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SYNTHETIC STUDIES TOWARDS SPHINGOSINE-RELATED METABOLITES

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Abstract

Metabolites of the thermophilic fungi *Myriococcum albomyces* and *Mycelia sterilia* such as myriocin (thermozymocidin, ISP-1), the mycestericins and the sphingofungins structurally resemble the sphingosines, important components of cell membranes. The close relation of the metabolites to the sphingosines suggests an important role in regulatory processes of eukaryotic cell membranes.

All the compounds revealed *in vitro* remarkable immunosuppressive activity and their pharmaceutical potential has led to the development of promising novel immunosuppressants. The derivative FTY720 is the first S1P receptor agonist and has a different mode of action than the commonly used calcineurin-inhibitors CsA (Neoral®) and FK506 (Prograf®), or the macrolides RAD (Certican™) and rapamycin. FTY720 is currently in clinical phase III trials for therapeutic use in the areas of transplantation and autoimmunity and was recently found to be effective in kidney transplantation in humans.

Studies on the sphingosines and Garner's aldehyde have prompted us to investigate sphingosine-related metabolites such as myriocin, the mycestericins, or the sphingofungins. Many of these metabolites bear an α-substituted serine moiety as a common feature, and the formation of this quaternary centre represents the main synthetic challenge in total syntheses of these metabolites.

The task of this thesis is to establish a synthetic route for the controlled, stereoselective formation of the quaternary carbon centre of α-substituted serine derivatives, with the option of choice of the absolute configuration. An efficient and stereoselective method for this is based on the principle of self-regeneration of stereocentres (SRS).

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This thesis is dedicated to Benz (1946-2001).

Basel, January 2006 Martin Brunner

Abbreviations

AcOH	acetic acid
$(Boc)_2O$	di-*tert*-butyl dicarbonate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	diisopropylethylamine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
FC	flash chromatography
HMPA	hexamethylphosphorous triamide
KHDMS	potassium bis(trimethyl)disilazane
LICA	lithium isopropylcylcohexylamide
MPM or PMB	*p*-methoxyphenylmethyl or *p*-methoxybenzyl
NaHMDS	sodium bis(trimethyl)disilazane
NMO	4-methylmorpholine *N*-oxide
PG	protecting group
PMP	*p*-methoxyphenyl
Pv	pivaloyl
Py	pyridine
TEA	triethylamine
TPAP	tetra-*n*-propylammonium perruthenate
Tsoc	triisopropylsilyloxycarbonyl

List of Publications

I **Highly Diastereoselective Methylation of Five-Ring *N*,*O*-Acetals**

M. Brunner, T. Straub, P. Saarenketo, K. Rissanen, A. M. P. Koskinen, *Lett. Org. Chem.* **2004**, *1*, 268-270.

II **Highly Diastereoselective Aldol Additions to Five-Ring *N*,*O*-Acetals**

M. Brunner, A. M. P. Koskinen. *Tetrahedron Lett.* **2004**, *45*, 3063-3065.

III **Stereocontrolled α-Alkylation of Fully Protected L-Serine**

M. Brunner, P. Saarenketo, T. Straub, K. Rissanen, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2004**, 3879-3883.

IV **Biology and Chemistry of Sphingosine-Related Metabolites**

M. Brunner, A. M. P. Koskinen, *Curr. Org. Chem.* **2004**, *8*, 1629-1645.

V **Diastereoselective Formation of Highly Functionalised α-Substituted Amino Acid Derivatives *via* Aldol Addition**

M. Brunner, M. Nissinen, K. Rissanen, T. Straub, A. M. P. Koskinen, *J. Mol. Struct.* **2005**, *734*, 177-182.

Contents

1. Introduction

The synthesis of the natural product glucose by Emil Fischer in 1890 is considered as a starting point for asymmetric organic synthesis.[1] Since that time many more highly complex molecules such as vitamin B_{12}, rapamycin, taxol and brevetoxin, have been synthesised and an impressive wealth of remarkably elegant synthetic methods and strategies have been developed.[2] While in the earlier times the interest lay clearly in the total synthesis of a molecule, the focus of the scientists of today is on the development of ever better and efficient methodologies as well. The search for practical stereoselective tools for the synthesis of complex molecules is of great economic interest.

Diastereoselective and, better, enantioselective reactions are needed to meet the industrial requirements to obtain the optically pure molecule in demand. Thus, it is essential to have access to each enantiomer of a possible drug candidate, a vitamin, a nutrient, or a fragrance. Stereoselective reactions can follow two basic principles. Optically active compounds can be obtained either *via* external asymmetric induction with a chiral catalyst or additive, or with the help of a chiral auxiliary which is removed after the synthesis. The methodology of internal asymmetric induction with a chiral auxiliary is traditionally the preferred synthetic strategy to control the formation of a specific stereoisomer. Chiral auxiliaries are frequently obtained from chiral starting compounds such as amino acids or carbohydrates.

The intriguing results of studies on stereoselective syntheses of sphingosines[3] with Garner's aldehyde[4] have prompted us to investigate sphingosine-related metabolites such as myriocin, the mycestericins, and the sphingofungins. Most of these metabolites bear an α-substituted serine moiety as a common feature, and the stereoselective formation of this quaternary centre is usually the main synthetic challenge in all published total syntheses so far.

The task of this thesis is to establish a synthetic route for the controlled, stereoselective formation of the quaternary carbon centre of α-substituted serine derivatives, with the option of choice of the absolute configuration. In other words, our synthetic strategy is expected to give rise to no less than the controlled, exclusive formation of the *R* or *S* configured chiral quaternary carbon in α-substituted serine fragments on demand, a challenging goal with many potential returns.

2. Sphingosine and sphingosine-related metabolites

2.1. Isolation of myriocin and mycestericins A to G

Biological membranes of living cells essentially consist of phospholipids, but many membranes also contain glycolipids and cholesterol. The backbones of the phospholipids are usually derived from glycerol. However, sphingomyelin is a sphingosine containing membrane component and belongs to the sphingolipids, which are important components of all mammalian membranes. Some play structural roles (*e. g.* sphingomyelin itself) whereas others appear to be important in cellular regulation (sphingosines, ceramides, glycosphingolipids). The basic structural units of sphingolipids, ceramides (*N*-acyl sphingosines) are synthesised in nature from serine and palmitoyl-CoA *via* the initially formed sphingosines (*vide infra*).[5] Besides the naturally occurring D-*erythro*-sphingosine a large amount of phytosphingosines are also known (Figure 1).[6]

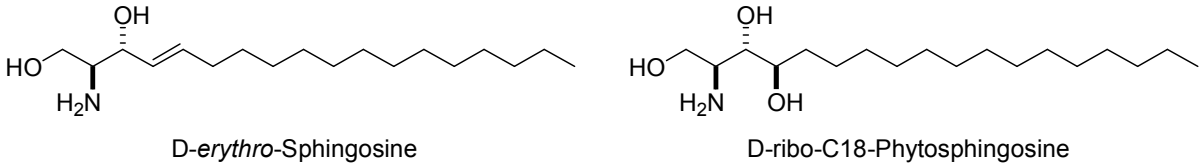


Figure 1. Some sphingosine structures

In the early seventies, two independent research groups in Canada and Italy discovered virtually simultaneously a metabolite, which strongly resembled the sphingosines. In 1971, Kluepfel and co-workers of the Ayerst Research Laboratories found a metabolite from the fermentation broth of the thermophilic fungus *Myriococcum albomyces* and named it myriocin (**1**). The novel compound showed strong *in vitro* antifungal, but no significant antimicrobial activity.[7] In 1972, Aragozzini and co-workers reported the discovery of thermozymocidin, a metabolite of the thermophilic mould *Mycelia sterilia*. Its structure and physical properties were identical to **1**.[8] Recently, the same compound was also isolated from the culture broth of *Melanconis flavovirens*, a fungus of the class of Pyrenomycetes,[9] and as a metabolite termed ISP-1 in the culture broth of the fungus *Isaria sinclairii* (*Cordyceps caespitosa*).[10] *Cordyceps* is a genus of fungus belonging to the Clavicipitacea family and is parasitic on insect larvae like *Lepidoptera adonata* (butterfly larva) or mature insects.

Vegetable wasps and plant worms carrying the parasitic fungus *Cordyceps sinensis* Sacc. have been used in traditional Chinese Medicine as a nostrum for eternal youth. Both *M. flavovirens* and *I. sinclairii* are non-thermophilic organisms.

Re-examination of the culture broth of the fungus *M. sterilia* yielded the novel immunosuppressants mycestericins A (**2**) to G (**8**).[11] Mycestericins are structurally closely related to myriocin (**1**) (Figure 2). Mycestericin A (**2**), B (**3**) and C (**4**) are congruent to **1** at the polar end with the same hydroxy group substitution pattern. Mycestericins D (**5**) to G (**8**) with only one of the secondary hydroxy groups form two pairs of diastereomers.

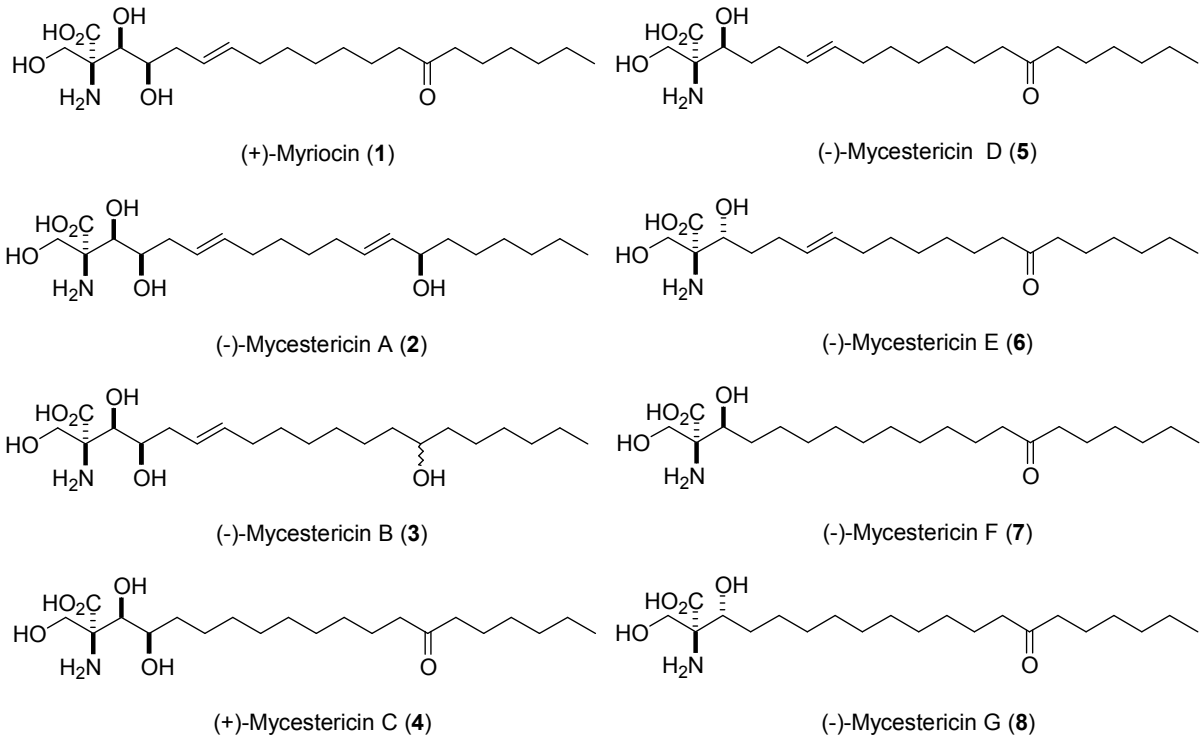


Figure 2. Metabolites from *M. sterilia*

2.2. Isolation of sphingofungins

In 1992, a series of compounds called sphingofungins were isolated from a strain of the thermotolerant fungus *Aspergillus fumigatus*,[12] the sphingofungins A (**9**) to D (**12**). Their structures show similarities to sphingolipids (sphingosines) and each of the four metabolites is synthetically accessible starting from the most abundant sphingofungin C (**11**).[13] The remaining sphingofungins E (**13**) and F (**14**) were isolated from the fermentation broth of the thermophilic fungus *Paecilomyces variotii* (Figure 3).[14] All sphingofungins are serine

palmitoyltransferase inhibitors and potent antifungal agents against various *Candida* species, but are essentially inactive against filamentous fungi and bacteria.[15]

