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SEEMS TO BE WORKING. TIME
TO EVOLVE AGAIN.

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Application of functionalized β-lactams for the selective construction of new aza- and oxaheterocyclic systems

Thesis submitted in fulfillment of the requirements
for the degree of doctor (PhD) in Applied Biological Sciences: Chemistry

Dutch translation of the title:

Aanwending van gefunctionaliseerde β-lactamen voor de selectieve constructie van stikstof- en zuurstofbevattende heterocyclische systemen

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Woord Vooraf

Dit doctoraatswerk bleek een werk van lange adem te zijn, een weg van mooie ups, maar toch ook downs, eigen aan het voltooien van een dergelijke onderneming. Ongetwijfeld clichés die menig doctoraatstudent zich al bedacht heeft. Hierbij wil ik graag even de tijd nemen om een aantal personen te bedanken die een belangrijke rol hebben gespeeld bij het voltooien van dit proefschrift.

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Lief klein wondertje, ik zie je nu al doodgraag en ik kijk enorm uit naar jouw komst!

Karen Mollet

Mei 2013

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List of Abbreviations

Boc: *tert*-butoxycarbonyl

CAN: ceric ammonium nitrate

Cbz: benzyloxycarbonyl

DAST: *N*,*N*-diethylaminosulfur trifluoride

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMAP: 4-(dimethylamino)pyridine

DMF: dimethylformamide

DMS: dimethylsulfide

DMSO: dimethylsulfoxide

er: enantiomeric ratio

*m*CPBA: 3-chloroperbenzoic acid

MES: 2-(*N*-morpholino)ethanesulfonic acid

Morph-DAST: morpholinosulfur trifluoride

Ms: methanesulfonyl

NBS: *N*-bromosuccinimide

PMB: *p*-methoxybenzyl (4-methoxybenzyl)

PMP: *p*-methoxyphenyl (4-methoxyphenyl)

TBAF: tetra-*n*-butylammonium fluoride

TBDMS: *tert*-butyldimethylsilyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TMAF: tetramethylammonium fluoride

TMS: trimethylsilyl

Ts: 4-toluenesulfonyl

1 Introduction and Goals

Since Fleming's accidental discovery of a penicillin-producing mold in 1928,[1] eighty years of steady progress has followed, and today the β-lactam class of antibiotics is one of the most succesful examples of natural product application and chemotherapy. The naturally or (semi)synthetic penicillins, cephalosporins, cephamycins, oxacephems, (carba)penems, monobactams, and nocardicins (Figure 1) all contain the β-lactam structural subunit and they all function by sequestering the catalytically active serine residue in bacterial penicillin binding proteins, transpeptidases responsible for the crucial cross-linking of peptidoglycan polymers as the final step of the bacterial cell wall synthesis, thus disturbing the integrity of the cell wall, finally leading to cell wall rupture and death.[2]

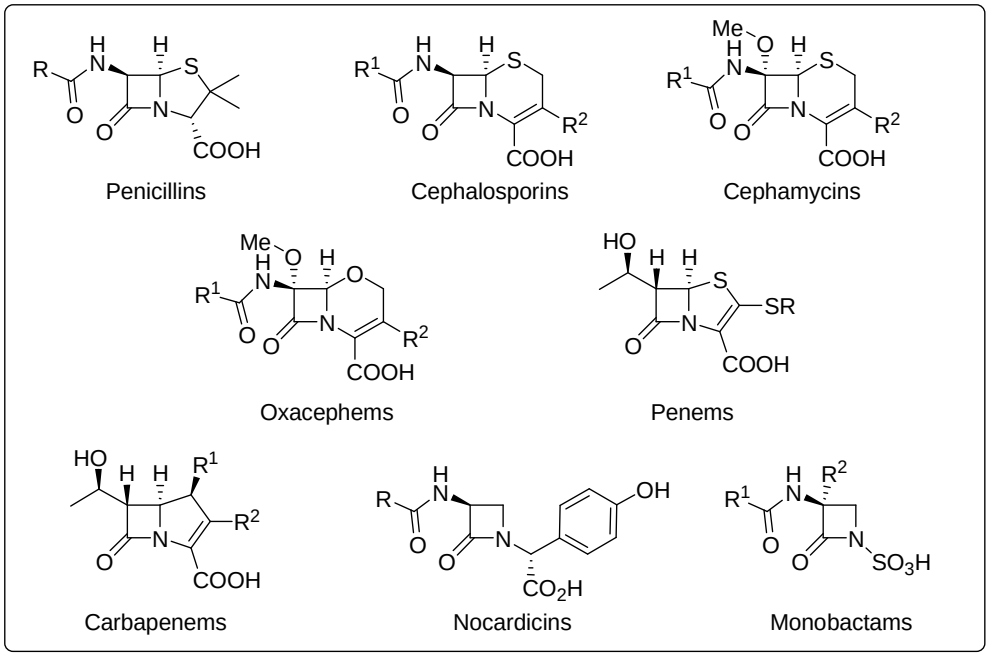


Figure 1

In light of the rapidly emerging bacterial resistance to β-lactam antibiotics, caused by their widespread use during the past decades, the preparation and biological evaluation of new types of β-lactams intended to overcome the defense mechanisms of the bacteria is a major topic in medicinal and pharmaceutical chemistry.[2]

On the other hand, in addition to the key role that β-lactams have played in the fight against pathogenic bacteria, a renewed interest has been focused on the synthesis of azetidin-2-ones possessing diverse pharmacological activities including cholesterol absorption inhibitory activity, antidiabetic, antitumor, anti-inflammatory, antiparkinsonian, anti-HIV and antimalarial activity.[3]

Besides their biological activity, the importance of β-lactams as synthetic intermediates has been widely recognized in organic synthesis. Selective bond cleavage of the β-lactam nucleus coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks. In this way, azetidin-2-ones act as important intermediates toward a wide variety of nitrogen-containing acyclic and heterocyclic target compounds.[4] In that respect, in previous studies at the Department of Sustainable Organic Chemistry and Technology (UGent), the synthetic potential of 1-, 3- and 4-(ω-haloalkyl)azetidin-2-ones **1a**, **1b** and **1c** has been elaborated in detail, leading to the preparation of different mono- and bicyclic heterocyclic compounds, including aziridines,[5,6,7] azetidines,[7,8,9] piperidines,[9,10,11] pyrrolidines,[9,12] azepanes,[11] pyrrolidin-2-ones,[13] oxolanes,[7,14] 1,4- and 3,4-fused bicyclic β-lactams,[11,14,15] and bicyclic γ-lactams (Figure 2).[16]

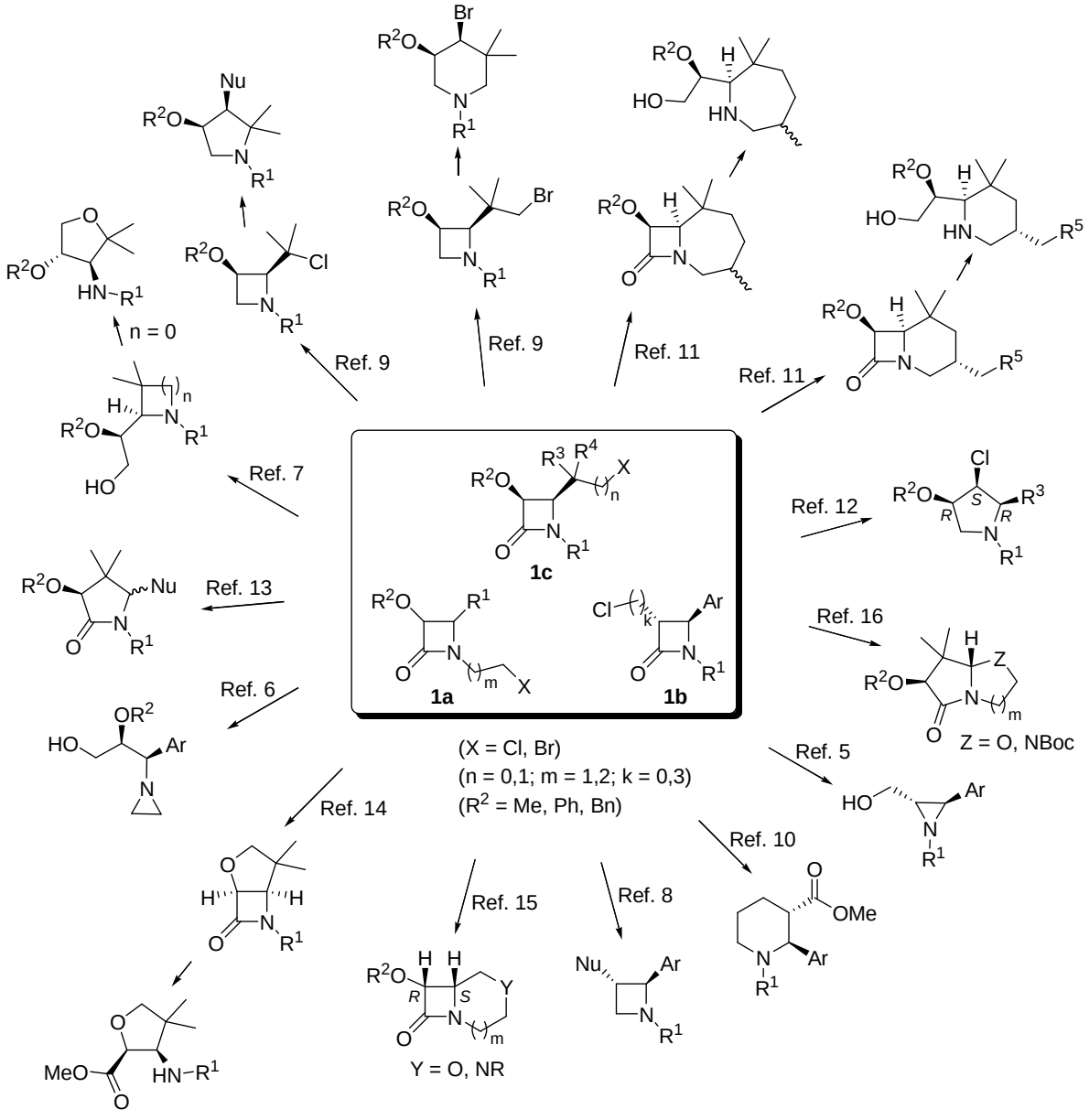
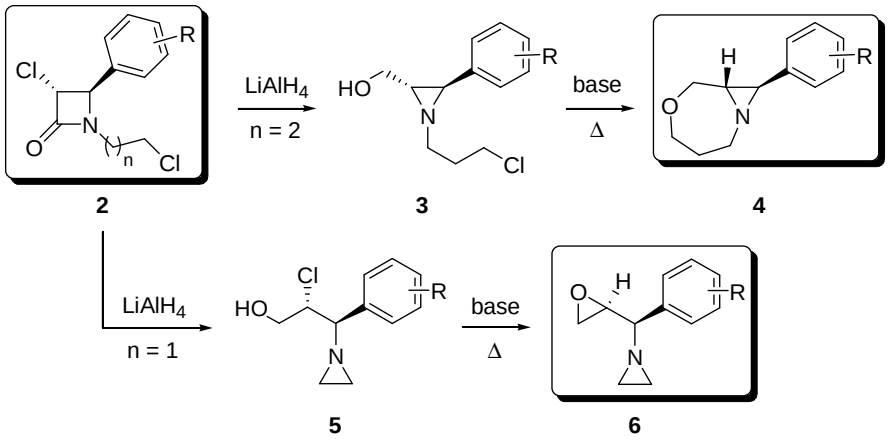


Figure 2

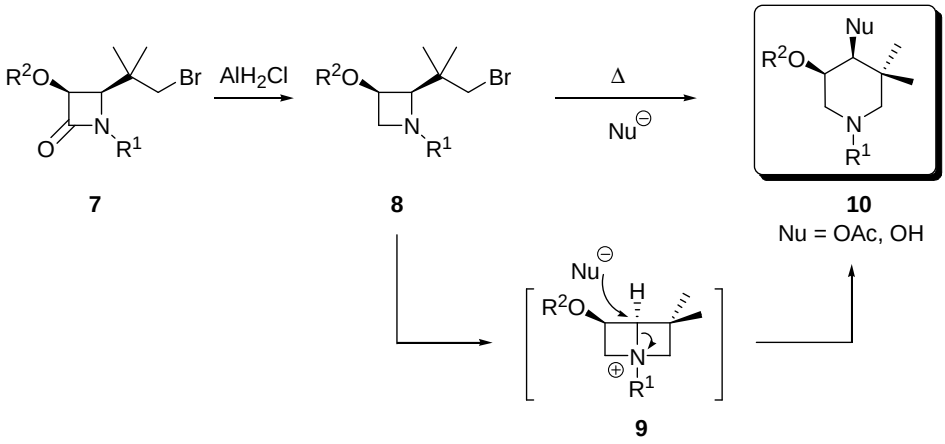
In continuation of the above-illustrated synthetic potential of β-lactams containing a halogenated side chain (Figure 2) as building blocks in the stereoselective construction of heterocycles, which can serve as lead compounds for the development of new biologically relevant targets, in a first topic of this PhD thesis special attention will be devoted to the reactivity of the unexplored class of halogenated β-lactams bearing a halogenated side chain. More specifically, as an extension of the previously reported $LiAlH_4$-induced ring contraction of 3-chloro-β-lactams and 1-(2-chloroethyl)-β-lactams toward the corresponding 3-(hydroxymethyl)aziridines[5] and 1-(3-hydroxypropyl)aziridines,[6] respectively, the aim of this part is to combine both structural features into one system. Thus, the reactivity of 3-chloro-1-(ω-chloroalkyl)azetidin-2-ones **2** toward $LiAlH_4$ will be evaluated, leading to the formation of 1-(3-chloropropyl)-3-(hydroxymethyl)aziridines **3** (n = 2) and 1-(2-chloro-3-hydroxypropyl)aziridines **5** (n = 1, Scheme 1). Subsequent treatment with a base would then furnish oxazepane-aziridine fused systems **4** and 1-(2-oxiranylmethyl)aziridines **6**, respectively (Scheme 1).



Scheme 1

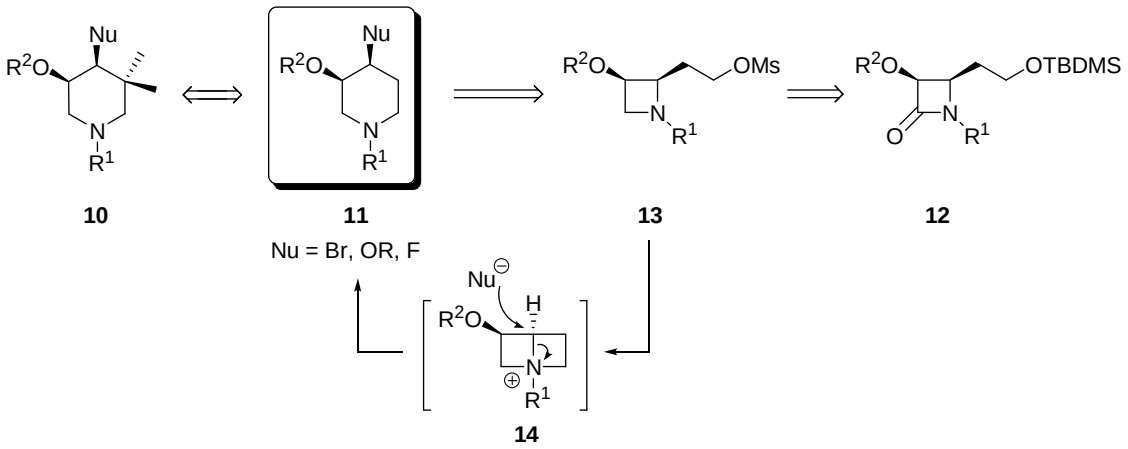
Substituted six-membered azaheterocycles in general and piperidines in particular are found in a whole variety of natural products and pharmaceutical compounds, and they continue to attract considerable attention due to their diverse and important biological activities. The pivotal position of piperidines is illustrated by the fact that several thousands of piperidine derivatives have been mentioned in clinical or preclinical studies.[17] The biological importance of this ring system makes short and versatile routes to substituted piperidines of high interest and value. Therefore, a continuous interest exists in the development of new methodologies for the synthesis of biologically active piperidines.[18] In light of this biological relevance, the synthetic applicability of 2-(2-bromo-1,1-dimethylethyl)azetidines **8** toward stereodefined 4-acetoxy- and 4-hydroxypiperidines **10** will be evaluated, as the latter compounds have become increasingly popular as building blocks toward bioactive compounds. Thus, the synthesis of *cis*-3,4-disubstituted 5,5-dimethylpiperidines **10** will be investigated starting from 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **7**. Monochloroalane-

mediated reduction of β-lactams **7** would afford azetidines **8**, which are susceptible to intramolecular ring closure toward intermediate bicyclic azetidinium salts **9**. Subsequent ring opening by the additional nucleophile would then give rise to the formation of the premised piperidines **10** (Scheme 2). The intermediacy of bicyclic azetidinium ions has previously been proposed in similar rearrangements,[9,19] and particular attention will be devoted to the study of their viability in this work.



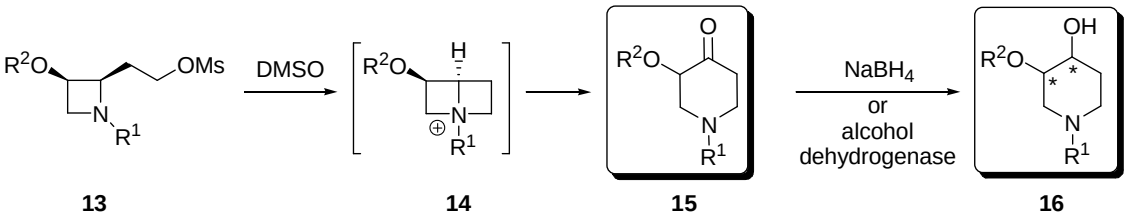
Scheme 2

However, the synthesis of analogous piperidines **11**, in which no 5,5-*gem*-dimethyl group is present, might open up interesting possibilities for the development of biologically and pharmaceutically relevant compounds as well. To achieve this goal, a different synthetic route will be developed. From a retrosynthetic point of view, the synthesis and subsequent ring enlargement of 2-(2-mesyloxyethyl)azetidines **13** *via* bicyclic azetidinium ions **14** could offer a convenient alternative and an easy access to this new class of 5-nonsubstituted piperidines **11**. Azetidines **13** will be prepared *via* 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12**, which will then undergo a AlH_2Cl-induced reduction and a TBAF-mediated deprotection toward the corresponding 2-(2-hydroxyethyl)azetidines, which will be further converted *via* functional group transformation of the alcohol moiety to the mesyloxy group (Scheme 3).



Scheme 3

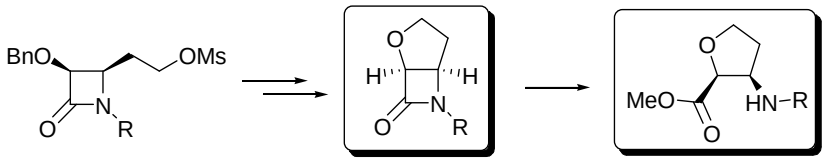
Next to piperidines, the piperidin-4-one ring also comprises an important structural unit both from a medicinal and a chemical point of view, as piperidin-4-ones are known to possess *inter alia* CNS stimulant,[20] antitumor,[21] analgesic,[22] and local anaesthetic[23] activities, and selective modification of the carbonyl moiety can lead to a variety of functionalized piperidines. For these reasons, the one-step ring enlargement of 2-(2-mesyloxyethyl)azetidines **13** toward novel piperidin-4-ones **15** *via* a ring expansion-oxidation protocol upon heating in DMSO will be examined as an efficient synthetic methodology toward this new class of functionalized piperidin-4-one scaffolds (Scheme 4). Furthermore, in order to demonstrate their synthetic usefulness, both a chemical and an enzymatic reduction of the carbonyl moiety will be investigated to provide a convenient entry into the biologically interesting 4-hydroxylated piperidines **16** (Scheme 4). Special attention will hereby be devoted to stereochemical implications.



Scheme 4

In addition to the generation of monocyclic (aza)heterocyclic target compounds from azetidin-2-ones, the β-lactam skeleton has been extensively used as a template to construct cyclic structures fused to the four-membered ring using the functionalization of the β-lactam nucleus as a stereocontrolling element.[4g,24] In that respect, a new pathway toward 3,4-fused bicyclic β-lactams will be developed, involving initial synthesis of 3-benzyloxy-4-(2-mesyloxyethyl)azetidin-2-ones **17**, which will undergo hydrogenolysis of the benzyl ether substituent followed by intramolecular

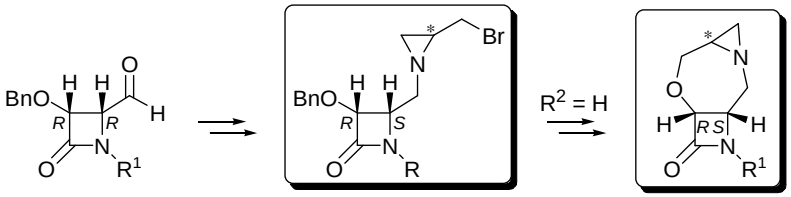
nucleophilic displacement to form 2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **18** (Scheme 5). Further hydrolysis of the amide bond in bicyclic β-lactams **18** would then give rise to the formation of constrained β-amino acid derivatives **19** (Scheme 5). β-Amino acids comprise a valuable class of compounds because of their broad biological and synthetic applicability.[25] In particular, cyclic β-amino acids are present in a variety of natural products and are metabolically more stable toward hydrolysis then their α-amino counterparts, which is of importance for the preparation of modified peptides.[26]



17 **18** **19**

Scheme 5

In previous studies at the Department of Sustainable Organic Chemistry and Technology (UGent), 2-(bromomethyl)aziridines have proven to be valuable synthons for the preparation of a wide variety of nitrogen-containing heterocyclic compounds and acyclic amines such as 4-amino-3-pyrrolidinylbutanenitriles,[27] 2-amino-1-aryloxy-3-methoxypropanes,[28] cyclopropanecarbonitriles,[29] β-fluoro amines,[30] 2-(*N*-sulfonylimino)azetidines,[31] pyrrolidin-2-ones,[32] morpholines,[33] 2-(*N*-ethylaminomethyl)aziridines,[34] piperidines,[35] thiazolines,[36] δ-lactams and γ-lactones.[37] The fact that both β-lactams and 2-(bromomethyl)aziridines have been shown amply to be valuable synthons in organic chemistry prompted us to design a strategy for the synthesis of new compounds in which these small ring systems are combined. In this way, initial selective manipulation of the β-lactam ring and/or the aziridine moiety followed by intramolecular rearrangements involving both structural units could provide a useful entry into a broad range of novel mono-, bi- and tricyclic target compounds. Thus, in a final section of this PhD thesis, β-lactam-aziridine hybrids **21** will be prepared through imination, bromination and reductive cyclization of β-lactam aldehydes **20**, and will then undergo intramolecular nucleophilic displacement of bromide by the C-3 alkoxide (obtained upon hydrogenolysis of the benzyl ether substituent and subsequent treatment with a base) to yield tricyclic β-lactams **22** (Scheme 6).



Scheme 6

2 Literature Overview

In this chapter, a literature overview of the main synthetic routes dealing with the transformation of functionalized β-lactams into azaheterocyclic six-membered ring systems by cleavage of the β-lactam ring through any of the three possibilities, i.e., N1-C2, C3-C4 or C4-N1 bond cleavage, is presented (Figure 3). As the synthesis and synthetic applicability of the azetidin-2-one moiety has been reviewed extensively,[4] the emphasis in this chapter lies on new literature data published during the period 2005-2012.

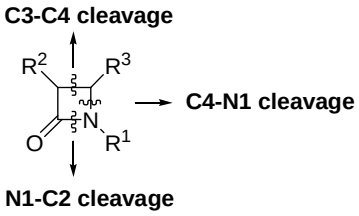
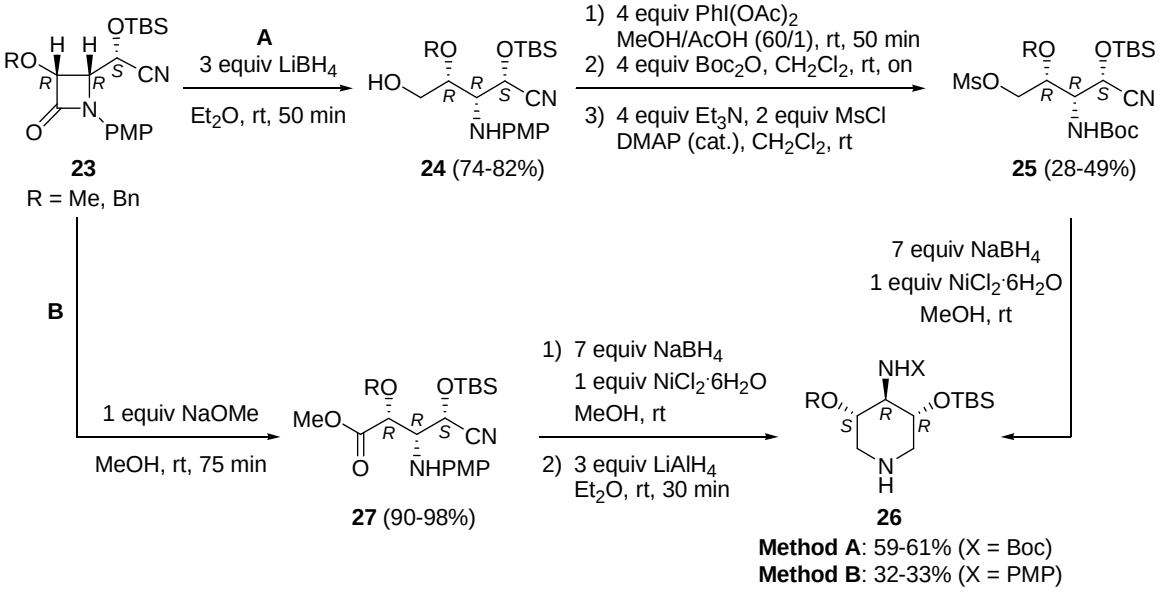


Figure 3

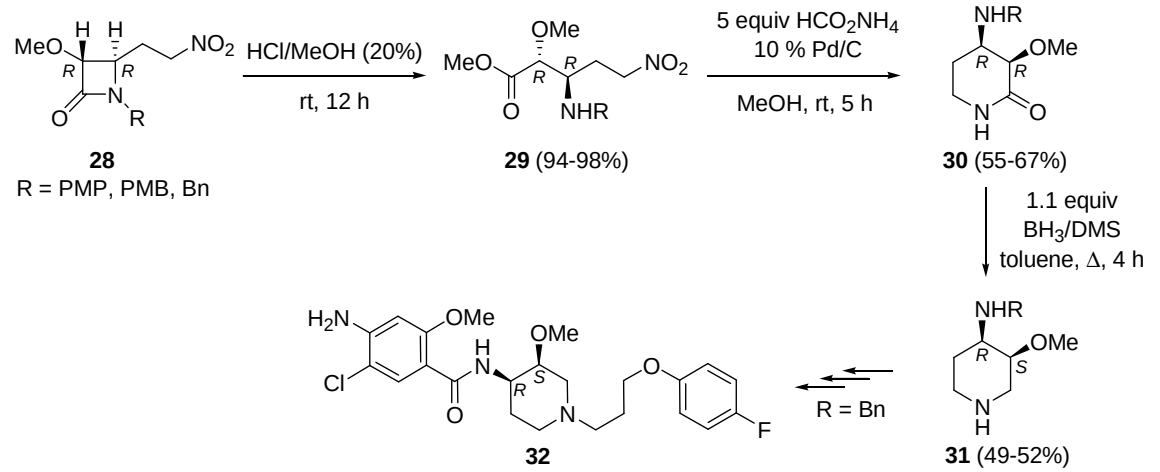
2.1 Ring transformation through N1-C2 bond cleavage

Two concise, complementary stereocontrolled routes to optically pure orthogonally protected *anti*,*anti*-4-amino-3,5-piperidinediols **26** have been described. Key features of the first approach (method A) include a chemoselective reductive ring opening of the β-lactam nucleus with $LiBH_4$ to 3-amino-5-hydroxypentanenitriles **24**, followed by reductive cyclization of conveniently functionalized δ-mesyloxynitriles **25** with $NaBH_4/NiCl_2$ (Scheme 7). The second approach (method B) involves a $LiAlH_4$-induced reduction of protected *anti*,*anti*-4-amino-3,5-dihydroxypiperidin-2-ones, which were easily obtained by chemoselective reduction of the cyano group in γ-cyano-β-amino esters **27** and subsequent intramolecular ring closure of the resulting diamino esters (Scheme 7).[38]



Scheme 7

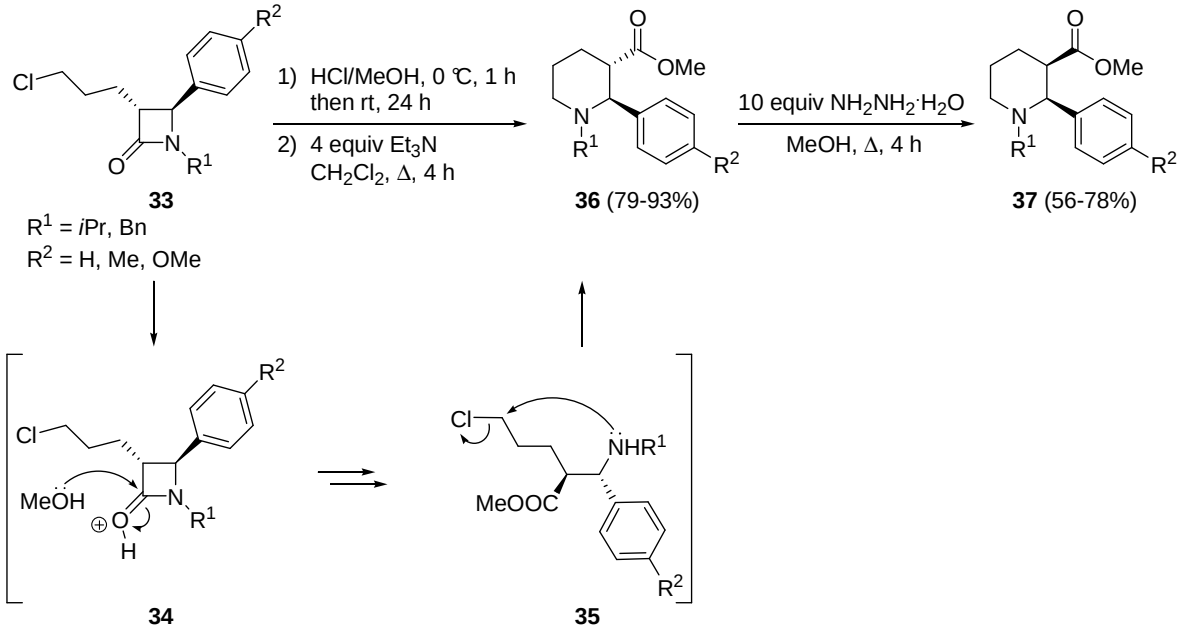
According to an analogous reaction sequence, β-lactams have been shown to play a key role in the synthesis of cisapride, a drug used for the treatment of various gastrointestinal disorders.[39] The synthetic strategy consists of methanolysis of nitro-β-lactams **28** followed by a Pd-catalyzed reductive cyclization by means of ammonium formate and reduction of the carbonyl moiety upon treatment with borane (Scheme 8).[40] The construction of the gastroprokinetic agent **32** was achieved in an additional three-step synthesis.[41]



Scheme 8

An alternative (diastereoselective) approach for the synthesis of piperidine derivatives from β-lactams has been developed at the Department of Sustainable Organic Chemistry and Technology (Ghent University) and comprises the ring transformation of 3-(3-chloropropyl)-β-lactams **33**, synthesized by treatment of *N*-(arylmethylidene)amines with 5-chloropentanoyl chloride in benzene

