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Synthesis of Iminosugars Through Diastereo/Enantioselective Diels-Alder Cycloaddition

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Synthesis of Iminosugars Through Diastereo/Enantioselective Diels-Alder Cycloaddition

Tese de Doutoramento em Ciências
Especialidade em Química

Trabalho efetuado sob a orientação do
Doutor António Gil Fortes

dezembro de 2013

"Não é o trabalho, mas o saber trabalhar, que é o segredo do êxito no trabalho. Saber trabalhar quer dizer: não fazer um esforço inútil, persistir no esforço até ao fim, e saber reconstruir uma orientação quando se verificou que ela era, ou se tornou, errada."

Fernando Pessoa

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Finalizada uma das etapas mais difíceis mas também mais realizadora da minha vida, é chegada a hora de expressar o meu profundo agradecimento a todos os que direta ou indiretamente contribuíram para a sua realização.

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ABSTRACT

Stereoselective Diels-Alder cycloaddition is a very important methodology in the synthesis of chiral organic compounds. In this thesis, the selectivity was achieved by means of a chiral auxiliary or by the use of chiral Lewis acid complex.

Diastereoselective Diels-Alder cycloaddition was achieved by reacting a 1,3-butadiene bearing 2,3,4,6-tetraacetyl glucosyl as chiral auxiliary with PTAD. Total facial selectivity was obtained in this process. The cycloadduct obtained was converted in the known (-)-1-azafagomine, and in (+)-5-*epi*-1-azafagomine. Two new 1-*N*-phenyl carboxamide derivatives of 1-azafagomine were obtained by partial reductive cleavage of the phenyltriazolidinone moiety. The inhibitory potency of these new compounds towards α- and β-glucosidases was evaluated, and with the compound related to (-)-1-azafagomine showing the best inhibitory activity against α-glucosidase. The biological mechanism of action of both enantiomers in yeast *α*-glucosidase was studied by molecular docking methodologies using the homologue *Saccharomyces cerevisiae* enzyme. The efficient packing of the aromatic ring of the *N*-phenyl carboxamide moiety into a hydrophobic subsite (pocket) in the enzyme's active site seems to be responsible for the improved binding affinity.

This process was very efficient in terms of facial discrimination; however a long sequence of reactions were needed to obtain the final products, due to the additional steps required to introduce and remove the chiral auxiliary. As an alternative, a shorter synthetic strategy was devised using a Diels-Alder cycloaddition catalysed by a bimetallic complex of Mg and Zn tethered to BINOL (LACASA-DA).

Combination of a D-erythrose 1,3-butadiene with maleimides and achiral 2*H*-azirine 3-carboxylate in a LACASA-DA cycloadditions gave in most cases total facial selectivity. In the case of cycloadduct obtained from 2*H*-azirine, both enantiomers were obtained depending of the chirality of BINOL. The (*R*)-cycloadduct, obtained with (*S*)-BINOL, is a precursor of neuraminic acid and D-swainsonine analogues.

Moreover, LACASA-DA methodology also gave excellent enantioselectivities (>99 %) with achiral reagents, such as 2,4-pentadienol (diene) and *t*-butyl 2*H*-azirine 3-carboxylate or DEAD (dienophiles). Both enantiomeric forms of cycloadducts were obtained only by changing BINOL stereochemistry. Cycloadducts obtained from 2*H*-

azirine were easily converted in two sets of polihydroxylated pipecolic acid derivatives, after 3 steps.

All new compounds were fully characterized by the usual spectroscopic technics (^{1}H NMR and ^{13}C NMR and IR), analytical techniques (mass spectrometry) and physical properties (optical rotation). The absolute stereochemistry of stereocentres included in the molecules was determined by X-ray crystallography, in cases where single crystals could be obtained, or by combination of coupling constants (*J*) in the ^{1}H NMR data with dihedral angles determined by molecular dynamics studies for the oils.

RESUMO

A reação de Diels-Alder estereosseletiva é uma metodologia muito importante na síntese de compostos orgânicos quirais. Neste trabalho, a seletividade foi conseguida utilizando um auxiliar quiral ou um ácido de Lewis quiral.

A reação de Diels-Alder diastereosseletiva entre um dieno contendo o 2,3,4,6-tetra-acetilglucopiranosilo como auxiliar quiral e o PTAD, originou o aducto correspondente com total seletividade facial. O cicloaducto obtido foi convertido em aza-açucares conhecidos: (-)-1-azafagomina e (+)-5-*epi*-1-azafagomina. A clivagem redutiva parcial da unidade de feniltriazolidinona originou dois novos derivados *N*-fenil-carboxamida da 1-azafagomina. Estes novos compostos foram avaliados quanto à sua atividade inibitória face às enzimas α- e β-glucosidases. O composto relacionado com a (-)-1-azafagomina exibiu a melhor atividade inibitória face à α-glucosidase. O mecanismo biológico de acção de ambos os enantiómeros na α-glucosidase (*baker's yeast*) foi estudado por metodologias de "docking" molecular utilizando a enzima homóloga *Saccharomyces cerevisiae*. O acondicionamento eficiente do anel aromático da unidade *N*-fenil carboxamida numa bolsa hidrofóbica presente no local activo da enzima parece ser responsável pelo aumento da inibição.

Esta metodologia mostrou-se muito eficiente em termos de discriminação facial, no entanto, era necessário uma longa sequência reacional para se obter os produtos finais, devido aos passos adicionais necessários para introduzir e remover o auxiliar quiral. Assim, enveredou-se por um processo mais curto que usa a cicloadição de Diels-Alder catalisada por um complexo bimetálico de Mg e Zn ligado ao BINOL (LACASA-DA).

A combinação de um dieno derivado da D-eritrose, com maleimidas e uma azirina não quiral, a 2*H*-azirina 3-carboxilato de *t*-butilo, usando a estratégia LACASA-DA gerou, na maioria dos casos, total seletividade facial. No caso do cicloaducto obtido a partir da azirina, foram obtidos ambos os enantiómeros dependendo da quiralidade do BINOL. O cicloaducto (*R*) obtido com o (*S*)-BINOL, é um precursor de análogos do ácido neuramínico e da D-swainsonina.

Adicionalmente, a metodologia LACASA-DA também originou produtos com excelentes enantiosseletividades (>99 %) usando reagentes não quirais, tais como, o 2,4-pentadienol (dieno) e a 2*H*-azirina 3-carboxilato de *t*-butilo ou o azodicarboxilato de dietilo (DEAD) (dienófilos). Ambas as formas enantioméricas dos cicloaductos foram

obtidas apenas alterando a estereoquímica do BINOL. Os cicloaductos obtidos a partir da 2*H*-azirina foram facilmente convertidos, em dois conjuntos de derivados polihidroxilados do ácido pipecólico, em apenas três passos reacionais.

Todos os compostos foram caracterizados pelas técnicas espetroscópicas usuais (^{1}H e ^{13}C RMN, e IV), técnicas analíticas (espetrometria de massa) e propriedades físicas (rotação ótica). A estereoquímica absoluta dos estereocentros incluídos nos produtos foram determinados por cristalografia de raio-X, nos casos em que os cristais puderam ser obtidos, ou por correlação das constantes de acoplamento (*J*) dos espetros de RMN de protão com os ângulos diedros determinados por estudos de dinâmica molecular, para os óleos.

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SYMBOLS AND ABBREVIATIONS LIST

δ	chemical shift (in ppm)
ν_{max}	maximum wavelength (in cm^{-1})
ABG	2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide
Ac	acetyl group
Ad	adamantyl group
aq.	aqueous
Ar	aromatic group
bd	broad duplet
BINOL	1,1′-bi(2-naphthol)
BLA	Bronsted acid-assisted chiral Lewis Acid
Bn	benzyl group
Boc	*t*-butyloxycarbonyl group
bs	broad singlet
Bu	butyl group
***t*-Bu**	*t*-butyl group
Bz	benzyl group
cat.	catalyst
conc.	concentration
^{13}C NMR	Carbon Nuclear Magnetic Resonance
cod	1,5-cyclooctadiene
Cy	cyclohexyl group
d	doublet
Δ	reflux
DA	Diels-Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dm	doublet of multiplets
DEAD	diethyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMSO	dimethylsulfoxide
DPP	2,6-diphenylpyridine
dq	doublet of quartets

dr	diasteriomeric ratio
dt	doublet of triplets
DTBMP	2,6-di-*t*-butyl-4-methylpyridine
DTBP	2,6-di-*t*-butylpyridine
ee	enantiomeric excess
ent	enantiomer
eq.	equivalent
Et	ethyl group
EtOAc	ethyl acetate
exc.	excess
FGT	Functional Group Transformation
HDA	Hetero Diels-Alder reaction
^{1}H NMR	Proton Nuclear Magnetic Resonance
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Correlation
HRMS	High Resolution Mass Spectrometry
IR	Infrared
K_i	inhibition constant
J	coupling constant (in Hertz)
LACASA-DA	Diels-Alder cycloaddition based on a Lewis Acid-Catalysed reaction of a "Self-Assembled" complex
lit.	literature
m	multiplet
M	mol/dm^3
Me	methyl group
MOM	methoxymethyl ether group
Ms	methanesulfonyl or mesyl group
MS	molecular sieves
Naph	naphthyl group
NMO	*N*-methylmorpholine *N*-oxide
NOE	Nuclear Overhauser Effect
mp	melting point
PAA	3-phenylacetylacetone
PE	petroleum ether
Ph	phenyl group

PLC	Preparative Liquid Chromatography
***i*-Pr**	isopropyl group
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
pyr	pyridine
q	quartet
rt	room temperature
s	singlet
sat.	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl group
TFA	trifluoracetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl group
Tr	triphenylmethyl or trityl
***p*-TsOH**	*p*-toluenesulfonic acid
VAPOL	2,2′-diphenyl-(4-biphenanthrol)

THESIS SUMMARY

The present dissertation is divided in four chapters and a brief description of each chapter is here depicted.

Chapter 1 is a brief introduction covering the reports of BINOL chiral ligands attached to any metals as catalysts in enantioselective Diels-Alder cycloaddition, focusing in the synthesis of chiral synthons leading to biologically important compounds.

Chapter 2 comprises a compilation of the articles published or submitted to international scientific journals, obtained during this dissertation. Each article is presented as a sub-chapter and the formatting presented does not correspond to the format of the journal where it was published or submitted. This second chapter is organized as follows:

2.1. "Advances in the Synthesis of Homochiral (-)-1-Azafagomine and (+)-5-*epi*-1-Azafagomine. 1-*N*-Phenyl Carboxamide Derivatives of both Enantiomers of 1-Azafagomine: Leads for the Synthesis of Active α-Glycosidase Inhibitors", *J. Org. Chem.* **2011**, *76*, 9584-9592.

2.2. "Diastereoselectivity in Diels–Alder Cycloadditions of Erythrose Benzylidene-acetal 1,3-Butadienes with Maleimides", *Synlett* **2012**, *23*, 1765-1768.

2.3. "Asymmetric Diels-Alder Cycloadditions of D-Erythrose 1,3-Butadienes to Achiral *t*-Butyl 2*H*-Azirine 3-Carboxylate" *Tetrahedron: Asymmetry* **2013**, *24*, 1063-1068.

2.4. "Enantioselective Diels-Alder Cycloadditions in the Synthesis of Two Enantiomeric Sets of Homochiral Polihydroxylated Pipecolic Acid Derivatives.", *submitted to Org. Lett.* **2013**.

Chapter 3 presents a general overview of results presented in Chapter 2.

Chapter 4 presents the conclusions of the research reported in this dissertation, as well as considerations for future work.

Chapter 1

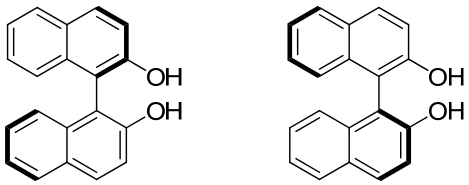
Introduction

1. Enantioselective Diels-Alder cycloadditions in the synthesis of important chiral synthons using (*R*)-/(*S*)-BINOL ligands

The Diels-Alder (DA) cycloaddition is one of the most important synthetic reactions to build up six-membered ring compounds. Four contiguous stereogenic centres are created in a single step. The stereochemistry control of these reactions is defined by 1) the preference of *endo vs exo* transition state or *vice-versa*, being the *endo* kinetics generally the favouring approach, and 2) the facial discrimination. If either the facial discrimination and the *endo*/*exo* diastereomery are excellent, homochiral products will be generated.[1]

It has been long known that coordination of metals attached to any of the reagents allows lowering the transition states energetics so much that reactions can often occur below 0 ºC. If metals used as catalyst are attached to chiral ligands, these complexes may be able to promote both catalysis and induce facial discrimination, leading to homochiral products.[2]

Since 1990 the enantiomeric atropoisomers of 1,1'-binaphtyl-2,2'-diol (BINOL) (Figure 1) have become widely popular as ligands in enantioselective oxidation, reduction, and C-C or C-X (X = N, O) bond forming reactions, including DA cycloaddition.[3]



(*R*)-(+)-BINOL (*S*)-(+)-BINOL

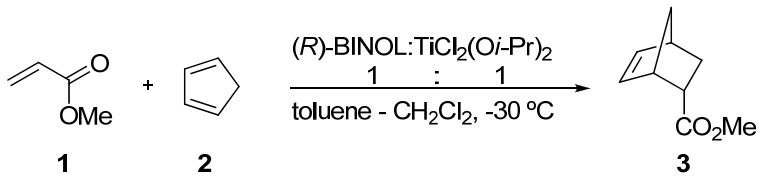
Figure 1 BINOL enantiomers.

In what enantioselective Diels-Alder reaction concerns at a first stage aluminium and boron dominates, but recently the focus has been shifted to transition-metal catalysts.[4]

This review is based on BINOL chiral ligands attached to any metals whenever used in enantioselective DA cycloaddition having in view the synthesis of chiral synthons leading to biologically relevant molecules.

1.1 Titanium-BINOL catalysts

The earlier studies in asymmetric DA reaction using BINOL-Ti complexes were reported by Reetz[5] and Seebach[6] using BINOL-$TiCl_2$ and BINOL-Ti(O*i*-Pr)$_2$, respectively. Seebach obtained the most promising result so far. It is represented in Scheme 1: methyl acrylate **1** was combined with cyclopentadiene **2** in the presence of (*R*)-BINOL-$TiCl_2$(O*i*-Pr)$_2$ complex. The cycloadduct **3** was formed in 77 % yield and 50 % of enantiomeric excesse (*ee*).

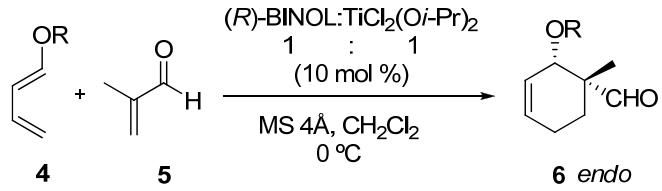


1 **2** **3**

Scheme 1 Asymmetric DA reaction of methyl acrylate **1** and cyclopentadiene **2**.

Mikami and Nakai[7,8] extended these first results on enantioselective DA reaction with BINOL, in which the key to the success was the use of the Ti-complex prepared *in situ* from Ti(O*i*-Pr)$_2$X$_2$ and (*R*)-BINOL in the presence of MS 4Å. The presence of MS facilitated the alkoxy-ligand exchange reaction, which is essential for the *in situ* preparation of the chiral catalyst. The reaction of 1,3-dienol derivatives **4** to methacroleine **5** afforded the *endo*-cycloadducts **6** in high *endo* ratio and good *ee* (71-86 %) (Table 1).

Table 1 DA cycloaddition of 1,3-dienol derivatives **4** with methacroleine **5** in the presence of (*R*)-BINOL:$TiCl_2(Oi\text{-}Pr)_2$ complex.



4 **5** **6** *endo*

Entry	R	solvent	T (ºC), t (h)	yield (%)	*endo*/*exo*	*ee* (%)
1	**4a**, $CONMe_2$	CH_2Cl_2	0 ºC, 58h	82	99.6/0.4	86
2	**4a**, $CONMe_2$	toluene	0 ºC, 48h	80	99.4/0.6	85
3	**4b**, CH_3	CH_2Cl_2	-30 ºC, 5h	43	87/13	71
4	**4c**, $COCH_3$	toluene	rt, 18h	81	98/2	80

The results achieved encouraged further application of this methodology to naphthoquinone. This resulted to be one of the most efficient entry to the asymmetric synthesis of anthracyclinone aglycones (Figure 2).[9]

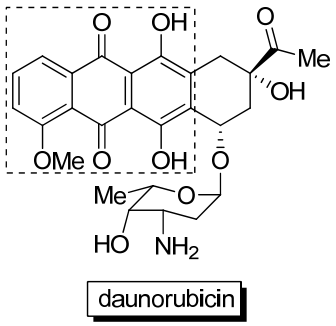
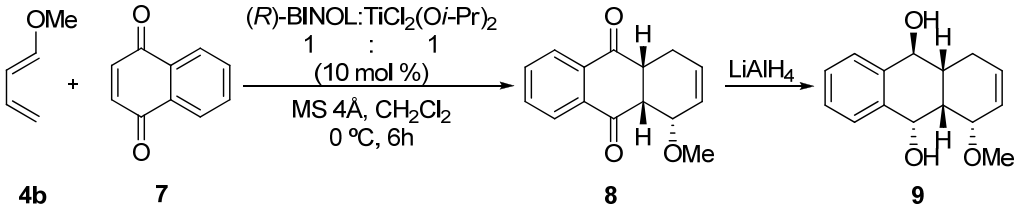


Figure 2 Structure of a known anthracyclinone aglycone.

The reaction of naphthoquinone **7** with diene **4b** catalysed by (*R*)-BINOL-$TiCl_2$ provided the chiral adduct **8** with complete *endo*-selectivity and a good facial discrimination. Carbonyl groups in compound **8** were stereoselectively reduced with $LiAlH_4$ leading to derivative **9**. Derivatization of **9** with (*S*)-MTPA allowed determination of the optical purity of **8** to be 85 % *ee* (Scheme 2). Adduct **8** is a synthetic intermediate in the synthesis of tetracycline antibiotics.

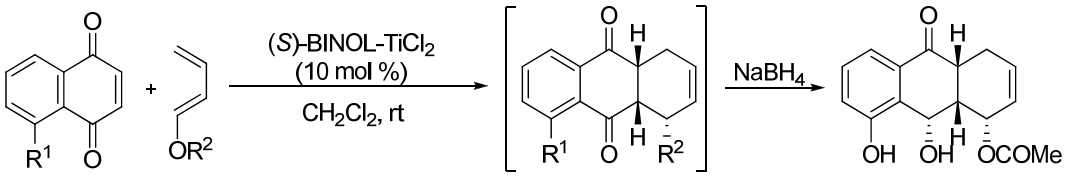


4b **7** **8** **9**

Scheme 2 DA cycloaddition of naphthoquinone **7** with diene **4b** catalysed by BINOL-Ti complex.

Later, Mikami[10] reported a full account of an enantioselective DA reaction of naphthoquinones **10** and methyl glyoxylate **11** with 1,3-dienol ethers and esters catalysed by the chiral BINOL-$TiCl_2$ complex (Mikami's catalyst) (Table 2).

Table 2 DA reaction of naphthoquinones **10** and dienes **4** catalysed by the BINOL-$TiCl_2$ system.



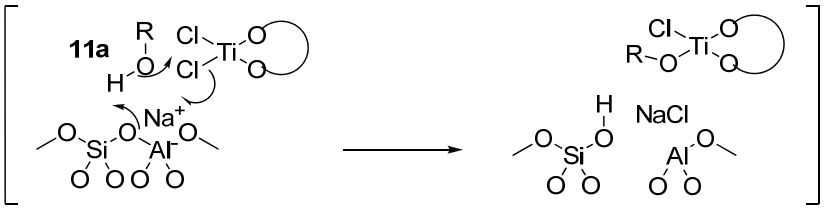
10 **4**

12a R^1 = OH, R^2 = COMe
12b R^1 = H, R^2 = Me

13

Entry	MS 4Å	R^1	R^2	yield (%)	*ee* (%)
1	yes	**10a**, OH	**4d**, COMe	__	9
2	removed	**10a**, OH	**4d**, COMe	86	96
3	yes	**10b**, H	**4b**, Me	__	85

The asymmetric catalytic Diels-Alder reaction of juglone (**10a**) with butadienyl acetate **4d** was catalysed by BINOL-$TiCl_2$ complex prepared *in situ* in the presence of MS 4Å. Cycloadduct **12a** was obtained with complete *endo*-selectivity, but with very low *ee*, 9 % (Table 2, entry 1) as determined in (*R*)-MTPA ester derivative of the more stable derivative **13**. The low enantioselectivity in this case is in marked contrast with the *ee* (85 %) obtained with naphthoquinone **10b** and diene **4b** under the same reaction conditions. These results suggested that the free hydroxyl group in **10a** might be binding to titanium, displacing chloride as outlined in Scheme 3 and be responsible for the low *ee* observed.

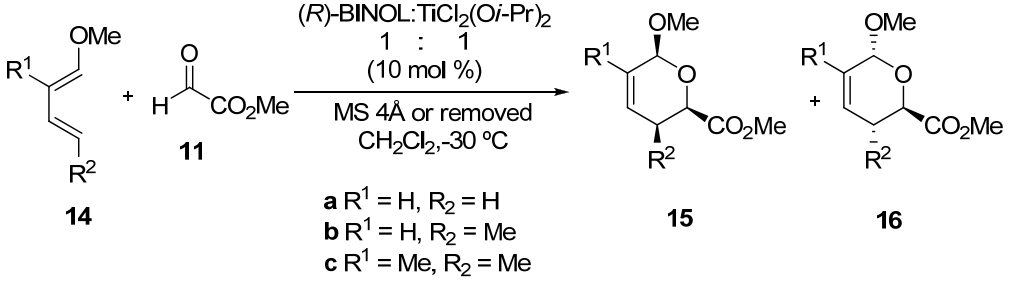


Scheme 3 Alkoxy-ligand exchange reaction between MS and BINOL-$TiCl_2$ complex.

To prevent this undesired reaction, a MS-free BINOL-titanium complex was obtained by MS centrifugation followed by decantation. Removal of isopropanol under reduced pressure gave BINOL-Ti complex as a solid. DA reaction of juglone **10a** and diene **4d** in the presence of Ms-free catalyst afforded adduct **12a** in high yield (86 %) and high optical purity (96 %). This adduct provides an efficient approach to the asymmetric synthesis of anthracycline and tetracycline antibiotics.

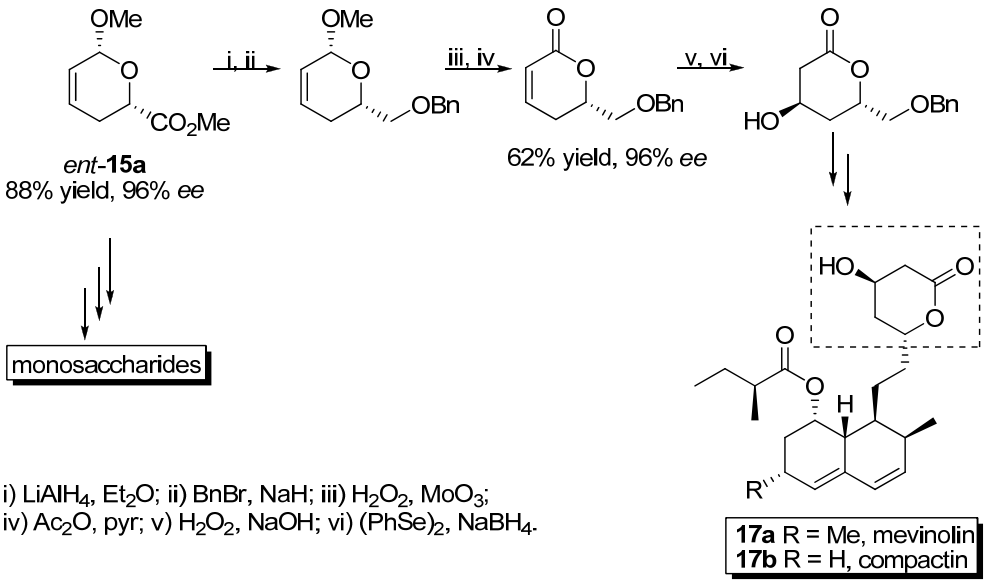
It was found that the use of MS-free catalyst also improved the *endo*- and enantioselectivity in the hetero Diels-Alder (HDA) reactions of glyoxylate **11** with methoxydienes **14**. The reaction proceeded smoothly to give the *endo*-adduct **15** with high facial selectivity (Table 3).

Table 3 HDA reaction catalysed by the BINOL:$TiCl_2$(O*i*-Pr)$_2$ system.



Entry	MS 4Å	R^1	R^2	yield (%)	**15** (*ee*)	**16** (*ee*)
1	yes	H	H	77	78 (94)	22 (>90)
2	removed	H	H	78	88 (96)	12 (>90)
3	yes	H	Me	63	97 (90)	3
4	removed	H	Me	58	>98 (93)	<2
5	yes	Me	Me	18	98 (88)	2
6	removed	Me	Me	32	>98 (>95)	<2

Applying the same reaction conditions, but in the presence of (*S*)-BINOL-$TiCl_2$ complex, was obtained *ent*-**15a**, a useful intermediate in the synthesis of monosaccharides,[11] and the lactone portion in mevinolin **17a**, compactin **17b**, coenzyme A redutase inhibitors (Scheme 4).[12]



Scheme 4 Synthesis of monosaccharides and lactone portion of mevinolin **17a** and compactin **17b** from precursor *ent*-**15a**.

Moreover, the Diels-Alder cycloadducts **15b** and **15c** could be part of the antibiotic indanomycin **18** (X-14547A) (left-wing portion)[13,14] and of the macrolide antibiotic erythromycins **19** (C1-C5 portion) (Figure 3).[15]

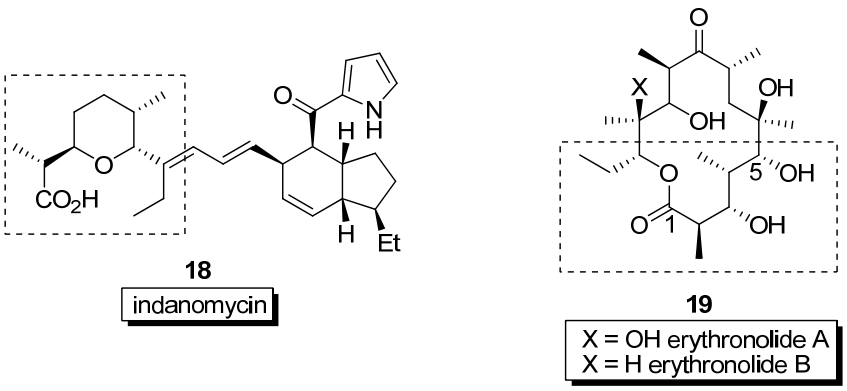
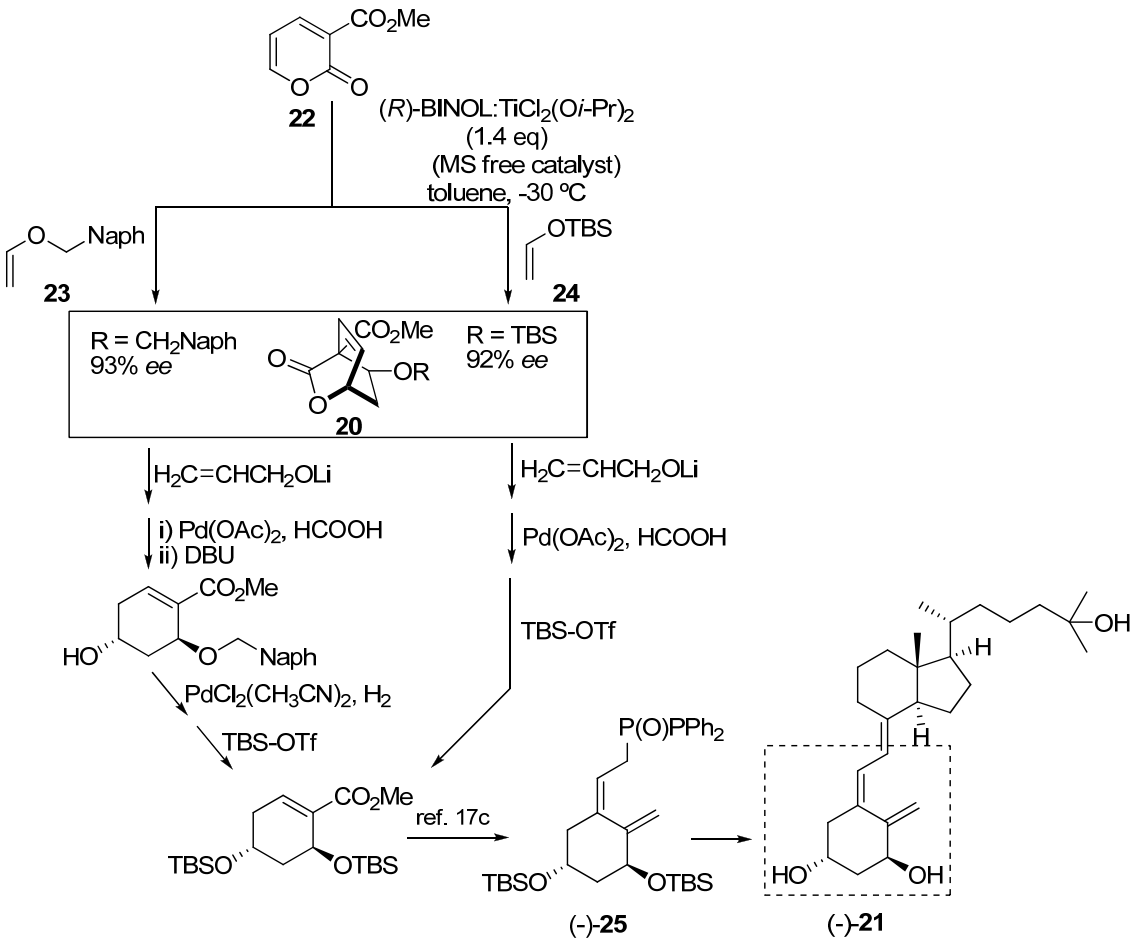


Figure 3 Structure of antibiotics indanomycin **18** and erythromycin **19**.

Posner[16] studied the stereo-control of DA cycloadditions with 2-pyrone dienes with the aim of obtaining useful and versatile bicyclic lactone adducts **20** (Scheme 5). Such bicyclic adducts could be converted into various biologically active compounds, *e.g.* calcitriol **21** (1α,25-dihydroxyvitamin D_3) (Scheme 5) and **21** analogues.[17]

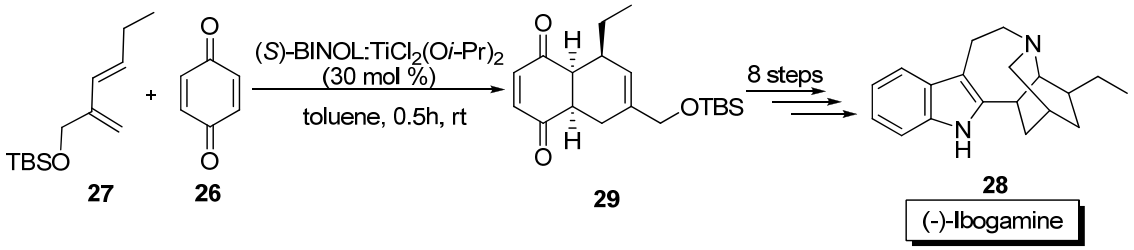
Calcitriol **21** has been known for a long time to be hormonally active in regulating calcium and phosphorus homeostasis in humans.[18]

Commercially available methyl 2-pyrone-3-carboxylate **22** reacted with 1-naphtylmethyl vinyl ether **23** and vinyl silyl ether **24** in the presence of (*R*)-BINOL:$TiCl_2$(O*i*-Pr)$_2$ mixture, affording the corresponding cycloadducts **20** with good yields (59-83 %) and high enantioselectivities (92-93 %). These adducts were converted in 5 or 4 steps into calcitriol intermediate (-)-**25** depending on the dienophile used (**23** or **24**) (Scheme 5).



Scheme 5 Synthesis of calcitriol precursor (-)-**25**.

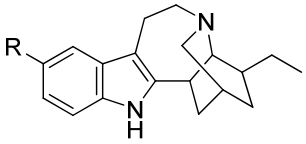
Later, White[19,20] described a high enantioselective cycloaddition of benzoquinone (**26**) to diene **27** in the presence of the Mikami's catalyst (Scheme 6). The cycloadduct was obtained in 65 % yield and 87 % *ee*. It is a useful chiral synthon in the synthesis of the indole alkaloid (-)-ibogamine **28**.[21,22]



Scheme 6 DA cycloaddition of benzoquinone (**26**) and diene **27** in the synthesis of the cycloadduct **29**, precursor of (-)-ibogamine.

Cycloadduct **29** was transformed into (-)-ibogamine **28** after eight steps, in 10 % overall yield (Scheme 6).

(-)-Ibogamine (**28**) and its congener (-)-ibogaine (**30**) have attracted much attention due to the evident property of reducing heroin and cocaine addiction (Figure 4).[23]



28, R = H, (-)-ibogamine
30, R = OMe, (-)ibogaine

Figure 4 Structure of indole alkaloids (-)-ibogamine **28** and (-)-ibogaine **30**.

Corey[24] was able to obtain excellent yields and *ee* of cycloadducts from DA reaction of quinones monoketals **31** and **32** with simple carbon open-chain dienes catalysed by (*S*)-BINOL:$TiCl_2(Oi\text{-}Pr)_2$ system in the presence of MS 4Å (Table 4 and Table 5). This method provided for decades a powerful synthon for construction of functionalized *cis*-decalin systems, part of steroid skeletons (Figure 5).[25]

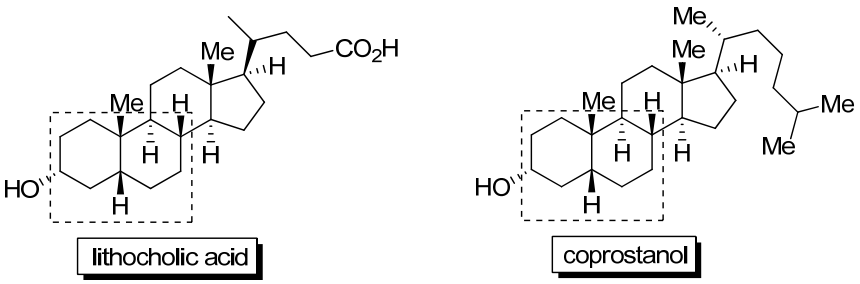
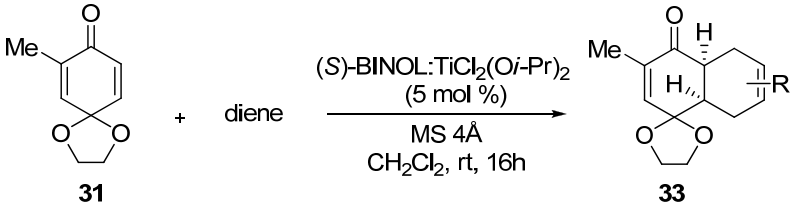
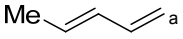
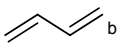
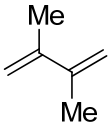
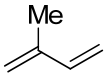


Figure 5 Examples of steroids with *cis*-decalin unities.

Enantioselectivities (81-84 % *ee*) were found to be somewhat lower for butadiene, 2,3-dimethylbutadiene and isoprene than for (*E*)-1,3-pentadiene (98 %). As usual reaction with isoprene suffers from another drawback, a poor regioselectivity (53:47) (Table 4).

Table 4 Enantioselective DA reactions of quinone monoketal **31** with various dienes catalysed by (*S*)-BINOL:$TiCl_2$(O*i*-Pr)$_2$, MS 4Å.

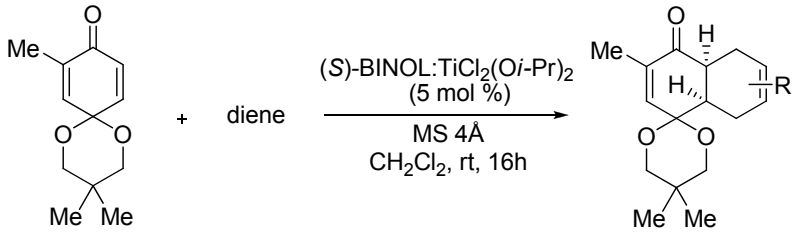


Entry	diene	yield (%)	*ee* (%)
1		97	98
2		91	81
3		88	84
4		91	84, 72[c]

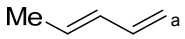
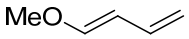
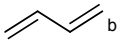
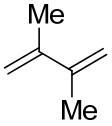
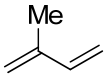
[a] *endo*/*exo* ratio >98:2. [b] Reaction at -20 ºC for 72h. [c] Mixture of *regio*-isomers (53:47).

Higher *ee* were obtained for products of reactions occurring under the same conditions with bulkier neopentyl ketals dienophiles **32**, instead of ethylene ketals **31** (Table 5).

Table 5 Enantioselective DA reactions of quinone monoketal **32** with various dienes catalysed by (*S*)-BINOL:$TiCl_2(OiPr)_2$, MS 4Å.