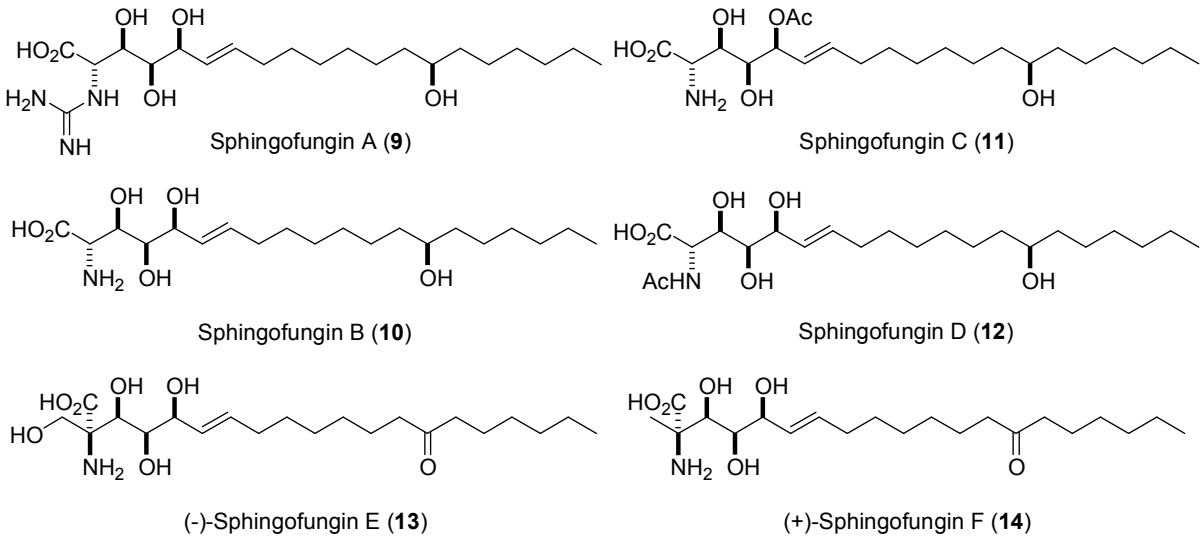


Figure 3. Structures of sphingofungins

2.3. Miscellaneous sphingosine-analogues

The antibiotic flavovirin (**15**) was found in the pyrenomycete *M. flavovirens* in the course of the isolation of **1** and is 5 to 10 times more active than **1** against filamentous fungi, but not against bacteria.[16] Malonofungin (**16**) has been isolated from fermentations of a fungus originating from Jamaican *Panicum maximum* leaves and identified as *Phaeoramularia fusimaculans*. Malonofungin exhibits an antifungal and antibacterial activity spectrum comparable to compounds **1** - **14** (Figure 4).[17]

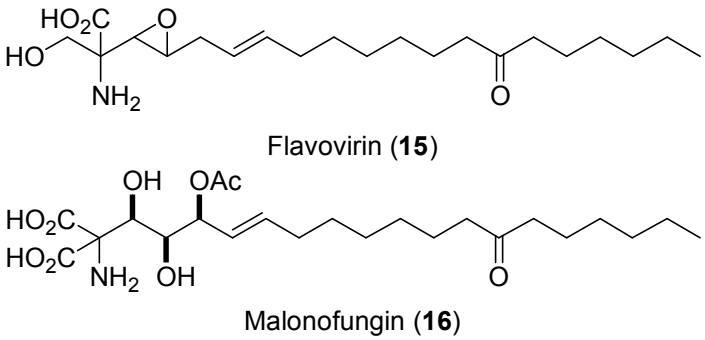
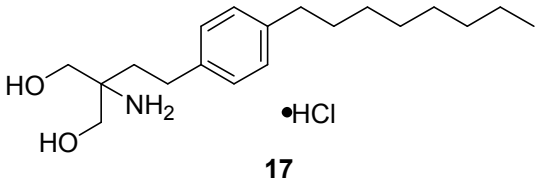


Figure 4. Miscellaneous sphingosine-analogues

2.4. Biology of sphingosine-analogues

Myriocin (**1**) is an immunosuppressive agent both *in vitro* and *in vivo*, equipotent to tacrolimus (FK506)[18] and 5 to 100 times more potent than cyclosporin A (CsA),[19] two currently clinically prescribed agents. Compared to **1**, the immunosuppressive activity of mycestericins A (**2**) to G (**8**) to the proliferation of lymphocytes in the mouse allogeneic mixed lymphocyte reaction (MLR) is lower.[11]

Structure-activity relationships (SAR) of myriocin (**1**) and mycestericins (**2**-**8**) in mouse allogeneic MLR *in vitro* were used to evaluate the influence of the structural features of **1** on the biological activity.[15] From these SAR studies, symmetric 2-amino-1,3-propanediols were developed and, eventually, the derivative FTY720 (**17**) has been identified as very effective immunosuppressant (Figure 5).[20] FTY720 (**17**) is the first S1P receptor agonist that protects organ grafts by reducing the recirculation of lymphocytes from lymphatics to blood and inflammatory tissues and has a different mode of action than the commonly used calcineurin-inhibitors CsA (Neoral®) and FK506 (Prograf®), or the macrolides RAD (Certican™) and rapamycin. FTY720 (**17**) is currently in clinical phase III trials for therapeutic use in the areas of transplantation and autoimmunity and was recently found to be effective in kidney transplantation in humans. FTY720 (**17**) may be superior to CsA and FK506 against infection associated with impaired immune defence.[21]



17

Figure 5. The structure of FTY720

Myriocin (**1**) has also been found to inhibit serine palmitoyltransferase (SPT), which catalyses the first step of the sphingolipid biosynthesis (Figure 6), and thus it induces apoptosis of the cell.[22] In the yeast *Saccharomyces cerevisiae*, **1** inhibits the synthesis of the intermediate ceramide by a rapid and specific decrease in the rate of transportation of GPI-anchored proteins to the Golgi apparatus. This effect is probably due to a rapid depletion of sphingolipids from the endoplasmic reticulum (ER).[23]

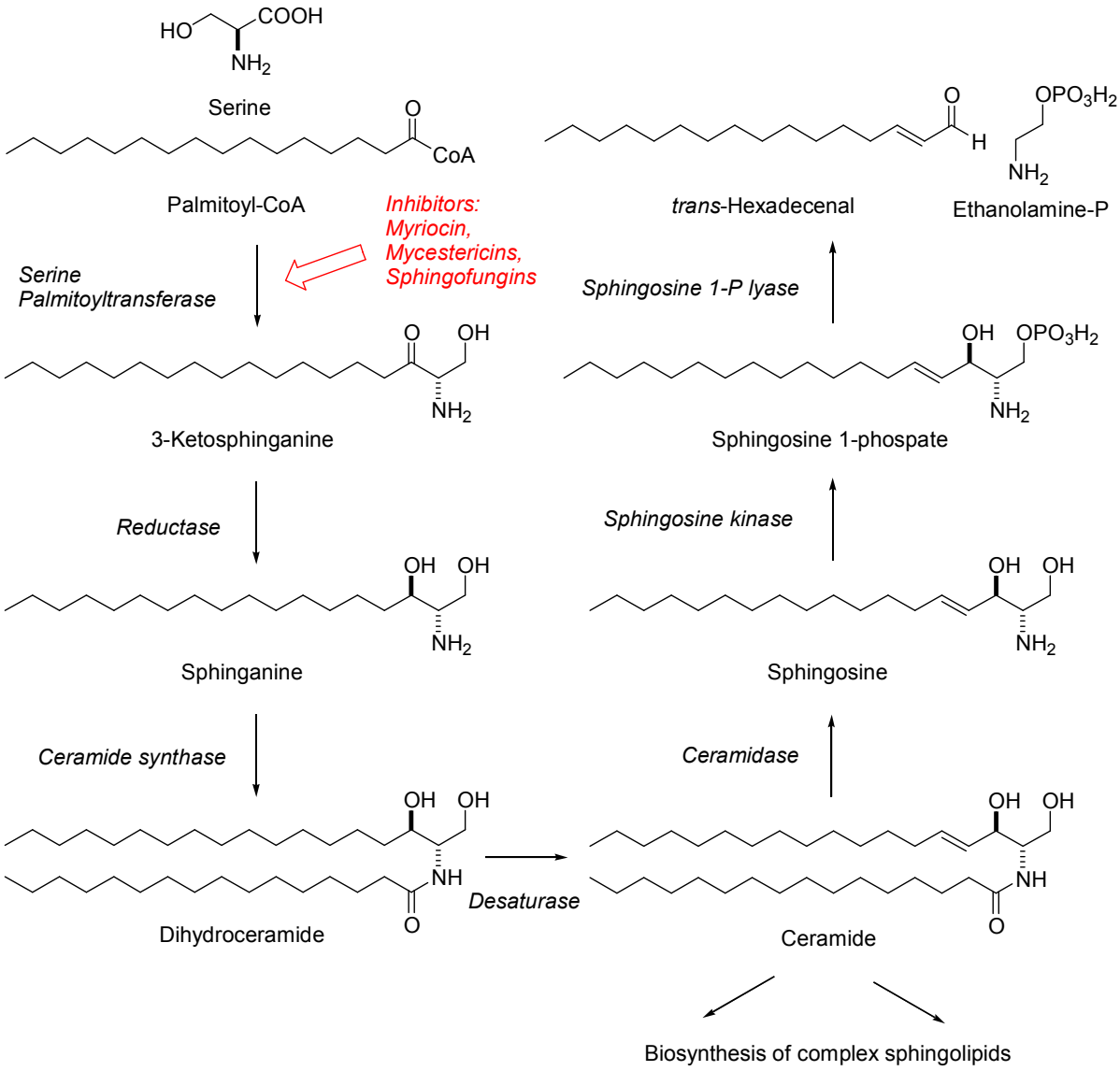


Figure 6. Simplified biosynthetic and catabolic sphingosine pathway

Recently, myriocin's ability to reduce the accumulation of free sphingoid bases was recognised.[24] The mycotoxins fumonisins (B_1, B_2 and B_3) are inhibitors of ceramide synthase, an enzyme in the *de novo* sphingolipid synthesis, which results in an increase of sphinganine concentration. Fumonisins are found in most corn containing food and feeds all over the world and are associated with outbreaks of equine leukoencephalomalacia (ELEM), swine pulmonary oedema syndrome, and other farm animal diseases.[25] The disease ELEM is usually mortal to animals like horses, but temporary reduction of sphinganine concentration by **1** may lead to treatments.[26]

3. Total syntheses of sphingosine-analogues

Although early attempts for the total synthesis of (+)-myriocin (**1**) were already made in the late seventies,[27,28] its first total synthesis was published only ten years after its discovery, in 1982. The same Italian group who isolated "thermozymocidin" used D-fructose as the chiral starting material and completed the synthesis in 13 linear steps.[29] A decade later the second total synthesis was accomplished in which another carbohydrate, 2-deoxy-D-glucose, acted as the chiral starting material.[30] At the same time, a new synthesis strategy used the non-natural amino acid D-valine in a highly diastereoselective aldol reaction of its corresponding Schöllkopf's bis-lactimether as a key step for a convergent synthesis with 13 linear steps for **1**[31] and in the very first total synthesis of sphingofungin F (**14**) in 1997. The linear side-chain aldehyde was prepared using the methodology of chiral Lewis-acid-controlled (CLAC) synthesis.[32] Achiral 1-trimetylsilylbuta-2,3-dienes were used as starting materials for **1**[33] as well as the first total synthesis of sphingofungin E (**13**)[34] from L-(+)-tartaric acid.

The close relationship of their structures allows facile chemical interconversion of sphingofungin A (**9**) and D (**12**),[13] but only few syntheses of these metabolites have been published so far.[32,35] Sphingofungin E (**13**) and F (**14**) bear the corresponding quaternary carbon of **1** to **8** and similar or identical synthesis strategies were therefore applied. Rather elaborate syntheses of **1**,[36] **13**,[37] and **14**[38] used an Overman rearrangement of allylic trichloroacetimidates derived from D-glucose as the key step. The most recent total syntheses for **1**,[39] **13**/**14**[40] employed chiral oxazolines obtained from L-serinol. Sphingofungin E (**13**) and F (**14**) were also obtained from *gem*-diacetates acting as carbonyl surrogates.[41] Formal approaches to **1**, which built the basis for another elaborate synthesis of **13,**[42] were made from D-glucose as the chiral starting material.[43,44]

To date, only few total syntheses of the mycestericins (**2** - **8**) have been published with major interest for the two diastereomeric pairs mycestericin D/E (**5**/**6**) and F/G (**7**/**8**). An enzymatic aldol reaction was used in the synthesis of **5** and **7,**[45] and the principle of self-regeneration of stereocentres (SRS)[46] was used in the first total syntheses of **6** and **8**.[47] Another enantioselective synthesis of **6** was accomplished by using a *Cinchona* alkaloid-catalysed asymmetric Baylis-Hillman reaction.[48] Total syntheses for mycestericins A (**2**) to C (**4**) have not been published, so far.

