines and their derivatives, substrates of choice for this work.

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[1] Righi, G.; Naponiello, G.C.M.; Mandic', E.; Bovicelli, P; Tirotta, I. *Tetrahedron, submitted*; Righi, G., Mandic',E.; Bovicelli, P.; Tirotta, I. manuscript in preparation.

[2] a) Kolb, H.C.; Van Nieuwenhze, M. S.; Sharpless, K.B. *Chem. Rev.,* **1994**, 94, *8,* 2483-2547; b) Kishi, Y.; Cha, J. K.; Christ, W. J. *Tetrahedron*, **1984**, *40*, 2247; c) Sharpless, K. B.; Kolb, H.C.; Pher, G. A. *J. Am. Chem. Soc.*, **1994**, *116*, 1270-1278; d) Hermitage S.A.; Murphy A.; Nielsen P.; Stanley M.R.; *Tetrahedron,* **1998**, *54*, 13185-13202;

[3] a) Kim,N.; Choi,J.; Cha,J. *J. Org. Chem.* **1993**, 58, *25*, 7096-7099; b) Yadav,J.S.; Raju,A.; Rao,P.; Rajaiah, G. *Tetrahedron: Asymm*. **2005,** 16, *19,* 3283-3290; Moran, E.;Tellew, J.; Zhao, Z.; Armstrong, E. *J. Org. Chem*. **1993**, 58, *27*, 7848-7859

Moreover, using a chiral ligand as the catalyst, it is possible to obtain high enantiomeric excesses. Sharpless [4] firstly reported the asymmetric dihydroxylation (AD) in 1980, using cinchona derivatives as ligands (Fig. 2), and the procedure has since been improved upon. Applying the AD to chiral substrates it is possible to combine the diastereoselection due to the substrate's capability to interact with the osmium tetroxide and the ligand effect, gaining access to very high diastereomeric ratio (double diastereoselection). In this work differently functionalised vinyl compounds have been submitted to both the non-asymmetric procedure and the AD in order to thoroughly investigate the effect of chiral centers on the stereochemistry of the reaction.

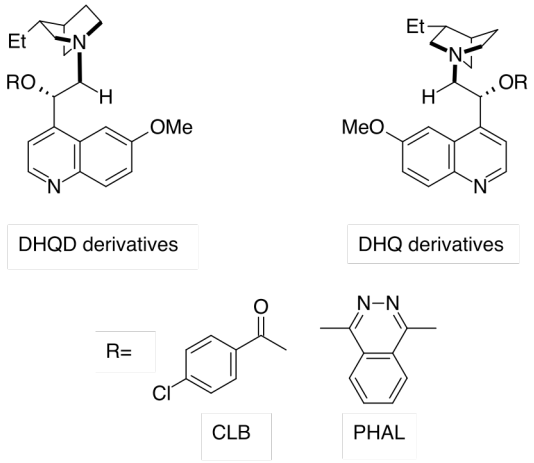



**Fig. 2 Cinchona derivatives as chiral ligands in the asymmetric dihydroxylation reaction.**

## 6. Results and discussion.

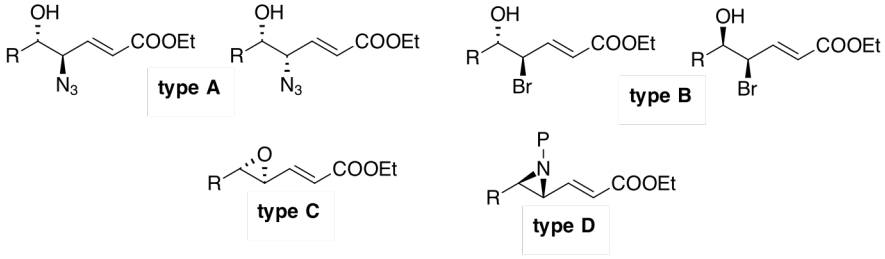


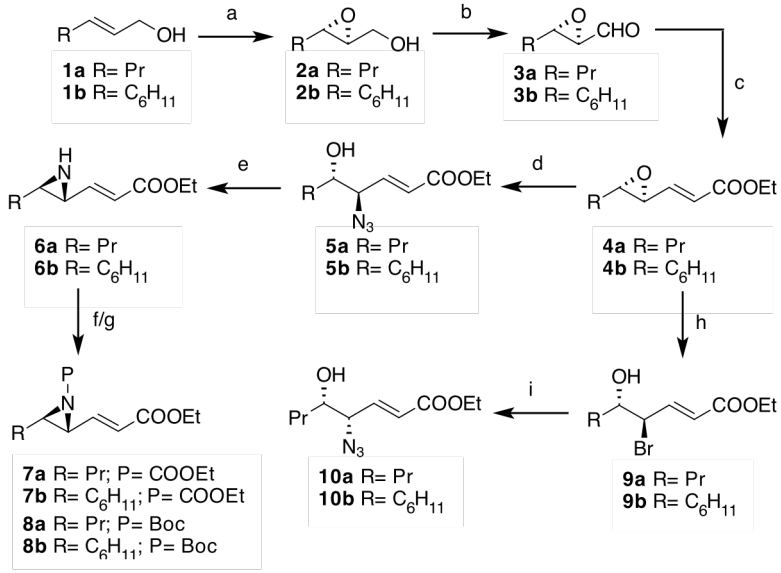

**Fig. 3 Substrates of choice**

With the purpose of identifying the substrate leading to the best stereochemical control of the dihydroxylation and therefore the most suitable for synthetic applications, the reactions were carried out on (Fig. 3): unsaturated azido alcohols (type **A**), bromohydrins (type **B**), epoxides (type **C**) and differently protected aziridines (type **D**). Moreover the R group and the protective group (P) on the aziridine ring were varied in order to investigate the possible influence of the steric hindrance on the diastereoselectivity of the reaction.

[4] Sharpless, K. B.; Hentges, S. G. *J. Am. Chem. Soc.*, **1980**, *102*, 4263-4265

*2.1. Synthesis of the substrates.*

All the substrates can be synthesized starting from the corresponding allylic alcohol[5] following the same synthetic path (Scheme 1).




**Scheme 1** *Reagents and conditions:* a) *m*-CPBA, $CH_2Cl_2$, 0°C, 3h (85-90%); b) TEMPO, IBDA, $CH_2Cl_2$, r.t., 2h (70-80%); c) LiOH, TEPA, THF, 70°C, 2h (85-95%); d) $BF_3{\cdot}Et_2O$, $TMSN_3$, $CH_2Cl_2$, 0°C-r.t, 1h (90-95%); e) $PPh_3$, acetonitrile, r.t.-70°C, o/n (90%); f) $Et_3N$, ClCOOEt, dry $Et_2O$, 0°C-r.t., o/n (98%); g) $Boc_2O$, DMAP, dry $CH_2Cl_2$, r.t., o/n (98%); h) LiBr, Amberlyst15, acetone, r.t., 4h (90-95%); i) $NaN_3$, dry DMF, r.t., o/n (90-95%).

Epoxy alcohols **2a** and **2b** were obtained via a non-asymmetric epoxidation reaction[6] and then converted into the corresponding epoxy aldehydes **3a** and **3b** using the well known TEMPO/IBDA method which is mild enough to preserve the epoxide function. A subsequent Horner-Emmons reaction afforded *trans* α,β-unsaturated epoxy esters **4a** and **4b**, which are the first substrates of study. The oxirane ring of compounds **4a** and **4b** was then regio- and stereoselectively opened using the $BF_3{\cdot}OEt_2/TMSN_3$ methodology[7] recently developed by our group (see Chapter 4), obtaining *anti* azido alcohols **5a** and **5b**. These compounds were then converted into the corresponding

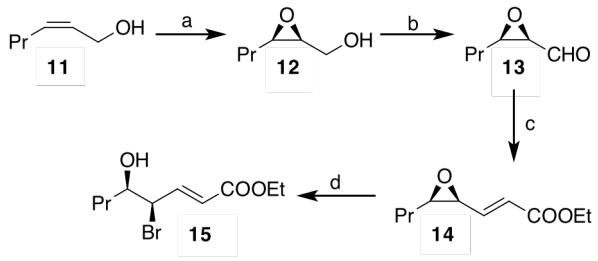
[5] For the substrates with R=cyclohexyl the appropriate alcohol **1b** is not commercially available and it was synthesized from the cyclohexanecarboxaldehyde. A Horner-Emmons reaction, followed by a reduction of the ester using DIBAL, led to alcohol **1b** with an overall yield of 97%.

[6] For the first part of this work it is not mandatory to have optically active compounds, all the molecules are intended as racemates and the stereochemistry is only reported as the relative one.

[7] Righi, G.; Salvati Manni, L.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett*., **2011**, *52*, 3895-3896

aziridines **6a** and **6b** via a well known procedure[8]. The aziridines were finally protected as ethyl and *tert*-butyl carbamate (compounds **7a**, **7b**, **8a**, **8b**). α,β-unsaturated esters **4a** and **4b** were also used to prepare four more substrates. A first regio- and stereoselective LiBr/Amb15 mediated ring opening reaction led to the corresponding *anti* bromohydrins **9a** and **9b**. Then a substitution reaction using $NaN_3$ in N,N-dimethylformammide (DMF) afforded *syn* azido alcohols **10a** and **10b**.

*Syn* bromohydrin **15** was obtained starting from *cis*-2-hexen-1-ol following the same synthetic pathway described before for compounds **9a** and **9b** (Scheme 2).




**Scheme 2** *Reagents and conditions:* a) m-CPBA, $CH_2Cl_2$, 0°C, 3h (83%); b) TEMPO, IBDA, $CH_2Cl_2$, r.t., 2h (72%); c) LiOH, TEPA, THF, 70°C, 2h (88%); d) LiBr, Amberlyst15, acetone, r.t., 5h (90%)

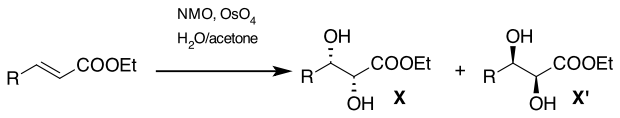
*2.2. Dihydroxylation reactions.*

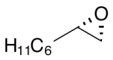
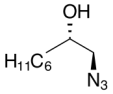
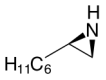
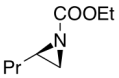
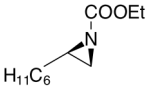
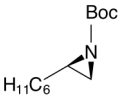
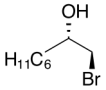
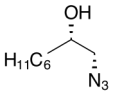
All the compounds synthesized were then submitted to the dihydroxylation reaction, using $OsO_4$ (5%) as catalyst, 4-methylmorpholine N-oxide (NMO) as cooxidant and an $H_2O$/acetone (1:8) mixture as solvent.

The results are summarized in Table 1. The ratio between the two diastereomers was calculated on the integrals of the $^1$H-NMR spectra of the crude mixture. The attribution of each signal to the right diastereomer was made in different ways depending on the class of the substrate.

[8] Legters, J.; Thijs, L.; Zwanemburg, B., *Recle. Trav. Chim. Pays-Bas*, **1992**, *111*, 1

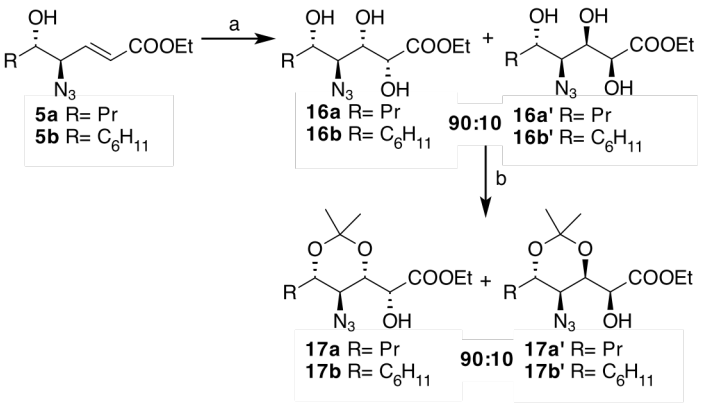
**Table 1 Non-asymmetric dihydroxylation reaction on differently functionalised vinyl compounds: results.**



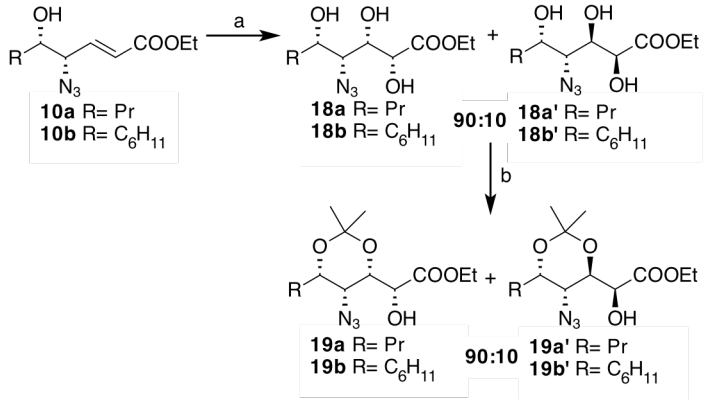

| Entry | Olefin | R | Diols | Ratio |
|---|---|---|---|---|
| 1 | 4a |  | 24a/24a' | 60:40 |
| 2 | 4b |  | 24b/24b' | 55:45 |
| 3 | 5a |  | 16a/16a' | 90:10 |
| 4 | 5b |  | 16b/16b' | 90:10 |
| 5 | 6a |  | 27a/27a' | 50:50 |
| 6 | 6b |  | 27b/27b' | 50:50 |
| 7 | 7a |  | 28a/28a' | 90:10 |
| 8 | 7b |  | 28b/28b' | 90:10 |
| 9 | 8a |  | 29a/29a' | 85:15 |
| 10 | 8b |  | 29b/29b' | 87:13 |
| 11 | 9a |  | 20a/20a' | 75:25 |
| 12 | 9b |  | 20b/20b' | 70:30 |
| 13 | 15 |  | 22a/22a' | 75:25 |
| 14 | 10a |  | 18b/18b' | 90:10 |
| 15 | 10b |  | 18a/18a' | 90:10 |

*2.2.1 Azido derivatives.*

As shown in Scheme 3 and Scheme 4 the osmilation reaction on both *anti* (**5a**, **5b**) and *syn* (**10a**, **10b**) azido derivatives led to a mixture of diols in a 90:10 diastereomeric ratio. In both cases the recognition of the stereochemistry of the major product was made converting the mixture into the corresponding 1,3-acetonides [9]. It is known [10] that these compounds have characteristic signals at the $^{13}$C-NMR depending on their stereochemistry: an *anti*-acetonide (e.g. compound **17a'**) shows a signal at ~100 ppm for the ketalic carbon and two very close signals at ~25 ppm for the $C(CH_3)_2$, whereas in a *syn*-acetonide (e.g. compound **17a**) the ketalic carbon shows a signal at ~98 ppm and the $C(CH_3)_2$ two different signals at ~19 and ~30 ppm.




**Scheme 3** *Reagents and conditions*: a) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (84-87%). b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, r.t., o/n (90-95%)




**Scheme 4** *Reagents and conditions*: a) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (85-89%). b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, r.t., o/n (90-95%)

In both cases the major product proved to be a *syn* acetonide indicating that the major diols were compounds **16a**, **16b**, **18a** and **18b**. These results seem to indicate that the stereochemistry of the reaction is not affected by the azide group in the allylic position and may be driven instead by the OH group in the homoallylic position. These data also indicate that the steric hindrance of the R group on the epoxide ring does not influence the stereochemistry of the reaction.

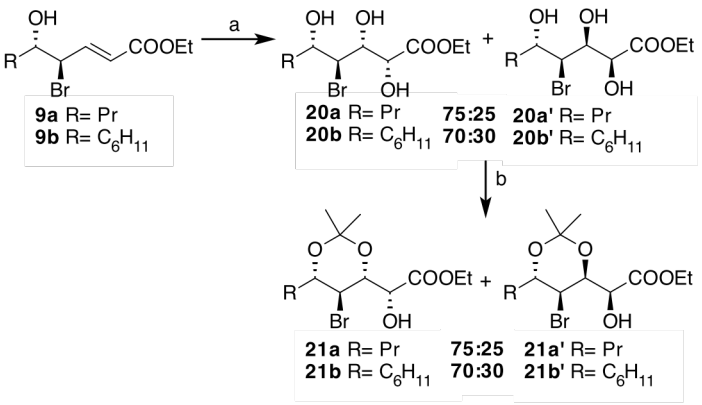
[9] The solely formation of the 1-3 acetonides is achieved performing the reaction at room temperature: as reported also in the experimental section, low temperatures favor the 1-2 acetonides. Moreover, 1-3 acetonides are easily distinguishable from 1-2 isomers, especially at the $^{13}$C-NMR: the ketalic carbon falls at ~98-100 ppm for the former, at ~110-112 ppm for the latter.

[10] Richnovsky, S.D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, 58, 3511-3515

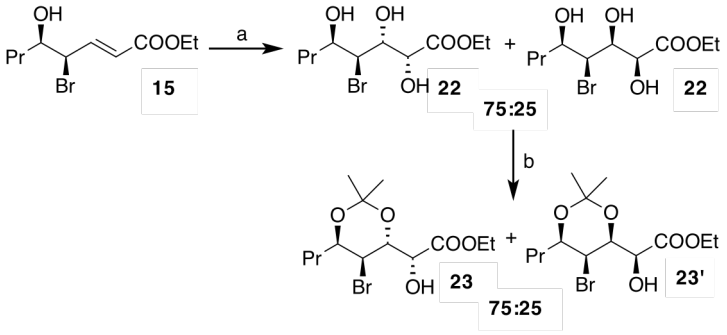
*2.2.2 Bromo derivatives.*

Similar considerations can be made for *anti* bromohydrins **9a** and **9b** (Scheme 5). We can assert again that the steric hindrance of the R group have none to little influence on the reaction. In this case the bromotriols mixtures obtained were chromatographically inseparable.