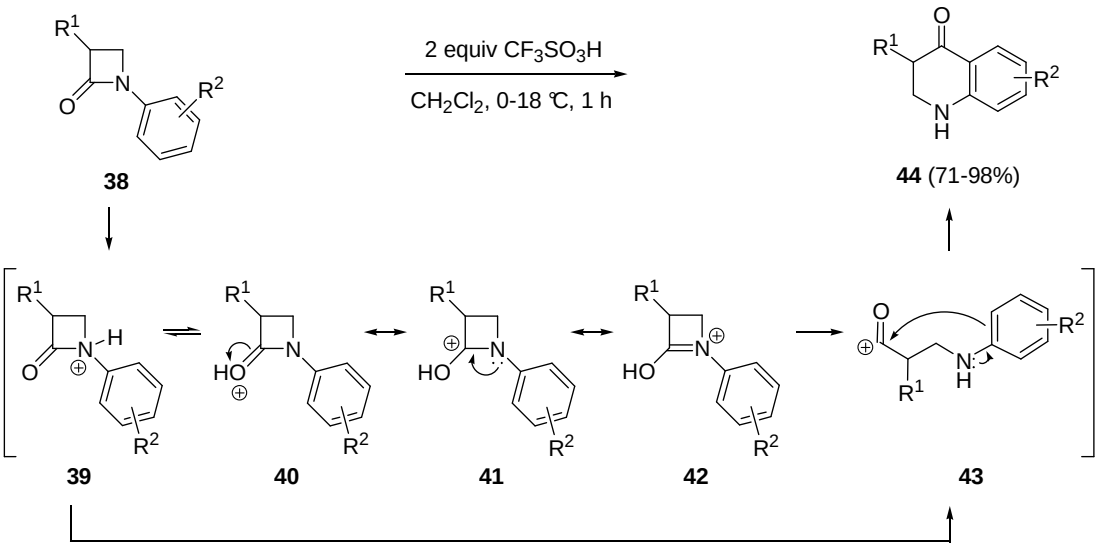
in the presence of 2,6-lutidine.[10] The synthetic strategy involves a two-step synthesis of *trans*-2-arylpiperidine-3-carboxylates **36**, compounds of significant interest due to their potential use in the treatment of Alzheimer's disease,[42] upon subsequent treatment of 3-(3-chloropropyl)-β-lactams **33** with hydrogen chloride in methanol and triethylamine in dichloromethane (Scheme 9). This reaction has been proposed to proceed through initial nucleophilic ring opening of the protonated β-lactam **34** by methanol, followed by intramolecular displacement of chloride by the *in situ* formed free amine **35** upon addition of the base (Scheme 9).[10] Interestingly, *cis*-piperidines would be expected, suggesting that epimerization has occurred during this transformation. Furthermore, these *trans*-2-arylpiperidine-3-carboxylates **36** were easily converted into their corresponding *cis*-isomers **37** by means of hydrazine monohydrate in methanol (Scheme 9).[10]



Scheme 9

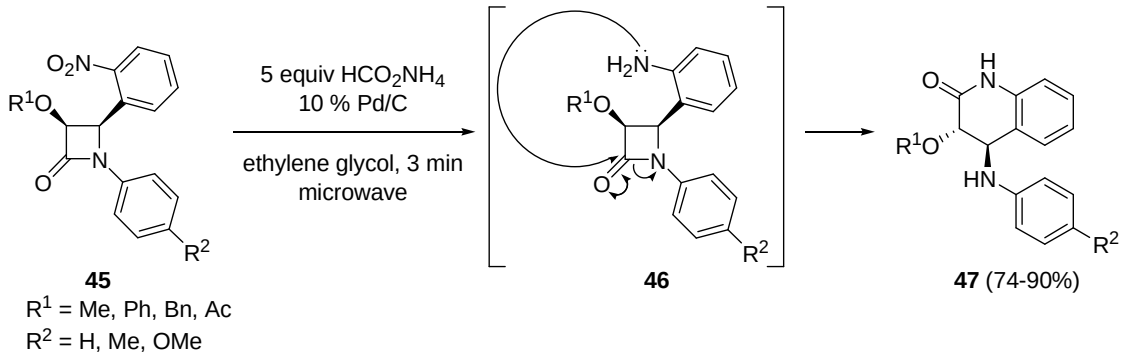
Several examples are known in which aryl-substituted β-lactams are rearranged into functionalized quinolone derivatives, a family of compounds with *inter alia* broad-spectrum antibiotic,[43] antidiabetic,[44] antidepressant, sedative and antiparkinson[45] properties. For example, 1-arylazetidin-2-ones **38**, synthesized by a Goldberg-Buchwald-type copper-catalyzed coupling of *N*-unsubstituted azetidin-2-ones with the appropriate aryl halides or using Mitsunobu cyclization processes,[46] have been treated with triflic acid under mild reaction conditions in CH_2Cl_2, which ensued a smooth Fries rearrangement delivering 2,3-dihydro-4(1*H*)-quinolinones **44** in good to high yields (71-98%) (Scheme 10).[46] This intramolecular Friedel-Crafts acylation is the result of an acid-mediated amide bond cleavage in β-lactams **38**, generating a highly reactive free acylium ion in intermediates **43**, which

subsequently undergo an intramolecular electrophilic aromatic substitution (Scheme 10). Recently, this transformation has been used in the synthesis of TRPV1 antagonists as analgesic agents.[47]



Scheme 10

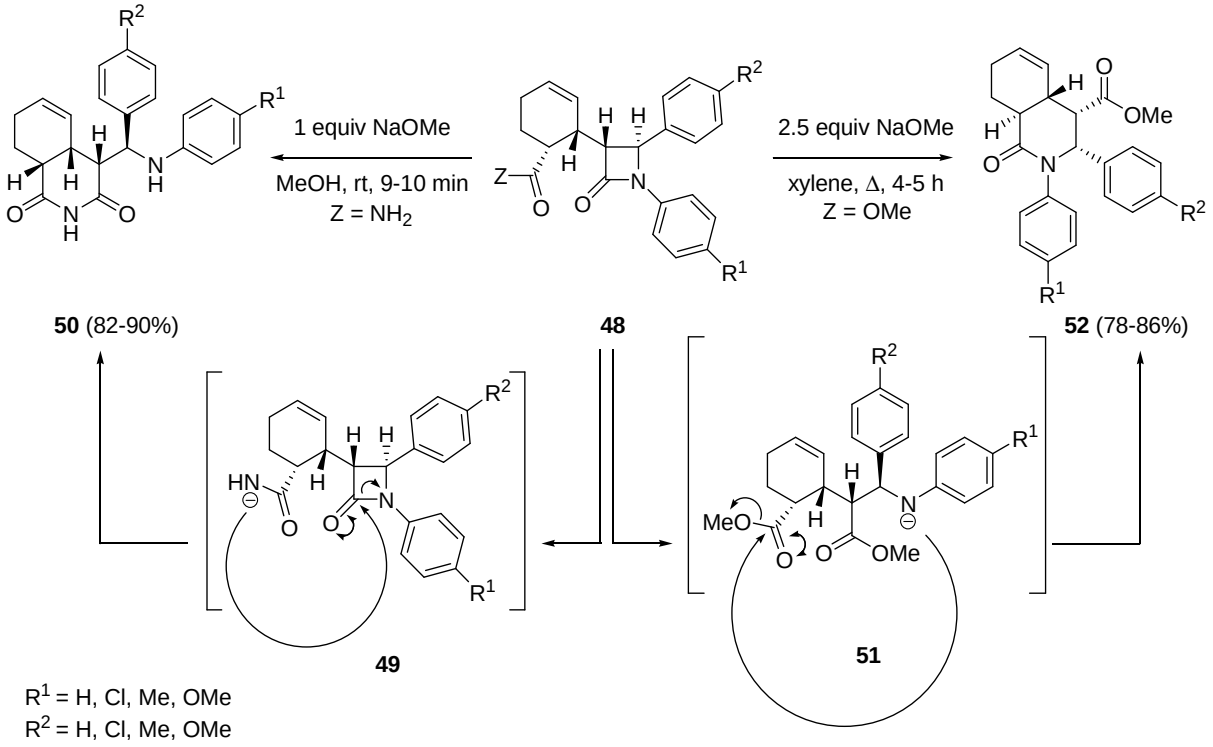
Another method for the construction of dihydroquinolinones from β-lactams starts with the microwave-assisted transfer hydrogenation of the *ortho*-nitro group in azetidinones **45**, synthesized *via* the Staudinger reaction, to afford intermediates **46** by using ammonium formate in ethylene glycol. Subsequent *in situ* intramolecular β-lactam ring opening provided 4-amino-3,4-dihydroquinolin-2-ones **47** in 74-90% yield (Scheme 11).[48]



Scheme 11

Isoquinoline-based scaffolds represent an important group of biologically active compounds and are attracting increasing attention in contemporary biomedical research and drug discovery programs. Several members of this group exhibit various pharmacological and biological activities, including potential anticancer properties.[49] In that respect, recently, the single-step diastereoselective

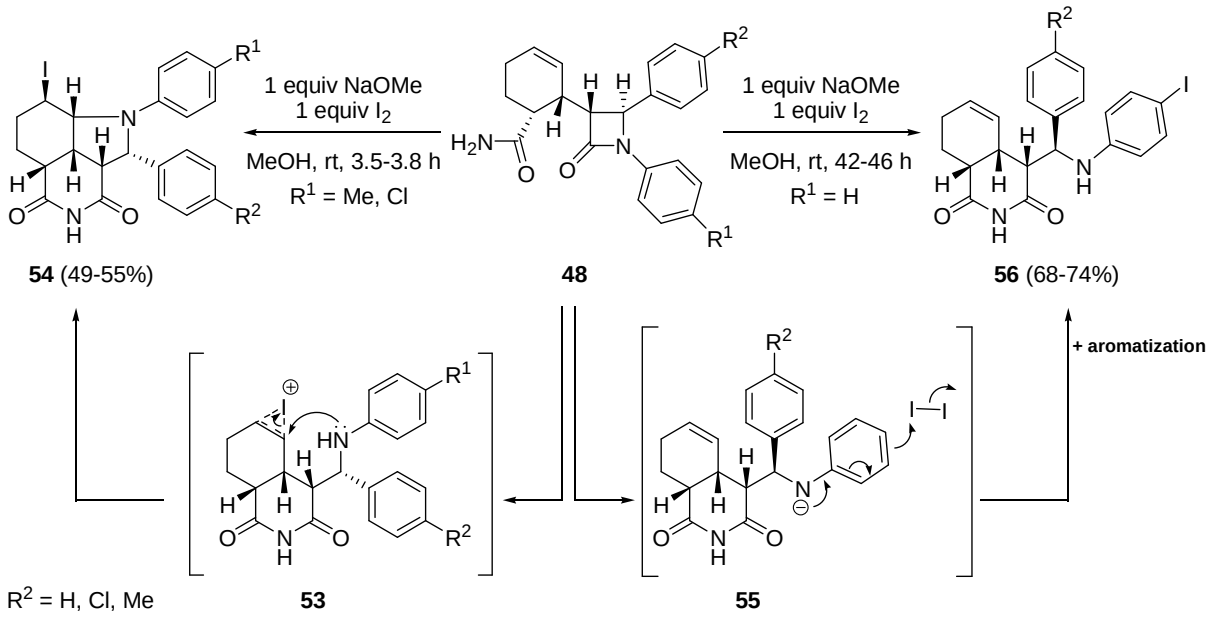
synthesis of functionalized hexahydroisoquinolinones **52** and tetrahydroisoquinoline-1,3-diones **50** has been realized by intermolecular NaOMe-induced amidolysis of 1-aryl-β-lactams **48** (Z = OMe) and subsequent intramolecular cyclization upon reflux in xylene, and by intramolecular base-induced amidolysis of 1-aryl-β-lactams **48** (Z = NH_2) with concomitant two-carbon ring enlargement by stirring in MeOH at room temperature, respectively (Scheme 12).[50]



Scheme 12

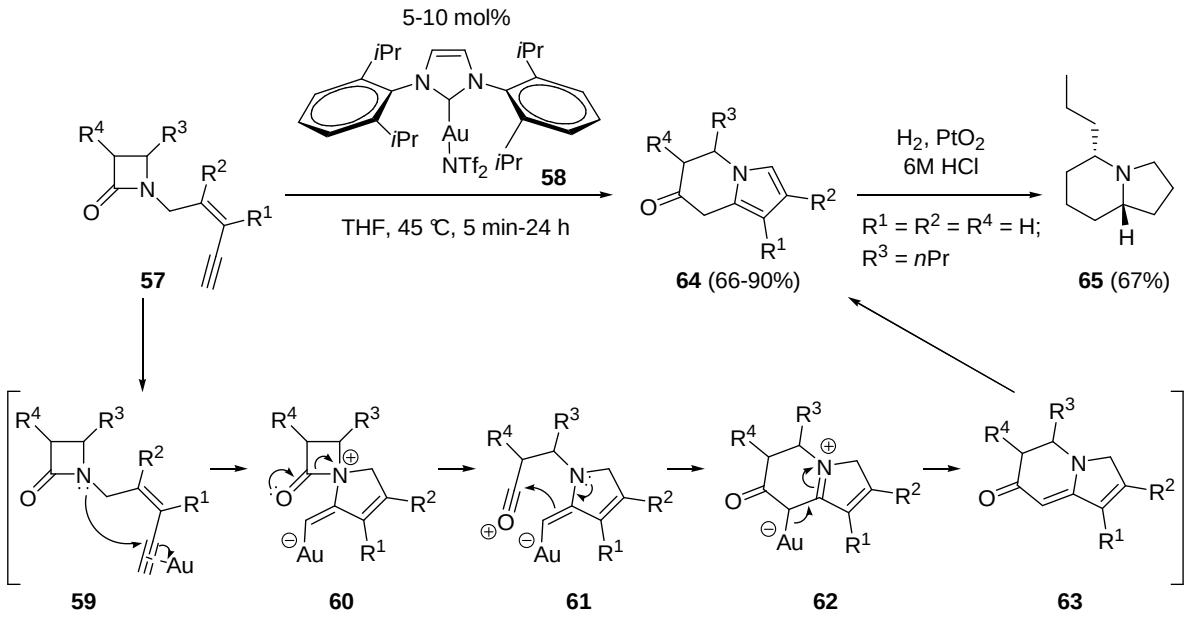
Furthermore, it has been observed that treatment of β-lactams **48** (Z = NH_2) with NaOMe and I_2 in methanol at room temperature gave rise to iodinated octahydropyrroloisoquinoline-1,3-diones **54** and 4-[(4-iodophenylamino)arylmethyl]tetrahydroisoquinoline-1,3-diones **56** depending upon the *N*-substituent of the β-lactam ring.[50] In the case *para*-substituted 1-arylazetidin-2-ones **48** (Z = NH_2, R^1 = Me, Cl) were deployed as synthetic precursors, electrophilic addition of molecular iodine across the double bond in the initially formed tetrahydroisoquinoline-1,3-dione derivatives **50** yielded intermediate iodonium ions **53**, which upon intramolecular cyclization afforded the corresponding functionalized tricyclic tetrahydropyrrole derivatives **54** in 49-55 % yield (Scheme 13).[50] Interestingly, *N*-phenyl-β-lactams **48** (Z = NH_2, R^1 = H) underwent electrophilic aromatic substitution instead of iodocyclization upon addition of I_2, which has been explained considering the initial formation of diketones **55** having a negative charge on the nitrogen atom. In this way, the electron density at the *para*-position of the phenyl substituent increases, thus favouring aromatic electrophilic substitution

with molecular iodine, resulting in the selective preparation of iodinated tetrahydroisoquinoline-1,3-diones **56** in 68-74% yield after re-aromatization (Scheme 13).[50]



Scheme 13

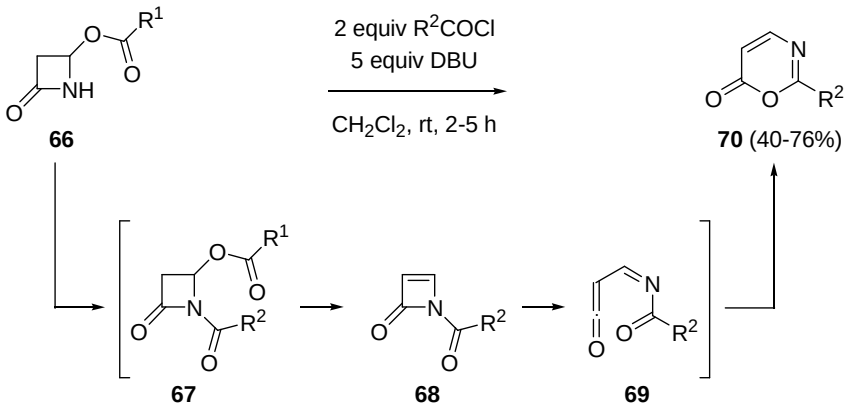
The synthetic usefulness of β-lactam to piperidinone transformations has also been demonstrated through the synthesis of dihydroindolizinones. Enynyl β-lactams **57** have been rearranged into 5,6-dihydro-8*H*-indolizin-7-ones **64** through a regiospecific Au-catalyzed β-lactam ring opening and recyclization sequence. The reaction mechanism of this ring expansion has been rationalized by considering an initial 5-*exo*-*dig* cyclization of the lactam nitrogen to the metal-activated alkyne moiety, followed by a heterocyclic fragmentation of the amide bond to generate acyl cations **61**, which subsequently undergo cyclization to the enamine moiety to afford bicyclic zwitterions **62**. Finally, recuperation of the Au-catalyst and subsequent 1,5-hydride migration gives bicyclic pyrroles **64** (Scheme 14).[51] This synthetic strategy was further extended by the development of naturally occurring indolizidine alkaloids, as demonstrated by the synthesis of racemic indolizidine 167B **65**, an alkaloid isolated from neotropical poison dart frogs (Scheme 14).[51]



R^1 = H, $BnOCH_2CH_2$, *c*Hex, *n*Pr; R^2 = H, Ph, *n*Hex; R^1R^2 = $(CH_2)_5$, $(CH_2)_6$;
R^3 = H, Me, Et, Bn, *n*Pr; R^4 = H, Me, Et, $(Et)_2$

Scheme 14

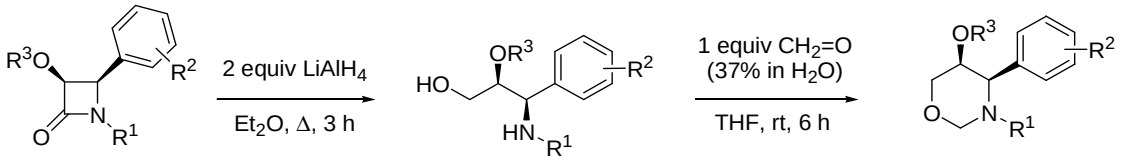
A one-step approach has been reported for the conversion of 4-acyloxy-β-lactams **66** into 1,3-oxazin-6-ones **70** by using acyl chlorides in the presence of DBU (Scheme 15).[52] After initial acylation of the β-lactam nitrogen, the acidity of the H-3 proton of the β-lactam nucleus is enhanced by the electron-withdrawing *N*-acyl group, thus making the β-lactam carbonyl group more "ketone-like". As a result, the organic base DBU promotes the elimination of the carboxylic acid (R^1CO_2H) across the β-lactam C3-C4 bond generating highly strained azetinones **68**, which rapidly experience a four-centered electrocyclic ring opening to *N*-acylimidoylketenes **69**, which in turn provide 1,3-oxazin-6-ones **70** in 40-76% yield through a six-centered electrocyclic ring closure (Scheme 15).[52]



R^1 = Me, Ph
R^2 = Ph, 4-ClC_6H_4, 2-furyl, *t*Bu, Et, 4-BrC_6H_4, (*E*)-C_6H_5-CH=CH

Scheme 15

Another example of a two-step ring transformation of β-lactams into nitrogen- and oxygen-containing six-membered heterocycles, developed at the Department of Sustainable Organic Chemistry and Technology (Ghent University), comprises the synthesis of 1,3-oxazinanes **73** *via* $LiAlH_4$-promoted reductive ring opening of *cis*-β-lactams **71** toward γ-aminoalcohols **72**, followed by recyclization using formaldehyde in THF (Scheme 16).[53] The biological importance of these classes of compounds has been demonstrated by evaluation of their *in vitro* antiplasmodial activity and cytotoxicity, pointing to their promising potential as a novel type of antimalarial agents.[53]

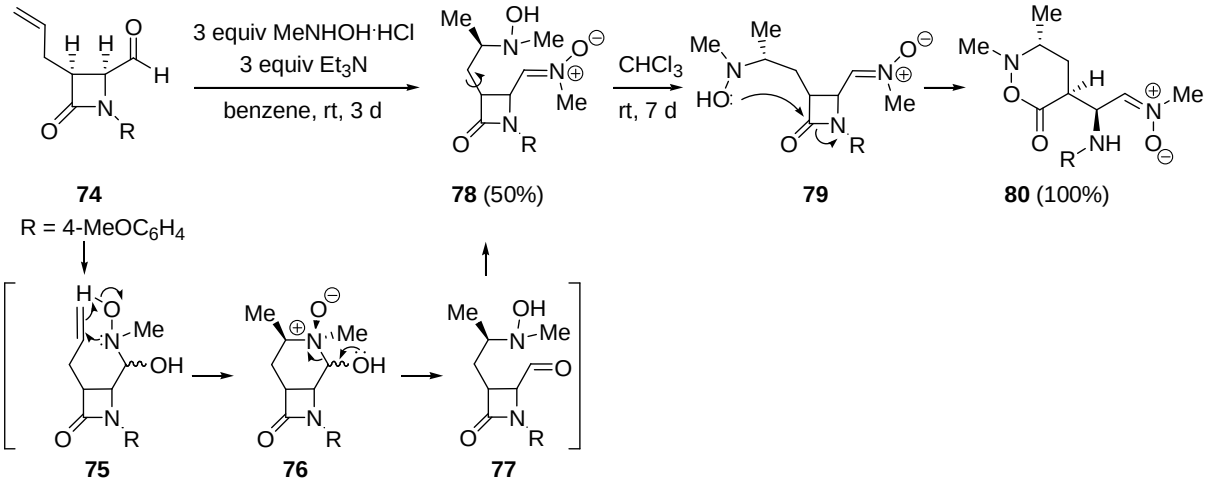


71 **72** (32-75%) **73** (50-74%)

R^1 = *i*Pr, *n*Pr, *i*Bu, *t*Bu, *c*Hex, Ph, Bn
R^2 = H, 4-Me, 3-OMe, 4-OMe, 4-Cl, 2-Br, 2-F
R^3 = Me, Ph, Bn

Scheme 16

In a single example, racemic 3-allyl-4-formyl-β-lactam **74** was treated with *N*-methylhydroxylamine hydrochloride in the presence of triethylamine, which, upon intramolecular protonation of the olefin moiety toward the corresponding zwitterionic bicyclic hemiaminal **76** followed by imination of the latent aldehyde, gave rise to the selective formation of nitrone **78** in 50% yield (Scheme 17). This nitrone **78** proved to be unstable in chloroform and after one week 1,2-oxazinane-6-one **80** was obtained in quantitative yield through intramolecular ring opening of the β-lactam nucleus *via* the N1-C2 bond (Scheme 17).[54]

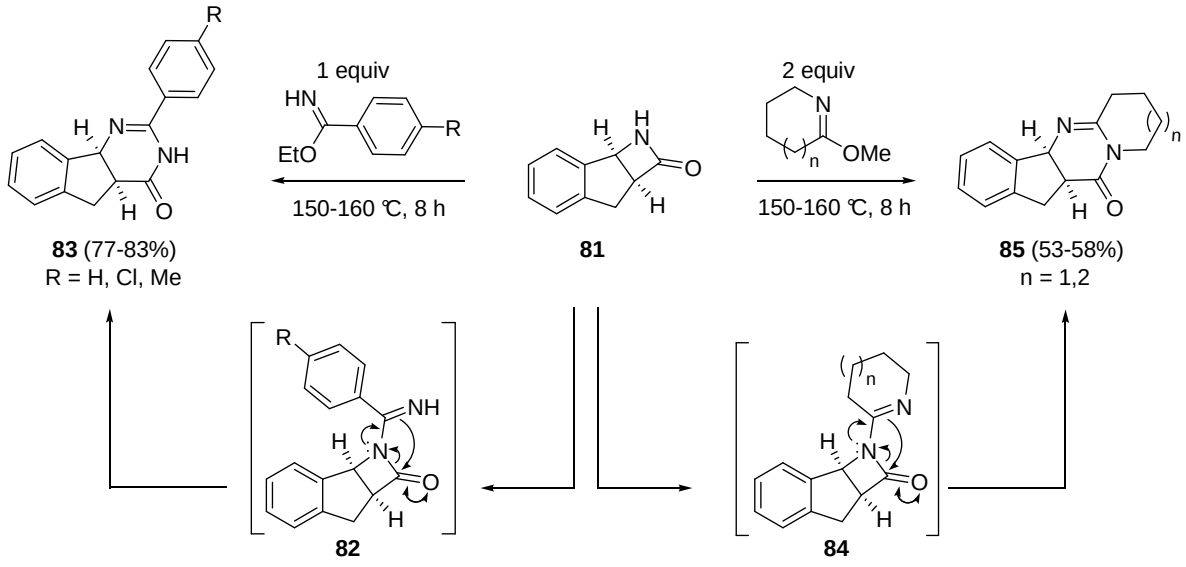


74 **78** (50%) **79** **80** (100%)

75 **76** **77**

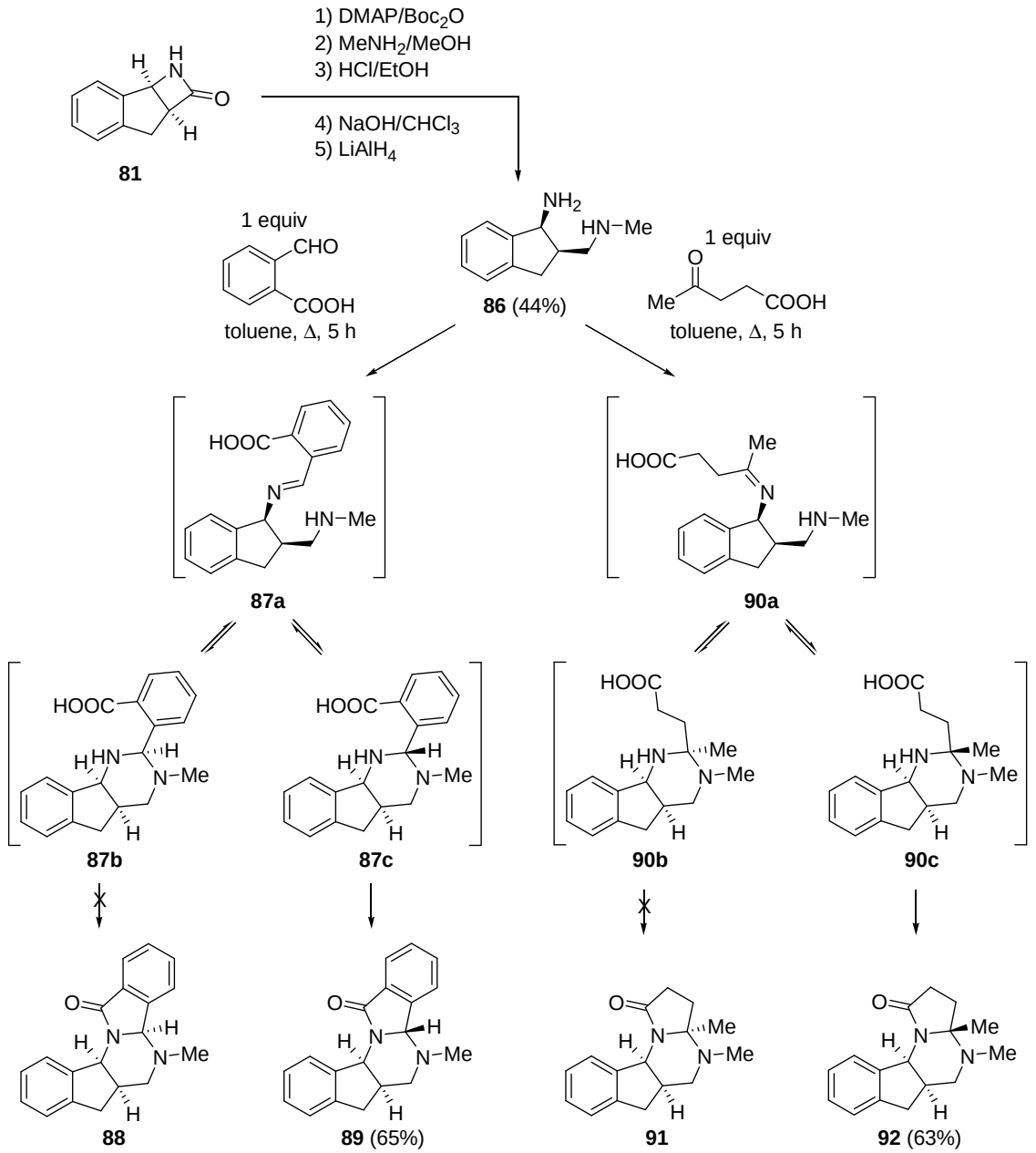
Scheme 17

Indane-fused dihydropyrimidinones **83** and **85** have been obtained by ring enlargement of 3,4-benzo-6-azabicyclo[3.2.0]heptan-7-one **81**, prepared from indene by chlorosulfonyl isocyanate addition, upon melting with imidates or lactim ethers at 150-160 °C for 8 hours (Scheme 18). The first step in the reaction is the formation of amidine intermediates **82** and **84**, which, after intramolecular transamidation with simultaneous N1-C2 bond fission, rearrange into tri- and tetracycles **83** and **85**, respectively (Scheme 18).[55]



Scheme 18

In addition, 1,3-diamine **86**, synthesized *via* N1-C2 bond cleavage of tricyclic β-lactam **81**, has been treated with 2-formylbenzoic acid or levulinic acid in boiling toluene, which ensued, after initial imination, a smooth two ring-closure sequence delivering indane-fused hexahydropyrimidines **89** and **92** with complete diastereoselectivity in 65% and 63% yield, respectively (Scheme 19).[55] The stereochemical outcome of this overall ring rearrangement has been rationalized assuming the formation of a tautomeric equilibrium between the intermediates **87** and **90**, respectively, in combination with a kinetic control governing the second cyclization step (Scheme 19).[55]

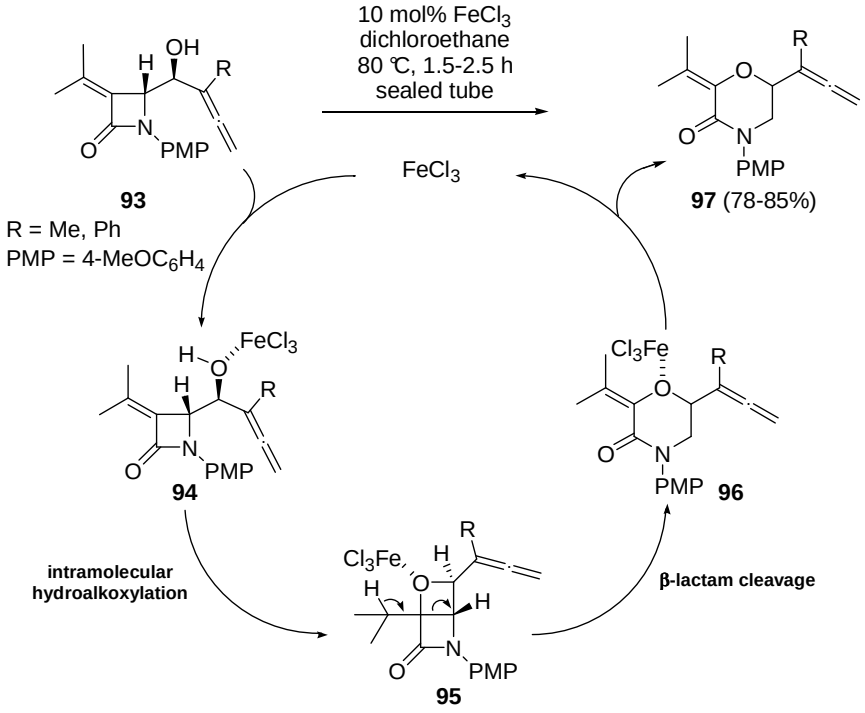


Scheme 19

2.2 Ring transformation through C3-C4 bond cleavage

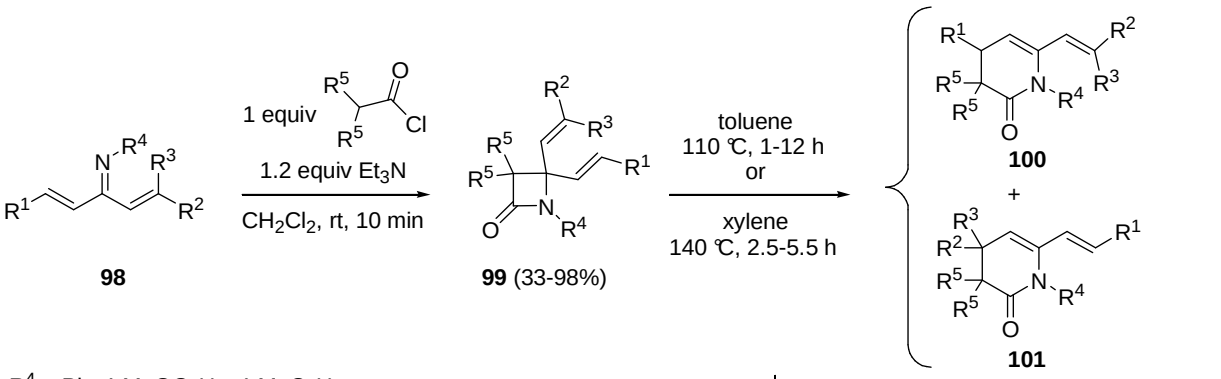
The tandem cycloetherification/β-lactam ring cleavage of racemic γ-olefinic α-allenols **93**, prepared from the appropriate 4-oxoazetidine-2-carboxaldehydes *via* a regiocontrolled indium-mediated Barbier-type carbonyl-allenylation in aqueous medium,[56,57] in the presence of catalytic iron(III) trichloride in dichloroethane at 80 °C in a sealed tube has been described to selectively afford allenic morpholinones **97** in good yields (78-85%) (Scheme 20).[57] Probably, the hydroxyl-iron complex **94**, formed initially through coordination of $FeCl_3$ to the oxygen atom of olefinic allenols **93**, considerably increases the acidity of the hydroxyl protons, thus inducing a chemo- and regioselective

intramolecular protonation of the alkene moiety with concomitant 4-*exo* oxycyclization to yield bicycles **95**, which, driven by relief of the strain associated with the four-membered ring, rapidly evolve to intermediates **96** through selective β-lactam ring cleavage. Finally, demetalation regenerates the iron catalyst and affords morpholinones **97** (Scheme 20).[57] Alternatively, initial activation by coordination of $FeCl_3$ to the olefinic double bond cannot be excluded.