4. α-Substituted amino acids

4.1. Introduction

Most of the sphingosine-analogues myriocin (**1**), mycestericins (**2** - **8**) and sphingofungins (**9** - **14**) bear an α-substituted serine moiety with the same absolute configuration (Figure 7). In general, the stereoselective synthesis of α-substituted quaternary α-amino acids can be achieved either by external (chiral catalysts) or by internal induction (chiral auxiliaries or chiral reacting molecules).[49] The most prominent internal induction methodology is probably Schöllkopf's, which employs bis-lactim ethers, derived from amino acids such as glycine or valine, for the stereoselective formation of α-amino acid derivatives.[50] An application of this methodology is found in a convergent synthesis of **1** with stereospecific additions to enolates of bis-lactim ethers derived from L-valine.[31] However, the formation of the bis-lactim ether auxiliaries and the separation of the products after cleavage involve rather "expensive" intermediates for the synthesis and constitute major disadvantages of this methodology.[50]

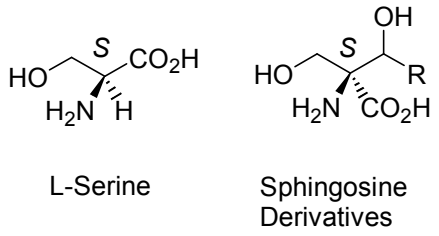


Figure 7. Absolute configuration of aldol adducts

4.2. Self-regeneration of stereocentres (SRS)

First observations where the absolute configuration of a reaction centre was restored in the course of the reaction without using any external (chiral) additive were independently made during syntheses of α-substituted α-hydroxy acids[51] and proline derivatives.[52] The additions to enolates of fully protected hydroxy and amino acids were highly diastereoselective and yielded mainly one product isomer. Analysis of these phenomena led

Seebach to describe a general principle, which he termed self-regeneration of stereocentres (SRS).[46,53]

The principle takes advantage of the reversible formation of chiral auxiliaries, *i*. *e*. the protection of amino and hydroxy groups as heterocyclic acetals. Amino or hydroxy acids such as di- and trifunctional amino-, hydroxy-, and sulfanylcarboxylic acids from the natural "pool of chiral building blocks"[54] are transformed to five-membered ring *N*,*N*-, *N*,*O*-, *N*,*S*-, *O*,*O*- or *O*,*S*-acetals. The large ring substituents control the stereoselective reaction of these acetals without any chiral additives. The dominant steric restrictions of the reacting chiral ring enolates direct the addition to the nucleophile, and the product formation is strongly dependent on the configuration of the temporary acetal stereocentre. A general procedure involving the SRS-principle can be summarised by the following steps:[55]

1. Formation of the *temporary* stereogenic centre.
2. Removal the of the *original* stereogenic centre.
3. Stereochemical regeneration reaction of the *original* stereogenic centre, induced by the *temporary* stereogenic centre.
4. Removal of the *temporary* stereogenic centre.

The cyclic acetals are exceptionally versatile auxiliaries because of their relative instability during the formation and removal as well as their relative stability during the stereoselective reactions. The SRS-principle has been applied mainly in reactions with enolisable compounds to synthesise enantiopure compounds with quaternary carbons.

A large array of alkylations, aldol or Michael additions, Diels-Alder reactions, cylcoadditions, and radical reactions are reported.[56] Furthermore, decarboxylation of trifunctional amino acids such as serine or threonine result in oxazolines with reversed reactivity at the former C2 of the amino acid[57] and the addition of a nucleophile creates the regenerated stereocentre.[58]

A variation of the SRS-principle in diastereoselective additions uses unstable chiral borane-amine adducts, which easily loose the borane under the reaction conditions, instead of the heterocyclic acetals, to synthesise compounds with quaternary substituted carbons.[59]

However, the utilisation of β-heterosubstituted amino acids such as cysteine, threonine, phenylserine, or serine for alkylation or aldol reactions is often accompanied by β-elimination under strongly basic conditions.[55] Especially in reactions with cysteine, the sulfide group cannot be prevented from undergoing β-elimination even in geometrically unfavourable situations. Elimination reaction took place in the five-membered ring of

enolate **18** or in the bicyclic system **19**, where the C-S bond is approximately perpendicular to the π orbital of the enolate (Figure 8, top).[60] It was also shown that enolate **18** can be trapped with methyl iodide at -78 ºC in reasonable yield,[61] but enolate **19** was obtained only when very special well-defined *in situ* conditions were maintained.[62]

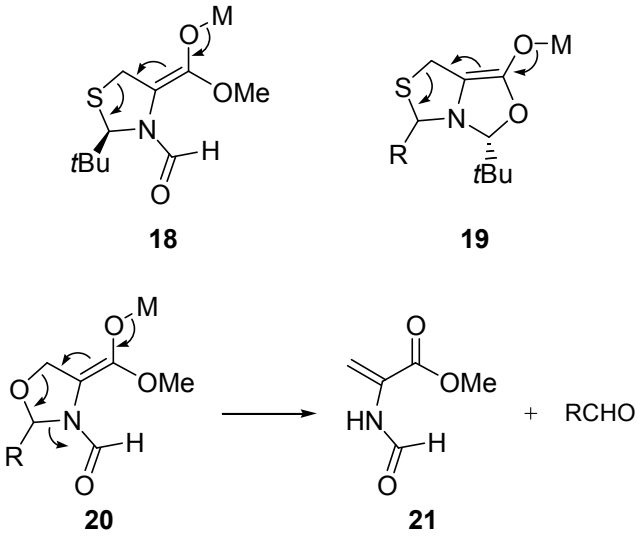


Figure 8. β-Elimination of *N,X*-acetals

The analogous observation has been reported for the *N*-formyl-serine enolates of type **20** and even very reactive electrophiles cannot compete with the β-elimination. The fragmentation reaction in the five-membered ring enolate **20** is very likely to happen since the leaving group is an aldehyde and the resulting enamine **21** is stabilised by the *N*-protection group (Figure 8, bottom). Despite these difficulties several possibilities exist to suppress the elimination reaction in favour of the addition of the electrophile. In the case of serine, an α-amino-β-hydroxycarboxylic acid, three possibilities are known.[55]

1. A poorer leaving group is introduced.
2. The anionic character of the enolate can be reduced by changing the metal or by delocalisation of the charge over the protection groups.
3. The critical C-O bond is fixed coplanar with respect to the atoms of the enolate π-system in order to make a β-elimination impossible because of stereoelectronic reasons.

Consequently, the utilised *N*,*O*-acetals can easily be modified by the choice of the *N*-protection group. Suitable amino protection groups for serine (or cysteine) should stereoelectronically minimise the possibility of β-elimination and act as a spectator, hindering reaction partners to attack the molecule from all faces. Besides, the basic nitrogen should be prevented from undergoing undesired reactions. Taking these requirements into consideration, the acyl and carbamoyl protection groups proved to be the most useful ones.[46]

For our investigation we chose the sterically demanding carbamates Cbz and Boc together with the bulky *t*-Bu ring substituent, which should force the five-ring *N*,*O*-acetals into a locked conformation. Thus, the rigid heterocyclic ring has to adopt a conformation where the hemiaminal substituent has a pseudoaxial position and one face of the ring is completely shielded. Although five-membered rings such as cyclopentane can undergo pseudo-rotation, the introduction of the heteroatoms and the substituents introduce a potential energy barrier suppressing any pseudo-rotation.[63] A potential alkylation or aldol reaction at the α-carbon will be controlled by the molecule's configuration. The reduced flexibility and the stereoelectronic requirements of the rather rigid molecule necessarily suppress β-elimination of the corresponding enolate. A molecule with fixed conformation, in the way that the critical bonds cannot adopt an antiperiplanar conformation, would also fulfil the minimal requirement for inhibition of the elimination reaction.

The experiments with the *N*-formyl oxazolidines were usually carried out with the *cis*-isomers and, therefore, the addition to the corresponding enolates occurred exclusively with retention of configuration. For imidazolidin-, oxazolidin- and dioxolanones, however, the *trans* isomers, yielding products of inversion, were prepared as well.[46] The SRS-principle is applicable to the *cis* or *trans* isomers of the *N*-Boc or *N*-Cbz oxazolidines. The sterically demanding substituents of either five-ring diastereomer shield one ring face completely and subsequent addition reactions are only possible from the opposite side. Thus, products of retention (*cis* isomer) or inversion (*trans* isomer) are obtained (Figure 9).

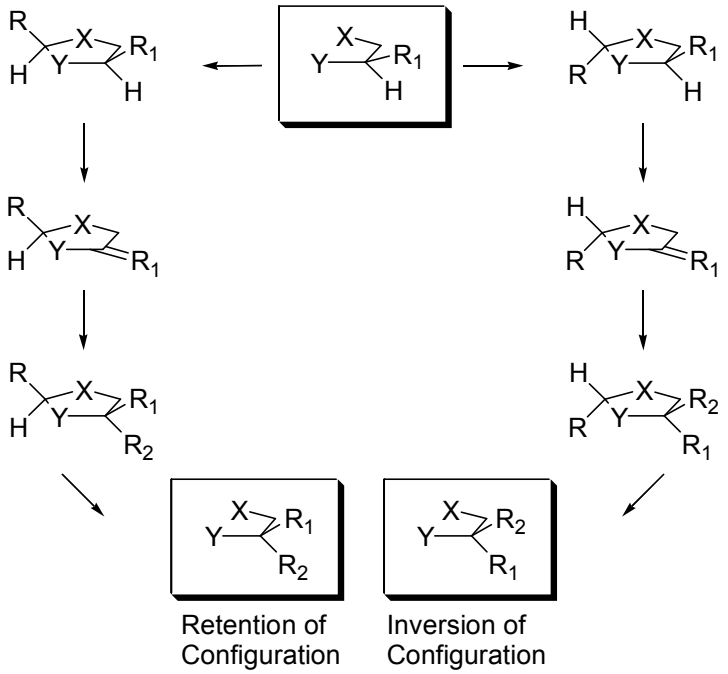


Figure 9. Substitution of α-hydrogen with retention or inversion of configuration

4.3. Synthesis of five-membered ring *N*,*O*-acetals

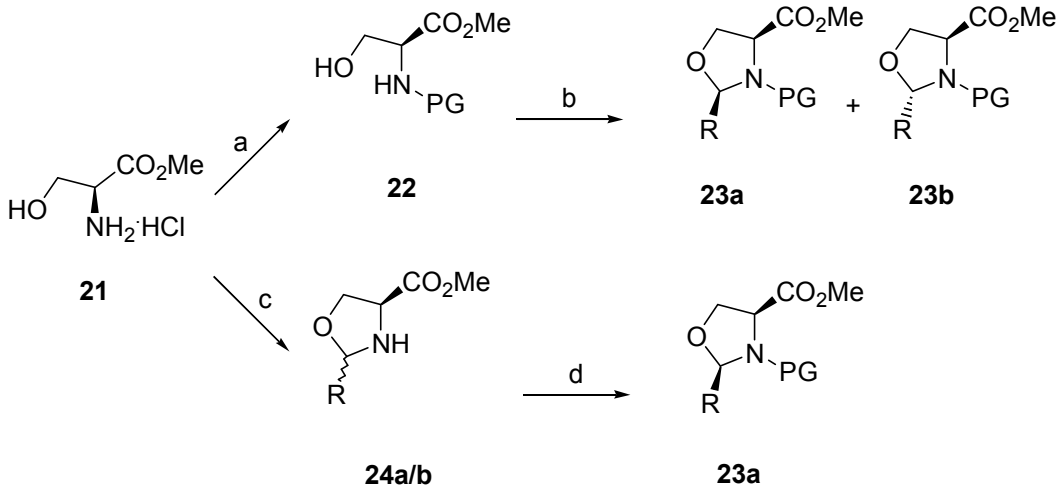
4.3.1. Introduction

Numerous *N*,*O*-acetals derived from serine have already been prepared with a variety of protecting groups. The methods generally used yielded the *cis* isomers exclusively.[46] However, these oxazolidines are obtainable in two diastereomeric forms where the ring substituents are either *cis* or *trans* to each other with respect to the five-membered ring. While the preparation of the *cis* isomers doesn't impose difficulties and several efficient and practicable methods exist, no reliable way to obtain the *trans* isomers as major products was found in the literature.