Therefore, to fully characterize the major products, the mixtures were converted into the corresponding 1,3-acetonides: the prevalent compounds turned out to be *syn* acetonides **21a** and **21b** thus indicating an *anti* correlation between the Br and the diol in compounds **20a** and **20b** (major products of the osmilation reaction).




**Scheme 5** *Reagents and conditions*: a) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (70-80%). b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, r.t., o/n (90-95%)

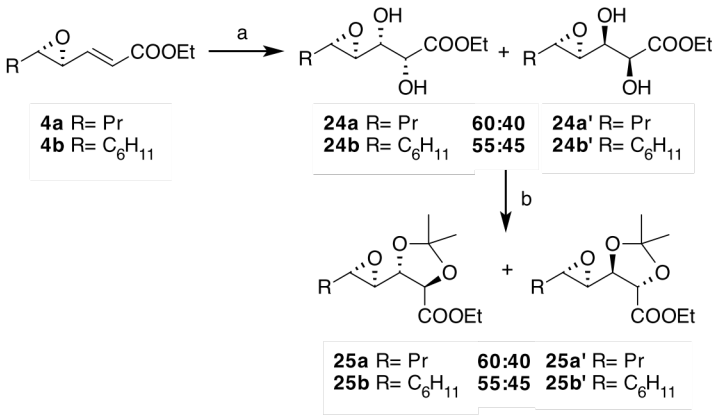



**Scheme 6** *Reagents and conditions*: a) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (75%). b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, r.t., o/n (93%)

An *anti* correlation between the bromine and the diol moiety was also observed in the osmilation of *syn*-bromohydrin **15** (Scheme 6). Unlike what observed with the azido alcohols, these results seem to indicate that the configuration of the bromine is actually able to influence the $OsO_4$ attack, leading in all cases to a product with an *anti* correlation between the Br and the diol moiety. This could be justified by the different steric hindrance exerted by the bromine and the $N_3$.

*2.2.3. Vinyl epoxides.*

In the case of vinyl epoxides, the oxirane ring didn't seem to effectively affect the diastereoselectivity of the dihydroxylation reaction: **4a** and **4b** gave an inseparable mixture with a *syn* correlation between the ring and the diol moiety in the main product (Scheme 7). At first the stereochemical assignment of the epoxy diols was based on their spectral characteristics. As reported in the literature[11], the general trend for epoxy alcohols is that the $^1$H-NMR signal for the CHOH of the *syn* diastereomer is more shielded than the one for the *anti* diastereomer (Fig. 4).

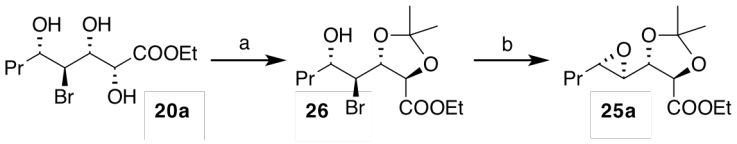



**Scheme 7** *Reagents and conditions*: a) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (70%); b) 2,2-dimethoxypropane, p-toluensulfonic acid, acetone, 0°C, o/n (80%)


**Fig. 4 Chemical shifts for a general CHOH adjacent to an oxirane ring as reported in the literature**

Our experimental data were in line with the literature: the signal of the CHOH adjacent to the oxirane ring falls at ~3.8 ppm for compounds **24a** and **24b** and is shifted 0.1 ppm upfield in compounds **24a'** and **24b'** (~4.0 ppm).

To confirm the stereochemical assignment, the previously determined stereochemistry of the bromotriols was exploited. **20a** was converted into a 1,2-acetonide (**26**), subsequently submitted to a ring closing reaction that gave an epoxy acetonide, which proved to be spectroscopically identical to **25a** (Scheme 8), the major epoxy acetonide obtained from the protection of the **24a**/**24a'** mixture.

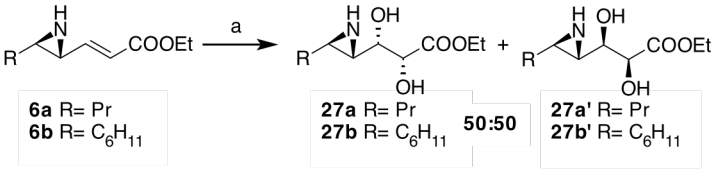



**Scheme 8** *Reagents and conditions*: a) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, -20°C, o/n (80%). b) KOH, MeOH, reflux, 1h (90%)

[11] a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *115*, 7226-7236; b) Miheclich, E.D. *Tetrahedron Lett.* **1979**, *20*, 4729-4732

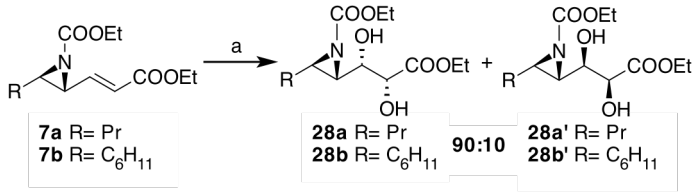
*2.2.4. Vinyl aziridines.*

The unprotected aziridine ring didn't affect at all the diastereoselectivity of the reaction leading for both compound **6a** and **6b** to a chromatographically inseparable mixture with a diastereomeric ratio of 50:50 (Scheme 9).



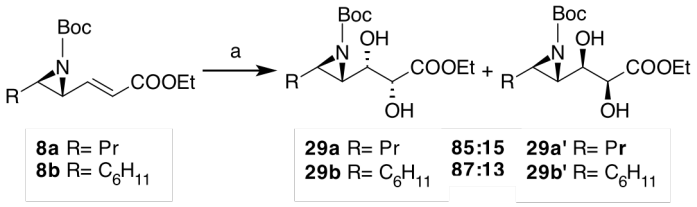

**Scheme 9** *Reagents and conditions*: a) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (70%).

As shown in Table 1, completely different results were obtained when the nitrogen was protected as carbamate. The osmilation reaction on both the COOEt protected compounds **7a** and **7b** led to a mixture with a 90:10 diastereomeric ratio (Scheme 10).




**Scheme 10** *Reagents and conditions*: $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (70-73%)

Similarly, the diols mixtures obtained from Boc protected compounds **8a** and **8b** showed a diastereomeric ratio of 85:15 and 87:13 (Scheme 11). This extremely different reactivity between protected and unprotected aziridines can be explained by the high steric hindrance exerted by the protective group on the double bond.




**Scheme 11** *Reagents and conditions*: $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (70-75%)

The stereochemical assignment of the major diastereomers was made, as well as for the epoxy-diols, by comparison with literature data[12], which pointed, in all our cases, towards the compounds with an *anti* correlation between the ring and the diol moiety as the major ones.

[12] a) Hwang, G.I.; Chung, J.H.; Lee, W.K. *J. Org. Chem.* **1996**, 61, 6183-6188; b) Andres, J.M.; de Elena, N.; Pedrosa, R.; Pretz-Encavo, A. *Tetrahedron* **1999**, 55, 14137-14144

*2.3. Asymmetric dihydroxylation.*

All the substrates were prepared in their enantiomerically pure form using the Sharpless protocol for the epoxidation reaction and were then submitted to the AD.

As noted before, performing this reaction on chiral olefins the ligand effect is summed to that of the stereogenic center and the diastereoselection is doubled. As shown in Fig. 5, the major diol obtained can have the same stereochemistry as the one obtained in the non-asymmetric reaction, and is therefore named as the *matched* compound, or the opposite one (*mismatched*).

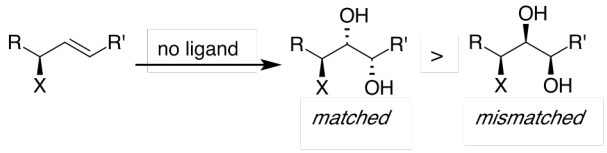



**Fig. 5 Double diastereoselection in chiral olefins**

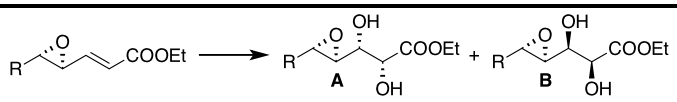
For each compound the first attempt was made using Sharpless procedure: commercially available ADmix-α or ADmix-β (source of the ligand and osmium tetroxide)[13] and 1 eq. of methanesulfonamide in a 1:1 $H_2O$/*t*-BuOH mixture at room temperature. However these conditions turned out to be unsuitable for the substrates of choice, therefore several variations (e.g. solvents, ligands, etc.) have been made in order to find the best reaction conditions for each substrate.

*2.3.1. Vinyl epoxides.*

As can be gathered from Table 2, using Sharpless procedure the conversion was very low, although with a good diastereomeric excess (Entries 2 and 3). Using instead 2% of $K_2OsO_4$ as the osmium source, 5% of $(DHQ)_2PHAL$ (or of $(DHQD)_2PHAL$), with 1 eq. of methanesulfonamide, 3eq of $K_2CO_3$ and $K_3Fe(CN)_6$, in a 1:1 $H_2O$/*t*-BuOH mixture at room temperature (Entries 4 and 5), after generally 12 hours the conversion of the substrate was complete and the diols were obtained in good yields and excellent diastereomeric ratio (from here on this procedure will be referred to as procedure B). It is particularly important to notice that it was possible to obtain either the *matched* or the *mismatched* product with very high diastereomeric excess.

[13] ADmix contains: $(DHQ)_2PHAL$ (α) or $(DHQD)_2PHAL$ (β) 0.16%, potassium carbonate 49,88%, potassium ferricyanide 49,88%, potassium osmate dihydrate 0.07%.

**Table 2 Dihydroxylation reaction on vinyl epoxides: results**



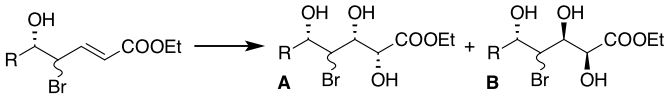

| Entry | Ligand | R = propyl | | R = cyclohexyl | | Main product |
|---|---|---|---|---|---|---|
| | | A:B | Yield (%) | A:B | Yield (%) | |
| **1** | - | 60:40 | 70 | 55:45 | 70 | |
| **2** | ADmix-α | 15:85 | 15 | - | - | *Mismatched* |
| **3** | ADmix-β | 90:10 | <10 | - | - | *Matched* |
| **4** | $(DHQ)_2PHAL$ | 15:85 | 70 | 20:80 | 80 | *Mismatched* |
| **5** | $(DHQD)_2PHAL$ | 90:10 | 70 | 85:15 | 84 | *Matched* |

*2.3.2. Bromo derivatives.*

As reported in Table 3, performing the Sharpless procedure on both *anti* and *syn* bromo derivatives (Entries 2 and 5) only a complex mixture was obtained, where the major compounds detected were the corresponding α,β-unsaturated epoxy esters and epoxy diols. Same results were obtained using procedure B (Entry 3).

A study aimed at finding the right reaction conditions for these substrates is still ongoing.

**Table 3 Dihydroxylation reaction on vinyl bromo-alcohols: results**



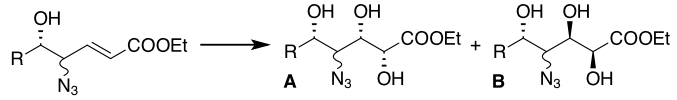

| Entry | Substrate | Ligand | R = propyl | | R = cyclohexyl | |
|---|---|---|---|---|---|---|
| | | | A:B | Yield (%) | A:B | Yield (%) |
| **1** | *anti* | - | 75:25 | 70 | 70:30 | 80 |
| **2** | | ADmix-α or β | Undesired product | | Undesired product | |
| **3** | | $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ | Undesired product | | - | |
| **4** | *syn* | - | 75:25 | 75 | - | |
| **5** | | ADmix-α or β | Undesired product | | - | |
| **6** | | $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ | - | | - | |

*2.3.4. Azido derivatives.*

When the Sharpless procedure was applied to both *syn* and *anti* azido alcohols no conversion of the substrate was observed (Entries 2 and 5 Table 4). Unexpectedly procedure B led to a complex mixture (Entries 3 and 6) where the major compound detected showed no signals of the ethyl ester. The same results were obtained using more equivalents of $K_2OsO_4$ (5%) and ligand (6%).

A study aimed at finding the right reaction conditions for these substrates is still ongoing.

**Table 4 Dihydroxylation reaction on vinyl azido-alcohols: results**



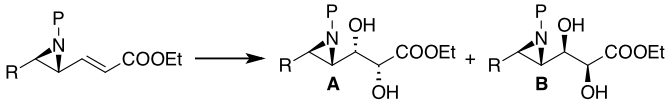

| Entry | Substrate | Ligand | R = propyl | | R = cyclohexyl | |
|---|---|---|---|---|---|---|
| | | | A:B | Yield (%) | A:B | Yield (%) |
| **1** | *anti* | - | 90:10 | 84 | 90:10 | 87 |
| **2** | | ADmix-α or β | - | | - | |
| **3** | | $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ | Undesired product | | Undesired product | |
| **4** | *syn* | - | 90:10 | 85 | 90:10 | 89 |
| **5** | | ADmix-α or β | - | | - | |
| **6** | | $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ | Undesired product | | Undesired product | |

*2.3.5. Vinyl aziridines.*

On both unprotected and N-Boc protected aziridines the ADmix procedure gained no conversion of the substrate (Entries 2 and 7 Table 6). Applying procedure B on unprotected aziridines again no conversion of the substrate was observed but increasing the equivalents of $K_2OsO_4$ (5%) and ligand (6%) a complex mixture was recovered where no aziridine ring was detected.

We finally had a breakthrough using $OsO_4$ (5%) as the osmium source and 15% of DHQ-CLB (dihydroquinine chlorobenzoate) as the ligand, 2 eq. of NMO as cooxidant in a 1:8 $H_2O$/acetone mixture at room temperature (from here on referred to as procedure C). Applying these conditions to N-Boc protected aziridine (R= cyclohexyl) only the *matched* diastereomer was obtained. Procedure C will be applied shortly on all N-Boc and N-COOEt protected aziridines.

**Table 5 Dihydroxylation reaction on vinyl aziridines: results**




| Entry | P | Procedure | R = propyl | | R = cyclohexyl | | Main product |
|---|---|---|---|---|---|---|---|
| | | | A:B | Yield (%) | A:B | Yield (%) | |
| **1** | **H** | Non-asymmetric | 50:50 | 70 | 50:50 | 70 | |
| **2** | | ADmix-α or β | - | | - | | - |
| **3** | | B | - | | - | | - |
| **4** | | B modified | Undesired product | | Undesired product | | - |
| **5** | **Boc** | - | 85:15 | 70 | 87:13 | 75 | |
| **6** | | ADmix-α or β | - | - | - | - | - |
| **7** | | C with $(DHQ)_2CLB$ | - | | >95:5 | 70 | *matched* |

## 7. Conclusions.

In conclusion, the results obtained from this study show that the presence of a bromo alcohol, an azido alcohol or a N-protected aziridine moiety on the double bond is able to induce a significative stereochemical control in the non-asymmetric dihydroxylation reaction. On the contrary, when the olefin is substituted with an epoxide or an unprotected aziridine almost no stereoselectivity is observed.

Performing the asymmetric reactions proved to be more difficult than expected and several variations of the reaction conditions were necessary.

Using procedure B, both *trans* α,β-unsaturated epoxy esters (R=propyl and cyclohexyl) were successfully converted into either the *matched* or the *mismatched* product with a diastereomeric excess >80%.

Azido derivatives, bromo derivatives and unprotected aziridines led unfortunately only to complex reaction mixtures.

Protected aziridines proved to be particularly unreactive but finally, using procedure C, N-Boc protected aziridine with R= cyclohexyl was successfully converted into the matched diastereomer with a diastereomeric excess >95%.

Currently procedure C is being applied to both protected and unprotected aziridines, bromo derivatives and azido derivatives.

The relevant diastereoselection obtained in some cases allows the preparation of attractive compounds having at least four contiguous stereogenic centers, useful intermediates in the synthesis of a wide range of biologically active compounds as, for example, azasugars. Studies in this direction are currently under investigation (see Chapter 7).

# 8. Experimental.

*4.1. General.*

$^{1}$H NMR spectra were recorded using a Varian Mercury 300 (300 MHz). Residual solvent peaks were used as internal references for $^{1}$H NMR spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. $^{13}$C spectra were recorded using a Varian Mercury 300 (75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak: chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml.

All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 aluminium sheets (Merck Italia) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)].

Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

*4.2. Synthesis of the substrates.*

For the synthesis of compounds **2a-b**/**6a-b** see Chapter 9 "Experimental"

*4.2.1. General procedure for the COOEt protection.*

Under nitrogen atmosphere 1 mmol of the appropriate substrate was dissolved in 3 ml of anhydrous diethyl ether. 1,2 mmol (121 mg, 0.2 ml) of $Et_3N$ and 1.2 mmol (130 mg, 0.1 ml) of ethyl chloroformate were then added and the reaction mixture stirred at room temperature for 3h or until consumption of the substrate (TLC monitoring). The mixture was then filtered through a celite pad and the solvent evaporated under reduced pressure to give the desired product, which was used without any purification.