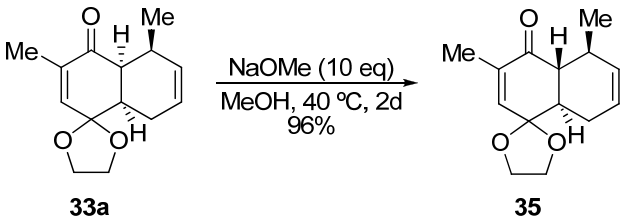


32 **34**

Entry	diene	yield (%)	*ee* (%)
1		90	99
2		90	99
3		95	95
4		95	90
5		91	96, 91[c]

[a] *endo*/*exo* ratio >99:1. [b] Reaction at -20 ºC for 72h. [c] Mixture of *regio*-isomers (56:44).

Isoprene afforded a mixture of *regio*-isomers as in previous cases. The *cis*-decalin precursors **33** and **34** can be successfully epimerized to the *trans*-isomer **35** with sodium methoxide (see Scheme 7 as an example). Aromatization was avoided in the epimerization process due to the quinone ketal moiety in the molecule. The 1,4-quinone would naturally led to aromatization during the process.

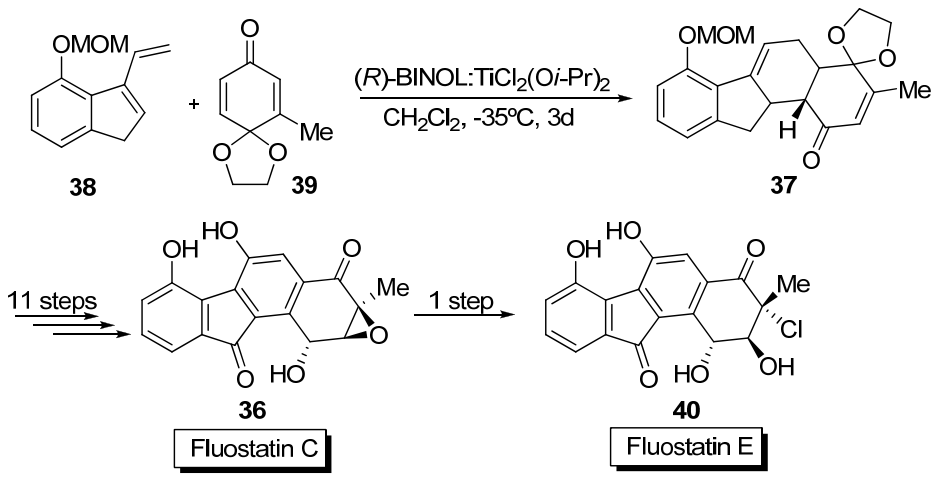


33a **35**

Scheme 7 Epimerization of *cis*-decalone monoketal **33a** to the corresponding *trans*-fused ketone **35**.

Fluostatin C (**36**) is a member of a larger family of fluostatins, it exhibits antibiotic and antitumor activities.[26] Enantioselective DA cycloaddition catalysed by BINOL-Ti complex was applied to the synthesis of fluostatin C precursor **37**.[27]

The cycloaddition step occurs between diene **38** and quinoneketal **39** in the presence of (*R*)-BINOL:$TiCl_2$(O*i*-Pr)$_2$ leading to the adduct **37** in 93 % yield and 65 % *ee*. The cycloadduct was submitted to several chemical transformations (11 steps) to achieve fluostatin C (**36**) in 3.3 % overall yield. Fluostatin C afforded fluostatin E (**40**) in 90 % yield by treatment with aqueous HCl (Scheme 8).

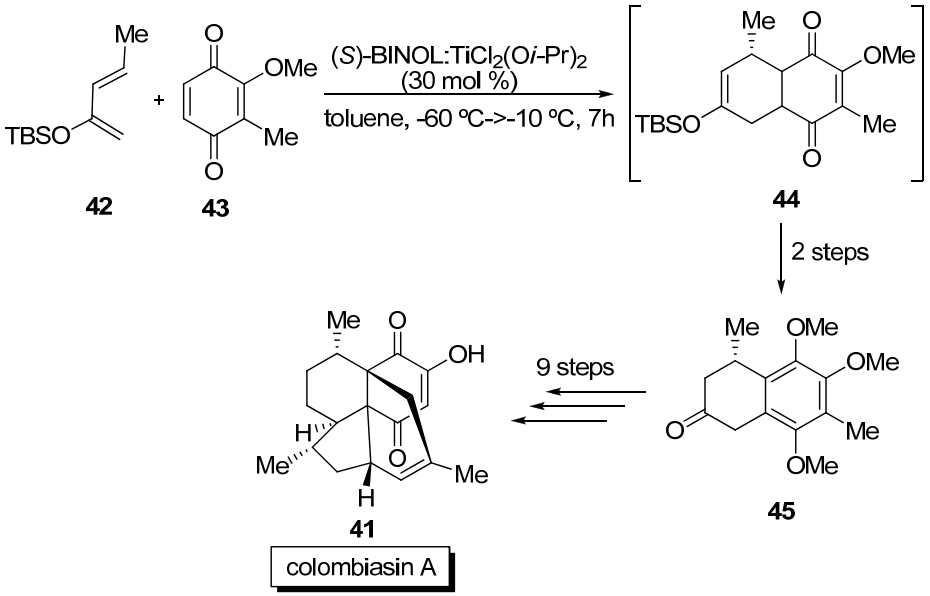


38 **39** **37** **36** **40**

Scheme 8 Synthesis of Fluostatin C (**36**) and E (**40**).

The first step of a total synthesis of terpenoid (-)-colombiasin A **41** is the DA cycloaddition catalysed by (*S*)-BINOL:$TiCl_2$(O*i*-Pr)$_2$ (Scheme 9). Nicolaou[28] combined a Danishefsky-type diene **42** with quinone **43** under the mentioned catalysis giving cycloadduct **44**, which was transformed *in situ* into **45** with 70 % yield and 94 % *ee*. After 9 steps, colombiasin A **41** was obtained in 4 % overall yield. The cycloaddition

between diene **42** and quinone **43** under Mikami's catalyst having (*R*)-BINOL as chiral inductor led to *ent*-**44** with the same *ee*.



Scheme 9 Synthesis of colombiasin A precursor **44**.

Danishefsky-type diene **46** has been used to synthesise useful synthons of alkaloids, such as octalindione,[29] the naphthoquinone core of streptovaricin U,[30] and 5-(3-furyl)-8-methyloctahydroindolizine[31] (Figure 6).

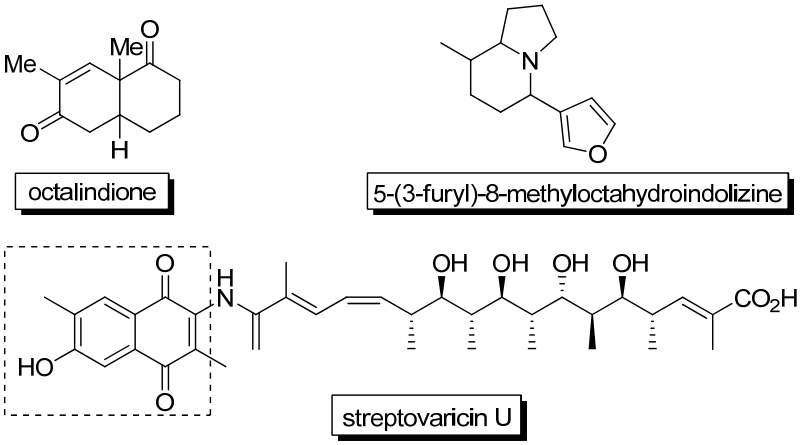
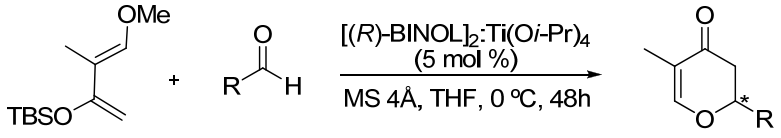


Figure 6 Structure of octalindione, streptovaricin U and 5-(3-furyl)-8-methyloctahydroindolizine.

The key products, 2,5-disubstituted dihydropyrones in its chiral form (**47**), were obtained from *trans*-1-methoxy-2-methyl-3-trimethylsilyloxybuta-1,3-diene (**46**) and aldehydes in the presence of [(*R*)-BINOL]$_2$:Ti(O*i*-Pr)$_4$.[32] This catalytic system proved to be very effective with a wide range of aldehydes, affording the corresponding products **47** in moderate to high yields and with high *ee* values (Table 6).

Table 6 Asymmetric synthesis of 2,5-disubstituted dihydropyrones **47** catalysed by [(*R*)-BINOL]$_2$-Ti(O*i*-Pr)$_4$ complex.



46 **47**

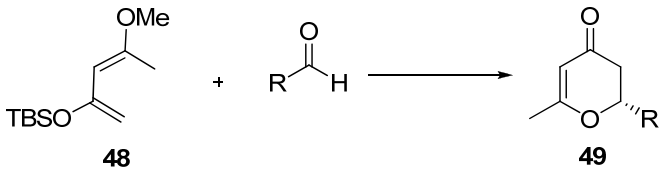
Entry[a]	aldehyde	yield (%)	*ee* (%)
1	benzaldehyde	86	99
2	2-chlorobenzaldehyde	99	90
3	2,4-dichlorobenzaldehyde	70	94
4	3-nitrobenzaldehyde	85	98
5	4-methoxybenzaldehyde	84	90
6	1-naphthaldehyde	40	97
7	4-fluorobenzaldehyde	73	94
8	4-cyanobenzaldehyde	95	92
9	2-pyridinecarboxaldehyde	99	98
10	2-furaldehyde	99	97
11	*n*-hexanal	41	87

[a] Reactions were carried out at 0 ºC in THF using 5 mol % [(*R*)-BINOL]$_2$-Ti(O*i*-Pr)$_4$ complex, in the presence of MS 4Å, over 48h.

Other related compounds (2,6-disubstituted dihydropyrones) also important intermediates in organic synthesis, were achieved firstly by Huang[33] and then by Yang.[34] Yang reported an HDA cycloaddition between diene **48** and different aldehydes catalysed by (*R*)-BINOL:Ti(O*i*-Pr)$_4$. A range of aromatic, hetero-aromatic, conjugated

and aliphatic aldehydes were used, affording the respective products **49** in moderate to high yields (up to 99 %) and excellent enantioselectivities (up to 99 %) (Table 7).

Table 7 Asymmetric HDA reaction of aldehydes with diene **48**.



48 **49**

Entry[a]	substrate	yield (%)	*ee* (%)
1	benzaldehyde	70	99
2	3-methylbenzaldehyde	73	>99
3	3-chlorobenzaldehyde	83	98
4	1-naphthaldehyde	78	>99
5	4-phenylbenzaldehyde	93	98
6	4-cyanobenzaldehyde	86	94
7	4-nitrobenzaldehyde	99	>99
8	4-methoxybenzaldehyde	83	>99
9	3-pyridinecarboxaldehyde	65	98
10	(*E*)-cinnamaldehyde	64	92
11	propionaldehyde	88	94
12	*n*-hexanal	77	91

[a] Reactions were carried out in the presence of MS 4Å, toluene and with 20 mol % catalyst loading (*R*)-BINOL:Ti(O*i*-Pr)$_4$ at 0 ºC for 48h.

A possible mechanism for asymmetric induction in this catalytic system is outlined as in Figure 7. When the (*R*)-BINOL-Ti(O*i*-Pr)$_4$ complex is used as the catalyst, the steric hindrance of the binaphthyl moiety shields the *si* face of the aldehyde, while the *re* face is available to accept the attacking diene to give the products as expected.

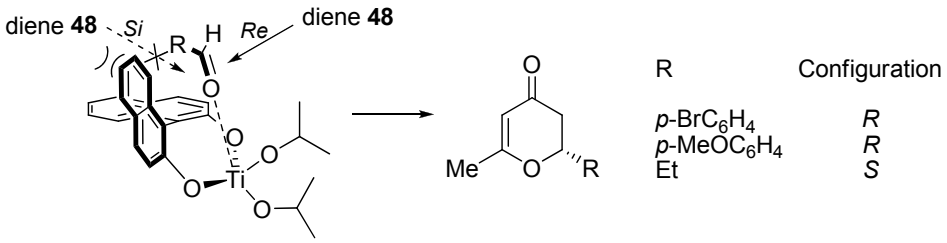
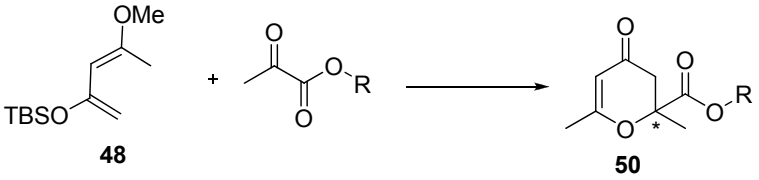


Figure 7 Proposed TS model of the HDA reaction of diene **48** with aldehydes catalysed by (*R*)-BINOL-Ti(O*i*-Pr)$_4$.

Some pyruvates were also explored as dienophiles under the same reaction conditions. The results obtained were not as good. When the reactions of pyruvates were carried out in the presence of 10 mol % of [(*R*)-BINOL]$_2$:Ti(O*i*-Pr)$_4$, 2,2,6-trisubstituted dihydropyrones **50** were obtained in good yields (76-85 %) and high *ee* values (94-99 %) (Table 8).[34]

Table 8 Asymmetric HDA reaction of pyruvates with diene **48**.



Entry[a]	substrate	yield (%)	*ee* (%)
1	ethyl pyruvate	85	99
2	methyl pyruvate	82	94
3	isopropyl pyruvate	76	96

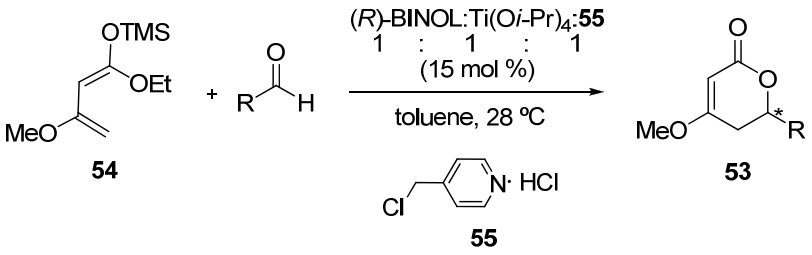
[a] Reactions were carried out in THF with 10 mol % catalyst loading [(*R*)-BINOL]$_2$:Ti(O*i*-Pr)$_4$ at 0 ºC for 72h.

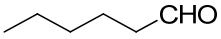
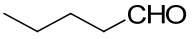
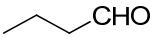
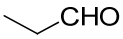
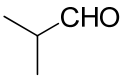
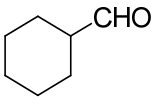
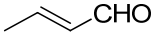
Combination of propionaldehyde and diene **48** in the presence of 20 mol % of (*R*)-BINOL:Ti(O*i*-Pr)$_4$ catalyst gave in one step the (*S*)-(-)-hepialone **49** compound in 88 % yield with 94 % *ee* (Table 7, entry 11). As expected, its enantiomer, (*R*)-(+)-hepialone, a male moth sex pheromone isolated from *Hepialus hecta L*. and *Hepialus californicus Bdv*,[35] was obtained in the same yield and *ee* by replacing (*R*)-BINOL for (*S*)-BINOL in the reaction conditions.

α,β-Unsaturated γ-lactones are key structural subunits of numerous natural and unnatural products with a wide range of biological activities.[36] Some of these compounds: kavain **51** and dihydrokavain **52** were isolated from kava plant *Piper methysticum* (Piperaceae). Kava root is commonly available in dietary supplements due to their anxiolytic and soporific properties. Analgesic, anaesthetic, antifungal, antithrombotic, anticonvulsive, and muscle-relaxing properties have also been reported.[37]

Feng[38] reported an efficient asymmetric HDA reaction leading to α,β-unsaturated γ-lactone derivatives **53** in moderate-to-good yields (46-79 %) with high enantioselectivities (81-88 %) by combining Brassard's diene **54** and aldehydes with (*R*)-BINOL:Ti(O*i*-Pr)$_4$ and 4-picolyl chloride hydrochloride **55** as additive (Table 9).

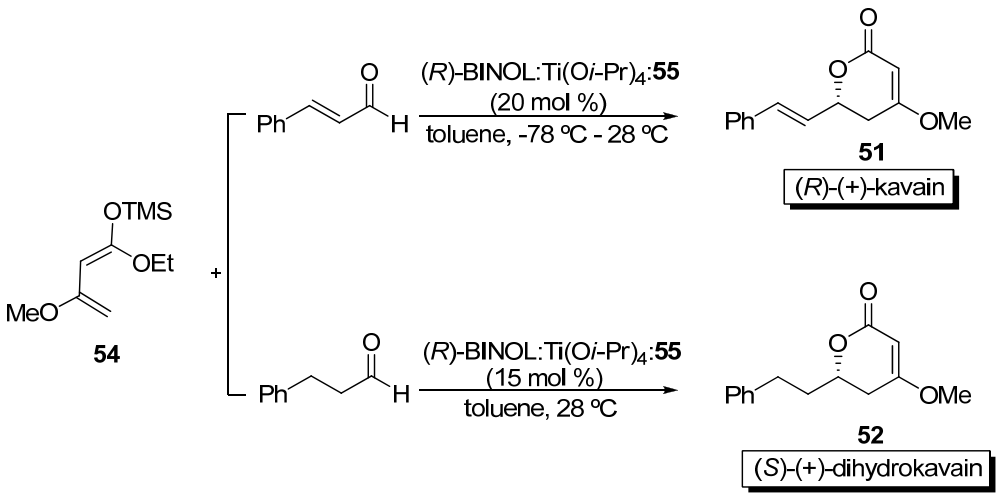
Table 9 HDA reaction of Brassard's diene **54** with aldehydes catalysed by (*R*)-BINOL-Ti(O*i*-Pr)$_2$:**55**.



Entry[a]	Aldehyde	yield (%)	*ee* (%)
1		74	83
2		46	82
3		79	84
4		72	88
5		54	83
6		65	81
7		79	85
8[b]	PhCHO	56	87[c]

[a] Reactions were carried out in toluene at 28 ºC for 115h in the presence of 15 mol % of (*R*)-BINOL:Ti(O*i*-Pr)$_4$:**55**. [b] Performed at 0 ºC. [c] The absolute configuration was determined to be *R* by comparison with literature data.[39]

Kavain **51** and dihydrokavain **52** were obtained in one step by HDA cycloaddition of Brassard's diene **54** with cinnamaldehyde and 3-phenylpropionaldehyde, respectively (Scheme 10). (*R*)-(+)-Kavain (**51**) was obtained in 56 % yield with 70 % *ee*, and purified by recrystallization to give homochiral (*R*)-(+)-kavain. (*S*)-(+)-dihydrokavain (**52**) was obtained in 57 % yield and 84 % *ee*.[38]



Scheme 10 One-step synthesis of (*R*)-(+)-Kavain and (*S*)-(+)-dihydrokavain.

Recently, Ward[40] described a total synthesis of (-)-cyathin A_3 (**56**), that includes an enantioselective DA cycloaddition as key step. The chiral induction was produced by a modified Mikami's catalyst. Cyathin A_3 (**56**), belon to the diterpenoids' family, can be isolated from various mushrooms and related basidiomycetes (Figure 8). Diverse biological activities has been noted, namely that certain cyathanes can stimulate the production of nerve growth factor (NGF), important to the survival of neuronal cells.[41,42]

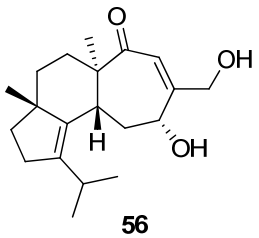
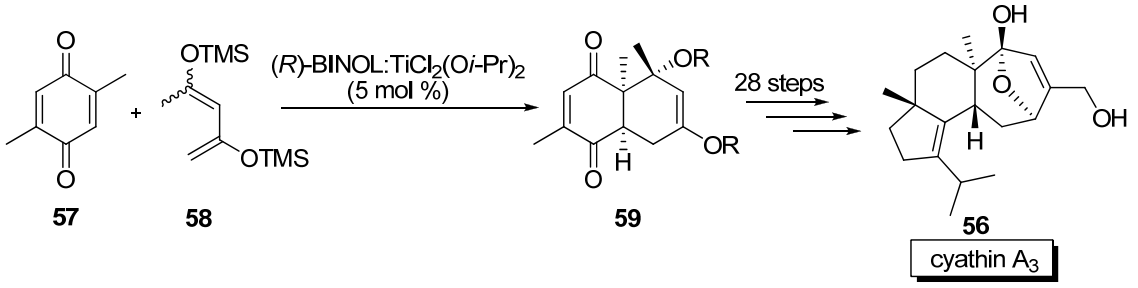


Figure 8 Structure of cyathin A_3.

The synthesis of cyathin A_3 (**56**) was achieved by a DA cycloaddition between 2,5-dimethyl-1,4-benzoquinone **57** and 2,4-bis(trimethylsilyloxy)-1,3-pentadiene **58** catalysed by Mikami's catalyst [(*R*)-BINOL-$TiCl_2$] modified by addition of Mg powder and silica gel (SiO_2). Mg powder added to remove HCl, and SiO_2 may preferentially absorb diene polimers as decomposition products or improve catalyst performance by immobilizing it in the SiO_2 surface.[43] The cycloadduct **59** was obtained in 90 % yield and 93 % *ee* in dienophile one gram scale. After 28 steps, cyathin A_3 **56** was achieved in 0.65 % overall yield from cycloadduct **59** (Scheme 11).



Scheme 11 Synthesis of cyathin A_3 precursor **59**.

Once cyathin A_3 **56** is easily transformed into allocyathin B_3 (**60**), neoallocyathin A_4 (**61**), cyathin B_3 (**62**), cyathin C_3 (**63**), and allocyathin B_2 (**64**), this route also constitutes a formal synthesis for these natural products.[44,45,46] In the other hand, cyathatriol (the 14-β-alcohol derivative of **56**)[45] has been proposed[47] as a (bio)synthetic precursor of the erinacines (e.g., **65** and **66**)[46], which are xylose-conjugated terpenoids possessing a cyathane core (Figure 9).

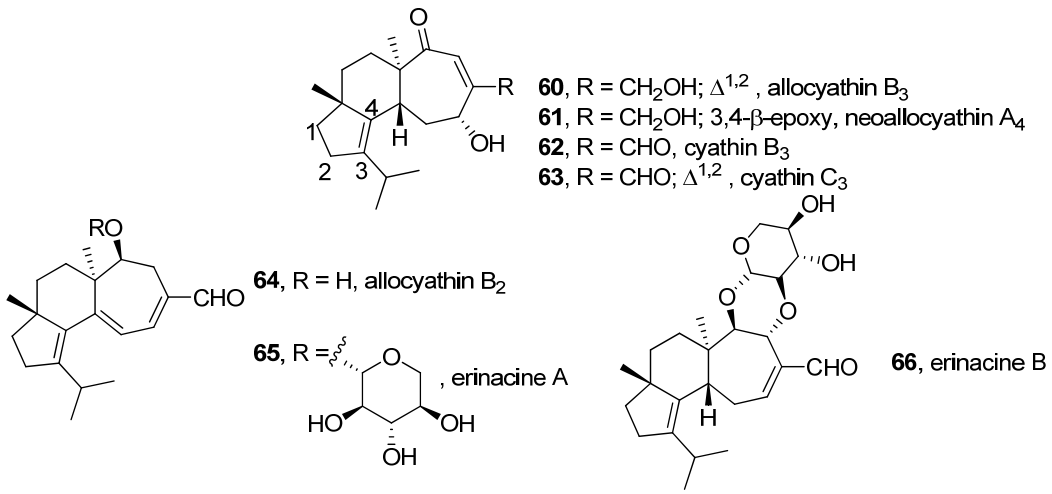
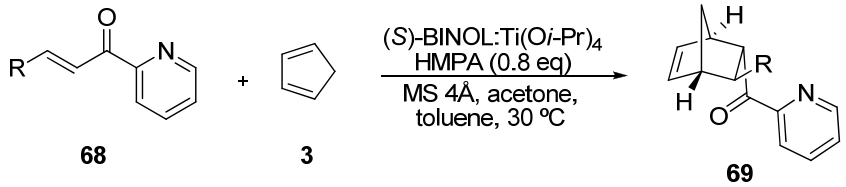


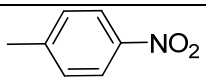
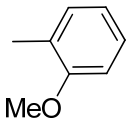
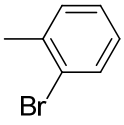
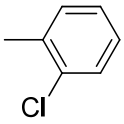
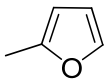
Figure 9 Selected cyathane diterpenes.

Yu[48] showed that BINOL-titanium complex also catalysed asymmetric Diels-Alder reactions of aza-chalcones **67** with cyclopentadiene **2** in the presence of hexamethylphosphoramide (HMPA) (80 mol %). Products **68** were obtained in moderate-to-good yields and with up to 87 % *ee* (Table 10). Other Lewis base additives such as quinine, imidazole, DMAP, Et_3N and quinoline proved to be less efficient than HMPA. Aza-chalcones have been reported to display a wide variety of biological activities and are valuable intermediates for Diels–Alder reactions.[49] Moreover, the DA reaction of aza-chalcones and cyclopentadiene **2** has been used in many studies as a benchmark reaction.[50]

Table 10 Asymmetric DA cycloaddition between aza-chalcones **68** and cyclopentadiene **3**.



68 **3** **69**

Entry	R	yield (%)	*ee* (%)
1		>99	52
2		91	87
3		53	70
4		76	72
5		49	79

In 2009, Kumaraswamy and co-workers[51] reported an enantioselective route to the synthesis of diospongins A **69** and B **70** and their enantiomers using catalytic hetero Diels-Alder cycloaddition as the first step.

Diospongins A **69** and B **70** were isolated from the rhizomes of *Discorea spongiosa*. They had shown interesting antiosteoporotic activity,[52] and are leads in the discovery of potent and novel antiosteoporotic agents (Figure 10).

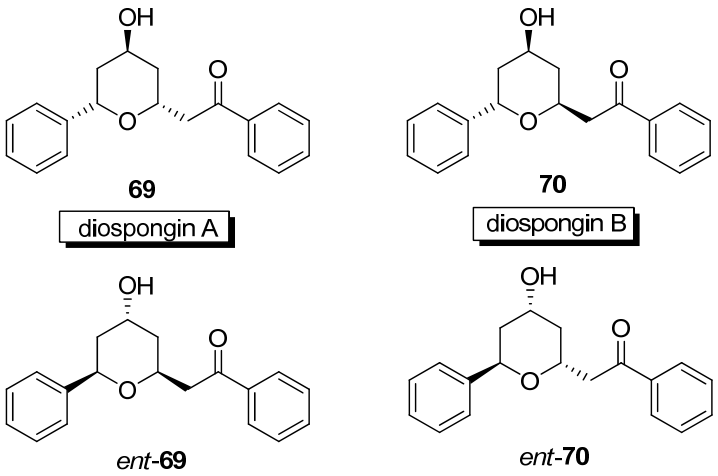
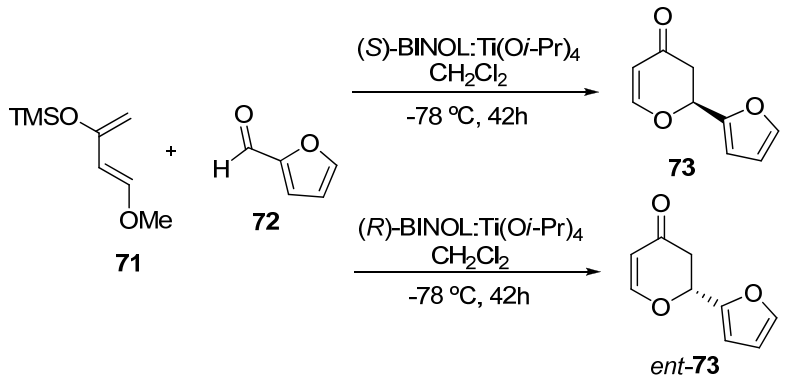


Figure 10 Dispongins A **69** and B **70** and their enantiomers.

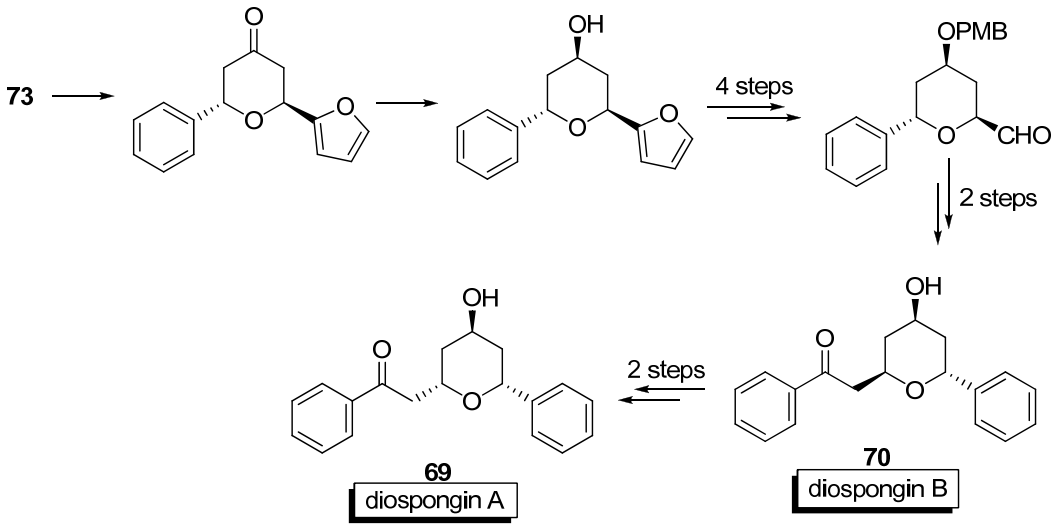
Despite their structural similarity, diospongins A and B exhibit remarkable differences in their biological profile. Diospongin B (**70**) displays a potent inhibitory activity on bone resorption induced by parathyroid hormone, while diospongin A **69** did not show any activity.

The enantioselective hetero Diels-Alder reaction between Danishefsky's diene (**71**) and furfuraldehyde (**72**) using 10 mol % of (*S*)-BINOL/Ti(O*i*-Pr)$_4$ catalyst gave dihydropyranone **73** in 60 % yield and 96 % *ee*. Recrystallization of the product resulted in 99.9 % enantiomeric excess. Dihydropyranone **73** and its enantiomeric form *ent*-**73** were obtained depending on the chiral nature of BINOL. After recrystallization *ent*-**73** was obtained in >99 % *ee* (Scheme 12).



Scheme 12 Synthesis of **73** and *ent*-**73**.

Adduct **73** was converted in diospongin B (**70**) in 8 steps with 56 % overall yield (Scheme 13). Further, diospongin B was transformed into diospongin A (**69**) in 79 % in 2 steps. By the same sequence, *ent*-**73** was converted into *ent*-**70** in 62 % yield, and *ent*-**70** into *ent*-**69** in 79 % yield.



Scheme 13 Synthesis of diospongins A and B.

Kwiatkowski *et al* [53] recently reported a new approach for the synthesis of bissetone **74** and its stereoisomers. Bissetone **74** is one of the metabolites of 1,5-anhydro-D-fructose, it showed antimicrobial activity, and can be isolated from Gorgonian soft coral *Briareum polyanthes* (Figure 11).[54]

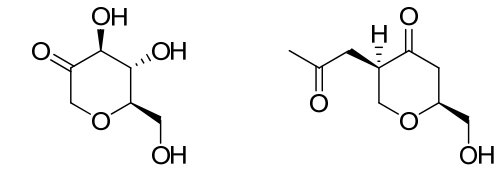
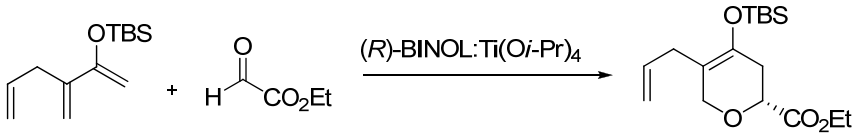


Figure 11 1,5-Anhydro-D-fructose and its metabolite (-)-bissetone **74**.

The key reaction in the synthesis of (-)-bissetone (**74**) is a highly enantioselective hetero Diels-Alder cycloaddition between triene **75** and ethyl glyoxylate **76** catalysed by a BINOL-Ti complex. Cycloadduct **77** was obtained in high yield and 90 % *ee*. Optimization of the reaction conditions showed that 2 mol % of $[BINOL]_2$:Ti complex in toluene gave the highest enantioselectivity (93 %), and good yield (80 %) (Table 11).

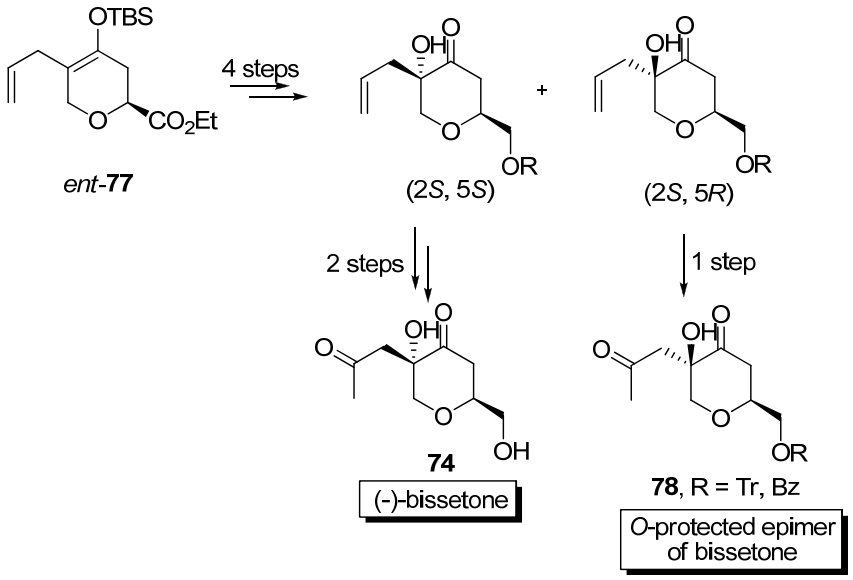
Table 11 Enantioselective HDA reaction between triene **75** and ethyl glyoxylate **76**.



75 **76** **77**

Entry	cat.	mol %	solvent	T (ºC)	t (h)	yield (%)	*ee* (%)
1	(*R*)-BINOL:Ti(O*i*-Pr)$_4$ (1:1)	5	CH_2Cl_2	0	4	89	90
2	(*R*)-BINOL:Ti(O*i*-Pr)$_4$ (2:1)	2	toluene	0	15	80	93

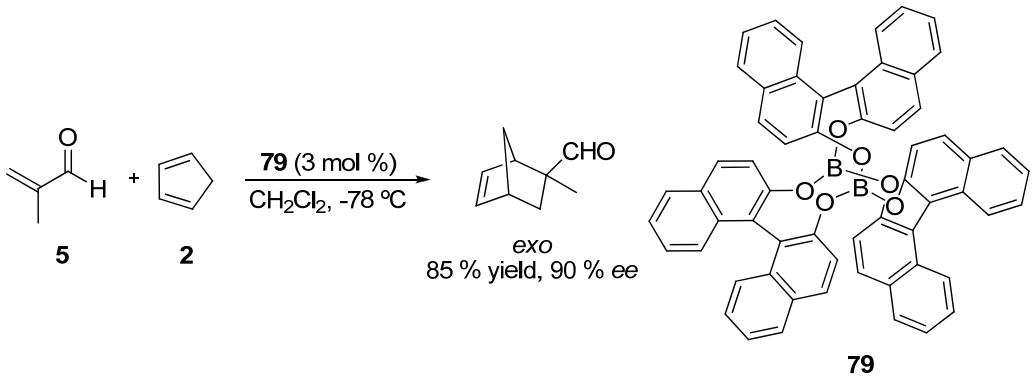
In the synthesis of natural (-)-bissetone **74**, a titanium catalyst based on (*S*)-BINOL was used to obtain cycloadduct *ent*-**77**. This adduct was then transformed in five steps into (-)-bissetone **74** in 54 % overall yield, and its *O*-protected epimer **78** with 53 % yield for R = Tr and 48 % yield for R = Bz (Scheme 14).



Scheme 14 The synthesis of (-)-bissetone and *O*-protected epimer of bissetone from *ent*-**77**.

1.2 Boron-BINOL catalysts

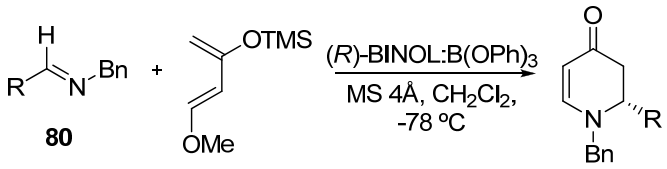
Chiral boron complexes have been explored as promoters of asymmetric Diels-Alder reactions. Kaufmann[55] reported the synthesis and X-ray of a C_3-symmetric tetradecacyclic diborate complex **79**, which efficiently catalysed the Diels-Alder reaction between methacrolein **5** and cyclopentadiene **2** (Scheme 15). The catalyst was prepared by mixing (*S*)-BINOL (3 eq.) and bromoborane-dimethyl sulphide complex (2 eq.).