Traditional Fischer esterification of L- or D-serine afforded the required serine methyl ester hydrochlorides (*e. g.* **21**), the general starting materials for the formation of oxazolidines.[64] From these, the *cis*- or *trans*-epimers were accessible in two steps by the same reaction sequence with changed order of events. The thermodynamically favoured *cis*-substituted *N*,*O*-acetals (*e. g.* **23a**) were obtained in three steps with high yields and very good diastereoselectivities by a slightly modified literature procedure (Scheme 1).[65]

The preparation of the *trans*-epimers required more elaborate methods. For instance, good selectivities in favour of the *trans* product were obtained when Rh(III)-catalysts were

used in acetalisation of aldehydes with Cbz-protected serine methyl and benzyl esters, but the *cis*/*trans* ratio for the latter esters shifted in favour of the *cis*-epimer with longer reaction time.[66] When we applied standard acetal formation conditions with physical removal of water, it was necessary to protect the basic amino nitrogen of L-serine methyl ester hydrochloride (**21**). Subsequent acid-catalysed acetalisation under azeotropic distillation with different aldehydes in pentane, benzene, or toluene gave diastereomeric mixtures of *cis*- and *trans*-epimers in low ratios and moderate yields; not surprisingly, extremely long reaction times were necessary with pentane. Boiling toluene decomposed the starting material, a consequence of Boc and Cbz group cleavage in acid-catalysed reactions at temperatures higher than 80 ºC. Significant improvements with higher yields and better diastereoselectivities of *cis*/*trans* ratios of 1:4 were achieved by chemical water removal by orthoformate esters in toluene in the presence of the catalyst PPTS at moderate temperatures.[65]



Conditions: a) TEA, $(Boc)_2O$, $MeOH/CH_2Cl_2$ or Cbz-Cl, sat. $NaHCO_3$; b) PPTS, aldehyde, toluene or pentane; c) aldehyde, TEA, pentane; d) $(Boc)_2O$ or Cbz-Cl, THF.

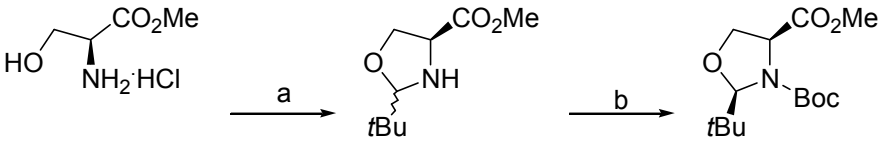
Scheme 1. General synthesis routes to *cis*- and *trans*-substituted *N*,*O*-acetals

We obtained the *cis*-epimers without detectable amounts of other products; however, the *trans*-epimers always had to be separated from a mixture of diastereomers. Acetalisations with acid catalysts yielded virtually inseparable mixtures by chromatography, but the solid products could be recrystallised from nonpolar solvents at low temperatures. The combination of *N*-protecting groups and aldehydes notably influenced the possibility of separation and Cbz-protected *N*,*O*-acetals were separated unsatisfactorily. The protecting group combination pivalaldehyde/Boc proved to be the most useful and the corresponding *trans N*,*O*-acetals were obtained in pure crystalline form in high yields.

Attempts to form hemiaminals *via* transketalisation of aldehyde acetals[67] in the presence of the Lewis acid catalyst $BF_3 \cdot Et_2O$, a general method for the synthesis of the well-known Garner aldehyde,[68] yielded *cis*/*trans*-epimer ratios of ca. 2:1.[69]

4.3.2. Synthesis of (2*S*,4*S*)- and (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate

Pivalaldehyde is a convenient protecting reagent for serine because of the steric bulk of the corresponding cyclic *N*,*O*-acetal as well as the chemical (the acetal carbon is fairly reactive) and physical properties (the obtained hemiaminals are often solid). Both diastereomers of oxazolidine **27** were prepared according to the modified procedures described above.[65,70] The *cis*-isomer was obtained *via* azeotropic distillation of a mixture of L-serine methyl ester hydrochloride (**21**), pivalaldehyde, and TEA in pentane. The 1:1-mixture of the oxazolidines **26a**/**b** was directly treated with $(Boc)_2O$ in THF at 0 ºC to yield exclusively **27a** (2*R*,4*S*) after removal of residual anhydride by fractional Kugelrohr distillation (Scheme 2).[65,70] In contrast to Baldwin's rules a ring-opening/ring-closure occurs under the applied reaction conditions and the more stable isomer is solely formed.[60]



21 **26a/b** **27a**

Conditions: a) TEA, pivalaldehyde, pentane, reflux, 1 d; b) $(Boc)_2O$, THF, 0 °C, 90% for two steps.

Scheme 2. Diastereoselective formation of **27a**

Epimerisation of asymmetrically substituted oxazolidines or thiazolidines seems to be a general phenomenon. It is known that *N*-formylation of a mixture of **26a**/**b** in Et_2O/dry-ice did not change the ratio of *N*-protected **26a**/**b.**[55,65b] *N*-Acetylation of thiazolidine-4-carboxylic acids with acetic anhydride and pyridine at room temperature or acetic anhydride in boiling water resulted in the formation of either the 2,4-*cis* or the 2,4-*trans* epimers, respectively.[71] In the latter case, the base-catalysed epimerisation proceeds through an open chain Schiff base intermediate prior to acetylation and any mechanism involving deprotonation/reprotonation at C2 of the thiazolidine ring can be ruled out.[71] In the same way oxazolidines derived from serine esters are prone to ring/chain tautomerism. Equilibrium studies of serine methyl and

ethyl esters with aromatic aldehydes in $CDCl_3$ showed three-component tautomeric mixtures where the open chain Schiff base intermediate was typically predominating.[72] Among the two ring forms the amount of the *cis*-epimer was always higher than the amount of the *trans*-epimer and unlike the thiazolidines no reaction conditions could be found to obtain only *trans*-substituted oxazolidines.[70a,b] In the case of the *t*-Bu substituted oxazolidines **26** we did not observe any open chain form in the ^{1}H NMR for solutions of **26a**/**b** or **27a**/**b** in $CDCl_3$ respectively and, in contrast to the *N*-formylated oxazolidines, we observed only one rotamer of **27a**.[65]

The determination of absolute and relative configuration of **27a** in the ^{1}H NMR spectrum was impossible. However, a detected NOESY correlation (Figure 10) between the methyl protons of *t*-Bu-C2 and the methylene proton H_β-C5 and the comparison with the NOESY and X-ray structure of **27b** (Figure 11) confirmed the absolute configuration (2*S*,4*S*) of **27a**.[73] The broad signals of the methine proton H-C4 and the methyl protons of the Boc group in the ^{1}H NMR spectrum of **27a** in $CDCl_3$ and benzene-d_6 indicate conformational restrictions of the molecule with rotational inflexibility of the Boc group.

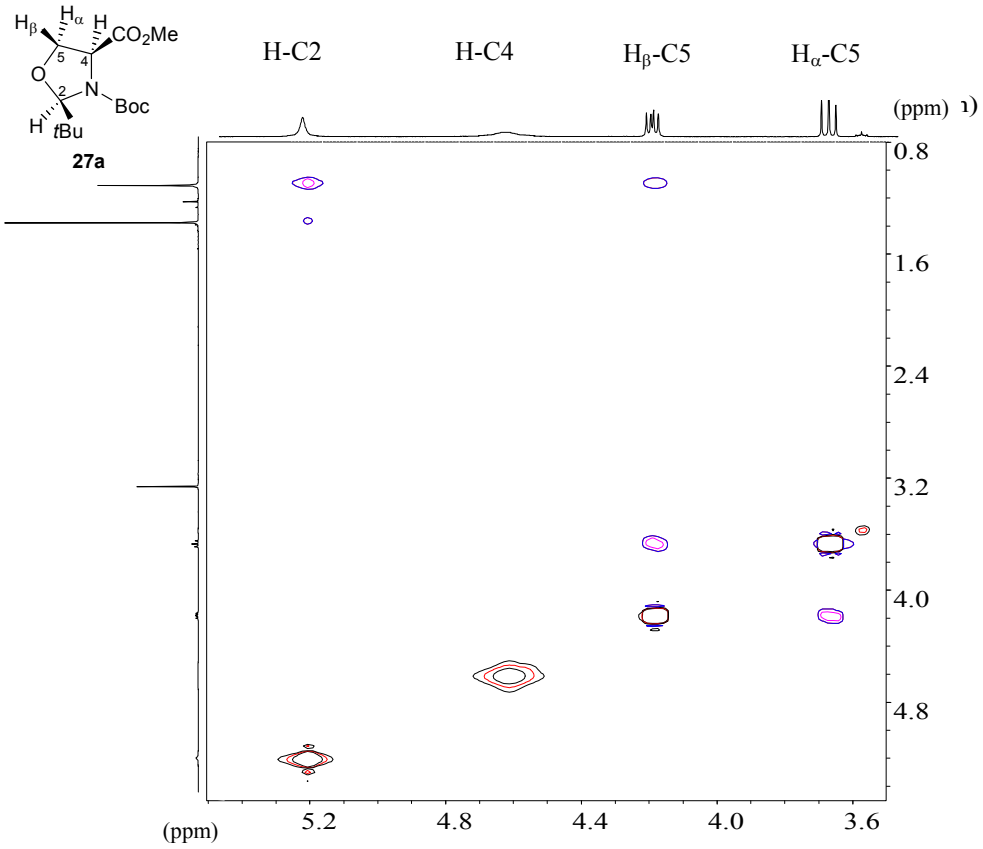
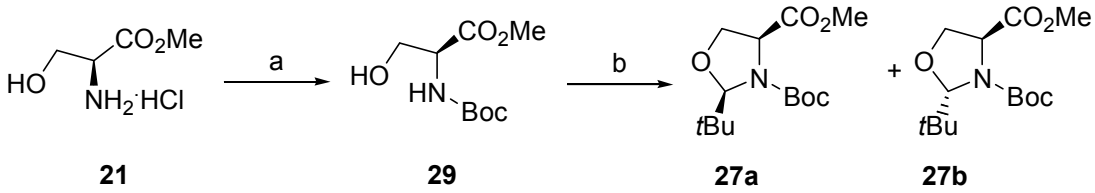


Figure 10. NOESY spectrum of **27a** in benzene-d_6

In the synthesis of the *trans*-epimer **27b** we changed the order of events and protected the nitrogen prior to the acetal formation. The common starting material L-serine methyl ester hydrochloride (**21**) was treated with $(Boc)_2O$ and TEA in $MeOH/CH_2Cl_2$ and the pure derivative **29** was obtained in quantitative yield**.** Azeotropic distillation of **29** in a solution of pivalaldehyde and PPTS in toluene or benzene yielded a 2:1 mixture of diastereomers in favour of the thermodynamically less stable **27b**. The severe reaction conditions destroyed the products, however, and the yields were generally not satisfying. Improved selectivities up to 1:4 for **27a**:**27b** were obtained when water was chemically removed with orthoformate esters[74] in toluene at lower temperatures. The desired *trans*-epimer **27b** was obtained after recrystallisation in hexane at -20 ºC as a 9:1 rotameric mixture as observed in the ^{1}H NMR (Scheme 3). There is a tendency for the formation of condensation products between the orthoester[75] and the serine derivative in such acetalisations and a cyclic orthoformic acid derivative may actually be an intermediate in these acetalistions.[66]



21 **29** **27a** **27b**

Conditions: a) TEA, $(Boc)_2O$, $MeOH/CH_2Cl_2$, quant.; b) PPTS, pivalaldehyde, triethyl orthoformate, toluene, 60% for **27b**.