**(*E*)-ethyl 3-((2*R**,3*R**)-3-(N-ethoxycarbonyl)propylaziridin-2-yl)acrylate (7a)**: pail yellow oil (248 mg, 97% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.40 (1H, dd, *J* 8.8, 15.4 Hz, C<u>H</u>=CHCO), 6.09 (1H, d, *J* 15.4, C<u>H</u>CO), 4.22-4.00 (4H, m, COC<u>H</u>$_2$CH$_3$ x2), 2.81 (1H, dd, *J* 2.8, 8.8 Hz, C<u>H</u>-CH=CH), 2.53-2.45 (1H, m, CH$_2$C<u>H</u>), 1.72-1.10 (10H, m, C<u>H</u>$_2$ x2 + C<u>H</u>$_3$ x2), 0.78 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.1, 160.7, 143.4, 124.0, 62.1, 60.13, 45.4, 43.2, 32.7, 19.8, 14.1, 13.9, 13.2; HRMS (ES Q-TOF): [M+H]+, found 256.1543 $C_{13}H_{21}NO_4$ requires 256.1549

**(*E*)-ethyl 3-((2*R**,3*R**)-3-(N-ethoxycarbonyl)cyclohexylaziridin-2-yl)acrylate (7b)**: pail yellow oil (289 mg, 98% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.29 (1H, dd, *J* 9.4, 15.4 Hz, C<u>H</u>=CHCO), 6.08 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.22-4.00 (4H, m, COC<u>H</u>$_2$CH$_3$ x2), 2.89 (1H, dd, *J* 2.8, 9.4 Hz, C<u>H</u>-CH=CH), 2.38-2.29 (1H, m, cyclohexyl-C<u>H</u>), 1.99-0.96 (17H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$ x2); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.2, 161.0, 143.6, 124.2, 62.3, 60.3, 50.3, 42.3, 39.5, 30.2, 29.6, 26.0, 25.5, 25.3, 14.1, 14.0; HRMS (ES Q-TOF): [M+H]+, found 296.1865. $C_{16}H_{25}NO_4$ requires 296.1862

*4.2.2. General procedure for the Boc protection.*

Under nitrogen atmosphere, 1 mmol of the appropriate substrate was dissolved in 10 ml of anhydrous dichloromethane. 1.1 mmol (248 mg, 0.2 ml) of $Boc_2O$ and a catalytic amount of DMAP were then added and the reaction mixture stirred at room temperature for 12h or until consumption of the substrate (TLC monitoring). The solvent was then evaporated under reduced pressure to give the desired product, which was used without any purification.

**(*E*)-ethyl 3-((2*R**,3*R**)-3-(N-tert-butoxycarbonyl)propylaziridin-2-yl)acrylate (8a)**: yellow oil (277mg, 98% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.40 (1H, dd, *J* 9.3, 15.9 Hz, C<u>H</u>=CHCO), 6.12 (1H, d, *J* 15.9 Hz, C<u>H</u>CO), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.81 (1H, dd, *J* 2.7, 9.3 Hz, C<u>H</u>-CH=CH), 2.50 (1H, m, CH$_2$C<u>H</u>), 1.80-1.45 (13H, m, C<u>H</u>$_2$ x2 + C(C<u>H</u>$_3$)$_3$), 1.30 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.98 (3H, t, J 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$ ); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.2, 159.2, 143.4, 124.0, 81.0, 60.5, 45.8, 43.1, 33.1, 31.2, 27.9, 14.4, 14.0; HRMS (ES Q-TOF): [M+H]+, found 284.1860. $C_{15}H_{25}NO_4$ requires 284.1862

**(*E*)-ethyl 3-((2*R**,3*R**)-3-(N-tert-butoxycarbonyl)cyclohexylaziridin-2-yl)acrylate (8b)**: pail yellow oil (317 mg, 98% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.33 (1H, dd, *J* 9.4, 15.4 Hz, C<u>H</u>=CHCO), 6.10 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.87 (1H, dd, *J* 2.8, 9.4 Hz, C<u>H</u>-CH=CH), 2.36-2.31 (1H, m, cyclohexyl-C<u>H</u>-N), 1.99-1.58 (5H, m, cyclohexyl), 1.42 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.25 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 1.22-1.07 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.7, 160.4, 144.2, 124.0, 81.7, 60.4, 50.4, 42.5, 39.7, 30.3, 29.8, 27.8, 26.0, 25.6, 25.4, 14.2; HRMS (ES Q-TOF): [M+H]+, found 324.2179. $C_{18}H_{29}NO_4$ requires 324.2175

*4.2.3. General procedure for the LiBr/Amb15 ring opening reaction.*

LiBr (4 mmol, 260 mg) and Amberlyst15 (1 mmol, 212 mg) were added to 1 mmol of the appropriate substrate dissolved in 8 ml of acetone and the mixture stirred overnight. After filtration the mixture was concentrated in vacuo and the residue taken up in ethyl acetate, neutralized and washed with brine. The organic layer was dried on $Na_2SO_4$ and the solvent evaporated under reduced pressure to give the desired product that was used without any purification.

***(E)* (4*R**,5*S**)-ethyl 4-bromo-5-hydroxyoct-2-enoate (9a)**: pail yellow oil (238 mg, 90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.03 (1H, dd, *J* 9.9, 15.4 Hz, C<u>H</u>=CHCO), 5.99 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.59 (1H, dd, *J* 3.3, 9.9 Hz, C<u>H</u>-Br), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.96-3.80 (1H, m, C<u>H</u>-OH), 2.40 (1H, br s, O<u>H</u>), 1.61-1.39 (4H, m, C<u>H</u>$_2$ x2), 1.30 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.92 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.12, 141.9, 124.2, 73.6, 60.5, 57.1, 35.7, 18.7, 13.9, 13.5; HRMS (ES Q-TOF): [M+H]+, found 265.0436. $C_{10}H_{17}BrO_3$ requires 265.0439

***(E)* (4*R*,5S**)-ethyl 4-bromo-5-cyclohexyl-5-hydroxypent-2-enoate (9b)**: pail yellow oil (289 mg, 95% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 7.15 (1H, dd, *J* 10.2, 15.6 Hz, C<u>H</u>=CHCO), 6.02 (1H, d, *J* 15.6 Hz, C<u>H</u>CO), 4.79 (1H, dd, *J* 3.8, 10.2 Hz, C<u>H</u>-Br), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.64 (1H, dd, *J* 3.8, 7.7 Hz, C<u>H</u>-OH), 2.8 (1H, br s, O<u>H</u>), 1.8-0.93 (14H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 140.7, 125.6, 76.9, 64.7, 60.9, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 305.0750. $C_{13}H_{21}BrO_3$ requires 305.0753

***(E)* (4*R*,5R**)-ethyl 4-bromo-5-hydroxyoct-2-enoate (15)**: pail yellow oil (238 mg, 90% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.90 (1H, dd, *J* 9.7, 15.4 Hz, C<u>H</u>=CHCO), 5.90 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.47 (1H, dd, *J* 5.1, 9.7 Hz, C<u>H</u>-Br), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.65-3.51 (1H, m, C<u>H</u>-OH), 2.96 (1H, br s, O<u>H</u>), 1.55-1.30 (4H, m, C<u>H</u>$_2$ x2), 1.20 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.80 (3H, t, J 6.7 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 143.4, 123.6, 73.0, 60.8, 58.6, 36.5, 18.7, 14.1, 13.8; HRMS (ES Q-TOF): [M+H]+, found 265.0438. $C_{10}H_{17}BrO_3$ requires 265.0439

*4.2.4. General procedure for the nucleophilic substitution (Br-$N_3$).*

Under nitrogen atmosphere $NaN_3$ (4 mmol, 260 mg) was added to 1 mmol of the appropriate substrate dissolved in 1 ml of anhydrous DMF and the mixture left stirring at room temperature until complete consumption of the substrate. The mixture was then diluted with ethyl acetate and washed with brine. The organic layer was dried on $Na_2SO_4$ and the solvent evaporated under reduced pressure to give the desired product, which was used without any purification.

**(E) (4*S*,5S**)-ethyl 4-azido-5-hydroxyoct-2-enoate (10a)**: yellow oil (204 mg, 90% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.78 (1H, dd, *J* 7.2, 15.9 Hz, C<u>H</u>=CHCO), 6.01 (1H, d, *J* 15.9 Hz, C<u>H</u>CO), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.95-3.75 (1H, m, C<u>H</u>N$_3$), 3.60-3.45 (1H, m, C<u>H</u>-OH), 2.40 (1H, br s, O<u>H</u>), 1.61-1.11 (4H, m, C<u>H</u>$_2$ x2), 1.30 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.92 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.34, 141.48, 124.41, 72.55, 67.31, 60.47, 35.17, 18.37, 13.80, 13.52; HRMS (ES Q-TOF): [M+H]+, found 228.1345. $C_{10}H_{17}N_3O_3$ requires 228.1348

**(E) (4*S*,5S**)-ethyl 4-azido-5-cyclohexyl-5-hydroxypent-2-enoate (10b)**: brown oil (254 mg, 95% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.83 (1H, dd, *J* 7.5, 15.8 Hz, C<u>H</u>=CHCO), 6.04 (1H, d, *J* 15.8 Hz, C<u>H</u>CO), 4.31-3.98 (3H, m, C<u>H</u>N$_3$ + COC<u>H</u>$_2$CH$_3$), 3.28 (1H, dd, J 5.4 Hz, C<u>H</u>-OH), 2.65 (1H, br s, O<u>H</u>), 1.94-0.93 (14H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.5,

141.9, 124.5, 77.2, 64.9, 60.7, 40.0, 29.6, 27.0, 26.0, 25.9, 25.7, 14.0; HRMS (ES Q-TOF): [M+H]+, found 268.1663. $C_{13}H_{21}N_3O_3$ requires 268.1661

*4.2.5. Synthesis of (2S*,3R*) 2,3-epoxy-hexan-1-ol (**12**).*

At 0°C, *m*-CPBA (1,5 mmol, 259mg) was added to a solution of *cis* hex-2-en-1-ol (1 mmol, 0.12 ml) in 1 ml of dichloromethane and the mixture left stirring for 1 hour or until consumption of the substrate (TLC monitoring). The organic layer was washed with aqueous solutions of $Na_2S_2O_3$ and NaCl and then dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product as a colourless oil, which was then used without any purification (96 mg, 83% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 3.86 (1H, dd, *J* 4.1, 12.1 Hz, C$\underline{H}_a$H$_b$-OH), 3.67 (1H, dd, *J* 6.8, 12.1 Hz, CH$_a$$\underline{H}_b$-OH), 3.16 (1H, dt, *J* 4.1, 6.8, 8.5 Hz C$\underline{H}$-CH$_2$OH), 3.08-2.95 (1H, m, CH$_2$CH$_2$-C$\underline{H}$), 1.80-1.40 (5H, m, C$\underline{H}_2$ x2 + O$\underline{H}$), 0.9 (3H, t, *J* 7.3 Hz, C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 61.9, 58.7, 55.9, 33.5, 19.1, 13.7.

All other experimental data were consistent with the ones reported in the literature[14].

*4.2.6. Synthesis of (2S*,3R*) 2,3-epoxy-hexanal (**13**).*

1 mmol of epoxy alcohol **12** (116 mg) was dissolved in 1 ml of anhydrous dichloromethane under argon atmosphere and then TEMPO (0,1 mmol, 16 mg) and IBDA (1,1 mmol, 354 mg) were added and the mixture stirred at room temperature for 3h or until consumption of the substrate (TLC monitoring). The reaction mixture was then diluted with dichloromethane and washed with saturated solutions of $Na_2S_2O_3$, $NaHCO_3$, and NaCl until pH=7. The organic layer was dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product as a colourless oil, which was used without any purification. (82 mg, 72% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 9.5 (1H, d, *J* 5.3 Hz, C$\underline{H}$O), 3.37-3.21 (2H, m, C$\underline{H}$-O-C$\underline{H}$), 1.72-1.4 (4H, m, C$\underline{H}_2$ x2), 0.97 (3H, t, *J* 7.3 Hz, CH$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 199.0, 58.9, 57.1, 34.3, 19.0, 13.5; HRMS (ES Q-TOF): [M+H]+, found 115.0754 $C_6H_{10}O_2$ requires 115.0759

*4.2.7. Synthesis of (E)-ethyl 3-((2S*,3R*)-3-propyloxiran-2-yl)acrylate (14).*

Aldehyde 13 (1 mmol, 115 mg), LiOH (1,1 mmol, 27 mg) and TEPA (1,1 mmol, 250 mg, 0,22 ml) were dissolved in 10 ml of THF and then stirred at the reflux temperature for 5h or until consumption of the substrate (TLC monitoring). A saturated solution of $NH_4Cl$ was then added and the reaction mixture concentrated in vacuo. The aqueous residue was then extracted with ethyl acetate and the organic layer washed with aq. $NH_4Cl$ and brine until pH=7. The combined organic extracts were dried over $Na_2SO_4$ and evaporated in vacuo to leave the crude that was then purified

[14] Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, 42, *23*, 6459-6464

by flash chromatography on silica gel (hexane/AcOEt 9:1) to give the desired product as a yellow oil (163 mg, 88% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.67 (1H, dd, *J* 6.6, 15.7 Hz, C<u>H</u>=CHCO), 5.99 (1H, dd, *J* 0.8, 15.7 Hz, C<u>H</u>CO), 4.15 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.38 (1H, ddd, *J* 0.8, 4.4, 6.6 Hz, C<u>H</u>CH=CH), 3.1-2.99 (1H, m, CH$_2$-C<u>H</u>), 1.47-1.26 (4H, m, C<u>H</u>$_2$ x2), 1.16 (3H, t, *J* 7.2, COCH$_2$C<u>H</u>$_3$ ), 0.89 (3H, t, *J* 6.8 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.3, 141.9, 124.9, 60.3, 59.3, 54.9, 29.4, 19.5, 14.0, 13.6; HRMS (ES Q-TOF): [M+H]+, found 185.1173 $C_{10}H_{16}O_3$ requires 185.1178

*4.3. General procedure for the dihydroxylation reaction.*

To a solution of 1 mmol of the appropriate substrate in 9 ml of acetone/water (8:1) were added 2 mmol (270 mg) of NMO and 0,63 ml of a 2,5% solution of OsO4 in t-butanol (0.05 mmol of OsO4) and the mixture left stirring overnight at room temperature. The reaction was then quenched with a saturated solution of $Na_2S_2O_3$, the mixture left stirring for 1h and then transferred in a separative funnel. The aqueous layer was extracted with ethyl acetate, the combined organic layers dried over Na2SO4 and the solvent removed under reduced pressure. The residue was then purified by chromatography on silica gel to give the mixture of the desired products.

The chromatographically inseparable mixtures **20a**/**20a**', **20b**/**20b**', **22a**/**22a**', **24a**/**24a**', **24b**/**24b**' were subsequently converted into the corresponding acetonides to allow a fully characterization.

**(2*R**,3*S**,4*S**,5*S**)-ethyl 4-azido-2,3,5-trihydroxyoctanoate (16a)**: (data given only for the major product) pail yellow oil (200 mg, 77% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 4.45 (1H, d, *J* 0.5 Hz, C<u>H</u>OH-CO), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.97-3.88 (1H, m, CH$_2$C<u>H</u>OH), 3.85 (1H, dd, *J* 0.5, 9.6 Hz, C<u>H</u>OH-CHOH), 3.62 (1H, dd, *J* 5.6, 9.6 Hz, C<u>H</u>N$_3$), 1.71-1.46 (7H, m, C<u>H</u>$_2$ x2 + O<u>H</u> x3), 1.3 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.9 (3H, t, *J* 6.6 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 173.3, 73.6, 73.2, 71.3, 65.9, 62.4, 34.7, 18.7, 14.2, 14.1; HRMS (ES Q-TOF): [M+H]+, found 262.1406. $C_{10}H_{19}N_3O_5$ requires 262.1403

**(2*R**,3*S**,4*S**,5*S**)-ethyl 4-azido-5-cyclohexyl-2,3,5-trihydroxypentanoate (16b)**: (data given only for the major product) pail yellow oil (241 mg, 80% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 4.43 (1H, d, *J* 0.5 Hz, C<u>H</u>OH-CO), 4.28-4.05 (4H, m, COC<u>H</u>$_2$CH$_3$ + C<u>H</u>OH-CHOH + cyclohexyl-C<u>H</u>OH), 3.65-3.63 (1H, m, C<u>H</u>N$_3$), 1.88-1.44 (8H, m, cyclohexyl + O<u>H</u> x3), 1.34-0.8 (9H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 173.1, 83.4, 78.1, 74.7, 71.5, 62.2, 40.4,

30.1, 29.2, 26.4, 25.9, 25.6, 14.2; HRMS (ES Q-TOF): [M+H]+, found 302.1711. $C_{13}H_{23}N_3O_5$ requires 302.1715

**(2*R*,3S*,4R*,5S*)-ethyl 4-azido-2,3,5-trihydroxyoctanoate (18a)**: (data given only for the major product) pail yellow oil (198 mg, 76% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.26 (1H, d, *J* 2.6 Hz, C<u>H</u>OH-CO), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.08 (1H, dd, *J* 2.6, 6.3 Hz, C<u>H</u>OH-CHOH), 3.78-3.70 (1H, m, CH$_2$C<u>H</u>OH), 3.38 (1H, dd, *J* 2.4, 6.3 Hz, C<u>H</u>N$_3$), 1.67-1.33 (7H, m, C<u>H</u>$_2$ x2 + O<u>H</u> x3), 1.27 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.9 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 173.4, 71.4, 71.1, 70.4, 65.5, 62.3, 36.3, 19.2, 14.2, 13.9. HRMS (ES Q-TOF): [M+H]+, found 262.1400. $C_{10}H_{19}N_3O_5$ requires 262.1403