Scheme 15 Enantioselective DA cycloaddition of cyclopentadiene **2** and methacrolein **5** catalysed by the diborate complex **79**.

Yamamoto[56,57] used a chiral boron complex generated *in situ* by mixing an equimolar amount of BINOL and triphenyl borate in CH_2Cl_2. This catalyst was used in the presence of MS 4Å in an aza-Diels-Alder reaction of imines **80** with Danishefsky's diene **71**. Cyclodducts **81** were obtained in moderate to good yields (45-89 %), and high enantiomeric purity (74-90 % *ee*) (Table 12).

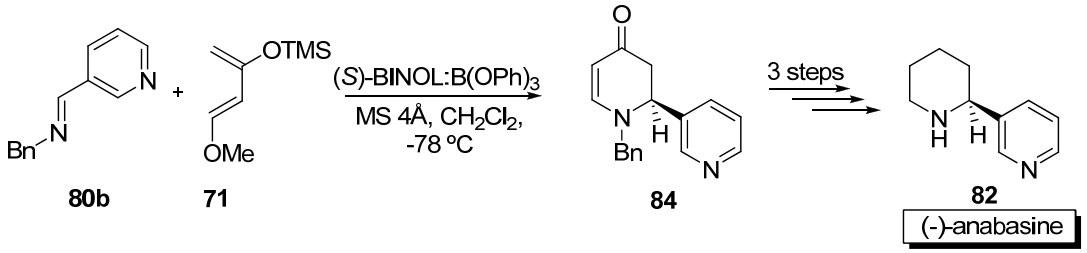
Table 12 Aza-Diels-Alder reaction catalysed by the (*R*)-BINOL/$B(OPh)_3$ system.



Entry[a]	R^1	yield (%)	*ee* (%)
1	Ph (**a**)	75	82
2	3-pyridyl (**b**)	71	90
3	Cyclohexanyl	45	76
4	3,5-$(MeO)_2C_6H_4$	89	74
5	2-naphthyl	83	84

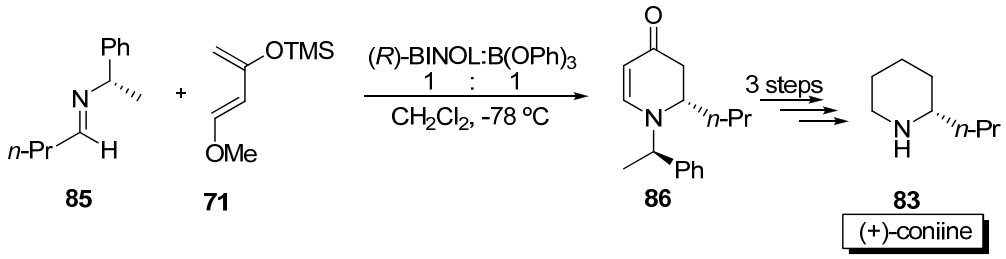
[a] Conditions: CH_2Cl_2, catalyst (1 eq.), and diene (1.2 eq.), -78 ºC, 5h.

Either (*R*)- and (*S*)-**81** were obtained as products by changing the chirality of the BINOL ligand. The methodology was applied to the synthesis of piperidine alkaloids (-)-anabasine (**82**), derived from nicotinic acid, and to (+)-coniine (**83**) (Scheme 16, Scheme 17).[57] The intermediate dihydropyridone **84** was obtained in 68 % yield and 90 % *ee*, and then converted to (-)-anabasine **82** in 3 steps with 49 % total yield from **84** (Scheme 16).



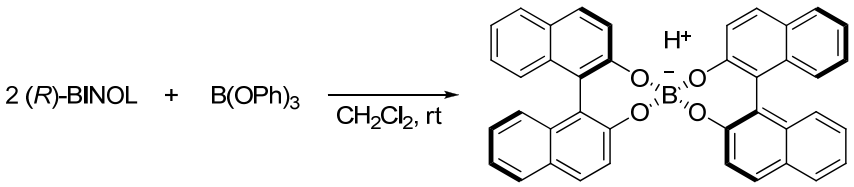
Scheme 16 Synthesis of (-)-anabasine.

On the other hand, the diastereomer **86** was obtained in its homochiral form in 41 % yield. Its FGT gave (+)-coniine **83** in 54 % overall yield from **86** (Scheme 17). Of course a double asymmetric induction is behind the DA process in this case. Boron Lewis acid was used in stoichiometric quantities in all cases.



Scheme 17 Asymmetric synthesis of (+)-coniine.

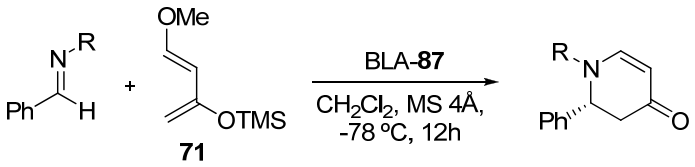
Yamamoto[58] showed the interest of a Bronsted acid-assisted chiral boron Lewis acid (BLA) **87**, obtained from a 2:3 mixture of BINOL and triphenylborate as a chiral inductor catalyst in DA cycloadditions (Scheme 18).



BLA-**87**

Scheme 18 Formation of the chiral BLA-**87** promoter.

Diels-Alder cycloaddition of benzylidenebenzylamine **80a** to Danishefsky's diene **71** in the presence of BLA afforded **89a** in 78 % yield and 86 % *ee*. The reaction of diene **71** with chiral aldimine **90** gave cycloadduct **89b** in a 64 % yield, and 99 % *ee* showing a matched double asymmetric induction (Scheme 19).



80a R = Bn
90 R = (*S*)-PhMeCH

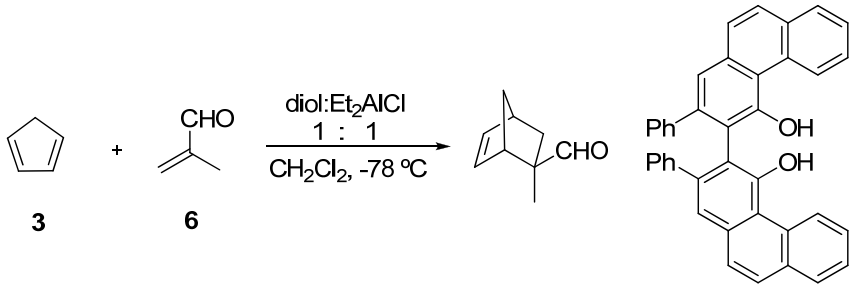
89a R = Bn
89b R = (*S*)-PhMeCH

Scheme 19 Asymmetric aza-Diels-Alder cycloadditions catalysed by BLA-**87**.

1.3 Aluminium-BINOL catalysts

Wulff worked on the influence of catalysts obtained from diethylaluminium chloride and BINOL.[59] *Exo*-selectivities were good to excellent in all cases, but enantiomeric excesses were modest (13-41 %). Enantioselectivities could be largely improved with a biaryl inductor, (VAPOL, **91**) (Table 13).

Table 13 Selectivity of the Diels-Alder reaction catalysed by the Et_2AlCl/diol system.



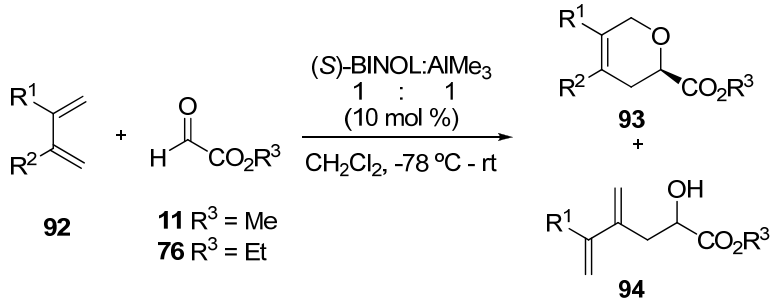
3 **6**

VAPOL (**91**)

Entry	diol	cat. (mol %)	yield (%)	*exo*/*endo*	*ee* (%)
1	(*S*)-BINOL	10	99	97/3	23
2	(*S*)-VAPOL	10	100	98/2	98
3	(*S*)-VAPOL	0.5	98	97/3	88

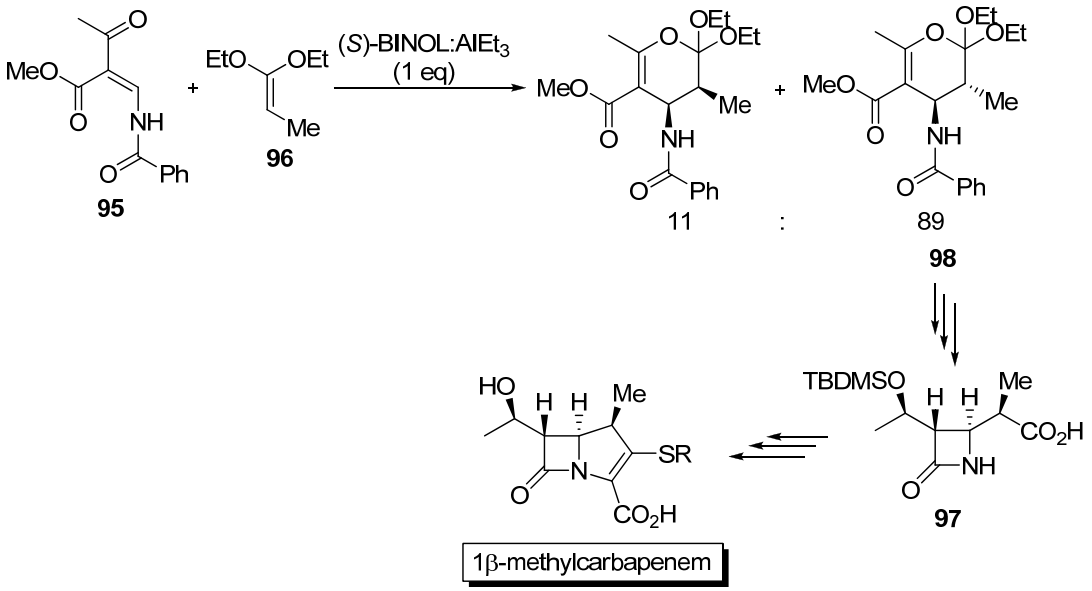
A BINOL-AlMe catalyst, obtained from (*S*)-BINOL and $AlMe_3$, has been used by Jörgensen to promote the hetero Diels-Alder cycloaddition preferentially to ene addition in the reaction between 1,3-butadienes **92** and glyoxylate esters (Table 14).[60] Simple dienes such as isoprene were also combined with glyoxylate esters under BINOL-Ti catalysts. In this case an ene reaction is concurrent giving the ene product as the major component.[8]

Table 14 Hetero Diels-Alder reaction catalysed by the aluminium-BINOL system.



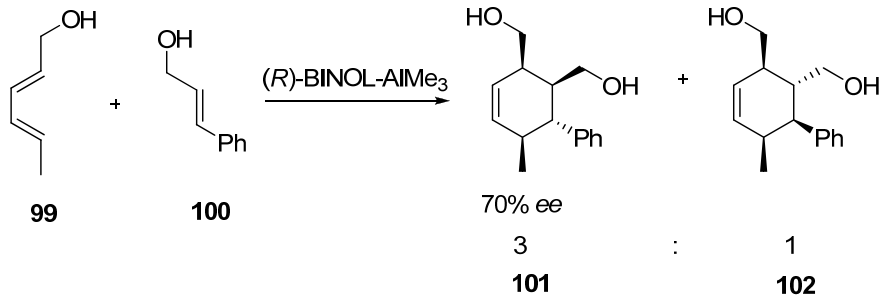
Entry	R^1	R^2	R^3	**93**		**94**	
				yield (%)	*ee* (%)	yield (%)	*ee* (%)
1	Me	Me	Et	73	97	9	88
2	Me	H	Et	29	97	14	88
3	Me	H	Me	13	70	3	27

Diels-Alder cycloaddition between methyl 2-(benzoylamino)methylene-3-oxobutanoate **95** and methylketene diethyl acetal (**96**) in the presence of an equimolar amount of (*S*)-BINOL-AlEt led **98** with a high *trans*-selectivity (76 %) and *ee*, after crystallization (74 %) (Scheme 20). Cycloadduct **98** was transformed first into **97**, an intermediate of 1β-methylcarbapenem antibiotic and then in the proper antibiotic.[61]



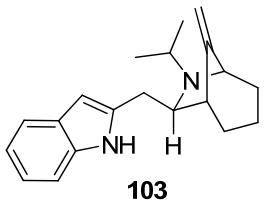
Scheme 20 HDA reaction leading to a key 1β-methylcarbapenem intermediate **98**.

Recently, Olson reported an interesting result as part of a study directed towards the feasibility of DA reaction of “noncompatible” diene **99** with dienophile **100** by means of a temporary tethering with Al or Zr.[62] This combination resulted in the one-step formation of substituted cyclohexene 1,2-bis-methanols **101** and **102**, in 58 % yield with excellent regioselectivity and significant *endo*/*exo*-selectivity (3:1) (Scheme 21).



Scheme 21 Aluminium tethered Diels-Alder reaction between diene **99** and dienophile **100**.

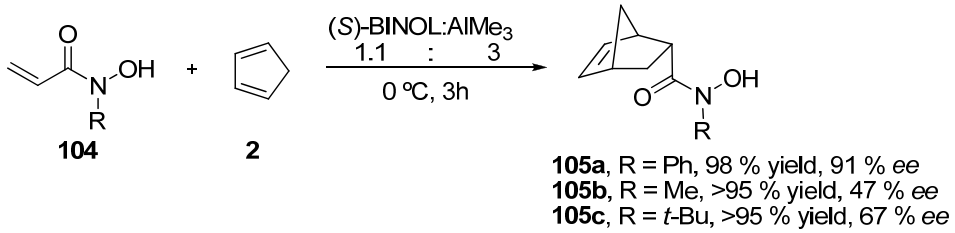
Later, Renaud[63] reported the use of hydroxamic acids as dienophiles in enantioselective Diels-Alder reactions. The chiral Lewis acid was prepared by mixing optically pure BINOL with 3 eq. of trimethylaluminium in the reaction of *N*-hydroxy-*N*-phenylacrylamide **104** with cyclopentadiene **2**. The product was obtained in high yield (>96 %) and moderate to good enantioselectivity. It was used in particular as a key intermediate in the synthesis of peduncularine **103**, a major alkaloid isolated from a Tasmanian shrub *Aristotelia peduncularis* (Figure 12).[64]



103

Figure 12 Structure of alkaloid peduncularine **103**.

Facile conversion of adducts **105** to the corresponding alcohols or aldehydes makes the hydroxamic acid products useful intermediates building blocks in synthesis (Scheme 22).

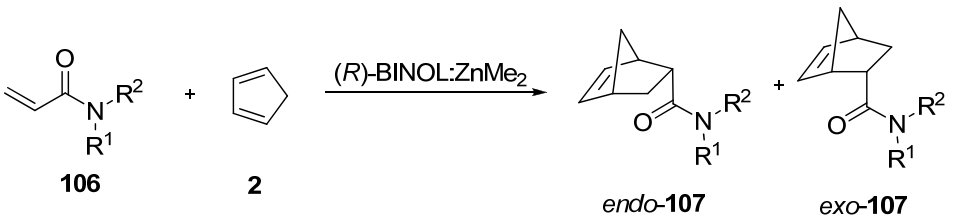


Scheme 22 Enantioselective DA reactions with *N*-hydroxy-*N*-phenylacrylamide **104**.

1.4 Zinc-Magnesium-BINOL catalysts

Dialkylzinc represents an attractive alternative to trialkylaluminium for preparation of mild Lewis acids.[65] The Lewis acid obtained from dimethylzinc and BINOL, known as Yamamoto's Zn-BINOL catalyst. It was examined in the Diels-Alder reaction between *N*-alkoxyacrylamides **106** and cyclopentadiene **2**.[66] Reactions proved to be very efficient and enantioselectivities obtained were up to 96 % *ee* (Table 15).

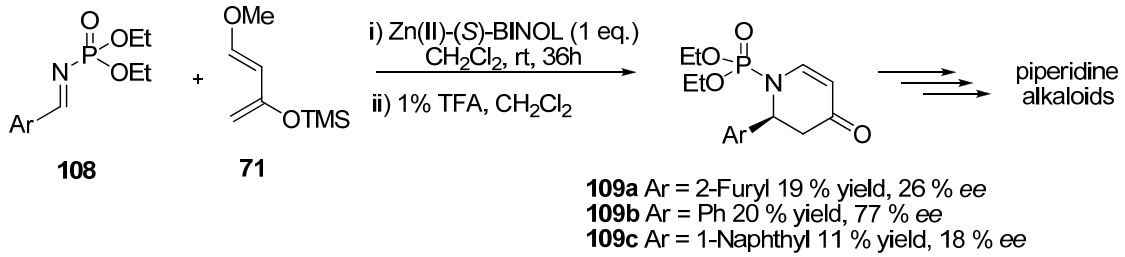
Table 15 Reaction of *N*-alkoxyacrylamides **106** with cyclopentadiene **2** catalysed by (*R*)-BINOL-Zn system.



Entry	R^1	R^2	eq. of catalyst	*endo*:*exo*	*ee* (*endo*) (%)
1	Me	OMe	1.1	7:1	89
2	Ph	OMe	1.1	54:1	96
3	Ph	OMe	0.25	41:1	90
4	Ph	OEt	1.1	29:1	86
5	Ph	O*i*-Pr	1.1	14:1	76

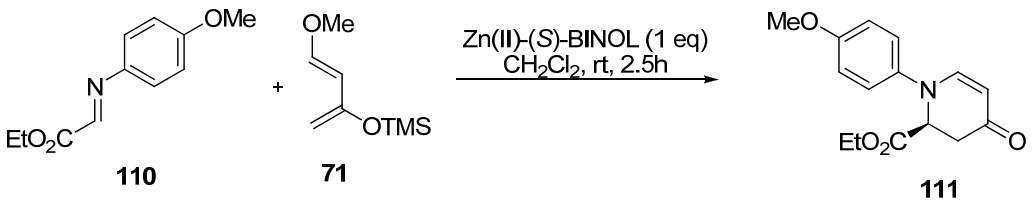
The simplicity of the Zn-BINOL experimental procedure makes it very attractive from a synthetic point of view. Conversion of *N*-alkoxyamide Diels-Alder cycloadducts **108** into useful building blocks is facilitated by the well-known synthetic versatility of Weinreb amides.

As part of a program aimed to developing new strategies for the preparation of readily elaborated chiral synthons for the synthesis of piperidine alkaloids, Whiting screened a number of different Lewis acids and chiral ligands to induce facial discrimination in aza-Diels-Alder reactions with *N*-imine functions.[67] Zn-BINOL system was the only one to provide some asymmetric induction in reaction between imine **108** and Danishefsky's diene **71**. Products were obtained in low yields and low to moderate *ee* (18-77 %), as outlined in Scheme 23.



Scheme 23 Asymmetric synthesis of cycloadducts **109** using Zn(II)-(*S*)-BINOL complex.

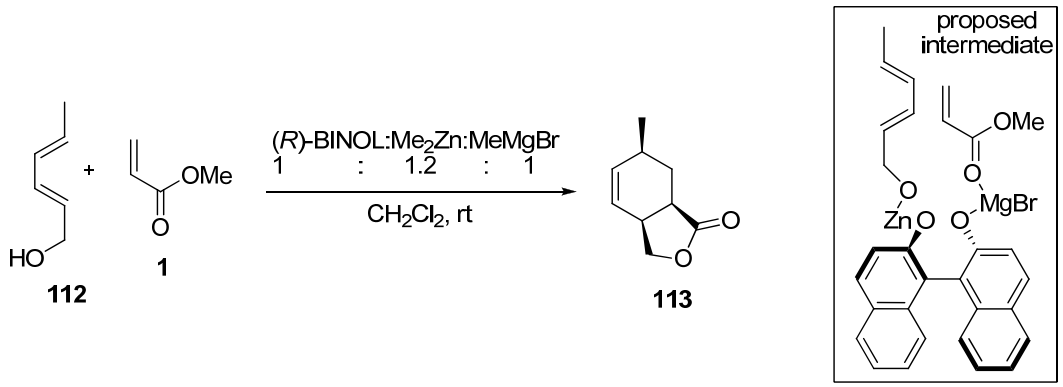
In further studies, Whiting[68] showed that the use of Zn-BINOL complex catalysed the asymmetric aza-Diels-Alder reaction of an ethyl glyoxylate-derived *N*-aryl imine **110** with Danishefsky's diene **71** affording the corresponding cycloadduct **111** with 78 % yield and 93 % *ee* (Scheme 24).



Scheme 24 BINOL-zinc complex catalysis of aza-Diels-Alder reaction between imine **110** and Danishefsky's diene **71**.

The ready availability of BINOL, the ease of preparation of the catalyst and reproducibility of the system makes this process highly attractive for piperidine alkaloid and related compound synthesis.

Later, Ward[69] reported a new strategy to control Diels-Alder cycloadditions based on a Lewis acid bimetallic complex of Mg and Zn, that "self-assemble" reagents and catalyse the process (LACASA-DA). In this approach, a simultaneous coordination of the diene, dienophile and BINOL in a Lewis acid template turns process a kind of "intramolecular" Diels-Alder reaction (see intermediate proposed in Scheme 25) with enhanced reactivity, regioselectivity and diastereo / enantioselectivivity. Combination of 2,4-hexadienol **112** with methyl acrylate **1** under these conditions and using (*R*)-BINOL as chiral inductor afforded cycloadduct **113** in excellent yield (95 %) and high enantioselectivity (96 % *ee*) (Scheme 25).



Scheme 25 LACASA-DA reaction of **112** with **1** using a multinuclear Lewis acid (*R*)-BINOL catalyst.

The synthetic potential of LACASA-DA strategy was demonstrated by Barriaud *et al* in the synthesis of the tricyclic core of Penostatin F **114** (Figure 13), a natural product isolated from *Penicillium sp.* Compound **114** is known to exhibit a significant cytoxicity against P388 Leukemia cells.[70]

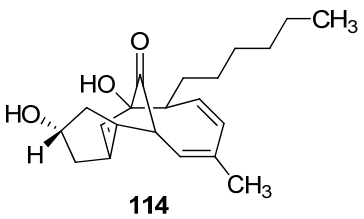
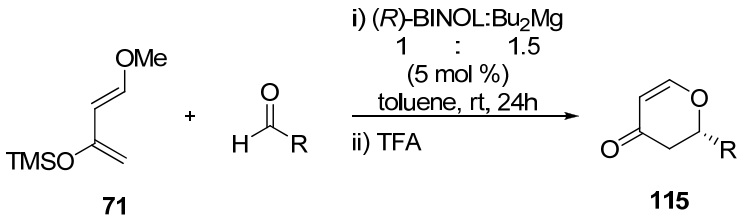


Figure 13 Structure of Penostatin F.

Recently, Ding[71] developed a magnesium binaphthoxide system (BINOL-Bu_2Mg) capable of efficiently catalyse the hetero Diels-Alder reaction of Danishefsky's diene **71** with aldehydes to afford a variety of 2-substituted 2,3-dihydro-4*H*-pyran-4-ones **115** in high yields and with excellent *ee* values (Table 16).

Table 16 Enantioselective HDA reactions of Danishefsky's diene **71** and aldehydes by catalysis of BINOL-Mg complexes.



71 **115**

Entry	R	yield (%)	*ee* (%)
1	C_6H_5	94	96
2	$C_6H_5CH_2CH_2$	54	63
3	(*E*)-C_6H_5CHCH	61	91
4	furan-2-yl	62	82
5	3-MeC_6H_4	99	94
6	4-BrC_6H_4	87	88
7	2-MeC_6H_4	77	92

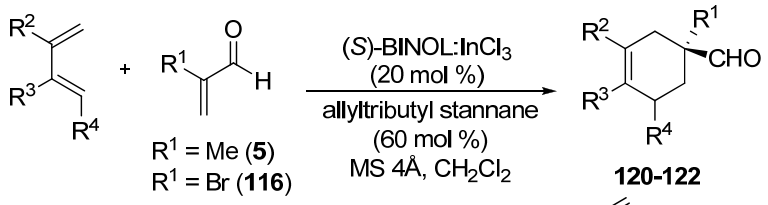
Approaches to the asymmetric synthesis of this type of six-membered oxo heterocycle have extensive applications in natural and unnatural product synthesis,[2-3, 36b, 65, 72] *e.g.* mevilonin **17a** and compactin **17b**.[2-3, 34b, 57, 64]

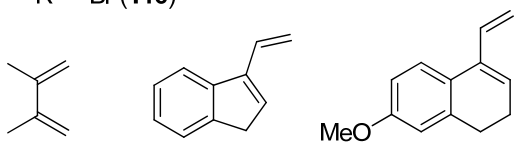
1.5 Indium-BINOL catalysts

Indium(III) complexes have gained a lot of attention in recent years due to their capability as Lewis acid catalysts for various organic synthetic transformations and for its aqueous media tolerance.[73,74]

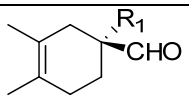
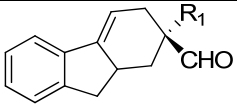
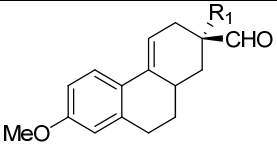
Loh described a new type of catalyst made by addition of (*S*)-BINOL-In(III) complex (pre-catalyst) to allyltributyl stannane (activator). The complex generated is a potent Lewis acid.[73] A variety of cyclic and open-chain dienes were combined to 2-methacrolein **5** and 2-bromocrolein **116** resulting in products **120**-**122** obtained in good yields and high *ee* (Table 17).

Table 17 Diels-Alder reaction of open-chain 1,3-dienes with 2-methacroleine **5** and 2-bromoacrolein **116** catalysed by chiral (*S*)-BINOL-In(III) complex.



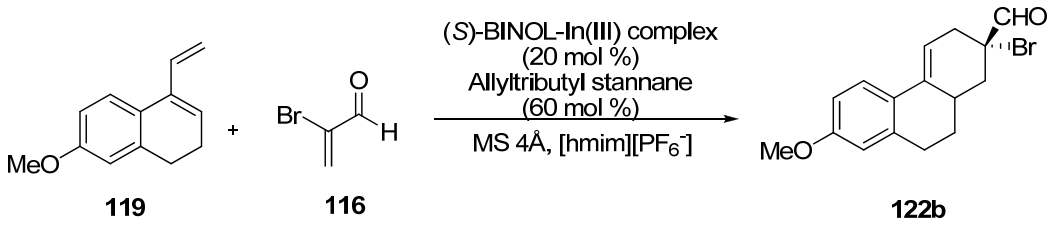


117 **118** **119**

Entry	Reactants	T (ºC), t (h)	Product	R^1	yield (%)	*ee* (%)
1	**117**+**5**	rt, 20		Me	63	98
2	**117**+**116**	-20, 20		Br	74	98
3	**117**+**116**	rt, 20 + H_2O	**120a** R^1 = Me **120b** R^1 = Br	Br	70	80
4	**118**+**5**	-20, 20		Me	71	98
5	**118**+**116**	-20, 20		Br	72	98
6	**118**+**116**	rt, 20 + H_2O	**121a** R^1 = Me **121b** R^1 = Br	Br	72	66
7	**119**+**5**	-20, 20		Me	75	97
8	**119**+**116**	-20, 20		Br	77	94
9	**119**+**116**	-20, 20 + H_2O	**122a** R^1 = Me **122b** R^1 = Br	Br	61	94

In further publications, Loh reported the usefulness of ionic liquids as "green" alternative to conventional solvent media in these reactions.[75] 2-Methacroleine **5**/ 2-bromocrolein **116** was reacted with cyclopentadiene, isoprene and diene **117** in the presence of BINOL-In(III) complex and allyltributyl stannane in [hmim][PF_6^-] ionic liquid.

Reaction proceeded with yields and enantioselectivities comparable to those obtained in CH_2Cl_2. In an attempt to apply this method to the synthesis of steroids, diene **119** was reacted with **116** (Scheme 26). Cycloadduct **122b** was obtained with 89 % yield and 92 % of enantiomeric excess.



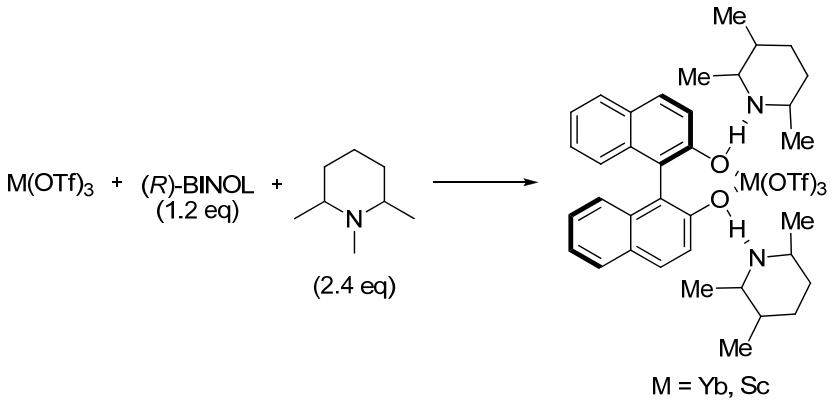
119 **116** **122b**

Scheme 26 Catalytic enantioselective DA reaction in ionic liquid via a chiral In(III) complex.

The chiral In(III) complex can be reused for seven successive cycles with comparable enantioselectivities and yields.

1.6 Lanthanide/Transition metals-BINOL catalysts (Sc, Yb)

Kobayashi, as part of his studies on lanthanide triflates as Lewis acids, reported a series of papers describing the enantioselectivity induced by BINOL-ytterbium[76] and BINOL-scandium triflates[77] in reactions of cyclopentadiene **2** with various acyl-1,3-oxazolidin-2-ones (**123**). Catalysts were prepared by mixing the metal triflate with BINOL in the presence of MS 4Å, followed by addition of a tertiary amine (Scheme 27).



Scheme 27 Preparation of chiral Yb or Sc catalysts.

The asymmetric induction observed in these reactions can be rationalized by assuming an octahedral metal-dienophile complex (Figure 14). The axial chirality of (*R*)-BINOL is transferred to the amine. The *re* face of acyl-1,3-oxazolidin-2-one is effectively shielded by the amine part, and the diene has to approach to dienophile from the *si* face. Cycloadduct was afforded in high enantioselectivity.

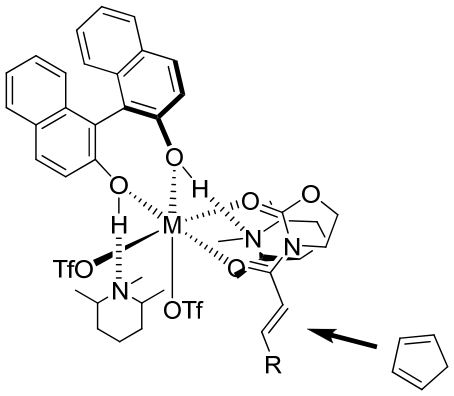
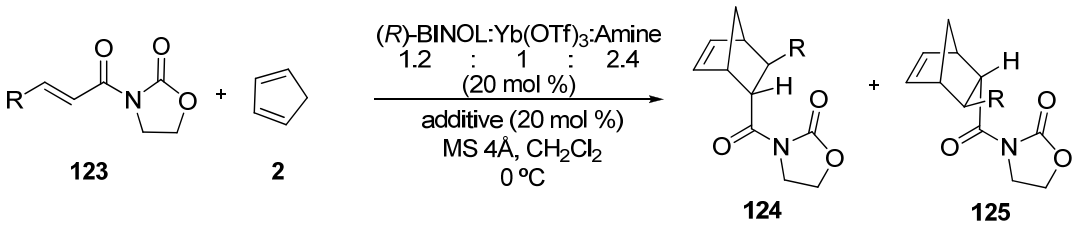


Figure 14 Assumed transition state.

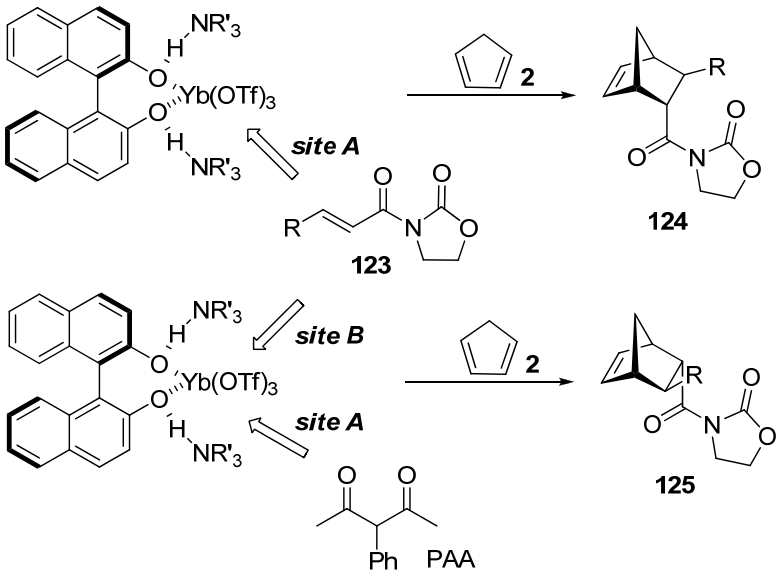
Kobayashi and other authors showed that both cycloadduct's enantiomers can be obtained with the same chiral BINOL, by adding an achiral ligand 3-phenylacetylacetone (PAA) as an additive to the ytterbium complex (Table 18, Scheme 28).[78]

Table 18 Results of DA reaction catalysed by chiral Yb catalyst with PAA additive.



Entry	additive	R	yield (%)	*endo*:*exo*	**124**:**125**	*ee* (%)
1	none	Me	77	89:11	97.5:2.5	95
2	PAA	Me	83	93:7	9.5:90.5	81
3	none	*n*-Pr	81	80:20	91.5:8.5	83
4	PAA	*n*-Pr	81	91:9	10:90	80

This result can be explained by the coordination's nature. Two binding sites are postulated for the ligands to ytterbium catalysts. Under equilibrium conditions, and in the absence of PAA, acyl-1,3-oxazolidin-2-ones **123** coordinates to ***site A***, stabilizing the original catalyst system. Thus, coordination forces cyclopentadiene to attack at the *si* face to afford cycloadduct **124**. However, when PAA was added, its coordination occur at ***site A*** forcing the dienophile to approach ***site B*** of the catalyst. This leaves the *re* face opened leading to cycloadduct **125** (Scheme 28).



Scheme 28 Synthesis of enantiomers **124** and **125** under the same chiral source and in the presence/absence of PAA.

Other lanthanides (Lu, Tm, Er, Ho, Y and Gd) were used to prepare catalysts with BINOL, but the *ee* of the products obtained strongly depends on the ionic radii of lanthanide. The yields and selectivity diminished rapidly with ionic radii enlargement.[78a]

Cycloadduct **124** (R = Me) is a valuable synthetic precursor of alkaloid 251F (Figure 15), a natural product detected in the skin's extract of the dendrobatid frog species *Minyobates bombetes*.[79]

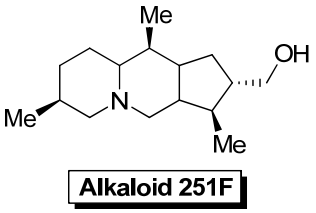
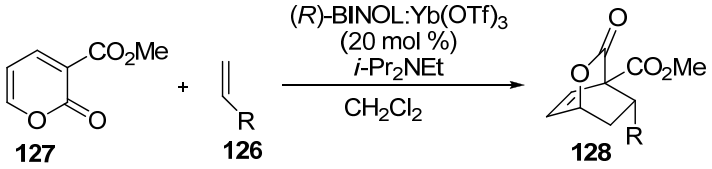


Figure 15 Structure of dendrobatid alkaloid 251F.

Marko[80], as part of a program aimed a rapid and efficient synthesis of complex natural products, used the Kobayashi catalyst in a Diels-Alder reaction between vinyl ethers or vinyl sulphides **126** and 3-carbomethoxy-2-pyrone (3-CMP), **127**. Under optimized conditions, high yields (90-91 %) and excellent enantioselectivities (>90 % *ee*) were obtained in some cases (Scheme 29).



R	yield (%)	*ee* (%)
OCy	90	92
OAd	91	93
SPh	91	>95

Scheme 29 Catalytic enantioselective inverse electron-demand DA reaction of vinyl ethers and sulphides **126** with 3-CMP **127**.

Byciclic lactones **128** are key intermediates of important subunits present in biologically active natural products, such as gibberellins (Figure 16). Gibberellins are a group of highly functionalised diterpenoids, which play an important role in plant growth and development.[81]

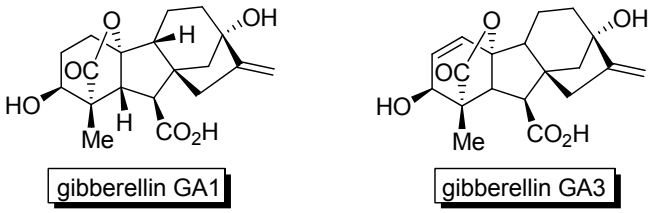
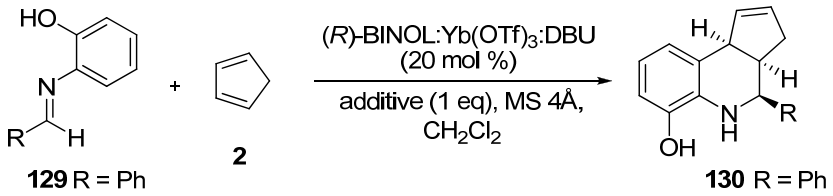


Figure 16 Structure of some relevant gibberellins.