Scheme 3. Formation of **27b**

The relative and absolute configuration of **27b** (2*R*,4*S*) was assigned with the help of an X-ray structure (Figure 11). An ORTEP[76]-plot of **27b** shows the Boc group forcing the ring nitrogen to be nearly planar and the substituent at C4 to occupy a pseudoaxial conformation.[73]

The ^{1}H NMR spectrum of **27b** in $CDCl_3$ reveals that the signal for the methine proton H-C4, which overlaps with the pseudoaxial methylene proton signal H_α-C5, appears at higher field (4.35 ppm) than the corresponding proton signal in **27a** (4.67 ppm).[77] The pseudoequatorial methylene proton H_β-C5 of **27b** is represented by a doublet at δ 4.02 ppm with $^2J_{HH}$ = 7.2 Hz, while both, the pseudoaxial H_α-C5 and the pseudoequatorial H_β-C5 of **27a** (*vide supra*), couple with H-C4 and thus appear as doublet of doublets. The aminal proton H-C2 singlet of **27b** appears 0.19 ppm downfield-shifted compared to the corresponding proton signal in **27a** and is significantly broadened due to rotational barrier

along the *t*-Bu-CO-N bond. Analogous observations were made in connection with the synthesis of *cis*- and *trans*-dioxalanones[52] and imidazolidinones (Figure 12).[78]

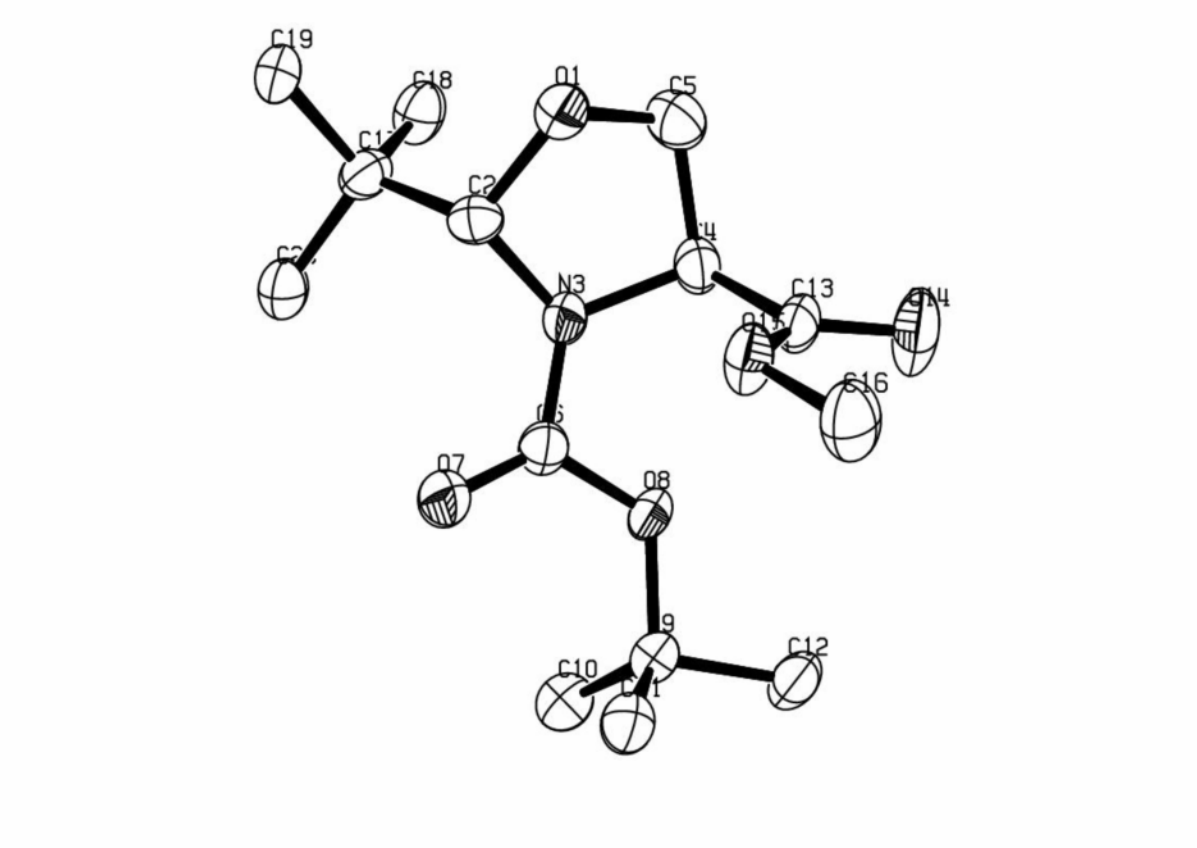
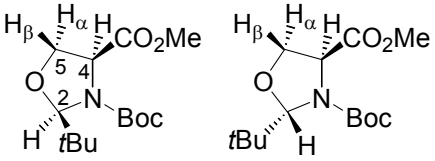


Figure 11. ORTEP[76]-plot of **27b**

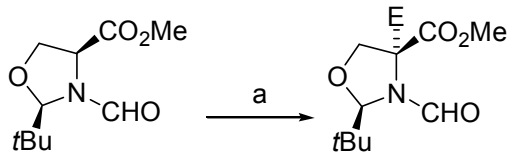


27a	**27b**	
Proton	**27a**	**27b**
H-C2	5.00	5.19
H-C4	4.67	4.35
H_{α}-C5	4.24	4.35
H_{β}-C5	4.11	4.02

Figure 12. ^{1}H NMR chemical shifts (ppm) in $CDCl_3$ of **27a**/**b**

4.4. Diastereoselective alkylation of (2*S*,4*S*)- and (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate

Alkylations of oxazolidine **30**[65] followed the SRS-principle with excellent diastereoselectivities (de >98%). The chiral enolate of **30** was alkylated with electrophiles in the presence of cosolvents (DMPU, HMPA) and in many cases only one diastereomer of type **31** was observed by ^{1}H and ^{13}C NMR (Scheme 4). The acetal auxiliary was usually cleaved after the reaction and the chiral amino acid was obtained in high enantiopurity.[65]

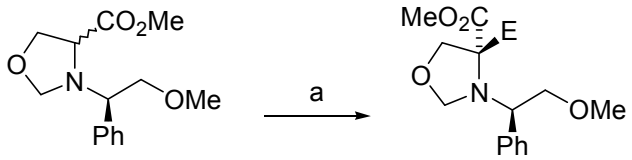


30 **31**

Conditions: a) LDA, EX (electrophile), THF, 10-71%.

Scheme 4. Additions to *N*-formyl protected oxazolidines

A 1:1-mixture of oxazolidine **32** with an exocyclic chiral appendage was used in diastereoselective alkylation reactions as well. The enolate was generated with potassium hexamethylsilazane (KHDMS) in this case and no additive (HMPA, DMPU, or LiBr) was needed to improve yields of **33** (Scheme 5). The diastereoselectivities for alkylations of **32** were comparable with the corresponding reactions of **30** only in the cases of electrophiles with iodide as leaving group. The best results were obtained with methyl and benzyl iodide whilst methyl bromoacetate gave only a moderate yield (29%).[79] Recently, the same methodology was applied in the asymmetric synthesis of quaternary tetrahydroisoquinolidine-3-carboxylic acid derivatives.[80]



32 **33**

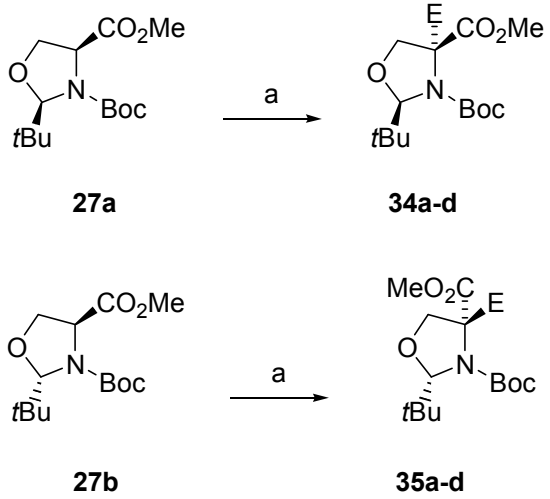
Conditions: a) KHMDS, EX (electrophile), THF, -78 ºC, 73-97%.

Scheme 5. Additions to oxazolidines with exocyclic chirality

In the diastereoselective alkylations of **27a** and **27b** standard conditions were applied.[65] The ester enolate was formed using LDA, which was prepared *in situ* from DIPA and a solution of *n*-BuLi in hexanes (Aldrich, 2.5 M).[81] Neither the Li-enolates of **27a**/**27b** nor of related compounds could be isolated and characterised so far. It is therefore unclear whether the configuration of the ester enolate is *E* or *Z*. Using 110 mol-% of LDA gave only good yields in the case of **27a,** but not for **27b**. Increasing the amount of base to 200 mol-% led to improved yields for both alkylated products **34**/**35a** – **34**/**35d**.

The electrophiles were added neat at -78 °C, after the indicated period and the reaction mixture was then warmed up to room temperature (Scheme 6). Using a period of 10 min for the formation of the enolate, we usually recovered only starting material indicating a very slow deprotonation of the sterically hindered oxazolidines. Prolonging the formation time up to one hour increased the yield of the alkylated products significantly. The different behaviour of the enolates of **27a** and **27b** is illustrated in deuteration experiments. Not only the yields differ considerably, also different side products were observed. While **34e** was accompanied only by starting material, **35e** and an additional product from protonation with inversion of configuration at C4 was observed for **27b**.

Higher reaction temperatures had no positive effect on the yield, but the formed enolates were surprisingly stable to β-elimination. The Li-enolates did not decompose completely at temperatures of -30 ºC and more than 50% starting material could be recovered after quenching the enolates at 0 °C.



Conditions: a) LDA, EX, THF, -78 °C; EX = D_2O, MeI, allyl bromide, BnBr, methyl bromoacetate; for yields: see Table 1.

Scheme 6. Diastereoselective alkylation of **27a** and **27b**

Alkylation of **27a**/**27b** with standard electrophiles such as methyl iodide, allyl bromide, benzyl bromide or methyl bromoacetate resulted exclusively in an addition *trans* to the *t*-Bu ring substituent with retention (**27a**) or inversion (**27b**) of configuration at the reaction centre as confirmed by ^{1}H NMR of the crude product. The corresponding alkylated oxazolidines **34a**/**35a** to **34d**/**35d** each form a pair of enantiomers with identical ^{1}H and ^{13}C NMR spectra and opposite optical rotation values. Alkylation reactions in the **27b** series gave systematically lower yields indicating different behaviour of the enolates of **27a** and **27b** (Table 1).

Entry	27	EX	Product	yield[a]	*dr*[b]
1	**a**	MeI	**34a**	92	99:1
2	**a**	allyl bromide	**34b**	45 (79)	99:1
3	**a**	BnBr	**34c**	(25)	99:1
4	**a**	$BrCH_2CO_2Me$	**34d**	67	99:1
5	**a**	D_2O	**34e**	64	99:1
6	**b**	MeI	**35a**	87	99:1
7	**b**	allyl bromide	**35b**	30 (67)	99:1
8	**b**	BnBr	**35c**	11	one isomer
9	**b**	$BrCH_2CO_2Me$	**35d**	20	one isomer
10	**b**	D_2O	**35e**	-	mixture

[a] crude yields in brackets. [b] diastereomer ratio (*dr*) determined by ^{1}H NMR.

Table 1. Diastereoselective alkylation

Both methylated oxazolidines **34a** and **35a** were obtained in high yields without further purification. The yields decreased significantly for the electrophiles allyl bromide, benzyl bromide, and methyl bromoacetate.[82] In contrast to the literature, the use of DMPU as a cosolvent did not improve the situation.[65] Reaction with benzyl bromide gave only poor yields for **34c**/**35c**, accompanied with significant amounts of 1,2-diphenyl-1-bromoethane. Similar difficulties were encountered in the alkylation of other sterically hindered enolates.[83]

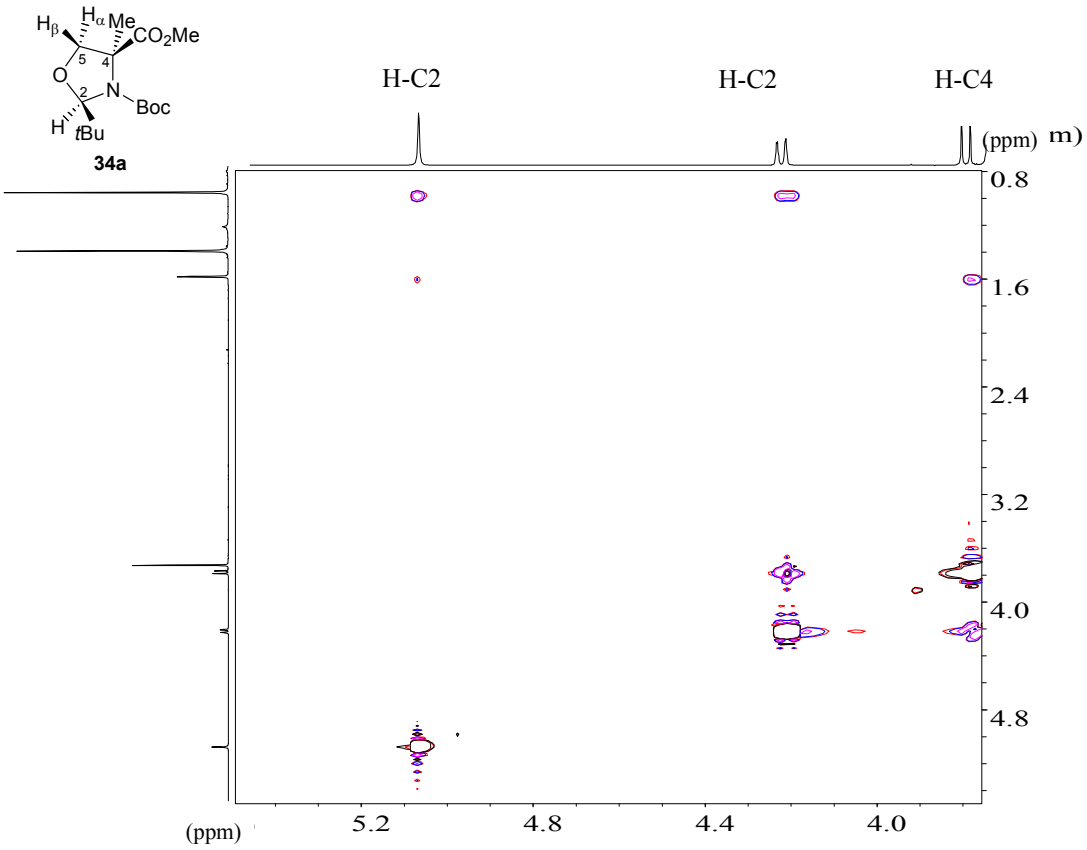
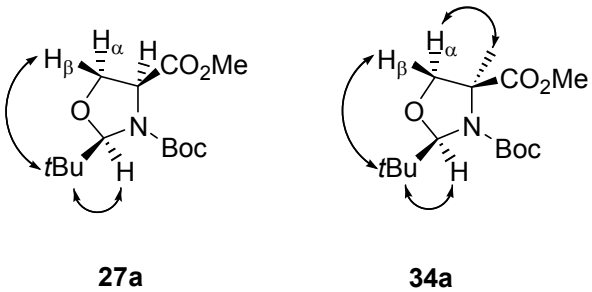