**(2*R*,3S*,4R*,5S*)-ethyl 4-azido-5-cyclohexyl-2,3,5-trihydroxypentanoate (18b)**: (data given only for the major product) pail yellow oil (236 mg, 78% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.36 (1H, d, *J* 2.6 Hz, C<u>H</u>OH-CO), 4.33-4.21 ( 3H, m, COC<u>H</u>$_2$CH$_3$ + C<u>H</u>OH-CHOH), 3.69 (1H, dd, *J* 2.0, 6.7 Hz, cyclohexyl-C<u>H</u>OH), 3.45 (1H, dd, J 2.0, 8.4 Hz, C<u>H</u>N$_3$), 2.0-1.50 (8H, m, cyclohexyl + O<u>H</u> x3), 1.34-0.8 (9H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.8, 75.9, 73.9, 71.0, 64.6, 62.5, 41.2, 29.1, 26.3, 25.9, 25.8, 25.5, 14.2; HRMS (ES Q-TOF): [M+H]+, found 302.1717. $C_{13}H_{23}N_3O_5$ requires 302.1715

**(2*R*,3S*)-ethyl 3-((2*S*,3R**)-3-propyl-(N-ethoxycarbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate (28a)**: (data given only for the major product) pail brown oil (182 mg, 63% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.37 (1H, d, *J* 1.7 Hz, C<u>H</u>OH-CO), 4.27 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.16 (2H, q, *J* 7.2 Hz, NCOC<u>H</u>$_2$CH$_3$), 3.99 (1H, dd, *J* 1.7, 4.9 Hz, C<u>H</u>OH-CHOH), 2.63-2.56 (1H, m, CH$_2$C<u>H</u>), 2.49 (1H, dd, J 3.4, 4.9 Hz, C<u>H</u>-CHOH), 2.1 (2H, br s, O<u>H</u> x2), 1.81-1.4 (4H, m, C<u>H</u>$_2$ x2), 1.35-1.20 (6H, m, COCH$_2$C<u>H</u>$_3$ x2), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.1, 160.7, 71.9. 69.1 62.1, 60.13, 45.4, 43.2, 32.7, 19.8, 14.1, 13.9, 13.2; HRMS (ES Q-TOF): [M+H]+, found 290.1600. $C_{13}H_{23}NO_6$ requires 290.1604

**(2*R*,3S*)-ethyl 3-((2*S*,3R**)-3-cyclohexyl(N-ethoxycarbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate (28b)**: (data given only for the major product) pail yellow oil (217 mg, 66% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.32 (1H, d, *J* 0.5 Hz, C<u>H</u>OH-CO), 4.29-4.06 (5H, m, COC<u>H</u>$_2$CH$_3$ x2 + C<u>H</u>OH-CHOH), 2.5 (1H, dd, J 3.6 Hz, C<u>H</u>N), 2.4 (1H, dd, J 3.6, 6.0 Hz, C<u>H</u>N), 2.21 (2H, br s, O<u>H</u> x2), 2.01-1.56 (5H, m, cyclohexyl), 1.36-0.96 (12H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$ x2); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.8, 172.7, 72.4, 69.7, 62.3, 62.2, 45.4, 43.0, 39.5, 30.8, 30.0, 26.3, 25.8, 25.6, 14.4, 14.2; HRMS (ES Q-TOF): [M+H]+, found 330.1914. $C_{16}H_{27}NO_6$ requires 330.1917

**(2*R*,3S**)-ethyl 3-((2*S*,3R**)-3-propyl-(N-tert-butoxycarbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate (29b)**: (data given only for the major product) pail brown oil (190 mg, 60% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.38 (1H, d, *J* 0.5 Hz, C<u>H</u>OH-CO), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.88 (1H, dd, *J* 0.5, 5.2 Hz, C<u>H</u>OH-CHOH), 2.58-2.50 (1H, m, CH$_2$C<u>H</u>N), 2.45 (1H, dd, *J* 3.3, 5.2 Hz, C<u>H</u>-CHOH), 2.3 (2H, br s, O<u>H</u> x2), 1.78-1.39 (13H, m, C<u>H</u>$_2$ x2 + C(C<u>H</u>$_3$)$_3$), 1.29 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.95 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165,2, 159,2, 80.9, 71.9, 69.1, 60.5, 45.8, 43.1, 33.1, 31.2, 27.9, 14.4, 14.0; HRMS (ES Q-TOF): [M+H]+, found 318.1917. $C_{15}H_{27}NO_6$ requires 318.1917

**(2*R*,3S**)-ethyl 3-((2*S*,3R**)-3-cyclohexyl-(N-tert-butoxycarbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate 29b**: (data given only for the major product) pail yellow oil (233 mg, 65% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.38 (1H, d, *J* 0.5 Hz, C<u>H</u>OH-CO), 4.25 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.97 (1H, dd, *J* 5.0, 1.8 Hz, C<u>H</u>OH-CHOH), 2.5 (1H, dd, *J* 3.5, 5.0 Hz, C<u>H</u>-CHOH), 2.36 (1H, dd, *J* 3.5, 7.5 Hz, cyclohexyl-C<u>H</u>), 2.05-1.59 (7H, m, cyclohexyl + O<u>H</u> x2), 1.4 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.34-1.00 (9H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.9, 161.1, 81.2, 72.4, 70.8, 62.2, 46.4, 42.7, 41.0, 39.7, 30.3, 28.0, 26.3, 25.8, 25.6, 14.2; HRMS (ES Q-TOF): [M+H]+, found 358.2225. $C_{18}H_{31}NO_6$ requires 358.2229

*4.4 General procedure for the acetonide formation.*

1 mmol of the appropriate substrate was dissolved in 10 ml of acetone. To the mixture 2,2-dimethoxypropane (1.4 mmol, 0.17 ml) and a catalytic amount of p-toluensulfonic acid were added and the mixture left stirring at room temperature until complete consumption of the substrate. The reaction crude was diluted with $Et_2O$ and filtered through a basic alumina pad; the solvent was then removed under reduced pressure and the residue purified by chromatography on silica gel to give the mixture of the desired products.

To obtain 1,2-acetonides the reaction needs to be carried out at -20° - 0°C (kinetic control conditions) whereas at room temperature for 1,3-acetonides (thermodynamic control conditions).

**(*R**)-ethyl 2-((4*S**,5*S**,6*S**)-5-azido-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxy acetate (17a)**: pail yellow oil (271 mg, 90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.37 (1H, d, *J* 1.9 Hz, C<u>H</u>OH), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.89 (1H, dd, *J* 1.9, 10.0 Hz, C<u>H</u>-CHOH), 3.6 (1H, ddd, *J* 2.5, 8.0, 10.0 Hz, CH$_2$C<u>H</u>), 3.35 (1H, dd, *J* 10.0 Hz, C<u>H</u>N$_3$), 2.53 (1H, br s, O<u>H</u>), 1.82-

1.41 (4H, m, C$\underline{H}_2$ x2), 1.37 (3H, s, CC$\underline{H}_3$), 1.33 (3H, s, CC$\underline{H}_3$), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$C$\underline{H}_3$), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.1, 98.9, 73.5, 71.8, 70.0, 61.8, 58.6, 35.0, 29.2, 19.2, 18.1, 14.3, 13.9; HRMS (ES Q-TOF): [M+H]+, found 302.1719. $C_{13}H_{23}N_3O_5$ requires 302.1716

**(*R**)-ethyl 2-((4*S**,5*S**,6*S**)-5-azido-2,2-dimethyl-6-cyclohexyl-1,3-dioxan-4-yl)-2-hydroxy acetate (17b)**: colourless oil (317 mg, 93% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.43 (1H, dd, *J* 1.8, 9.0 Hz, C$\underline{H}$OH), 4.2 (2H, q, *J* 7.2 Hz COC$\underline{H}_2$CH$_3$), 3.9 (1H, dd, J 1.8, 9.4 Hz, C$\underline{H}$-CHOH), 3.65-3.45 (2H, m, C$\underline{H}$-CHN$_3$ + C$\underline{H}$N$_3$), 2.9 (1H, d, *J* 9.0 Hz, O$\underline{H}$), 1.84-1.57 (5H, m, cyclohexyl), 1.39-1.11 (15H, m, cyclohexyl + C(C$\underline{H}_3$)$_2$ + COCH$_2$C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.8, 99.0, 75.8, 73.7, 70.3, 61.9, 54.9, 39.1, 30.0, 29.3, 26.8, 26.5, 26.4, 25.7, 19.2, 14.0; HRMS (ES Q-TOF): [M+H]+, found 342.2023. $C_{16}H_{27}N_3O_5$ requires 342.2029

**(*R**)-ethyl 2-((4*S**,5*R**,6*S**)-5-azido-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxy acetate (19a)**: yellow oil (277 mg, 92% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.44-4.11 (3H, m, COC$\underline{H}_2$CH$_3$ + C$\underline{H}$OH), 3.91 (1H, dd, *J* 1.7, 10.0 Hz, C$\underline{H}$-CHOH), 3.6 (1H, ddd, *J* 2.5, 7.9, 10.0 Hz, CH$_2$C$\underline{H}$), 3.38 (1H, dd, *J* 10.0 Hz, C$\underline{H}$N$_3$), 2.5 (1H, br s, O$\underline{H}$), 1.82-1.41 (4H, m, C$\underline{H}_2$ x2), 1.37 (3H, s, CC$\underline{H}_3$), 1.33 (3H, s, CC$\underline{H}_3$), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$C$\underline{H}_3$), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.1, 98.9, 73.6, 71.9, 70.0, 61.8, 58.6, 35.1, 29.8, 19.2, 18.2, 14.4, 13.9; HRMS (ES Q-TOF): [M+H]+, found 302.1719. $C_{13}H_{23}N_3O_5$ requires 302.1716

**(*R**)-ethyl 2-((4*S**,5*R**,6*S**)-5-azido-2,2-dimethyl-6-cyclohexyl-1,3-dioxan-4-yl)-2-hydroxy acetate (19b)**: colourless oil (325 mg, 95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.45 (1H, dd, *J* 4.3, 7.4 Hz, C$\underline{H}$OH), 4.2 (2H, q, *J* 7.2 Hz COC$\underline{H}_2$CH$_3$), 3.80 (1H, dd, *J* 3.0, 7.4 Hz, C$\underline{H}$-CHOH), 3.60 (1H, dd, *J* 4.8 Hz, C$\underline{H}$-CHN$_3$), 3.35 (1H, dd, *J* 3.0, 4.8 Hz, C$\underline{H}$N$_3$), 2.6 (1H, d, *J* 4.3 Hz, O$\underline{H}$), 1.84-1.57 (5H, m, cyclohexyl), 1.39-1.11 (15H, m, cyclohexyl + C(C$\underline{H}_3$)$_2$ + COCH$_2$C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 170.8, 99.0, 75.8, 73.7, 70.3, 61.9, 54.9, 40.0, 30.0, 29.3, 26.8, 26.5, 26.4, 25.7, 19.2, 14.3; HRMS (ES Q-TOF): [M+H]+, found 342.2023. $C_{16}H_{27}N_3O_5$ requires 342.2029

**(*R**)-ethyl 2-((4*R**,5*S**,6*S**)-5-bromo-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxy acetate (21a)**: light orange oil (229 mg, 68% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.57 (1H, dd, *J* 1.7, 9.2 Hz, C$\underline{H}$OH), 4.41-4.14 (3H, m, C$\underline{H}$-Br + COC$\underline{H}_2$CH$_3$), 3.95-3.86 (2H, m, C$\underline{H}$-O x2), 2.85 (1H, d, *J* 9.2 Hz, O$\underline{H}$), 1.82-1.41 (4H, m, C$\underline{H}_2$ x2), 1.37 (3H, s, CC$\underline{H}_3$), 1.33 (3H, s, CC$\underline{H}_3$), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$C$\underline{H}_3$), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ:

172.3, 98.9, 75.5, 73.4, 70.7, 61.8, 48.3, 35.4, 29.4, 19.3, 18.1, 14.5, 13.9; HRMS (ES Q-TOF): [M+H]+, found 339.0805. $C_{13}H_{23}BrO_5$ requires 339.0807

**(*R**)-ethyl 2-((4*R**,5*S**,6*R**)-5-bromo-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxy acetate (23)**: pail brown oil (237 mg, 70% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.54 (1H, dd, *J* 4.2, 8.4 Hz, C<u>H</u>-Br), 4.41 (1H, dd, *J* 1.2 Hz, C<u>H</u>OH), 4.34-4.13 (3H, m, C<u>H</u>-CHOH + COC<u>H</u>$_2$CH$_3$), 3.76 (1H, ddd, *J* 4.2, 8.0, 12.2 Hz, CH$_2$-C<u>H</u>), 2.45 (1H, br s, O<u>H</u>), 1.71-1.19 (13H, m, C<u>H</u>$_2$ x2 + C(C<u>H</u>$_3$)$_2$ + COCH$_2$C<u>H</u>$_3$), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 172.3, 101.8, 76.4, 74.5, 69.0, 62.0, 54.9, 35.9, 23.9, 23.6, 18.8, 14.3, 13.9; HRMS (ES Q-TOF): [M+H]+, found 339.0809. $C_{13}H_{23}BrO_5$ requires 339.0807

**(4*R**,5*S**)-ethyl 2,2-dimethyl-5-((2*R**,3*S**)-3-propyloxiran-2-yl)-1,3-dioxolane-4-carboxylate (25a)**: colourless oil (147 mg, 57% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.44 (1H, d, *J* 7.7 Hz, C<u>H</u>-COOEt), 4.2 (2H, q, *J* 7.2 Hz COC<u>H</u>$_2$CH$_3$), 4.02 (1H, dd, *J* 5.0, 7.7 Hz, C<u>H</u>-CHCOOEt), 2.99 (1H, ddd, *J* 2.2, 5.2, 7.4 Hz, CH-O-C<u>H</u>-CH), 2.93 (1H, dd, J 2.2, 5.0 Hz, CH$_2$-C<u>H</u>), 1.64-1.48 (4H, m, C<u>H</u>$_2$ x2), 1.46 (3H, s, CC<u>H</u>$_3$), 1.43 (3H, s, CC<u>H</u>$_3$), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 170.4, 112.2, 78.9, 76.3, 61.7, 57.7, 56.1, 33.8, 26.7, 25.9, 19.4, 14.3, 14.0; HRMS (ES Q-TOF): [M+H]+, found 259.1549. $C_{13}H_{22}O_5$ requires 259.1545

**(4*R**,5*S**)-ethyl 2,2-dimethyl-5-((2*R**,3*S**)-3-cyclohexyloxiran-2-yl)-1,3-dioxolane-4-carboxylate (25b)**: colourless oil (155 mg, 52% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 4.44 (1H, d, *J* 7.7 Hz, C<u>H</u>-CO), 4.2 (2H, q, *J* 7.2 Hz COC<u>H</u>$_2$CH$_3$), 4.02 (1H, dd, *J* 5.0, 7.7 Hz, C<u>H</u>-CHCO), 2.99 (1H, dd, J 2.2, 5.0 Hz, CH-O-C<u>H</u>), 2.93 (1H, dd, J 2.2, 5.4 Hz, cyclohexyl-C<u>H</u>), 1.84-1.57 (5H, m, cyclohexyl), 1.46 (3H, s, CC<u>H</u>$_3$), 1.43 (3H, s, CC<u>H</u>$_3$), 1.39-1.11 (9H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 170.4, 112.2, 79.3, 76.4, 61.7, 60.3, 56.7, 39.7, 29.8, 29.4, 26.3, 25.7, 25.6, 14.3; HRMS (ES Q-TOF): [M+H]+, found 299.1854. $C_{16}H_{26}O_5$ requires 299.1858

# Chapter 7. Total synthesis of azasugars through asymmetric dihydroxylation of optically active vinyl epoxides.

## 6. Introduction.

As described in Chapter 6, interesting results were obtained in the asymmetric dihydroxylation of vinyl epoxides. It was possible to obtain both the *matched* and the *mismatched* product in high diastereomeric excesses and yields, using the appropriate ligand (Fig. 1).

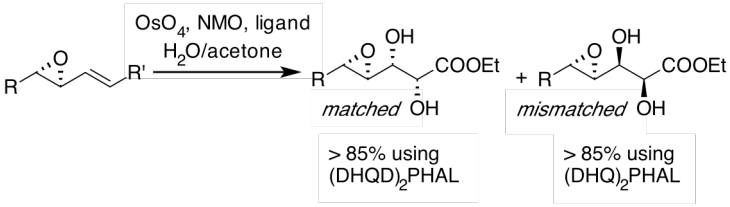



**Fig. 1 Asymmetric dihydroxylation of vinyl epoxides.**

These molecules, containing four adjacent stereogenic centers, could be further elaborated using the already described ring-opening methodologies, giving access to amino polyalcoholic fragments (Fig. 2), common motifs in many natural occurring and biologically active compounds. In the last few months of my PhD I've become interested in the total synthesis of azasugars, as a synthetic application of the knowledge gathered through my whole career.