Kobayashi[82] reported the first example of catalytic asymmetric aza-Diels-Alder reaction using a chiral lanthanide Lewis acid. *N*-Benzylideneaniline was reacted with cyclopentadiene **2** in the presence of 20 mol % of chiral ytterbium Lewis acid prepared from $Yb(OTf)_3$, (*R*)-BINOL, and 1,3,5-trimethylpiperidine (TMP). The reaction proceeded smoothly to afford the desired tetrahydroquinoline derivative in 53 % yield, however no chiral induction was observed. Believing that a bidentate coordination of the substrate might be necessary for chiral induction, the aromatic imine **129** was used as diene. The product was obtained with high yield, but low enantiomeric excess (6 %). The selectivity was greatly improved by using DBU instead of TMP as additive. Two DBU unities should interact with BINOL hydrogens, and the phenolic hydrogen of the diene would interact best to form N···H-O hydrogen bond with an additive, such as *N*-methylimidazole (NMI), DTBP, 2,6-dimethylpyridine (DMP), or 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) (Table 19). If DBU interacts with the phenolic hydrogen a decrease of selectivity is observed.

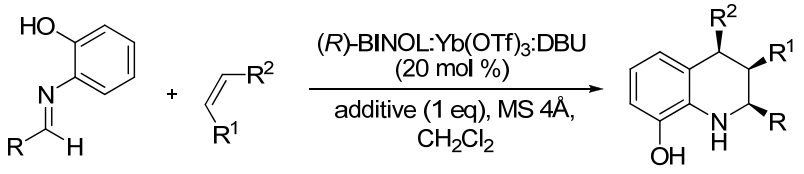
Table 19 Effect of additive in DA reaction of imine **129** and cyclopentadiene **2**.

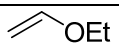
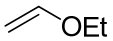
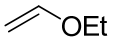
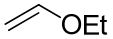
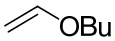


Entry	Additive	T (ºC)	yield (%)	*cis*:*trans*	*ee* (%) (*cis*)
1	____	-15 to 0	48	99:1	68
2	DTBP	0	67	99:1	61
3	DMP	0	14	98:2	56
4	DTBMP	-15	82	>99:1	70
5	DTBP	-15	92	>99:1	71

Other dienes and dienophiles were tested under similar conditions (Table 20). The corresponding tetrahydroquinolines **131** were obtained in 58-90 % yield, with a *cis*:*trans* selectivity greater than 90:10, and *ee* ranging from 68-91 % for the major (*cis*) isomer.

Table 20 Asymmetric synthesis of tetrahydroquinolines derivatives **131**.



Entry	R	alkene	additive	yield (%)	*cis*:*trans*	*ee* (%) (*cis*)
1[a]	Ph		DTBP	52	94:6	77
2	α-Naph		DTBP	69	>99:1	86
3	α-Naph		DPP	65	99:1	91
4	α-Naph		DTBMP	74	>99:1	91
5	α-Naph		DTBMP	80	66:34	70
6	α-Naph		DTBMP	90	91:9	78
7	α-Naph		DPP	67	93:7	86
8	α-Naph		DTBMP	69	>99:1	68
9	c-C_6H_{11}		DTBMP	58	>99:1	73

[a] Conditions: 10 mol % of ytterbium catalyst at -45 ºC.

The proposed transition state that accounts for the experimental results is depicted in Figure 17. DBU establishes hydrogen bonds with the coordinated (*R*)-BINOL transferring axial chirality of the alcohol to the aza-diene region favouring the chiral induction. According to the transition state in Figure 17, the imine is fixed to Yb(III) in a bidentate coordination, and DTBP additive interacts with the phenolic hydrogen creating a rigid structure. The top face of the imine diene is shielded by DBU,

and so the dienophile must approach the diene from the bottom face. This leads to good levels of facial selectivity (see Table 19 and Table 20).

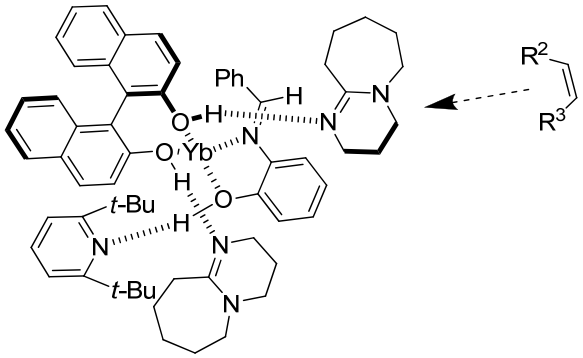


Figure 17 Transition state proposed for reaction of imine **129** and different dienophiles.[a]

[a] Triflate anions are omitted for clarification.

2. Conclusions

Advances in enantioselective DA cycloaddition with titanium, boron, aluminium, zinc, magnesium, indium and lanthanides Lewis acids attached to BINOL is reviewed from 1990 to the present. The focus of this work is made on the synthesis of chiral synthons used to build up biologically active compounds. Generally cycloadducts were obtained in high levels of facial selectivities. Some titanium, boron and aluminium systems require stoichiometric amounts of the catalyst, but in most cases only catalytic amounts are involved.

3. References

1. Kobayashi, S.; Jorgensen, K. A., *Cycloaddition Reactions in Organic Synthesis*. Wiley-VCH Verlag GmbH: **2001**; p 5.

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Chapter 2

Results and discussion as a compilation of articles

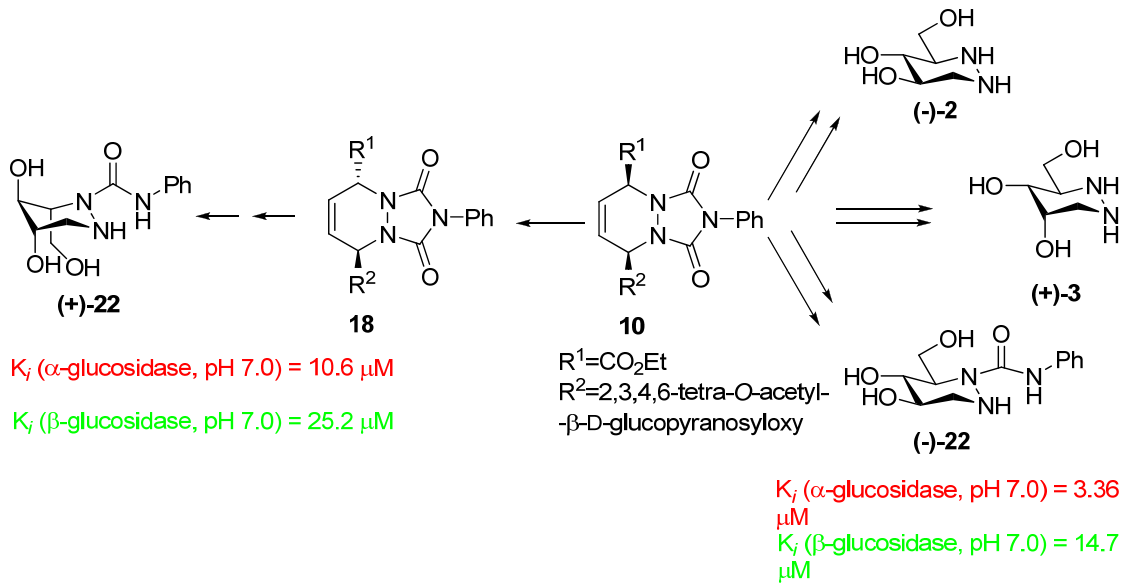
2.1

Advances in the Synthesis of Homochiral (-)-1-Azafagomine and (+)-5-*epi*-1-Azafagomine. 1-*N*-Phenyl Carboxamide Derivatives of both Enantiomers of 1-Azafagomine: Leads for the Synthesis of Active α-Glycosidase Inhibitors.

M. José Alves; Flora T. Costa; Vera C. M. Duarte; António Gil Fortes; José A. Martins; Nuno M. Micaelo *J. Org. Chem.* **2011**, *76*, 9584-9592.

Index

1. Abstract

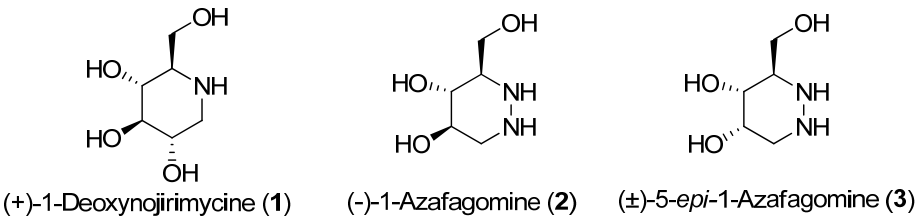


A new expeditious preparation of homochiral (-)-1-azafagomine and (+)-5-*epi*-1-azafagomine has been devised. Stoodley's diastereoselective cycloaddition of dienes bearing a 2,3,4,6-tetraacetyl glucosyl chiral auxiliary to 4-phenyl-1,2,4-triazole-3,5-dione was merged with Bols's protocol for functionalizing alkenes into molecules bearing a glucosyl framework. Homochiral (+)-5-*epi*-1-azafagomine was synthetized for the first time. Partial reductive cleavage of the phenyltriazolidinone moiety afforded new homochiral 1-*N*-phenyl carboxamide derivatives of 1-azafagomine. Both enantiomers of these derivatives were synthetized and tested, displaying a very good enzymatic inhibition toward baker's yeast α-glucosidase. The molecular recognition mechanism of the 1-*N*-phenyl carboxamide derivative of 1-azafagomine by α-glucosidase from baker's yeast was studied by molecular modelling. The efficient packing of the aromatic ring of the 1-*N*-phenyl carboxamide moiety into a hydrophobic subsite (pocket) in the enzyme's active site seems to be responsible for the improved binding affinity in relation to underivatized (-)-1-azafagomine and (+)-1-azafagomine.

2. Introduction

The synthesis of iminosugars is receiving increasing interest because many of these structures are biological tools and potential therapeutics. The first iminosugar medicine registered was miglitol (Glyset, PHARMACIA, and UPJOHN).[1] The biological properties of iminosugars arise from their interference with glycosidases, the natural carbohydrate degrading enzymes, and with carbohydrate-recognizing receptors spread

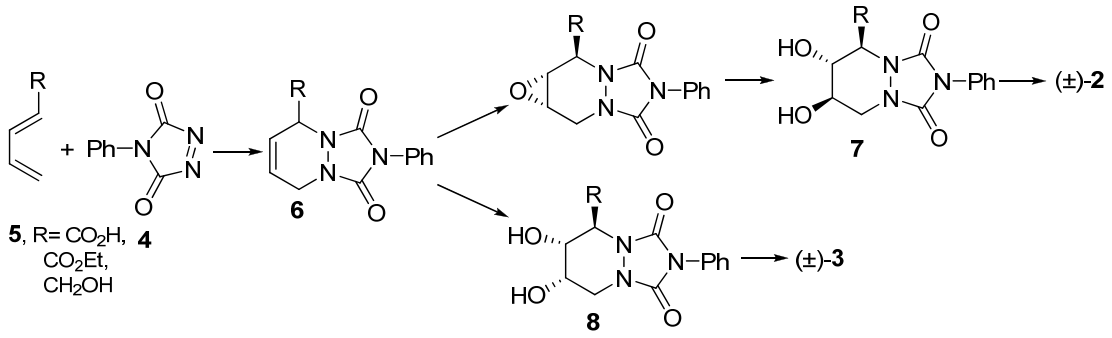
in all living organisms. 1-Deoxynojirimycine (**1**) is a natural iminosugar resembling the structure of glucose. The biological activity of this compound seems to be dependent on its conjugated ammonium form mimicking the transition state for glycoside cleavage.[2] Bols and co-workers have demonstrated that (-)-1-azafagomine (**2**) is a potent competitive inhibitor of almond β-glucosidase (*Ki* = 0.32 *μ*M), yeast α-glucosidase (*Ki* = 6.9 *μ*M), and isomaltase (*Ki* = 0.27 *μ*M).[3] On the other hand, racemic (±)-5-*epi*-1-azafagomine (**3**) was found to be a much weaker glycosidase inhibitor of almond β-glucosidase (*Ki* = 137 *μ*M) and *Escherichia coli* β-galactosidase (*Ki* = 149 *μ*M) (Figure 1).[4] 5-*epi*-1-Azafagomine (**3**), as far as we could find, was previously unknown in any of the enantiomeric pure forms.



(+)-1-Deoxynojirimycine (**1**) (-)-1-Azafagomine (**2**) (±)-5-*epi*-1-Azafagomine (**3**)

Figure 1 Structure of some known iminosugars.

The synthesis of homochiral (-)-1-azafagomine (**2**) was accomplished by Bols and co-workers through a synthetic sequence based on the Diels-Alder cycloaddition to 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) **4** to achiral dienes: 2,4-pentadienoic acid, methyl 2,4-pentadienoate, and 2,4-pentadienol (**5**).[4] The racemic cycloadduct **6** obtained from 2,4-pentadienol and PTAD was resolved by lipase-mediated transesterification. The olefin portion of each enantiomer's precursor of **2** was oxidized to oxirane and further opened under highly acidic conditions to yield the glucosyl framework of 1-azafagomine, compound **7**. After hydrazinolysis, both enantiomers of 1-azafagomine were obtained in 9 % total yield[5] (Scheme 1). Osmilation of the double bond on the racemic cycloadduct **6** led to racemic diol **8**, which after hydrazinolysis gave 5-*epi*-1-azafagomine (**3**). Bols[3] also achieved the synthesis of (-)-1-azafagomine (**2**) from relatively expensive L-xylose in six steps. L-2,3,5-Tribenzyl xylofuranose was isolated as an intermediate after three steps with no explicit yield. 1-Azafagomine was then isolated in 37 % overall yield from this intermediate.[6,7]



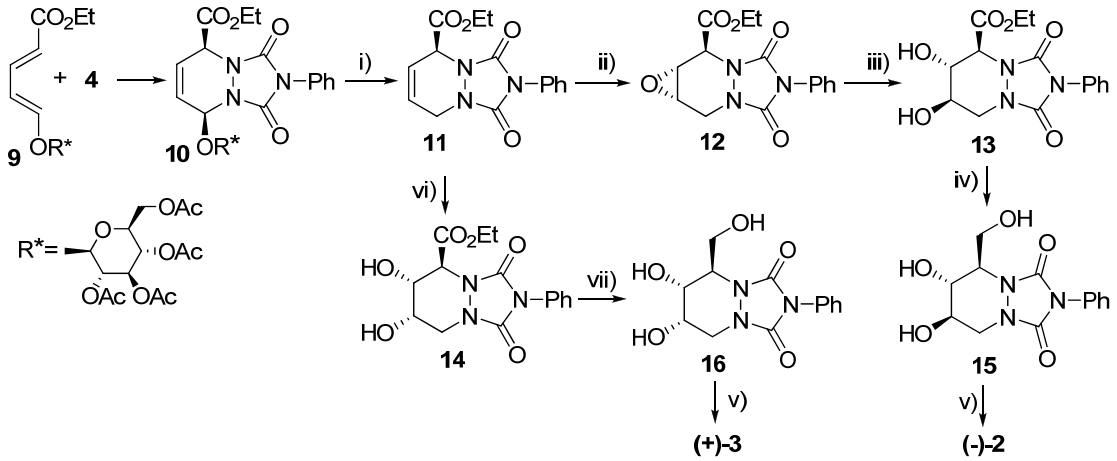
Scheme 1

Alternatives to the enzymatic resolution of racemic adducts of type **6** are desirable for the production of chiral synthons for further elaboration into homochiral compounds. Stoodley, in the 1990's, combined 2,4-pentadienoates, bearing a tetraacetyl glucosyl chiral auxiliary in the position 1, compound **9a**, with PTAD to obtain cycloadduct **10** in 70 % yield and in a high degree of diastereoselectivity (Scheme 2).[8,9] The chemistry of cycloadduct **10** had been pushed forward for the synthesis of dehydropiperazic acid, a non proteinogenic amino acid constituent of antrimycins-linear heptapeptides with antitubercular activity.[10] Lately, dienes bearing oxazolidinone chiral auxiliary were combined with PTAD to generate (*S*)-piperazinic acid.[11] To the best of our knowledge, nobody has merged the Stoodley cycloaddition entry into chiral alkenes of type **11** with Bols' olefin functionalization methodology for synthetizing enantiopure iminosugars.

3. Results and discussion

3.1. New Synthetic Sequence for Preparing Homochiral (-)-1-Azafagomine and (+)-5-epi-1-Azafagomine

In this paper we report a new synthetic route for obtaining homochiral (-)-1-azafagomine (-)-**2** and (+)-5-*epi*-1-azafagomine (+)-**3** from chiral alkene (-)-**11** (Scheme 2).



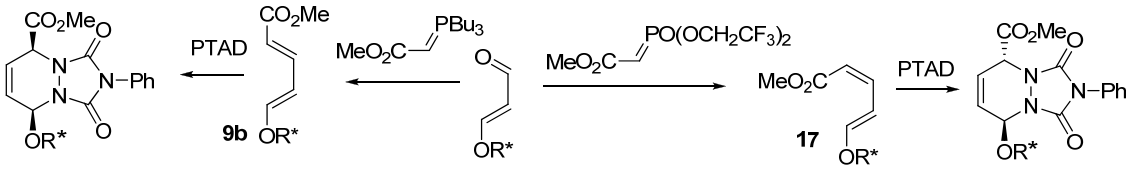
Scheme 2

Reagents: i) Et_3SiH, TFA, DCM, 5h, rt, 61 %; ii) oxone®, CF_3COCH_3, $NaHCO_3$, CH_3CN/H_2O (3.5:2), 24h, 65 % iii) H_2O (exc.), H_2SO_4 (cat.), reflux, 8h, 52 %; iv) $NaBH_4$ (3 eq.), EtOH, 3d, rt, 59 %; v) $NH_2NH_2.H_2O$, 100 ºC, 18h, 68 % (-)-**2**; 64 % (+)-**3**; vi) OsO_4, NMO, Acetone:H_2O (2:1), 5d, rt, 79 %; vii) $NaBH_4$ (3 eq.), EtOH, 3d, rt, 52 %.

Cycloadduct **10** was submitted to reductive cleavage with triethylsilane, according to Stoodley's protocol, to generate known compound (-)-**11**.[9] Treatment of **11** with oxone/trifluoroacetone in the presence of $NaHCO_3$ at room temperature for 1 day generated a 3:1 mixture of oxiranes as reported previously by Bols for his racemic compounds.[4] Selective crystallization afforded the major isomer **12** in 65 % yield. Opening of oxirane **12** was achieved with total regio- and stereoselectivity by refluxing in aqueous H_2SO_4 giving **13**. Osmilation of compound **11** produced *cis*-diol **14** with total stereoselectivity. Selective reduction of *trans*-diol **13** and *cis*-diol **14** with $NaBH_4$ gave, respectively, triols **15** and **16**. These compounds were further treated with hydrazine under reflux to produce the target compounds: (-)-1-azafagomine (**2**) in 14 % overall yield and (+)-5-*epi*-1-azafagomine (**3**) in 26 % overall yield from alkene (-)-**11** (Scheme 2). Whereas (-)-1-azafagomine **2** is a known compound, (+)-5-*epi*-1-azafagomine **3** was obtained displays NMR spectra compatible with the data published for the racemic compound **3**. The specific optical rotation obtained for (+)-5-*epi*-1-azafagomine is $[\alpha]_D$ = +65º (*c* 0.70, H_2O). The specific optical rotation value measured for (-)-1-azafagomine, $[\alpha]_D$ = -20º (*c* 0.85, H_2O), differs from the one reported in the literature, $[\alpha]_D$ = -9.8º (*c* 0.85, H_2O).[3]

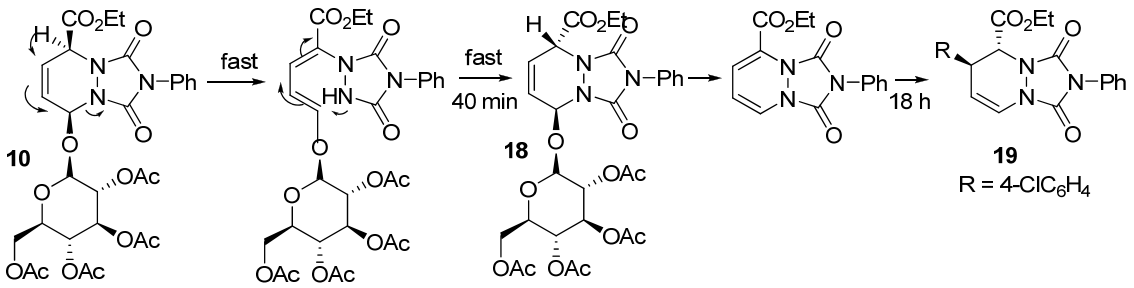
3.2. New Synthetic Sequence for Preparing Homochiral 1-N-Phenyl Carboxamide Derivatives of 1-Azafagomine (+)-22 and (−)-22

Stoodley was able to prepare the precursors of (-)-**22** and (+)-**22** from (*E*,*E)*-diene **9b** and (*E*,*Z*)-diene **17**, respectively, by the method described in Scheme 3.[9]



Scheme 3 Stoodley´s synthetic sequence for precursors related to compounds (-)-**2**, (-)-**22** and (+)-**22**.

(*E*,*E*)-Diene **9b** was isolated in 70 % yield and (*E*,*Z*)-diene **17** in 14 % yield. Applying Still's olefination, the yield of the (*E*,*Z*)-diene could be improved to 36 %[9] (Scheme 3). Having in mind the shortcomings in the synthesis of compound **17**, epimerization of compound **10** obtained by Stoodley's method was tried in various conditions: (i) triethylamine in MeOH, (ii) NaN_3 in MeOH, and (iii) triethylamine/*p*-chlorothiophenol in MeOH (Scheme 4). When triethylamine was the sole reagent, isolation of compound **18** was difficult because of the competing elimination of glucosyl moiety giving the 1,3-diene compound. The same applied for the attempt with NaN_3. The mixture of triethylamine/*p*-chlorothiophenol afforded after 40 min of reaction 88 % yield of compound **18**. This represents an important achievement concerning the synthesis of compound **18**. Extending the reaction time, a Michael addition of *p*-chlorothiophenol occurs, leading to compound (±)-**19** (Scheme 4).



Scheme 4 Epimerization of compound **10** into compound **18**.

Reagents: NEt_3, *p*-chlorothiophenol, MeOH, 0ºC -> rt.

The structure of compound **18** was unambiguously confirmed by X-ray crystallography (Figure 2).

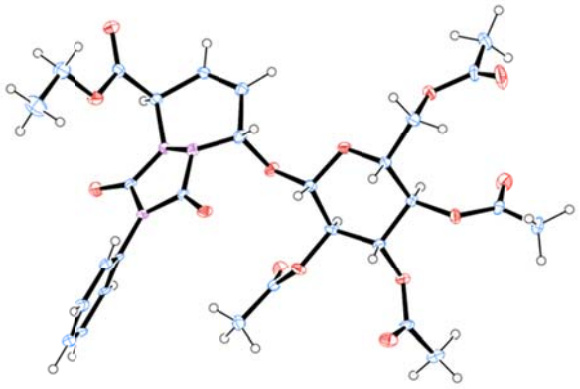


Figure 2 ORTEP view of compound **18**.

3.3. Reduction of the Ester and Urea Groups in the Triazolidinone Moiety

*i) In the Synthesis of Compound (-)-**21***

When compound (-)-**11** was treated with 7 equivalents of freshly opened $LiAlH_4$, a new compound formed, according to ^1H NMR spectroscopy. If the $LiAlH_4$ was not strictly fresh, a mixture of two compounds was observed on the ^1H NMR spectrum. Further treatment with $LiAlH_4$ converted the mixture into the same compound observed before. The structure of the intermediate in the reduction process was determined by X-ray crystallography and identified as compound **20** (Figure 3).

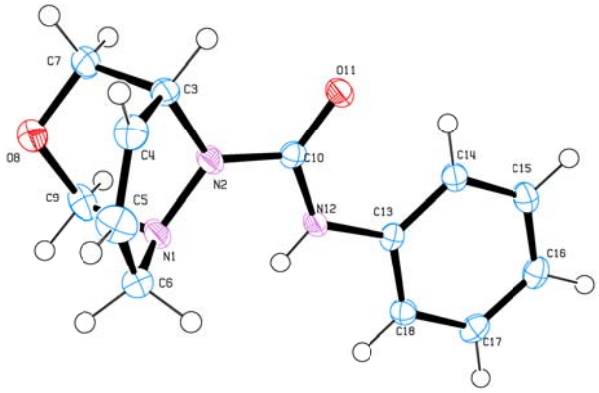
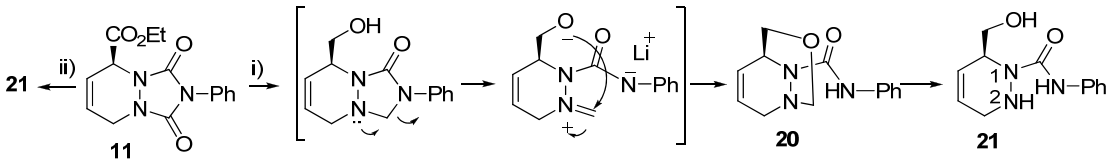


Figure 3 ORTEP view of compound **20**.

Knowledge of the bridged structure of compound **20** allowed us to propose a plausible mechanism for its formation and the formation of compound **21** (Scheme 5).



Scheme 5

Reagents: i) $LiAlH_4$ (7 eq.)[a)], THF, 4h, 0 ºC -> rt, 86 %; ii) $LiAlH_4$ (15 eq.)[b)], THF, 4h, 0 ºC -> rt, 48 %.

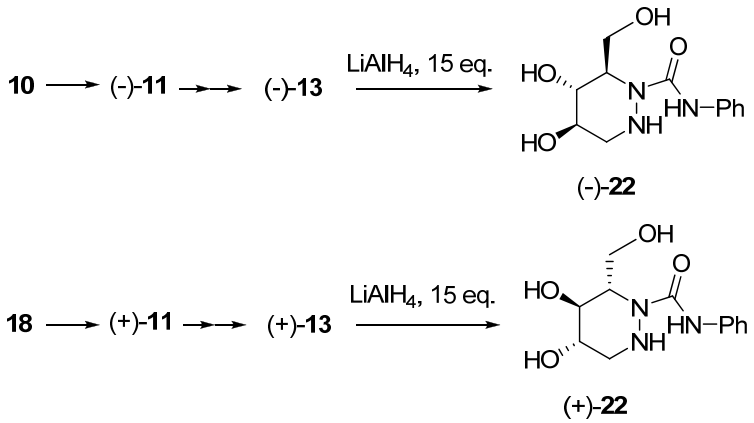
a) from a long-time opened bottle

b) from a recently opened bottle

The Schiff salt initially formed by reduction of one of the carbonyl groups is trapped by internal nucleophilic attack of the alcohol function. A large excess of hydride was necessary to cleave intermediate **20** to final product **21**. Compounds **20** and **21** display a major difference in their ^{13}C NMR spectra: a peak at δ_C = 86.3 ppm, assigned to the methylene attached to the oxygen and nitrogen atoms in compound **20**, is not apparent in the ^{13}C NMR spectrum of compound **21**.

*ii) In the Synthesis of Compounds (-)-**22** and (+)-**22***

Attempted epoxidation of compound **21** was unsuccessful, leading to a complex mixture. As an alternative, compound (-)-**13** was subjected to treatment with $LiAlH_4$ in THF to give compound (-)-**22**. The synthesis of compound (+)-**22** was obtained from **18** (Scheme 4) by reductive cleavage of the glucosyl moiety to give (+)-**11** followed by the functional group transformation described in Scheme 6.



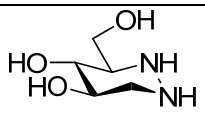
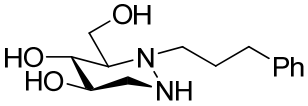
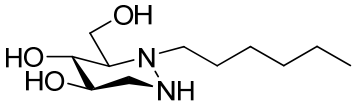
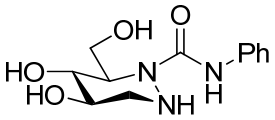
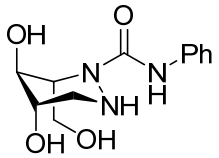
Scheme 6

The enantiopure compounds (-)-1-*N*-phenyl carboxamide 1-azafagomine (-)-**22** and (+)-1-*N*-phenyl carboxamide 1-azafagomine (+)-**22** were obtained following the same sequence of reactions in 29 and 10 % overall yield starting from compounds **10** and **18**, respectively.

3.4. 1-*N*-Phenyl Carboxamide Derivatives of 1-Azafagomine: New Leads for the Synthesis of Potent α-Glycosidase Inhibitors

A structure-activity relationship study of a series 2-*N*-alkylated 1-azafagomines as glycosidase inhibitors revealed that these compounds are better β-glycosidase inhibitors than α-glycosidase inhibitors. Moreover, the inhibition constant (*Ki*) was found to be dependent on the chain length. The best results have been obtained with the *N*-propylphenyl derivative **23** (*Ki* = 0.032 *μ*M) and the *N*-hexyl derivative **24** (*Ki* = 0.055 *μ*M)[12] (Table 1).

Table 1 *Ki* Values (μM) for the inhibition of α- and β-glucosidases by compounds **22** and other azasugars at different pH values.

Compound		α-glucosidase (bakers' yeast)	β-glucosidase (almonds)	α/β-selectivity
	(-)-**2**[3]	6.90[a]	0.32[a]	22
	**23**[12]	158[a]	0.032[a]	4938
	**24**[12]	278[a]	0.55[a]	5054
	(-)-**22**	3.36[b] [c,d]	14.7[b] 67.4[c]	0.23
	(+)-**22**	10.6[b] [c,d]	25.2[b] 90.0[c]	0.42

[a] pH 6.8. [b] pH 7.0. [c] pH 5.0. [d] Enzyme inactive.

The *N*-propylphenyl derivative **23** is around an order of magnitude more effective as a β-glucosidase inhibitor than (-)-1-azafagomine **2**. On the other hand, derivative **23** is a much weaker inhibitor of α-glucosidase than its parent compound (**2**), making compound **23** a potent inhibitor selective for β-glucosidase.[12]

The most striking results of the inhibition studies with the 1-*N*-phenyl carboxamide derivatives of 1-azafagomines **22** are *Ki* values toward α-glucosidase substantially lower than the *N*-propylphenyl derivative **23**. Compound (-)-**22**, displaying the same stereochemistry as (-)-1-azafagomine **2**, is around two times more active, whereas its isomer (+)-**22** is slightly less active. Both enantiomers of compound **22** display lower activity toward β-glucosidase than their parent compound **2** and the *N*-propylphenyl derivative. A moderate α/β selectivity was observed for compounds **22**. The low *Ki* values obtained for compounds **22** toward α-glucosidase suggests an efficient recognition mechanism between both enantiomers and the enzyme. The levorotatory isomer was slightly more active than the dextrorotatory isomer (Table 1). This observation is in contrast with the results reported by Bols, who demonstrated that

(-)-1-azafagomine is the active enantiomer, whereas (+)-1-azafagomine is virtually inactive toward the same α-glucosidase that was used in this study.[3]

The yeast α-glucosidase enantioselective discrimination toward (+)-**22** and (-)-**22** was studied using molecular docking methodologies. This enzyme, as well as the *Saccharomyces cerevisiae* enzyme used for the homology modelling,[13] belongs to the glycoside hydrolase family 13 (GH 13). This family of retaining glucosidases is characterized by strong recognition of the glucoside moiety of synthetic *p*-nitrophenyl glucosides and heterogeneous substrates such as sucrose, while being inactive toward hydration of D-glucal and the hydrolysis of *p*-nitrophenyl α-2-deoxyglucosides.[14,15] The active site structure in Figure 4 illustrates that this enzyme retains the nucleophile aspartate 214 and the catalytic residues glutamate 276 and aspartate 349. Our theoretical binding affinity estimate for (+)-**22** and (-)-**22** against yeast α-glucosidase are of -7.8 and -7.5 kcal/mol, respectively. The binding affinity free energy difference between the two enantiomers is within the docking standard error (∼2 kcal/mol), and consequently, it suggests low enantiomeric discrimination of (+)-**22** and (-)-**22**. However, our experimental *Ki* data (Table 1) indicates a preferential binding of (-)-**22** when compared to (+)-**22**. This discrepancy can be explained by the lack of mobility of enzyme to reorganize during the docking experiments and, consequently, to properly recognize the most potent enantiomeric compound, (-)-**22**. Despite this, the observation of the binding pose of both enantiomers of **22** provides a structural explanation of their binding mechanism (Figure 4) and a rational approach for their future improvement. These complexes correspond to lowest binding energy pose. They belong to the most populated cluster of docking solutions, 7 and 8 docking poses out of 20, respectively, for each enantiomer.

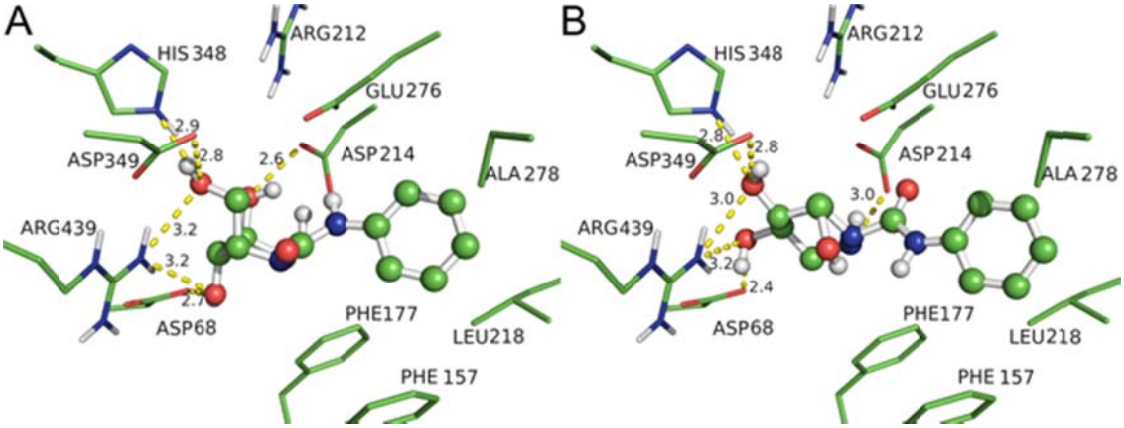


Figure 4 Structure of the lowest binding free energy complexes between yeast *α*-glucosidase binding site and the enantiomers of compound **22**: (A) (+)-**22** and (B) (-)-**22**. The figure is rendered with Corey-Pauling-Koltun (CPK) colouring scheme. Selected side-chain residues of the yeast α-glucosidase binding pocket are rendered in sticks and labelled with the three-letter amino acid code name and sequence residue number. Compounds are rendered in ball-and-stick style.

The *α*-glucosidase enzyme active site is characterized by two distinct regions: a highly polar region due to the presence of histidine 348, glutamate 276, aspartate 68, 214, and 349, and arginine 212 and 439 and a hydrophobic pocket flaked by phenylalanine 157 and 177, leucine 218, and alanine 278 (Figure 4). The binding affinity between the two **22** enantiomers and yeast α-glucosidase is the result of several strong hydrogen bonding interactions between two hydroxyl and amine groups of (+)-**22** and (-)-**22** with aspartate 68, 214, and 349, arginine 212 and 439, and histidine 348 of the α-glucosidase enzyme active site. The highlighted nonbonded interactions of (-)-**22** with histidine 348, arginine 439, and aspartate 68 are shorter for this enantiomer when compared to (+)-**22**, suggesting a stronger interaction of (-)-**22** with the enzyme. On the basis of these observations, the molecular modelling study suggests that the binding affinity can be improved either by (a) increasing the length of the *N*-phenyl-1-carboxamide moiety or (b) introducing donor/acceptor moieties on the *p*-position of the aromatic ring. These avenues are being currently pursued in order to improve the binding affinity and, ideally, selectivity.

4. Conclusions

In this paper we report the preparation of homochiral 1-azafagomine (-)-**2** and (+)-5-*epi*-1-azafagomine (+)-**3**. The synthetic route devised merges Stoodley diastereoselective Diels-Alder cycloaddition methodology with Bols protocol for functionalizing alkenes into molecules bearing sugar-like frameworks. Novel 1-*N*-phenyl carboxamide derivatives of 1-azafagomine **22** were obtained in enantiomeric pure forms. The epimerization of cycloadduct **10** was revealed to be the key step in the synthesis of the dextrorotatory compound **22**. This methodology represents an advantageous alternative to other more conventional approaches for obtaining enantiopure (+)-**2** (not isolated in this work) and its derivatives (e.g., *N*-phenyl carboxamides). Compounds **22** were tested as inhibitors against α- and β-glucosidases. Both enantiomeric forms of **22** are potent inhibitors of α-glucosidase, in contrast to the current wisdom that only (-)-**2** enantiomer of 1-azafagomine is active toward α- and β-glucosidase. The low *Ki* value determined toward α-glucosidase inhibition is particularly relevant in comparison with its analogue *N*-propylphenyl azafagomine, the compound in Table 1 with a closer side chain length. The molecular recognition mechanism between the enantiomeric compounds **22** and the α-glucosidase studied by molecular modeling has shown that the aromatic group is accommodated in a hydrophobic pocket of the enzyme binding site with polar characteristics at its end. This evidence has provided further clues for improving the binding affinity and, possibly, the α/β selectivity by increasing the length of the *N*-carboxamide moiety and the introduction of donor/acceptor hydrogen bond groups on the aromatic ring.