Scheme 20

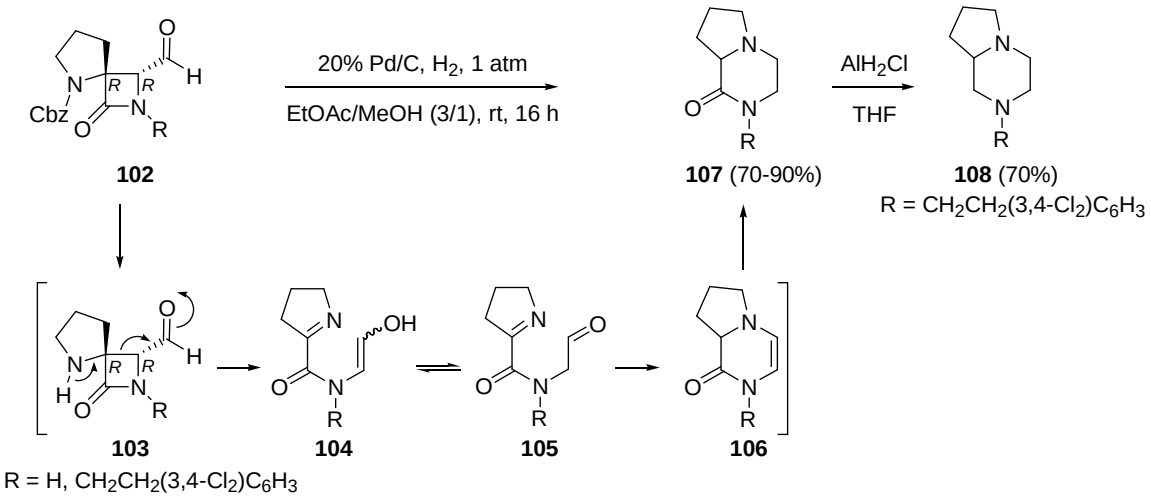
As described above, β-lactams are excellent substrates for the synthesis of functionalized piperidinone derivatives through selective fragmentation of the N1-C2 amide bond of the β-lactam nucleus followed by ring expansion. Also, β-lactams have been proven to be suitable building blocks for the ring enlargement toward dihydropyridones, as demonstrated by the thermally induced [1,3]-sigmatropic rearrangement with concomitant C3-C4 bond cleavage of 4,4-dienyl-β-lactams **99**, which have been obtained through [2+2]-cyclocondensation of azatrienes **98** with the appropriate ketenes, upon heating in toluene or xylene (Scheme 21).[58] When the starting β-lactams **99** have two different vinyl substituents (R^1 = Ph; R^2 = CO_2Et; R^3 = H or R^1 = Ph, CO_2Et; R^2 = R^3 = Me), the regioselectivity of the rearrangement reaction depends on steric factors and on the electronic demands of the substituents. Whereas in the former case (R^1 = Ph; R^2 = CO_2Et; R^3 = H) the predominant formation of dihydropyridones **100** can be attributed to the benzylic stabilization of the developing carbenium ion, in the latter case (R^1 = Ph, CO_2Et; R^2 = R^3 = Me) steric factors play a predominant role rather than electronic factors, inducing reaction at the monosubstituted diene C-terminus even if the substituent is an electron-withdrawing ethoxycarbonyl group (Scheme 21).[58]



R^4 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, Bn, *i*Pr, *n*Pr, NMe_2 R^5 = Ph, Me	$R^1 = R^2$ = Ph; R^3 = H	**100** = **101** (98-99%)
	R^1 = Ph; $R^2 = CO_2Et$; R^3 = H	**100**+**101** (77-99%); **100**/**101**: 81-87/13-19
	R^1 = Ph, CO_2Et; $R^2 = R^3$ = Me	**100** (48-95%)

Scheme 21

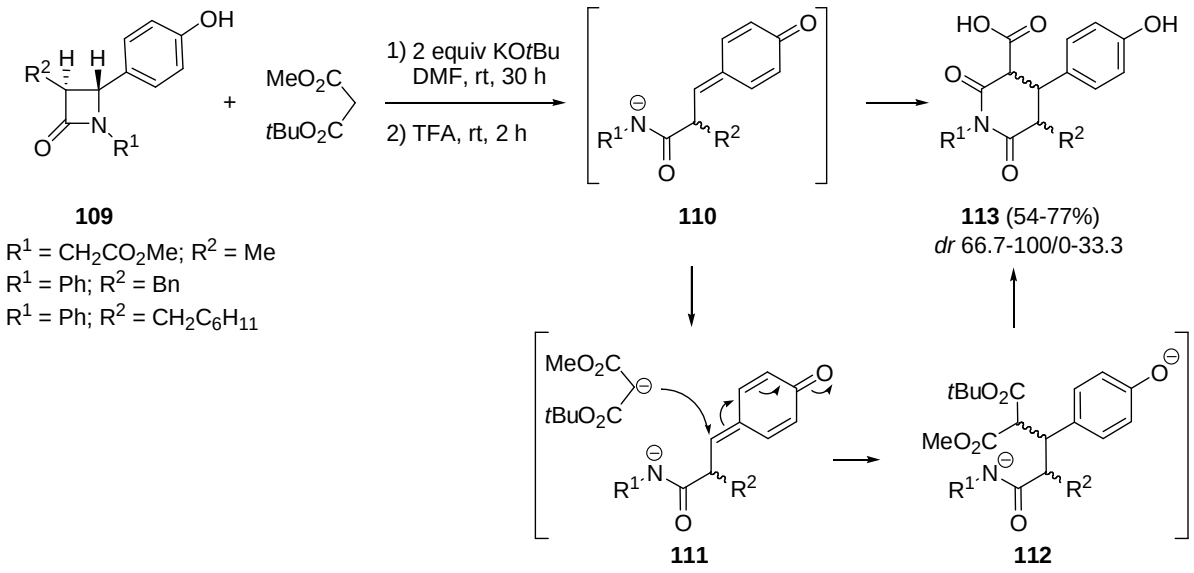
A β-lactam to piperazinone rearrangement has been reported in the synthesis of 1,4-diazabicyclo[4.3.0]nonanones **107** from 4-formyl-spiro-β-lactams **102** by means of a Pd-catalyzed hydrogenation. This ring transformation involves, after initial hydrogenolytic removal of the benzyloxycarbonyl protecting group, a retro-Mannich process, which induces β-lactam ring opening through selective C3-C4 bond fission, affording intermediate enols **104** (Scheme 22).[59] Further hydrogenation, nucleophilic addition of the *in situ* liberated secondary amine to the aldehyde group and elimination finalizes the reaction pathway, generating pyrrolidine-fused pyrazinones **107** in good yields (70-90%) (Scheme 22).[59] 1,4-Diazabicyclo[4.3.0]nonanes comprise remarkable structural units encountered in several biologically active products, as demonstrated by their potential use in the treatment of *inter alia* schizophrenia, depression, memory dysfunction,[60] filariasis[61] and angina pectoris.[62] In that respect, further derivatization of bicyclic piperazinone **107** [R = $CH_2CH_2(3,4\text{-}Cl_2)C_6H_3$], i. e., monochloroalane-mediated reduction of the carbonyl functionality, enabled the synthesis of 1,4-diazabicyclo[4.3.0]nonane **108** (Scheme 22),[59] a compound claimed for the treatment of central nervous system disorders.[63]



Scheme 22

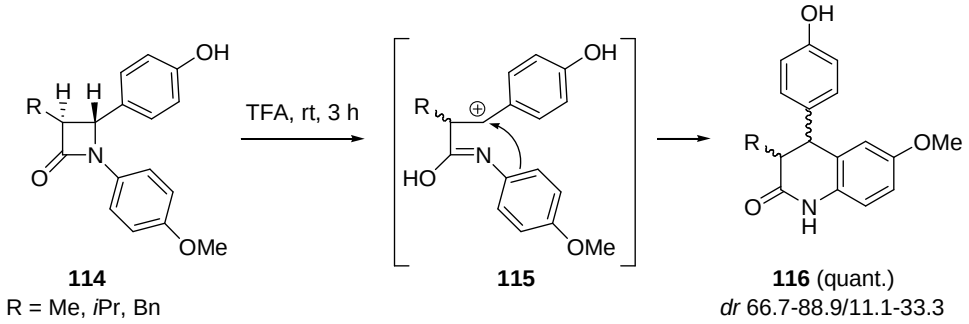
2.3 Ring transformation through C4-N1 bond cleavage

The first two-carbon ring expansion of a β-lactam through cleavage of the C4-N1 bond has been described in the synthesis of 1,3,4,5-tetrasubstituted glutarimides. The presence of a 4-hydroxyphenyl substituent at the 4-position in the starting 3-alkylazetidin-2-ones **109** enabled a base-mediated C4-N1 bond fission upon treatment with potassium *tert*-butoxide in DMF, which induced the formation of the corresponding phenolate anions followed by rearrangement to intermediate quinone methides **110** with simultaneous C4-N1 bond cleavage (Scheme 23).[64] The latter reactive quinone methides **110** are subsequently quenched by the *tert*-butyl methyl malonate anion in a Michael-type 1,6-conjugate addition at the benzylic carbon atom and are transformed into glutarimides **113** upon cyclization and removal of the *tert*-butyl group with trifluoroacetic acid (Scheme 23). The stereochemistry of the ring expansion proved to be dependent on the specific C3-substituent of the starting β-lactams **109**.[64]



Scheme 23

Next to the base-catalyzed ring opening of 4-(4-hydroxyphenyl)-β-lactams, the latter azetidinones are also cleaved under acidic conditions. It has been observed that treatment of β-lactams **114** with neat trifluoroacetic acid gave rise to the formation of intermediates **115**, which upon intramolecular Friedel-Crafts alkylation ensued to recyclize toward 3,4-dihydroquinolin-2-ones **116** in quantitative yields (Scheme 24).[65] It has to be noted that the 4-(4-hydroxyphenyl) substituent in the starting β-lactams **114** induces C4-N1 bond cleavage, whereas in the absence of a C4-substituent cleavage of the amide bond occurs upon treatment with trifluoroacetic acid (Scheme 10).



Scheme 24

2.4 Conclusion

Despite the β-lactam skeleton being just a four-membered cyclic amide, it is a useful and versatile building block exhibiting an extremely rich organic chemistry. The selective bond cleavage of the β-lactam nucleus has proven to have many applications in stereocontrolled synthesis, including the synthesis of azaheterocyclic six-membered ring systems (Figure 4).

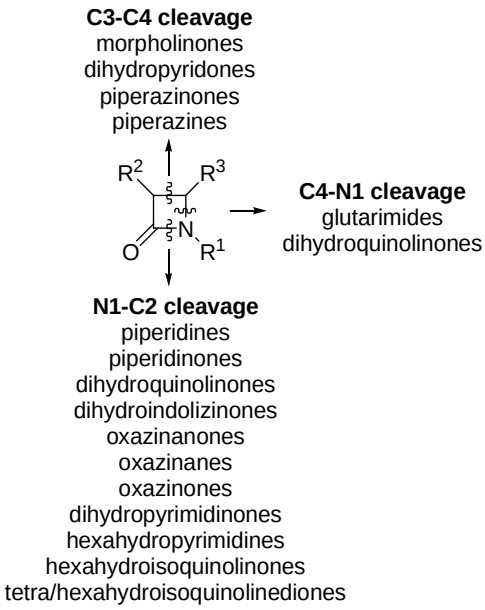


Figure 4

In this PhD thesis, the potential of substituted azetidin-2-ones as building blocks for the stereoselective preparation of various functionalized piperidines, piperidinones, oxazin-3-ones, morpholin-3-ones and pyrazinones will be explored with the intention to provide new entries toward biologically interesting scaffolds.

3 Results and Discussion

This PhD-thesis is partly based on the following SCI-papers, referred to in the text by the Roman numerals I-VI:

I. Transformation of *trans*-4-Aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones into 3-Aryl-2-(ethylamino)propan-1-ols via Intermediate 1-(1-Aryl-2-chloro-3-hydroxypropyl)aziridines and *trans*-2-Aryl-3-(hydroxymethyl)aziridines. **Mollet, K.**; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 264. (SCI IF 4.45)

II. Synthesis of stereodefined 3,4-disubstituted piperidines through rearrangement of 2-(2-bromo-1,1-dimethylethyl)azetidines. **Mollet, K.**; Broeckx, L.; D'hooghe, M.; De Kimpe, N. *Heterocycles* **2012**, *84*, 431. (SCI IF 1.00)

III. Stereoselective Synthesis of *cis*-3,4-Disubstituted Piperidines through Ring Transformation of 2-(2-Mesyloxyethyl)azetidines. **Mollet, K.**; Catak, S.; Waroquier, M.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 8364. (SCI IF 4.45)

IV. Stereoselective synthesis of bicyclic tetrahydrofuran-fused β-lactams and their conversion into methyl *cis*-3-aminotetrahydrofuran-2-carboxylates. **Mollet, K.**; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2012**, *68*, 10787. (SCI IF 3.03)

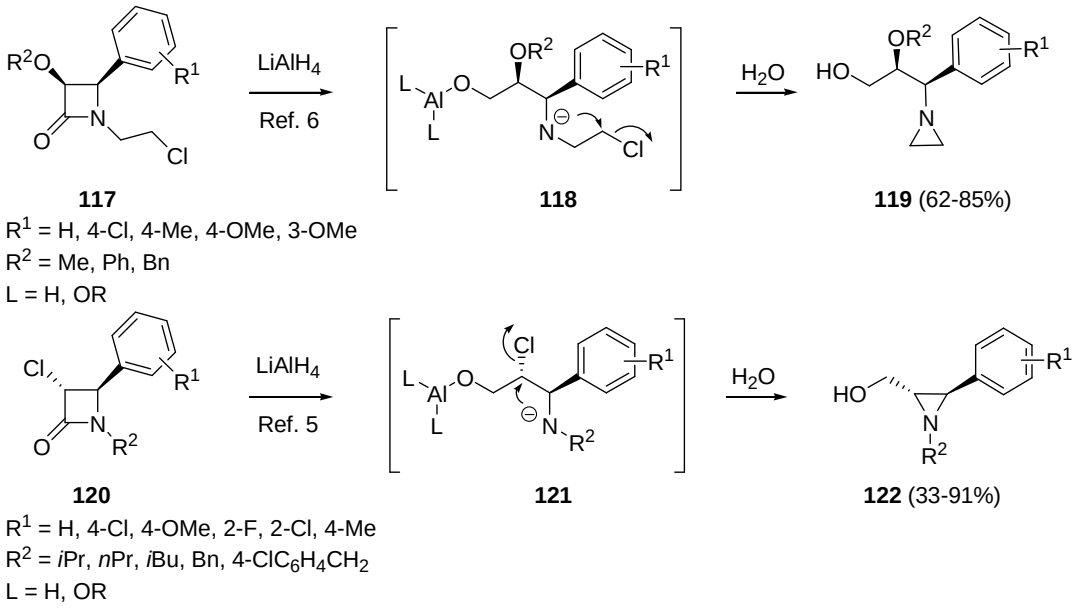
V. Synthesis of piperidin-4-ones starting from 2-(2-bromo-1,1-dimethylethyl)azetidines and 2-(2-mesyloxyethyl)azetidines through a ring expansion-oxidation protocol. **Mollet, K.**; D'hooghe, M.; Broeckx, L.; Danneels, B.; Desmet, T.; De Kimpe, N. *Tetrahedron* **2013**, *69*, 2603. (SCI IF 3.03)

VI. Synthesis of 2-Hydroxy-1,4-oxazin-3-ones through Ring Transformation of 3-Hydroxy-4-(1,2-dihydroxyethyl)-β-lactams and a Study of Their Reactivity. **Mollet, K.**; Goossens, H.; Piens, N.; Catak, S.; Waroquier, M.; Törnroos, K. W.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *Chem. Eur. J.* **2013**, *19*, 3383. (SCI IF 5.93)

3.1 Reactivity of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones toward $LiAlH_4$ (Paper I)

Both halogenated azetidin-2-ones and azetidin-2-ones bearing halogenated side chains are useful starting materials for rearrangements due to their high intrinsic reactivity, which is based on the combination of a strained four-membered ring system, a nucleophilic nitrogen (obtained after further elaboration) and an electrophilic carbon center. In that respect, in previous studies at the Department of Sustainable Organic Chemistry and Technology (Ghent University), intensive research on the synthetic applicability of the mainly unexplored class of 4-(haloalkyl)azetidin-2-ones **1c** has resulted in the efficient and diastereoselective preparation of a wide variety of functionalized azaheterocyclic compounds, including aziridines,[7] azetidines,[7,9] piperidines,[9,11] pyrrolidines,[9,12] azepanes,[11] pyrrolidin-2-ones,[13] oxolanes,[7,14] 1,4- and 3,4-fused bicyclic β-lactams,[11,14] and bicyclic γ-lactams (Figure 2).[16]

One of the most straightforward transformations of β-lactams comprises their reductive ring opening toward γ-aminoalcohols.[6,66] The presence of halogenated carbon atoms in these substrates is of synthetic relevance, as this can lead further to rearrangements toward azaheterocyclic compounds. In previous studies at the Department of Sustainable Organic Chemistry and Technology (Ghent University), the applicability of halogen-bearing β-lactams for the construction of stereodefined aziridines upon treatment with $LiAlH_4$, *e.g.*, the conversion of *N*-(2-chloroethyl)azetidin-2-ones **117** into 1-(3-hydroxypropyl)aziridines **119**[6] and the reductive ring contraction of 3-chloro-β-lactams **120** into 3-(hydroxymethyl)aziridines **122**[5], has been demonstrated (Scheme 25). However, up to now, the reactivity of halogenated β-lactams **2** bearing a halogenated side chain toward $LiAlH_4$ has not been explored in the literature.



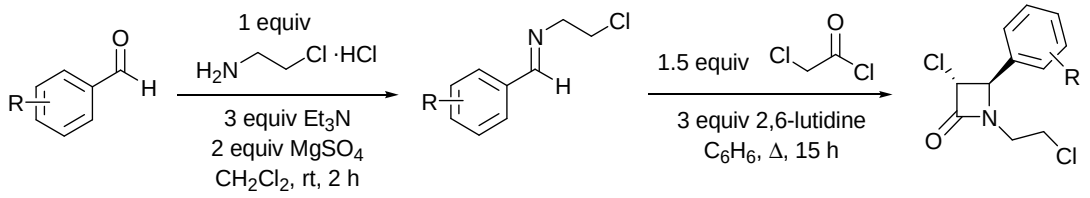
Scheme 25

The chemistry of 3-chloro-β-lactams comprises a mainly unexplored field in the literature, although these compounds are very useful substrates for further elaboration due to their unique synthetic properties, *e.g.*, dehalogenation toward 3-unsubstituted azetidinones[67] and conversion into different 3-substituted azetidines.[8] In addition, also the use of *N*-(ω-haloalkyl)-β-lactams has been studied to a very limited extent, for example toward the synthesis of 1,4-diazepan-5-ones[68] and bicyclic β-lactams.[15] In this chapter, both structural features were combined into a new type of substrates, i.e., 3-chloro-1-(2-chloroethyl)-β-lactams, which were evaluated for their reactivity toward $LiAlH_4$. Although other reducing agents such as $LiBEt_3H$ and $LiBH_4$ could be used,[66] the choice for $LiAlH_4$ was based on previous experiments conducted at the Department of Sustainable Organic Chemistry and Technology (Ghent University).

3.1.1 Synthesis of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones

The synthesis of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **2a-d**, in which the two halogen atoms reside in β-position with respect to the nitrogen atom, was accomplished by Staudinger's ketene-imine cyclocondensation reaction. Thus, treatment of *N*-(arylmethylidene)-(2-chloroethyl)amines **124a-d**, prepared *via* imination of benzaldehydes **123a-d** in dichloromethane in the presence of $MgSO_4$ and Et_3N utilizing one equiv of 2-chloroethylamine hydrochloride, with 1.5 equiv of chloroacetyl chloride and three equiv of 2,6-lutidine in benzene gave the premised *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **2a-d** in 60-75% yield (Scheme 26).

In accordance with previous results on β-lactam synthesis,[5a,8] the latter β-lactams **2a-d** were obtained stereoselectively (*cis*/*trans* 3-5/95-97) after a reflux period of 15 hours, and separation of both isomers was performed by means of column chromatography on silica gel. The *trans*-selectivity could be deduced based on the ^{1}H NMR spectra of β-lactams **2a-d**, as the observed coupling constants between the 3-H and 4-H protons varied between 1.1 and 2.0 Hz (^{1}H NMR, $CDCl_3$), which corresponds well with those reported in the literature for *trans*-β-lactams.[69] It should be noted that dichlorinated β-lactams **2** represent a novel class of substrates suitable for further elaborations.



123a-d

124a (R = 4-Me, 79%)
124b (R = H, 87%)
124c (R = 4-Cl, 79%)
124d (R = 3-OMe, 84%)

2a (R = 4-Me, 75%, *cis*/*trans* = 3/97)
2b (R = H, 60%, *cis*/*trans* = 3/97)
2c (R = 4-Cl, 69%, *cis*/*trans* = 5/95)
2d (R = 3-OMe, 66%, *cis*/*trans* = 5/95)

Scheme 26

The stereochemical outcome of this Staudinger reaction can be rationalized as follows. Next to different experimental factors, such as the choice of the solvent, base and reaction temperature,[70] it is well known that the specific ketene substituent plays an important role in the diastereoselectivity of the Staudinger reaction.[71] When the ketene, *in situ* generated from an acid chloride in the presence of a base, is substituted with a chloro atom (Moore ketene), *E*/*Z*-isomerisation across the iminium bond of the zwitterionic intermediate, formed by nucleophilic attack of the imine across the less hindered site of the ketene, followed by conrotatory ring closure will mostly afford the thermodynamically more stable *trans*-β-lactams (Figure 5), while electron-donating ketene substituents, *e.g.*, in Bose-Evans ketenes (alkoxy ketenes), generally accelerate the direct conrotatory ring closure, leading to a preference of *cis*-β-lactam formation.[71]

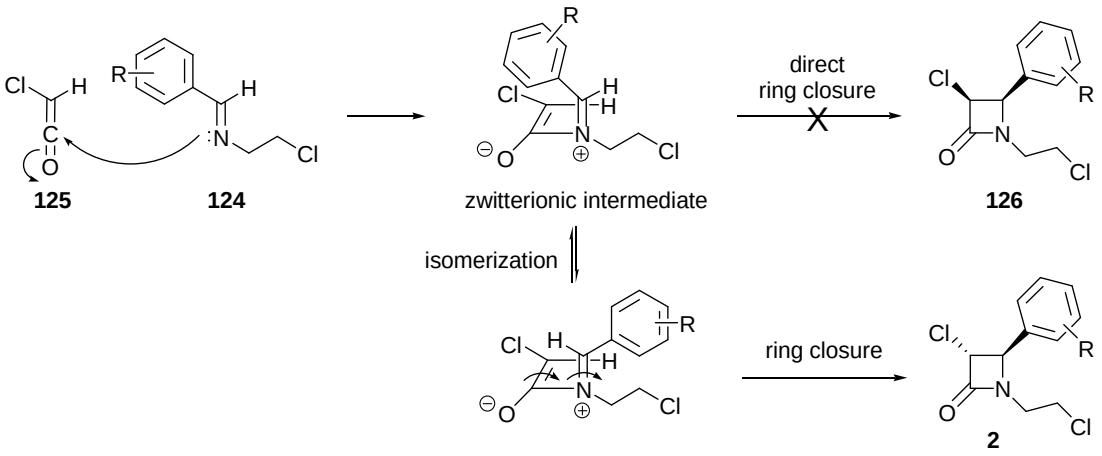
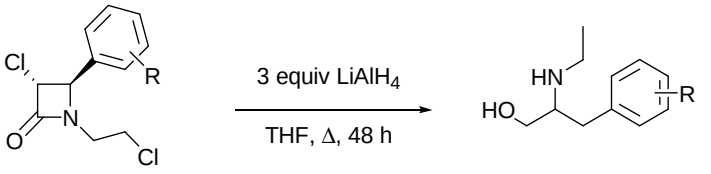


Figure 5

3.1.2 Synthesis of 3-aryl-2-(ethylamino)propan-1-ols

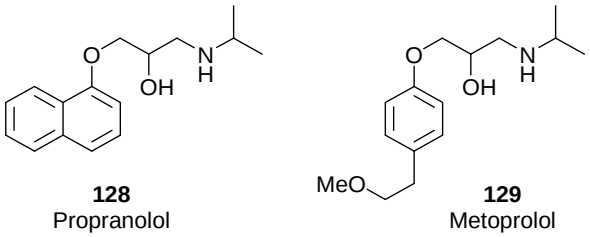
The reductive ring opening of azetidin-2-ones by means of $LiAlH_4$ has been described as an efficient approach toward β- en γ-aminoalcohols.[5,6,53,66] In analogy, *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **2a-d** were treated with three molar equiv of $LiAlH_4$ in THF under reflux for 48 hours, resulting in full conversion of the starting material. Quite unexpectedly, spectroscopic analysis of the obtained reaction products revealed their molecular structure to be 3-aryl-2-(ethylamino)propan-1-ols **127a-d** (Scheme 27).



127a (R = 4-Me, 61%)
127b (R = H, 70%)
127c (R = 4-Cl, 65%)
127d (R = 3-OMe, 68%)

Scheme 27

The synthesis of β-aminoalcohols merits considerable attention since these compounds play an important role in synthetic organic chemistry, for example as auxiliaries and ligands in asymmetric synthesis.[72] The two heteroatoms allow great flexibility, as one or both can be bound to a Lewis acid, transition metal or achiral starting material.[72] In addition, a variety of β-aminoalcohols exhibit various pharmacological properties, and the β-aminoalcohol moiety is present as a key structural unit in different biologically active compounds. For example, the β-blockers propranolol **128** and metoprolol **129** are used for treating abnormal heart rhythm, high blood pressure, heart failure and angina (Figure 6).[73]



128
Propranolol

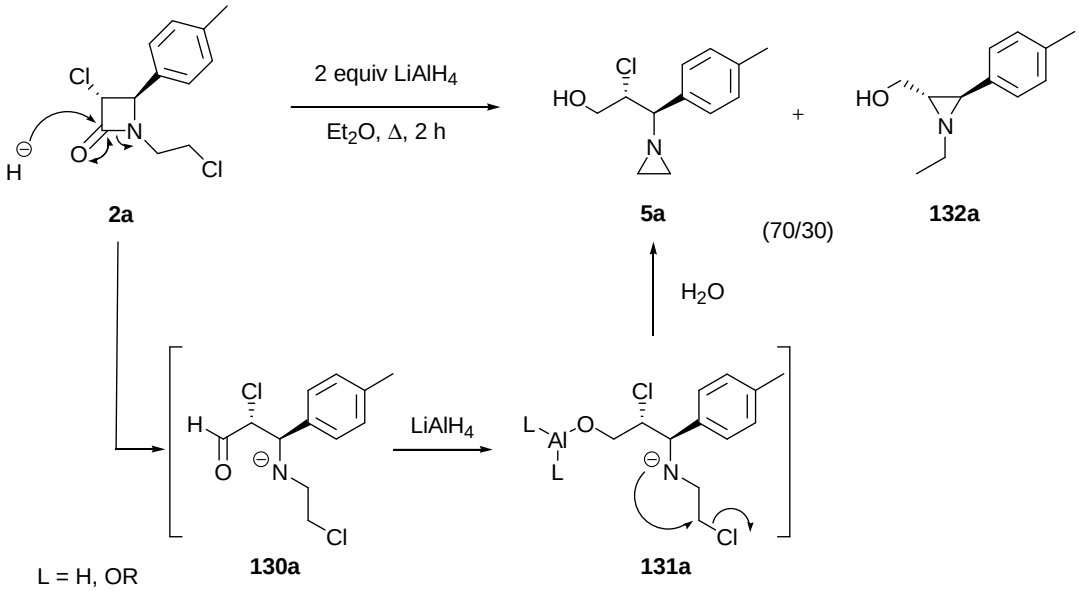
129
Metoprolol

Figure 6

3.1.2.1 Elucidation of the reaction mechanism

In order to elucidate the mechanistic background of this intriguing transformation, β-lactam **2a** was subjected to different reaction conditions, involving variation of the reaction time, reaction temperature, solvent and number of molar equiv of $LiAlH_4$. First, *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)-β-lactam **2a** was treated with two molar equiv of lithium aluminium hydride in diethyl ether under reflux for two hours.

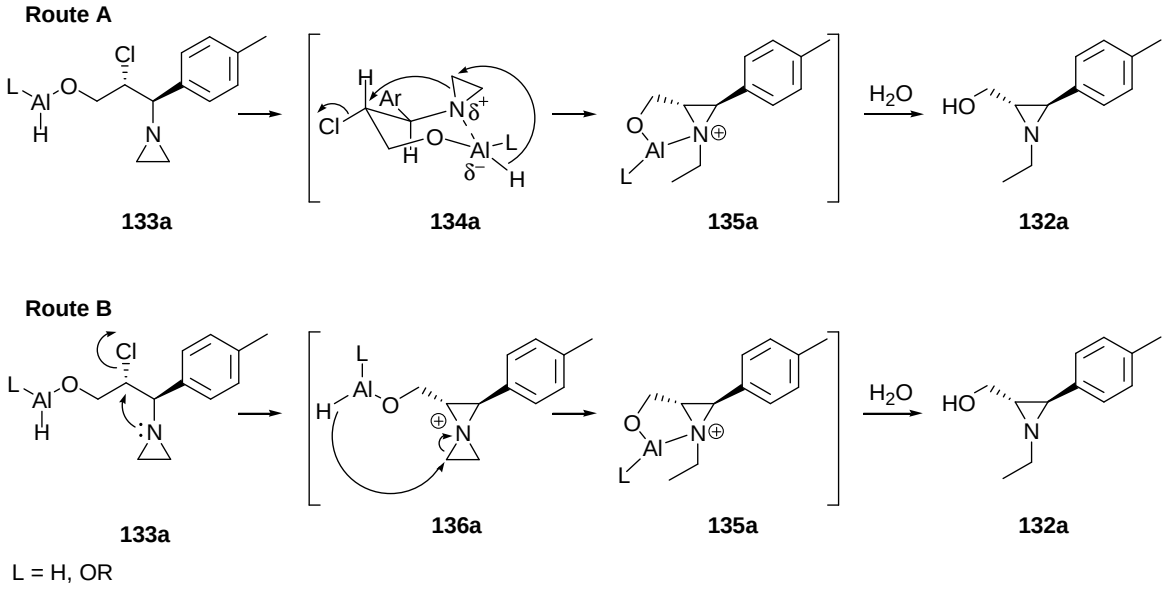
This process resulted in 1,2-fission of the amide bond, followed by intramolecular displacement of the chloride at the primary carbon atom by the nucleophilic nitrogen, giving rise to the initially expected 1-[2-chloro-3-hydroxy-1-(4-methylphenyl)]aziridine **5a**. Interestingly, next to the latter aziridine **5a**, a substantial amount of *trans*-1-ethyl-3-hydroxymethyl-2-(4-methylphenyl)aziridine **132a** was observed in the crude reaction mixture as well (Scheme 28, ratio **5a**/**132a**: 70/30).[5]



Scheme 28

The unexpected formation of *N*-ethylaziridine **132a** can be rationalized in two ways. In a first approach, the nucleophilic nitrogen in intermediate **131a**, formed after cleavage of the amide bond

of β-lactam **2a**, displaces the chloride at the secondary carbon atom to afford aziridine **132a** in a direct way. Since a primary electrophilic carbon atom is more likely to be attacked than a secondary, this competition could not explain the observed ratio (70/30). Alternatively, the presence of the latter aziridine **132a** can be explained by a possible ring transformation of aziridine **5a**. Considering the *in situ* activation of the aziridine moiety by the Lewis acid character of aluminium in chair-like intermediate **134a**, aziridine **132a** can be formed by hydride-induced ring opening followed by intramolecular substitution of the chloro atom (Scheme 29, Route A). Alternatively, initial displacement of chloride by the nucleophilic aziridine nitrogen to form an *N*-spiro bis-aziridinium intermediate **136a**, followed by hydride-induced ring opening toward aziridine **132a** cannot be excluded (Scheme 29, Route B).