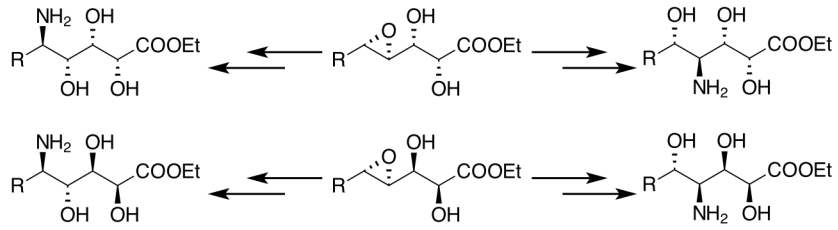



**Fig. 2 Possible further elaborations of the epoxide ring.**

Azasugars, or iminosugars, are structural analogues of traditional carbohydrates where the ring oxygen is replaced by a nitrogen atom. These natural compounds belong to the polyhydroxylated alkaloids family and, as for sugars, can be found as five terms cycles (azafuranose) and six terms cycles (azapyranose). They can be divided in five classes (Fig. 3): piperidines, pyrrolidines, pyrrolizidines, nortropanes and indolizidines.

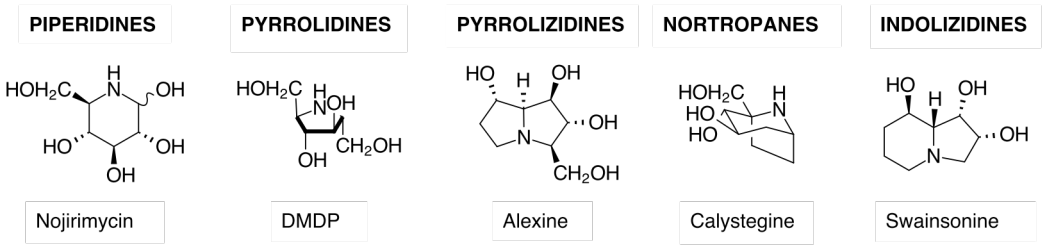



**Fig. 3 Five classes of azasugars.**

Their most valuable property is the ability to inhibit glycosidase and glycosyltransferase enzymes by mimicking the corresponding natural substrates[1]. Therefore these sugar mimics have a tremendous therapeutic potential against a vast array of diseases, from viruses infections to tumoral metastases, and this has led to an increasing interest in their synthesis,[2] particularly given their low natural abundance.

Most of the syntheses reported to date make use of carbohydrates as precursors, for their structural similarity[3] (Fig. 4).

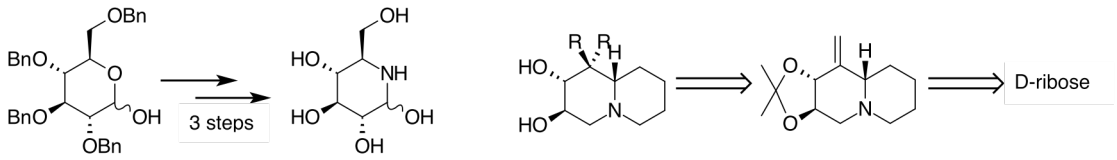



**Fig. 4 Synthesis of azasugars from carbohydrates.**

Fewer are the ones starting from linear molecules, and those often make use of the dihydroxylation reaction to generate new stereocenters[4] (Fig. 5).

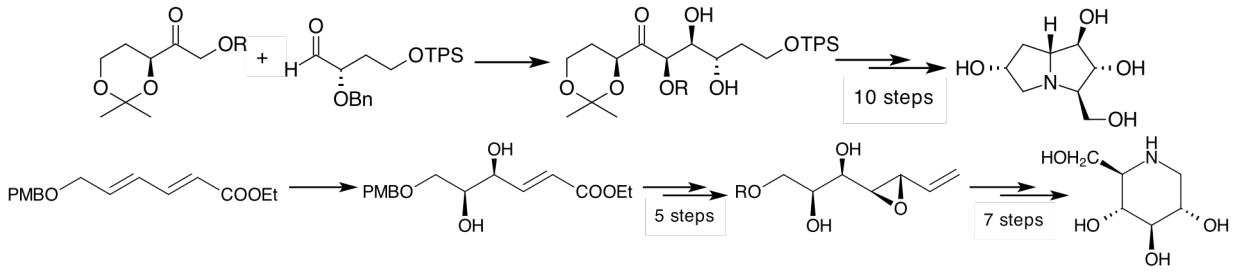



**Fig. 5 Synthesis of azasugars from linear molecules.**

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[1] a) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, 120, *13*, 3007-3018; b) Asano, N; Nash, R.J.; Molyneux, R.J.; Fleet, G.W.J. *Tetrahedron:Asymmetry* **2000**, 11, *8*, 1645-1680

[2] a) Afarinkia, K.; Bahar, A. *Tetrahedron:Asymmetry* **2005,** 16, 7, 1239-1287; b) Stocker, B.L.; Dangerfield,E.M.; Win-Mason, A.L.; Haslett, G.W.; Timmer , M.S.M. *Eur. J. Org. Chem.* **2010**, 9, 1615-1637

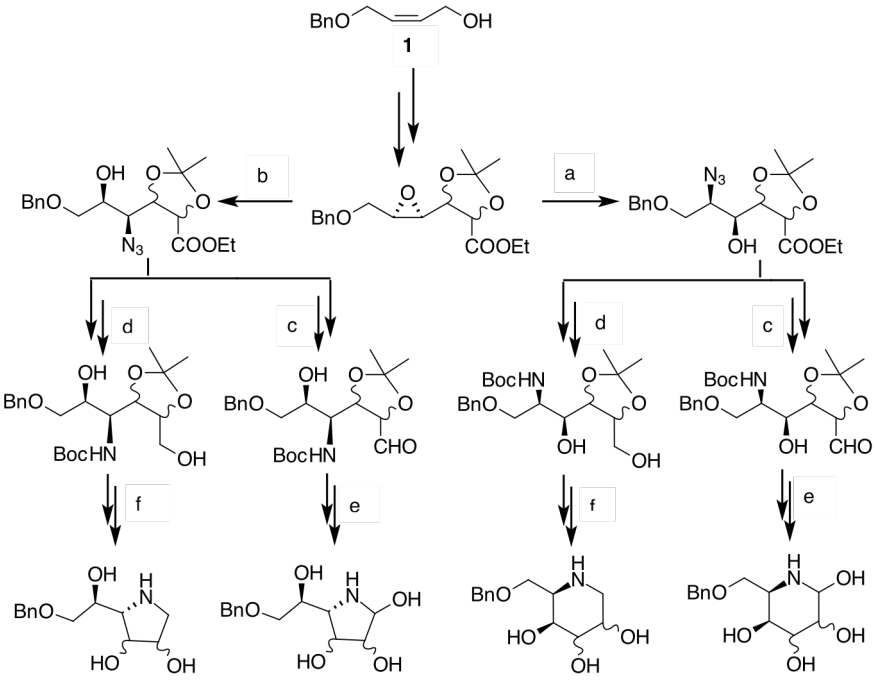
[3] Somfai, *Tetrahedron Lett*. **1998**, *39*, 7173; b) Wennekes, T. *et al. J. Med. Chem*. **2010**, 53, *2*, 689; c) Ganesh, P. *et al. Org.Biomol.Chem.*, **2009**, *7*, 3300

[4] a) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Org. Lett.* **2007**, *9*, 77–80. b) Somfai, P.; Marchand, P.; Torsell, S.; Lindstrom, U. L., *Tetrahedron* **2003**, *59*, 1293

What we present is a 9-10 steps divergent synthesis, which, starting from the same commercially available allylic alcohol, could lead to four different azasugars (two piperidines and two pyrrolidines), creating four stereogenic centers in a completely controlled fashion. This strategy aims at becoming of general value, with the possibility of being applied to different precursors in order to obtain different functionalization on the target molecules.

## 7. Results and discussion.

Having in mind to use the asymmetric dihydroxylation of vinyl epoxides and the subsequent elaboration of the heterocyclic ring as key steps of the synthesis, a synthetic path starting from allylic alcohol **1** was developed (Scheme 1). Crucial steps are the regio- and stereo controlled opening of the epoxide ring (steps a and b) that would gain the 4- or 5-azido-alcohols, key intermediates for the formation of the five or six terms cycles. Moreover, is important to notice that from the azido alcohols the synthetic path uses the same reactions for all four structures (steps c, d, e, f).

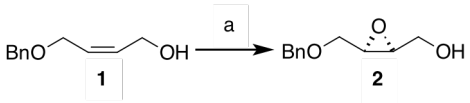



**Scheme 1 Proposed divergent synthetic strategy.**

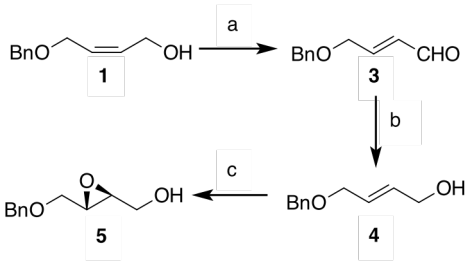
*2.1. Studies towards the asymmetric epoxidation of (cis)-4-(benziloxy)-2-buten-1-ol.*

The first step of the synthetic strategy would have obviously been an asymmetric epoxidation of the commercially available (*cis*)-4-(benziloxy)-2-buten-1-ol. Unfortunately this reaction has proved to be anything but easy to carry out.

Using Sharpless procedure for *cis* allylic alcohols (Scheme 2) only 30% of the substrate was converted into the desired epoxide **2**, and the enantiomeric excess was very low (55% e.e.). Increasing the purity of the reagents and the temperature gave no better results.




**Scheme 2** *Reagents and conditions*: molecular sieves, (+)-DET, $Ti(O\text{-}iPr)_4$, TBHP, dry $CH_2Cl_2$, -20°C, 3 days (30%).

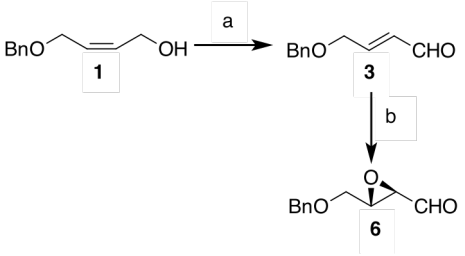



**Scheme 3** *Reagents and conditions*: a) Pyr/SO3 complex, $Et_3N$, DMSO, $CH_2Cl_2$, r.t., 2h (96%); b) $NaBH_4$, MeOH, r.t., 30' (85%); molecular sieves, (+)-DET, $Ti(O\text{-}iPr)_4$, TBHP, dry $CH_2Cl_2$, -20°C, 3 days (30%)

Given the known lack of efficiency of the Sharpless procedure on *cis* allylic alcohols, **1** was isomerized in order to perform the epoxidation on the *trans* isomer. An oxidation of the hydroxyl moiety using $Pyr/SO_3$ complex and a subsequent reduction of the aldehyde, afforded trans allylic alcohol **4** in an 81% yield over two steps (Scheme 3).

However, the Sharpless procedure gave the same results obtained on the *cis* isomer.

The last attempt was made using an altogether different approach. Following Jorgensen work,[5] *cis* alcohol **1** was converted into the corresponding *trans* α,β-unsaturated aldehyde **3**, which was then epoxidised using aq. $H_2O_2$ in the presence of a catalyst (Scheme 4). Unfortunately the desired epoxy aldehyde **6** was recovered only in 20% yield, even though with an enantiomeric excess of 95%.

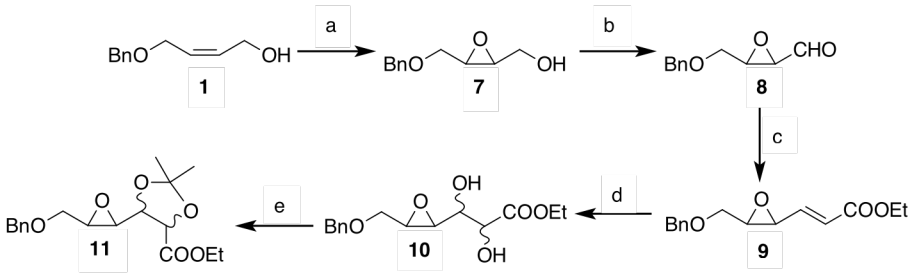



**Scheme 4** *Reagents and conditions*: a) $Pyr/SO_3$ complex, $Et_3N$, DMSO, $CH_2Cl_2$, r.t., 2h (96%); b) aq. $H_2O_2$, catalyst, $CH_2Cl_2$, r.t., 4h (20%)

[5] Marigo, M; Franzén, J; Poulsen, T.B; Zhuang, W; Jørgensen, K.A *J. Am. Chem. Soc*. **2005**, 127, *19*, 6964-6965

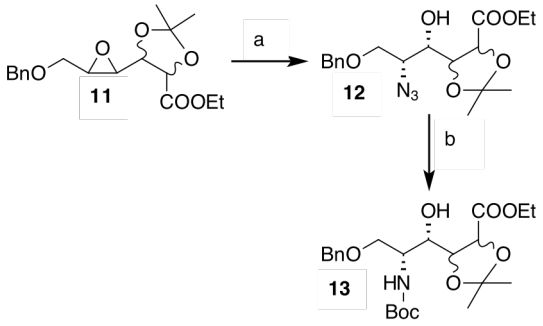
*2.2. Synthesis of ethyl 5-(3-((benzyloxy)methyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **11**.*

Given the difficulty to obtain optically active substrates the synthetic path was performed on racemic compounds in order to verify, in the meanwhile, the applicability of all the reactions and to fine-tune the conditions. The osmilation reaction was performed using non-asymmetric conditions. Starting from alcohol **1**, a non-asymmetric epoxidation, followed by the oxydation of the hydroxyl moiety and a subsequent Horner/Emmons reaction, afforded vinyl epoxide **9** (Scheme 5). This was then submitted to the non-asymmetric osmilation reaction, which led to the 1:1 chromatographically inseparable diastereomeric mixture **10**[6]. This was then converted into the 1,2-acetonides mixture **11**, key intermediate of the synthetic strategy.




**Scheme 5** *Reagents and conditions*: a) *m*-CPBA, $CH_2Cl_2$, r.t., 4h (90%); b) TEMPO, IBDA, $CH_2Cl_2$, r.t., 3h (90%); c) TEPA, LiOH, THF, 70°C, o/n (85%); d) $OsO_4$, NMO, $H_2O$/acetone, r.t., o/n (85%); e) *p*-toluensulphonic acid, DMP, acetone, r.t., o/n (75%)

*2.3. Synthesis of ethyl 5-((1S*,2R*)-2-(N-tert-butoxycarbonyl)amino-3-(benzyloxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **13** - route towards piperidinic azasugars.*




**Scheme 6** *Reagents and conditions*: a) $NaN_3$, $NH_4Cl$, EtOH, 70°C, o/n (85%); b) Pd/C, $H_2$, $Boc_2O$, AcOEt, r.t., o/n (95%)

For the route towards piperidinic azasugars, **11** was regio- and stereoselectively opened using[7] $NaN_3$ and $NH_4Cl$ in EtOH at 70°C, leading only to **12** in an 85% yield[8]. The azide group was subsequently reduced to NHBoc to give **13** in a 95% yield (Scheme 6).

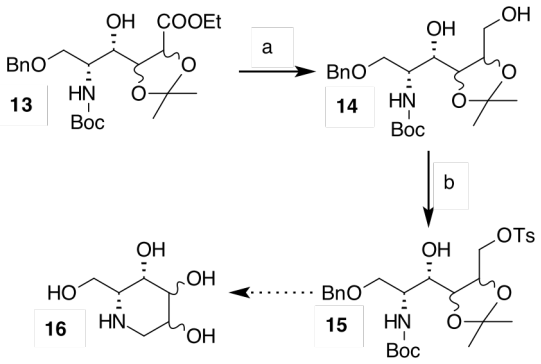
[6] From the epoxy diols mixture **9** on, the compounds characterization isn't complete yet, since the diastereomers are chromatographically inseparable. For the same reason all compounds showed are intended as diastereomeric mixtures.

[7] Behrens, C.H; Sharpless, K.B *J. Org. Chem.,* **1985**, 50, 26, 5696-5704

[8] All compounds are racemates and the stereochemistry reported is intended as the relative one.

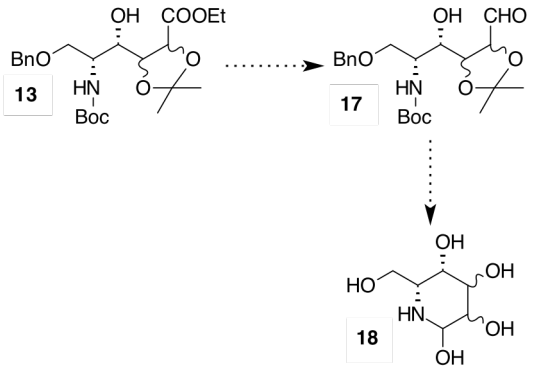
*2.4. Study towards the synthesis of analogues of 1-deoxynojirimycin – route towards deoxy piperidinic azasugars.*

For the route towards deoxy- piperidinic azasugars, a reduction of **13** and a subsequent protection led to tosyl derivative **15** in a 75% yield. A subsequent ring-closing reaction will lead to **16**, first target of our synthesis (Scheme 7).




**Scheme 7** *Reagents and conditions*: a) $NaBH_4$, THF, r.t., 4h (90%); b) $Et_3N$, DMAP, TsCl, dry $CH_2Cl_2$, -15°C, o/n (83%)

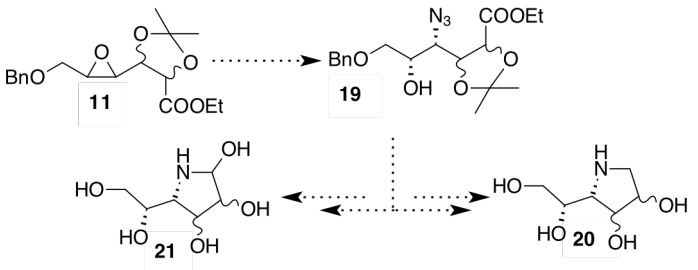
*2.4. Future developments.*




**Scheme 8 Route towards nojirimycin analogues.**

Amino alcohol **13** is the key intermediate also for the synthesis of nojirimycin analogues. A reduction to aldehyde and subsequent ring-closing reaction should easily lead to **18**, second target of our synthesis (Scheme 8).