Figure 13. NOESY spectrum of **34a** in benzene-d_6

Relative and absolute configurations of the alkylation products were assigned by NOESY experiments and an X-ray structure of **34d**.

The correlation in the NOESY spectrum of **27a** between the methyl protons of the *t*-Bu and the acetal proton at C2 are observed in **34a**, too. Further, these methyl protons correlate with H_β-C5 in both compounds. Together with the correlation of H_α-C5 and the protons of Me-C4, this is conclusive for the relative *trans* configuration of **34a** (Figure 13 and Figure 14).



27a **34a**

Figure 14. Observed NOESY correlations of educt **27a** and its methylation product **34a**

The X-ray structure of **34d** synthesised by addition of methyl bromoacetate to **27a** is shown in Figure 15.

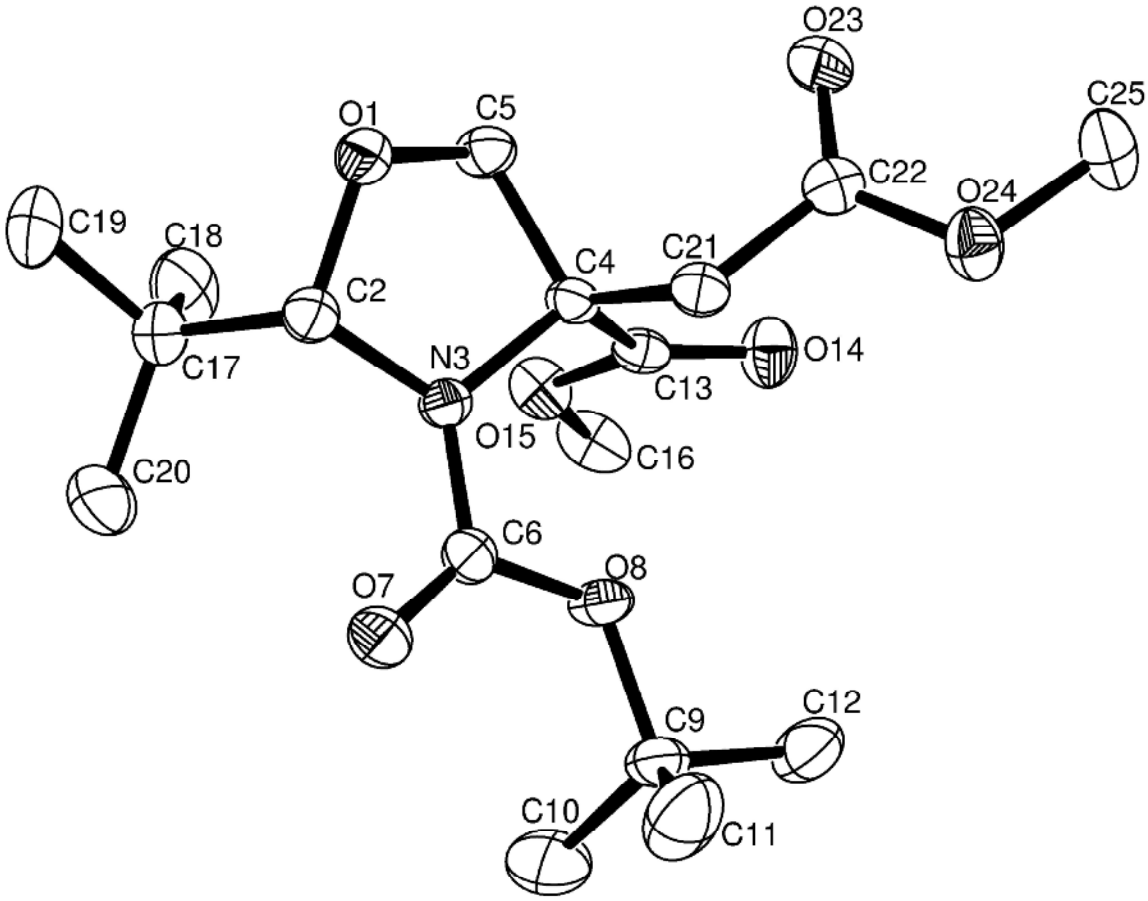


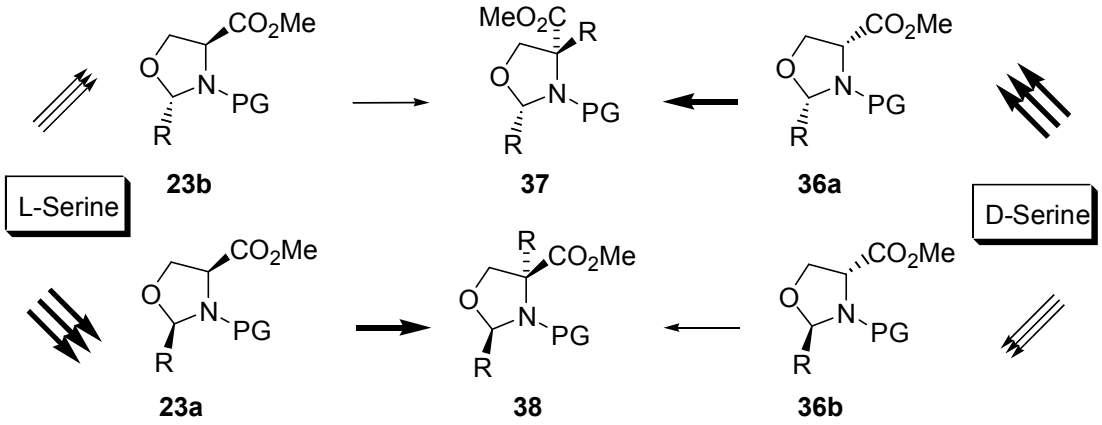
Figure 15. ORTEP[76]-plot of alkylation product **34d**

In summary, the new α-substituted amino acid derivatives from highly substituted **23a** and **23b**, respectively, gave products with retention (SRS-principle) or inversion of configuration.[46] Hence, it is possible to obtain both α-substituted amino acid enantiomers (**37**, **38**) from the starting amino acid of choice (Scheme 7).

The final step in the formal synthesis of α-substituted amino acids is the hydrolysis[46] of the protected species, *e. g.* **37** or **38**, under appropriate conditions. Elaborating these conditions, using selected compounds of this project, is beyond the scope of these investigations, but will certainly make an intriguing topic for a short project, such as a diploma thesis.

The hydrolysis of racemic Boc-protected glycine derivatives 2-*tert*-butyl-4-methoxy-2,5-dihydro-imidazole-1-carboxylates (Boc-BDI) invokes a separation step of the formed

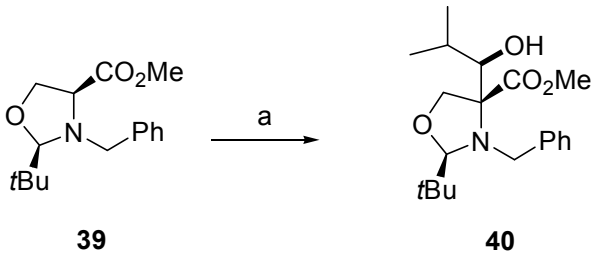
enantiomer, to obtain the pure compounds. We elegantly circumvent this separation problem by providing pure diastereomers for the hydrolysis.[84]



Scheme 7. Routes to α-substituted serine derivatives[85]

4.5. Diastereoselective aldol addition of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate to achiral carbonyl compounds

Diastereoselective aldol additions to **27a** and **27b** have the advantage of simultaneously creating a pair of stereocentres, which is a powerful tool for the preparation of β-hydroxy serine derivatives such as myriocins, mycestericins, and sphingofungins. Aldol additions of the Li-enolate of *N*-formyl protected five-ring *N*,*O*-acetals to acetone and benzaldehyde resulted in the formation of a single isomer while with the sterically more demanding benzophenone no adduct is formed at all.[65]



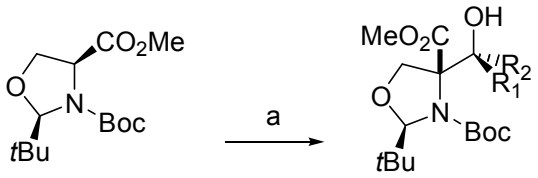
Conditions: a) LDA, LiBr, isobutyraldehyde, THF, 51%.

Scheme 8. Aldol addition to *N*-benzyl-protected oxazolidine

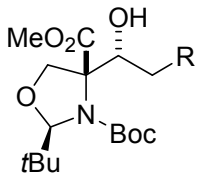
Applications of this strategy by Corey and co-workers in the synthesis of the microbial product lactacystin with *cis*-oxazolidine **39** and isobutyraldehyde yielded the

β-hydroxy amino ester **40** in >98% diastereomeric purity and 51% yield after recrystallisation. An excess of lithium bromide was necessary to obtain good yield and stereoselectivity (Scheme 8).[86]

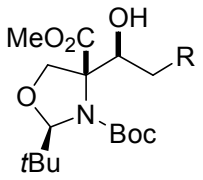
As in the alkylation series where we observed different behaviour in the enolisation step, the aldol reactions with more easily accessible oxazolidine **27a** gave better results than with its epimer **27b**. Here again, the sterically demanding *t*-Bu group shields one face of the *N,O*-acetal and allows the attack of the electrophile only from the less hindered face of the chiral enolate of **27a** (Scheme 9).



27a **41-47**



41a (R = Bn)
42a (R = Pr)
43a (R = Ph)



41b (R = Bn)
42b (R = Pr)

Conditions: a) LDA, R_1R_2CHO, THF, -78 °C to r.t., 25-57%.

Scheme 9. Diastereoselective aldol addition

Addition to simple unbranched aldehydes gave good results, but α-branched aldehydes and ketones were not very reactive. The aldol reactions with pivalaldehyde, isobutyraldehyde, and acetone gave zero to moderate yield. Valeraldehyde, hydrocinnam-aldehyde, and nonenolisable aromatic aldehydes were converted completely (>90%) and, as expected, only two of the four possible diastereomers were observed, as determined by ^{1}H NMR and HPLC (Table 2).

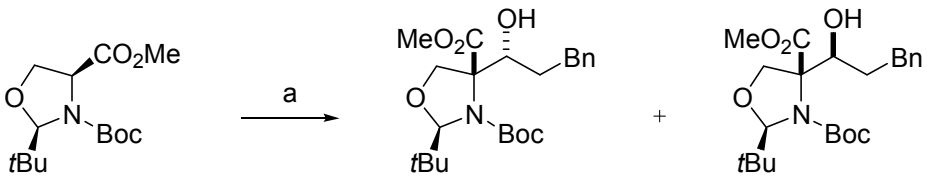
The conversions were satisfying for α-unbranched aldehydes (entries 1 and 7 in Table 2), but decreased rapidly for carbonyl compounds with α-substituents (entries 2 and 3). α-Unbranched aldehydes gave two equally distributed aldol products. Aromatic aldehydes like anisaldehyde, *p*-nitrobenzaldehyde and, especially, benzaldehyde (entries 4 to 6) yielded moderate to good diastereomeric ratios. Besides the products, the major amount of compound found in all reactions was recovered starting material.