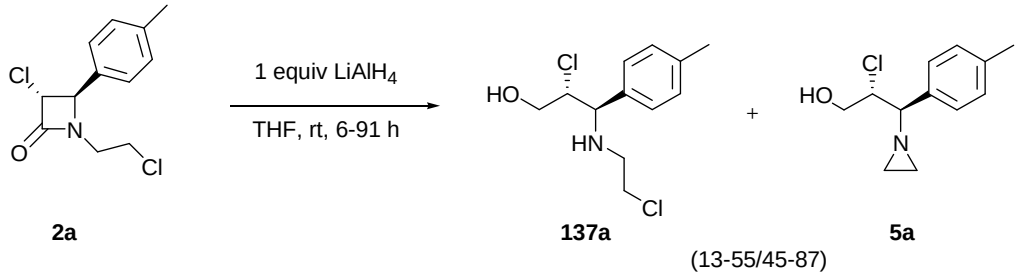


Scheme 29

It should be mentioned that non-activated aziridines are generally known to be highly reluctant toward hydride-induced ring opening,[74] and little information can be found in the literature concerning the corresponding intramolecular versions as in the case of intermediate **134a**. Furthermore, although reaction mechanisms consistent with the formation of bicyclic aziridinium salts are known,[75] the occurence of 1-azoniaspiro[2.2]pentanes **136** as such has not been described in the literature, apart from one paper in which the *N*-spiro bis-aziridinium ion is suggested to be a stable and isolable molecule based on *ab initio* studies.[76]

In order to prevent hydride-induced ring transformation of aziridine **5a** toward aziridine **132a**, milder reaction conditions were applied for the reduction of β-lactam **2a**. Thus, treatment of β-lactam **2a** with one molar equiv of $LiAlH_4$ in THF at room temperature for 6-91 hours afforded a mixture of γ-

aminoalcohol **137a** and aziridine **5a** in varying amounts (Scheme 30, Table 1). From a mechanistic point of view, these results can be rationalized considering the conversion of β-lactam **2a** into aziridine **5a** *via* intermediate γ-aminoalcohol **137a**, as mentioned before. In this way, 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines **5a,b** were isolated in pure form and in good yields after purification by column chromatography on silica gel (Table 2). Interestingly, all four hydrogen atoms of aziridines **5a,b** were observed as separate doublets of doublets with characteristic aziridine chemical shifts (1.05-2.20 ppm, $CDCl_3$). Also, spectroscopic analysis by ^{13}C NMR revealed different δ-values for the two aziridine carbon atoms (25.22-25.28 ppm and 31.62-31.64 ppm, $CDCl_3$). These findings are in accordance with analogous results reported in the literature for *C*-unsubstituted aziridines.[6,77]



Scheme 30

Table 1. Reduction of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)-β-lactam 2a in THF at room temperature

Number of molar equiv $LiAlH_4$	Solvent	Temperature	Time	Result
1	THF	rt	6 h	**137a**/**5a** = 55/45
1	THF	rt	19 h	**137a**/**5a** = 25/75
1	THF	rt	91 h	**137a**/**5a** = 13/87

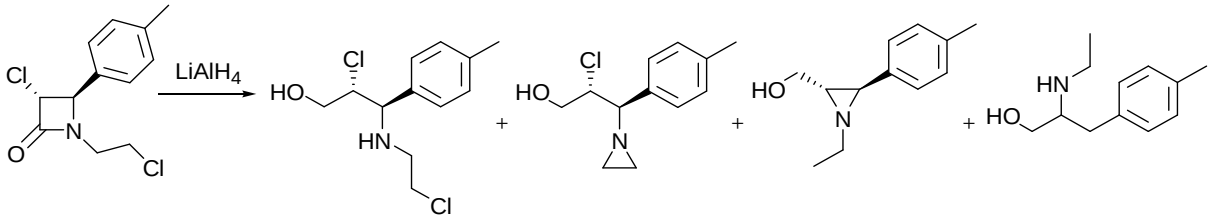
Table 2. Transformation of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams 2a,b into 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines 5a,b

Substrate	R	Reaction conditions	Compound (yield)[a]
2a	4-Me	1 molar equiv $LiAlH_4$, THF, rt, 91 h	**5a** (40%)
2b	H	1 molar equiv $LiAlH_4$, THF, rt, 91 h	**5b** (55%)

[a] After purification by column chromatography (SiO_2).

In the next stage, different attempts were made to tune the reaction selectivity toward aziridine **132a** starting from β-lactam **2a** upon treatment with $LiAlH_4$ (Scheme 31, Table 3). From the presented results, it can be deduced that although complete conversion of aziridine **5a** into aziridine

132a was achieved by establishing more forcing reaction conditions, the inherent reactivity of the intermediate 2-arylaziridine **132a** toward $LiAlH_4$ resulted in fast ring opening toward β-aminoalcohol **127a** at higher temperatures. In this transformation, $LiAlH_4$ is responsible for both the activation of the aziridine ring, resulting in a considerable weakening of the C2-N bond due to benzylic stabilisation of the developing carbenium ion, and for the delivery of the nucleophilic hydride which subsequently induces ring opening in a regioselective manner.[5a]



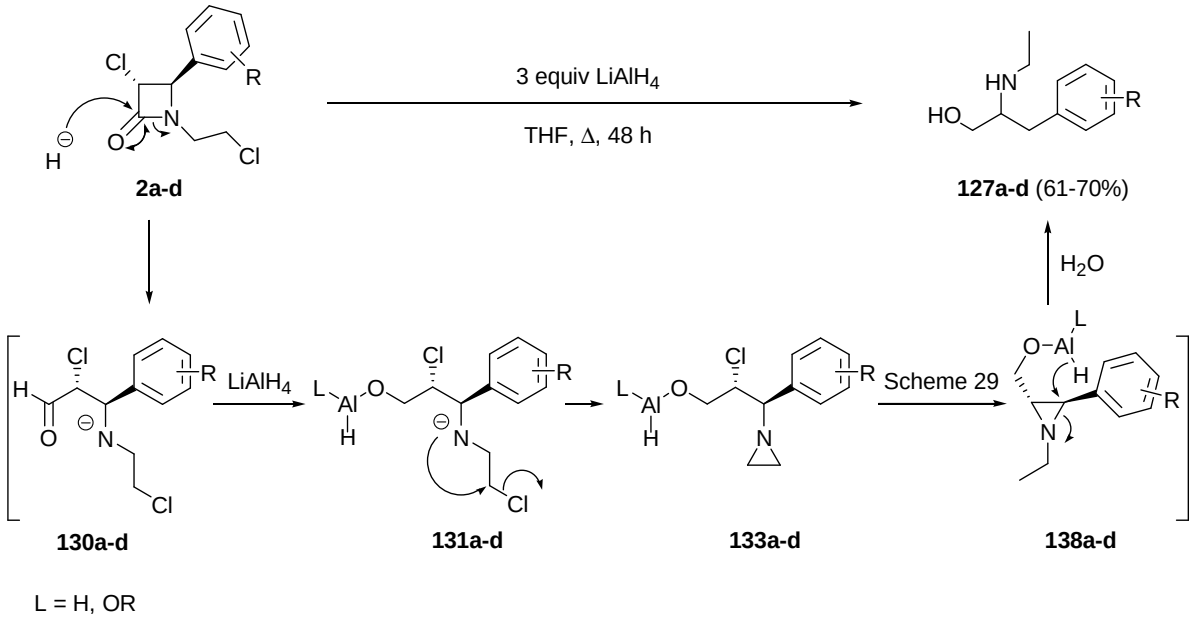
2a **137a** **5a** **132a** **127a**

Scheme 31

Table 3. Reduction of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)-β-lactam 2a under different reaction conditions

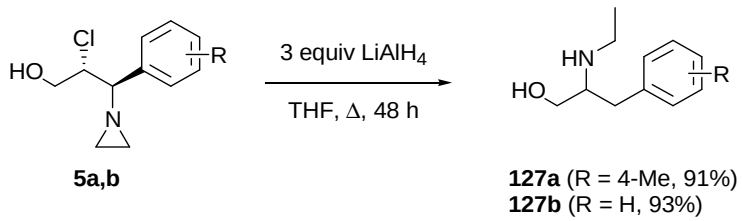
Entry	Number of molar equiv $LiAlH_4$	Solvent	Temperature	Time	Result	Yield
1	1	THF	reflux	2 h	**137a**/**5a**/**132a** = 45/45/10	80%
2	2	THF	reflux	2 h	**5a**/**132a** = 72/28	85%
3	2	THF	rt	18 h	**5a**/**132a** = 67/33	81%
4	2	THF	rt	20 h	**5a**/**132a** = 62/38	82%
5	2	THF	rt	100 h	**5a**/**132a** = 67/33	75%
6	2	Et_2O	reflux	1 h	**5a**/**132a** = 73/27	68%
7	2	Et_2O	reflux	2 h	**5a**/**132a** = 70/30	72%
8	2	Et_2O	reflux	3 h	**5a**/**132a** = 62/38	87%
9	2	Et_2O	reflux	4 h	**5a**/**132a**/**127a** = 48/33/19	83%
10	2	THF	reflux	7 h	**132a**/**127a** = 50/50	65%
11	3	Et_2O	reflux	1 h	**5a**/**132a** = 71/29	69%
12	3	Et_2O	reflux	5 h	**5a**/**132a**/**127a** = 58/22/20	79%
13	3	Et_2O	reflux	20 h	**132a**/**127a** = 25/75	82%
14	3	THF	reflux	48 h	**127a**	82%
15	4	THF	reflux	1 h	**132a**/**127a** = 58/42	73%

These detailed experiments finally culminated in a straightforward and efficient synthesis of 3-aryl-2-(ethylamino)propan-1-ols **127a-d** from *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **2a-d** upon treatment with three molar equiv of $LiAlH_4$ in THF under reflux for 48 hours (Table 3, Entry 14) through formation and subsequent conversion of intermediates **131a-d**, **133a-d** and **138a-d** (Scheme 32).



Scheme 32

To provide additional evidence for this reaction mechanism, 3-aryl-2-(ethylamino)propan-1-ols **127a,b** were synthesized in excellent yields by reduction of 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines **5a,b** using three molar equiv of $LiAlH_4$ in THF under reflux for 48 hours (Scheme 33).



Scheme 33

In conclusion, an efficient approach toward novel β-aminoalcohols is described by means of a $LiAlH_4$-mediated transformation of 3-chloro-1-(2-chloroethyl)-β-lactams. It is clear that the presence of two halogenated carbon atoms allows high synthetic flexibility, and selective manipulation of one electrophilic carbon center (followed by intramolecular rearrangements) opens new ways for the synthesis of biologically relevant target structures.

3.2 Diastereoselective synthesis of 3,4-disubstituted piperidines through rearrangement of azetidines

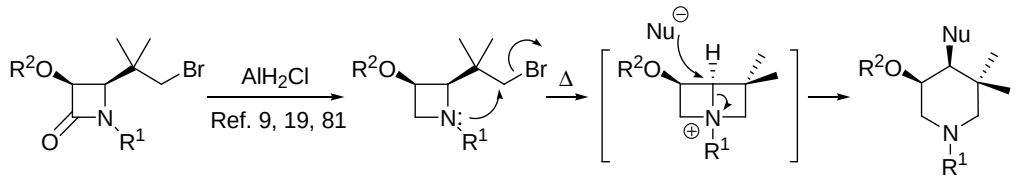
As substituted six-membered azaheterocycles are among the most common building blocks in natural products and biologically active compounds, the preparation of piperidine-based organic scaffolds has been widely studied.[17,18] To date, their synthesis still represents a major challenge in medicinal chemistry, as more and more (complex) piperidine-containing compounds are designed in order to improve the selectivity and reduce the side effects of potential new drugs.

Ring enlargements of small-ring nitrogen heterocycles comprise very useful reactions because they can provide a straightforward and efficient access to different nitrogen-containing target molecules.[78] These reactions frequently involve strained ring systems in which strain release acts as a driving force for the ring enlargement. In that respect, substituted azetidines have been proven to be suitable starting materials to perform rearrangements toward pyrroles, pyrrolidines, pyrrolidinones, imidazolidinones, isoxazolidines, piperidines, 1,2-oxazines, piperidin-2-ones, 2-iminopiperidines, azepanes and azepan-2-ones.[79] Moreover, the introduction of a leaving group in one of the substituents of these small-ring heterocycles enables intramolecular transformations toward intermediate bicyclic azetidinium ions, which are subsequently prone to undergo ring opening (mostly implying ring expansion) by the expelled leaving group or by an additional nucleophile.[9,12,79a,80]

In the present chapter, the scope and synthetic applicability of the latter methodology is examined toward the preparation of novel piperidines by treatment of functionalized azetidines with different nucleophiles.

3.2.1 Synthesis of 3,4-disubstituted 5,5-dimethylpiperidines through rearrangement of 2-(2-bromo-1,1-dimethylethyl)azetidines (Paper II)

In previous studies at the Department of Sustainable Organic Chemistry and Technology (UGent), the diastereoselective ring expansion of 2-(2-bromo-1,1-dimethylethyl)azetidines **8**, prepared *via* monochloroalane reduction of the corresponding β-lactams **7**, toward *cis*-3,4-disubstituted 5,5-dimethylpiperidines **10** upon treatment with NaOH, KCN, NaN_3 and Me_4NF has been described, and has been proposed to proceed *via* trapping of intermediate bicyclic azetidinium ions **9** (Scheme 34).[9,19,81]



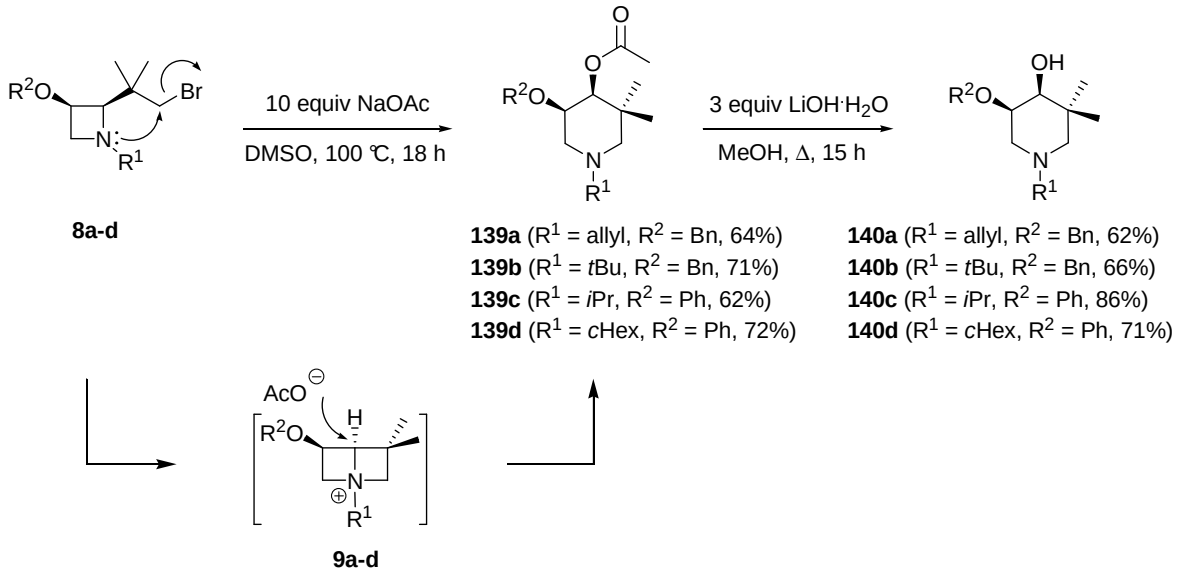
Nu = Br; R^1 = *t*Bu, Bn, allyl, *c*Hex; R^2 = Me, Bn
Nu = OH; R^1 = allyl, R^2 = Bn
Nu = CN; R^1 = allyl, R^2 = Bn
Nu = N_3; R^1 = allyl, R^2 = Bn
Nu = F; R^1 = allyl, *t*Bu, *i*Pr, *c*Hex, R^2 = Bn, Ph

Scheme 34

3.2.1.1 Synthesis of 4-acetoxy- and 4-hydroxy-5,5-dimethylpiperidines

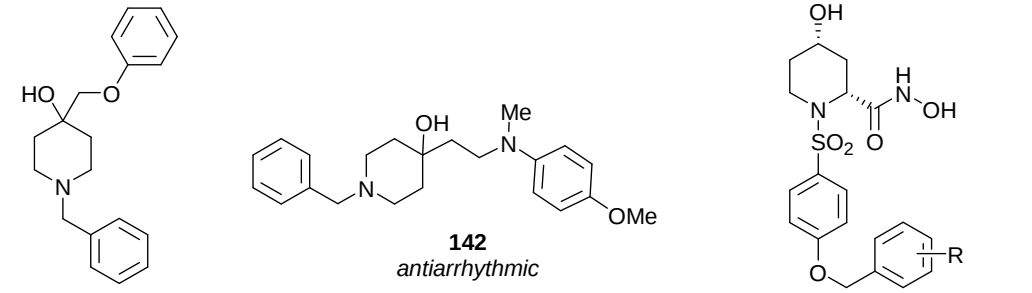
To broaden the scope of the above-described nucleophile-induced ring transformation of 2-(2-bromoethyl)azetidines **8** toward novel stereodefined piperidines, the feasibility of introducing other nucleophiles than bromide, fluoride, hydroxide, cyanide and azide was evaluated by employing sodium acetate. Thus, treatment of azetidines **8a-d**[19] with ten equiv of NaOAc in DMSO at 100 °C for 18 hours resulted in the selective formation of 4-acetoxy-5,5-dimethylpiperdines **139a-d** in good yields (Scheme 35). The relative *cis*-stereochemistry was demonstrated by the vicinal coupling constants between the protons at C-3 and C-4 (3.0-3.3 Hz, ^{1}H NMR, $CDCl_3$), which are in accordance with literature data concerning 3,4-dioxygenated piperidines,[82] and was rationalized considering the *in situ* formation and consecutive ring opening of bicyclic azetidinium intermediates **9a-d** (Scheme 35). This reaction mechanism is based on the intramolecular displacement of bromide by the nucleophilic nitrogen lone pair of azetidines **8a-d** toward reactive bicyclic intermediates **9a-d**, which are subsequently prone to undergo ring opening by the nucleophilic counterion, i.e., acetate, at the bridgehead carbon atom in a S_N2 fashion to furnish the thermodynamically more favoured six-membered piperidines **139a-d** (Scheme 35).[19]

The synthetic relevance of these novel 4-acetoxypiperidines **139a-d** was demonstrated by means of their transformation into the biologically important class of 4-hydroxylated piperidines,[83] producing the corresponding 4-hydroxypiperidines **140a-d** upon hydrolysis of the ester moiety by means of three equiv of LiOH in methanol under reflux for 15 hours (Scheme 35).



Scheme 35

Indeed, a vast array of molecules containing the 4-hydroxypiperidine skeleton has been reported in the treatment of arrhythmia,[83c] hypotension,[83d] tuberculosis,[83h] and diarrhea,[83i] and others are known as anti-inflammatory agents,[83e] CCR1 chemokine receptor antagonists[83f] and TNF-α converting enzyme (TACE) inhibitors[83g] useful for the treatment of rheumatoid arthritis, multiple sclerosis and Crohn's disease (Figure 7).



141
antihypotensive

142
antiarrhythmic

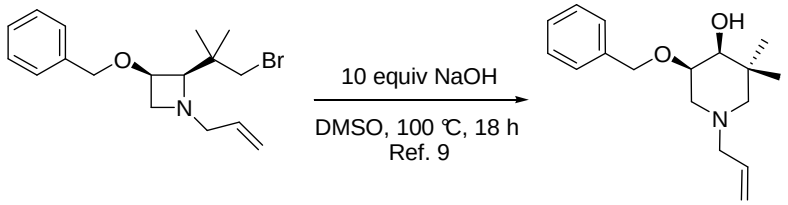
143
TNF-α converting enzyme inhibitors

R = H, 4-F, 3-F, 2-F, 4-Cl, 3-Cl, 2-Cl, 4-Me, 3-Me, 2-Me, 3-OMe, 2-OMe, 2-CF_3, 4-CN, 3-CN, 2-Ph

Figure 7

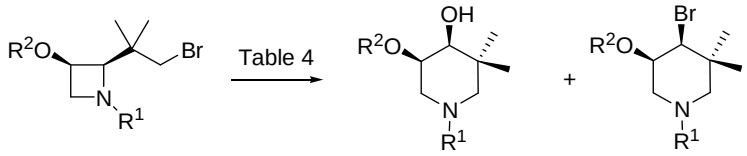
Following a protocol previously developed at the Department of Sustainable Organic Chemistry and Technology (UGent) concerning a one-step ring enlargement of *cis*-1-allyl-3-benzyloxy-2-(2-bromo-1,1-dimethylethyl)azetidine **8a** into the corresponding 4-hydroxypiperidine **140a** by means of sodium hydroxide in DMSO (Scheme 36),[9] different attempts were made to prepare the latter 4-hydroxypiperidines **140b-d** selectively through NaOH- and/or H_2O-mediated ring transformation of 2-

(2-bromoethyl)azetidines **8b-d** (Scheme 37, Table 4). However, in all cases the competition between hydroxide and bromide to induce ring enlargement resulted in a mixture of 4-hydroxypiperidines **140b-d** and 4-bromopiperidines **144b-d** in varying ratios (Table 4).



8a **140a** (86%)

Scheme 36



8b-d **140b-d** **144b-d**

(17/83 - 71/29)

Scheme 37

Table 4. Attempts toward the synthesis of 4-hydroxy-5,5-dimethylpiperidines 140b-d *via* a one-step ring expansion of 2-(2-bromo-1,1-dimethylethyl)azetidines 8b-d

Substrate	R^1	R^2	Reaction conditions	Result[a]
8b	*t*Bu	Bn	10 equiv NaOH, DMSO, 100 °C, 18 h	**140b/144b** = 29/71
8c	*i*Pr	Ph	10 equiv NaOH, DMSO, 100 °C, 18 h	**140c/144c** = 43/57
8d	*c*Hex	Ph	10 equiv NaOH, DMSO, 100 °C, 18 h	complex mixture
8b	*t*Bu	Bn	H_2O/DMSO (5/1), 80 °C, 15 h	**140b/144b** = 71/29
8b	*t*Bu	Bn	1 equiv NaOH, H_2O/DMSO (3/1), 80 °C, 5 h	**140b/144b** = 63/37
8b	*t*Bu	Bn	H_2O/DMSO (1/1), 80 °C, 6 h	**140b/144b** = 55/45
8c	*i*Pr	Ph	H_2O/DMSO (1/1), 80 °C, 6 h	**140c/144c** = 20/80
8d	*c*Hex	Ph	11 equiv NaOH, DMSO, 80 °C, 3 h	complex mixture
8d	*c*Hex	Ph	H_2O/DMSO (3/1), 80 °C, 15 h	complex mixture
8d	*c*Hex	Ph	1 equiv NaOH, H_2O/DMSO (3/1), 80 °C, 19 h	**140b/144b** = 17/83
8d	*c*Hex	Ph	10.3 equiv NaOH, DMSO, 80 °C, 3 h	complex mixture
8d	*c*Hex	Ph	15 equiv NaOH (1M), DMSO, 80 °C, 3 h	complex mixture

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

As a result, it can be concluded that the two-step synthesis of 4-hydroxypiperidines **140a-d** *via* 4-acetoxypiperidines **139a-d** comprises an improved alternative in terms of selectivity and efficiency.

In conclusion, 2-(2-bromo-1,1-dimethylethyl)azetidines were proven to be useful starting materials to perform rearrangements toward substituted six-membered azaheterocycles. These reactions presumably involve the intermediacy of 1-azoniabicyclo[2.2.0]hexanes, which are subsequently prone to undergo a nucleophile-induced ring enlargement toward a wide variety of highly functionalized piperidines. In particular, this methodology allowed the development of novel stereodefined 4-hydroxypiperidines, which are of high importance in pharmaceutical chemistry.

3.2.2 Synthesis of 3,4-disubstituted 5,5-dinor-dimethylpiperidines through rearrangement of 2-(2-mesyloxyethyl)azetidines (Paper III, IV and V)

In the next part of this work, the synthesis of analogous dinor-dimethylpiperidines **11** was envisaged (Figure 8), as the absence of a 5,5-*gem*-dimethyl group might have a pronounced influence on the biological profile of this class of compounds. From a retrosynthetic point of view, the synthesis and subsequent ring expansion of 2-(2-mesyloxyethyl)azetidines **13**, prepared *via* mesylation of the corresponding alcohols, could offer a convenient alternative and an easy access to this new class of 5-unsubstituted piperidines **11**. The present paragraph will focus on the reactivity of 2-(2-mesyloxyethyl)azetidines **13** with regard to different nucleophiles to develop new pathways toward biologically relevant piperidines **11** (Figure 8).

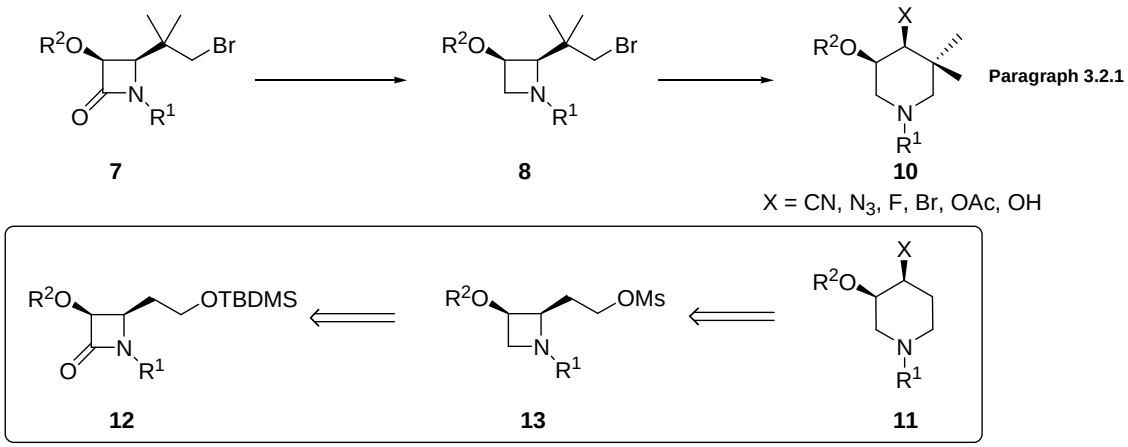
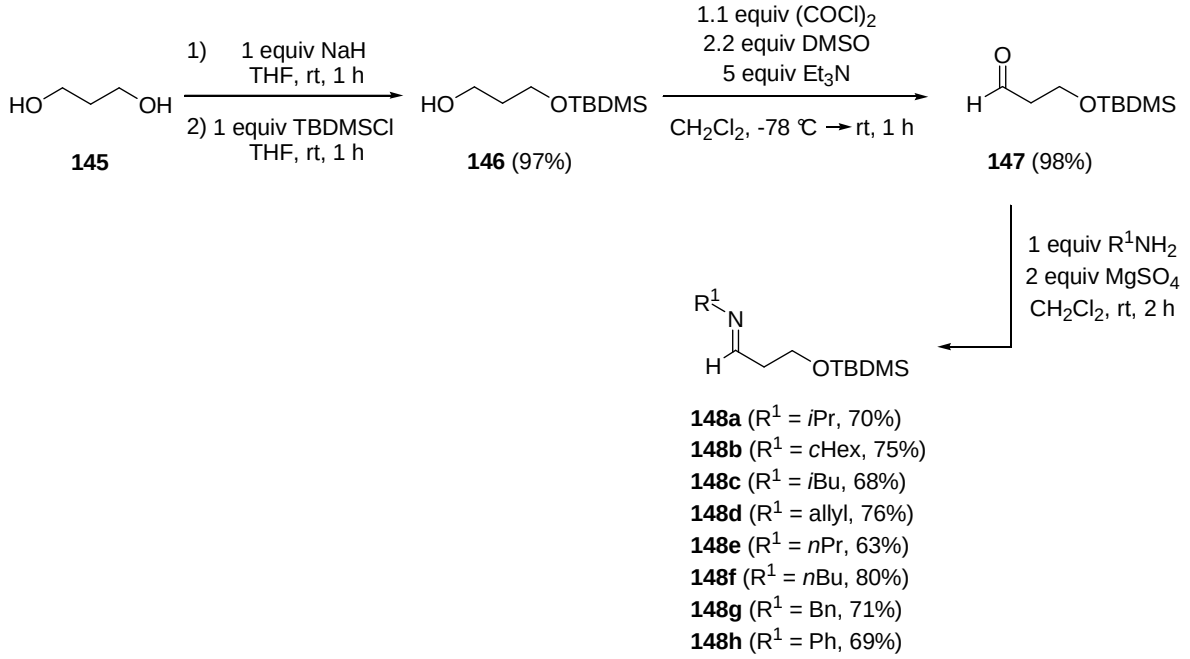


Figure 8

3.2.2.1 Synthesis of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones

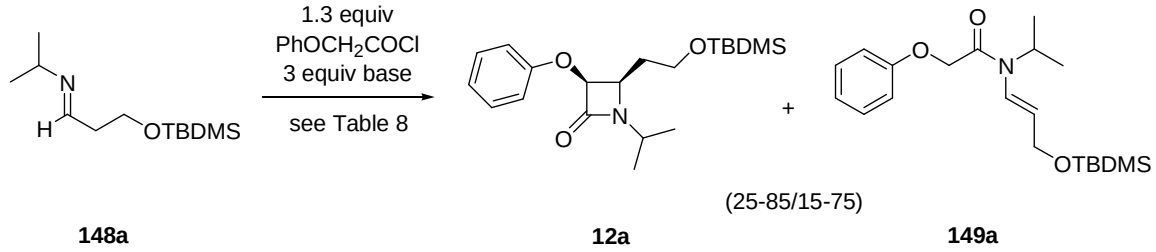
In order to achieve a selective oxidation and to circumvent difficulties associated with the presence of a free hydroxyl group during β-lactam formation, 1,3-propanediol **145** was first monoprotected as its *tert*-butyldimethylsilyl ether **146** using a literature protocol, involving silylation of the monosodium salt (obtained upon treatment of diol **145** with one equiv of NaH in THF) with one equiv of *tert*-butyldimethylsilyl chloride (TBDMSCl) in THF,[84] and was then oxidized to the corresponding

aldehyde **147** by means of a Swern oxidation using oxalyl chloride, DMSO and Et_3N in CH_2Cl_2 (Scheme 38).[85] Subsequent imination of 3-(*tert*-butyldimethylsilyloxy)propanal **147** with one equiv of the corresponding primary amines in dichloromethane in the presence of $MgSO_4$ as a drying agent led to the formation of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]alkylamines **148a-h** in good yields (Scheme 38).



Scheme 38

Subsequently, in order to evaluate the Staudinger synthesis of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12**, *N*-isopropylimine **148a** was selected as a model substrate and was subjected to different reaction conditions, involving variation of the solvent, base, temperature and reaction time (Scheme 39, Table 5). In almost all cases, mixtures of *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one **12a** and *N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]-*N*-isopropyl-2-phenoxyacetamide **149a** were obtained (**12a**/**149a** 25-85/15-75), next to negligible amounts of unidentified side products. Furthermore, different attempts to tune the reaction selectivity toward β-lactam **12a** by applying more harsh reaction conditions were not successful, as the ratio of compounds **12a** and **149a** remained unaffected independent of the reaction temperature and the temperature of acid chloride addition (Table 5, Entry 6-8).