As for the synthesis of pyrrolidinic azasugars, studies on the regioselective opening of **11** to 1,2-amino alcohol **19** are still ongoing (Scheme 9). From **19** the synthetic path will be the same described before for the synthesis of **16** and **18** and will lead to 3,4-dihydroxy-2-1',2'-dihydroxyethylpyrrolidine **20** and 3,4,5-trihydroxy-2-1',2'-dihydroxyethylpyrrolidine **21,** last two targets of our synthesis.




**Scheme 9 Route towards pyrrolidinic azasugars.**

## 8. Conclusions.

The synthetic strategy presented could lead to four different azasugars starting from the same, commercially available, allylic alcohol. Regio- and stereocontrolled reactions will create four adjacent stereogenic centers in a completely controlled fashion, allowing the synthesis of different analogues.

Two crucial steps have already been fine-tuned: regioselective ring-opening of **11** to 1,2-hydroxyl azide **12** and reduction of **13** to alcohol **14**. Studies on the asymmetric dihydroxylation of α,β-unsaturated epoxy ester **9**, reduction of **13** to aldehyde **17** and regioselective ring-opening of **11** to 1,2-amino alcohol **19** are still ongoing.

## 9. Experimental.

*4.1. General.*

$^{1}$H NMR spectra were recorded using a Varian Mercury 300 (300 MHz). Residual solvent peaks were used as internal references for $^{1}$H NMR spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. $^{13}$C spectra were recorded using a Varian Mercury 300 (75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak: chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml.

All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254

aluminium sheets (Merck Italia) and visualization was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)].

Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

*4.2. Synthesis of (E)-4-(benzyloxy)but-2-enal (3).*

*cis* 4-(benziloxy)-2-buten-1-ol (1 mmol, 178 mg) was diluted in 7.5 ml di $CH_2Cl_2$, $Et_3N$ (4 mmol, 404 mg, 0.5 ml) was added and the mixture cooled to 0°C. Then Py-$SO_3$ complex (3 mmol, 477 mg), dissolved in 3 ml of DMSO, was added and the mixture left stirring at room temperature until complete consumption of the substrate (TLC monitoring). The crude was diluted with a 2:1 mixture of hexane and diethyl ether and washed with aq. $NaHCO_3$. The aqueous layer was extracted twice with a 4:1 mixture of hexane and diethyl ether and then again with only diethyl ether. The organic layers were washed with a 1M aqueous solution of $NaH_2PO_4$, dried over $Na_2SO_4$, and the solvent was removed in vacuo to leave the crude, which was then purified by chromatography on silica gel (Pet. Spirit/$Et_2O$ 9:1) to give the desired product as a colourless oil (169 mg, 96%): $^1$H NMR (300 MHz $CDCl_3$) δ: 9.58 (1H, d, *J* 7.9 Hz, C<u>H</u>O), 7.42-7.27 (5H, m, Ph), 6.85 (1H, dt, *J* 4.1, 15.8 Hz, C<u>H</u>=CHCO), 6.41 (1H, ddt, *J* 1.9, 7.9, 15.8 Hz, C<u>H</u>CO), 4.59 (2H, s, C<u>H</u>$_2$Ph), 4.29 (2H, dd, *J* 1.9, 4.1 Hz, C<u>H</u>$_2$O); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 193.3, 153.1, 137.2, 131.9, 128.6, 128.1, 127.8, 73.1; 68.7

All other experimental data were consistent with the ones reported in the literature[9].

*4.3. Synthesis of (E)-4-(benzyloxy)but-2-en-1-ol (4).*

(E)-4-(benzyloxy)but-2-enal (1 mmol, 179 mg) was diluted in 2 ml of methanol and cooled to 0°C. $NaBH_4$ (2 mmol, 76 mg) was added and the mixture left stirring at room temperature until

[9] Anderson, J.C.; McDermott, B.P.; Griffin, E.J. *Tetrahedron*, **2000,** 56, *44*, 8747 - 8768

complete consumption of the substrate (TLC monitoring). The reaction mixture was concentrated in vacuo, diluted with diethyl ether and washed with aq. $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$, and the solvent removed in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 6:4) to give the desired product as a colourless oil (136 mg, 85%): $^1$H NMR (300 MHz $CDCl_3$) δ: 9.58 (1H, d, *J* 7.9 Hz, C<u>H</u>O), 7.42-7.27 (5H, m, Ph), 6.85 (1H, dt, *J* 4.1, 15.8 Hz, C<u>H</u>=CHCO), 6.41 (1H, ddt, *J* 1.9, 7.9, 15.8 Hz, C<u>H</u>CO), 4.59 (2H, s, C<u>H</u>$_2$Ph), 4.29 (2H, dd, *J* 1.9, 4.1 Hz, C<u>H</u>$_2$O), 2.6 (1H, br s, O<u>H</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 137.86, 132.37, 128.49, 128.36, 127.88, 72.53, 65.68, 58.80.

All other experimental data were consistent with the ones reported in the literature[10].

*4.4. Synthesis of ((2S,3S)-4-(benzyloxy)-2,3-epoxybutan-1-ol (5).*

In a three neck round bottom flask at -20°C and under argon atmosphere, 89 mg of activated molecular sieves were dissolved in 1.5 ml of anhydrous dichloromethane. Were subsequently added: $Ti(Oi\text{-}Pr)_4$ (0.28 mmol, 0.1 ml, 79 mg), (+)-DET (0.28 mmol, 0.05 ml, 58 mg) and TBHP (2 mmol, 0.4 ml, 180 mg) drop-wise, and the mixture left stirring for 30 minutes. (*E*)-4-(benzyloxy)but-2-en-1-ol (1 mmol, 0.1 ml, 178 mg) was diluted in 0.5 ml of anhydrous dichloromethane and added drop-wise, and the mixture left stirring at overnight at -20°C. The mixture was warmed to 0°C, a cold aqueous solution $FeSO_4$ (330 mg) and tartaric acid (100 mg) in 0.5 ml of $H_2O$ was added and the mixture left stirring vigorously for 5-10 minutes. The mixture was transferred in a separative funnel, the layers separated, and the aqueous one extracted twice with diethyl ether. A 30% solution of NaOH in brine was added to the organic layers and the mixture left stirring vigorously at 0°C for 1 hour. The mixture was transferred in a separative funnel, the layers separated, and the aqueous one extracted twice with diethyl ether. Finally the organic layers were dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 7:3) to give the desired product as a colourless oil (58 mg, 30%): $[\alpha]^D_{20}$=-13.5 (c. 3.5, chloroform); $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.27 (5H, m, Ph), 4.5 (2H, s, C<u>H</u>$_2$Ph), 3.77-3.42 (4H, m, C<u>H</u>$_2$O x2), 3.23-3-16 (1H, m, C<u>H</u>-$CH_2$), 3.09-3-(1H, m, C<u>H</u>-$CH_2$), 2.9 (1H, br t, *J* 5.4 Hz, O<u>H</u>); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 137.6, 128.4, 127.7, 127.69, 73.2, 69.5, 61.1, 55.7, 54.2

[10] Yoshimitsu, T; Fukumoto, N; Tanaka, T. *J. Org. Chem*., **2009**, 74, *2*, 696 - 702

All other experimental data were consistent with the ones reported in the literature[11].

*4.5. Synthesis of (2R,3S)-4-benzyloxy-2,3-epoxybutanal (6).*

(E)-4-(benzyloxy)but-2-enal (1mmol, 178 mg) was dissolved in 2 ml of $CH_2Cl_2$ and were subsequently added: *(S)*-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinmethanol trimethylsilyl ether (0,1 mmol, 60 mg), and 1.3 mmol of a 35% aqueous solution of $H_2O_2$ and the mixture left stirring at room temperature until complete consumption of the substrate (TLC monitoring). The mixture was diluted with dichlorometane and washed with aq. $Na_2S_2O_4$ and brine. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 85:15) to give the desired product as a colourless oil (38 mg, 20%): $[\alpha]^{D}_{20}$=-41.8 (c. 4.1, chloroform); $^1$H NMR (300 MHz, $CDCl_3$) δ: 9.05 (1H, d, *J* 6.4 Hz, C<u>H</u>O), 7.42-7.27 (5H, m, Ph), 4.61 (1H d, *J* 12.0 Hz, C<u>H</u>$_a$H$_b$Ph), 4.59 (1H d, *J* 12.0 Hz, CH$_a$<u>H</u>$_b$Ph), 3.85 (1H, dd, *J* 11.5, 2.7 Hz, C<u>H</u>$_a$H$_b$O), 3.59 (1H, dd, *J* 11.5, 5.0 Hz, CH$_a$<u>H</u>$_b$O), 3.48 (1H, dt, *J* 5.0, 2.0 Hz, CH$_2$C<u>H</u>), 3.34 (1H, dd, *J* 6.4, 2.0 Hz, C<u>H</u>-CHO); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 197.5, 137.3,128.5,128.0,127.7, 73.5, 68.3, 56.2, 55.1

All other experimental data were consistent with the ones reported in the literature[12].

*4.6. Synthesis of cis 4-(benzyloxy)-2,3-epoxybutan-1-ol (7).*

(*cis*)-4-(benziloxy)-2-buten-1-ol (1mmol, 178 mg) was dissolved in 10 ml of $CH_2Cl_2$ and the mixture cooled to 0°C. *m*-CPBA (1.5 mmol, 259 mg) was added and the mixture left stirring at room temperature for 4 hours or until complete consumption of the substrate (TLC monitoring). The mixture was filtered, diluted with dichloromethane and washed with saturated solutions of $NaHCO_3$, $Na_2SO_3$ and NaCl until pH 7. The organic layer was dried over $Na_2SO_4$ and the solvent removed in vacuo to give the desired product as colourless oil (162 mg, 90%). $^1$H NMR (300 MHz $CDCl_3$) δ: 7.36-7.27 (5H, m, Ph), 4.64-4.49 (2H, m, C<u>H</u>$_2$Ph), 3.77-3.59 (4H, m, C<u>H</u>$_2$O x2), 3.1 (1H,

[11] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc*., **1987**, *109*, 5765-5780.

[12] Pettersson-Fasth,H; Riesinger, SW; Backvall, J.E. *J. Org. Chem.* **1995**, *60*, 6091-6096

dt, *J* 4.5, 5.8 Hz, C<u>H</u>-$CH_2O$), 3.0 (1H, dt, *J* 4.5, 6.0 Hz, C<u>H</u>-$CH_2O$); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 137.2; 128.3; 127.7; 127.6; 73.1; 67.7; 60.3; 55.6; 54.6

All other experimental data were consistent with the ones reported in the literature[13].

*4.7. Synthesis of cis 4-(benzyloxy)-2,3-epoxybutanal (8).*

*cis* 4-(benzyloxy)-2,3-epoxybutan-1-ol (1mmol, 194 mg) was dissolved in 1 ml of $CH_2Cl_2$ and TEMPO (0.1 mmol, 7 mg) and BAIB (1.1 mmol, 354 mg) were added and the mixture left stirring at room temperature for 3 hours. The reaction crude was diluted with 5 ml of $CH_2Cl_2$ and washed with 0.7 ml aq $Na_2S_2O_4$. The aqueous layer was extracted twice with and the organic layers washed with aqueous solutions of $NaHCO_3$ and NaCl, dried over $Na_2SO_4$ and the solvent removed in vacuo to leave the crude product, which was used without purification, as a yellow oil (189 mg, 90%); $^1H$ NMR (300 MHz $CDCl_3$) δ: 9.43 (1H, d, *J* 7.0 Hz, C<u>H</u>O), 7.36-7.27 (5H, m, Ph), 4.58 (2H, s, $CH_2Ph$), 3.82 (1 H dd, *J* 8.2, 3.2 Hz, C<u>H</u>$_a$H$_b$O), 3.80 (1H, dd, *J* 8.2, 2.2 Hz, CH$_a$<u>H</u>$_b$O), 3.50 (dt, *J* 3.2, 2.2 Hz, $CH_2$C<u>H</u>), 3.34 (1H, dd, *J* 7.0, 2.2 Hz, C<u>H</u>-CHO); 3.2 (1H, br s, O<u>H</u>); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 197.2, 137.0, 128.5, 128.0, 127.8, 73.6, 66.2, 58.0, 57.3;

All other experimental data were consistent with the ones reported in the literature (see ref. 13).

*4.8. Synthesis of cis (E)-ethyl 3-(3-((benzyloxy)methyl)oxiran-2-yl)acrylate (9).*

*cis* 4-(benzyloxy)-2,3-epoxybutanal (1 mmol, 192 mg), LiOH (1.1 mmol, 27 mg) and TEPA (1.1 mmol, 250 mg, 0,22 ml) were dissolved in 10 ml of THF and the mixture left stirring at the reflux temperature until complete consumption of the substrate (TLC monitoring). The mixture was diluted with brine and concentrated in vacuo. The aqueous residue was extracted with AcOEt and the organic layer was neutralized with aq. $NH_4Cl$ and washed with brine. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 9:1) to give the desired product as a yellow oil (223 mg, 85%): $^1H$ NMR (300 MHz $CDCl_3$) δ: 7.50-7.21 (5H, m, Ph), 6.52 (1H, dd, *J* 6.4, 15.5 Hz, C<u>H</u>=CHCO), 6.13 (1H, d, *J* 15.5 Hz, C<u>H</u>CO), 4.64-4.40 (2H, m, $CH_2Ph$), 4.19 (2H, q, *J* 7.2 Hz,

[13] Escudier, J.M.; Baltas, M.; Gorrichon, L. *Tetrahedron*, **1993**, 49, *24*, 5253 - 5266

$COCH_2CH_3$), 3.6-3.5 (3H, m, $CH_2O$ + CH-CH=CH), 3.48-3.45 (1H, m, $CH_2$-CH); $^{13}C$ NMR (75 MHz $CDCl_3$) δ:165.5; 141.1; 137.9; 128.7; 128.0; 127.9; 125.9; 73.5; 67.6; 60.8; 57.7; 54.4; 14.4

All other experimental data were consistent with the ones reported in the literature[14].

*4.9. Synthesis of ethyl 3-(3-((benzyloxy)methyl)oxiran-2-yl)-2,3-dihydroxypropanoate (10).*

cis (E)-ethyl 3-(3-((benzyloxy)methyl)oxiran-2-yl)acrylate (1 mmol, 262 mg) was dissolved in a 1:8 mixture of $H_2O$/acetone (9 ml/1.4 ml). NMO (2 mmol, 0.270 g) and a 2,5w% of $OsO_4$ in tBuOH (0.05 mmol, 0.013 g, 0.6 ml) were added and the mixture left stirring at room temperature until complete consumption of the substrate (TLC monitoring). The reaction was quenched with $Na_2S_2O_3$, diluted with ethyl acetate and washed with brine. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 7:3) to give the desired product as a pail yellow oil (252 mg, 85%).

*4.10. Synthesis of ethyl 5-(3-((benzyloxy)methyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (11).*

Ethyl 3-(3-((benzyloxy)methyl)oxiran-2-yl)-2,3-dihydroxypropanoate (1 mmol, 296 mg) was dissolved in 9 ml di acetone and DMP (1.4 mmol, 0.15 ml) and a catalytic amount of *p*-toluensolfonic acid were added. The mixture was left stirring at room temperature until complete consumption of the substrate (TLC monitoring), then diluted with diethyl ether and washed with aq. $NaHCO_3$, the aqueous layer was extracted several times with diethyl ether and the organic layers washed with brine and then dried over $Na_2SO_4$. The solvent was evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 9:1) to give the desired product as a colourless oil (252 mg, 75%).

*4.11. Synthesis of ethyl 5-((1S*,2R*)-2-azido-3-(benzyloxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (12).*

[14] Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem. Int. Ed.,* **2005**, 44, *32*, 5094 - 5097

Ethyl 5-(3-((benzyloxy)methyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (1 mmol, 336 mg, $NaN_3$ (5 mmol, 325 mg) and $NH_4Cl$ (2 mmol, 107 mg) were dissolved in 10ml of EtOH and the mixture left stirring at 70°C until complete consumption of the substrate (TLC monitoring). The mixture was filtered, concentrated in vacuo and the residue taken up with ethyl acetate and washed with brine. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 7:3) to give the desired product as a colourless oil (322 mg, 85%).

*4.12. Synthesis of ethyl 5-((1S*,2R*)-2-(N-tert-butoxycarbonyl)amino-3-(benzyloxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (13).*

Ethyl 5-((1S*,2R*)-2-azido-3-(benzyloxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (1 mmol, 379 mg) was dissolved in the minimum amount of ethyl acetate and a catalytic amount of 10% Pd/C and $(Boc)_2O$ (1.1mmol, 0.37 ml) were added. The mixture was left stirring under 5atm $H_2$ pressure, at room temperature, until complete consumption of the substrate (TLC monitoring). The mixture was concentrated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 7:3) to give the desired product as a colourless oil (424 mg, 95%).