Entry	Carbonyl Compound	Conversion	*dr*[a] (^{1}H NMR)	*dr*[a] (HPLC)	
1	valeraldehyde	95%	3/2	1/1	**42a**/**b**
2	isobutyraldehyde	25%	7/1	9/1	-
3	pivalaldehyde	10%	3/2	3/2	-
4	anisaldehyde	95%	10/1	-	-
5	benzaldehyde	100%	>23/1	1 isomer	**43a**
6	*p*-nitrobenzaldehyde	100%	5/1	5/1	-
7	hydrocinnamaldehyde	100%	1/1	1/1	**41a**/**b**
8	acetone	-	-	-	-

[a]*dr*: diastereomeric ratio

Table 2. Diastereoselectivity of aldol additions to **27a**

The pure *anti*- and *syn*-diastereomers **41a** and **41b**, from the aldol reaction of **27a** with hydrocinnamaldehyde were obtained in equimolar amounts after separation by chromatography. The ^{1}H NMR of the crude product also contained signals assigned to traces of starting material and side products (Scheme 10).



27a **41a** **41b**

Conditions: a) LDA, hydrocinnamaldehyde, THF, -78 °C to r.t, 25% for each diastereomer.

Scheme 10. Aldol addition with hydrocinnamaldehyde

The pure *anti*- and *syn*-diastereomers **42a** and **42b**, from the aldol reaction of **27a** with valeraldehyde, were obtained after chromatography. The diastereomeric ratios from ^{1}H NMR and HPLC differ slightly, but indicate equimolar amounts as well. The crude mixture did not contain further products according to NMR data, but small amounts of starting material (<10%) were present. The combined isolated yields of the *syn*- and *anti*-product were 87% (57% *anti* and 30% *syn*) respectively.

The major isomer **43a** of the reaction between **27a** and benzaldehyde was recrystallised and identified as the *anti*-adduct. All obtained products were stable to retro-aldol reaction and storage in acidic solution did not decompose the products.

Aldol additions with long-chain aldehydes like 1-decanal or 1-octadecanal were not successful, probably due to low solubility of the aliphatic aldehydes under reaction conditions (THF at -78 ºC) and only starting material was recovered.

As with the products of the alkylation series, the aldol addition products were assigned based on NOESY correlation studies, an X-ray structure of the *anti*-product **41a**, and analogy considerations. The addition of the carbonyl compounds to the enolate occurred from the face opposite to the bulky *t*-Bu group (Figure 16).

The aldol adducts **42a**/**b** were assigned by comparison with ^{1}H NMR data of the hydrocinnamaldehyde adducts **41a**/**b**.

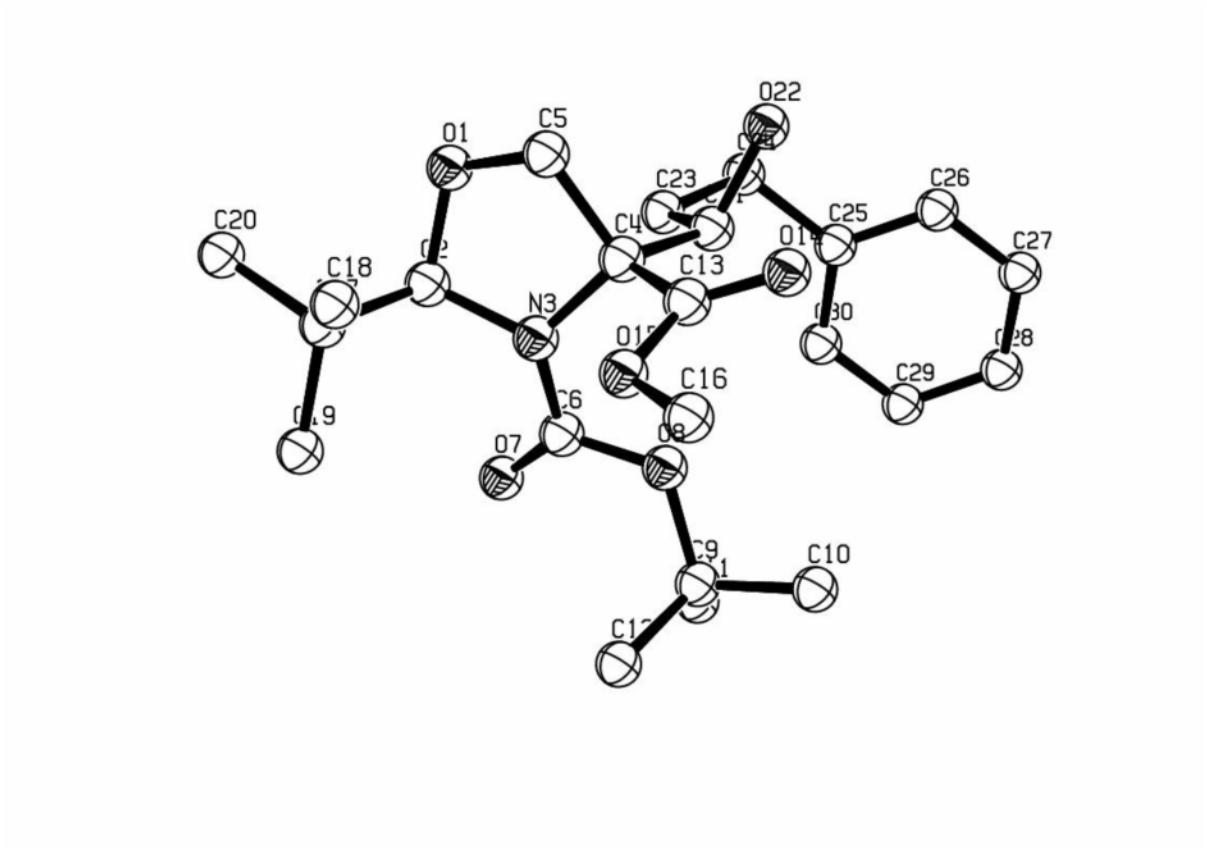


Figure 16. ORTEP[76]-plot of *anti*-aldol product **41a**

The chemical shifts of the characteristic signals in the ^{1}H NMR spectra of both, the *anti*- and *syn*-diastereomers **41a**/**b** and **42a**/**b**, differ significantly. The signal of the methine proton H-C4'[87] in the *syn*-isomer **41b**, geminal to the newly formed hydroxy group in β-position, is shifted 0.67 ppm and the equatorial methylene proton signal H_{β}-C5 of **41b** 0.37 ppm to higher field with respect to the corresponding signals of **41a**. On the other hand, the H-C4' proton signal in the *anti*-isomer **42a** is upfield shifted by ca. 0.45 ppm while the H_{β}-C5 signal in **42a**/**b** differ only marginally in this case (Table 3).

Proton	*anti*-product **41a** (1'*R*,2*R*,4*S*)	*syn*-product **41b** (1'*S*,2*R*,4*S*)	*anti*-product **42a** (1'*R*,2*R*,4*S*)	*syn*-product **42b** (1'*S*,2*R*,4*S*)
H-C2	5.07	5.23	5.00	5.20
H-C4'	4.58	3.91	3.48	3.89-3.82
H_α-C4"	2.98-2.90	3.08-3.01	1.60-1.20	1.48-1.20
H_β-C4"	2.77-2.63	2.82-2.68	1.60-1.20	1.48-1.20
H_α-C5	4.53	4.73	4.51	4.41
H_β-C5	4.10	3.73	4.02	3.89-3.82
H-OC4	3.60	5.45	-[a]	-[a]

[a] The hydroxy group proton could not be localised in ^{1}H NMR

Table 3. ^{1}H NMR data of **41a**/**b** and **42a**/**b**

Aldol additions of achiral carbonyl compounds to chiral enolates can theoretically lead to an equimolar mixture of two products. However, variation of reagents is a versatile tool to manipulate the stereoselectivity.[88] Our attempts to influence the *syn*/*anti*-product distribution in the aldol addition of **27a** to hydrocinnamaldehyde under various different reaction conditions were only little successful (Table 4).

Entry	**Reagent (200 mol-%)/Solvent**	**T/°C**	27a/ **mol-%**	A[a]/ **mol-%**	***dr*** **(**41a/b**)** **NMR**	***dr*** **(**41a/b**)** **HPLC**
1	LDA/THF	-78	100	250	1:2	1:2
2	LICA / THF	-78	100	250	2:3	2:3
3	$TiCl_4$, TEA / CH_2Cl_2	-78	100	250	1:1	1:1
4	$TiCl_4$, TEA/ CH_2Cl_2	0	100	250	SM	-
5	$SnCl_4$, DIPEA / CH_2Cl_2	-78	100	250	1:1	1:1
6	$SnCl_4$, DIPEA / CH_2Cl_2	0	100	250	5:2	-
7	NaHDMS / THF	-78	100	250	2:5	1:1
8	KHDMS / THF	-78	100	250	SM	-

[a]**A**: hydrocinnamaldehyde

Table 4. Reagent controlled aldol reaction

We observed a preference for the *syn* product **41b** when we used alkali metal containing bases, and best results were obtained with LDA and LICA, which may be explained with a slightly favoured six-membered ring transition state.[89] The diastereo-

selectivities of the latter reactions were comparable, but clearly superior to the silazane bases as such as NaHDMS or KHDMS. No selectivity was observed when we used Lewis acid/base systems in CH_2Cl_2.

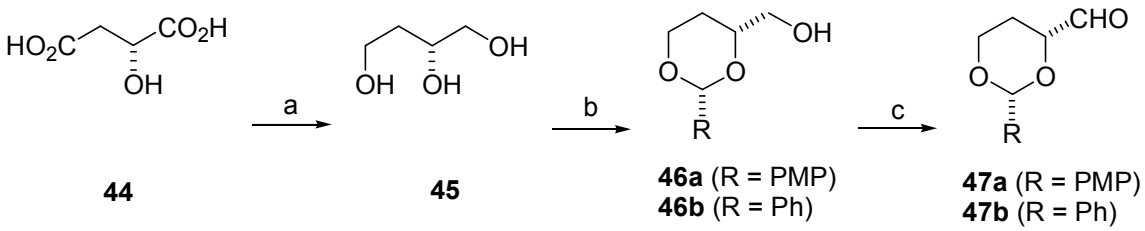
4.6. Diastereoselective aldol addition of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate to chiral aldehydes

4.6.1. Introduction

The previous aldol reactions with oxazolidine **27a** which produced achiral carbonyl compounds were only poorly diastereoselective. The *cis*/*trans* and *syn*/*anti* selectivity in these reactions is strongly dependent on the conformational restrictions of the *N*,*O*-acetals. However, aldol additions of a chiral aldehyde to oxazolidines of type **27** showed high diastereoselectivity.[90] As a consequence, the combination of the chiral enolates of **27a** with chiral aldehydes or ketones has to lead to a single product isomer. During synthetic studies for kaitocephalin, such an aldol reaction of Corey's oxazolidine **39** and its corresponding aldehyde yielded predominantly one single isomer, although in moderate yield only.[90]

4.6.2. Synthesis of (2*S*,4*R*)-2-(4-methoxyphenyl)-[1,3]dioxane-4-carbaldehyde

With respect to a potential total synthesis of myriocin (**1**) or its analogues, we used chiral aldehydes of type **47** which are easily prepared from malic acid in three steps. Borane reduction of D-malic acid (**44**) to triol **45** was followed by cyclisation, where exclusively the thermodynamically more stable diequatorial dioxane **46a** was obtained in 64% yield for these two steps.[91] The subsequent Swern[92] oxidation yielded the unstable α-alkoxy aldehyde **47a**[93] in 62% yield after chromatography (Scheme 11). Yields for PMP and phenyl acetals were comparable.



44 **45** **46a** (R = PMP) **46b** (R = Ph) **47a** (R = PMP) **47b** (R = Ph)

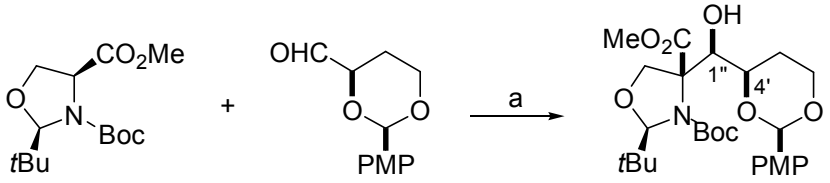
Conditions: a) $BH_3 \cdot SMe_2$, $B(OMe)_3$, THF, 0 °C to r.t.; b) PPTS, $PMPCH(OMe)_2$ or $PhCH(OMe)_2$, CH_2Cl_2, reflux, 64% for 2 steps; c) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, -60 °C to r.t., 62%.