The results of this study suggest that 1-*N*-phenyl carboxamide derivatives of 1-azafagomine are potential new leads for the synthesis of potent α-glycosidase inhibitors.

5. Experimental section

5.1. General Methods

Solvents were distilled under anhydrous conditions. The (*S*)-ethyl 2-phenyl-2,4,9-triazabicyclo[4.3.0]non-6-ene-1,3-dione-5-carboxylate (-)-**11** was obtained according to Stoodley's protocol for the (*S*)-methyl carboxylate derivative; 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide (ABG) was prepared according to the literature,[16]

and potassium 3-hydroxypropenal[17] was combined to ABG[18] followed by addition of tributylphosphorane.[9] The diene obtained was subjected to 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) to obtain the adduct **10**. The glucose moiety was removed by reduction with triethylsilane.[10] Compound **7** (R = CH_2OH) was obtained according to the literature.[4] Functionalization of the double bond was obtained by osmilation with OsO_4 in acetone/water or with oxone, trifluoromethylacetone, in the presence of $NaHCO_3$ and aqueous acetonitrile. Reduction of the oxazolidinone was done either with freshly opened $LiAlH_4$ 1 M in THF or with long-term opened bottles (over a month) of $LiAlH_4$ 1 M in THF. All reagents were purchased and used without further purification. Glassware was dried prior to use. Compounds were purified by dry flash chromatography using silica 60, <0,063 mm and water pump vacuum or by flash chromatography using silica 60Å 230−400 mesh as stationary phases. TLC plates (silica gel 60 F_{254}) were visualized either at a UV lamp or in I_2.

5.2. Synthesis of ethyl 5-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-2,4-pentadienoate 9

To a solution of ethyl tributyl phosphorane[9] (3.37 g; 11.70 mmol) in DCM (15 mL) was added 3-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-1-propenal[17] (1.32 g; 3.42 mmol); the orange solution formed was stirred at rt for 24 h. The solvent was evaporated, giving an oil subjected to dry-flash chromatography (petroleum ether/diethyl ether; gradient of polarity) (**9**; 1.17 g; 63 %).

$[\alpha]_D^{20}$ +27.0° (*c* 1, CH_2Cl_2). ν_{max} (nujol) 2955, 2934, 1736, 1698, 1635 cm^{-1}. ^1H NMR (δ_H, 300 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, CH_3), 2.01, 2.03, 2.04, 2.08 (12H, 4 × s, 4 × CH_3CO_2), 3.81 (1H, ddd, *J* 9.0, 6.0, 3.0 Hz, H-5′), 4.13 (1H, dd, *J* 9.0, 3.0 Hz, H-6′), 4.18 (2H, q, *J* 6.0 Hz, CH_2), 4.26 (1H, dd, *J* 12.0, 3.0 Hz, H-6′), 4.87 (1H, d, *J* 9.0 Hz, H-1′), 5.08−5.29 (3H, m, H-2′ + H-3′ + H-4′), 5.78 (1H, d, *J* 15.0 Hz, H-2), 5.90 (1H, t, *J* 12.0 Hz, H-4), 6.81 (1H, d, *J* 12.0 Hz, H-5), 7.20 (1H, dd, *J* 15.0, 12.0 Hz, H-3) ppm. ^{13}C NMR (δ_C, 75.5 MHz, $CDCl_3$) 14.2 (CH_3), 20.5, 20.5, 20.7 (CH_3CO_2), 60.1 (CH_2), 61.6 (C-6′), 67.8, 70.6, 72.3 (C-2′, C-3′, C-4′), 72.4 (C-5′), 99.7 (C-1′), 110.1 (C-4), 118.7 (C-2), 140.9 (C-3), 152.6 (C-5), 167.0 (C=O ester), 169.1, 169.2, 170.1, 170.5 (CH_3CO_2) ppm.

5.3. Synthesis of (5*S*,8*S*)-ethyl 8-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-2-phenyl-2,4,9-triazabicyclo[4.3.0]non-6-eno-1,3-dione-5-carboxylate 10

To a solution of diene **9** (1.31 g; 2.86 mmol) in DCM (15 mL) was added 4-phenyl-1,2,4-triazole-3,5-dione (0.50 g; 2.86 mmol), giving a red colored solution that quickly lost its color. The reaction mixture was stirred for a further 30 min and then evaporated. The residue was tritured with ethyl ether. A white solid was formed and filtered, giving the title compound (**10**; 1.302 g; 70 %).

$[\alpha]_D^{20}$ +23,8° (*c* 1, CH_2Cl_2). ν_{max} (nujol) 2954, 2853, 1743, 1620, 1635, 1218 cm^{-1}. ^1H NMR (δ_H, 300 MHz, $CDCl_3$) 1.35 (3H, t, *J* 6.0 Hz, CH_3), 2.00, 2.01, 2.02, 2.04 (12H, 4 × s, 4 × CH_3CO_2), 3.87 (1H, ddd, *J* 12.0, 6.0, 3.0 Hz, H-5′), 4.05 (1H, dd, *J* 12.0, 3.0 Hz, H-6′), 4.27 (1H, dd, *J* 15.0, 9.0 Hz, H-6′), 4.34 (2H, dq, *J* 7.2, 1.2 Hz, CH_2), 5.01 (2H, m, H-5 + H-2′), 5.09 (1H, t, *J* 9.9 Hz, H-4′), 5.19−5.26 (2H, m, H-3′ + H-1′), 6.06-6.12 (2H, m, H-8 + H-7), 6.19-6.26 (1H, m, H-6), 7.39-7.56 (5H, m, Ph) ppm. ^{13}C NMR (δ_C, 75.5 MHz, $CDCl_3$) 14.0 (CH_3), 20.5, 20.6, 20.6 (CH_3CO_2), 56.7 (C-5), 61.5 (C-6′), 62.9 (CH_2), 67.8 (C-4′), 71.0 (C-2′), 72.1 (C-5′), 72.8 (C-3′), 74.6 (C-8), 97.2 (C-1′), 123.3 (C-7), 124.9 (C-6), 125.4 (CH, Ph), 128.5 (CH, Ph), 129.2 (CH, Ph), 130.7 (Cq, Ph), 150.2 (C=O), 151.4 (C=O), 165.6 (C=O ester), 169.4, 169.4, 170.2, 170.7 (CH_3CO_2) ppm. HRMS (FAB): calcd for $C_{29}H_{33}N_3O_{14}$: 648.2041; found, 648.2041.

5.4. Synthesis of (*S*)-ethyl 2-phenyl-2,4,9-triazabicyclo[4.3.0]-non-6-ene-1,3-dione-5-carboxylate (-)-11

To a solution of the cycloadduct **10** (1.31 g; 2.03 mmol) in DCM (20 mL) were added triethylsilane (12.7 mL; 0.78 mol) and trifluoroacetic acid (12.7 mL; 0.17 mol). The resulting yellow suspension was kept under stirring at rt for 5 h. The solvent was removed under vacuum and the residue redissolved in DCM (30 mL). The solution was washed with an aq saturated solution of $NaHCO_3$ (3 × 50 mL) and water (50 mL). The combined organic layers were dried over magnesium sulphate and filtered, and the solvent was evaporated. From the residual oil crystallized a white solid that was washed with diethyl ether and proved to be the title compound ((-)-**11**; 0.313 g; 51 %).

$[\alpha]_D^{20}$ −311.0° (*c* 2.15, CH_2Cl_2). mp 140−142 °C. ν_{max} (nujol) 2954, 2923, 1742, 1714 cm^{-1}. ^1H NMR (δ_H, 300 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, CH_3), 3.99-4.06 (1H, dm, H-8), 4.25 (2H, q, *J* 7.2 Hz, CH_2), 4.38-4.45 (1H, dm, H-8), 5.09-5.12 (1H, m, H-5),

6.05−6.16 (2H, m, H-6 + H-7), 7.38−7.57 (5H, m, Ph) ppm. ^{13}C NMR (δ_C, 75.5 MHz, $CDCl_3$) 14.1 (CH_3), 43.1 (C-8), 55.9 (C-5), 62.4 (CH_2), 119.7 (C-6 or C-7), 123.3 (C-6 or C-7), 125.6 (CH, Ph), 128.2 (CH, Ph), 129.1 (CH, Ph), 131.1 (Cq, Ph), 152.3 (C=O), 153.3 (C=O), 166.7 (C=O ester) ppm. EA calcd for $C_{15}H_{15}N_3O_4$: C, 59.79%; H, 5.02%; N, 13.95%; found: C, 59.90%; H, 4.93%; N, 13.86%.

5.5. Synthesis of (*R*)-ethyl 2-phenyl-2,4,9-triazabicyclo[4.3.0]-non-6-ene-1,3-dione-5-carboxylate (+)-11

To a solution of the cycloadduct **18** (1.03 g; 1.59 mmol) in DCM (25 mL) were added triethylsilane (9.85 mL; 0.78 mol) and trifluoroacetic acid (9.85 mL; 0.17 mol). The resulting yellow solution was kept under stirring at rt for 5 h. The solvent was removed under vacuum, and the residue was redissolved in DCM (25 mL). The solution was washed with an aq saturated solution of $NaHCO_3$ (3 × 25 mL) and water (25 mL). The combined organic layers were dried over magnesium sulphate and filtered, and the solvent was evaporated. From the residual oil crystallized a white solid that was washed with diethyl ether and proved to be the title compound ((+)-**11**; 0.292 g; 61 %).

$[\alpha]_D^{20}$ +370.0° (*c* 1, CH_2Cl_2).

5.6. Synthesis of (5*S*,6*R*,7*S*)-ethyl 6,7-epoxy-2-phenyl-2,4,9-triazabicyclo [4.3.0]nonane-1,3-dione-5-carboxylate (−)-12

To a solution of compound (-)-**11** (0.48 g; 1.59 mmol) in acetonitrile (28.0 mL), water (16.0 mL) and 1,1,1-trifluoracetone (3.21 mL), were added solid $NaHCO_3$ (2.44 g; 29.02 mmol) and oxone® (12.00 g; 39.04 mmol) for 20 min at 0 °C. The mixture was stirred for 18 h. A new portion of solid $NaHCO_3$ (2.44 g; 29.02 mmol) and oxone® (12.00 g; 39.04 mmol) was added and stirred for another 4 h. Then water (100 mL) was added to the reaction mixture, which was extracted with $CHCl_3$ (8 × 40 mL). The organic layers were combined and dried with magnesium sulphate. After removal of the solvent, recrystallization with diethyl ether gave a white solid identified as the title compound ((-)-**12**; 0.329 g; 65 %).

$[\alpha]_D^{20}$ -238.0° (*c* 0.8, CH_2Cl_2). mp 218−220 °C. ν_{max} (nujol) 2950, 2923, 1775, 1750, 1715, 1458, 1094,1034 cm^{-1}. ^{1}H NMR (δ_H, 300 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz, CH_3),3.53-3.65 (2H, m, H-7 + H-8), 3.89 (1H, dd, *J* 5.6, 3.8 Hz, H-6), 4.19-4.40 (2H, m,

CH_2), 4.47 (1H, dd, *J* 13.6, 1.4 Hz, H-8), 5.01 (1H,d, *J* 5.7 Hz, H-5), 7.33-7.51 (5H, m, Ph) ppm. ^{13}C NMR (δ_C, 75.5 MHz, $CDCl_3$) 14.1 (CH_3), 43.0 (C-8), 49.0 (C-6), 50.1 (C-7), 54.8 (C-5), 62.7 (CH_2), 125.6 (CH, Ph), 128.4 (CH, Ph), 129.1 (CH, Ph), 130.9 (Cq, Ph), 153.3 (C=O), 153.56 (C=O), 165.6 (C=O ester) ppm. HRMS (FAB): calcd for $C_{15}H_{16}N_3O_5$: 318.1089; found, 318.1087.

5.7. Synthesis of (5*R*,6*S*,7*R*)-ethyl 6,7-epoxy-2-phenyl-2,4,9-triazabicyclo [4.3.0]nonane-1,3-dione-5-carboxylate (+)-12

To a solution of compound (+)-**11** (0.37 g; 1.21 mmol) in acetonitrile (21.1 mL), water (12.3 mL), and 1,1,1-trifluoracetone (2.40 mL) were added solid $NaHCO_3$ (1.86 g; 29.02 mmol) and oxone® (9.15 g; 39.04 mmol) for 20 min at 0 °C. The mixture was stirred for 18 h. A new portion of solid $NaHCO_3$ (1.86 g; 29.02 mmol) and oxone® (9.15 g; 39.04 mmol) was added and stirred for another 4 h. Then water (60 mL) was added to the reaction mixture, which was extracted with DCM (10 × 40 mL). The organic layers were combined and dried with magnesium sulphate. After removal of the solvent, recrystallization with diethyl ether gave a white solid identified as the title compound ((+)-**12**; 0.233 g; 60 %).

$[\alpha]_D^{20}$ +232.8° (*c* 0.8, CH_2Cl_2).

5.8. Synthesis of (5*S*,6*R*,7*R*)-ethyl 6,7-dihydroxy-2-phenyl-2,4,9-triazabicyclo[4.3.0]nonane-1,3-dione-5-carboxylate (−)-13

To a solution of epoxide (-)-**12** (0.20 g; 0.63 mmol) in water (30 mL) was added concentrated H_2SO_4 (0,5 mL), and the mixture was refluxed for 8 h. After this time, solid $NaHCO_3$ (0.86 g; 10.24 mmol) was added, and the water was evaporated until dryness. The residue was dissolved in ethyl acetate (100 mL) and washed with NaCl (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (100 mL). The organic phases were combined and dried with magnesium sulphate, filtered, and concentrated in the rotary evaporator. The yellowish solid obtained was washed with diethyl ether and found to be the title compound ((-)-**13**; 0.110 g; 52 %).

$[\alpha]_D^{20}$ −22.8° (*c* 2, acetone). ν_{max} (nujol) 3596−3540, 2954, 2923, 1729, 1698, 1122, 1088 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 1.24 (3H, m, CH_3), 3.64 (1H, d, *J* 12.0 Hz, H-8), 3.95 (1H, bs, H-7), 3.99 (1H, d, *J* 12.8 Hz, H-8), 4.13-4.28 (2H, m, CH_2), 4.46 (1H, t,

J 2.8 Hz, H-6), 4.74 (1H, d, *J* 2.8 Hz, H-5), 7.38−7.50 (5H, m, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 13.9 (CH_3), 44.3 (C-8), 59.4 (C-5), 62.6 (CH_2), 65.9 (C-7), 67.4 (C-6), 125.9 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 131.0 (Cq, Ph), 152.1 (C=O), 154.1 (C=O), 167.3 (C=O ester) ppm. HRMS (FAB): calcd for $C_{15}H_{18}N_3O_6$: 336.1196; found: 336.1207.

5.9. Synthesis of (5*R*,6*S*,7*S*)-ethyl 6,7-dihydroxy-2-phenyl-2,4,9-triazabicyclo[4.3.0]nonane-1,3-dione-5-carboxylate (+)-13

To a solution of epoxide (+)-**12** (0.23 g; 0.73 mmol) in water (35 mL) was added concentrated H_2SO_4 (0.7 mL), and the mixture was refluxed for 10 h. After this time, solid $NaHCO_3$ (1.42 g; 16.90 mmol) was added, and the water was evaporated until dryness. The residue was dissolved in ethyl acetate (100 mL) and washed with NaCl (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The organic phases were combined and dried with magnesium sulphate, filtered, and concentrated in the rotary evaporator. The yellowish solid obtained was washed with diethyl ether and found to be the title compound ((+)-**13**, 0.121 g; 49 %).

$[\alpha]_D^{20}$ +26.9° (*c* 0.5, acetone).

5.10. Synthesis of (5*S*,6*R*,7*S*)-ethyl 6,7-dihydroxy-2-phenyl-2,4,9-triazabicyclo[4.3.0]nonane-1,3-dione-5-carboxylate 14

To a solution of (-)-**11** (0.30 g; 1.00 mmol) in acetone (1 mL) and water (0.5 mL) were added 4-methylmorpholine *N*-oxide (0.18 g; 1.49 mmol) and a solution of OsO_4 in water 4 % (108 mL). The mixture of stirred for 5 days. Then an aq. solution of $Na_2S_2O_3$ 5 % (25 mL) was added to mixture, which was stirred for 15 min. The solution was extracted with ethyl acetate (4 × 30 mL) and the organic phases were washed with water (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to give a white solid (**14**; 0.26 g; 79 %).

$[\alpha]_D^{20}$ -110.6° (*c* 2.05, acetone); ν_{max} (nujol) 3425, 1768, 1749, 1736, 1287, 1204 cm^{-1}. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, CH_3), 3.35 (1H, d, *J* 10.8 Hz, H-8), 3.83 (1H, ddd, *J* 10.0, 5.2, 2.8 Hz, H-7), 4.03 (1H, dd, *J* 11.6, 5.2 Hz, H-8), 4.24 (2H, q, *J* 7.2 Hz, CH_2), 4.52 (1H, t, *J* 2.8 Hz, H-6), 4.90 (1H, d, *J* 3.6 Hz, H-5), 7.40−7.49 (5H, m, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 14.0 (CH_3), 43.2 (C-8), 60.6 (C-5), 62.8

(CH2), 65.1 (C-7), 67.2 (C-6), 125.8 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 130.9 (Cq, Ph), 151.4 (C=O), 153.8 (C=O), 166.4 (C=O ester) ppm. HRMS (FAB): calcd for $C_{15}H_{18}N_3O_6$: 336.1196; found: 336.1195.

5.11. Synthesis of (5*S*,6*R*,7*R*)-6,7-dihydroxy-5-hydroxymethyl-2-phenyl-2,4,9-triazabicyclo[4.3.0]nonane-1,3-dione 15

To a solution of the diol (-)-**13** (0.07 g; 0.22 mmol) in ethanol (3 mL) was added $NaBH_4$ (8 mg; 0.22 mmol) under magnetic stirring at room temperature. After 1 h, an aliquot was quenched with HCl 0.4 M, extracted with ethyl acetate, dried over magnesium sulphate, and concentrated. ^{1}H NMR spectrum showed that the reaction was not completed, so a new amount of $NaBH_4$ (8 mg; 0.22 mmol) was added, and the mixture was stirred for another 4 h. The procedure was repeated with addition of $NaBH_4$ (8 mg; 0.22 mmol). The reaction was quenched with aq. HCl 0.4 M (4.4 mL); the mixture was stirred for 10 min and evaporated. The residue was dissolved in water (10 mL) and extracted with ethyl acetate (8 × 15 mL). The organic phases were combined and dried over magnesium sulphate. Evaporation of the solvent gave a white solid identified as the title compound (**15**, 0.037 g; 59 %).

$[\alpha]_D^{20}$ -70.4° (*c* 1.2, acetone).

The spectroscopic data of the racemic mixture was reported before.[4]

5.12. Synthesis of (5*S*,6*R*,7*S*)-6,7-dihydroxy-5-hydroxymethyl-2-phenyl-2,4,9-triazabicyclo[4.3.0]-nonane-1,3-dione 16

To a solution of the diol **14** (0.224 g; 0.73 mmol) in ethanol (7 mL) was added $NaBH_4$ (0.083 g). The mixture was stirred at room temperature overnight. After addition of aq. HCl 0.4 M (15.3 mL), the mixture was stirred for 15 min. Then the solvent was removed under vacuum, and the residue was dissolved in water (20 mL) and saturated aq. solution of $NaHCO_3$ (10 mL) and extracted with ethyl acetate (14 × 25 mL). The organic layers were combined, dried over magnesium sulphate, and concentrated. It obtained a white solid identified as the title compound (**16**, 0.112 g; 52 %).

$[\alpha]_D^{20}$ -8.0° (*c* 0.75, acetone).

The spectroscopic data of the racemic mixture was reported before.[4]

5.13. Synthesis of ethyl (5*R*,8*S*)-8-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-2-phenyl-2,4,9-triazabiciclo[4.3.0]non-6-ene-1,3-dione-5-carboxylate 18

To a suspension of compound **10** (0.22 g; 0.33 mmol) in methanol (5 mL) were added 4-chorothiophenol (0.10 g; 0.68 mmol) and triethylamine at 0 °C and under magnetic stirring. After 40 min, the solvent was evaporated, and the crude was subjected to dry-flash chromatography (petroleum ether/ether 1:3). The product was obtained as a white solid (**18**; 0.187 g; 88 %).

$[\alpha]_D^{20}$ +219.7° (*c* 1, acetone); mp 154−157 °C. ν_{max} (nujol) 2955, 2924, 1744, 1723, 1226 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2 Hz, CH_3), 1.88, 1.98, 2.02, 2.07 (12H, 4 × s, 4 × CH_3CO_2), 3.74-3.79 (1H, m, H-5′), 4.15 (1H, dd, *J* 12.4, 2.4 Hz, H-6′), 4.23 (2H, q, *J* 7.2 Hz, CH_2), 4.25 (1H, dd, *J* 12.0, 4.4 Hz, H-6′), 4.95 (1H, dd, *J* 9.6, 8.0 Hz, H-2′), 5.07 (1H, t, *J* 10.0 Hz, H-4′), 5.15 (1H, dd, *J* 5.2, 2.0 Hz, H-5), 5.18-5.23 (2H, m, H-1′ + H-3′), 5.96 (1H, d, *J* 4.8 Hz, H-8), 6.07 (1H, ddd, *J* 10.0, 4.4, 2.0 Hz, H-6), 6.31 (1H, ddd, *J* 10.0, 5.2, 0.8 Hz, H-7), 7.27-7.56 (5H, m, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 14.0 (CH_3), 20.5, 20.5, 20.7 (CH_3CO_2), 56.0 (C-5), 61.6 (C-6′), 62.7 (CH_2), 68.0 (C-4′), 71.1 (C-2′), 72.2 (C-5′), 72.6 (C-3′), 76.0 (C-8), 99.6 (C-1′), 123.9 (C-7), 124.1 (C-6), 125.6 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 130.8 (Cq, Ph), 151.5 (C=O), 153.4 (C=O), 166.0 (C=O ester), 169.2, 169.4, 170.1, 170.6 ($CH_3\underline{C}O_2$) ppm. EA calcd for $C_{29}H_{33}N_3O_{14}$: C, 53.79%; H, 5.14%; N, 6.49%; found: C, 53.58%; H, 5.23%; N, 6.38%.

5.14. Synthesis of (*S*)-*N*-phenyl-3-oxa-1,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylate 20

To a solution of ester (-)-**11** (0.205 g; 0.68 mmol) solubilized in dry THF (13 mL) was added $LiAlH_4$ 1 M in THF (7 eq., 5.2 mL), from a flask containing a white deposit, at 0 °C. The mixture was kept under stirring for 4 h at rt. The reaction was quenched with a sequence addition of water (1 drop), aq. NaOH 15 % (2 drops), and water (1 drop), during which time a large amount of H_2 was released. Then a portion of water (15 mL) was added, and the mixture was extracted with ethyl acetate (4 × 25 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (25 mL) and brine (25 mL) and then dried over $MgSO_4$. After evaporation of the ethyl acetate, a yellowish crude crystallized giving **20** (0.088 g; 48 %).

$[\alpha]_D^{20}$ −57.5° (*c* 0.4, $CHCl_3$). ν_{max} (nujol) 3320, 1670, 1604, 1591, 1530 cm^{-1}. ^1H NMR (δ_H, 300 MHz, $CDCl_3$) 3.45 (1H, dd, *J* 18.3, 1.2 Hz, H-8), 3.71 (1H, d, *J* 10.5 Hz, H-4), 3.90 (1H, dd, *J* 2.7, 11.1 Hz, H-4), 4.00 (1H, dd, *J* 18.3, 1.2 Hz, H-8), 4.56 (1H, d, *J* 10.5 Hz, H-2), 4.66 (1H, bs, H-5), 4.69 (1H, d, *J* 10.5 Hz, H-2), 6.07 (2H, bs, H-6 + H-7), 7.04 (1H, t, *J* 7.2 Hz, CH, Ph), 7.31 (2H, t, *J* 7.2 Hz, CH, Ph), 7.49 (2H, d, *J* 7.2 Hz, CH, Ph), 8.00 (1H, bs, NH) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 44.4 (C-5), 50.7 (C-8), 66.7 (C-4), 86.3 (C-2), 118.7 (CH, Ph), 122.9 (CH, Ph), 127.8 (C-7 or C-6), 128.9 (C-6 or C-7), 128.9 (CH, Ph), 138.5 (Cq, Ph), 153.1 (C=O) ppm. HRMS (FAB): calcd for $C_{13}H_{16}N_3O_2$: 246.124252; found: 246.124172.

5.15. Synthesis of (*S*)-6-(hydroxymethyl)-*N*-phenyl-2,3-dihydropyridazine-1(6*H*)-carboxamide 21

To the ester (-)-**11** (0.15 g; 0.5 mmol) solubilized in dry THF (10 mL) was added $LiAlH_4$ 1 M in THF (15 eq.; 13.5 mL), freshly open, at 0 °C. The mixture was kept under stirring for 4 h at rt. The reaction was quenched by a drop of water followed by 2 drops of aq. NaOH 15 % and another drop of water, during which time a large amount of H_2 was released. Then a portion of water (40 mL) was added, and the mixture was extracted with ethyl acetate (5 × 40 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (50 mL) and brine (50 mL) and then dried over $MgSO_4$. After evaporation of the ethyl acetate, a yellowish crude was obtained, from which crystallized a solid (**21**; 0.10 g; 86 %).

$[\alpha]_D^{20}$ -150.8° (*c* 0.4, $CHCl_3$). ν_{max} (nujol) 3359, 3268, 3058, 1636, 1601, 1592, 1536 cm^{-1}. ^1H NMR (δ_H, 300 MHz, $CDCl_3$) 3.30 (1H, bd, *J* 17.2 Hz, H-3), 3.48-3.55 (1H, m, H-3), 3.75 (1H, dd, *J* 10.8, 5.2 Hz, CH_2OH), 3.95 (1H, dd, *J* 11.2, 3.2 Hz, CH_2OH), 4.20 (1H, dd, *J* 11.2, 2.4 Hz, OH), 4.78 (1H, bs, H-6), 5.83 (1H, dm, *J* 8.4 Hz, H-4 or H-5), 6.13 (1H, dm, *J* 8.4 Hz, H-4 or H-5), 7.02 (1H, t, *J* 7.6 Hz, CH, Ph), 7.30 (2H, t, *J* 7.6 Hz, CH, Ph), 7.47 (2H, d, *J* 7.6 Hz, CH, Ph), 8.60 (1H, bs, NH) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 45.3 (C-6), 50.7 (C-3), 65.1 (CH_2OH), 122.7 (CH, Ph), 124.5 (C-4 or C-5), 128.3 (C-5 or C-4), 128.9 (CH, Ph), 138.7 (Cq, Ph), 155.0 (C=O) ppm. HRMS (FAB): calcd for $C_{12}H_{16}N_3O_2$: 234.124432; found: 244.124252.

5.16. Synthesis of (4*R*,5*R*,6*R*)-4,5-dihydroxy-6-(hydroxymethyl)-*N*-phenylhexahydropyridazine-1-carboxamide (−)-22

To a solution of (-)-**13** (0.06 g; 0.18 mmol) in dry THF (8 mL) was added at 0 °C a solution of $LiAlH_4$ 1 M in THF (7 eq.; 2.51 mL). The reaction mixture stirred for 3 h at rt, and then the quenching was followed by sequential addition of 1 drop of water, one drop of aq. NaOH 15 %, and water (20 mL). The aqueous solution was extracted with ethyl acetate (6 × 60 mL). The organic layers were combined, dried, and evaporated, giving an oil that was submitted to PLC (DCM/methanol 10 %), giving the title compound (-)-**22** (0.014 g; 29 %).

$[\alpha]_D^{20}$ -54.4° (*c* 0.6, methanol). ν_{max} (neat) 3346, 2925, 1656, 1592, 1534 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 2.92 (1H, dt, *J* 1.2, 14.8 Hz, H-3), 3.32 (1H, dd, *J* 14.8, 2.0 Hz, H-3), 3.69−3.73 (1H, m, H-6), 3.82 (1H, dd, *J* 12.0, 4.8 Hz, CH_2OH), 3.90−3.92 (1H, m, H-4), 4.11(1H, dd, *J* 12.2, 9.0 Hz, CH_2OH), 4.44-450 (1H, m, H-5), 7.19−7.43 (5H, m, Ph). ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 46.4 (C-3), 56.1 (C-5), 59.0 (CH_2OH), 64.8 (C-6), 66.2 (C-4), 121.5 (CH, Ph), 125.0 (CH, Ph), 129.1 (CH, Ph), 138.0 (Cq, Ph), 153.6 (C=O) ppm. HRMS (FAB): calcd for $C_{12}H_{18}N_3O_4$: 268.1219; found: 268.1222.

5.17. Synthesis of (4*S*,5*S*,6*S*)-4,5-dihydroxy-6-(hydroxymethyl)-*N*-phenylhexahydropyridazine-1-carboxamide (+)-22

To a solution of (+)-**13** (0.12 g; 0.36 mmol) in dry THF (10 mL) was added at 0 °C a solution of $LiAlH_4$ 1 M in THF (7 eq.; 5.03 mL). The reaction mixture was stirred for 1.5 h at rt, and then the quenching was followed by sequential addition of 1 drop of water, one drop of aq. NaOH 15 %, and water (50 mL). The aqueous solution was extracted with ethyl acetate (10 × 40 mL). The organic layers were combined, dried, and evaporated, giving an oil that was submitted to PLC (DCM/methanol 10 %), giving the title compound (+)-**22** (0.010 g; 10 %).

$[\alpha]_D^{20}$ +51.3° (*c* 1, methanol).

5.18. Measurement of Glycosidase Inhibition

α-Glucosidase from baker's yeast (EC 3.2.1.20, Sigma G-5003) and β-glucosidase from almonds (EC 3.2.1.21, Sigma G-0395) were used as model glycosidases. Enzyme assays were conducted in 96 well Nunc plates, using 4-

nitrophenyl α-D-glucopyranoside or 4-nitrophenyl β-D-glucopyranoside as substrates, in phosphate buffer 100 mM, pH 7.0 or citrate buffer 100 mM, pH 5.0 at 25 °C. A range of substrate concentrations from 3.3×10^{-5} M to 2.0×10^{-3} M (11 different concentrations), in a final volume of 300 μL, was tested using 0.2 units/mL of β-glucosidase or 0.15 units/mL of α-glucosidase, in the absence and in the presence of inhibitor ((+)- and (-)-**22**, 5×10^{-6} M and 10×10^{-6} M). Blanks were set containing all reaction components but enzyme. All assays were performed in triplicate.

The formation of 4-nitrophenol was monitored for 20 min at 25 °C, measuring the absorbance (1 reading each minute) at 400 nm. A value of ε l = 787.73 M^{-1} (pH 7.0) or 28.29 M^{-1} (pH 5.0), determined in the same conditions as used for the enzyme assays, was used to convert absorbance into product concentration. Initial velocities were calculated from the slopes of the absorbance vs time graphs for each concentration of substrate and used to construct Michaelis-Menten plots. The kinetic parameters K_M and V_{max} were determined by fitting the experimental results to a rectangular hyperbole using the Origin 8 Graph Pad and by Lineweaver-Burk analysis. The inhibition type was established as competitive for all enzymes and inhibitors tested, using two different concentrations of inhibitors (in duplicate) and by examining the Lineweaver-Burk plot. For each inhibitor concentration, individual *Ki* values were obtained using the expression for competitive inhibition ($Ki = [I]/((K_{Mapp}/K_M)-1)$, where K_M and K_{Mapp} represent the Michaelis−Menten constant in the absence and in the presence of inhibitor, respectively. Reported *Ki* values are expressed as average of two independent *Ki* determinations.

5.19. Structural Molecular Modelling Studies

Structural enzyme-compound complexes and theoretical binding free energy of (-)-**2**, (+)-**2**, and **22** toward yeast α-glucosidase structure were done with computational docking methodologies using AUTODOCK 4.[19] The modelling of the enzyme-compound complexes with almond β-glucosidase was not calculated because, to the best of our knowledge, no structure or protein sequence is available. In the docking calculations, all possible torsions of the compounds were set flexible except the amide bonds in both enantiomers of compound **22**. The protonation state of the amine *N*-1 and *N*-2 of the compounds was set neutral, in agreement with previous NMR evidence.[20] The grid for probe-target energy calculations was placed with its centre at the enzyme-binding site. The docking grid size was 42 × 40 × 42 grid points with 0.375 Å spacing. For each ligand, 20 runs using the Lamarckian genetic algorithm with 150

individuals in each population were carried out. The maximum number of generations was set to 27 × 103 and the maximum number of energy evaluations to 5 × 106. The resulting docking solutions were clustered using AUTODOCK with a structural root-mean-square deviation cutoff of 1Å. Since no experimental structure exists for the yeast *α*-glucosidase enzyme, a theoretical structural model of this enzyme was derived using MODELER,[21] employing the crystal structure of isomaltase from *S. cerevisiae* structure (PDB ID: 3A4A)[13] as template. Isomaltase and α-glucosidase from *S. cerevisiae* share 72 % sequence similarity. Twenty models were generated using an initial alignment between the isomaltase and α-glucosidase enzyme sequences. The model with the lowest objective function[21] was chosen, and its quality was evaluated on the basis of its stereochemistry given by Procheck.[22] A high quality model of the yeast α-glucosidase enzyme was obtained with no residues in disallowed regions in the Ramachandran plot. The protonation states of the acidic and basic residues were set to their standard state found in aqueous solution at pH 7.

6. Acknowledgments

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2.2

Diastereoselectivity in Diels-Alder Cycloadditions of Erythrose Benzylidene-acetal 1,3-Butadienes with Maleimides

Daniela A. L. Salgueiro; Vera C. M. Duarte; Cristina E. A. Sousa; Maria J. Alves; António Gil Fortes *Synlett*, **2012**, *23*, 1765-1768.

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1. Abstract

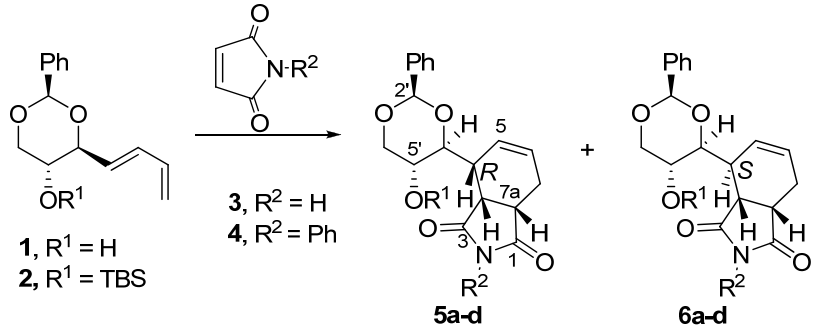
Maleimides were combined with D-erythrose benzylidene-acetal 1,3-butadienes to study the facial selectivity of the Diels-Alder cycloadditions. The selectivity was found to range from moderate to good. The reaction diastereotopicity can be reversed with the temperature. Simultaneous coordination of the diene, having a free hydroxyl group, and maleimide to a chiral bimetallic Lewis acid catalyst (LACASA-DA reaction) occurs with complete diastereocontrol to give a single adduct, using an extra chiral inductor either (*R*)- or (*S*)-BINOL.

2. Results and discussion

Small chiral synthons are becoming more and more appealing to synthetic chemists to build up target molecules possessing multistereogenic centers. We have been investigating the utility of D-erythrose 1,3-butadienes, such as **1** and **2**,[1] as chiral counterparts in diastereoselective Diels-Alder cycloadditions. In the past a high diastereotopicity was demonstrated in Diels-Alder reactions of these dienes with 2-methoxycarbonyl-*p*-benzoquinones.[1] In a previous study in our laboratory a complete chiral induction was also found in [4π+2π] cycloadditions of certain D-erythrose benzylidene-acetal 1,3-butadienes, having ether protection at C-5, with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD).[2] Maleimide (**3**) and *N*-phenylmaleimide (**4**) were now combined with D-erythrose dienes **1** and **2**. The facial selectivities were moderate to good under elevated temperatures, and interestingly the topicity was reversed when the cycloadditions were carried out at 5 ºC. Self-assembly of the reaction components on a Lewis acid template made the selectivity complete in two cases.

D-Erythrose benzylidene-acetal 1,3-butadienes possessing the alcohol function protected (*e.g.,* **2**) reacted with PTAD to give solely the *endo*, (*S*)-configuration adduct at the new stereogenic centre.[2] The reaction turned out to be less selective when the diene bore an unprotected hydroxyl group at C-5 (**1**). However, when reacting diene **2** with *N*-phenylmaleimide in dichloromethane (the solvent used in reactions with PTAD) the selectivity was reduced to a 2:1 ratio of *endo*-diastereomers; the major being the *R* isomer (**5**) and the minor, its (*S*)-diastereomer (**6**). The selectivity dropped to zero when diene **1** reacted with *N*-phenylmaleimide (**4**). The best selectivity with maleimides occurs when at least one of the reagents has the possibility of acting as a proton donor in a hydrogen bond. Thus combination of diene **2** and maleimide (**3**) affords a 3:1 (*R*/*S*) ratio of isomers; while reaction of diene **1** with maleimide (**3**) also yields the same ratio

of isomers. Scheme 1 depicts the four possible combinations of the reagents and reaction conditions, and the yields of products are collected in Table 1.