148a **12a** **149a**

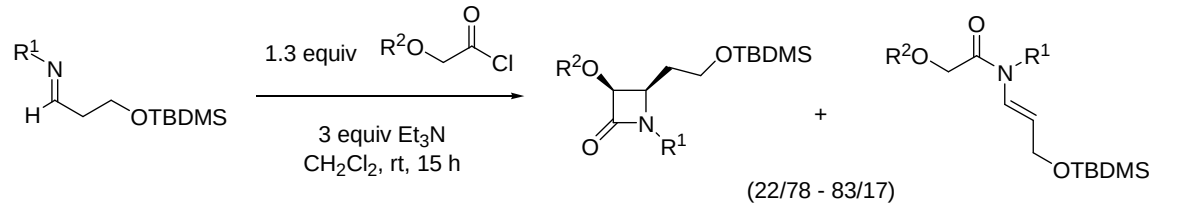
Scheme 39

Table 5. Staudinger reaction of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isopropylamine 148a under different reaction conditions

Entry	Solvent	Base	Acid chloride added at	Reaction temperature and time	Result[a]
1	C_6H_6	Et_3N	reflux	reflux, 1 h; rt, 15 h	**12a**/**149a** = 25/75
2	C_6H_6	2,6-lutidine	reflux	reflux, 15 h	complex mixture
3	C_6H_6	Et_3N	reflux	reflux, 15 h	**12a**/**149a** = 30/70
4	CH_2Cl_2	PPh_3	0 °C	rt, 15 h	complex mixture
5	CH_2Cl_2	Et_3N	0 °C	rt, 15 h	**12a**/**149a** = 83/17
6	CH_2Cl_2	Et_3N	0 °C	reflux, 15 h	**12a**/**149a** = 80/20
7	CH_2Cl_2	Et_3N	reflux	reflux, 15 h	**12a**/**149a** = 81/19
8	CH_2Cl_2	Et_3N	reflux	reflux, 1 h; rt, 15 h	**12a**/**149a** = 85/15

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

In the next phase, the synthesis of a number of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12** was evaluated according to the optimal reaction conditions as described in Table 5, Entry 5. Thus, treatment of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]alkylamines **148** with 1.3 equiv of phenoxy- or benzyloxyacetyl chloride in dichloromethane in the presence of three equiv of Et_3N resulted in the corresponding mixtures of β-lactams **12** and *N*-acyl enamines **149** (22/78 – 83/17) after 15 hours at room temperature (Scheme 40, Table 6). It should be noted that the specific *N*-substituent in imines **148** has a pronounced influence on the ratio of β-lactams **12** and *N*-acyl enamines **149**, as the presence of an isobutyl, allyl or benzyl group favors the formation of the corresponding *N*-acyl enamines **149**, while an isopropyl group leads to the corresponding β-lactams **12**. The Staudinger synthesis of β-lactams **12** proceeded in a highly diastereoselective way, which can be attributed to the electron-donating benzyloxy or phenoxy group present in the Boose-Evans ketenes (see paragraph 3.1.1).[71] As the coupling constant between the protons at C-3 and C-4 in ^{1}H NMR ($CDCl_3$) was between 4.1 and 5.2 Hz, the relative stereochemistry of β-lactams **12** was assigned as *cis*.[69] It should be noted that the reported yields are yields obtained after purification by column chromatography on silica gel.



148

12a (R^1 = *i*Pr, R^2 = Ph, 47%)
12b (R^1 = *i*Pr, R^2 = Bn, 35%)
12c (R^1 = *c*Hex, R^2 = Bn, 55%)
12d (R^1 = *i*Bu, R^2 = Bn, 5%)

149d (R^1 = *i*Bu, R^2 = Bn, 66%)

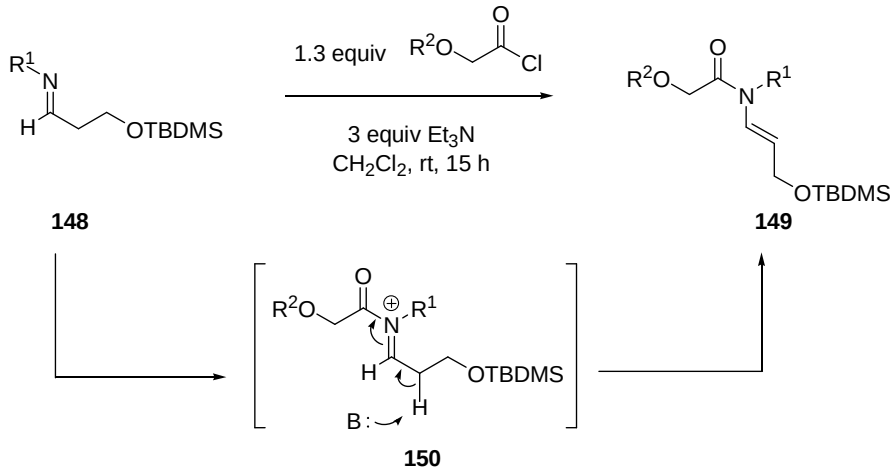
Scheme 40

Table 6. Synthesis of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones 12 and *N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]acetamides 149

Substrate	R^1	R^2	Result[a]
148a	*i*Pr	Ph	**12a**/**149a** = 83/17
148a	*i*Pr	Bn	**12b**/**149b** = 75/25
148b	*c*Hex	Bn	**12c**/**149c** = 67/33
148c	*i*Bu	Bn	**12d**/**149d** = 40/60
148d	allyl	Bn	**12e**/**149e** = 22/78
148b	*c*Hex	Ph	**12f**/**149f** = 33/67
148e	*n*Pr	Ph	complex mixture
148f	*n*Bu	Bn	complex mixture
148g	Bn	Ph	**12g**/**149g** = 33/67
148h	Ph	Bn	complex mixture

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

The presence of *N*-acyl enamines **149** can be explained as follows. Nucleophilic addition of imines **148** across the acid chloride and subsequent α-deprotonation with respect to the *in situ* formed iminium moiety **150** can account for the formation of the observed enamides **149** (Scheme 41). It is known that *N*-(alkylmethylidene)amines are less reactive toward [2+2]-cyclocondensation reactions as compared to *N*-(arylmethylidene)amines, sometimes resulting in the full and selective formation of enamides instead of azetidin-2-ones.[10,86] The *E*-stereochemistry assigned to the olefinic moiety in enamides **149** is supported by the observed vicinal coupling constants between both olefinic protons (J = 13.8 Hz, ^{1}H NMR, $CDCl_3$).



Scheme 41

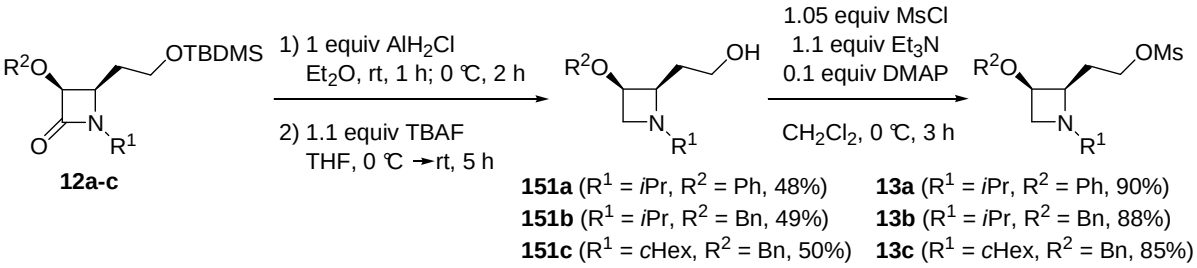
Although the chemistry of β-lactams has been thoroughly investigated in the past,[4] very little is known about the synthetic applicability of the latter class of 2-azetidinones **12**, pointing at the unexplored nature of this subject. Indeed, β-lactams **12** hold interesting potential for further elaboration due to the presence of a strained four-membered ring and an oxygenated carbon center in the side chain. Therefore, a thorough investigation was executed to reveal the synthetic applicability of these new β-lactam scaffolds, which will be presented in the following sections.

3.2.2.2 Synthesis of 2-(2-mesyloxyethyl)azetidines

In accordance with the synthesis of 3,4-disubstituted 5,5-dimethylpiperidines from 2-(2-bromo-1,1-dimethylethyl)azetidines (see paragraph 3.2.1), a similar strategy was contemplated for the preparation of piperidines from 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12a-c**. This methodology involves an initial reduction toward the corresponding azetidines in order to enhance the nucleophilicity of the nitrogen atom, followed by the introduction of a leaving group in γ-position with respect to the azetidine nitrogen. In this way an intramolecular substitution reaction toward bicyclic azetidinium intermediates can take place, which are prone to undergo ring opening by the liberated leaving group or by an additional nucleophile, furnishing the premised piperidine derivatives.

In order to perform a selective reduction of the carbonyl moiety without affecting the four-membered ring system, β-lactams **12a-c** were treated with monochloroalane (AlH_2Cl), as this method had already been proven to be a suitable method for the synthesis of functionalized azetidines.[66a,87] Also in the present case, reductions of highly functionalized β-lactams **12a-c** were performed successfully in that respect. Thus, 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12a-c**, obtained in analytically pure form after column chromatography on silica gel, were treated with one

molar equiv of AlH_2Cl, prepared *in situ* from three molar equiv of $LiAlH_4$ and one equiv of $AlCl_3$, in diethyl ether at 0 °C for two hours, affording novel 2-(2-hydroxyethyl)azetidines **151a-c** in good yields (48-50%) after deprotection of the silyl ether using 1.1 equiv of tetra-*n*-butylammonium fluoride (TBAF) in THF (Scheme 42). It has to be noted that in all cases significant amounts of 2-(2-hydroxyethyl)azetidines **151a-c** (40-85%) were present in the crude reaction mixtures after monochloroalane reduction of the corresponding β-lactams **12a-c** without subsequent introduction of TBAF. Furthermore, it was necessary to perform an inverse addition by adding β-lactams **12a-c** to one molar equiv of AlH_2Cl in diethyl ether.



12a-c

151a (R^1 = *i*Pr, R^2 = Ph, 48%) **13a** (R^1 = *i*Pr, R^2 = Ph, 90%)
151b (R^1 = *i*Pr, R^2 = Bn, 49%) **13b** (R^1 = *i*Pr, R^2 = Bn, 88%)
151c (R^1 = *c*Hex, R^2 = Bn, 50%) **13c** (R^1 = *c*Hex, R^2 = Bn, 85%)

Scheme 42

The reductive removal of the carbonyl group in β-lactams **12a-c** proceeded with the expected retention of the stereochemistry as defined during the Staudinger synthesis of these β-lactams. The relative stereochemistry of azetidines **151a-c** with regard to the protons at C-2 and C-3 was assigned as *cis* based on the coupling constants between these protons (6.6-7.7 Hz, ^{1}H NMR, $CDCl_3$), in accordance with literature data.[9,75b,87]

In general, azetidines are an important class of azaheterocyclic systems, as the strained four-membered ring is found in many naturally occurring and synthetic organic compounds with interesting biological and pharmacological properties.[88] In addition, azetidines have been shown to be excellent building blocks in organic synthesis.[79,80,19] Also, 2-(2-hydroxyethyl)azetidines **151a-c** were expected to furnish a broad scala of reactivities, although little has been reported on the synthesis and reactivity of this type of functionalized azetidines. In this way, the hydroxyl moiety in azetidines **151a-c** was activated upon treatment with 1.05 equiv of mesyl chloride (MsCl) in the presence of a base and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at 0 °C for three hours (Scheme 42), in order to provide the dinor-dimethyl analogues of 2-(2-bromo-1,1-dimethylethyl)azetidines **8** (see paragraph 3.2.1) as eligible substrates for ring expansion toward novel piperidine derivatives (Figure 9).

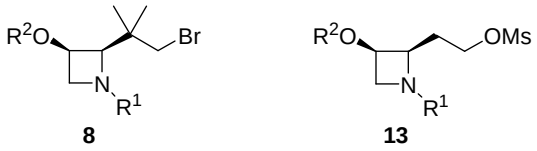
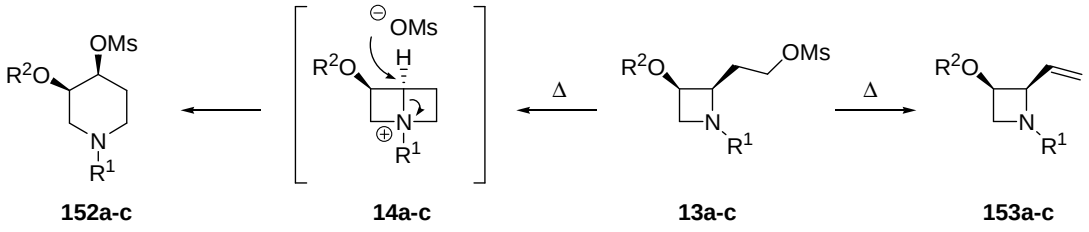


Figure 9

It should be stressed that during workup of the obtained mesylated azetidines **13a-c**, careful monitoring of the temperature proved to be very important, as evaporation of the solvent *in vacuo* at temperatures higher than 25 °C led to the spontaneous formation of reasonable amounts (4-35%) of ring-expanded 4-mesyloxypiperidines **152a-c**, which can be explained considering the formation and subsequent mesylate-induced ring opening of intermediate 1-azoniabicyclo[2.2.0]hexanes **14a-c**. In addition, small amounts of 2-vinylazetidines **153a-c** (3-12%) were observed as well in the crude reaction mixtures (Scheme 43). It should be mentioned that the transformation of the hydroxyl group in 2-(2-hydroxyethyl)azetidines **151** into other leaving groups, such as a tosylate or a chloride, is expected to result in the formation of analogous ring-expanded piperidines and vinylazetidines due to the high inherent instability of the azetidine-containing substrates.



Scheme 43

3.2.2.3 Synthesis of 3,4-disubstituted 5,5-dinor-dimethylpiperidines

In this section, the above-described synthetic methodology concerning the nucleophile-induced ring expansion of 2-(2-bromo-1,1-dimethylethyl)azetidines **8** toward functionalized piperidine derivatives *via* intermediate 1-azoniabicyclo[2.2.0]hexanes **9** is extended toward the synthesis of their dinor-dimethyl variants, as, given the broad medicinal relevance of piperidines in general, the absence of a 5,5-*gem*-dimethyl moiety can modify the related bioactivity due to changes in conformational properties (Figure 10).

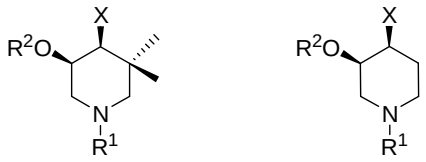
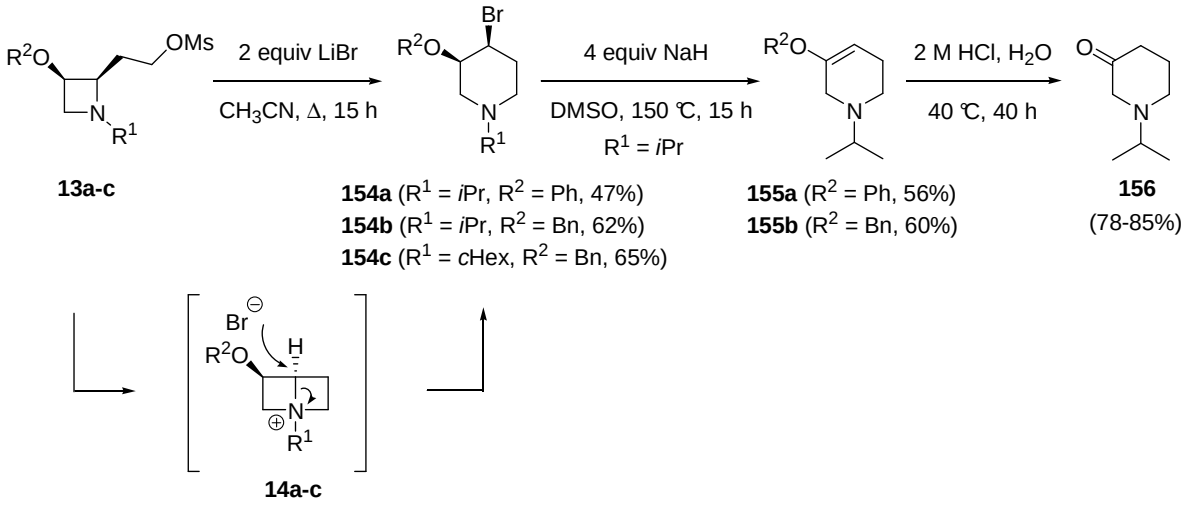


Figure 10

3.2.2.3.1 Synthesis of 4-bromopiperidines

In a first part, treatment of 2-(2-mesyloxyethyl)azetidines **13a-c** with two equiv of LiBr in acetonitrile for 15 hours under reflux resulted in the selective formation of 4-bromopiperidines **154a-c** in good yields (47-65%) after column chromatography on silica gel or recrystallization from absolute ethanol (Scheme 44). The *cis*-stereochemistry of 3-oxygenated 4-bromopiperidines **154a-c** was assessed based on the coupling constants between the protons at positions 3 and 4 (3.6-3.9 Hz, ^{1}H NMR, $CDCl_3$), which are in accordance with those reported in the literature for *cis*-vicinal substituted piperidines.[82] Furthermore, also the fact that dehydrobromination occurred upon treatment of piperidines **154a,b** with dimsylsodium (four equiv) in DMSO at 150 °C for 15 h was indicative of a *cis*-relationship between the C-3 and C-4 substituents, which is required to obtain an *anti*-elimination (Scheme 44). The obtained cyclic enol ethers **155a,b** could be easily hydrolysed to give 1-isopropylpiperidin-3-one **156** by reaction with aq 2 M HCl at 40 °C for 40 h (Scheme 44). Piperidin-3-ones constitute a class of compounds of high biological interest as they are considered as pharmacophores in medicinal sciences and their synthesis is often associated with the preparation of biologically relevant compounds.[89]



Scheme 44

From a mechanistic point of view, the observed *cis*-stereochemistry of piperidines **154a-c** can be rationalized considering the *in situ* formation and consecutive ring opening of bicyclic azetidinium intermediates **14a-c** (Scheme 44). This reaction mechanism is based on the intramolecular displacement of the mesyloxy substituent by the nucleophilic nitrogen lone pair of azetidines **13a-c** toward reactive bicyclic intermediates **14a-c**, which are subsequently prone to undergo ring opening by a nucleophile, i.e., bromide, at the bridgehead carbon atom in an S_N2 fashion to furnish the thermodynamically more favored six-membered 4-bromopiperidines **154a-c** (Scheme 44). An alternative reaction pathway, involving direct nucleophilic substitution of the mesyloxy group by bromide followed by ring expansion *via* bicyclic azetidinium ions **14a-c** should not be excluded. The selective formation of 4-bromopiperidines **154a-c** over 4-mesyloxypiperidines **152a-c** can be attributed to the considerably stronger nucleophilicity of bromide in acetonitrile as compared to the mesyloxy anion.

Upon detailed spectroscopic analysis, small amounts of 2-vinylazetidines **153a-c** (5-9%) were observed as well in the crude reaction mixtures, as characteristic azetidine chemical shifts and typical signals for vinylic protons were detected in the ^{1}H NMR spectra of these mixtures ($CDCl_3$, Table 7).

Table 7. Conversion of 2-(2-mesyloxyethyl)azetidines 13a-c toward 4-bromopiperidines 154a-c

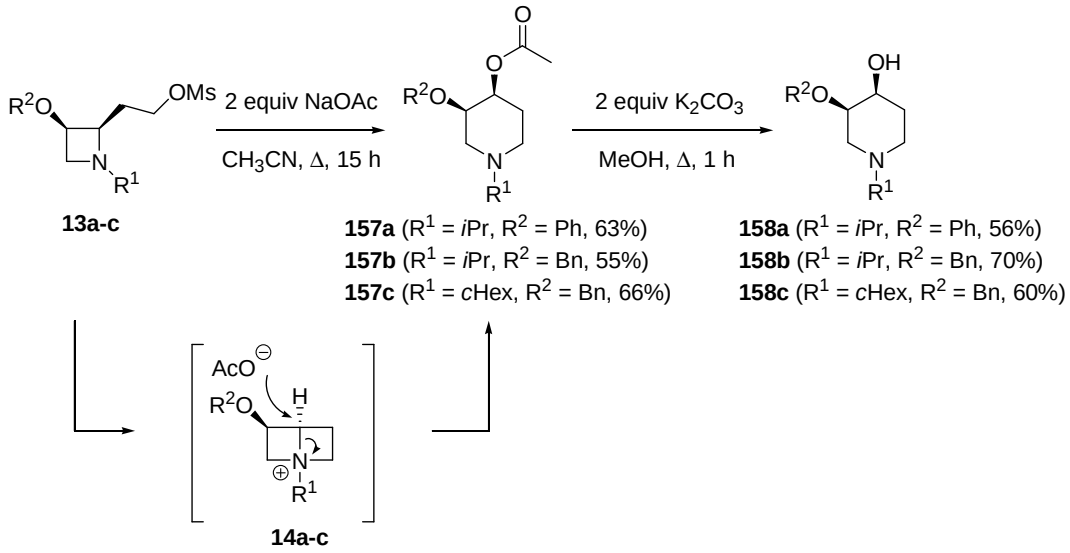
Substrate	R^1	R^2	Result[a]
13a	*i*Pr	Ph	**153a**/**154a** = 6/94
13b	*i*Pr	Bn	**153b**/**154b** = 5/95
13c	*c*Hex	Bn	**153c**/**154c** = 9/91

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

3.2.2.3.2 Synthesis of 4-acetoxy- and 4-hydroxypiperidines

The scope of this synthetic methodology was further extended toward other 4-substituted piperidine derivatives. The possibility of introducing other nucleophiles than bromide was first tested through the addition of sodium acetate. Thus, treatment of azetidines **13a-c** with two equiv of NaOAc in acetonitrile under reflux for 15 hours resulted in the selective formation of 4-acetoxypiperidines **157a-c** in good yields after purification (Scheme 45). The relative *cis*-stereochemistry controlled by the Staudinger synthesis of β-lactams **12a-c** was transferred through the reaction sequence, affording *cis*-piperidines **157a-c** in a stereoselective way as demonstrated by the vicinal coupling constants between the protons at C-3 and C-4 (2.9-4.0 Hz, ^{1}H NMR, $CDCl_3$), which are in accordance with literature data concerning *cis*-3,4-dioxygenated piperidines.[82] Again, small amounts of 2-vinylazetidines **153a-c** (2-6%) were present in the crude reaction mixtures as well (Table 8).

Next, the reactivity of 4-acetoxypiperidines **157a-c** was evaluated with the intention to provide a convenient entry into the biologically relevant class of 4-hydroxylated piperidines,[83] yielding the corresponding 4-hydroxypiperidines **158a-c** in 56-70% yield *via* methanolysis of the ester moiety upon treatment with two equiv of K_2CO_3 in methanol under reflux for one hour (Scheme 45).



Scheme 45

Table 8. Conversion of 2-(2-mesyloxyethyl)azetidines 13a-c toward 4-acetoxypiperidines 157a-c

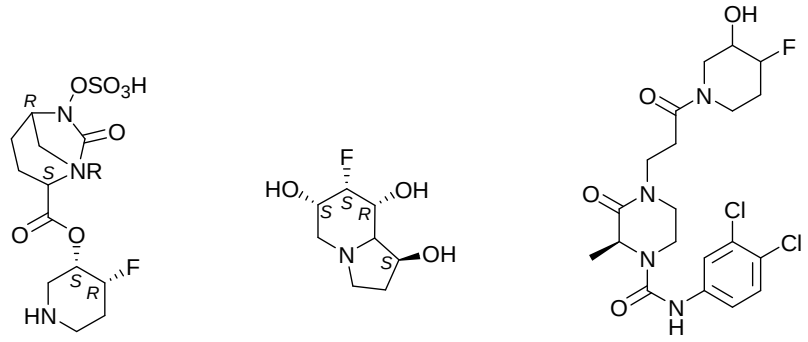
Substrate	R^1	R^2	Result[a]
13a	*i*Pr	Ph	**153a**/**157a** = 2/98
13b	*i*Pr	Bn	**153b**/**157b** = 6/94
13c	*c*Hex	Bn	**153c**/**157c** = 3/97

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

3.2.2.3.3 Attempts toward the synthesis of 4-fluoropiperidines

In the pharmaceutical industry, about 20% of the prescribed pharmaceuticals and 30% of the leading 30 blockbuster drugs by sales contain a C-F bond, as illustrated by *inter alia* Lipitor (inhibits cholesterol synthesis), Advair Discus (anti-asthmatic), and Prevacid (antacid/stomach ulcer).[90] In addition, organofluorine compounds have also achieved significant advances in the area of agrochemistry.[91] This is mainly due to the fact that the replacement of a hydrogen atom with fluorine often gives rise to drastic changes in biological activity because of the altered electronic distribution and changes in conformational properties.[92] Consequently, during the last decades, much effort has been devoted to synthesize site-specific fluorinated compounds, and the development of new synthetic approaches and new commercial applications are the subject of intense research in organic chemistry and related disciplines.[93]

In particular, fluorinated azaheterocyclic compounds attract widespread attention, and fluorine-containing piperidines are important building blocks from a medicinal point of view.[93a-e,94] The numerous patents concerning fluorinated piperidines emphasize the possibility of these compounds as substituents to modulate the activity of different active compounds, such as antidiabetic,[95] anticancer,[96] antidepressant,[97] antibacterial,[98] anti-inflammatory and immunomodulatory agents[99] and compounds for the treatment of neurological and psychiatric diseases (Figure 11).[100]

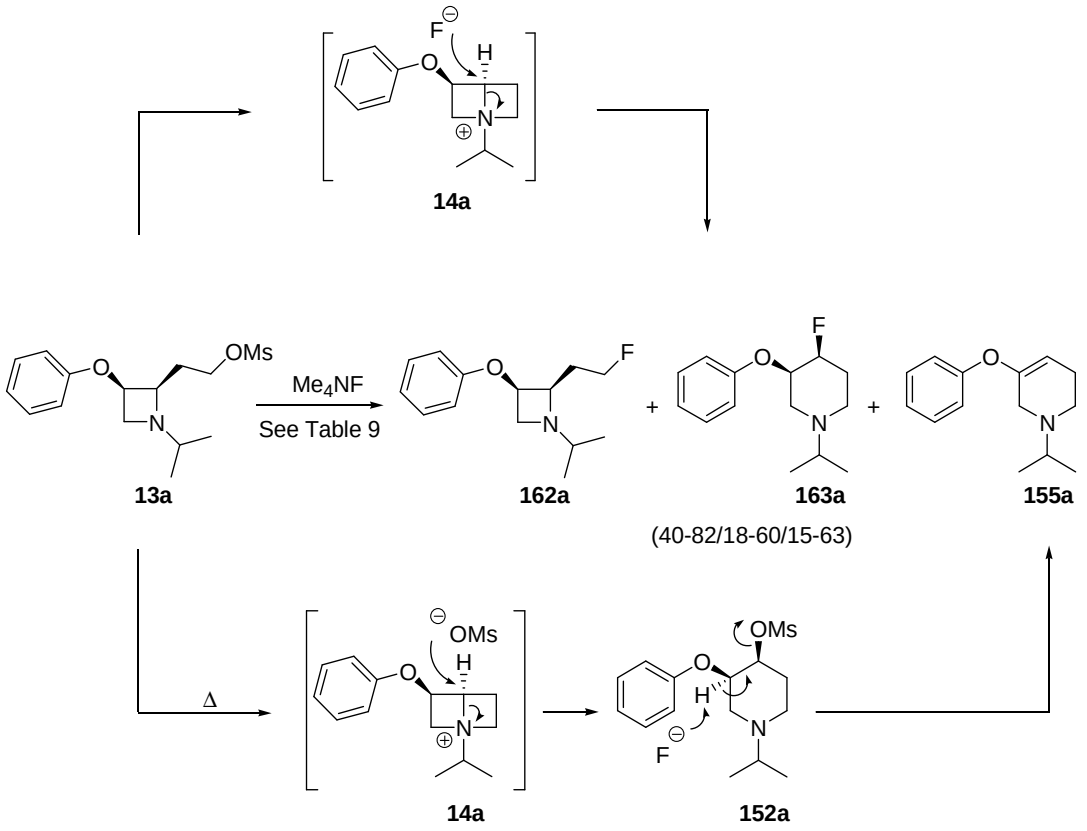


159 *antibacterial* **160** *antidiabetic* **161** *anti-inflammatory*

Figure 11

In light of this biological importance, efforts were made in order to perform a ring enlargement of 2-(2-mesyloxyethyl)azetidines **13a-c** as a convenient synthetic approach toward new 4-fluorinated piperidines lacking a 5,5-dimethyl moiety.

In analogy with the previously described ring expansion of 2-(2-bromo-1,1-dimethylethyl)azetidines **8** toward 4-fluoropiperidines,[19] 2-(2-mesyloxyethyl)azetidine **13a** was treated with tetramethylammonium fluoride (TMAF or Me_4NF) under different reaction conditions, involving variation of the number of equiv of Me_4NF (2, 10), solvent (DMSO, DMF, CH_3CN), temperature (35 °C, 60 °C, 100 °C, reflux), reaction time (15-48 h), and time of TMAF-addition (0–3 h), inevitable leading to the formation of mixtures of 2-(2-fluoroethyl)azetidine **162a**, 4-fluoropiperidine **163a** and tetrahydropyridine **155a** in varying ratios (40-82/18-60/15-63, Scheme 46, Table 9), next to negligible amounts of 2-vinylazetidine **153a** (< 8%).



Scheme 46

Table 9. Attempts toward the selective synthesis of *cis*-4-fluoro-1-isopropyl-3-phenoxypiperidine 163a through TMAF-mediated ring expansion of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine 13a

Entry	Number of equiv of Me_4NF	Solvent	Temperature	Me_4NF added at	Time after addition	Result[a]
1	2	DMSO	100 °C	0 h	18 h	**162a**/**163a** = 80/20
2	2	DMF	60 °C	0 h	18 h	**162a**/**163a** = 82/18
3	2	DMSO	100 °C	0 h	48 h	**162a**/**163a** = 78/22
4	10	DMSO	60 °C	0 h	18 h	**162a**/**163a** = 81/19
5	2	CH_3CN	35 °C - reflux	5 min (35 °C)	15 h (reflux)	**162a**/**163a**/**155a** = 60/25/15
6	2	CH_3CN	35 °C - reflux	30 min (35 °C)	15 h (reflux)	**162a**/**163a**/**155a** = 40/30/30
7	2	CH_3CN	35 °C - reflux	1 h (35 °C)	15 h (reflux)	**163a**/**155a** = 60/40
8	2	CH_3CN	35 °C - reflux	2 h (35 °C)	15 h (reflux)	**163a**/**155a** = 45/55
9	2	CH_3CN	35 °C - reflux	3 h (35 °C)	15 h (reflux)	**163a**/**155a** = 37/63

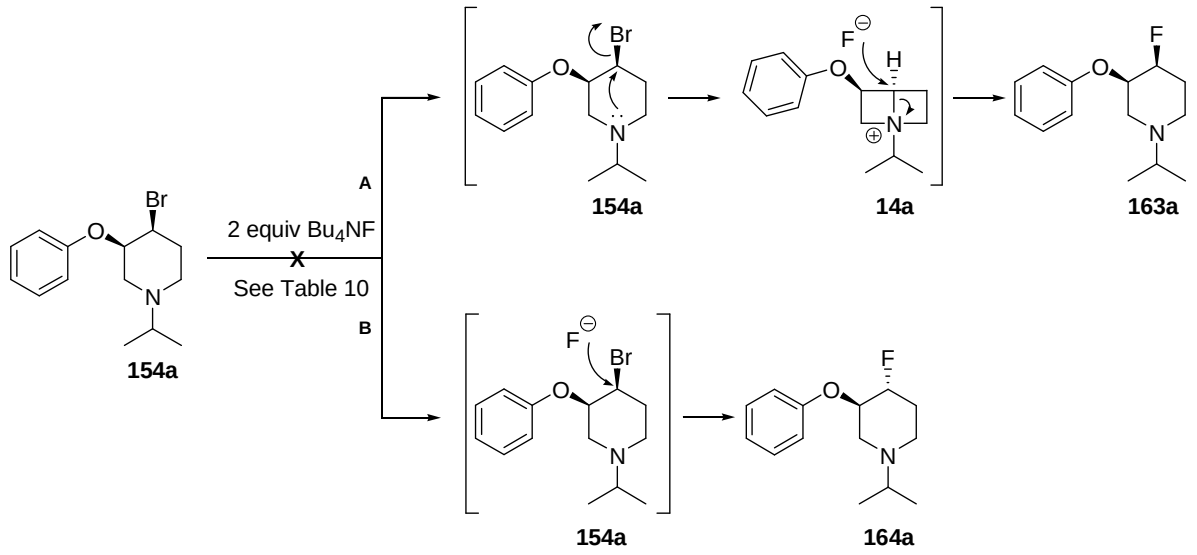
[a] Based on ^1H NMR analysis of the crude reaction mixture.