*4.13. Synthesis of (1S*,2R*)-2-(N-tert-butoxycarbonyl)amino-3-(benzyloxy)-1-(5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (14).*

Ethyl 5-((1S*,2R*)-2-(N-tert-butoxycarbonyl)amino-3-(benzyloxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (1 mmol, 436 mg) was dissolved in 10 ml of THF and 1 ml of $H_2O$, the mixture cooled to 0°C and $NaBH_4$ (4 mmol, 150 mg) was added. The mixture was left stirring at room temperature until complete consumption of the substrate (TLC monitoring) and then diluted with water and concentrated in vacuo. The aqueous residue was extracted with ethyl acetate and the organic layer washed with aq. $NaHCO_3$, $H_2O$ and brine. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was used without purification, to give the desired product as a colourless oil (356 mg, 90%).

*4.14. Synthesis of (1S*,2R*)-2-(N-tert-butoxycarbonyl)amino-3-(benzyloxy)-1-(5-((O-tosyl)-hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (15).*

(1S*,2R*)-2-(N-tert-butoxycarbonyl)amino-3-(benzyloxy)-1-(5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (1 mmol, 396 mg) was dissolved in 3 ml of anhydrous dichloromethane under nitrogen atmosphere at -15°C and were subsequently added: DMAP (1.5 mmol, 183 mg), $Et_3N$ (1.1 mmol, 111 mg, 0.14 ml) and TsCl (1 mmol, 191 mg) and the mixture was left stirring at -15°C until complete consumption of the substrate (TLC monitoring). The mixture was warmed to room temperature and diluted with dichloromethane and then washed with aq. HCl, $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$ and the solvent evaporated in vacuo to leave the crude, which was then purified by chromatography on silica gel (Hexane/AcOEt 7:3) to give the desired product as a colourless oil (450 mg, 83%).

# Chapter 8. Conclusions.

During my three years of PhD I've been focusing my attention on the study of epoxides and aziridines reactivity, engaging in different projects:

1. **Preparation of tryptophan derivatives from aziridine-2-carboxylates.** During the six months I spent in Melbourne, Australia, I've had the opportunity of working for Prof. Craig Hutton, studying the coupling reaction between aziridine-2-carboxylates and indoles, catalysed by Lewis acids.

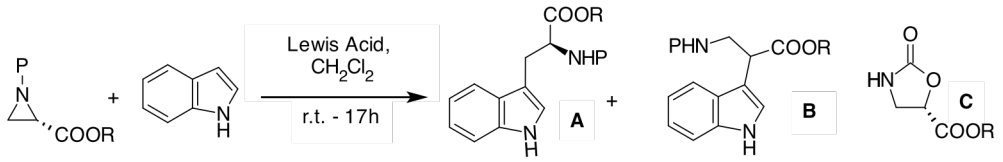



**Fig. 1 Aziridine-2-carboxylate indole coupling.**

The reaction is characterised by two competing processes: a "ring opening" process, leading to the tryptophan derivative, and a "ring expansion" process, leading to an oxazolidinone. The ratio between the two products can be controlled choosing the appropriate conditions: oxophilic Lewis acids (such as $Sc(OTf)_3$) and aziridine protective groups not able to form carbocation (such as 2,2,2-trichloroethanecarbonyl group) favour the ring opening process, thus providing an higher yield of the tryptophan derivative, whereas azaphilic Lewis acids (such as $Hf(OTf)_3$) and aziridine protective groups that easily form carbocation (such as tert-butoxycarbonyl group) favour the oxazolidinone formation. The reaction occurs generally with complete stereoselectivity and high regioselectivity, only using $Sc(OTf)_3$ the regioselectivity is lower and this can be attributed to the lower chelating ability of the Scandium.

2. **Study on the azidolysis reaction of vinyl epoxides and aziridines.** A methodology recently reported on a particular epoxy ester was applied for the first time on vinyl epoxides and aziridines (Fig.2). The reaction is a nucleophilic attack of an azide group to the heterocyclic ring, catalysed by a Lewis acid: $TMSN_3$ is the azide source and $BF_3 \bullet Et_2O$

the Lewis acid. The reaction, characterised by a very broad scope and high reproducibility, is fast (0.5-2 hours), clean and has high yields (>95% on average), occurs with complete stereoselectivity and its regiochemistry is solely due to the peculiar reactivity of the allylic position. The influence of the ring and double bond functionalizations was investigated. The steric hindrance of the R group has no influence on the reaction, an electron-withdrawing nature of R' is essential for the regioselectivity of the reaction (>95% when R'= COOEt, CN) and a carbamate aziridine protective group is required in order to activate the ring.

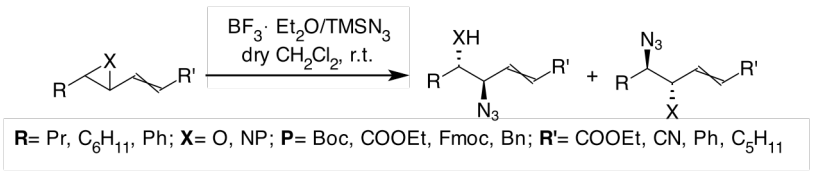



**Fig. 2 Azidolysis reaction on differently functionalized vinyl epoxides and aziridines.**

3. **Regio- and stereocontrolled opening of three-membered heterocyclic rings: a greener approach.** Four nucleophilic ring-opening methodologies, extensively studied by our group in the past years, were upgraded to greener conditions. The methodologies examined are ring-opening reactions mediated by: $MgBr_2$, LiBr/Amb15, NaBr/Amb15, $TMSN_3$/ $BF_3$•$Et_2O$. Substrates of these reactions were epoxy alcohols, O-sylilated aziridino alcohols, epoxy esters, aziridino esters, vinyl epoxides and aziridines, all of which were differently functionalized on the heterocyclic ring and with different protective groups for the aziridine nitrogen (Fig. 3). In all cases the reactions were carried out at room temperature (even the ones that were reported at low temperatures) in DMC, a green solvent, replacing the harmful solvents usually used (e.g. acetone, $Et_2O$, dichloromethane); the work-ups were simplified to filtrations and in vacuo removal of the solvent upon addition of four volumes of methanol; regio- and stereoselectivity were proved to be consistent (if not better) with the ones already reported.

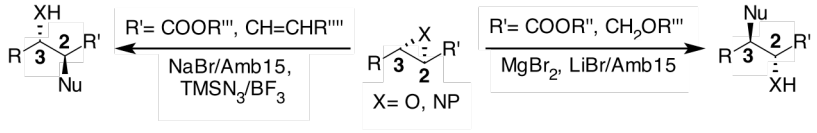



**Fig. 3 Nucleophile mediated ring-opening reactions on differently functionalised epoxides and aziridines.**

4. **One-pot procedure for the synthesis of di-protected amino alcohols from unprotected vinyl aziridines.** During an attempt at protecting a vinyl aziridine as N-acyl derivative an unexpected reaction was observed: instead of the desired protected product, only a di-protected amino alcohol was recovered. The reaction was thoroughly studied in order to verify its reproducibility, scope and the influence of the aziridine functionalizations on it (Fig.4). The study showed that, when the reaction is performed using 3 eq. of acyl chloride and 1 eq. of $Et_3N$, in anhydrous dichloromethane at room temperature, *syn* di-protected amino alcohols can be recovered in a 60-70% yield. The reaction is fairly clean and fast, can be performed on variously functionalised vinyl aziridines using different acyl chlorides; it proceeds with complete regio- and stereoselectivity. The steric hindrance of R (propyl or cyclohexyl) has no influence on the reaction, whereas when R is a phenyl group the regioselectivity is opposite to the one observed for alkyl substituted compounds, and this is probably due to the higher reactivity of the benzylic position (as opposed to the allylic one).

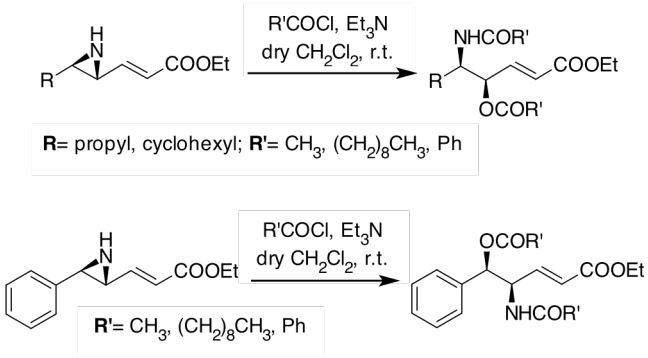



**Fig. 4 Acyl chloride mediated ring-opening reaction of vinyl aziridines.**

5. **Study on the stereochemical control of the dihydroxylation reaction of optically active vinyl epoxides and derivatives.** The $OsO_4$ catalysed dihydroxylation reaction was applied to vinyl epoxides, aziridines and bromo and azido derivatives (Fig. 5). The steric hindrance of the R group proved to have none to little influence on the diastereoselectivity of the reaction.

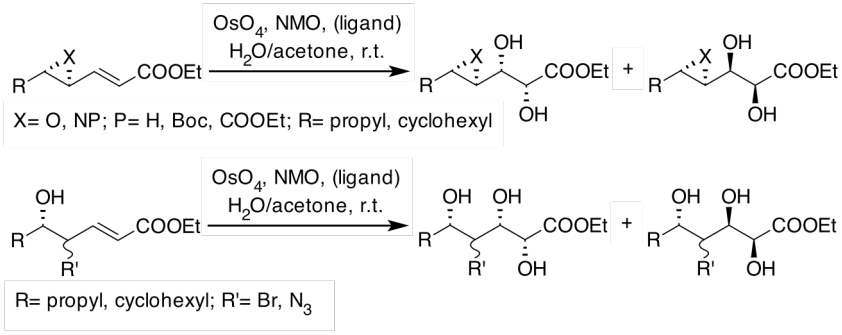



**Fig. 5 Dihydroxylation reaction on vinyl epoxides, aziridines, azido derivatives and bromo derivatives.**

The non-asymmetric reaction, characterized by a syn stereospecificity, proved to be diastereoselective when applied to chiral compounds. Particularly when applied to N-protected aziridines, *syn* and *anti* azido-alcohols and *syn* and *anti* bromohydrins, the diols mixture obtained was characterised by a very high diastereomeric ratio (80:20-90:10). On the other hand epoxides and unprotected aziridines showed none to little influence on the stereoselectivity of the reaction, leading to approximately 1:1 diastereomeric ratios. Vinyl epoxides were submitted to the asymmetric procedure and, selecting the appropriate ligand, it was possible to obtain either one of the diastereomers with high diastereomeric excesses (>80%).

6. **Total synthesis of azasugars through asymmetric dihydroxylation of optically active vinyl epoxides.** During the last few months of my PhD I've become interested in the total synthesis of azasugars, as a synthetic application of the knowledge gathered through my whole career.

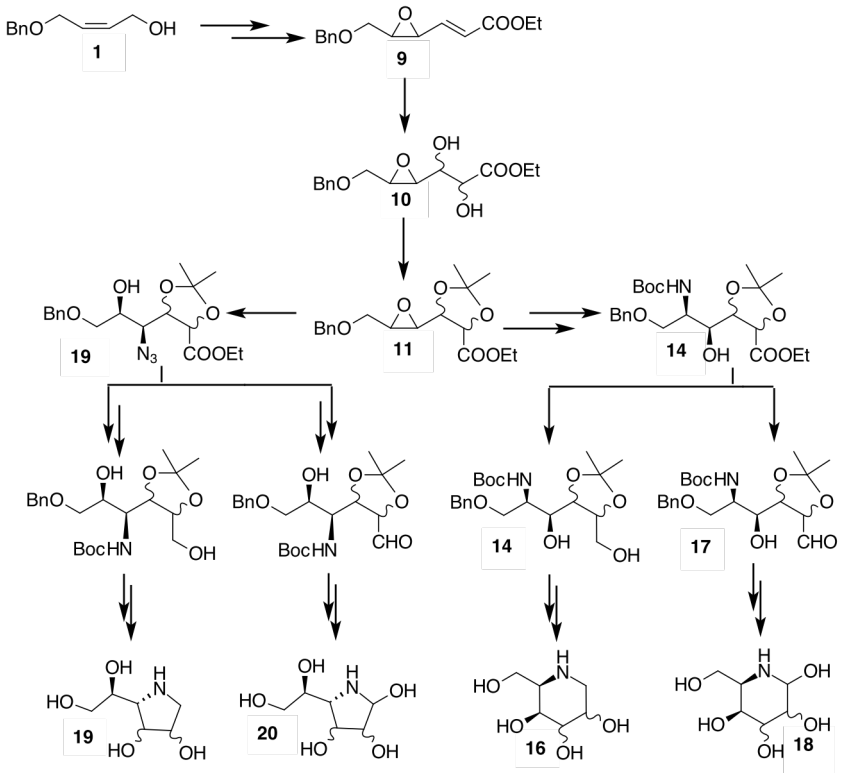



**Fig. 6 Total divergent synthesis of azasugars**

The synthetic strategy presented is a divergent synthesis that, starting from the same, commercially available, allylic alcohol, could lead to four different azasugars (two piperidines and two pyrrolidines), forming four adjacent stereogenic centres through

stereo- and regiocontrolled reactions. Two crucial steps have already been fine-tuned: regioselective ring-opening of **11** to 1,2-hydroxyl azide **12** and reduction of **13** to alcohol **14**. Studies on the asymmetric dihydroxylation of α,β-unsaturated epoxy ester **9**, reduction of **13** to aldehyde **17** and regioselective ring-opening of **11** to 1,2-amino alcohol **19** are still ongoing (Fig. 6). From **19** the synthetic path will be the same as for the synthesis of **16** and **18,** and will lead to 3,4-dihydroxy-2-1',2'-dihydroxyethylpyrrolidine **20** and 3,4,5-trihydroxy-2-1',2'-dihydroxyethylpyrrolidine **21,** last two targets of our synthesis.

# Chapter 9. Experimental.

## 1. General.

$^{1}$H NMR spectra were recorded using a Varian Mercury 300 (300 MHz). Residual solvent peaks were used as internal references for $^{1}$H NMR spectra: chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm) and methanol (δ 3.31 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. $^{13}$C spectra were recorded using a Varian Mercury 300 (75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the residue solvent peak: chloroform (77.00), acetone (δ 30.83 ppm) and methanol (49.05)

HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml.

All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 aluminium sheets (Merck Italia) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), n-butanol (100mL)].

Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

## 2. Synthesis of common substrates

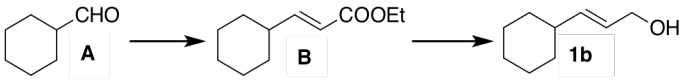



**Fig. 1 Synthesis of (E)-3-cyclohexyl-2-propen-1-ol (1b)**

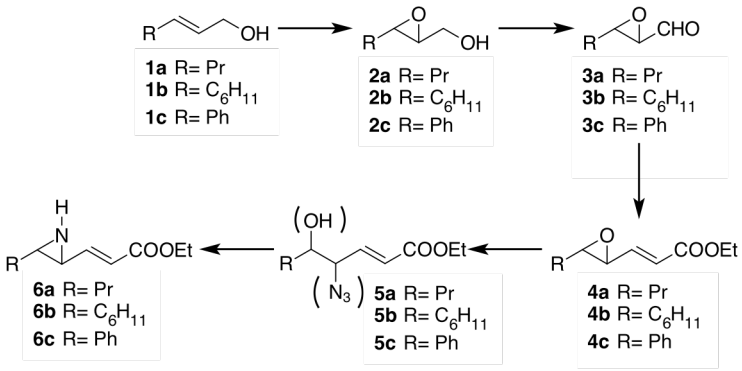



**Fig. 2 Common synthetic path**

*2.1. General procedure for the epoxidation with m-CPBA.*

At 0°C, *m*-CPBA (1,5 mmol, 259mg) was added to a solution of the appropriate allylic alcohol (1 mmol) in 1 ml of $CH_2Cl_2$. and the mixture left stirring for 1 hour or until consumption of the substrate (TLC monitoring). The organic layer was washed with saturated solutions of $Na_2S_2O_3$ and NaCl and then dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was then used without any purification.

**(*2S*,3S**) 2,3-epoxy-hexan-1-ol (2a)**: colourless oil (85% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 3.83 (1H, ddd, *J* 2.2, 4.9, 14.5 Hz, C$\underline{H}_a$H$_b$-OH), 3.53 (1H, ddd, *J* 4.9, 10.7, 17.4 Hz, CH$_a\underline{H}_b$-OH), 2.97-2.77 (2H, m, C$\underline{H}$-O-C$\underline{H}$), 2.3 (1H, br s, O$\underline{H}$), 1.57-1.3 (4H, m, C$\underline{H}_2$ x2), 0.9 (3H, t, *J* 7.3 Hz, C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 61.9, 58.7, 55.9, 33.5, 19.1, 13.7

**(*2S*,3S**) 3-cyclohexyl-2,3-epoxy-propan-1-ol** (**2b)**: colourless oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 3.87-3.76 (1H, m, C$\underline{H}_a$H$_b$-OH), 3.55-3.44 (1H, m, CH$_a\underline{H}_b$-OH), 2.98 (1H, bs, O$\underline{H}$), 2.92 (1H, ddd, *J* 2.5, 4.9, 7.4 Hz, C$\underline{H}$-CH$_2$OH), 2.68 (1H, dd, *J* 2.5, 6.8 Hz, cyclohexyl-C$\underline{H}$), 1.84-

1.52 (5H, m, cyclohexyl), 1.28-0.93 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 62.1, 60.4, 57.6, 39.5, 29.6, 28.9, 26.2, 25.6, 25.5.