Scheme 1 Four possible combinations of dienes **1** and **2** to maleimides **3** and **4** giving compounds **5** and **6**.

Considering the unexpected behavior of maleimides in relation to PTAD, Figure 1 shows a possible explanation for the observation. Reagent superimposition in situations **A**, **B** and **C** show the dienophiles approach to the *re* face of the diene, leading to the (*S*)-configuration of products. In case **A** the proximity in space between the two electronegative atoms of the diene and dienophile may result in repulsion between reagents and render such an approach unlikely. Approach **B** does not indicate repulsion due to the nature of maleimides, which may favor such an approach. Finally, as shown in approach **C**, attack on the *si* face would result in the least hindered interaction between reagents, which may explain the (*R*)-configured compounds as the major isomers in most reactions.

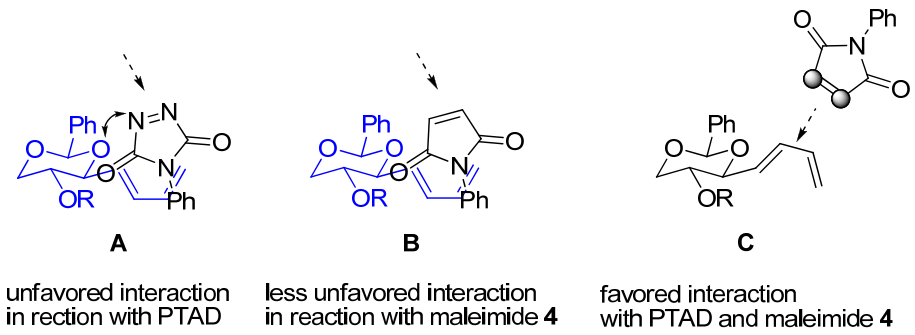


Figure 1 Different interaction at the rear double bond in maleimides and PTAD with the erythrose dienes (**A**, **B**, and **C**).

Table 1 displays some relevant reaction conditions employed in Diels-Alder reactions between erythrose dienes **1** and **2** and maleimides **3** and **4**. In the majority of the cases a higher yield of the (*R*)-configured product is observed. The reactions usually require several days, but in one case reaction was shortened from 5 days to 15 hours by increasing the temperature to 40 ºC with some loss of selectivity (Table 1, compare entries 3 and 4). Diene **1** and maleimide (**3**) were also combined at 5 ºC (Table 1, entry 2) when (*S*)-diastereomer became the major product, showing that the manner of approach of reagents is highly dependent on temperature. A possible interpretation for this fact may be the development of a hydrogen bond in the approach of maleimide by the *re* face of the diene as shown in Figure 2 which is influential at lower temperatures. There is a good deal of information in the literature that relates the outcome of Diels-Alder cycloadditions with possible hydrogen-bonding effects between reactants.[3a-g] This is reinforced by the result of the experiment carried out at 5 ºC between diene **2** and *N*-phenylmaleimide (**4**), which has no possibility of forming a hydrogen bond. The major isomer has the (*R*)-configuration at both temperatures (Table 1, entries 5 and 6), with some selectivity improvement at the lower temperature, showing a different trend from the one in entries 2 and 3 (Table 1).

Table 1 DA cycloadditions of dienes **1** and **2** with maleimide (**3**) and *N*-phenylmaleimide (**4**).

Entry	Diene	Dienophile (2 eq.)	Product	Solvent	T (ºC)	Time	dr (*R*/*S*)	η (%) 5*R*/6*S*
1	**1**	**4**	**5a/6a**	toluene	rt	3 d	1[a]:1	22 – 23
2	**1**	**3**	**5b/6b**	CH_2Cl_2	5	18 d	1:2	30 – 19
3	**1**	**3**	**5b/6b**	CH_2Cl_2	rt	5 d	3:1	[b]
4	**1**	**3**	**5b/6b**	CH_2Cl_2	40	15 h	2:1	33 – 21
5	**2**	**4**	**5c/6c**	CH_2Cl_2	rt	9 d	2:1	43 – 20
6	**2**	**4**	**5c/6c**	CH_2Cl_2	5	18 d	3:1	22 – 4[c]
7	**2**	**3**	**5d/6d**	CH_2Cl_2	rt	5 d	3:1	41–39[d]

[a] Submitted to X-Ray crystal structure analysis.

[b] Not isolated; dr obtained by ^{1}H NMR spectroscopy.

[c] An additional 11 % of a 1:1 mixture of (*S*)- and (*R*)-isomers was isolated. The ratio was based up on ^{1}H NMR spectroscopic analysis of the sample.

[d] 39 % is not pure *S* isomer; it is formed by a 1:2.9 (*R*/*S*) mixture of isomers based on ^{1}H NMR spectroscopic analysis of the sample.

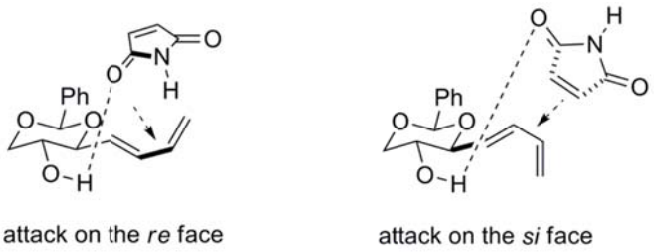


Figure 2 Approach of maleimide (**3**) to diene **1** in the *re* / *si* face showing the formation of a hydrogen bond between reagents.

The (*R*)-/(*S*)-configurations of the products were found by comparison of ^{1}H NMR spectra of both isomers in each case to compounds **5a**/**6a**.[4] The identity of **5a** was unequivocally confirmed by X-ray crystallography (Figure 3). The chemical shifts of H-5 / H-2' differ between isomers, and the difference is reproducible in every case.[5] Product **6a** is an *endo* product as **5a**, according to NOE experiments; irradiation of H-5' and H-7a leading to an increase in intensity of H-4 signals by 6.27 % and 10.4 %, respectively.

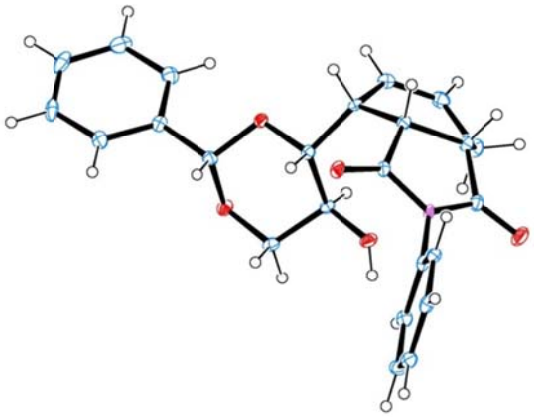
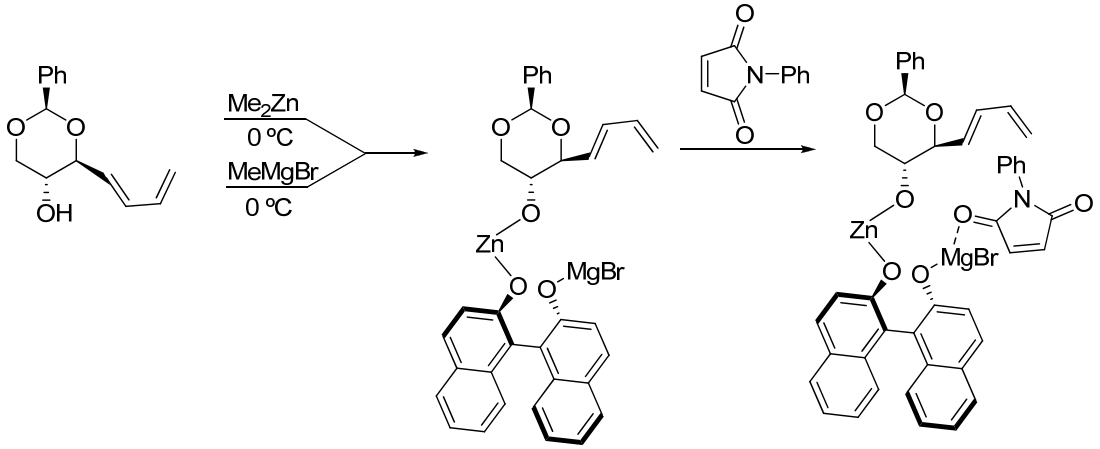


Figure 3 ORTEP view of diastereomer **5a**.

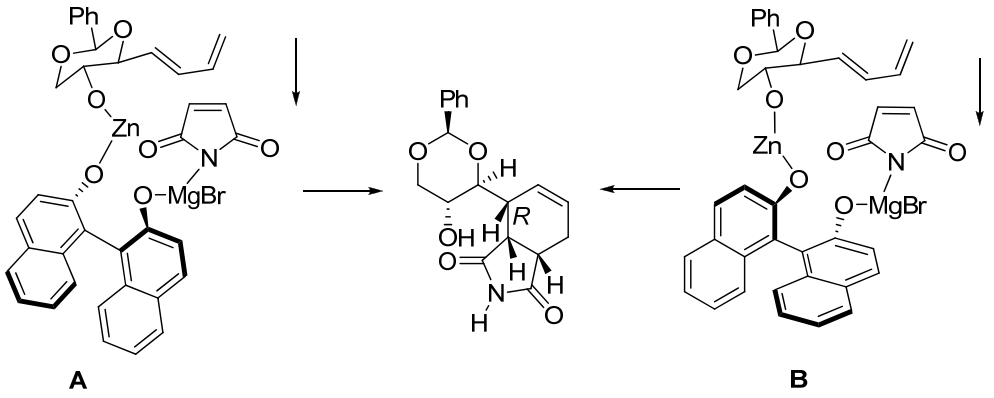
To improve the facial selectivity of these cycloadditions it was decided to self-assemble the reagents by tethering erythrose diene **1** and maleimides **3** and **4** in a LACASA-Diels-Alder cycloaddition using bimetallic complexes of Mg(II) and Zn(II) in which (*R*)- and (*S*)-BINOL were chiral inducers. This brings an important advantage over simple Lewis acid catalysts because covalent bonds to the metals are established, and the reaction occurs effectively by an intramolecular cycloaddition as shown in

Scheme 2. This method has been first developed by Inomata[6a,b] using a tartaric acid-zinc complex in reaction of nitroso dienophiles with a dienol, and later by Ward.[7a,b]



Scheme 2 Bimetallic complex of Mg(II) and Zn(II) assembling together diene **1**, *N*-phenylmaleimide (**4**) and (*R*)-BINOL.

The reaction combining (*S*)-BINOL (**A**), maleimide, and diene **1** was completely selective, forming exclusively the (*R*)-product in 33 % yield.[8] Scheme 3 represents the assembly of the reagents, and the direction of attack of maleimide to the front face of the diene leading to the (*R*)-configured product. The high selectivity observed is probably due to the covalent bond between the Mg and the nitrogen atom that forces the antarofacial interaction. The assembly of (*R*)-BINOL (**B**), *NH*-maleimide, and diene **1** give also a single (*R*)-configured product (29 %). This means that although the flexibility of the complex is higher in the case of **B**, a similar approach takes place.



Scheme 3 Coordination of the erythrose diene **1** with maleimide (**1**) using bimetallic complex of Mg(II) and Zn(II) with (*S*)-BINOL (**A**) and (*R*)-BINOL (**B**).

When *N*-phenylmaleimide (**4**) was used in place of maleimide (**3**) with (*R*)-BINOL and diene **1** a 2.5:1 ratio of isomers was obtained, in 50 % yield, favoring the (*S*)-compound. These products were isolated in 35 % (*S*) and 15 % (*R*) yields. In this case no covalent bond could have been established, and the reaction attack of the dienophile could now occur by the less bulky rear face of the diene.

In conclusion maleimides **3** and **4** reacted with erythrose dienes **1** and **2** showing at its best a 1:3 ratio of isomer products. It was found possible to reverse the selectivity on lowering the reaction temperature. Pure (*R*)-isomers were isolated in moderate yields in the case of maleimide (**3**) and diene **1** by using bimetallic complex templates of Zn(II) and Mg(II) and (*R*)- or (*S*)-BINOL. Combination of diene **1**, *N*-phenylmaleimide (**4**) and (*R*)-BINOL under the same conditions led to the (*S*)-isomer (35 % yield) together the (*R*)-isomer (15 % yield).

3. Acknowledgments

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4. **Analytical data for some typical compounds**

Compound **5a**: $[\alpha]_D^{20}$ -92.4° (*c* 0.45, EtOAc). ν_{max} (nujol) 3441, 1690, 1457 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 2.22-2.32 (1H, m, H-7), 2.75-2.90 (2H, m, H-7+ H-3a), 3.35 (1H, tdd, *J* 11.6, 5.8, 3.5 Hz, H-4), 3.60 (1H, td, *J* 11.2, 0.8 Hz, H-6'), 3.83 (1H, bs, H-5'), 3.96 (1H, dt, *J* 15.0, 7.5 Hz, H-7a), 4.28 (1H, t, *J* 9.0 Hz, H-4'), 4.36 (1H, ddd, *J* 11.0, 5.1, 2.3 Hz, H 6'), 5.52 (1H, s, H-2'), 6.02-6.13 (1H, m, H-6), 6.17 (1H, dt, *J* 9.4, 3.2 Hz, H-5), 7.11-7.18 (2H, m, Ph), 7.32-7.54 (8H, m, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 24.27 (C-7), 39.23 (C-3a), 40.41 (C-4), 41.43 (C-7a), 66.44 (C-5'), 71.89 (C-6'), 80.46 (C-4'), 101.10 (C-2'), 126.06 (C-H, Ph), 126.42 (C-H, Ph), 128.13 (C-6), 128.23 (C-H, Ph), 128.83 (C-H, Ph), 128.94 (C-H, Ph), 129.12 (C-H, Ph), 130.14 (C-5), 131.56 (Cq, Ph), 137.49 (Cq, Ph), 178.53 (C=O), 179.81 (C=O) ppm. HRMS (ESI): calcd for $C_{24}H_{23}NNaO_5$: 428.1467; found: 428.1468.

Compound **6a**: $[\alpha]_D^{20}$ -118.2° (*c* 0.45, EtOAc). ν_{max} (nujol) 3442, 1690, 1411, 1072 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 2.17-2.31 (1H, m, H-7), 2.64-2.76 (1H, m, H-4), 2.83 (1H, ddd, *J* 15.4, 7.0, 1.6 Hz, H-7), 3.27 (1H, td, *J* 8.0, 1.6 Hz, H-3a), 3.65 (1H, t, *J* 10.4 Hz, H-6'), 3.81 (2H, dd, *J* 9.0, 5.5 Hz, H-7a + H-5'), 4.27 (1H, dd, *J* 10.8, 5.1 Hz, H-6'), 4.44 (1H, t, *J* 9.6 Hz, H-4'), 5.64 (1H, s, H-2'), 6.02 (1H, ddt, *J* 12.9, 6.5, 3.3 Hz, H-6), 6.41 (1H, dt, *J* 9.4, 3.5 Hz, H-5), 7.19-7.22 (2H, m, Ph), 7.35-7.40 (4H, m, Ph), 7.43-7.47 (2H, m, Ph), 7.50-7.52 (2H, m, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 25.00 (C-7), 39.50 (C-3a), 40.09 (C-7a), 41.32 (C-4), 68.05 (C-5'), 71.24 (C-6'), 79.47 (C-4'), 100.79 (C-2'), 126.08 (C-H, Ph), 126.54 (C-H, Ph), 127.54 (C-6), 128.19 (C-H, Ph), 128.60 (C-H, Ph), 128.85 (C-H, Ph), 129.08 (Cq, Ph), 130.62 (C-5), 131.89 (Cq, Ph), 137.70 (Cq, Ph), 177.21 (C=O), 179.05 (C=O) ppm. HRMS (ESI): calcd for $C_{24}H_{23}NNaO_5$: 428.1473; found: 428.1468.

5. Compound **5a**: H-5: 6.40 (dt, *J* 3.2, 9.2 Hz), H-2': 5.64 (s); Compound **5b**: H-5: 6.38 (dt, *J* 3.6, 9.2 Hz), H-2': 5.66 (s); Compound **5c**: H-5: 6.34 (dt, *J* 3.6, 9.2 Hz); H-2': 5.67 (s); Compound **5d**: H-5: 6.28 (dt, *J* 3.6, 9.2 Hz), H-2': 5.67 (s); Compound **6a**: H-5: 6.17 (dt, *J* 3.2, 9.2 Hz), H-2': 5.51 (s); Compound **6b**: H-5: 6.12 (dt, *J* 3.6, 9.6 Hz), H-2': 5.54 (s); Compound **6c**: H-5: 6.16 (bs), * H-2': 5.42 (s); Compound **6d**: H-5: 6.08 (br t, *J* 2.0 Hz), *H-2': 5.42 (s).* These signals coincide with H-6.

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8. **Preparation of solution A**

A solution of diene **1** (0.05 g; 0.22 mmol) in dry toluene (1.0 mL) was added to a solution of Me_2Zn (1.2 M) in toluene (178 µL; 0.22 mmol) at 0 ºC and stirred for 5 min.

Preparation of solution B

A solution of (*S*)-BINOL (0.061 g; 0.22 mmol) in dry toluene (1.0 mL) was added to a solution of MeMgBr (1.4 M in toluene-THF; 152 µL; 0.22 mmol) at 0 ºC and stirred for 5 min. Solution **A** was added to solution **B**, the mixture diluted with dry toluene (1.8 mL) and stirred for 5 min. This mixture was refrigerated at -78 ºC and a solution of maleimide (**3**, 0.02 g; 0.22 mmol) in dry toluene (1.5 mL) was then added. The temperature was allowed to rise gradually to rt. The reaction was complete after 17 d and was quenched with an aq. sat. solution of $NaHCO_3$ (1 mL), filtered through a pad of Celite®, and the Celite® was washed with EtOAc (4 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give a yellow oil that was submitted to “dry-flash” chromatography using a mixture of PE (40-60)-Et_2O. (*S*)-BINOL was recovered (0.035 g; 57 %) from PE-Et_2O (1:1), and the product was eluted with PE-Et_2O (1:2.3) (0.024 g; 33 %).

2.3

Asymmetric Diels-Alder Cycloadditions of D-Erythrose 1,3-Butadienes to Achiral *t*-Butyl 2*H*-Azirine 3-Carboxylate

Duarte, V. C. M.; Faustino, H.; Alves, M. J.; Gil Fortes, A.; Micaelo, N. *Tetrahedron: Asymmetry* **2013**, *24*, 1063-1068.

Index

1. Abstract

Two D-erythrose 1,3-butadienes were reacted with electrophilic achiral *t*-butyl 2*H*-azirine 3-carboxylate giving cycloadducts with good yields and moderate selectivity. The isomers could be separated to give the major (*R*)-isomers at C-2 in approximately 50 % yield in both cases. Alternatively LACASA-DA methodology was applied to one of the reactions leading to homochiral (*R*)- and (*S*)-products by changing the chiral nature of an extra chiral BINOL inductor used.

2. Introduction

D-Erythrose is an important chiral synthon used in many syntheses.[1-5] However, the use of its 1,3-butadiene derivatives **1** is not common. The lack of interest in these dienes, namely as counterparts in Diels-Alder cycloadditions (DA), is probably due to the poor facial selectivity associated with DA thermal processes, although exceptions are known.[6,7] Nevertheless, a series of interesting compounds could be envisaged by functional group transformations (FGT) of these DA cycloadducts mainly in the field of sugars/aza-sugars. Therefore we attempted to better understand the facial selectivity of dienes **1** with dienophiles in order to improve the selectivity. At first, 5-membered ring dienophiles (maleimides and 4-phenyl/methyl-1,2,4-triazoline-3,5-dione) were examined. The major or exclusive isomer obtained [(*S*) at C-2] was formed by the attack of the dienophile at the *si* face of the diene.[7] Having in mind that the DA cycloadduct of D-erythrose-1,3-butadienes to 2*H*-azirines enables the synthesis of analogue precursors of neuraminic acid **3**, especially if the C-2 (*R*)-configuration isomers could be formed in reasonable yields, we tested this C=N dienophile to see if an approach by the *re* face would be preferred. Figure 1 represents the close relationship of neuraminic acid with the (*R*)-cycloadduct **4a**. Functionalization of the C=C bond would give an epimeric analogue of compound **3** at C-6.

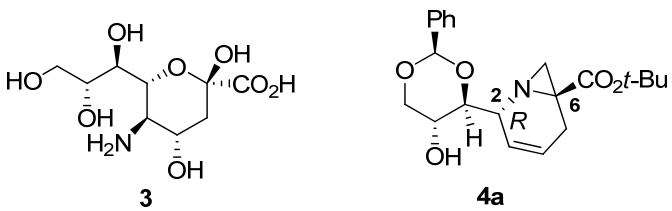
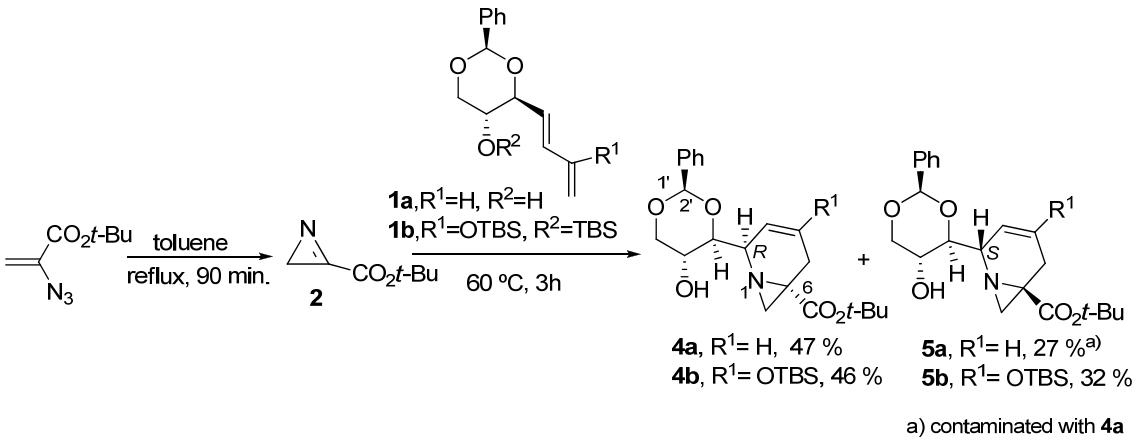


Figure 1 Structural comparison of neuraminic acid **3** and (2*R*)-cycloadduct **4a**.

3. Results and discussion

Two D-erythrose butadienes **1a**,**b** were prepared according to the literature[6,7] and combined with *t*-butyl 2*H*-azirine 3-carboxylate, obtained *in situ* from *t*-butyl α-azido acrylate;[9] the reaction occurs at 60 ºC. Two products were formed in each reaction in the same ratio. Primary cycloadducts obtained by the reaction of diene **1b** lost the *t*-butyldimethylsilyl group attached to the erythrose moiety according to ^{1}H and ^{13}C NMR spectra, thus giving the free alcohols **4b** and **5b** (Scheme 1).



Scheme 1 Thermal cycloaddition of 2*H*-azirine **2** to diene **1**.

The regiochemistry of the cycloaddition results from the attack of the nucleophilic terminal of the diene to the electrophilic center in the azirine.[8] Such an approach can develop a hydrogen bond interaction between the nitrogen azirine ring atom of the dienophile and the hydroxyl group at the diene, favouring an attack at the *si* face (bottom representation in Figure 2) over *re* face (top representation depicted in Figure 2). However the stereochemistry of the products is incompatible with such reagent interactions: an approximate (*R*):(*S*) ratio of 2.5:1 was obtained in the thermal reaction of diene **1a** to azirine **2** (Scheme 1).

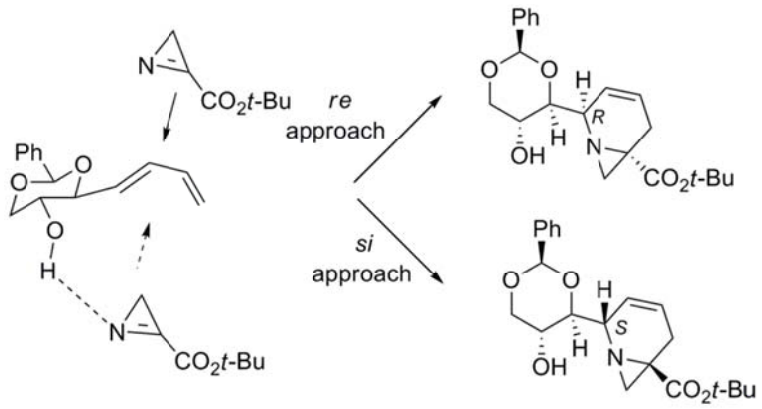


Figure 2 The *endo* facial approaches of 2*H*-azirine **2** to diene **1**.

The identification of the products (oils) was based on conformation analysis using molecular dynamics simulations. The two lowest free energy conformers of the (*R*)-diastereomer (structures **A** and **B**), and (*S*)-diastereomer (structures **C** and **D**) were obtained. In every case, the hydroxyl group establishes an intramolecular hydrogen bond within *O*-1 in the dioxanyl moiety (Figure 3). This obviously predicts the same *O*-H-*O* interaction trend to occur in the diene reagent, leaving no room for a possible hydrogen bond with the nitrogen atom of the approaching azirine that would favour the C-2 (*S*)-configuration product predicted by the approach outlined in Figure 2.

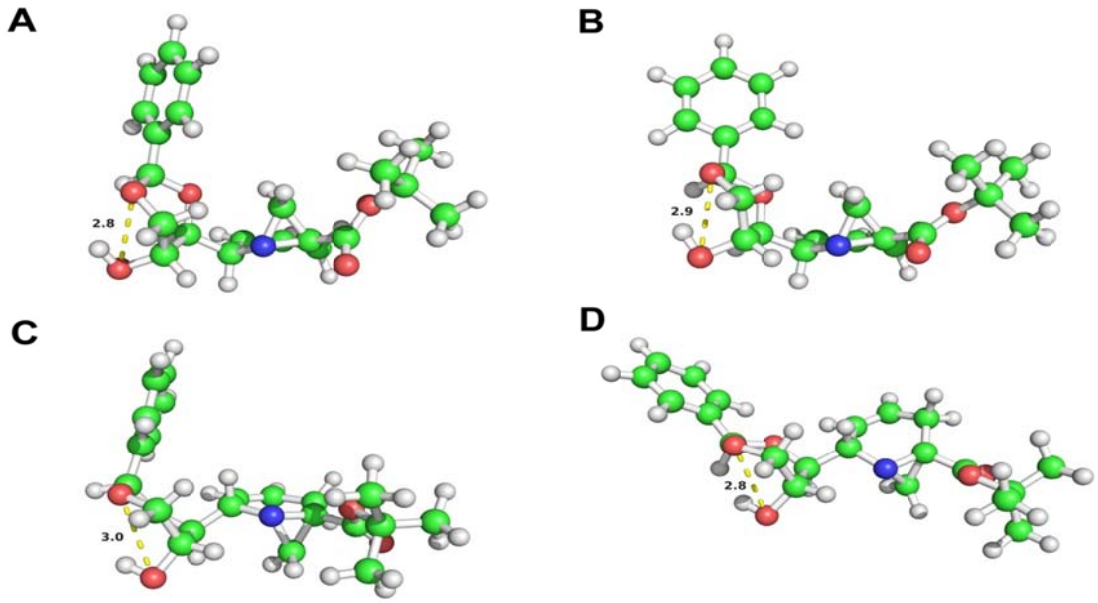


Figure 3 Lowest free energy conformations of (*R*)-**4a**/(*S*)-**5a**-diastereomers. (*R*)-diastereomer: conformations **A** and **B**; (*S*)-diastereomer: conformations **C** and **D**. Structures are rendered in ball-and-stick mode with carbon in green, oxygen in red, nitrogen in blue, and hydrogen in white. Intramolecular interactions and distances are highlighted with a dashed yellow line.

Figure 4 shows an alternative interaction of the approaching azirine to the *re/si* faces of the diene. The *re* approach shows a proximity between the nitrogen lone pair of the azirine and the π current of the aromatic ring. Attractive interactions at the van der Waals' distance were explored by using aromatic rings with a wide range of substituents in triptycene scaffold.[10] Many examples of such a positive interaction have also been reported between the oxygen atom of carbonyls and the aromatic groups in proteins, within an average of 3.5 Å distance.[11] In the *si* approach, the lone pair of the nitrogen is too far from the phenyl group due to the different directions of attack. The (*R*)-configuration product would also be favoured from a kinetic profile point of view.

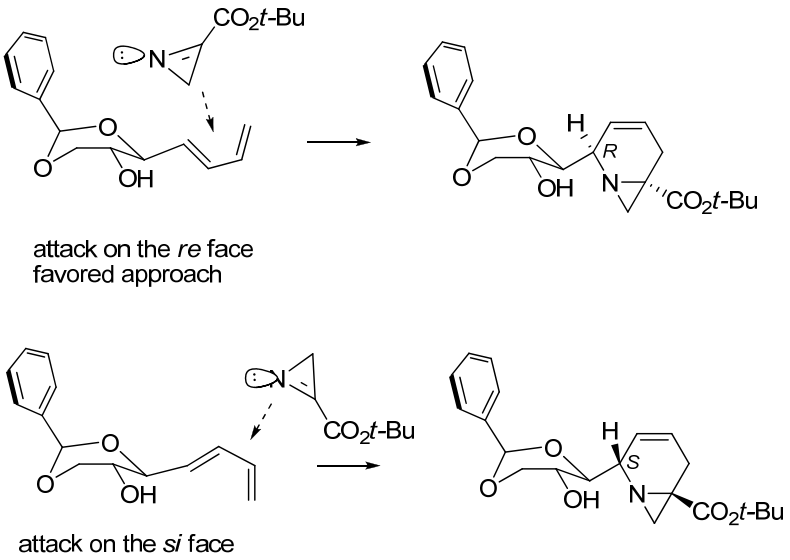


Figure 4 The two possible *endo* approaches of 2*H*-azirine **2** to diene **1a**.

On the other hand, the conformational free energy difference between the (*R*)- and (*S*)-diastereomers using computational free energy perturbation methods was determined to be -8.9 kcal/mol, meaning that the (*S*)-product is thermodynamically preferred relative to the (*R*)-product. The isomeric ratio of products **4a**/**5a** probably reflects the major importance of kinetics over thermodynamics in this cycloaddition.

The identification of isomers **4a**/**5a** was made by measuring the dihedral angle between the two six-membered ring moieties in the more stable conformers **A**, **B** [(*R*)-isomer], and **C**, **D** [(*S*)-isomer] (Figure 3). Both **A** and **B** display small dihedral angles: **A** 68º, **B** 47º; these values are in accordance with the small coupling constant shown in the ^{1}H NMR spectrum (*J* ~2 Hz) for (*R*)-diastereomer. Considering that conformers **A** and **B** make up 98 % of the total population in chloroform an obvious relationship of the

(*R*)-isomer with the small coupling constant of H-2 to H-4'occurs. In contrast, **C** and **D** show larger dihedral angles: **C** 174º, **D** 176º, and so a large coupling constant of H-2 to H-4' is predicted. In fact, the *J* is *c.a.* 10 Hz in the other (*S*)-isomer. The **C** and **D** population corresponds to 91 % of the total conformation species solubilized in chloroform with 63 % and 28 %, respectively. An equivalent computational conformational analysis of compounds **4b**/**5b** was also made, however due to the lack of force field parameters for silicon, the *t*-butyldimethylsilyl group was replaced with *t*-butyl. The same dihedral angle/coupling constant trend was obtained for compounds **4b/5b**. The (*R*)-isomer shows 99 % of its population to be in the **E** (89 %) and **F** conformers (10 %). The dihedral angles H-C_2-C_4-H in the two conformers are both small: 53º **E** and 61º **F**, which is consistent with the small coupling constant of H-2 to H-4' (2.2 Hz) in the ^{1}H NMR spectrum (Figure 5). The (*S*)-isomer showed 94 % of its population to be in the **G** conformer (74 %) and **H** conformer (20 %). The dihedral angles of these conformers are both large angles: 167º **G** and 162º **H**, which is consistent with the large coupling constant of H-2 to H-4' (10.1 Hz) (Figure 5).

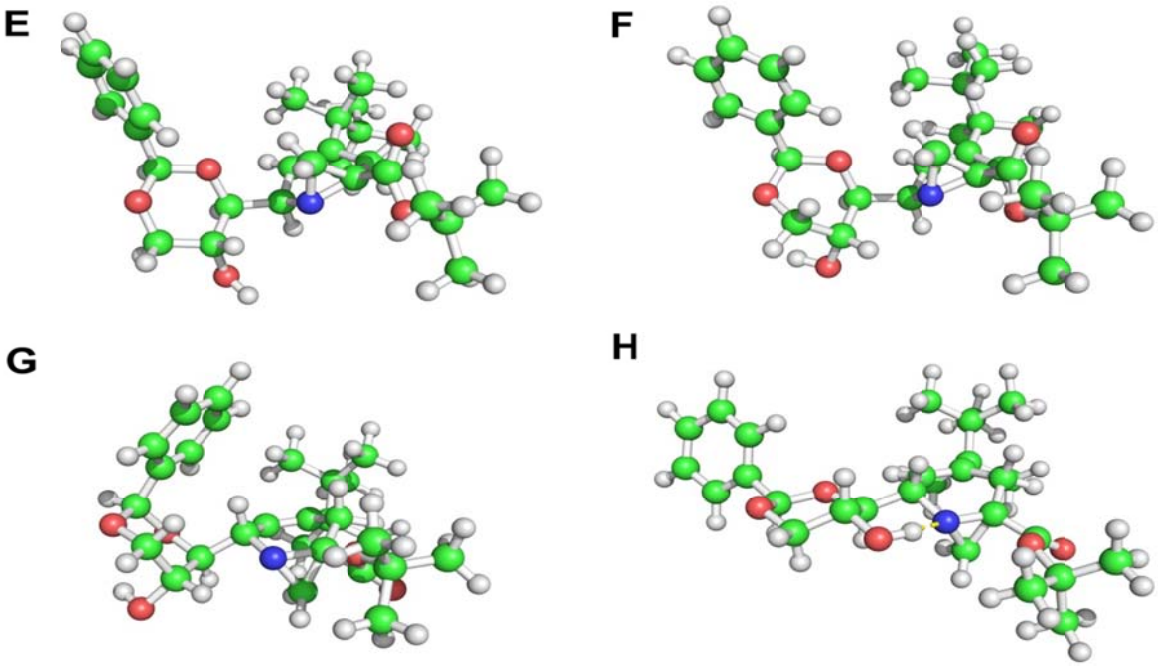
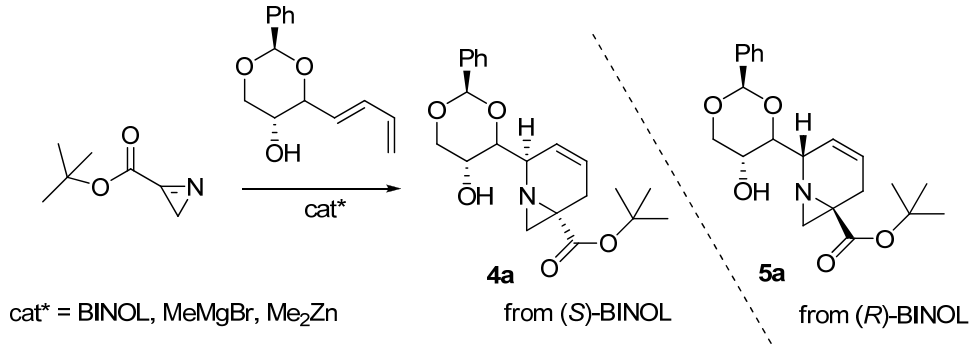


Figure 5 Lowest free energy conformations of (*R*)-**4b**/(*S*)-**5b** diastereomers. (*R*)-diasteromer: conformations **E** and **F**; (*S*)-diastereomer: conformations **G** and **H**. Structures as rendered in ball-and-stick mode with carbon in green, oxygen in red, nitrogen in blue, and hydrogen in white. Intramolecular interactions and distances are highlighted with a dashed yellow line.

With the aim of enhancing the formation of compound **4a** *versus* **5a**, we thought that a coordination reaction might induce kinetics to completely control the process. Previous experience with a bimetallic complex of Mg(II) and Zn(II) having (*R*)-/(*S*)-BINOL as a chiral ligand was applied before in a Diels-Alder cycloaddition based on a Lewis acid-catalysed reaction of a "self-assembled" complex (LACASA-DA). This method involves the existence of a free hydroxyl group in the diene and a carbonyl in the dienophile to coordinate all reagents and led to very good facial selectivities. 2,4-Pentadienol was combined to nitroso dienophiles,[12,13] and to methyl acrylate[14,15] in the presence of tartaric acid or BINOL with excellent selectivities. We have previously reported on some control in reactions of diene **1a** with maleimides.[16]

Combining diene **1a** with azirine **2** at low temperatures gave homochiral compounds **4a** or **5a** depending on the stereochemistry of the BINOL (Scheme 2). Compound **5a** was obtained in 47 % yield in the presence of (*R*)-BINOL, and **4a** in 28 % yield in the presence of (*S*)-BINOL. The excess reacting diene remained untouched according to ^{1}H NMR spectra, even after the addition of fresh portions of azirine or prolonged reaction times.