Scheme 11. Synthesis of chiral aldehydes **47**

The alternative mild oxidation method by Ley, where alcohol **46** was treated with the catalyst tetrapropylammonium perruthenate (TPAP) and NMO,[94] yielded, neither in CH_2Cl_2 nor in CH_2Cl_2/CH_3CN, satisfying yields and the reactions usually stopped before 20% of starting material was converted. The modified version with molecular oxygen instead of NMO gave similar results.[95]

4.6.3. Aldol reaction with double stereodifferentiation

Reaction of the chiral enolate of **27a** with the chiral aldehyde **47a** yielded a single diastereomer with less than 50% of the starting material consumed. The obtained *syn*-adduct **48** was isolated in 25% yield after chromatography. The utilisation of additives or modified stoichiometric ratios did not improve the results. It is very likely that the unstable β-substituted aldehyde **47a** polymerises much faster than the enolate of **27a** is formed (Scheme 12). The reactions mixtures usually had to be quenched with acid prior to warming up to avoid retro-reactions of the alcoholate-adducts under the basic reaction conditions. Slow retro-aldol reaction of isolated **48** was nevertheless observed while storing it at +5 °C for several weeks.

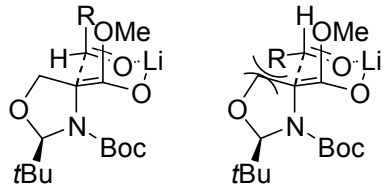


27a **47a** **48**

Conditions: a) LDA, THF, -78 °C to r.t., 20%.

Scheme 12. Aldol addition with double stereodifferentiation

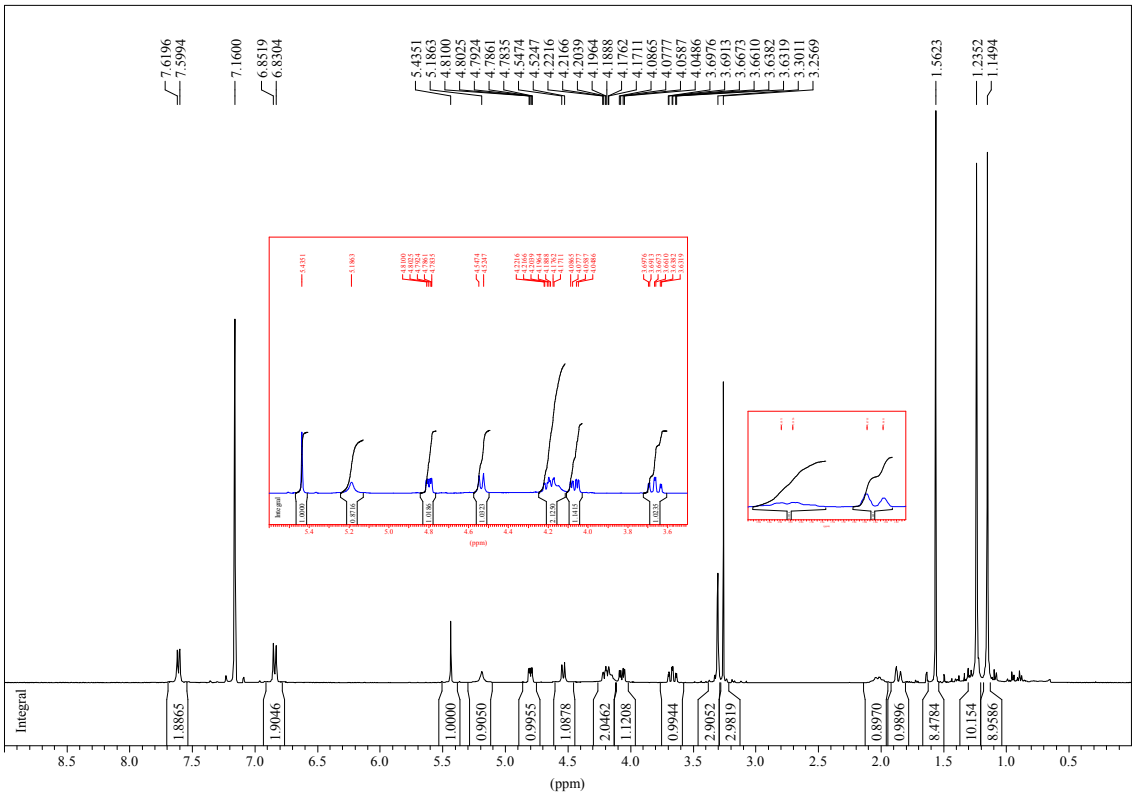
Modelling suggests that the attack of the nucleophile takes place from the less shielded *Si*-face of the enolate of **27a**, although the α-substituent groups of the aldehydes adopt the unfavourable axial position to avoid repulsion with the methylene group of the enolate in the corresponding Zimmerman-Traxler[89] transition state **49a** (Figure 17).

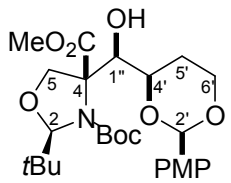


49a **49b**

Figure 17. Zimmerman-Traxler transition states for transformation **27a** → **48** (Scheme 12)

Hence, addition to the nucleophile's *Si*-face occurs rather *via* transition state **49a** to yield the anti-Felkin[96] product **48** (2*R*,4*R*,1"*R*,4'*R*). The ^{1}H NMR spectrum of **48** in benzene-d_6 revealed well-resolved signals for all protons. In $CDCl_3$ and benzene-d_6, respectively, the PMP acetal proton H-C2' was represented by a sharp singlet with significant downfield shift with respect to the broad signal of the corresponding hemiaminal proton, which indicates a more restricted conformation of the oxazolidine moiety compared to the dioxane moiety of **48**. The methine proton signal H-C1"at δ 4.19 ppm partly overlapped with the methylene proton signal H_β-C5. The signal for the methine proton H-C1" yields a doublet at δ 4.80 ppm with observed $^{3}J_{HH}$ = 7.0 Hz to H-C4'. This large $^{3}J_{HH}$ value indicates an average dihedral angle of ca. 30° for H-C1"-C4'-H.[97] The signals of the two methylene protons at H-C5' have chemical shifts of 4.06 and 3.66 ppm with an observed geminal coupling constant $^{2}J_{HH}$ = 11.5 Hz (Figure 18).



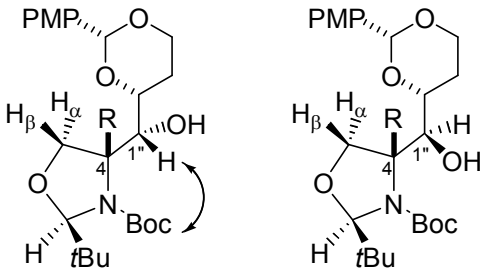


48

Figure 18. ^{1}H NMR spectrum of *syn*-**48** in benzene-d_6

From NOESY correlation experiments we assigned the relative configuration of compound **48**. The weak correlation of the Boc-group methyl protons and the methine proton H-C1" is in good agreement with the Zimmerman-Traxler transition state model only possible for the *syn* (4*R*,1"*R*) product (Figure 19).[89] The *anti*-product (4*R*,1"*S*) with opposite configuration at C1" would have passed the unfavourable transition state **49b** (Figure 17) where the aldehyde substituent has an equatorial position, and an unfavourable interaction with the enolate's methylene group.

Unfortunately, compound **48** was assigned incorrectly (1"*S*) in our Tetrahedron Letters paper (**2004**, *45*, 3063-3065).



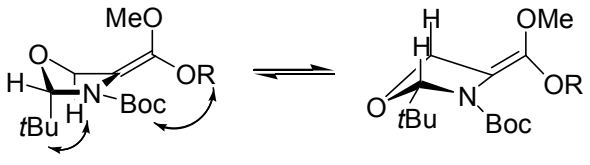
syn-**48** *anti*-**48**

Figure 19. NOE correlations of aldol adduct **48** (R = CO_2Me)

4.7. Crystallographic analysis of the alkylation and aldol products

The obtained X-ray structures of oxazolidine **27b**, its derivative **34d**, and of the *anti* aldol product **41a** from the reaction of **27a** with hydrocinnamaldehyde show some remarkable conformational properties. These rigid *N*,*O*-acetal derivatives represent further examples exhibiting a powerful allylic 1,3-strain ($A^{1,3}$-strain) in reactions of their corresponding enolates with an *N*-carbamoyl group next to the exocyclic double bond.[98,99]

Of related compounds it is known that the *N*-acyl group influences the reactivity and selectivity significantly and is not simply a spectator in reactions. It is reported that, due to the more electron-withdrawing acyl group, enolates of *N*-formylated *N*,*O*-acetals show a higher stability and exhibit less $A^{1,3}$-strain than the corresponding enolates of *N*-carbamoyl *N*,*O*-acetals such as compounds **50** (Figure 20).[100]



50a **50b**

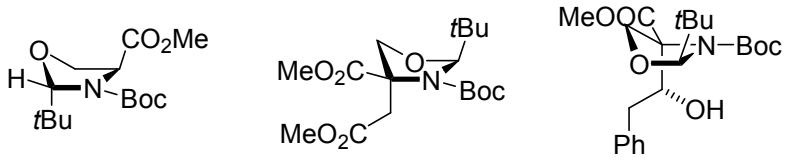
Figure 20. Conformations in five-membered ring *N*,*O*-acetals

The magnitude of $A^{1,3}$-strain in the enolate of oxazolidine **27b** is related to the steric demand of the *N*-protecting group Boc (Figure 21). Alkylations and aldol additions of the enolates of **27a** or **27b** are less feasible than with five-membered ring *N*,*O*-acetals with the more flexible *N*-formyl or *N*-Cbz protecting groups. However, the reactions with compounds

27a or **27b** have shown pronounced diastereoselectivities, because the enolate's *Re*-faces are perfectly shielded and allow an approach of the elecrophile exclusively from the opposite *Si*-face.

The five-membered rings in the crystal structures of **27b**, **34d**, and **41a** adopt a typical puckered envelope conformation with the protected amine nitrogen being close to planar and in the same plane with three of the five ring atoms. The ring-oxygen in **27b** is out of plane while the bulky substituents of the ring-carbon atoms take quite untypical quasi-axial positions. The methyl ester group at C4 is nearly perpendicular to the above-mentioned ring plane and the twisted orientation of the Boc group forms a dihedral angle of 13.4° with the *t*-Bu-C2 group. The *Re*-face of the enolate of **27b** is completely shielded by both the bulky *t*-Bu ring substituent and the twisted Boc group and the conformation relieves $A^{1,3}$-strain.

The two α-substituted compounds **34d** and **41a** adopt a slightly twisted puckered envelope conformation with the C5 carbon being out of the plane. The *t*-Bu-C2 groups in each compound and the larger substituent at C4 are both in quasi-axial position with dihedral angles for the *t*-Bu-C2 and the Boc groups of 2° (**34d**) and 24° (**41a**). The large angle value in the latter compound indicates a strongly distorted Boc group (Figure 21).



27b **34d** **41a**

Figure 21. Conformations of *N*,*O*-acetals

4.8. Conclusions

Stereospecific alkylations of *N*-formyl protected *N*,*O*-acetals, which are obtained from amino acids such as serine, yielded a single diastereomer in good yields. Thus, the well established principle of SRS represents an interesting tool for short and stereoselective syntheses for novel routes to sphingosine-analogues such as myriocin (**1**), mycestericins (**2**-**8**), and sphingofungin E/F (**13**/**14**), which contain a quaternary stereocentre. The known conformationally rigid Boc-protected five-ring *N*,*O*-acetals of type **27** were used in corresponding alkylation reactions to obtain chiral intermediates for the synthesis of the

above-mentioned natural products. The corresponding chiral enolates of these *N*,*O*-acetals adopt unusual conformations and significantly affect the product formation. Depending on the used oxazolidine isomers the desired single diastereomer was obtained with retention or inversion of configuration in good to moderate yield. While the alkylation reactions exclusively deal with the α-carbon stereocentre, the aldol reactions simultaneously form a pair of vicinal stereocentres, the ideal feature for the above mentioned natural products. Combinations of tailor-made chiral carbonyl compounds and *N*,*O*-acetals in aldol reactions exclusively resulted in the formation of the desired diastereomers, which are versatile intermediates for the syntheses of the sphingosine related metabolites myriocin (**1**), mycestericins (**2** - **8**) and sphingofungin E/F (**13**/**14**).

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