From a mechanistic viewpoint, mesylated azetidine **13a** probably undergoes competition between intermolecular S_N2-substitution at the electrophilic oxygenated carbon center leading to the formation of 2-(2-fluoroethyl)azetidine **162a** on the one hand, and intramolecular nucleophilic substitution toward bicyclic azetidinium intermediate **14a**, followed by regiospecific ring opening by

the nucleophilic fluoride at the bridgehead carbon atom in an S_N2 fashion to yield the premised 4-fluoropiperidine **163a** on the other (Scheme 46, Table 9, Entry 1-4).

In order to circumvent the formation of 2-(2-fluoroethyl)azetidine **162a**, 2-(2-mesyloxyethyl)azetidine **13a** was first allowed to rearrange toward bicyclic azetidinium salt **14a** by heating in CH_3CN at 35 °C without the addition of the fluorine source (Table 9, Entry 5-9). Indeed, as the heating time before Me_4NF-addition was prolonged, the ratio gradually changed in favor of the premised fluorinated piperidine **163a**, but ^1H NMR analysis revealed that substantial amounts (15-63%) of cyclic enol ether **155a** were present in the crude reaction mixtures as well. The latter observation can be rationalized considering the initial formation of the ring expanded 4-mesyloxypiperidine **152a**, followed by the fluoride-induced mesylate elimination toward cyclic enol ether **155a**, as the ability of the fluoride anion to act as a base is well known in the literature.[101] Consequently, this strategy for the selective synthesis of fluorinated piperidines was abandoned.

In a second approach toward the synthesis of fluorinated piperidines, a totally different synthetic route starting from 4-bromopiperidine **154a** was contemplated, involving either an initial bromine dislocation induced by the nitrogen lone pair leading to the formation of azetidinium salt **14a** followed by a regiospecifically fluoride-mediated ring opening toward 4-fluoropiperidine **163a** due to a double Walden inversion (Scheme 47, Route A), or a direct S_N2-substitution at the brominated carbon atom toward the corresponding *trans*-derivative **164a** (Scheme 47, Route B). Following this rationale, *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **154a** was initially heated in acetonitrile, DMF or DMSO in the presence of two equiv of tetrabutylammonium fluoride (TBAF or Bu_4NF), unfortunately resulting in complete recovery of the starting material (Table 10, Entries 1, 5, 9). Subsequently, extensive efforts using different silver salts ($AgBF_4$, Ag_2CO_3) in order to enhance halide dissociation driven by the precipitation of the resulting silver bromide failed, as the starting compound was recovered completely or the formation of rather complex reaction mixtures was observed in which no typical signals for the expected substitution product could be detected, as shown by GC and ^1H NMR analysis (Table 10).



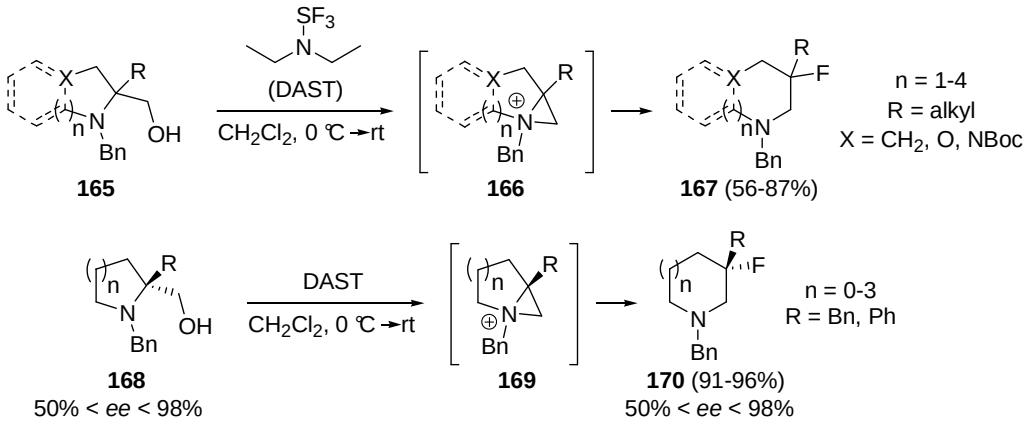
Scheme 47

Table 10. Attempts toward the synthesis of 4-fluoro-1-isopropyl-3-phenoxypiperidine 163a/164a from *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine 154a

Entry	Additive	Solvent	Temperature	Time	Result[a]
1	-	CH_3CN	reflux	22 h	no reaction
2	Ag_2CO_3 (5 equiv)	CH_3CN	rt	15 h	no reaction
3	Ag_2CO_3 (5 equiv)	CH_3CN	reflux	3 h	complex mixture
4	$AgBF_4$ (5 equiv)	CH_3CN	reflux	2 h	complex mixture
5	-	DMF	60 °C	18 h	no reaction
6	Ag_2CO_3 (5 equiv)	DMF	rt	15 h	no reaction
7	Ag_2CO_3 (5 equiv)	DMF	80 °C	2 h	complex mixture
8	$AgBF_4$ (5 equiv)	DMF	80 °C	1.5 h	complex mixture
9	-	DMSO	100 °C	22 h	no reaction
10	$AgBF_4$ (5 equiv)	DMSO	rt	18 h	no reaction
11	Ag_2CO_3 (5 equiv)	DMSO	60 °C	2 h	complex mixture
12	$AgBF_4$ (5 equiv)	DMSO	100 °C	2 h	complex mixture

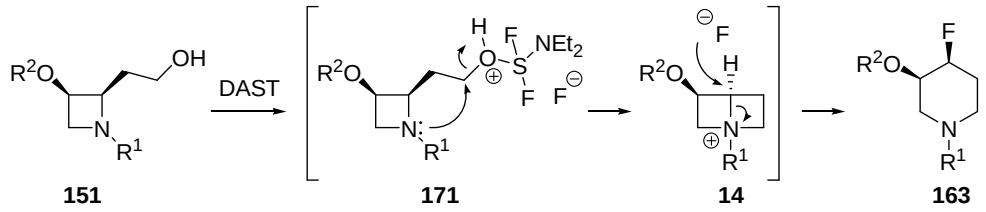
[a] Based on ^{1}H NMR and/or GC analysis of the crude reaction mixture.

Among the broad variety of fluorinating agents used to fulfill the increasing demand for site-selective fluorination of organic compounds, *N*,*N*-diethylaminosulfur trifluoride (DAST) has emerged as a powerful reagent to convert alcohols into the corresponding monofluorinated target molecules.[102] This reagent is described to initiate rearrangements through anchimeric assistance of an electron-rich group (*e.g.*, in compounds with methoxy,[103] amino,[104] oxiranyl,[105] azido[106] groups, or with a double bond[103c]) due to the formation of a very good leaving group. In that respect, the selective and efficient ring expansion of cyclic α-(hydroxymethyl)amines **165** and **168** toward cyclic β-fluoro amines **167** and **170** upon treatment with DAST has been reported very recently (Scheme 48).[104b]



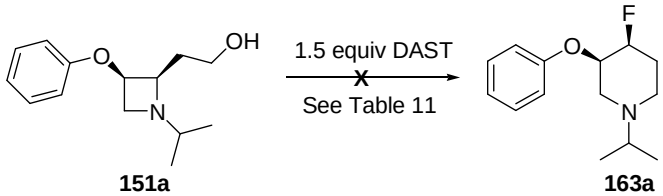
Scheme 48

Accordingly, a similar strategy was envisaged for the rearrangement of cyclic 2-(hydroxyethyl)azetidines **151** into cyclic γ-fluoro amines **163**. This methodology involves a DAST-mediated activation of the hydroxyl functionality in γ-position with respect to the azetidine nitrogen. Subsequent intramolecular nucleophilic substitution by the nitrogen lone pair in intermediate azetidines **171** toward azetidinium salts **14** can take place, which can finally furnish 4-fluoropiperidines **163** through ring opening by fluoride (Scheme 49).



Scheme 49

In order to achieve this goal, *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **151a** was selected as a model substrate and treated with 1.5 equiv of DAST in different solvents and at different temperatures (Scheme 50, Table 11). Unfortunately, no formation of the desired 4-fluoropiperidine **163a** was observed and only complex reaction mixtures were obtained. Consequently, this methodology was abandoned as well.



Scheme 50

Table 11. Attempts toward the selective synthesis of *cis*-4-fluoro-1-isopropyl-3-phenoxypiperidine 163a through DAST-mediated ring expansion of *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine 151a

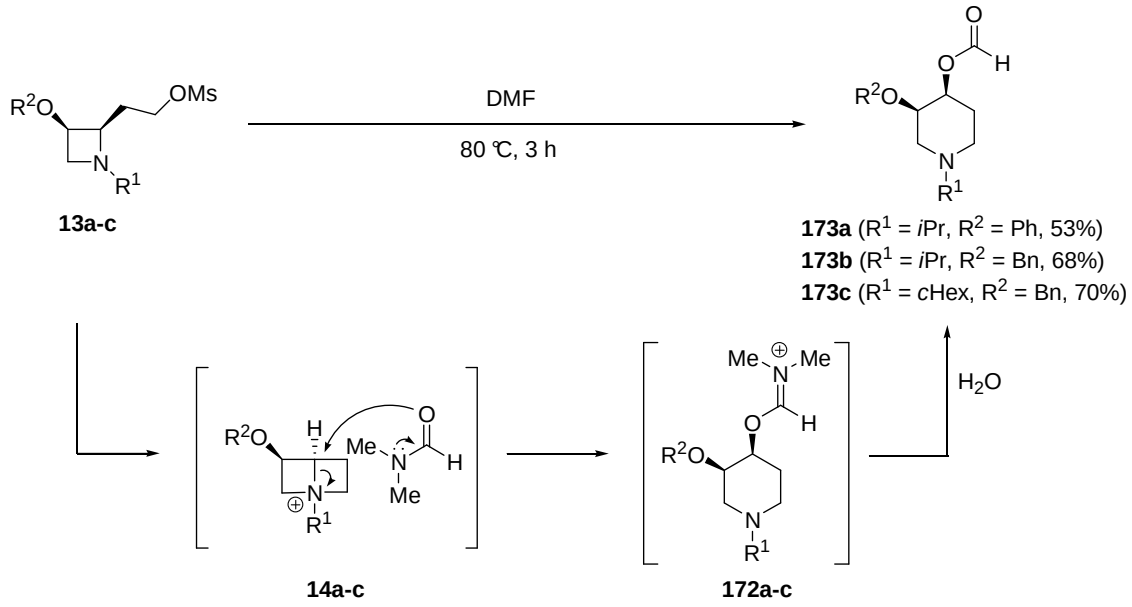
Solvent	Conditions	Result[a]
CH_2Cl_2	0 °C, 1 h then rt, 1 h	complex mixture
CH_2Cl_2	-78 °C, 1 h then rt, 1 h	complex mixture
THF	0 °C, 1 h then rt, 1 h	complex mixture
acetone	0 °C, 1 h then rt, 1 h	complex mixture
acetone	-78 °C, 1 h then rt, 1 h	complex mixture
THF + 3 equiv Et_3N	0 °C, 1 h then rt, 1 h	complex mixture

[a] Based on ^{1}H NMR and/or GC analysis of the crude reaction mixture.

It is clear that the transformation of 2-(2-mesyloxyethyl)azetidines and 2-(2-hydroxyethyl)azetidines into the corresponding 4-fluoropiperidines remains troublesome applying the proposed methodologies. Nevertheless, the TMAF-mediated ring expansion of 2-(2-mesyloxyethyl)azetidines clearly needs further elaboration, as *cis*-4-fluoro-1-isopropyl-3-phenoxypiperidine **163a** was formed in 18-60% through ring enlargement of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **13a**.

3.2.2.3.4 Synthesis of 4-(formyloxy)piperidines

In order to further assess their intrinsic reactivity, azetidines **13a-c** were heated in DMF at 80 °C for three hours. Surprisingly, next to small amounts of 2-vinylazetidines **153a-c** (3-7%, Table 12), azetidines **13a-c** were almost exclusively converted into 4-(formyloxy)piperidines **173a-c** (Scheme 51). A plausible explanation for this transformation involves the formation of intermediate azetidinium salts **14a-c**, followed by nucleophilic ring opening by dimethylformamide at the bridgehead carbon atom. Subsequent hydrolysis of intermediates **172a-c** during aqueous workup afforded the corresponding piperidines **173a-c** in high yields (53-70%) after purification by column chromatography on silica gel. Again, the relative *cis*-stereochemistry obtained during the Staudinger synthesis of β-lactams **12a-c** was retained, thus affording *cis*-piperidines **173a-c** as can be derived from the coupling constants between the protons at C-3 and C-4 (3.9-4.1 Hz, ^{1}H NMR, $CDCl_3$).[82]



Scheme 51

Table 12. Conversion of 2-(2-mesyloxyethyl)azetidines 13 toward 4-(formyloxy)piperidines 173

Substrate	R^1	R^2	Result[a]
13a	*i*Pr	Ph	**153a**/**173a** = 5/95
13b	*i*Pr	Bn	**153b**/**173b** = 3/97
13c	*c*Hex	Bn	**153c**/**173c** = 7/93

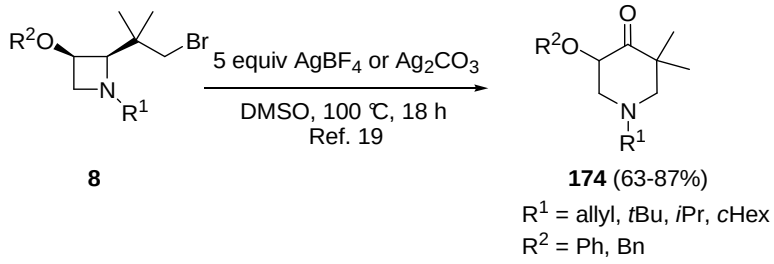
[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

In addition to the elegant nature of this transformation (no additional reagents required), 4-(formyloxy)piperidines thus obtained exhibit interesting structural characteristics, making them suitable substrates for further elaboration. The presence of a formyloxy substituent at the 4-position of the piperidine backbone provides an entry into functionalized piperidines through further modification of the ester functionality.

3.2.2.3.5 Synthesis of piperidin-4-ones through a ring expansion-oxidation protocol

Piperidin-4-ones represent an important class of bioactive azaheterocycles attracting a progressive interest due to their observed biological and pharmaceutical properties, such as antiviral, antitumor,[21] analgesic,[22] local anaesthetic,[23] antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, CNS stimulant and depressant activities.[20] Furthermore, piperidin-4-ones have been used as eligible intermediates in the synthesis of a variety of biologically active compounds, including functionalized piperidines, through further modification of the carbonyl moiety.[107]

At the Department of Sustainable Organic Chemistry and Technology (UGent), 2-(2-bromo-1,1-dimethylethyl)azetidines **8** have been rearranged into 5,5-dimethylpiperidin-4-ones **174** in high purity upon treatment with five equiv of silver carbonate or silver tetrafluoroborate in DMSO for 18 hours at 100 °C.[19] During these transformations, the presence of a silver salt proved to be indispensable. This smooth rearrangement probably proceeded through nucleophilic attack of the nitrogen lone pair onto the electrophilic halogenated carbon atom, affording an intermediate azetidinium salt. Hereby, the exempted bromide was unable to induce ring enlargement toward 4-bromopiperidines due to complexation with the silver ion. The necessity of the silver counterion was thus based on trapping of the bromide so that ring transformation toward brominated piperidines was excluded. The intermediate bicyclic azetidinium salts were subsequently converted into piperidin-4-ones **174** upon DMSO-mediated ring enlargement, followed by abstraction of the acidic proton at the oxygenated carbon atom and liberation of dimethylsulfide.[19]

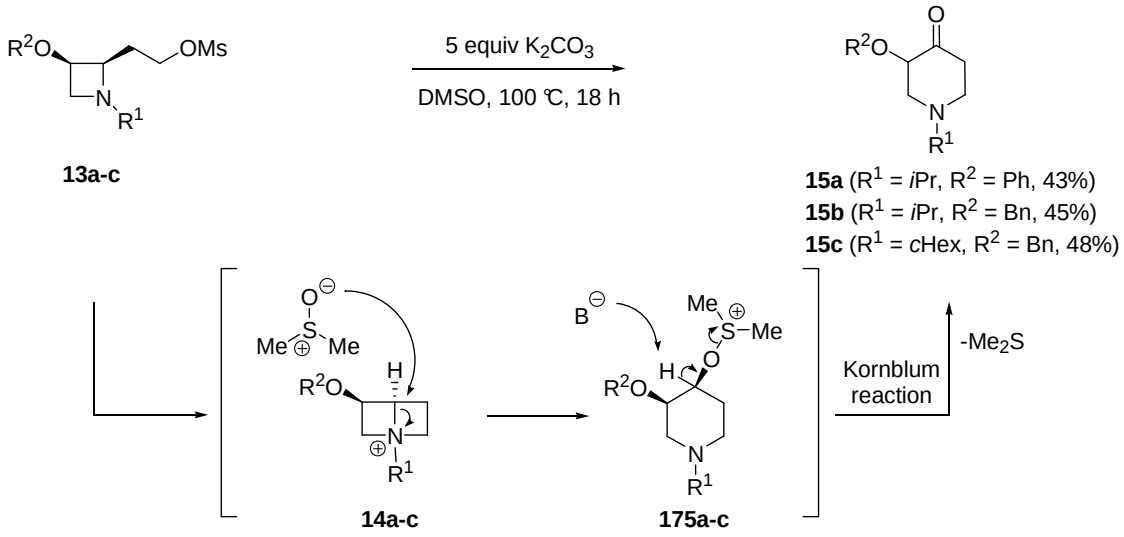


8 **174** (63-87%)
R^1 = allyl, *t*Bu, *i*Pr, *c*Hex
R^2 = Ph, Bn

Scheme 52

In order to broaden the scope of this synthetic transformation, the ring enlargement of 2-(2-mesyloxyethyl)azetidines **13a-c** *via* a similar ring expansion-oxidation mechanism was envisaged. In that respect, azetidines **13a-c** were stirred in DMSO at 100 °C for 18 hours in the presence of five equiv of K_2CO_3,[89g] resulting in full conversion of the starting material toward the desired piperidin-4-ones **15a-c** in 43-48% yield (Scheme 53), together with minor amounts of unidentified side products (8-27%). However, when wet DMSO was used, in some cases a substantial amount (up to 70%) of 4-hydroxypiperidines **158a-c** was obtained along with piperidin-4-ones **15a-c** after heating of azetidines **13a-c** in DMSO, which might be the result of an incomplete oxidation reaction or direct hydrolysis of the strained intermediates **14a-c**, probably due to the presence of water in DMSO. Moreover, the addition of K_2CO_3 appeared to be essential, as piperidin-4-ones **15a-c** were formed in very low yields (5-8%) if the reaction was performed in the absence of K_2CO_3. In analogy with the above-described reaction mechanism, the initially formed bicyclic azetidinium ions **14a-c** undergo a Kornblum-type reaction and are ring opened by DMSO at the bridgehead carbon atom in an S_N2-type fashion to yield intermediate piperidines **175a-c**, which are subsequently transformed into the corresponding piperidin-4-ones **15a-c** upon proton abstraction. The preferential formation of piperidin-4-ones **15a-c**

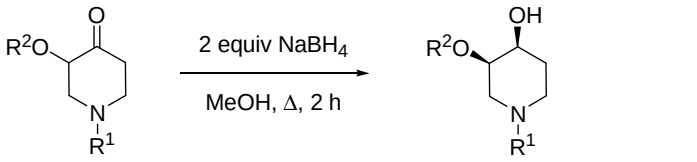
over 4-mesyloxypiperidines can be attributed to the relative higher nucleophilicity of DMSO as compared to the mesylate anion, making inactivation of the latter by complexation unnecessary. This stands in contrast with the necessity of a silver salt for the selective ring expansion-oxidation of 2-(2-bromoethyl)azetidines **8** toward piperidin-4-ones **174**. It should be stressed that this type of transformations is peculiar, as DMSO is known to directly oxidize organic halides and tosylates to the corresponding carbonyl compounds, as demonstrated amply by the Kornblum reaction and its variants.[108]



Scheme 53

3.2.2.3.5.1 Reduction toward 4-hydroxypiperidines

As mentioned before, the 4-hydroxypiperidine moiety comprises a privileged scaffold that is encountered in many bioactive compounds.[83] In that respect, the reduction of piperidin-4-ones **15a-c** was contemplated in the next phase. At first, treatment with two molar equiv of $NaBH_4$ in MeOH was performed, affording the corresponding 4-hydroxypiperidines **158a-c** in 73-88% yield after reflux for two hours (Scheme 54). It should be noted that this $NaBH_4$-mediated reduction of racemic piperidin-4-ones **15a-c** toward 4-hydroxypiperidines **158a-c** proceeded with complete *cis*-diastereoselectivity. The relative *cis*-stereochemistry at positions 3 and 4 is a direct result of the steric approach control, resulting in a preferential equatorial attack of the reducing agent with respect to the sterically hindered six-membered ring.[109]

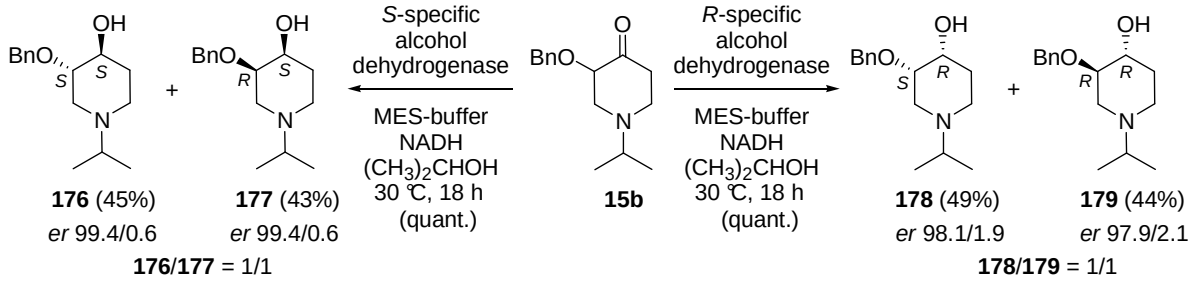


15a-c

158a (R^1 = *i*Pr, R^2 = Ph, 88%)
158b (R^1 = *i*Pr, R^2 = Bn, 79%)
158c (R^1 = *c*Hex, R^2 = Bn, 73%)

Scheme 54

In a second approach, an enzyme-mediated enantioselective reduction of piperidin-4-ones was investigated using alcohol dehydrogenases. The reduction of carbonyl compounds by alcohol dehydrogenases and their cofactors has numerous advantages compared to classical chemical reactions, such as the high level of enantioselectivity and the environmentally benign reaction conditions, and this field of research has gained an increased relevance over the past few years, especially concerning the synthesis of important intermediates for pharmaceuticals and bioactive compounds.[110] As a selected example, racemic 3-benzyloxy-1-isopropylpiperidin-4-one **15b** was treated with a commercially available *S*-specific[111] or *R*-specific[112] alcohol dehydrogenase in aqueous MES-buffer [2-(*N*-morpholino)ethanesulfonic acid] at 30 °C in the presence of NADH. This biocatalytic reduction reaction was performed by colleagues at the Department of Biochemical and Microbial Technology (UGent). In contrast to the chemical reduction process, the merit of this enzymatic approach comprises the *S*- and *R*-enantioselective reduction of the carbonyl functionality, in each case resulting in the formation of two diastereoisomers (ratio 1/1, based on ^{1}H NMR, Scheme 55). The four enantiomers **176**, **177**, **178** and **179** were obtained in analytically pure form in 43-49% yield by separation of the latter diastereoisomeric mixtures through column chromatography on silica gel. In order to establish their enantiomeric ratio, esterification of hydroxypiperidines **176**, **177**, **178** and **179** was performed utilizing one equivalent of (1*S*)-(-)-camphanic chloride in CH_2Cl_2 at room temperature for 15 hours in the presence of 0.1 equiv of DMAP [4-(dimethylamino)pyridine] and two equiv of Et_3N, pointing to a diastereoisomeric ratio of 99.4/0.6, 99.4/0.6, 98.1/1.9 and 97.9/2.1 for piperidines **176**, **177**, **178** and **179**, respectively (based on GC/MS-analysis). Consequently, an enantiomeric ratio of 99.4/0.6, 99.4/0.6, 98.1/1.9 and 97.9/2.1 could be assigned to 4-hydroxypiperidines **176**, **177**, **178** and **179** (Scheme 55). The absolute configurations were assigned by comparison of the observed rotation of piperidines **176** (α_D = +27.7°, CH_2Cl_2), **177** (α_D = +7.6°, $CHCl_3$), **178** (α_D = -7.6°, $CHCl_3$) and **179** (α_D = -27.7°, CH_2Cl_2) with optical rotations described in the literature for similar 3,4-dioxygenated piperidines.[113] Based on these findings, both chemical and enzymatic reductions can be used in a complementary way to effect a diastereoselective or enantioselective synthesis of 4-hydroxypiperidines from piperidin-4-ones, respectively.



176 (45%) *er* 99.4/0.6 | **177** (43%) *er* 99.4/0.6 | **176**/**177** = 1/1 | **15b** | **178** (49%) *er* 98.1/1.9 | **179** (44%) *er* 97.9/2.1 | **178**/**179** = 1/1

Scheme 55

3.2.2.3.6 Theoretical rationalization

As described in the previous paragraphs, the reactivity of 2-(2-mesyloxyethyl)azetidines with regard to different nucleophiles was evaluated for the first time, resulting in the stereoselective preparation of a variety of new 4-acetoxy-, 4-hydroxy-, 4-bromo-, and 4-(formyloxy)piperidines. These diastereoselective ring expansions are expected to proceed *via* transient 1-azoniabicyclo[2.2.0]hexanes, which are subsequently prone to undergo an S_N2-type ring opening at the bridgehead carbon atom to afford the final heterocycles. To assess the feasibility of this process and the relative stability of the intermediates, Density Functional Theory (DFT) calculations were conducted by colleagues at the Center for Molecular Modeling, Ghent University, on both the formation of bicyclic azetidinium ion **14a** and its ring opening by acetate, leading to the formation of the corresponding 4-acetoxypiperidine **157a** (Scheme 45).

The formation of bicyclic azetidinium intermediate **14a** occurs *via* intramolecular nucleophilic attack of the nitrogen lone pair in azetidine **13a** and simultaneous displacement of the mesylate anion as depicted **TS1** (Figure 12). Three explicit acetonitrile molecules were used to stabilize the nucleophuge, each interacting with one of the mesylate oxygen atoms through charge-dipole interactions. Subsequently, ring opening of bicyclic intermediate **14a** occurs *via* acetate-mediated nucleophilic attack at the bridgehead carbon atom, as shown in **TS2** (Figure 13). Analogously, the incoming acetate anion is stabilized by explicit interactions with two acetonitrile molecules.

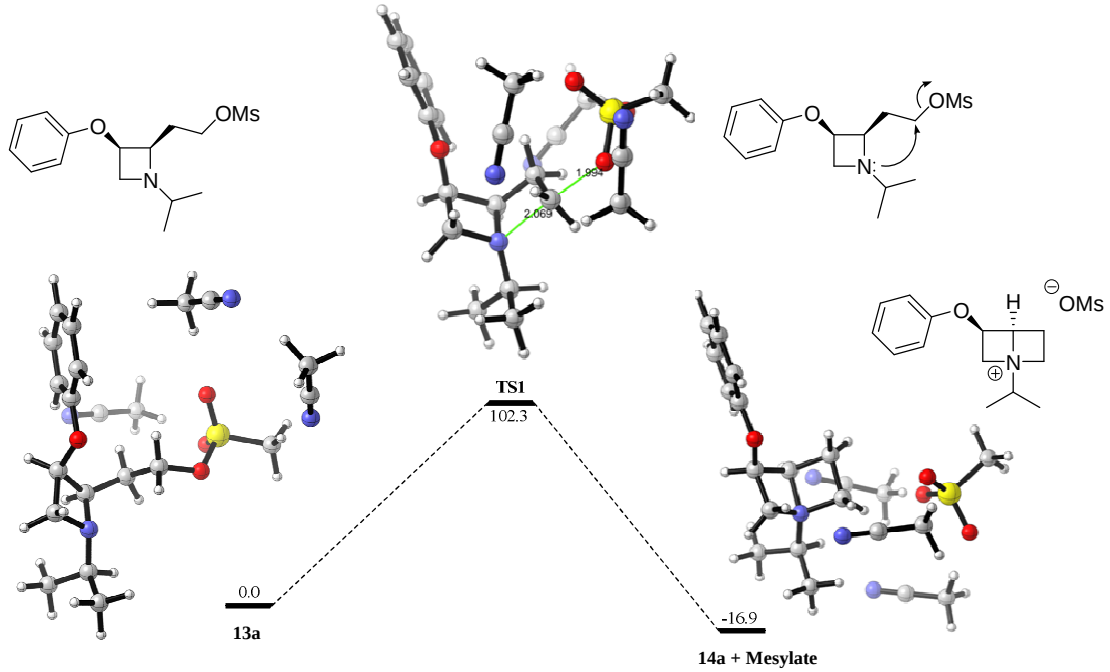


Figure 12. Formation of bicyclic azetidinium ion 14a, solvated by explicit acetonitrile molecules (M06-2X/6-311++G(d,p)//B3LYP/6-31+G(d,p)); critical distances in Å

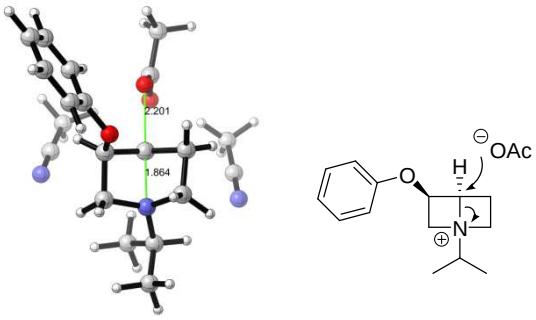


Figure 13. Transition state structure (TS2) for the acetate-induced ring opening of bicyclic azetidinium ion 14a, solvated by explicit acetonitrile molecules (B3LYP/6-31+G(d,p) geometries); critical distances in Å

The relative free energies along the reaction path for the formation and consecutive ring opening of bicyclic intermediate **14a** were calculated using two different solvation schemes, namely microsolvation (explicit solvation) and mixed solvation (explicit/implicit solvation). Explicit solvation involves placing discrete solvent molecules around the chemically active species to form a so-called "supermolecule" structure. However, in order to account for possible long-range interactions with the solvent environment, the supermolecule was immersed in a dielectric continuum using two different models (C-PCM and SMD). For all three solvation models, energies were refined using five different DFT methods (Table 13).

Compared to non-solvated gas-phase results [relative free energy of **TS1** in gas-phase = 136.6 kJ/mol, BMK/6-311++G(d,p)//B3LYP/6-31+G(d,p)], explicit solvation lowers barriers by an average of 15

kJ/mol by means of stabilizing the forming charge through intermolecular interactions. Results for both mixed solvation models, i.e., C-PCM and SMD, indicate that implicit solvation lowers the barriers by an additional 20 kJ/mol, bringing the barrier for the formation of bicyclic intermediate **14a** down to ~100 kJ/mol (Table 13). These results indicate that the formation of intermediate **14a** is a feasible process and, furthermore, its stability is comparable to that of the starting azetidine **13a**. Nucleophilic ring opening (**TS2**) of bicyclic azetidinium ion **14a** occurs readily, as illustrated in the small barriers and highly exergonic nature of this reaction step (Table 13).

Table 13. Relative Gibbs free energies (kJ/mol, 298K and 1atm) for the formation and consecutive nucleophilic ring opening of bicyclic azetidinium intermediate 14a[a-c]

		Formation of intermediate 14a			Ring opening of intermediate 14a		
		13a	**TS1**	**14a + mesylate**	**14a + acetate**	**TS2**	**157a**
Explicit solvation	B3LYP	0.0	123.2	26.1	0.0	37.6	-141.1
	BMK	0.0	124.8	1.4	0.0	60.4	-120.3
	M06-2X	0.0	121.1	6.8	0.0	52.8	-142.6
	CAM-B3LYP	0.0	127.2	17.3	0.0	47.6	-141.4
	ωB97X-D	0.0	111.2	-1.8	0.0	57.6	-118.6
Explicit/implicit solvation with C-PCM	B3LYP	0.0	104.3	3.4	0.0	43.8	-134.9
	BMK	0.0	105.9	-21.4	0.0	65.4	-114.7
	M06-2X	0.0	102.3	-16.9	0.0	58.5	-135.3
	CAM-B3LYP	0.0	108.1	-5.7	0.0	53.1	-135.3
	ωB97X-D	0.0	92.2	-25.0	0.0	63.3	-111.9
Explicit/implicit solvation with SMD	B3LYP	0.0	103.3	-2.7	0.0	45.1	-135.3
	BMK	0.0	105.5	-26.8	0.0	66.2	-116.1
	M06-2X	0.0	102.2	-22.1	0.0	59.2	-136.8
	CAM-B3LYP	0.0	107.3	-11.6	0.0	54.2	-136.2
	ωB97X-D	0.0	91.8	-30.4	0.0	64.2	-113.1

[a] B3LYP/6-31+G(d,p) optimized structures. [b] Single point energy calculations at all levels of theory with 6-311++G(d,p) basis set. [c] Implicit solvation in acetonitrile, ε = 36.6.