Scheme 2 The LACASA-Diels-Alder cycloaddition between diene **1a** and 2*H*-azirine **2** tethered in a bimetallic complex of Mg(II) and Zn(II) having (*R*)-/(*S*)-BINOL as a chiral ligand.

4. Conclusion

D-Erythrose 1,3-butadienes were combined with *t*-butyl 2*H*-azirine 3-carboxylate. Thermal reactions occur at 60 ºC with moderate facial selectivity, favouring the (*R*)-enantiomer at C-2. The approach of the reagents has been inversed relative to other cases in the literature. The two (*R*)-products were separated to give the major isomer in 46 % and 47 % yield in cases **a** and **b** respectively. The moderate selectivity was explained by the antagonism of thermodynamics and kinetics of the

cycloadditions. An LACASA-DA methodology using Zn/Mg bimetallic complexes and BINOL as an extra chiral inductor gave pure (*R*)- and (*S*)-products. A significant improvement in the yield was achieved in the case of the (*S*)-product but not in the (*R*)-product. The relative configuration of the new stereocentre in the products was obtained by combining the results of the conformational analysis with the ^{1}H NMR coupling constants.

5. Experimental section

5.1. General

Starting with D-erythrose 1,3-butadienes **1a**,**b** were obtained from (2*R*,4*R*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxane-4-carbaldehyde according to the literature.[6,7] 2*H*-Azirine was prepared *in situ* from α-azido *t*-butyl acrylate.[9] All other reagents were purchased and used without further purification. Solvents employed in reactions were dried: CH_2Cl_2 was freshly distilled under CaH_2, and toluene was submitted to simple distillation to remove the head fraction. The petroleum ether 40-60 ºC used in flash chromatography was previously distilled, while all other solvents were used as purchased. Glassware was dried prior to use. Compounds were purified by dry flash chromatography, using silica 60 <0,063 mm as the stationary phase and water pump vacuum. TLC plates (Silica Gel 60 F_{254}, Macherey-Nagel) were visualized either at a UV lamp or in I_2. ^{1}H NMR and ^{13}C NMR were run on a Varian Unity Plus 300, or Brucker Avance III 400 or Bruker BioSpin GmbH spectrometers. Infrared spectra were recorded on a Bomem MB 104 or on a Perkin-Elmer spectrophotometer. Samples were run as nujol mulls and oils as thin films. MS spectra were recorded on a VG Autospec M. spectrometer.

5.2. Reaction of D-erythrose diene 1a to *t*-butyl 2*H*-azirine 3-carboxylate 2

5.2.1. Synthesis of cycloaducts 4a and 5a

5.2.1.1. Thermal Method

The α-azido acrylate[9] (0.151 g; 0.893 mmol) was dissolved in toluene (16 mL) and refluxed under a nitrogen atmosphere for 90 min. The heating source was then removed and when the temperature reached 60 ºC, a solution of diene **1a** (0.041 g; 0.177 mmol) in a 1:1 mixture of toluene/DCM (2 mL) was added. The mixture was

maintained at 60 ºC for 3h. The solvent was evaporated until dryness and the crude subjected to flash chromatography in a 1:4 mixture of petroleum ether/ethyl ether. Two isomeric oily products were obtained. The (*S*)-Isomer, **5a**, (0.018 g; 27 %) was contaminated with the (*R*)-isomer **4a**, and isomer (*R*)-**4a** was obtained pure (0.031 g; 47 %).

Isomer (*R*)-**4a**: $[\alpha]_D^{20}$ -14.9° (*c* 1.5, CH_2Cl_2). ν_{max} (neat) 3368, 2977, 1723, 1158 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 1.48 (9H, s, 3 × CH_3), 2.06 (1H, s, H-7), 2.36 (1H, s, H-7), 2.65 (2H, t, *J* 4.0 Hz, H-5), 3.67 (1H, t, *J* 10.4 Hz, H-6'), 3.77 (1H, dd, *J* 9.3, 3.1 Hz, H-4'), 4.20 (1H, d, *J* 2.0 Hz, H-2), 4.33 (1H, dd, *J* 10.6, 5.3 Hz, H-6'), 4.38-4.50 (1H, m, H-5'), 5.44 (1H, s, H-2'), 5.46-5.54 (1H, m, H-3), 5.78 (1H, ddt, *J* 10.4, 5.4, 3.4 Hz, H-4), 7.33-7.35 (3H, m, H*m* and H*p*, Ph), 7.42-7.45 (2H, m, H*o*, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 22.4 (C-5), 27.8 (CH_3), 27.9 (CH_3), 28.0 (CH_3), 30.9 (C-7), 36.8 (C-6), 53.0 (C-2), 61.0 (C-5'), 71.1 (C-6'), 81.5 (C-6), 81.6 (Cq, *t*-Bu), 85.0 (C-4'), 101.4 (C-2'), 123.5 (C-3), 123.6 (C-4), 126.1 (C*o*, Ph), 128.1 (C*m*, Ph), 128.8 (C*p*, Ph), 138.1 (Cq, Ph), 172.0 (C=O) ppm. HRMS (ESI): calcd for $C_{21}H_{28}NO_5$: 374.1960; found: 374.1962.

Isomer (*S*)-**5a**: $[\alpha]_D^{20}$ -11.2° (*c* 1.05, $CHCl_3$). ν_{max} (neat) 3366, 2977, 1724, 1155 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 1.47 (9H, s, 3 × CH_3), 2.00 (1H, s, H-7), 2.22 (1H, s, H-7), 2.67 (2H, dd, *J* 4.4, 1.6 Hz, H-5), 3.46 (1H, dd, *J* 9.6, 8.4 Hz, H-4'), 3.69 (1H, t, *J* 10.8 Hz, H-6'), 5.51 (1H, s, H-2'), 3.96 (1H, d, *J* 10.0 Hz, H-2), 4.03 (1H, ddd, *J* 10.1, 8.7, 5.2 Hz, H-5'), 4.38 (1H, dd, *J* 10.8, 5.2 Hz, H-6'), 5.75-5.84 (2H, m, H-3 + H-4), 7.35-7.38 (3H, m, H*m* + H*p*, Ph), 7.47-7.50 (2H, m, H*o*, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 22.3 (C-5), 27.9 (3×CH_3; C-7), 39.4 (C-6), 59.9 (C-2), 68.1 (C-5'), 70.5 (C-6'), 80.4 (C-4'), 81.6 (Cq, *t*-Bu), 101.0 (C-2'), 120.8 (C-3 or C-4), 123.8 (C-3 or C-4), 126.0 (C*o*, Ph), 128.2 (C*m*, Ph), 128.9 (C*p*, Ph), 137.6 (Cq, Ph), 170.6 (C=O) ppm. HRMS (ESI): calcd for $C_{21}H_{28}NO_5$: 374.1952; found: 374.1962.

5.2.1.2. LACASA-DA Methodology

*i) Synthesis of cycloadduct **4a***

Solution A: a solution of diene **1a** (0.100 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of Me_2Zn (1.2 M) in toluene (359 µL; 0.43 mmol) at 0 ºC, and stirred for 5 min.

Solution B: a solution of (*S*)-BINOL (0.123 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of MeMgBr (1.4 M) in toluene/THF (307 µL; 0.43 mmol) at 0 ºC, and stirred for 5 min.

Solution A was added to solution B, diluted with dry toluene (3.6 mL), and stirred for 5 min. This mixture was cooled to -78 ºC and a solution of *t*-butyl 2*H*-azirine-3-carboxylate (0.061 g; 0.43 mmol) in dry toluene (3 mL) was then added. The reaction was stirred at -20 ºC for 24 h. A new portion of *t*-butyl 2*H*-azirine-3-carboxylate was then added and the reaction was stirred at rt for 5 days. The reaction was quenched with $NaHCO_3$ aq. sat. sol. (1 mL), filtered through a pad of Celite®, and the Celite® was washed with EtOAc (4 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give an orange oil corresponding to a 2:1 mixture of diene starting material and the expected product. The crude was submitted to 'dry-flash' chromatography using a mixture of PE (40-60)-Et_2O. The (*S*)-BINOL was recovered from PE-Et_2O 1:1 (0.069 g; 56 %) and the product was eluted with PE/Et_2O 2:3 to give the (*R*)-isomer as an oil (0.044 g; 28 %).

*ii) Synthesis of cycloadduct **4b***

Solution A: a solution of diene **1a** (0.100 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of Me_2Zn (1.2 M) in toluene (359 µL; 0.43 mmol) at 0 ºC, and stirred for 5 min.

Solution B: a solution of (*R*)-BINOL (0.123 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of MeMgBr (1.4 M) in toluene/THF (307 µL; 0.43 mmol) at 0 ºC, and stirred for 5 min.

Solution A was added to solution B, diluted with dry toluene (3.6 mL), and stirred for 5 min. This mixture was cooled to -78 ºC and a solution of *t*-butyl 2*H*-azirine-3-carboxylate (0.061 g; 0.43 mmol) in dry toluene (3 mL) was added. After mixturing the reagents, the temperature was allowed to rise gradually to rt. The reaction was quenched with $NaHCO_3$ aq. sat. sol. (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (4 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give an orange oil, consisting of a 1:1 mixture of starting diene and product. The crude was submitted to 'dry-flash' chromatography using a mixture of PE (40-60)-Et_2O. The (*R*)-BINOL was recovered from PE-Et_2O 3:1 (0.076 g; 62 %) and the product was eluted with PE-Et_2O 1:1 to give the (*S*)-isomer as an oil (0.076 g; 47 %).

5.2.2. Reaction of D-erythrose diene (1b) and *t*-butyl 2*H*-azirine 3-carboxylate (2)

5.2.2.1. Thermal Method

The *t*-butyl α-azido acrylate (0.340 g; 2.01 mmol) was dissolved in toluene (30 mL) and refluxed under a nitrogen atmosphere for 90 min. The heating source was removed and when the reaction mixture temperature reached 60 ºC, a solution of diene **1b** (0.184 g; 0.386 mmol) in DCM (4 mL) was added. The mixture was maintained at 60 ºC for 5h. A second portion of azirine was prepared (0.180 g; 1.06 mmol) in dry toluene (18 mL) and added to the reaction mixture and stirred further at 60 ºC for 1.5 h. The solvent was evaporated until dryness, after which flash chromatography was carried out using petroleum ether/ethyl ether 30 % as the eluent. Two isomeric compounds were obtained in 78 % overall yield, and separated as oils: (*S*)-isomer **5b** (0.063g; 32 %) and (*R*)-isomer **4b** (0.090g; 46 %).

Isomer (*R*)-**4b**: viscous oil. $[\alpha]_D^{20}$ -40.5° (*c* 1.05, $CHCl_3$). ν_{max} (neat) 3746, 3682, 3093, 3067, 3037, 3005, 1727, 1678, 1164, 1135, 1090, 1030, 841 cm^{-1}. ^1H NMR (δ_H, 800 MHz, $CDCl_3$) 0.10 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3), 0.92 (9H, s, SiCCH_3), 1.50 (9H, s, OCCH_3), 2.06 (1H, s, H-7), 2.30 (1H, s, H-7), 2.54 (1H, d, *J* 17.8 Hz, H-5), 2.64 (1H, bs, O*H*), 2.74 (1H, d, *J* 17.7 Hz, H-5), 3.66-3.70 (2H, m, H-4' + H-6'), 4.33-4.37 (2H, m, H-6' + H-2), 4.41 (1H, td, *J* 9.8, 5.4 Hz, H-5'), 4.58 (1H, br t, *J* 2.2 Hz, H-3), 5.43 (1H, s, H-2'), 7.31-7.38 (3H, m, CH, Ph), 7.42-7.47 (2H, m, CH, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) -4.6 (Si*C*H_3) -4.4 (Si*C*H_3), 18.0 (Si*C*$(CH_3)_3$), 25.6 (SiC(*C*$H_3)_3$), 27.7 (C-5), 28.0 (C-*C*H3), 30.9 (C-7), 54.0 (C-2), 38.4 (Cq, *t*-Bu), 61.3 (C-5'), 71.1 (C-6'), 81.7 (Cq), 84.9 (C-4'), 99.2 (C-3), 101.3 (C-2'), 126.0 (CH, Ph), 128.1 (CH, Ph), 128.7 (CH, Ph), 138.1 (Cq, Ph), 147.3 (C-4), 171.6 (C=O) ppm. HRMS (FAB): calcd for $C_{27}H_{42}NO_6Si$: 504.2781; found: 504.2786.

Isomer (*S*)-**5b**: viscous oil. $[\alpha]_D^{20}$ -4.0° (*c* 1.8, $CHCl_3$). ν_{max} (neat) 3566, 3554, 3092, 3068, 3036, 1727 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 0.15 (3H, s, SiCH_3), 0.16 (3H, s, SiCH_3), 0.93 (9H, s, SiC(C$H_3)_3$), 1.47 (9H, s, OC(C$H_3)_3$), 1.99 (1H, s, H-7), 2.21 (1H, s, H-7), 2.56 (1H, dd, *J* 17.6, 0.7 Hz, H-5), 2.77 (1H, dtd, *J* 17.6, 2.5, 1.1 Hz, H-5), 3.42 (1H, dd, *J* 9.5, 8.8 Hz, H-4'), 3.68 (1H, t, *J* 10.8, H-6'), 4.00 (1H, ddd, *J* 10.1, 8.7, 5.2 Hz, H-2), 4.07 (1H, d, *J* 9.7 Hz, H-5'), 4.38 (1H, dd, *J* 10.8, 5.2 Hz, H-6'), 4.84-4.91 (1H, m, H-3), 5.52 (1H, s, H-2'), 7.33-7.40 (3H, m, C-H, Ph), 7.45-7.50 (2H, m, C-H, Ph) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) -4.5 (Si*C*H_3), -4.4 (Si*C*H_3), 18.0 (Si*C*$(CH_3)_3$), 25.6 (SiC(*C*$H_3)_3$), 27.9 (C-*C*H_3), 28.1 (C-5), 28.2 (C-7), 40.9 (Cq, *t*-Bu), 60.4 (C-5'), 68.0 (C-

2), 70.4 (C-6'), 81.2 (C-4'), 81.8 (Cq), 95.8 (C-3), 100.7 (C-2'), 125.8 (CH, Ph), 128.2 (CH, Ph), 128.8 (CH, Ph), 137.6 (Cq, Ph), 148.1 (C-4), 170.4 (*C*=O) ppm. HRMS (FAB): calcd for $C_{27}H_{42}NO_6Si$: 504.2781; found: 504.2779.

5.3. Material and methods

Molecular dynamic (MD) simulations were performed with the GROMACS package version 4.5.4 using de AMBER03/GAFF force field. The geometry of each azirine enantiomer was optimized with a quantum mechanical method at the Hartree-Fock level with the 6-31G(d) basis set using GAMESS. This optimized geometry and the quantum mechanical electrostatic potential was used to calculate the partial atomic charges using the RESP fitting method. The azirine molecules were solvated with 500 chloroform solvent molecules in a cubic box with dimension of 4.4 × 4.4 × 4.4 nm. The equations of motion were numerically integrated using a timestep of 2 fs. The nonbonded interactions were treated with a cut off of 0.9 nm and updated every 5 steps. Long-range electrostatic interactions were treated with particle-mesh-ewald (PME) using a fourier spacing of 1.2 nm and a PME order of 4. The system was simulated in an isothermal and isochoric ensemble using the Berendsen thermostat at 300 K and relaxation time of 0.1 ps. The pressure coupling was also accomplished with the Berendsen barostat with a relaxation time of 0.5 ps and isothermal compressibility of 4.5 x 10^{-5} bar. All bonds were constrained using the LINCS algorithm. An initial energy minimization consisting of 5000 steps was performed using the steepest descent algorithm. We performed one long MD simulation of 400 ns for each system. Conformations were recorded every 1 ps.

From these long MD simulations the multidimensional free energy landscape of each azirine enantiomer was calculated. The multidimensional free energy landscape was calculated using a principal component analysis (PCA) approach based on the structural dissimilarity of all pairs of conformations recorded. The protocol for the PCA calculations and identification of the lowest free energy conformations used herein was the same as described by Sara *et al*.[17]

6. Acknowledgments

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2.4

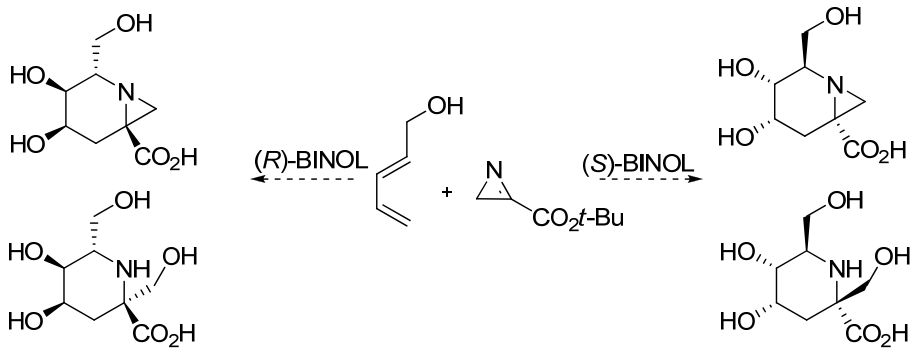
Enantioselective Diels-Alder Cycloadditions in the Synthesis of Two Enantiomeric Sets of Homochiral Polihydroxylated Pipecolic Acid Derivatives.

Duarte, V. C. M.; Alves, M. J.; Gil Fortes, A. *submitted to Org. Lett.* **2013**.

Index

1. Abstract

1,4-Pentadienol was combined with electrophilic *t*-butyl 2*H*-azirine 3-carboxylate under a self-assembly LACASA-DA methodology, using BINOL as chiral inductor. Cycloadducts were obtained with very high enantioseletivity (>99 % *ee*), and yields, in both enantiomeric forms, by changing the chirality of BINOL. Cycloadducts led to polihydroxylated pipecolic acids of two types, after two simple chemical transformations.



2. Results and Discussion

L-Pipecolic acid **1** (Figure 1) is a natural non proteinogenic α-amino acid commonly found in plants. Hydroxypipecolic acids can be considered as expanded hydroxylated homoprolines or as constrained serine derivatives. As such, replacement of natural amino acids in bioactive compounds by this fragment may affect the physiological and pathological processes in which they are implicated.[1] Also many polihydroxylated pipecolic acids have been reported with biological interest: e.g. α-homonojirimycin (**2**), a potent inhibitor of intestinal α-glucosidases;[2] a compound related to α-homonojirimycin, **3**, which is a potential immunosuppressive agent;[3] and a fused aziridine **4**, known as an inactivator of glucosidases[4] (Figure 1). Therefore much effort has been directed towards the development of efficient syntheses of pipecolic acid related compounds. Most of the synthetic approaches involve chiral reagents as starting materials, but new strategies have emerged employing asymmetric catalysis instead.[5]

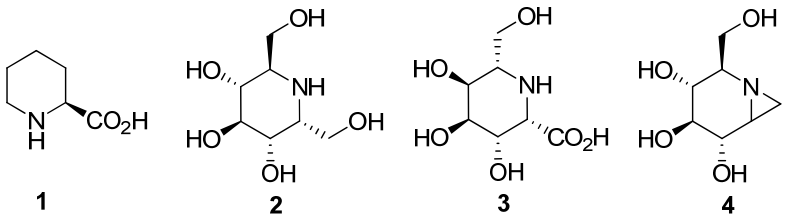
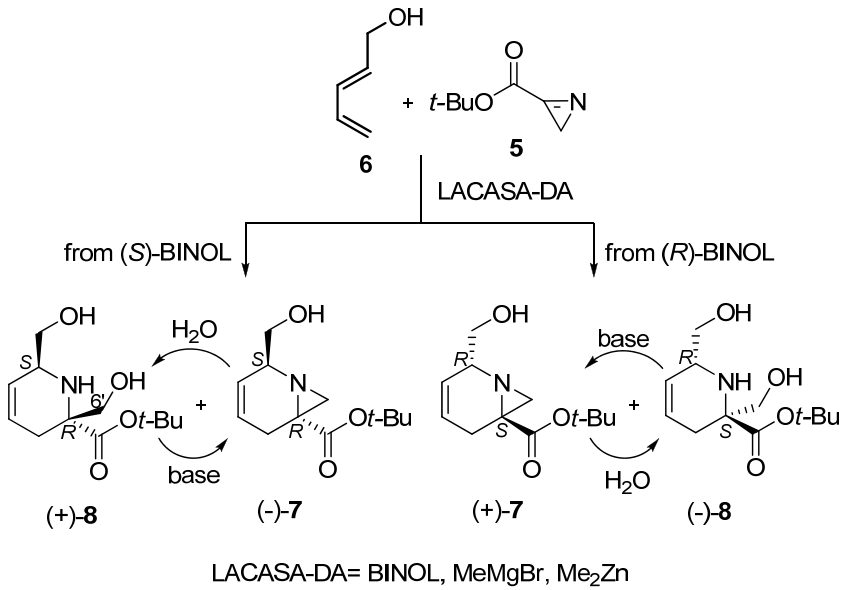


Figure 1 Pipecolic acid (**1**) and some related compounds (**2**-**4**).

Our group has been engaged in the stereoselective synthesis of polihydroxylated piperidines having Diels-Alder cycloaddition (DA) as the key step.[6] *E.g. t*-butyl 2*H*-azirine 3-carboxylate **5** was combined with a D-erythrose 1,3-butadiene in a LACASA-DA leading to the synthesis of a neuraminic acid precursor.[7] In the present work the same electrophilic dienophile (**5**) was combined to the achiral 2,4-pentadienol (**6**) aiming the DA cycloadduct, precursor of pipecolic acid related compounds.

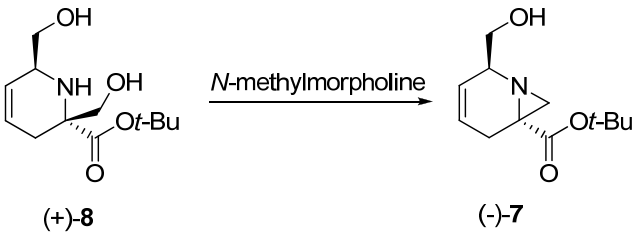
2,4-Pentadienol (**6**) was reacted to *t*-butyl 2*H*-azirine 3-carboxylate (**5**), obtained in situ from *t*-butyl α-azido acrylate at 120 ºC, in a DA cycloaddition.[8] The reaction was catalysed by a bimetallic complex of Mg and Zn tethering the reagents to (*R*)- /(*S*)-BINOL (Figure 2). The reactions proceeded smoothly at -20 ºC to give the expected cycloadducts **7** in moderate yields (47-49 %) (Scheme 1). A minor product was obtained in each reaction together with the major compound **7**. Their structure was identified as being **8**, formed by opening the aziridine moiety in compound **7**. Major features of compounds **8** are ^{1}H NMR spectra showing the presence of two sets of doublets at δ 3.46 and 3.66 ppm due to the germinal protons H-6', instead of the typical singlets of methylene aziridine protons at δ ~2 ppm with zero coupling constant between them.[9]



LACASA-DA= BINOL, MeMgBr, Me_2Zn

Scheme 1

The formation of compounds **8** is explained by the presence of residual water in toluene (the solvent of the reaction), which under the acidic reaction conditions promote the nucleophilic attack that would be otherwise ineffective. When freshly distilled toluene, dried over Na(s), was used in the reaction, the amount of **8** was considerably reduced. Fortunately the hydrolysis can be reverted by treatment of compound **8** with base giving back cycloadduct **7**. This was shown for the reaction mixture obtained in the cycloaddition carried out with (*S*)-BINOL chiral ligand. The obtained cycloadduct **7** showed to be levorotatory and the sub-product **8** of this same reaction switches the monochromatic light to the *dextra*. Treatment of compound (+)-**8** with *N*-methylmorpholine for 3 hours, gives back cycloadduct (-)-**7** in quantitative yield. The absolute value of optical rotation of the obtained product is exactly the same as for cycloadduct (-)-**7**, which shows that the stereocentres are maintained untouched during the ring opening-closing processes (Scheme 2). Being so, the yields of cycloadducts can be largely improved from moderate to high (89-93 %).



Scheme 2

The optical purity of cycloadducts **7**, obtained from reactions with the (*S*)- and (*R*)-BINOL were determined by the ^{1}H NMR analysis of (*S*)-camphanoate derivatives. A single set of singlets appears in spectra for methylene aziridine protons. Also only one set of singlets are due for methyl groups of the camphor unit, appearing at δ 0.76, 0.87 and 0.93 ppm, assuring the presence of a unique enantiomer **7** in each reaction.

Cycloadditions followed the typical *endo* approach of reagents of 2*H*-azirines to 1,3-dienes in general, except for furan and derivatives, in which the *exo* approach is preferential.[10] Products formed by the *endo* approach are easily identified by the effect of electronic current of the C=C bond at the rear of the structure which creates an anisotropic effect over the aziridine methylenic protons, shielding these protons, that show up at *ca* 2 ppm.[9]

Figure 2 depicts the arrangement of all components tethered together in the transition state of cycloadditions. According to arrangement **A** (*S*)-BINOL induces the dienophile to attack the *si* face of the diene (bottom face). Otherwise (*R*)-BINOL leaves open the *re* face of the diene (top face) as represented in approach **B**.

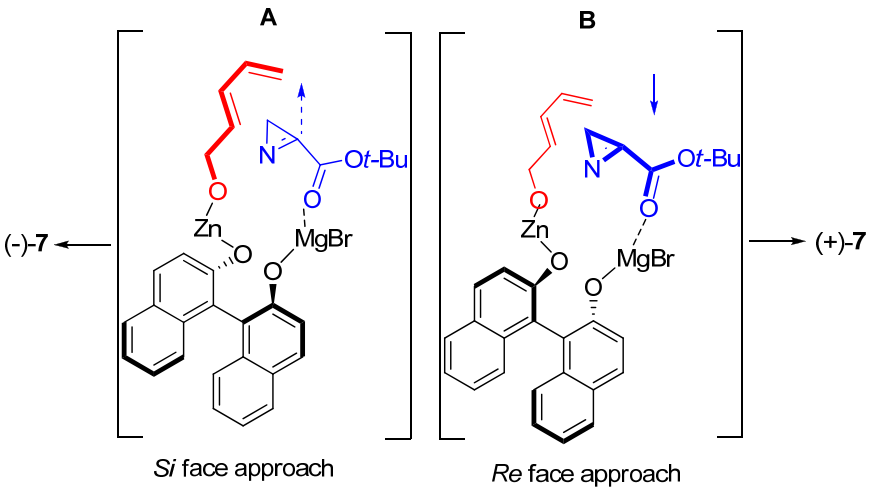
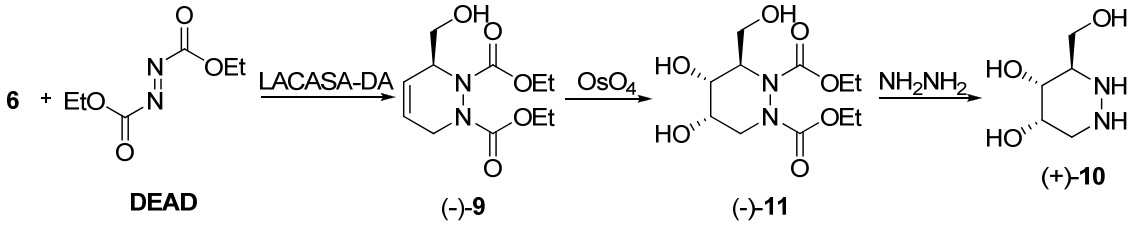


Figure 2 Different approaches of 2*H*-azirine **5** to 2,4-pentadienol (**6**) in the presence of (*S*)-BINOL (**A**) or (*R*)-BINOL (**B**).

In the impossibility of getting appropriate crystals of camphanoate derivatives of cycloadducts **7** or **8** for a single crystal X-ray analysis to acknowledge the stereocentres configuration of compounds **7**/**8**, a search in the lit. provided information of LACASA-DA cycloadditions between 2,4-pentadienol or 1-methoxy-2,4-hexadiene and methyl acrylate in the presence of (*S*)-BINOL. In both cases the dienophile attacks

the *si* face of the diene.[7] To improve the evidence in the definition of the absolute configuration in products **7**/**8**, it was decided to react an aza-dienophile, to which the same kind of interaction with Mg is expected relatively to 2*H*-azirine, with the aim of obtaining a known compound.[6,11] For this purpose 2,4-pentadienol (**6**) and diethyl azodicarboxylate (DEAD) was self-assembled on a Lewis acid template incorporating (*S*)-BINOL as chiral ligand. The product, cycloadduct (-)-**9**, was then transformed to the known 5-*epi*-1-azafagomine (+)-**10**, by osmilation with formation compound (-)-**11** followed its hydrazinolysis (Scheme 3). The product obtained showed an optical rotation value of + 22.7º which is in accordance with optical rotation of homochiral 5-*epi*-1-azafagomine **10** in lit.[6]



LACASA-DA = (*S*)-BINOL, MeMgBr, Me_2Zn

Scheme 3

Figure 3 shows the coordination and spatial arrangement of 2*H*-azirine **5** and DEAD in the reactive template incorporating (*S*)-BINOL. It is most likely that the absolute stereochemistry of products **7** and **8** will correspond to the approach of the azirine to the *si* face of diene **6** as occurs to DEAD. The reactions with (*R*)-BINOL gave products with the same ^{1}H and ^{13}C NMR spectra as those obtained with (*S*)-BINOL, but with the opposite optical rotation, showing that the azirine is attacking the *re* face of the diene this time. The stereochemistry of the products is opposite to that obtained in the reaction with (*S*)-BINOL.

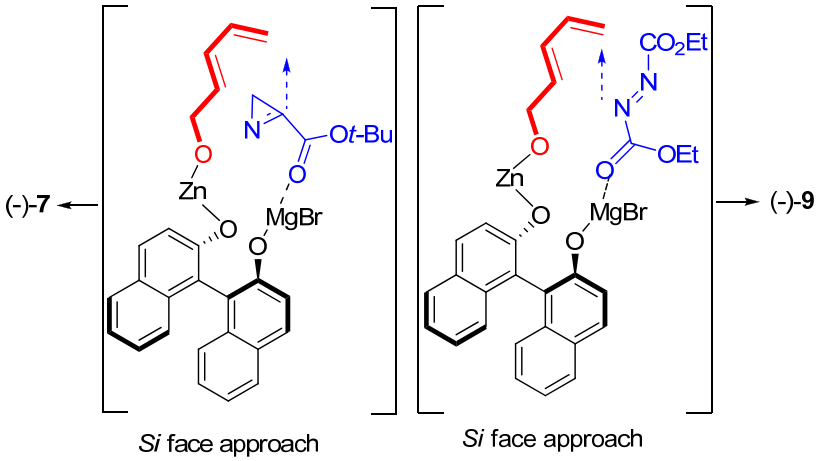
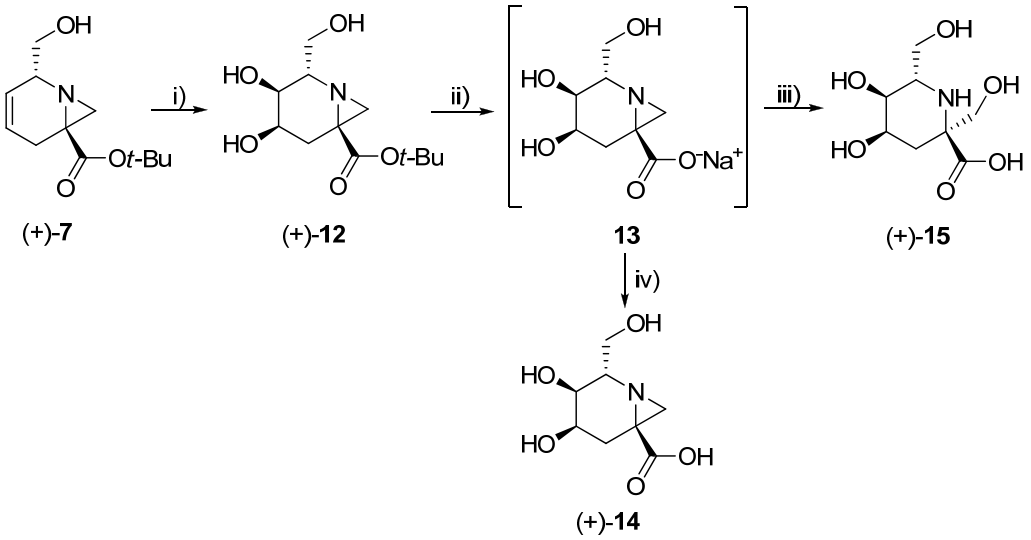


Figure 3 Comparison of azirine (**5**) and DEAD approaches to the *si* face of 2,4-pentadienol (**6**).

Functionalization of (+)-**7** was carried in two steps. First, oxidation occurred under OsO_4/NMO leading to a 5:1 mixture of stereoisomers; the major isomer (+)-**12** was isolated in 58 % yield by simply washing the crude material with ether. The major isomer (+)-**12** was hydrolysed by treatment with aq. NaOH 1M at rt to furnish compound **13**. After a 10 min stirring the reaction was complete. The obtained sodium salt was solubilized in water, stirred for another 10 min in the presence of Resin-H^+ to give the carboxylic acid (+)-**14**, together with an open chain compound (+)-**15**. If the resin treatment was prolonged for 1h, pure compound (+)-**15** was obtained in 35 % yield. To avoid the aziridine opening the reaction mixture obtained from sodium hydroxide treatment was filtered through a short column of Resin-H^+, previously washed with water to reduce its acidity. Pure product (+)-**14** was obtained in 43 % yield by this procedure (Scheme 4).



Scheme 4

Conditions: i) OsO_4, NMO, acetone/H_2O 8:1, 7h, rt, 66 %; ii) NaOH 1M, 10 min, rt; iii) Resin-H^+, 1h, rt, 35 %; iv) Resin-H^+ column, 43 %.

Enantiomers of compounds (+)-**14**, *ent*-**14**, and (+)-**15**, *ent*-**15**, were obtained from cycloadduct (-)-**7** following the sequence described in Scheme 4 for cycloadduct (+)-**7**.

In conclusion, the combination of *t*-butyl 2*H*-azirine 3-carboxylate with 2,4-pentadienol using a bimetallic complex of Zn, Mg tethered with BINOL gave primary adducts **7** and its hydrolysis products **8** in high yields and total enantioselectivity. Both enantiomers **7** were obtained by changing the chirality of BINOL. It was found that compounds **8** can be easily and cleanly transformed into **7** and vice-versa. Osmilation of the double bond, followed by *t*-butyl ester cleavage led to a two set of polihydroxylated pipecolic acids, **14** and **15** for each enantiomer. The absolute stereochemistry of products was proposed on the basis of similar reactions in lit. and by cycloaddition of 2,4-pentadienol to DEAD using (*S*)-BINOL, in which a known product with established configuration at the stereocentres was obtained.

3. Experimental section

3.1. General Methods

2*H*-Azirine 5 was prepared in situ from α-azido *t*-butyl acrylate.[8] All other reagents were purchased and used without further purification. Solvents employed in

reactions were dried: CH_2Cl_2 was freshly distilled under CaH_2 and toluene was submitted to simple distillation to remove the head fraction. Petroleum ether 40-60 ºC used in flash chromatography was previously distilled, and all other solvents were used as purchased. Glassware was dried prior to use. Compounds were purified by dry flash chromatography, using silica 60 <0.063 mm as the stationary phase and water pump vacuum. TLC plates (Silica Gel 60 F_{254}, Macherey-Nagel) were visualized either at UV lamp or in I_2. ^1H NMR and ^{13}C NMR were run on a Varian Unity Plus 300, or Brucker Avance III 400 or Bruker BioSpin GmbH spectrometers. Infrared spectra were recorded on a Bomem MB 104. Samples were run as nujol mulls and oils as thin films. Melting points are uncorrected. MS spectra were recorded on a VG Autospec M. spectrometer.

3.2. Synthesis of (2*S*,6*R*)-*t*-butyl 2-(hydroxymethyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (-)-7 and (2*R*,6*S*)-*t*-butyl 2,6-bis(hydroxymethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (+)-8

Solution A: a solution of Me_2Zn 1.2 M in toluene (0.991 mL; 1.19 mmol) was added to a solution of penta-2,4-dien-1-ol (0.10 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and the mixture stirred for 5 min.

Solution B: a solution of MeMgBr 1.4 M in toluene/THF (0.849 mL; 2,38 mmol) was added to a solution of (*S*)-BINOL (0.340 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and mixture stirred for 5 min.

Solution A was diluted with dry toluene (10 mL), added to solution B, stirred for 5 min and then refrigerated at -78 ºC. To this mixture was added a solution of *t*-butyl 2*H*-azirine-3-carboxylate (0.168 g; 1.19 mmol) in dry toluene (10 mL) during 5 min. The temperature was allowed to rise gradually to -20 ºC and the reaction mixture was transferred into a freezer for 24h and kept stirring. A new portion of *t*-butyl 2*H*-azirine-3-carboxylate (0.168 g; 1.19 mmol) was added, and the reaction stirred for another 7 days. The reaction was quenched with saturated solution of $NaHCO_3$ (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (2 × 20 mL). The filtrates were combined and concentrated under reduced pressure giving an orange oil. The crude mixture was purified by “dry-flash” chromatography (silica, petroleum ether/ diethyl ether, increasing polarity). (*S*)-BINOL was recovered with petroleum ether (3): ether (1) (0.250 g; 74 %); the minor isomer (+)-**8** with petroleum ether (1)/ diethyl ether (3) (0.063 g; 22 %), and major isomer (-)-**7** with diethyl ether (0.130 g; 49 %) as orange oils.