**(*2S*,3S**) 3-phenyl-2,3-epoxy-propan-1-ol (2c)**: colourless oil (95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.46-7.17 (5H, m, Ph), 4.05 (1H, ddd, *J* 4.0, 6.2, 12.0 Hz, C$\underline{H}_a$-$H_b$OH), 3.93 (1H, d, *J* 2.1 Hz, Ph-C$\underline{H}$), 3.79 (1H, ddd, *J* 4.0, 6.2, 12.0 Hz, $CH_a$-$\underline{H}_b$OH), 3.24 (1H, ddd, *J* 2.1, 4.0 Hz, C$\underline{H}$-$CH_2$OH), 2.56 (1H, t, *J* 6.2 Hz, O$\underline{H}$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 136.8, 128.6, 128.4, 125.8, 62.6, 61.4, 55.8.

For all compounds above, all other experimental data were consistent with the ones reported in the literature[1].

*2.2. General procedure for the TEMPO/IBDA oxidation.*

1 mmol of the appropriate substrate was dissolved in 1 ml of anhydrous dichloromethane under argon atmosphere and then TEMPO (0,1 mmol, 16 mg) and IBDA (1,1 mmol, 354 mg) were added and the mixture stirred at room temperature for 3 hour or until consumption of the substrate (TLC monitoring). The reaction mixture was then diluted with dichloromethane and washed with saturated solutions of $Na_2S_2O_3$, $NaHCO_3$, and NaCl till pH=7. The organic layer was dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product that was used without any purification.

**(*2S*,3S**) 2,3-epoxy-hexanal (3a)**: colourless oil (70% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 9.01 (1H, d, *J* 6.2 Hz, C$\underline{H}$O), 3.22 (1H, ddd, *J* 2.0, 4.9, 6.9 Hz, $CH_2$-C$\underline{H}$), 3.13 (1H, dd, *J* 2.0, 6.2 Hz, C$\underline{H}$-CHO), 1.72-1.4 (4H, m, C$\underline{H}_2$ x2), 0.97 (3H, t, *J* 7.3 Hz, C$\underline{H}_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 198.9, 59.4, 56.7, 33.5, 19.3, 13.8.

All other experimental data were consistent with the ones reported in the literature[2].

**(*2S*,3S**) 3-cyclohexyl-2,3-epoxy-propanal (3b)**: colourless oil (80% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 8.96 (1H, d, *J* 6.3 Hz, C$\underline{H}$O), 3.16 (1H, dd, *J* 2.0, 6.3 Hz, C$\underline{H}$-CHO), 3.01 (1H, dd, *J* 2.0, 6.6 Hz, cyclohexyl-C$\underline{H}$), 1.88-1.59 (5H, m, cyclohexyl), 1.41-0.98 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 198.7, 60.9, 58.1, 39.5, 29.6, 28.7, 26.2, 25.6, 25.5.

All other experimental data were consistent with the ones reported in the literature[3].

---

[1] Sharpless, B.K. *et al. J. Am. Chem. Soc.* **1987**, 109, *19*, 5765-5779

[2] Nair, V; Jahnke, T.S. *Tetrahedron*, **1987**, 43, *19*, 4257 - 4264

**(*2S*,3S**) 3-phenyl-2,3-epoxy-propanal (3c)**: pail yellow oil (85% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 9.2 (1H, d, *J* 6.2 Hz, C<u>H</u>O), 7.5-7.2 (5H, m, Ph), 4.17 (1H, d, *J* 1.6 Hz, Ph-C<u>H</u>), 3.44 (1H, dd, *J* 1.6, 6.2 Hz, C<u>H</u>-CHO); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 197.2, 129.5, 129.2, 125.7, 63.1, 56.7

All other experimental data were consistent with the ones reported in the literature[4].

*2.3. General procedure for the Horner - Emmons reaction.*

The appropriate compound (1 mmol), LiOH (1,1 mmol, 27 mg) and TEPA (1,1 mmol, 250 mg, 0,22 ml) were dissolved in 10 ml of THF and then stirred at the reflux temperature for 5h or until consumption of the substrate (TLC monitoring). A saturated solution of $NH_4Cl$ was then added and the reaction mixture concentrated in vacuo. The aqueous residue was then extracted with ethyl acetate and the organic layer washed with $NH_4Cl$ saturated solution and brine until pH=7. The combined organic extracts were dried over $Na_2SO_4$ and evaporated in vacuo to leave the crude product that was then purified by flash chromatography on silica gel (hexane/AcOEt 9:1) to give the desired product.

**(*E*)-ethyl 3-cyclohexylacrylate (B):** colourless oil (99% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.89 (1H, dd, *J* 6.8, 15.8 Hz, C<u>H</u>=CHCO), 5.73 (1H, dd, *J* 1.4, 15.8 Hz, C<u>H</u>CO), 4.2 (2H, q, *J* 7.2 Hz, COC<u>$H_2$</u>$CH_3$), 2.18-2.04 (1H, m, C<u>$H_{cyclohexyl}$</u>), 1.85-1.4 (10H, m, cyclohexyl), 1.26 (3H, t, *J* 7.2 Hz, $COCH_2C$<u>$H_3$</u>); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 167.2, 154.3, 119.1, 60.2, 40.5, 31.8, 26.1, 25.8, 14.4.

All other experimental data were consistent with the ones reported in the literature[5].

**(*E*)-ethyl 3-((*2*S,3S**)-3-propyloxiran-2-yl)acrylate (4a):** yellow oil (85% yield); $^{1}$H NMR (300 MHz $CDCl_3$) δ: 6.60 (1H, dd, *J* 7.2, 15.9 Hz, C<u>H</u>=CHCO), 6.04 (1H, d, *J* 15.9 Hz, C<u>H</u>CO), 4.2 (2H, q, *J* 7.2 Hz, COC<u>$H_2$</u>$CH_3$), 3.14 (1H, dd, *J* 2.2, 7.2 Hz, C<u>H</u>-CH=CH), 2.82 (1H, ddd, *J* 2.2, 5.5, 7.4 Hz, $CH_2C$<u>H</u>), 1.56-1.34 (4H, m, C<u>$H_2$</u> x2), 1.21 (3H, t, *J* 7.2, $COCH_2C$<u>$H_3$</u>), 0.89 (3H, t, *J* 6.6 Hz,

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[3] Lee, S; MacMillan, D.W.C. *Tetrahedron*, **2006**, 62, *49*, 11413 - 11424

[4] Yang, S.G. et al. Tetrahedron, **2007**, 63, *24*, 5184 - 5188

[5] Barrett, AG. M.; *et al. Tetrahedron*, **1996**, 52, *48*, 15325 - 15338

$CH_2CH_2C\underline{H}_3$).$^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.3, 144.6, 123.2, 61.0, 60.2, 56.0, 33.6, 18.9, 13.9, 13.6.

All other experimental data were consistent with the ones reported in the literature[6].

**(*E*)-ethyl 3-((*2*S,3S**)-3-cyclohexyloxiran-2-yl)acrylate (4b)**: pail yellow oil (95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.65 (1H, dd, *J* 7.2, 15.4 Hz, C$\underline{H}$=CHCO), 6.08 (1H, d, *J* 15.4 Hz, C$\underline{H}$CO), 4.2 (2H, q, *J* 7.2 Hz, COC$\underline{H}_2$CH$_3$), 3.25 (1H, dd, *J* 2.2, 7.2 Hz, C$\underline{H}$-CH=CH), 2.67 (1H, dd, *J* 2.2, 6.6 Hz, cyclohexyl-C$\underline{H}$-O), 1.90-1.59 (5H, m, cyclohexyl), 1.26 (3H, t, *J* 7.2 Hz, COCH$_2$C$\underline{H}_3$), 1.20-1.0 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 144.9, 123.2, 65.6, 60.4, 55.0, 39.9, 29.3, 28.8, 26.1, 25.5, 25.4, 14.1; HRMS (ES Q-TOF): [M+H]+, found 225.1491. $C_{13}H_{20}O_3$ requires 225.1491.

**(*E*)-ethyl 3-((*2*S,3S**)-3-phenyloxiran-2-yl)acrylate (4c)**: pail yellow oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.38-7.23 (5H, m, Ph), 6.79 (1H, dd, *J* 6.9, 15.7 Hz, C$\underline{H}$=CHCO), 6.17 (1H, d, *J* 0.8, 15.7 Hz, C$\underline{H}$CO), 4.2 (2H, q, *J* 7.2 Hz, COC$\underline{H}_2$CH$_3$), 3.80 (1H, d, *J* 1.6 Hz, Ph-C$\underline{H}$), 3.45 (1H, ddd, *J* 0.8, 1.6, 6.9 Hz, C$\underline{H}$-CH=CH), 1.26 (3H, t, *J* 7.2 Hz, COCH$_2$C$\underline{H}_3$).$^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.6, 143.5, 136.1, 128.6, 125.5, 124.0, 60.9, 60.6, 60.5, 14.2.

All other experimental data were consistent with the ones reported in the literature[7].

*2.4. Synthesis of (E)-3-cyclohexyl-2-propen-1-ol (**1b**)*

A 2.5% toluene solution of DIBAL (3 mmol, 426 mg; 20 ml) was added drop-wise to a stirred solution of (*E*)-ethyl 3-cyclohexylacrylate (1 mmol, 182 mg) in 10 ml of anhydrous THF under argon atmosphere at -40°C. After 10h the reaction mixture was allowed to warm at 0°C and a saturated solution of $NH_4Cl$ was added until formation of a gel, which was then dissolved by adding drop-wise an HCl 6N solution till pH=2. The mixture was then concentrated and the aqueous solution extracted with ethyl acetate for three times. The combined organic layers were then washed with $NaHCO_3$ saturated solution and brine till pH=7 and then dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product, which was purified by chromatography on silica gel (hexane/AcOEt 95:5) to give the desired alcohol as a colourless oil (98%). $^1$H NMR (300 MHz

[6] Miyashita, M. *et al. Angew. Chem. Int. Ed.* **2005**, 44, *32*, 5094 - 5097

[7] Yadav, JS. *et al. Tetrahedron: Asymmetry*, **2005**, 16, *19*, 3283 - 3290

$CDCl_3$) δ: 5,65-5,48 (2H, m, C<u>H</u>=C<u>H</u>), 4.03 (2H, d, *J* 4.8 Hz, C<u>H</u>$_2$), 2.18 (1H, br s, O<u>H</u>), 1.76-1.55 (5H, m, cyclohexyl), 1.32-0.95 (6H, m, cyclohexyl); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 138.9, 126.5, 63.8, 40.3, 32.8, 26.2, 26.1. All other experimental data were consistent with the ones reported in the literature[8].

*2.5. General procedure for the $BF_3$/$TMSN_3$ mediated ring-opening reaction.*

To a stirred solution of the appropriate substrate (1 mmol) in dichloromethane (3.3 ml) were added drop-wise, under argon atmosphere at 0°C, $TMSN_3$ (1 mmol, 115 mg. 0.13 ml) and $BF_3$·OEt (2 mmol, 28 mg, 0.25 ml). After 1h the reaction mixture was diluted with dichloromethane and washed with saturated solutions of $NaHCO_3$ and NaCl until pH7. The organic layer was dried on $Na_2SO_4$ and evaporated in vacuo to leave the crude product that was used without any purification.

**(*4R*,5S*,E*)-ethyl 4-azido-5-hydroxyoct-2-enoate (5a)**: pale orange oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.89 (1H, dd, *J* 7.2, 15.4 Hz, C<u>H</u>=CHCO), 6.08 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4,20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.08 (1H, dd, *J* 3.9, 7.2 Hz, C<u>H</u>-N$_3$), 3.79-3.70 (1H, m, C<u>H</u>-OH), 2.17 (1H, br s, O<u>H</u>), 1.61-1.34 (4H, m, C<u>H</u>$_2$ x2), 1.30 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.92 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 165.2, 140.4, 124.7, 72.2, 66.9, 60.3, 34.2, 18.3, 13.6, 13.3.

All other experimental data were consistent with the ones reported in the literature (see ref. 6).

**(4*R*,5S*,E*)-ethyl 4-azido-5-cyclohexyl-5-hydroxypent-2-enoate (5b)**: pail yellow oil (95% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.92 (1H, dd, *J* 7.8, 15.7 Hz, C<u>H</u>=CHCO), 6.05 (1H, d, *J* 15.7 Hz, C<u>H</u>CO), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 4.12 (1H, dd, *J* 4.5, 7.8 Hz, C<u>H</u>-N$_3$), 3.41 (1H, dd, *J* 4.5, 7.1 Hz, C<u>H</u>-OH), 2.48 (1H, bs, O<u>H</u>), 1.96-0.85 (14H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$)δ: 165.6, 140.7, 125.6, 76.9, 64.7, 60.9, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2.; HRMS (ES Q-TOF): [M+H]+, found 268.1665. $C_{13}H_{21}N_3O_3$ requires 268.1661.

**(4*R*,5S*,E*)-ethyl-5-azido-4-hydroxy-5-phenylpent-2-enoate (5c)**: yellow oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 7.44-7.3 (5H, m, Ph), 6.92 (1H, dd, *J* 4.8, 15.7 Hz, C<u>H</u>=CHCO), 6.05 (1H, d, *J* 1.7, 5.7 Hz, C<u>H</u>CO), 4.63 (1H, d, *J* 6.0 Hz, C<u>H</u>-N$_3$), 4.44 (1H, ddd, *J* 1.7, 4.8, 6.0 Hz, C<u>H</u>-OH), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.45 (1H, br s, O<u>H</u>), 1.27 (3H, 7, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$);

[8] Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J. *Tetrahedron*, **1996**, 52, *48*, 15325 - 15338

$^{13}$C NMR (75 MHzCDCl$_3$) δ: 169.9; 143,2; 136.1, 128.7; 128.5; 126.7, 123.1; 70.6; 60.5, 43.9; 13.9; HRMS (ES Q-TOF): [M+H]+, found 262.1190. $C_{13}H_{15}N_3O_3$ requires 262.1192.

*2.6. General procedure for the aziridine ring formation.*

To a stirred solution of the appropriate substrate (1 mmol) in anhydrous acetonitrile (1 ml), $PPh_3$ (1,2 mmol, 314 mg) was added under nitrogen atmosphere and the flask equipped with a monitoring device for the nitrogen release. After 2h the reaction mixture was brought to the reflux temperature and stirred for 12 h. The solvent was then removed under reduced pressure, the crude dissolved in cold $Et_2O$, filtered, concentrated and purified by flash chromatography on silica gel (hexane/AcOEt 7:3) to give the desired product.

Phenyl aziridine 6c was obtained keeping the reaction at room temperature for the whole time, in order to avoid rearrangements[9].

**(*E*)-ethyl 3-((2*R**,3*R**)-3-propylaziridin-2-yl)acrylate (6a)**: pail brown oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.30 (1H, dd, *J* 8.8, 15.4 Hz, C<u>H</u>=CHCO), 5.87 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.20 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.13 (1H, dd, *J* 2.2, 8.8 Hz, C<u>H</u>-CH=CH), 1.94-1.85 (1H, m, CH$_2$C<u>H</u>-N), 1.42-1.21 (5H, m, C<u>H</u>$_2$ x2 + N<u>H</u>), 1.11 (3H, t, *J* 7.2 Hz, COCH$_2$C<u>H</u>$_3$), 0.78 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 166.2, 148.6, 121.4, 60.2, 40.5, 37.8, 35.4, 20.4, 14.1, 13.7; HRMS (ES Q-TOF): [M+H]+, found 184.1335. $C_{10}H_{17}NO_2$ requires 184.1338

**(*E*)-ethyl 3-((2*R**,3*R**)-3-cyclohexylaziridin-2-yl)acrylate (6b)**: pail yellow oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ: 6.41 (1H, dd, *J* 8.8, 15.4 Hz, C<u>H</u>=CHCO), 5.99 (1H, d, *J* 15.4 Hz, C<u>H</u>CO), 4.18 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 2.31 (1H, dd, *J* 2.8, 8.8 Hz, C<u>H</u>CH=CH), 1.82 (1H, dd, *J* 2.8, 7.7 Hz, cyclohexyl-C<u>H</u>-NH), 1.77-1.56 (6H, m, cyclohexyl + N<u>H</u>), 1.20-0.85 (9H, m, cyclohexyl + COCH$_2$C<u>H</u>$_3$); $^{13}$C NMR (75 MHz $CDCl_3$) δ: 166.0, 148.9, 121.2, 60.2, 46.0, 41.8, 36.7, 30.9, 30.3, 26.2, 25.7, 25.6, 14.1.; HRMS (ES Q-TOF): [M+H]+, found 224.1655. $C_{13}H_{21}NO_2$ requires 224.1651.

**(*E*)-ethyl 3-((2*R**,3*R**)-3-phenylaziridin-2-yl)acrylate (6c)**: yellow oil (90% yield); $^1$H NMR (300 MHz $CDCl_3$) δ : 7.38-7.16 (5H, m, Ph), 6.56 (1H, dd, *J* 8.9, 15.5 Hz, C<u>H</u>=CHCO), 6.04 (1H, d, *J* 15.7 Hz, C<u>H</u>CO), 4.2 (2H, q, *J* 7.2 Hz, COC<u>H</u>$_2$CH$_3$), 3.04 (1H, d, *J* 1.3 Hz, Ph-C<u>H</u>), 2.56 (1H,

[9] Coldham, I.; Collis, A. J.; Mould, R. J.; Robinson, D. E. *Synthesis*, **1995**, 1147 - 1150

dd, *J* 1.3, 8.9 Hz, C<u>H</u>-CH=CH), 1.9 (1H, m, N<u>H</u>), 1.26 (3H, t, *J* 7.2 Hz, $COCH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz $CDCl_3$) δ: 165.6, 147.5, 138.1, 128.6, 127.5, 125.0, 122.1. 60.9, 42.4, 41.8, 14.2

All other experimental data were consistent with the ones reported in the literature (see ref. 9).