3.2.3 Conclusions

In summary, next to their established reactivity toward the synthesis of 4-bromo-, 4-cyano-, 4-azido-, 4-fluoro-, and 4-oxo-5,5-dimethylpiperidines, 2-(2-bromo-1,1-dimethylethyl)azetidines were proven to be useful starting materials to perform rearrangements toward 4-acetoxy- and 4-hydroxypiperidines as well. Furthermore, the reactivity of 2-(2-mesyloxyethyl)azetidines, lacking a *gem*-dimethyl group, toward different nucleophiles was evaluated for the first time, pointing to a useful transformation of the former into the class of *cis*-3,4-disubstituted 5,5-dinor-dimethylpiperidines, resulting in the stereoselective preparation of a variety of new 4-acetoxy-, 4-hydroxy-, 4-bromo-, 4-formyloxy-, and 4-oxopiperidines in moderate to high yields. This approach constitutes a convenient alternative for the preparation of the former class of 5,5-dimethylpiperidines and 5,5-dimethylpiperidin-4-ones, as the corresponding 5,5-dinor-dimethyl

variants provide interesting opportunities within the field of drug development, which can be of high importance in pharmaceutical and medicinal chemistry. In addition, the synthetic applicability of the latter 5,5-dinor-dimethylpiperidin-4-ones was demonstrated by means of both a chemical and an enzymatic reduction. Whereas the $NaBH_4$-induced reduction is characterized by a *cis*-diastereoselectivity, the alcohol dehydrogenase-mediated reductions proceeded with *S*- or *R*-enantioselectivity at the carbonyl functionality.

During these reactions, transient 1-azoniabicyclo[2.2.0]hexanes were prone to undergo an S_N2-type ring opening at the bridgehead carbon atom to afford the final azaheterocycles in a stereoselective way. The *cis*-diastereoselectivity is thus controlled by the Staudinger synthesis of the starting β-lactams and the S_N2-ring opening of the intermediate bicyclic azetidinium ions.

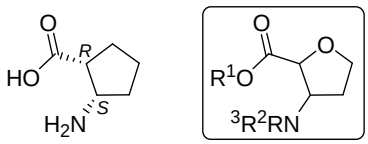
In addition to the experimental results, the intermediacy of transient 1-azoniabicyclo[2.2.0]hexanes in these transformations was further validated by means of high-level computational analysis. These results show that the bicyclic intermediate could be localized on the potential energy surface as a stable species.

3.3 Synthesis of bicyclic tetrahydrofuran-fused β-lactams and their conversion into methyl *cis*-3-aminotetrahydrofuran-2-carboxylates (Paper IV)

In addition to the generation of different biologically interesting nitrogen-containing (heterocyclic) systems from azetidin-2-one derivatives by selective bond cleavage and rearrangements,[4] as demonstrated in the previous paragraphs, the azetidin-2-one skeleton has also been extensively used as a template to construct cyclic structures fused to the four-membered ring using the functionalization of the β-lactam nucleus as a stereocontrolling element.[4g,24] Among them, 3,4-fused (*C*-fused) bicyclic β-lactams have received much less attention as compared to their celebrated *N*-fused analogues.[4g,14,24,114] However, in many cases the resistance to β-lactam antibiotics can be attributed to a high level of expression of class C β-lactamases, which are reported to be selectively inhibited by 3,4-bridged monobactam derivatives, as some β-lactams *C*-fused with a cyclopentene,[115] pyrrolidine[116] or thiazolidine[117] ring have been found to possess promising β-lactamase inhibitory activities. In addition, recently, bicyclic β-lactams *C*-fused with carbocycles and a carbohydrate unit have been reported to exhibit promising activities against malaria,[118a] leishmaniasis[118b] and several types of cancer.[118c]

Although the tetrahydrofuran motif is ubiquitous as a structural feature in bioactive natural and synthetic molecules,[119] relatively few methods are available for the construction of tetrahydrofuran-based β-lactams.[114a-i] For example, the transition metal-catalyzed heterocyclization of azetidin-2-one-tethered γ-allenols[114a,114c] and γ-alkynols[114d] and the Ag-mediated intramolecular 1,3-dipolar cycloaddition of oxo-*N*-propargylamides[114b] comprise regiocontrolled routes to β-lactams bearing an oxygen-containing 3,4-fused five-membered ring system. Very recently, chlorinated tetrahydrofuro[3,2-*c*]azetidin-2-ones have been prepared by a copper(I)-catalyzed atom transfer radical cyclization.[114e] The radical-mediated ring closure of 3-benzyloxy-4-ethynylazetidin-2-ones has been described toward the corresponding *C*-fused bicyclic *cis*-β-lactams,[114g] and a *cis*-4-(2-fluorophenyl)-3-hydroxy-β-lactam was transformed into a tricyclic β-lactam *via* an (η^6-arene)tricarbonylchromium(0) complex through a number of reaction steps.[114f]

In view of the continuous quest for new lead compounds in the pharmaceutical industry, the synthesis of new (cyclic) β-amino acid derivatives comprises an important research field in modern organic chemistry. The selective synthesis of β-amino acids[120] has been the subject of tremendous effort principally due to their important biological activities[121] as for example enzyme inhibitors or α-amino acid surrogates in the construction of peptides possessing unique conformational properties (β-peptides).[122] Furthermore, cyclic β-amino acids in which the amino group and the acid functionality are vicinally attached to an aliphatic ring system represent an important challenge due to their biological utility.[123] Cispentacin **180**,[124] an antifungal agent against various *Candida* strains and a subunit of the natural antibiotic amipurimycin,[125] comprises a relevant example and has attracted considerable attention to these five-membered β-amino acids (Figure 14).[126] Their oxaheterocyclic analogues, i.e., tetrahydrofurancarbocyclic acid derivatives, vicinally substituted with an amino group, are known to possess antimycotic activities.[127] Consequently, the synthesis of oxolane β-amino acid derivatives such as **181** constitutes a relevant challenge in organic chemistry (Figure 14).



180
cispentacin

181

Figure 14

At the Department of Sustainable Organic Chemistry and Technology (UGent), *cis*-3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)-β-lactams **7** have been transformed into *cis*-4,4-dimethyl-2-oxa-6-

azabicyclo[3.2.0]heptan-7-ones **182**, which served as eligible intermediates for the preparation of *cis*-3-amino-4,4-dimethyletrahydrofuran-2-carboxylates **183** *via* acidic methanolysis (Figure 15).[14] In line with paragraph 3.2 and in continuation of the interest in the use of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12** as versatile synthons, the present chapter focuses on the synthesis of *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **18** and *cis*-3-aminotetrahydrofuran-2-carboxylates **19**, thus providing an easy access to the 4,4-dinor-dimethyl variants as valuable templates in medicinal chemistry (Figure 15).

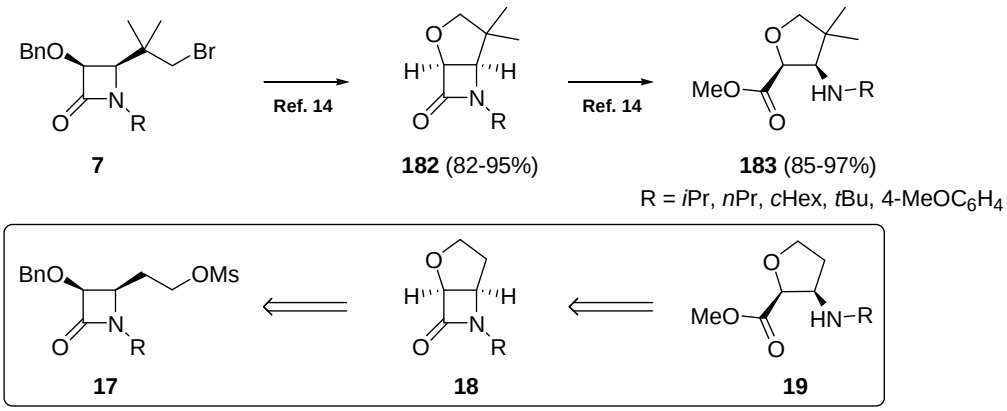


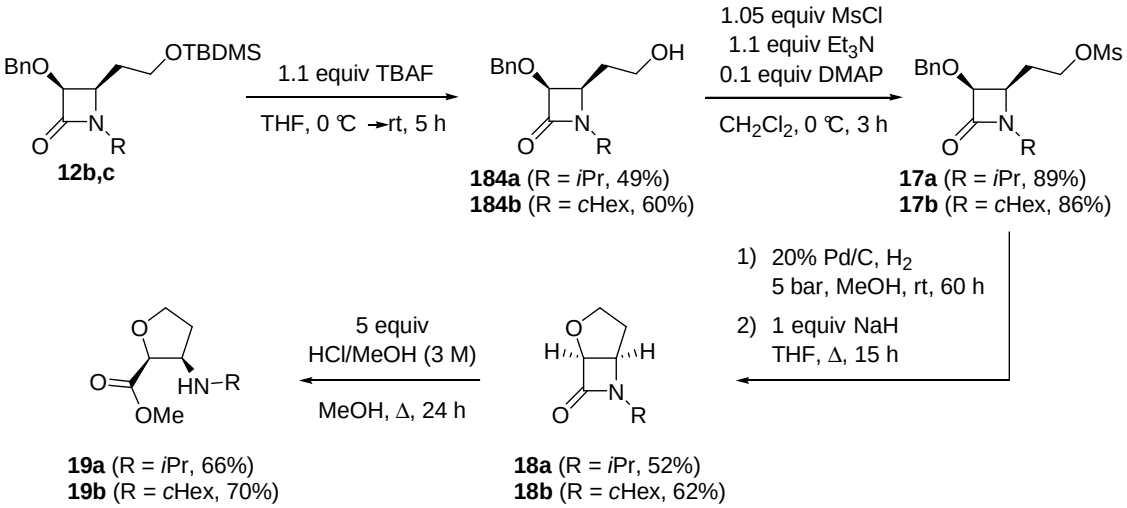
Figure 15

Thus, the potential of 3-benzyloxy-β-lactams **12b,c** as selected synthons in the synthesis of bicyclic azetidin-2-ones was investigated. Deprotection of the silyl ether in β-lactams **12b,c** using 1.1 equiv of tetra-*n*-butylammonium fluoride (TBAF) in THF, followed by treatment with 1.05 equiv of mesyl chloride (MsCl) in the presence of a base (1.1 equiv of Et_3N) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at 0 °C for three hours furnished the corresponding *cis*-3-benzyloxy-4-(2-mesyloxyethyl)azetidin-2-ones **17a,b** in 86-89% yield (Scheme 56). The latter β-lactams hold interesting potential for further elaboration due to the presence of a strained four-membered ring and a leaving group in one of the side chains.

Subsequently, hydrogenolysis of the benzyl ether substituent of the latter *cis*-3-benzyloxy-4-(2-mesyloxyethyl)azetidin-2-ones **17a,b** using 20% (w/w) palladium on activated carbon in methanol at room temperature for 60 hours afforded the corresponding *cis*-3-hydroxy-β-lactams in high purity (> 90%, ^{1}H NMR), which were used as such for further elaboration. Indeed, the latter 3-hydroxy-β-lactams were subjected to ring closure *via* intramolecular substitution of the mesyloxy functionality upon treatment with one equiv of NaH in THF under reflux for 15 hours, yielding the premised new *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **18a,b** in high yields (52-62%) after purification by column chromatography on silica gel. The *cis*-stereochemistry of bicyclic β-lactams **18a,b**, which is a direct consequence of the relative stereochemistry defined during the Staudinger synthesis of the starting

β-lactams **12b,c**, was unambiguously assigned based on the coupling constants between the protons at C-1 and C-5 (3.3 Hz, ^{1}H NMR, $CDCl_3$), pointing to a *cis*-configuration of the bicyclic framework.[14,114g] It has to be mentioned that this comprises the first synthesis of β-lactams *C*-fused with an unsubstituted tetrahydrofuran unit, in which the oxygen atom is connected to the C-3 β-lactam carbon atom.

As mentioned before, (cyclic) β-amino acids are important constituents of biologically active natural products and pharmaceutical agents.[121,122,123] In addition, oligomers of β-amino acids, for example β-peptides, have attracted considerable attention as useful peptidomimetics because of their proteolytic stability relative to natural α-peptides and their propensity to adopt stable secondary structures.[122] Since the use of β-lactams as synthons for the synthesis of β-amino acids with a pre-determined stereochemistry is well known in the literature,[4h,128] hydrolysis of the amide functionality in bicyclic-β-lactams can lead to the selective formation of (hetero)cyclic β-amino acids. In that respect, the reactivity of bicyclic β-lactams **18a,b** toward methanolic hydrogen chloride was evaluated with the intention to develop an efficient and straightforward route toward the class of 3-aminotetrahydrofuran-2-carboxylates **19a,b**. Treatment of β-lactams **18a,b** with five equiv of HCl in MeOH (3 M) under reflux for 24 hours resulted in the selective formation of novel methyl *cis*-3-aminotetrahydrofuran-2-carboxylates **19a,b** in good yields and purity (Scheme 56). The observed coupling constants between the protons at C-2 and C-3 in β-amino esters **19a,b** (5.5-6.6 Hz, ^{1}H NMR, $CDCl_3$) were in good accordance with those reported for their 4,4-dimethyl variants.[14] In this way, the transfer of the stereochemical information, introduced by the stereoselective Staudinger synthesis of β-lactams **12b,c**, through the reaction pathway enables the selective preparation of *cis*-3-aminotetrahydrofuran-2-carboxylates **19a,b**.



Scheme 56

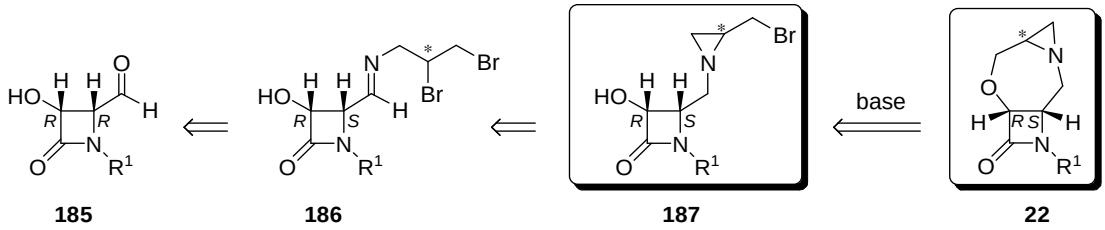
3.4 Synthesis of 2-hydroxy-1,4-oxazin-3-ones through ring transformation of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams (Paper VI)

Within the general objective of this thesis to synthesize new nitrogen-containing (a)cyclic target compounds based on novel fragmentations and rearrangements of the β-lactam ring, the fusion of the β-lactam ring and a second strained small-ring heterocycle in one chemical entity might give rise to the development of novel classes of highly reactive compounds. The interest in these fused bicyclic compounds stems from the combination of different reactive ring systems, which can (after initial selective manipulation) interact intramolecularly with each other, thus leading to the preparation of novel mono-, bi- and tricyclic target compounds.

Next to β-lactams, aziridines display an uncommon combination of reactivity and synthetic utility as well.[129] In particular, 2-(bromomethyl)aziridines are frequently deployed as versatile synthetic intermediates for the regio- and stereoselective preparation of a variety of (a)cyclic amines, including β-fluoro amines, piperidines, thiazolines, δ-lactams and γ-lactones.[27-37]

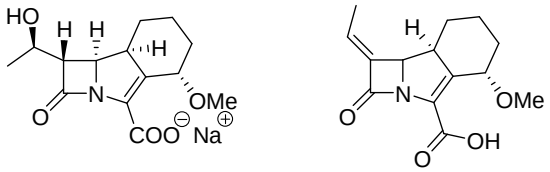
In view of the expertise at the Department of Sustainable Organic Chemistry and Technology (UGent) regarding the synthetic potential of both functionalized β-lactams and 2-(bromomethyl)aziridines, the introduction of the reactive [2-(bromomethyl)aziridin-1-ylmethyl] substituent at the 4-position in β-lactams **187** *via* imination and subsequent reductive ring formation of 4-formyl-β-lactams **185**, synthesized starting from (*R*)-glyceraldehyde acetonide, was investigated (Scheme 57). β-Lactam hybrids **187** comprise an unexplored class of compounds with high synthetic potential due to the presence of a reactive β-lactam ring, a strained aziridine moiety and a halogenated electrophilic carbon atom. In this way, initially, a synthetic concept was devised based on intramolecular nucleophilic displacement of bromide in β-lactams **187** by the C-3 alkoxide (obtained upon treatment with a base) to provide a convenient entry into the interesting class of tricyclic β-lactams **22** (Scheme 57). Indeed, due to increased bacterial resistance, the discovery of tricyclic β-lactam antibiotics ('trinems') and β-lactamase inhibitors[130] has triggered a renewed interest in the preparation and biological evaluation of new polycyclic β-lactam systems in an attempt to move away from the classical structures. For example, Sanfetrinem **188** shows a broad-spectrum antibacterial activity against *inter alia Streptococcus pneumoniae*, *Acinetobacter calcoaceticus*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis*,[130h,i] and LK-157 **189** exhibits inhibitory activity against a variety of class A and class C β-lactamases (Figure 16).[130g] In that respect, as in the case of their bicyclic analogues, the construction of 3,4-fused tricyclic β-lactams comprises an interesting

challenge as an alternative for their 1,4-fused counterparts, both from a synthetic and biological viewpoint, as very little information regarding this type of potential antibacterials and/or β-lactamase inhibitors can be found in the literature.



185 **186** **187** **22**

Scheme 57



188 Sanfetrinem **189** LK-157

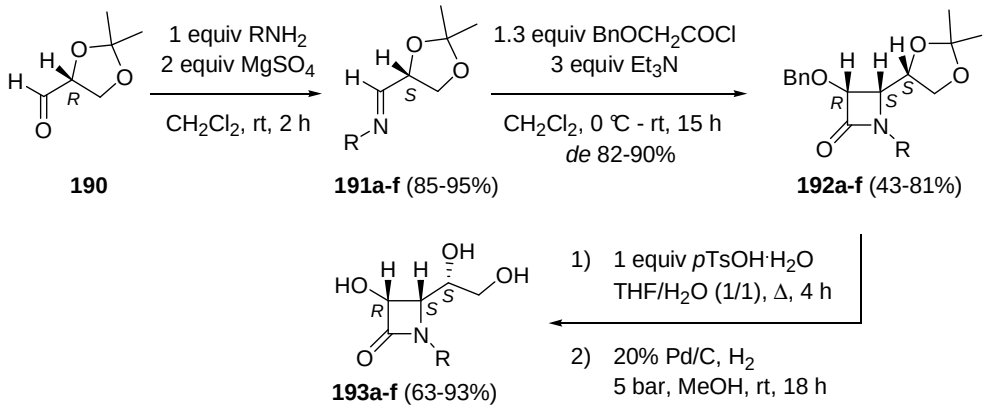
Figure 16

In order to evaluate the synthesis of 4-[2-(bromomethyl)aziridin-1-ylmethyl]-3-hydroxy-β-lactams **187** and their reactivity toward oxazepane-tethered tricyclic β-lactams **22**, the synthesis of 4-formyl-3-hydroxyazetidin-2-ones **185** was envisaged.

3.4.1 Synthesis of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams

The synthesis of the starting β-lactams **193a-f** was performed by means of a two-step literature procedure.[15,131] Thus, (*R*)-glyceraldehyde acetonide **190** was condensed with different primary amines in dichloromethane in the presence of $MgSO_4$ as drying agent, and the resulting chiral imines **191a-f** were used as substrates in the Staudinger synthesis of β-lactams **192a-f**. Therefore, imines **191a-f** were treated with benzyloxyacetyl chloride in dichloromethane in the presence of triethylamine to afford the corresponding optically active β-lactams **192a-f** in 43-81% yield and with high diastereomeric excess (Scheme 58, Table 14). The *cis*-diastereoselectivity could be deduced from the ^{1}H NMR spectra of β-lactams **192a-f**, as the coupling constants between the 3-H and 4-H protons on the β-lactam ring varied between 4.8 and 5.0 Hz (^{1}H NMR, $CDCl_3$), which correspond well with those reported in the literature for *cis*-β-lactams.[69] Subsequently, the latter azetidin-2-ones **192a-f** could be easily converted into the premised chiral 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193a-f** by consecutive hydrolysis in THF/H_2O (1/1) using one equiv of *p*-toluenesulfonic acid under reflux for four hours and hydrogenolysis of the benzyl ether moiety by using 20% (w/w) palladium on

activated carbon in methanol at room temperature for 18 hours, yielding β-lactams **193a-f** in 63-93% yield after column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30/1).



Scheme 58

Table 14. Synthesis of imines 191a-f, 3-benzyloxy-β-lactams 192a-f and 3-hydroxy-β-lactams 193a-f

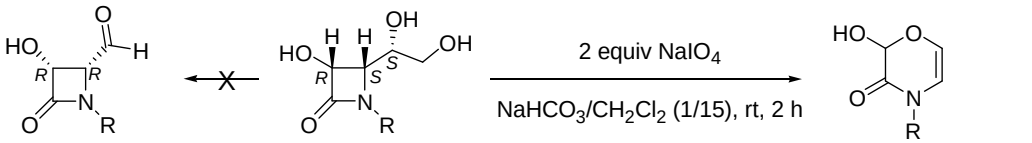
R	Compound 191 (yield)	Compound 192 (yield)[a]	*dr* (192)[b]	Compound 193 (yield)[a]
*i*Pr	**191a** (93%)	**192a** (81%)	91/9	**193a** (83%)
*i*Bu	**191b** (94%)	**192b** (50%)	92.5/7.5	**193b** (74%)
*n*Bu	**191c** (95%)	**192c** (43%)	92.5/7.5	**193c** (63%)
*c*Hex	**191d** (90%)	**192d** (65%)	93.5/6.5	**193d** (88%)
*n*Pr	**191e** (92%)	**192e** (70%)	95/5	**193e** (68%)
*i*Pent	**191f** (85%)	**192f** (50%)	94/6	**193f** (93%)

[a] After purification by column chromatography (SiO_2) or recrystallization. [b] Determined by ^{1}H NMR and GC.

3.4.2 Synthesis of 2-hydroxy-1,4-oxazin-3-ones

In the next stage, the reactivity of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193a-f** with regard to the oxidant sodium periodate ($NaIO_4$) was investigated as a potential entry into the synthetically useful class of 4-formyl-β-lactams,[15,131] which are known to be attractive synthons for further elaboration. Indeed, a significant interest has been focused on the synthesis and reactivity of 4-formyl-β-lactams as viable intermediates in (medicinal) organic synthesis, as illustrated by their use in the asymmetric synthesis of bi- and polycyclic β-lactams, different kinds of heterocycles, alkaloids, non proteinogenic α- and β-amino acids, amino sugars, taxoids, and complex natural products like biotin and sphingosines.[54,130e,132] In analogy, 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193a-f** were treated with two equiv of $NaIO_4$ in a two-phase system of saturated aqueous sodium bicarbonate and dichloromethane (1/15) at room temperature for two hours, but the expected 4-formyl-3-hydroxy-β-lactams **185** were not detected. Nonetheless, full and selective substrate conversion

occurred, and detailed spectroscopic analysis finally revealed the molecular structure of the obtained reaction products to be exclusively 2-hydroxy-1,4-oxazin-3-ones **194a-e**, which were isolated in good yields (69-94%, Scheme 59). Only in the case of an *n*-propyl unit as the *N*-substituent, a complex reaction mixture was obtained. This remarkable reactivity stands in sharp contrast with the known $NaIO_4$-mediated oxidation of 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams, which exclusively leads to the corresponding 4-formyl-β-lactam derivatives under the same reaction conditions.[15,131]



185 **193a-d,f**

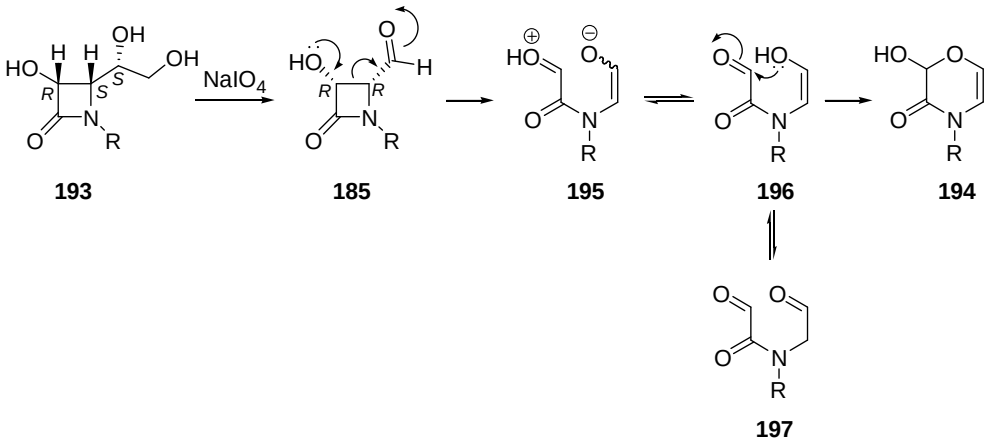
194a (R = *i*Pr, 69%)
194b (R = *i*Bu, 73%)
194c (R = *n*Bu, 75%)
194d (R = *c*Hex, 94%)
194e (R = *i*Pent, 70%)

Scheme 59

From a mechanistic point of view, the formation of the latter 2-hydroxy-1,4-oxazin-3-ones **194** can be rationalized considering the initial oxidation of the starting 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193** toward the corresponding 4-formyl-β-lactams **185**, which proved to be unstable under the given reaction conditions. Considering the presence of an electron-donating hydroxyl functionality at C-3, a subsequent C3-C4 bond cleavage in β-lactams **185** toward intermediates **195**/**196** is facilitated, whether or not periodate-promoted through activation of the aldehyde. Finally, ring closure of the latter intermediates **196** results in the selective formation of 2-hydroxy-1,4-oxazin-3-ones **194** (Scheme 60).

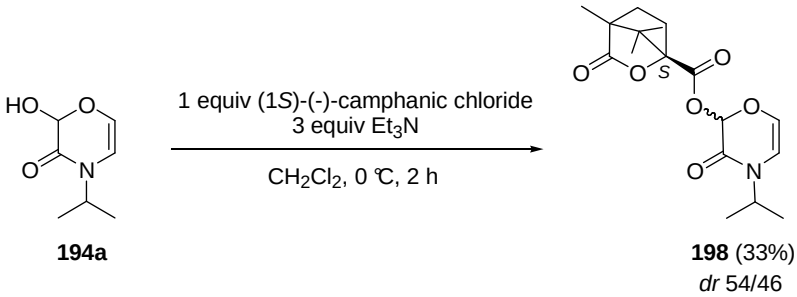
In an attempt to further assess the intrinsic reactivity of 4-formyl-β-lactams **185**, 3-benzyloxy-4-formyl-1-isopropyl-β-lactam[15] was subjected to hydrogenolysis (one bar H_2) as a possible entry into the corresponding 4-formyl-3-hydroxy-β-lactam **185a**. However, as could be anticipated, the substrate was overreduced to provide the 3-hydroxy-4-(hydroxymethyl)azetidin-2-one system instead. Subsequent Swern oxidation of the primary alcohol using oxalyl chloride, DMSO, and Et_3N gave rise to the exclusive formation of 2-hydroxy-1,4-oxazin-3-one **194a** and no traces of the desired 4-formyl-3-hydroxy-β-lactam **185a** could be found in the reaction mixture, pointing to the high intrinsic reactivity of 4-formyl-3-hydroxy-β-lactams **185** as probably the main driving force governing this new ring-expansion reaction. The presence of periodate is apparently not essential to effect this rearrangement, although it might have a propitious influence by coordinating to the carbonyl moiety

in intermediates **185**. As mentioned before, it should be stressed that this ring-expansion reaction is not compatible with β-lactam substrates bearing an alkoxy or phenoxy group at the C-3 position.



Scheme 60

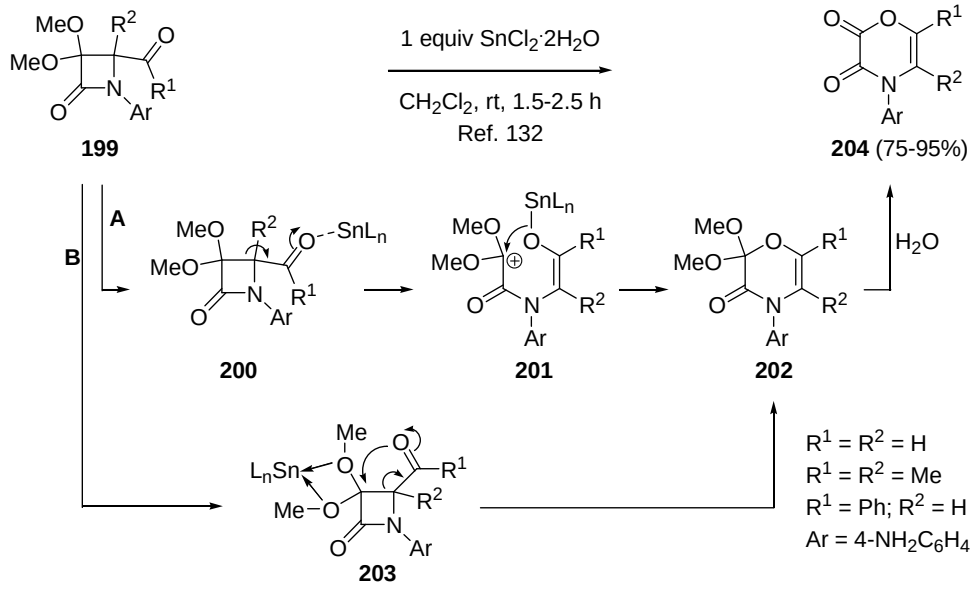
According to this reaction mechanism, the observed ring expansion of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193** toward 2-hydroxy-1,4-oxazin-3-ones **194** should proceed with loss of chirality, which was supported experimentally by measurement of the optical rotation of 4-cyclohexyl-2-hydroxy-1,4-oxazin-3-one **194d** (α_D = 0.0°, c = 1.22, CH_2Cl_2). By the way, the stereocenter of the hemiacetal is also subject to lability in terms of stereochemical integrity. In addition, esterification of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a** with one equiv of (1*S*)-(-)-camphanic chloride in CH_2Cl_2 at 0 °C for two hours in the presence of three equiv of triethylamine afforded the corresponding 2-camphanoyloxy-4-isopropyl-1,4-oxazin-3-one **198** as a mixture of two diastereoisomers in a ratio of 54/46 (based on ^{1}H NMR and GC analysis), pointing to the racemic character of 2-hydroxy-1,4-oxazin-3-ones **194** (Scheme 61).