Major isomer (-)-**7**: $[\alpha]_D^{20}$ -54.4° (*c* 2.0, $CHCl_3$). ν_{max} (nujol) 3234, 1731, 1659 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 1.47 (9H, s, 3 × CH_3), 1.93 (1H, s, H-1'), 2.01 (1H, s, H-1'), 2.58-2.65 (1H, m, H-5), 2.65-2.73 (1H, m, H-5), 3.60 (1H, dd, *J* 10.8, 8.4 Hz, H-2'), 3.67 (1H, dd, *J* 11.2, 4.8 Hz, H-2'), 3.78-3.80 (1H, m, H-2), 5.27-5.31 (1H, dm, *J* 10.4 Hz, H-4), 5.73-5.79 (1H, m, H-3) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 22.6 (C-5), 27.7 (C-1'), 27.9 (3 × CH_3), 38.5 (C-6), 56.7 (C-2), 65.0 (C-2'), 81.4 (Cq, *t*-Bu), 121.8 (C-4), 124.4 (C-3), 171.4 (C=O) ppm. HRMS (ESI): calcd for $C_{12}H_{20}NO_3$: 226.1438; found: 226.1435.

Minor isomer (+)-**8**: $[\alpha]_D^{20}$ +51.4 (*c* 1.8, $CHCl_3$). ν_{max} (neat) 3407, 1725, 1642 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$) 1.47 (9H, s, 3 × CH_3), 2.13 (1H, dm, *J* 16.8 Hz, H-3), 2.50-2.70 (2H, bs, 2 × OH), 2.62 (1H, dddd, *J* 16.8, 5.8, 2.5, 1.0 Hz, H-3), 3.46 (1H, d, *J* 9.8 Hz, H-2'), 3.54 (1H, dd, *J* 10.8, 4.4 Hz, H-6'), 3.65 (1H, dd, *J* 11.0, 3.8 Hz, H-6'), 3.66 (1H, d, *J* 10.0 Hz, H-2'), 3.91-3.96 (1H, m, H-6), 5.57 (2H, dm, *J* 10.0 Hz, H-5), 5.79 (1H, ddt, *J* 10.2, 5.8, 2.2 Hz, H-4) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$) 27.9 (3 × CH_3), 32.4 (C-3), 40.6 (C-2'), 53.6 (C-6), 61.1 (C-2), 65.3 (C-6'), 82.3 (Cq, *t*-Bu), 124.1 (C-4), 126.8 (C-5), 171.6 (C=O) ppm. HRMS (ESI): calcd for $C_{12}H_{22}NO_4$: 244.1549; found: 244.1520.

3.3. Synthesis of (2*R*,6*S*)-*t*-butyl 2-(hydroxymethyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (+)-7 and (2*S*,6*R*)-*t*-butyl 2,6-bis(hydroxymethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (-)-8

Solution A: a solution of Me_2Zn 1.2 M in toluene (0.991 mL; 1.19 mmol) was added to a solution of penta-2,4-dien-1-ol (0.10 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and stirred for 5 min.

Solution B: a solution of MeMgBr 1.4 M in toluene/THF (0.849 mL; 2.38 mmol) was added to a solution of (*R*)-BINOL (0.340 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and stirred for 5 min.

Solution A was diluted with dry toluene (10 mL), added to solution B, stirred for 5 min, and then refrigerated at -78 ºC. To this mixture was added a solution of *t*-butyl 2*H*-azirine-3-carboxylate (0.168 g; 1.19 mmol) in dry toluene (10 mL) during 5 min. The temperature was allowed to rise gradually to -20 ºC and the reaction mixture was transferred into a freezer for 24h and kept stirring. A new portion of *t*-butyl 2*H*-azirine-3-carboxylate (0.168 g; 1.19 mmol) was added, and the reaction stirred for another 7

days. The reaction was quenched with saturated solution of $NaHCO_3$ (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (2 × 20 mL). The filtrates were combined and concentrated under reduced pressure giving an orange oil. The crude oil was purified by "dry-flash" chromatography (silica, petroleum ether / diethyl ether). (*R*)-BINOL was recovered with petroleum ether (3) : ether (1) (0.246 g; 72 %); the minor isomer (-)-**8** with petroleum ether (1) : diethyl ether (3) (0.081 g; 28 %) and major isomer (+)-**7** with diethyl ether (0.127 g; 47 %) as orange oils.

Major isomer (+)-**7**: $[\alpha]_D^{20}$ +78.0° (*c* 0.75, $CHCl_3$)

Minor isomer (-)-**8**: $[\alpha]_D^{20}$ -45.6° (*c* 1.5, $CHCl_3$)

3.4. Synthesis of camphanoate derivative of compound (-)-7

To a solution of (-)-**7** (0.011 g; 0.045 mmol) in dry CH_2Cl_2 (6 mL) was added DMAP (4 mg), triethylamine (98 µL) and (*S*)-camphanic acid chloride (22 mg; 0.09 mmol). The reaction was stirred at rt for 40 min. The solvent was removed by reduced pressure; the residuum was dissolved in ethyl acetate (10 mL), filtered through a pad of silica and washed with ethyl acetate (2 × 10 mL). The filtrate was concentrated, giving a yellow oil (0.018 g; 96%), which proved by ^{1}H NMR to be an unique diastereomer.

^{1}H NMR (δ_H, 400 MHz, C_6D_6) 0.75 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.26 (2H, dt, *J* 10.0, 4.8 Hz, H-8'), 1.34 (9H, s, 3×CH_3), 1.72 (1H, ddd, *J* 13.6, 9.0, 5.0 Hz, H-9'), 1.81 (1H, s, H-1'), 2.07 (1H, s, H-1'), 2.10 (1H, ddd, *J* 13.4, 10.2, 4.9 Hz, H-9'), 2.31 (1H, dd, *J* 18.4, 6.5 Hz, H-5), 2.74 (1H, dtdd, *J* 18.4, 3.3, 2.3, 1.3 Hz, H-5), 3.65 (1H, bs, H-2), 3.87 (1H, dd, *J* 11.2, 4.4 Hz, H-2'), 4.27 (1H, dt, *J* 12.7, 6.4 Hz, H-2'), 4.94 (1H, dm, *J* 10.4 Hz, H-3), 5.36 (1H, dddd, *J* 10.3, 6.6, 3.0, 2.2 Hz, H-4) ppm.

3.5. Synthesis of camphanoate derivative of compound (+)-7

To a solution of (+)-**7** (0.025 g; 0.11 mmol) in dry CH_2Cl_2 (13.5 mL) was added DMAP (9 mg), triethylamine (178 µL) and (*S*)-camphanic acid chloride (50 mg; 0.22 mmol). The reaction was stirred at rt for 30 min. The solvent was removed at reduced pressure and the residuum was dissolved in ethyl acetate (10 mL), filtered through a short pad of silica, and washed with ethyl acetate (2 × 10 mL). Filtrate was concentrated, giving a yellow oil (0.019 g; 41 %), which proved by ^{1}H NMR to be a single diastereomer.

^{1}H NMR (δ_H, 400 MHz, C_6D_6) 0.76 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.26 (2H, dt, *J* 10.0, 4.8 Hz, H-8'), 1.33 (9H, s, 3×CH_3), 1.72 (1H, ddd, *J* 13.6, 9.0, 5.0 Hz, H-9'), 1.82 (1H, s, H-1'), 2.05 (1H, s, H-1'), 2.10 (1H, ddd, *J* 13.4, 10.2, 4.9 Hz, H-9'), 2.31 (1H, dd, *J* 18.4, 6.5 Hz, H-5), 2.74 (1H, dtdd, *J* 18.4, 3.3, 2.3, 1.3 Hz, H-5), 3.66 (1H, bs, H-2), 3.87 (1H, dd, *J* 11.2, 4.4 Hz, H-2'), 4.28 (1H, dd, *J* 11.1, 6.9 Hz, H-2'), 4.94 (1H, dm, *J* 10.4 Hz, H-3), 5.36 (1H, dddd, *J* 10.3, 6.6, 3.0, 2.2 Hz, H-4) ppm.

3.6. Conversion of (+)-8 into (-)-7

To a solution of a 3:1 mixture of (+)-**8** and (-)-7 (0.122 g; 0.50 mmol) in acetone (1.6 mL) and water (0.2 mL) was added *N*-methylmorpholine (81 µL; 0.75 mmol), and the reaction mixture stirred for 3h at rt, then diluted with CH_2Cl_2 (10 mL) and washed with water (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving compound (-)-**7** (0.112 g; 99 %).

3.7. Synthesis of (*S*)-diethyl 3-(hydroxymethyl)pyridazine-1,2(3*H*,6*H*)-dicarboxylate (-)-9

Solution A: a solution of Me_2Zn 1.2 M in toluene (991 µL; 1.19 mmol) was added to a solution of penta-2,4-dien-1-ol (0.100 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and stirred for 5 min.

Solution B: a solution of MeMgBr 1.4 M in toluene/THF (849 µL; 1.19 mmol) was added to a solution of (*S*)-BINOL (0.340 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and stirred for 5 min.

Solution A was diluted with dry toluene (10 mL), added to solution B, stirred for 5 min, and then refrigerated at -78 ºC. To this mixture was added a solution of diethyl azodicarboxylate (543 µL; 1.19 mmol) in dry toluene (10 mL). The temperature was allowed to rise gradually to rt and the reaction mixture was stirred for 18h. The reaction was quenched with saturated solution of $NaHCO_3$ (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (3 × 20 mL). The filtrates were combined and concentrated under reduced pressure giving a yellow oil. The crude oil was purified by "dry-flash" chromatography (silica, petroleum ether / diethyl ether). (*S*)-BINOL was recovered with petroleum ether (1) : ether (1) (0.200 g; 69 %) and product (-)-**9** with diethyl ether (0.225 g; 73 %) as a yellow oil.

$[\alpha]_D^{20}$ -23.4º (*c* 1.25, $CHCl_3$). ν_{max} (neat) 3483, 1707 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$)* 1.23-1.30 (12H, m, 4 × CH_3, A+B), 2.58 (1H, bs, OH), 3.35 (1H, dd, *J* 12.3, 9.5 Hz, H-3', A), 3.45 (1H, dd, *J* 12.0, 9.8 Hz, H-3', B), 3.56-3.69 (2H, m, 2 ×H-3', A+B), 3.77 (1H, dd, *J* 13.5, 4.3 Hz, H-6, A), 3.91 (1H, bs, H-6, B), 4.11-4.26 (8H, m, 4 × CH_2, A+B), 4.30 (1H, tdd, *J* 6.0, 3.9, 2.2 Hz, H-6, B), 4.34-4.44 (1H, m, H-6, A), 4.72 (2H, bs, H-3, A+B), 5.66-5.88 (4H, m, H-4 + H-5, A+B) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$)** 14.3 (CH_3, A), 14.4 (CH_3, B), 42.2 (C-6, A), 43.6 (C-6, B), 55.9 (C-3, A), 56.9 (C-3, B), 61.9 (C-3', A+B), 62.6, 62.7, 62.8, 62.9 (CH_2, A+B), 123.4, 124.2, 124,6, 125.2 (C-4 or C-5, A+B), 154.9, 155.7, 156.2, 156.3 (C=O, A+B) ppm. HRMS (ESI): calcd for $C_{11}H_{18}N_2NaO_5$: 281.1108; found: 281.1109.

* ^1H NMR analysis showed a 1:1 mixture of rotamers A and B, due to inversion of the nitrogen atoms lone pair within the six membered ring.

** ^{13}C NMR also showed peak duplication.

3.8. Synthesis of (3*R*,4*R*,5*S*)-diethyl 4,5-dihydroxy-3-(hydroxymethyl)piperazine-1,2-dicarboxylate (-)-11

To a solution of (-)-**9** (0.115 g; 0.45 mmol) in acetone (0.5 mL) and water (0.25 mL) was added *N*-methylmorpholine *N*-oxide (NMO) (0.079 g; 0.67 mmol) and solution of OsO_4 4 % in water (48.6 µL; 0.017 eq.). The reaction mixture was stirred for 5 days at rt. The reaction was quenched with an aqueous solution of $Na_2S_2O_3$ 5 % (10 mL) and the mixture was stirred for 15 min. Then, the solution was concentrated under reduced pressure; the residuum was dissolved in EtOAc and filtered through a short column of silica. Concentration of filtrate gave compound (-)-**11** as a colourless oil (0.079 g; 60 %).

$[\alpha]_D^{20}$ -17.0º (*c* 3.65, MeOH). ν_{max} (neat) 3419, 2983, 2937, 1698 cm^{-1}. ^1H NMR (δ_H, 400 MHz, $CDCl_3$)* 1.23-1.32 (12H, m, 4 × CH_3, A+B), 3.12 (1H, bd, *J* 10.8 Hz, H-6, A), 3.21 (1H, bd, *J* 10.8 Hz, H-6, B), 3.50 (2H, t, *J* 11.6 Hz, H-3', A), 3.62 (1H, d, *J* 8.0 Hz, H-3', B), 3.65-3.95 (4H, bs, H-4 + H-5, A+B), 4.01 (2H, dd, *J* 13.2, 5.6 Hz, H-6, A), 4.10-4.25 (9H, m, H-6, B + 4×CH_2, A+B), 4.52-4.64 (2H, bs, H-3, A+B) ppm. ^{13}C NMR (δ_C, 100 MHz, $CDCl_3$)** 14.3, 14.4 (CH_3, A+B), 44.0, 45.7 (C-6, A+B), 58.4, 59.0 (C-3, A+B), 61.9, 62.8 (C-3', A+B), 63.0, 63.1 (CH_2, A or B), 63.2, 63.3 (CH_2, A or B), 64.0, 64.3 (C-4 or C-5, A+B), 66.4, 66.7 (C-4 or C-5, A+B), 1555.2, 156.5 (C=O, A+B), 157.1, 157.3 (C=O, A+B) ppm. HRMS (ESI): calcd for $C_{11}H_{20}N_2NaO_7$: 315.1163; found: 315.1163.

* ^{1}H NMR analysis showed a 1:1 mixture of rotamers A and B, due to inversion of the nitrogen atoms lone pair within the six membered ring.

** ^{13}C NMR also showed peak duplication.

3.9. Synthesis of (3*R*,4*R*,5*S*)-3-(hydroxymethyl)piperazine-4,5-diol (+)-10

A solution of (-)-**11** (0.060 g; 0.21 mmol) in $NH_2NH_2.H_2O$ (3 mL) was stirred in an oil bath during 18h, at 100 ºC. The mixture was concentrated under reduced pressure and the residuum was submitted to a "dry-flash" chromatography (silica; ethanol / NH_4OH 25 %). The product was eluted with a 14:1 mixture of ethanol / NH_4OH 25 % as a colourless oil ((+)-**10**; 0.026 g; 86 %).

$[\alpha]_D^{20}$ +22.7º (*c* 1.6, H_2O)

The spectroscopic data of the racemic mixture was reported before.[11]

3.10. Synthesis of (2*S*,3*S*,4*R*,6*S*)-*t*-butyl 3,4-dihydroxy-2-(hydroxymethyl)-1-azabicyclo[4.1.0]heptane-6-carboxylate (+)-12

To a solution of (+)-**7** (0.075 g; 0.33 mmol) in acetone (1.60 mL) and water (0.20 mL) was added NMO (0.057 g; 0.49 mmol) and solution of OsO_4 4 % in water (35 µL; 0.06 mmol), and stirred at rt for 7h. The reaction was quenched with aqueous solution of $Na_2S_2O_3$ 5 % (7.40 mL), and stirred for 10 minutes. The solvent was removed by reduced pressure; the residuum obtained was washed ethanol (3 × 20 mL), filtered through a short column of silica and concentrated yielding a brown solid which by ^{1}H NMR spectrum proved to be a 5:1 mixture of isomers. The mixture was washed with diethyl ether and filtrated under vacuum, giving the major isomer (+)-**12** as beige solid (0.057 g; 66 %).

$[\alpha]_D^{20}$ +73.3° (*c* 1, THF). mp 161-163 ºC. ν_{max} (nujol) 3334, 3187, 1726 cm^{-1}. ^{1}H NMR (δ_H, 400 MHz, THF-*d*$_4$) 1.40 (9H, s, 3×CH_3), 1.77 (1H, d, *J* 1.6 Hz, H-1'), 1.93 (1H, dd, *J* 14.8, 4.0 Hz, H-5), 1.97 (1H, d, *J* 1.2 Hz, H-1'), 2.83 (1H, dd, *J* 14.8, 4.0 Hz, H-5), 3.21-3.28 (1H, m, H-3 or H-4), 3.28-3.34 (1H, m, H-3 or H-4), 3.65 (1H, dd, *J* 5.9, 3.6 Hz, H-2), 3.69 (1H, bd, *J* 3.2 Hz, OH), 3.73 (1H, bd, *J* 5.6 Hz, OH), 3.74-3.82 (3H, m, 2×H-2'+OH) ppm. ^{13}C NMR (δ_C, 100 MHz, THF-*d*$_4$) 28.0 (3×CH_3), 30.3 (C-5), 35.3 (C-1'), 36.0 (C-6), 57.1 (C-3 or C-4), 64.3 (C-2'), 66.7 (C-2), 67.6 (C-3 or C-4), 80.1 (Cq, *t*-Bu), 172.5 (C=O) ppm. HRMS (ESI): calcd for $C_{12}H_{22}NO_5$: 260.1420; found: 260.1429.

3.11. Synthesis of (2*S*,3*S*,4*R*,6*S*)-3,4-dihydroxy-2-(hydroxymethyl)-1-azabicyclo[4.1.0]heptane-6-carboxylic acid (+)-14

To a solution of (+)-**12** (0.009 g; 0.035 mmol) in 1,4-dioxane (2 mL) was added NaOH (1M, 3 mL) and stirred at rt for 10 min. The reaction mixture was filtrated through a column of resin-H^+ (Dowex 50 WX8 16-40 Mesh) and filtrate was concentrated by reduced pressure, giving the product as yellow oil ((+)-**14**; 0.003 g; 43 %).

$[\alpha]_D^{20}$ +52.8° (*c* 0.6, MeOH). ν_{max} (neat) 3422, 1653 cm^{-1}. ^1H NMR (δ_H, 400 MHz, D_2O) 1.86 (1H, s, H-1'), 1.95 (1H, s, H-1'), 2.29 (1H, dd, *J* 15.2, 3.6 Hz, H-3), 2.63 (1H, dd, *J* 15.2, 4.4 Hz, H-3), 3.33-3.41 (1H, m, H-6), 3.50 (1H, dd, *J* 9.0, 2.2 Hz, H-4 or H-5), 3.81 (1H, dd, *J* 12.0, 6.4 Hz, H-6'), 3.88-3.93 (2H, m, H-6' + H-4 or H-5) ppm. ^{13}C NMR (δ_C, 100 MHz, D_2O) 30.7 (C-3), 33.8 (C-1'), 38.8 (C-2), 55.6 (C-6), 62.1 (C-6'), 65.8 (C-4 or C-5), 66.1 (C-4 or C-5), 179.9 (C=O) ppm. HRMS (ESI): calcd for $C_8H_{14}NO_5$: 204.0794; found: 204.0801.

3.12. Synthesis of (2*S*,4*R*,5*S*,6*S*)-4,5-dihydroxy-2,6-bis(hydroxymethyl)piperidine-2-carboxylic acid (+)-15

To a solution of (+)-**12** (0.010 g; 0.04 mmol) in 1,4-dioxane (2 mL) was added NaOH (1M; 3 mL) and the mixture was stirred at rt for 10 min. Resin-H^+ (Dowex 50 WX8 16-40 Mesh) was added and the mixture stirred for 1h. The resin was filtered off and filtrate was concentrated by reduced pressure, giving a brown oil ((+)-**15**; 0.003 g; 35 %).

$[\alpha]_D^{20}$ +44.4° (*c* 0.6, MeOH). ν_{max} (neat) 3435, 1646, 1212 cm^{-1}. ^1H NMR (δ_H, 400 MHz, D_2O) 2.19 (1H, dd, *J* 15.2, 2.4 Hz, H-3), 2.74 (1H, dd, *J* 15.2, 4.0 Hz, H-3), 3.64 (2H, s, H-2'), 3.88 (1H, dd, *J* 11.0, 2.6 Hz, H-5), 3.91 (1H, dd, *J* 12.2, 6.2 Hz, H-6'), 3.99-4.04 (1H, m, H-6), 4.10 (1H, dd, *J* 12.4, 3.2 Hz, H-6'), 4.18-4.22 (1H, m, H-4) ppm. ^{13}C NMR (δ_C 100 MHz, D_2O) 33.8 (C-3), 38.1 (C-2'), 51.8 (C-6), 55.4 (C-6'), 60.9 (C-2), 63.1 (C-4), 63.3 (C-5), 169.0 (C=O) ppm. HRMS (ESI): calcd for $C_8H_{16}NO_6$: 222.0899; found: 222.0902.

4. Acknowledgements

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Chapter 3

Overview of Results

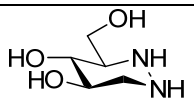
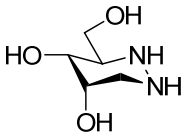
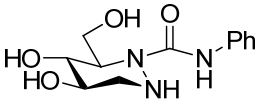
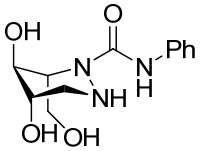
In this chapter, the title compounds achieved during the work presented in this thesis were summarized for an easy overview of results. The corresponding precursors were not included. The number of the subchapter was added to the number used in each article, in order to avoid confusion between different compounds with the same number but belonging to different subchapters: for example, compound **5a** in subchapter 2.2 is now **2.2-5a**.

The compounds for which biological activity studies were carried out, the values obtained were also presented.

In the case of facial selectivity studies, a summary of results were presented in tables for an easy comparison of the reaction conditions used either for thermal and catalysed reactions.

Chapter 2.1 "Advances in the Synthesis of Homochiral (-)-1-Azafagomine and (+)-5-*epi*-1-Azafagomine. 1-*N*-Phenyl Carboxamide Derivatives of both Enantiomers of 1-Azafagomine: Leads for the Synthesis of Active α-Glycosidase Inhibitors." *J. Org. Chem.* **2011**, *76*, 9584-9592.

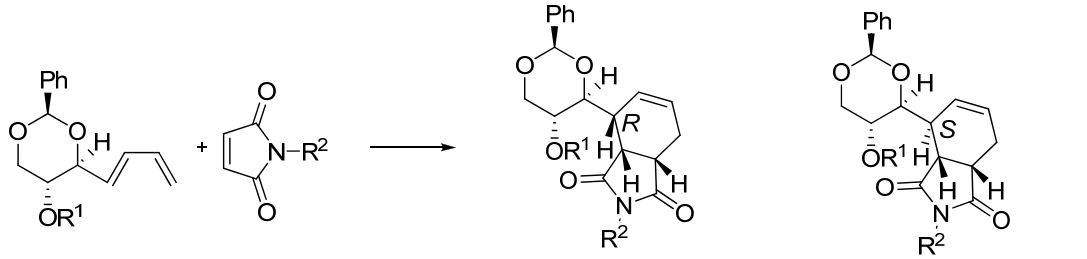
Table 21 K*i* Values (μM) for the inhibition of α- and β-glucosidases for compounds **2.1-22** and other relative azasugars.

Compound	Structure	α-glucosidase (baker's yeast)	β-glucosidase (almonds)
2.1-(-)-**2**		6.9[a]	0.32[a]
2.1-(+)-**3**		>1000[b]	137[b]
2.1-(-)-**22**		3.36[c] ___[d,e]	14.7[c] 67.4[d]
2.1-(+)-**22**		10.6[c] ___[d,e]	25.2[c] 90.0[d]

[a] pH 6.8. [b] Values obtained for the racemic mixture. [c] pH 7.0. [d] pH 5.0. [e] Enzyme inactive.

Chapter 2.2 "Diastereoselectivity in Diels-Alder Cycloadditions of Erythrose Benzylidene-acetal 1,3-Butadienes with Maleimides" *Synlett* **2012**, *23*, 1765-1768.

Table 22 Comparison of the facial selectivities achieved in thermal and catalysed cycloadditions of D-erythrose benzylidene-acetal 1,3-butadienes with maleimides.



2.2-5a R^1 = H, R^2 = Ph
2.2-5b R^1 = H, R^2 = H
2.2-5c R^1 = TBS, R^2 = H
2.2-5d R^1 = Ph, R^2 = H

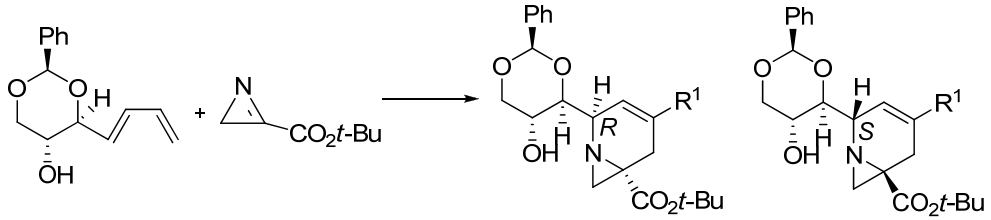
2.2-6a R^1 = H, R^2 = Ph
2.2-6b R^1 = H, R^2 = H
2.2-6c R^1 = TBS, R^2 = H
2.2-6d R^1 = Ph, R^2 = H

Product	Thermal reaction[a]	Catalysed reaction[b]	
		using (*R*)-BINOL	using (*S*)-BINOL
2.2-5a/**2.2-6a**	1(*R*):1(*S*)	1(*R*):2.5(*S*)	___
2.2-5b/**2.2-6b**	3(*R*):1(*S*)	(*R*)	(*R*)
2.2-5c/**2.2-6c**	2(*R*):1(*S*)	___	___
2.2-5d/**2.2-6d**	3(*R*):1(*S*)	___	___

[a] Reactions performed at rt. [b] LACASA-DA methodology.

Chapter 2.3 "Asymmetric Diels-Alder Cycloadditions of D-Erythrose 1,3-Butadienes to Achiral *t*-Butyl *2H*-Azirine 3-Carboxylate" *Tetrahedron: Asymmetry* **2013**, *24*, 1063-1068.

Table 23 Comparison of the facial selectivities achieved in thermal and catalysed cycloadditions of D-erythrose benzylidene-acetal 1,3-butadienes and *t*-butyl 2*H*-azirine 3-carboxylate.



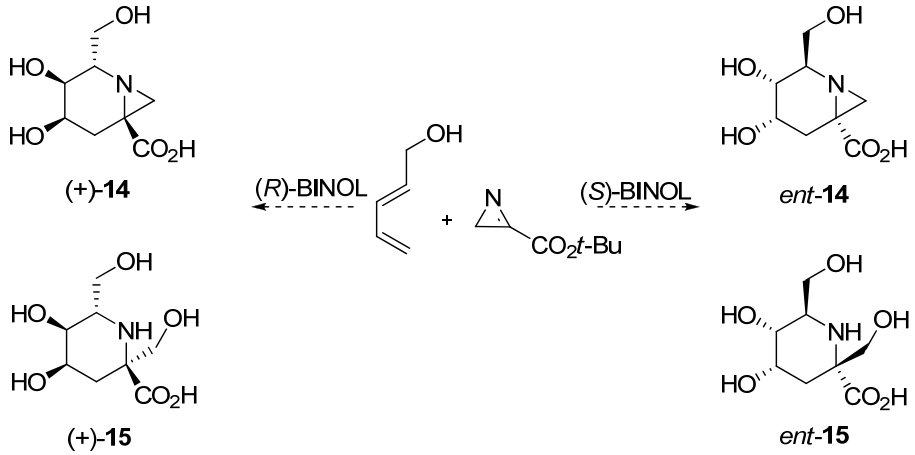
2.3-4a R^1 = H
2.3-4b R^1 = OTBS

2.3-5a R^1 = H
2.3-5b R^1 = OTBS

Product	Thermal reaction[a]	Catalysed reaction[b]	
		using (*R*)-BINOL	using (*S*)-BINOL
2.3-4a/**2.3-5a**	2.5(*R*):1(*S*)	(*S*)	(*R*)
2.3-4b/**2.3-5b**	1.4(*R*):1(*S*)	___	___

[a] Reactions performed at rt. [b] LACASA-DA methodology.

Chapter 2.4 "Enantioselective Diels-Alder Cycloadditions in the Synthesis of Two Enantiomeric Sets of Homochiral Polihydroxylated Pipecolic Acid Derivatives.", *submitted to Org. Lett.* **2013**.



Scheme 30 Synthesis of two enantiomeric sets of homochiral polihydroxylated pipecolic acid derivatives.

A 1,3-butadiene bearing a 2,3,4,6-tetraacetylglucosyl unit at position 1 was reacted by PTAD to give a homochiral cycloadduct, that was used as precursor of known iminosugars and its derivatives. This strategy allowed to obtaining 1-azafagomine in both enantiomeric forms, and for the first time (+)-5-*epi*-1-azafagomine. FGT of the cycloadduct afforded two new derivatives of 1-azafagomine: the *N*-phenyl carboxamides. These compounds were evaluated as glucosidase inhibitors; (-)-1-azafagomine derivative had shown the best inhibitory activity against baker's yeast α-glucosidase (K*i* = 3.39 μM) (Subchapter 2.1).

Combination of a D-erythrose diene with maleimides and an achiral 2*H*-azirine 3-carboxylate using a LACASA-DA methodology proved to be very efficient, giving in most cases total facial selectivity. In contrast thermal reactions produced a 3:1 ratio of diastereomers resulting from facial selectivity. A matched double asymmetric induction was observed in the catalysed reaction (Subchapters 2.2 and 2.3).

Combination of achiral reagents: 2,4-pentadienol (diene), 2*H* azirine and DEAD (dienophiles), in a LACASA-DA cycloaddition afforded the corresponding cycloadducts with total enantioselectivity. Cycloadducts were produced in both enantiomeric forms. In the case of the aziridine-fused cycloadduct, FGT led to the synthesis of polihydroxylated pipecolic acid derivatives (Subchapter 2.4).

Chapter 4

Conclusions and future prospects

1. Conclusions

The focus of this thesis has been put on the stereoselective synthesis of iminosugars with potential biological activity. Diels-Alder cycloaddition is the key step in every case.

The work started with a diastereoselective DA reaction. The inhibitory activity of the products obtained was tested in its α- and β-glucosidases, and the results were compared to analogues reported in lit.

The method demonstrated to be very efficient in terms of facial discrimination, but with a relatively long chain of reactions. A much more simplified and versatile process was established for the same compounds by an enantioselective methodology attaching the reagents to a Zn/Mg complex with BINOL. Homochiral products were obtained in both enantiomeric forms by changing the BINOL chirality.

The highlights of the obtained results are summarized next:

- chapter 2.1

A new expeditious preparation of homochiral (-)-1-azafagomine and (+)-5-*epi*-1-azafagomine was presented. The key step of the methodology employed consisted in a diastereoselective Diels-Alder cycloaddition of a diene bearing a 2,3,4,6-tetraacetyl glucosyl chiral auxiliary at position 1 with PTAD. New homochiral derivatives of both enantiomeric forms of 1-azafagomine: 1-*N*-phenyl carboxamide were synthetized and tested as glucosidase inhibitors face to α- and β-glucosidases. Both showed very good enzymatic inhibition toward baker's yeast α-glucosidase, one is twice more potent than (-)-1-azafagomine. Molecular modelling studies were performed in *Saccharomyces cerevisae* enzyme used for homology modelling, to understand the recognition mechanism of 1-*N*-phenyl carboxamide derivatives by baker's yeast α-glucosidase. The accommodation of the aromatic ring present in the 1-*N*-phenyl carboxamide moiety into a hydrophobic pocket in the enzyme's active site seems to be responsible for the improved inhibition observed relatively to the underivatized 1-azafagomine enantiomers.

- chapter 2.2

Maleimides were combined with D-erythrose benzylidene-acetal 1,3-butadienes in order to study the facial selectivity of the Diels-Alder cycloadditions. In thermal cycloadditions, the best result obtained was a 1:3 ratio of isomer products. It was found possible to reverse the selectivity to 2:1 by lowering the reaction temperature to 5º C. Tethering *N*H-maleimide, D-erythrose benzylidene-acetal 1,3-butadiene bearing the hydroxyl group unprotected to the chiral BINOL bimetallic Lewis acid catalyst (LACASA-DA reaction), allowed the synthesis of pure (*S*)-isomers in moderate yields, either in the presence of (*R*)- or (*S*)-BINOL.

- chapter 2.3

Two D-erythrose benzylidene-acetal 1,3-butadienes were reacted with electrophilic *t*-butyl 2*H*-azirine 3-carboxylate. Thermal cycloaddition occurred at 60 ºC with moderate facial selectivity, giving as major product the (*R*)-isomer. The moderate selectivity was explained by the antagonism of thermodynamics and kinetics in the reaction mechanism. Computational free energy perturbation methods together with ^{1}H NMR data led to the identification of the isomers formed. It was also shown that the (*S*)-product was thermodynamically preferred to the (*R*)-product. Pure (*R*)- and (*S*)-isomers were obtained by LACASA-DA methodology using Zn/Mg bimetallic complexes and BINOL as an extra chiral inductor.

- chapter 2.4

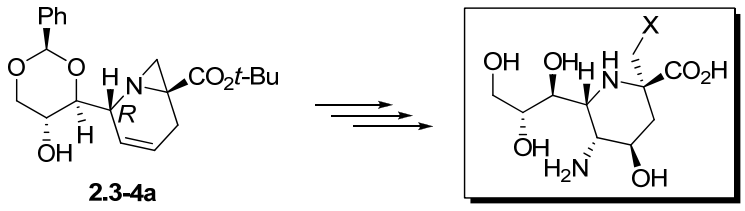
A bimetallic complex of Zn, Mg tethering BINOL, *t*-butyl 2*H*-azirine 3-carboxylate and 2,4-pentadienol led to a Diels-Alder cycloaddition with complete facial selectivity. Cycloadducts were obtained in high yields in both enantiomeric forms. The BINOL chirality is the factor responsible for the selectivity discrimination in each case. Cycloadduct's hydrolysis easily occurs under cycloaddition conditions, but proved to be reversible. The aziridine and the open-ring aziridine product led to two types of final products. Two simple chemical transformations furnished final polihydroxylated pipecolic acids. The absolute stereochemistry of products was proposed on the basis of similar reactions described in lit. and by cycloaddition of 2,4-pentadienol to DEAD,

using (*S*)-BINOL, in which a known product with established configuration at the stereocentres is obtained.

2. Future Prospects

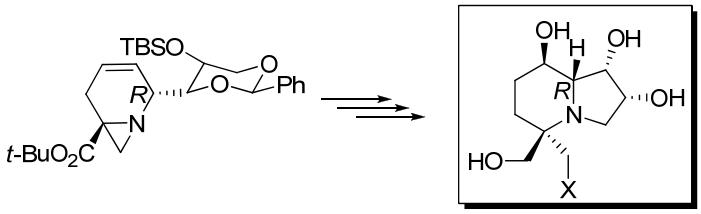
1) In an attempt to obtain piperidine iminosugars, 2,4-pentadienol was combined with a glyoxylate imine in a LACASA-DA cycloaddition. This system showed to be unreactive. To improve the reactivity the diene was substituted by a nucleophilic diene (Danishefsky's diene) and a boron catalyst was used instead of Zn/Mg complex. The catalyst was obtained from BINOL and $B(OPh)_3$. ^1H and ^{13}C NMR spectra of cycloadduct obtained showed that the diene skeleton was not included in the molecule. The full identification of this compound is still ongoing.

2) LACASA-DA methodology allows the synthesis of the cycloadducts precursors of important molecules, such as neuraminic acid and D-swainsonine analogues. The transformation of these cycloadducts into the final products is to be pursued. The (*R*)-cycloadduct (**2.3-4a**) obtained by LACASA-DA cycloaddition of D-erythrose 1,3-butadiene and *t*-butyl 2*H*-azirine 3-carboxylate, could be transformed into epimeric neuraminic acid analogue by trivial functional group transformations (Scheme 31).



Scheme 31 Conversion of cycloadduct **2.3-4a** in neuraminic acid analogue.

Disubstituted swainsonine analogues in position 5 will be accessed from cycloadduct **2.3-4a** by FGT (Scheme 32).



Scheme 32 FGT of cycloadduct to D-swainsonine analogue.

Other final compounds could be achieved from imines and azodicarboxylates starting materials (see Figure 18).

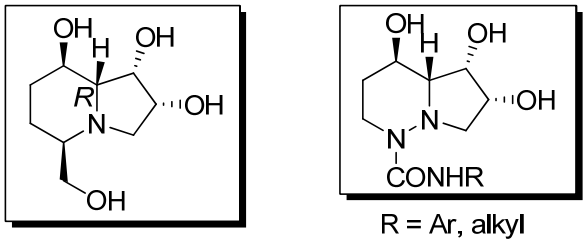


Figure 18 Structures of D-swainsonine and aza-D-swainsonine.