Scheme 61

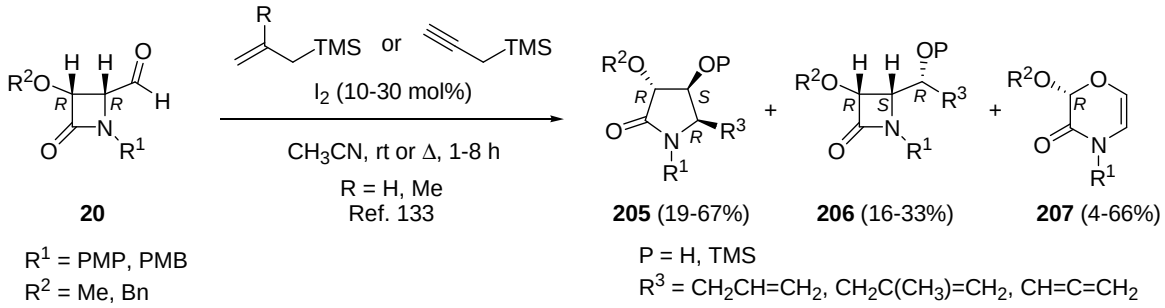
Albeit starting from different substrates and triggered by different reaction conditions, two other approaches involving ring enlargement of appropriate β-lactam derivatives toward morpholinone scaffolds have been reported in the literature. The first method involves a $SnCl_2 \cdot 2H_2O$-promoted

carbenium ion rearrangement of 4-acyl-β-lactams **199** bearing an acetal functionality at the C-3 carbon, yielding the corresponding 1,4-oxazin-2,3-diones **204** in good yields (75-95%).[133] Two possible reaction pathways, involving initial coordination of tin to the carbonyl moiety in β-lactams **200** followed by a C3-C4 bond cleavage due to the enhanced reactivity of the double bond and the ability of the acetal functionality to stabilize the emerging carbenium ion in intermediates **201** (Method A) and dicoordination of tin at the acetal functionality in β-lactams **199** to yield intermediates **203**, which subsequently evolve through a concerted or stepwise six-electron rearrangement (Method B), may account for the observed reactivity (Scheme 62).[133]



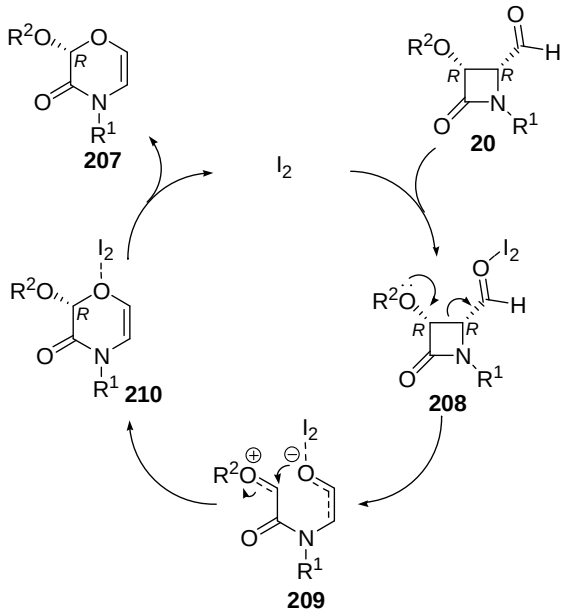
Scheme 62

The second approach comprises a single-step molecular iodine-catalyzed rearrangement of 3-alkoxy-4-formyl-β-lactams **20** into monocyclic γ-lactams **205** upon treatment with allylic and propargylic trimethylsilanes, inevitable leading to 2-alkoxy-1,4-oxazin-3-ones **207** as minor constituents (4-9%), except for the reaction of 4-formyl-3-methoxy-1-(4-methoxybenzyl)azetidin-2-one **20** (R^1 = PMB, R^2 = Me) with allyltrimethylsilane (R = H) which gave rise to the corresponding morpholinone **207** in 66% yield (Scheme 63).[134]



Scheme 63

Although a similar reaction mechanism was proposed (Scheme 64), the achiral outcome observed in the above-described ring expansion of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193** toward the corresponding 2-hydroxy-1,4-oxazin-3-ones **194** contradicts with the reported formation of optically pure 2-alkoxy-1,4-oxazin-3-ones **207** as minor constituents in the molecular iodine-catalyzed rearrangement of chiral 3-alkoxy-4-formyl-β-lactams **20** (Scheme 63).[134] In the latter case, although not discussed in the original paper, the chiral outcome could be explained by the partial carbenium ion character of the Zwitterionic intermediates **209** controlling the subsequent intramolecular nucleophilic attack to occur from the same side from which the initial β-lactam C3-C4 bond was cleaved (Scheme 64). A similar stereochemical control ("memory effect") has been described in the literature for reactions of carbenium ions in which the latter "remember" how they were formed before taking part in the second step.[135] In our case, however, the hydroxyl group in intermediates **195**, formed after C3-C4 bond cleavage of the intermediate 4-formyl-β-lactams **185**, can induce prototropy toward intermediates **196**. Since these intermediates **196** possess a planar configuration due the presence of a polycentric molecular orbital (PCMO) spread over the entire molecule, there is no stereocontrol during the subsequent intramolecular nucleophilic attack, resulting in the formation of racemic 2-hydroxy-1,4-oxazin-3-ones **194** (Scheme 60).



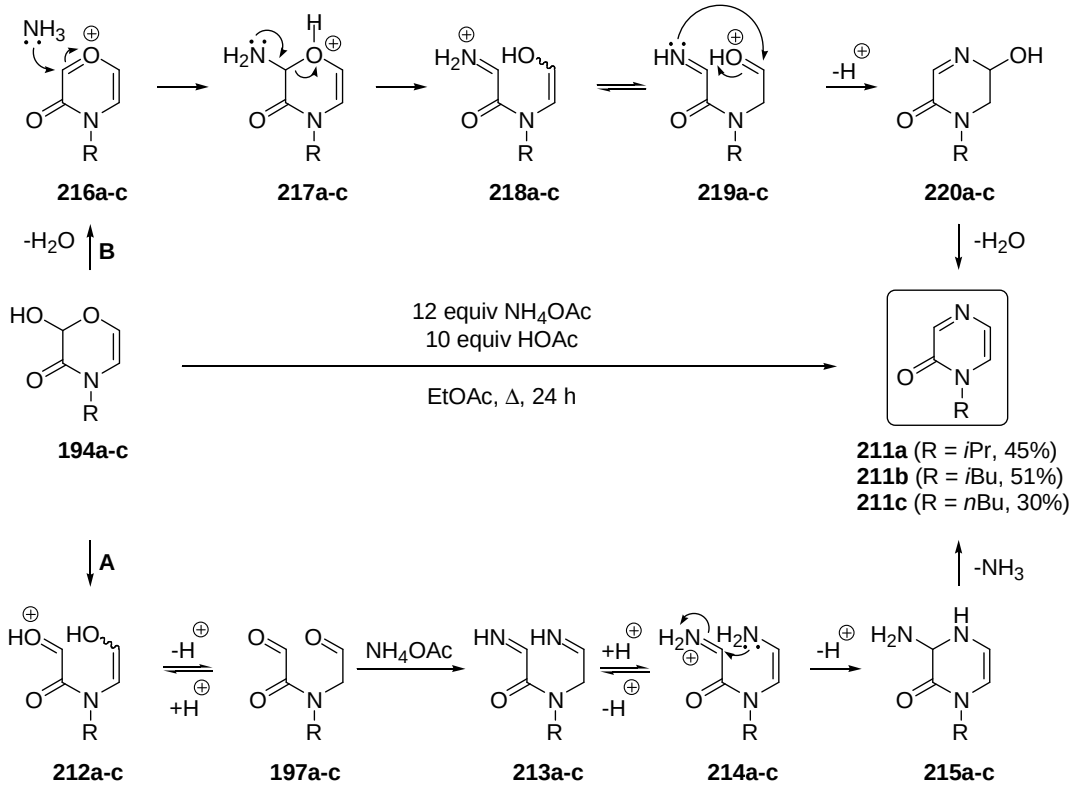
Scheme 64

Although a less expensive, achiral approach toward 2-hydroxy-1,4-oxazin-3-ones **194** starting from the oxidation of the commercially available racemic solketal[136] can be developed applying the same reaction sequence as mentioned above, the use of optically pure (*R*)-glyceraldehyde acetonide **190** provided some additional mechanistic insights into this unexpected transformation.

Whereas in these two reported routes 4-acyl- and 4-formyl-β-lactams **199** and **20** have been prepared as the substrates to perform the ring enlargement, in the above-described ring enlargement a different type of starting compounds, i.e., 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **193**, served as substrates for the ring rearrangement.

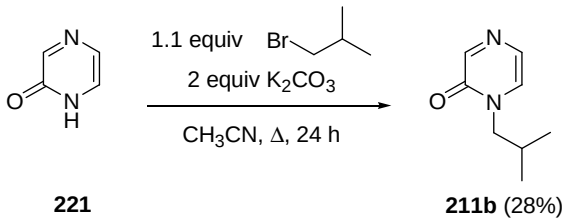
Subsequently, with the intention to support the proposed mechanistic rationale, the synthesis of the aza-analogues of the former 2-hydroxy-1,4-oxazin-3-ones **194** was envisaged. Thus, treatment of the latter compounds **194a-c** with 12 equiv of NH_4OAc and ten equiv of HOAc in ethyl acetate furnished the corresponding 1*H*-pyrazin-2-ones **211a-c** in 30-51% yield after a reflux period of 24 hours (Scheme 65, the synthesis of 1*H*-pyrazin-2-ones **211b,c** was performed by a colleague[137]).[138] This transformation suggests a reaction mechanism in which acetic acid-mediated hydrolysis of the hemi-acetal in 2-hydroxy-1,4-oxazin-3-ones **194** gives rise to the selective formation of dialdehydes **197**, which are subsequently transformed into the corresponding diimines **213** and enamino imines **214** through the action of ammonium acetate. Finally, ring closure followed by the elimination of ammonia results in the selective formation of 1*H*-pyrazin-2-ones **211** (Scheme 65, Route A). However, alternative reaction pathways should not be excluded. For example, initial elimination of water followed by the addition of ammonia can account for the formation of 2-amino-1,4-oxazin-3-

ones **217**, which subsequently undergo an acetic acid-mediated ring opening toward the corresponding intermediates **218**/**219**. Finally, ring closure and elimination of water give rise to the formation of 1*H*-pyrazin-2-ones **211** (Scheme 65, Route B).



Scheme 65

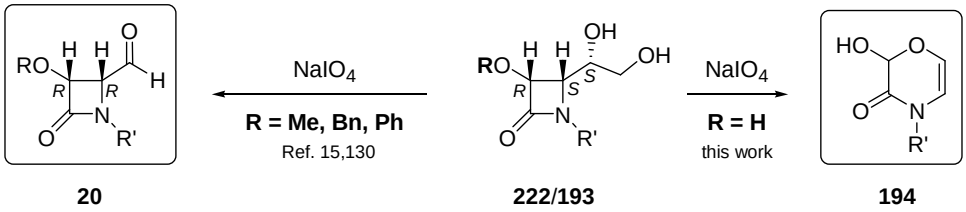
In order to confirm the formation of 1*H*-pyrazin-2-ones **211**, an independent synthesis was performed. Alkylation of 1*H*-pyrazin-2-one **221** by means of 1.1 equiv of isobutyl bromide and two equiv of potassium carbonate in acetonitrile under reflux afforded the expected 1-isobutyl-1*H*-pyrazin-2-one **211b** in 28% yield (Scheme 66),[139] which was identical to the compound obtained from 1-isobutyl-2-hydroxy-1,4-oxazin-3-one **194b** (Scheme 65).



Scheme 66

3.4.2.1 Theoretical rationalization

As mentioned before, the above-described four- to six-membered ring-expansion reaction is only compatible for substrates bearing a hydroxyl group at the C-3 position, and not for substrates bearing a alkoxy or phenoxy group, as 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams **222** (R = Me, Bn, Ph) are known to be oxidized to the corresponding 4-formyl-β-lactam derivatives **20** under the same reaction conditions without subsequent rearrangement into six-membered heterocycles (Scheme 67).[15,131] In order to shed light on this remarkable difference in reactivity and to provide additional insights into the mechanism (Scheme 60) and the factors governing this new ring-expansion reaction, Density Functional Theory calculations were conducted by colleagues at the Center for Molecular Modeling, Ghent University.



Scheme 67

The first step in the proposed transformation of β-lactams **185** toward oxazin-3-ones **194** comprises the ring opening of the β-lactam nucleus (Scheme 60, R = Me). This ring opening could give rise to an unstable zwitterionic species **195**, which is easily converted to intermediate **196** by proton transfer. However, a concerted reaction mechanism in which β-lactam **185** is directly converted to intermediate **196** was found more plausible. Indeed, the Gibbs free energy of activation ($\Delta G^{\ddagger}$) for the β-lactam ring opening involving a simultaneous proton transfer is 35.6 kJ/mol lower in energy than that for the formation of the zwitterionic intermediate **195** (Figure 17, **TS(185-196)** and **TS(185-195)**, respectively). The subsequent ring closure of intermediate **196** toward oxazin-3-one **194**, which also involves a simultaneous proton transfer, has a relatively high Gibbs free energy of activation ($\Delta G^{\ddagger}$ = 145.6 kJ/mol), indicating that this model might be inappropriate to represent the system. Finally, a concerted reaction mechanism in which β-lactam **185** is directly converted to oxazin-3-one **194** by simultaneous ring opening and ring closure was considered. The Gibbs free energy of activation for this conversion was found to be higher than that for the conversion of β-lactam **185** to intermediate **196** or zwitterionic intermediate **195** and therefore seems very unlikely.

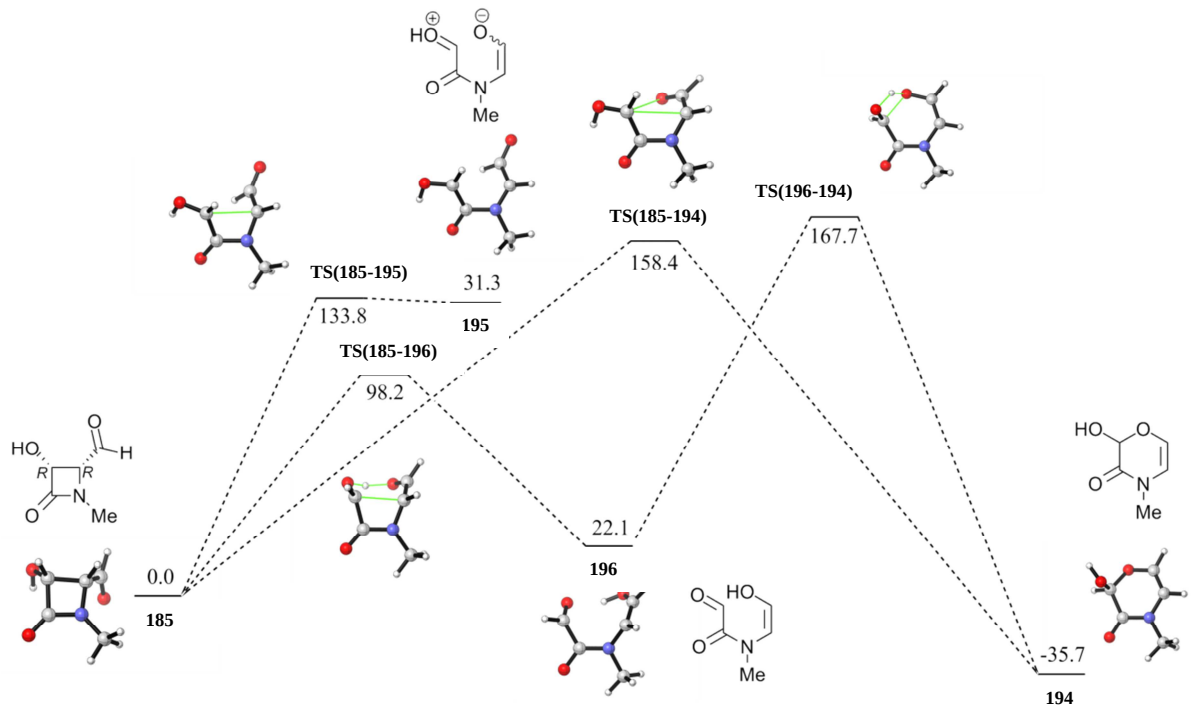


Figure 17. Gibbs free energy profile for the ring transformation of 4-formyl-3-hydroxy-β-lactams 185 to 2-hydroxy-1,4-oxazin-3-ones 194, without assistance of a second β-lactam (M06-2X/6-31+G(d,p)//B3LYP/6-31+G(d,p), ε=8.93; free energies in kJ/mol at 298K and 1 atm)

This ring transformation is not observed for β-lactam substrates bearing an alkoxy or phenoxy group instead of a hydroxyl group at the C-3 position. For comparative purposes, the hypothetical ring transformation of 4-formyl-3-methoxy-β-lactam **20** to 2-methoxy-1,4-oxazin-3-one **224** was investigated as well (Figure 18). The reaction mechanism with the ring opening of the starting β-lactam **20** to an unstable zwitterionic species **223** has a free energy of activation of 138.4 kJ/mol, which is higher than that for compound **185** (Figure 17). Moreover, if this relatively high Gibbs free energy of activation would be overcome, the formed very unstable species **223** will readily go back to β-lactam **20** instead reacting further to the oxazin-3-one **224** ($\Delta G^{\ddagger}$ = 0.9 kJ/mol and 105.4 kJ/mol, respectively). Furthermore, the concerted reaction mechanism in which β-lactam **20** is directly converted to oxazin-3-one **224** has a high Gibbs free energy of activation ($\Delta G^{\ddagger}$ = 167.0 kJ/mol).

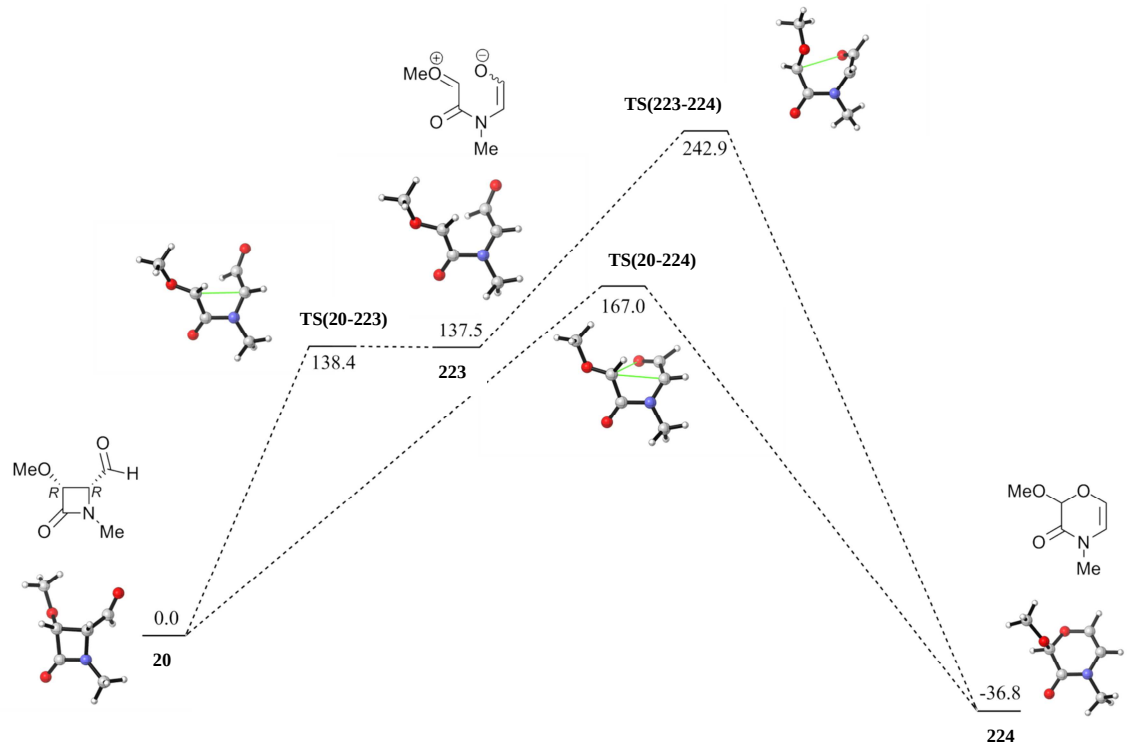


Figure 18. Gibbs free energy profile for the ring transformation of 4-formyl-3-methoxy-β-lactams 20 to 2-methoxy-1,4-oxazin-3-ones 224 (M06-2X/6-31+G(d,p)//B3LYP/6-31+G(d,p), ε=8.93; free energies in kJ/mol at 298K and 1 atm)

To make the model more realistic, a second β-lactam was added to the system. All barriers were brought down by β-lactam assistance (Figure 19). In case of proton transfer, the hydroxyl group of the second β-lactam acts as a proton conduit, accepting the proton from the first β-lactam and donating its own. If no proton transfer takes place, the second β-lactam stabilizes transition states and reactants due to intermolecular H-bonds. The reaction mechanism proposed for compound **185**, ring opening to intermediate **196** and subsequent ring closure toward oxazin-3-one **194** with simultaneous proton transfer in both steps, was found to be most plausible. Indeed, the Gibbs free energy of activation for the β-lactam ring opening with a simultaneous proton transfer is lower in energy than that for the ring opening with formation of the zwitterionic intermediate **195** and for the simultaneous ring opening and ring closure ($\Delta G^{\ddagger}$ = 91.1, 120.1 and 140.3 kJ/mol for **TS(185-196)**+B, **TS(185-195)**+B and **TS(185-194)**+B, respectively). Moreover, the Gibbs free energy of activation for the subsequent ring closure of intermediate **196** with simultaneous proton transfer was brought down significantly ($\Delta G^{\ddagger}$ = 145.6 kJ/mol for **TS(196-194)** and 84.1 kJ/mol for **TS(196-194)**+B, Figure 17 and Figure 19, respectively), demonstrating the need for the assistance of a second β-lactam for the reaction to proceed.

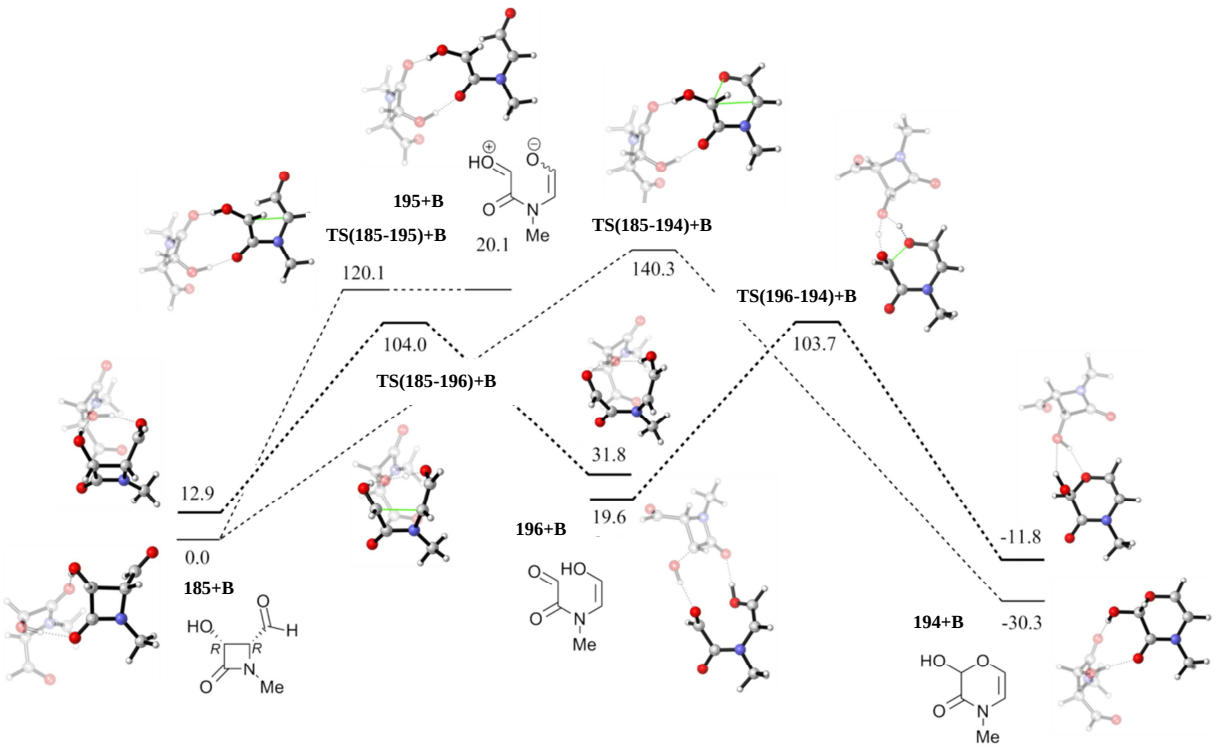


Figure 19. Gibbs free energy profile for the ring transformation of 4-formyl-3-hydroxy-β-lactams 185 to 2-hydroxy-1,4-oxazin-3-ones 194, with assistance of a second β-lactam (M06-2X/6-31+G(d,p)//B3LYP/6-31+G(d,p), ε=8.93; free energies in kJ/mol at 298K and 1 atm)

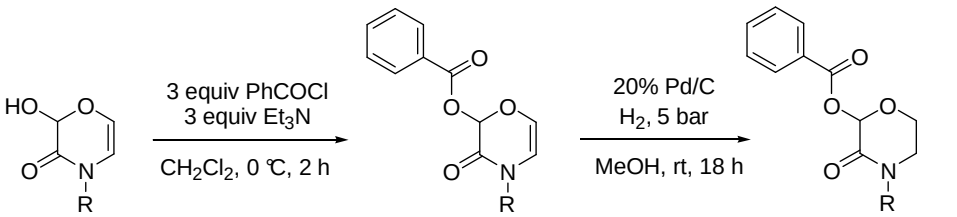
Thus, the transformation of 4-formyl-3-hydroxy-β-lactams **185** into 2-hydroxy-1,4-oxazin-3-ones **194** is facilitated by the proton transfer of the hydroxyl group and the assistance of the hydroxyl group of a second β-lactam. Both mechanisms are not feasible for β-lactam substrates bearing an alkoxy or phenoxy group.

2-Hydroxy-1,4-oxazin-3-ones **194** exhibit a number of interesting structural characteristics, making them suitable substrates for further elaboration. For example, the presence of a double bond in the oxazin-3-one backbone provides an entry into highly substituted monocyclic morpholinone derivatives upon treatment with electrophilic species. Additionally, the double bond can be deployed in intermolecular cycloaddition reactions leading to bicyclic morpholinones, and the free hydroxyl group can be used in coupling reactions with biologically relevant pharmacophores.

In order to show the capacity of the above-described method to prepare a broad array of oxazin-3-ones and morpholin-3-ones bearing chemical diversity, several functionalities in 2-hydroxy-1,4-oxazin-3-ones **194** were selectively manipulated, which will be discussed in the next section.

3.4.3 Reactivity study of 2-hydroxy-1,4-oxazin-3-ones

In a first approach, the hydroxyl group in the latter heterocycles **194a-d** was protected upon treatment with three equiv of benzoylchloride in dichloromethane in the presence of three equiv of triethylamine, furnishing the corresponding 2-benzoyloxy-1,4-oxazin-3-ones **225a-d** after two hours at 0 °C (Scheme 68, Table 15, the synthesis of 2-benzoyloxy-1,4-oxazin-3-ones **225b,c** was performed by a colleague[137]). As morpholine chemistry is of significant importance because of the occurence of these scaffolds in a large number of biologically active compounds useful in different therapeutical areas,[140] the search for new, functionalized morpholine derivatives remains a relevant issue in medicinal chemistry. In particular, morpholin-3-one derivatives[141] have attracted considerable interest owing to their biological and pharmacological activity, as they comprise key features in HIV-protease inhibitors,[142] non-peptide ligands with high affinity and selectivity for tachykinin receptors,[143] cornea permeable calpain inhibitors exhibiting anticataract properties,[144] A549 lung cancer cell inhibitors,[145] and potassium channel openers useful in the treatment of urinary incontinence (Figure 20).[146] In that respect, the attention was turned to the catalytic hydrogenation of the double bond in 2-benzoyloxy-1,4-oxazin-3-ones **225a-d** to provide an entry to the morpholin-3-one framework. Thus, the latter compounds **225a-d** were converted into the corresponding 2-benzoyloxymorpholin-3-ones **226a-d** in high yields (69-89%) and purity upon treatment with 20% (w/w) palladium on activated carbon in methanol at room temperature for 18 hours while applying five bar of hydrogen gas (Scheme 68, Table 15, the synthesis of 2-benzoyloxymorpholin-3-ones **226b,c** was performed by a colleague[137]).



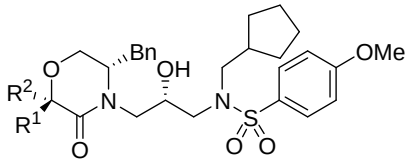
194a-d **225a-d** (34-93%) **226a-d** (69-89%)

Scheme 68

Table 15. Synthesis of 2-benzoyloxy-1,4-oxazin-3-ones 225a-d and 2-benzoyloxymorpholin-3-ones 226a-d

R	Compound 225 (yield)[a]	Compound 226 (yield)[a]
*i*Pr	**225a** (45%)	**226a** (69%)
*i*Bu	**225b** (64%)	**226b** (79%)
*n*Bu	**225c** (93%)	**226c** (82%)
*c*Hex	**225d** (34%)	**226d** (89%)

[a] After purification by column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30/1).

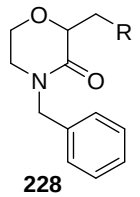


227

HIV-protease inhibitors

R^1 = allyl; R^2 = H

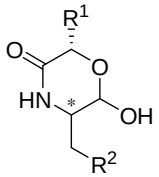
$R^1R^2 = (CH_2)_5$



228

non-peptide ligands for tachykinin receptors

R = C_6H_5, 3-indolyl

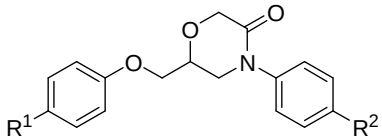


229

cornea permeable calpain inhibitors

R^1 = *i*Bu, *i*Pr, Bn

R^2 = Ph, Bn, 2-naphthyl, 4-HOC_6H_5, 4-$MeOC_6H_5$, 4-$BuOC_6H_5$

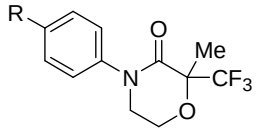


230

A549 lung cancer cell inhibitors

R^1 = Cl, NO_2

R^2 = H, Cl, OMe



231

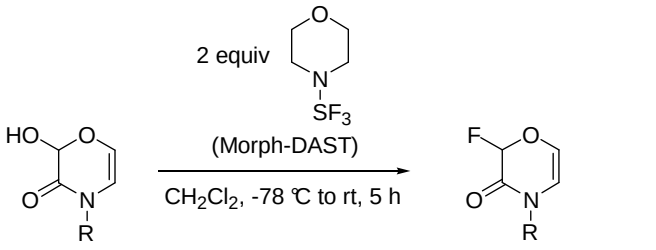
potassium channel openers

R = COC_6H_5, CF_3, $SO_2N(CH_3)_2$

Figure 20

As mentioned before, the incorporation of fluorine in organic compounds can tune their physicochemical characteristics due to the unique physical, chemical and biological properties of fluorine as a substituent.[92] In that respect, it became of interest to verify whether the use of appropriate fluorinating agents could introduce fluorine in a site-selective manner in the above synthesized heterocyclic compounds. In a first attempt, selective deoxyfluorination of 2-hydroxy-1,4-oxazin-3-ones **194a-d** was effected in the presence of two equiv of Morph-DAST in dichloromethane, resulting in a complete conversion toward 2-fluoro-1,4-oxazin-3-ones **232a-d** in 78-94% yield (Scheme 69, the synthesis of 2-fluoro-1,4-oxazin-3-ones **232b,c** was performed by a colleague[137]). The presence of a monofluorinated carbon center was unambiguously assigned based on the coupling constants between the proton and the fluoro atom at C-2, as the observed *J*-values of 52.7-53.7 Hz (^{1}H NMR, ^{19}F NMR, $CDCl_3$) correspond well with those reported in the literature (50-57 Hz, ^{1}H

NMR, $CDCl_3$).[147] Also, the ^{13}C NMR spectra revealed a coupling between the carbon and the fluorine at the C2-position, characterized by *J*-values between 233.1 and 234.2 Hz (^{13}C NMR, $CDCl_3$). These results are in good accordance with ^{13}C NMR data ($CDCl_3$) reported in the literature for compounds bearing similar structural subunits.[147b,148]

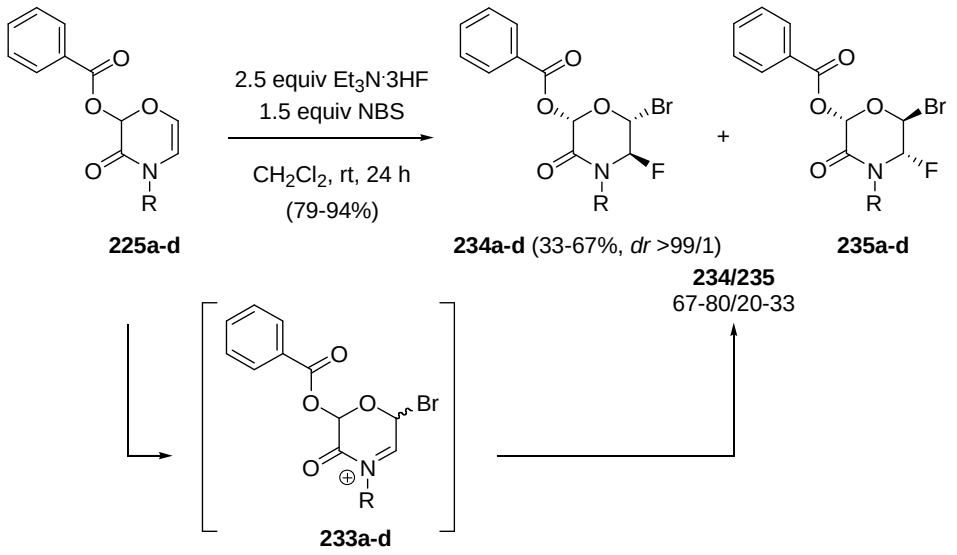


194a-d

232a (R = *i*Pr, 87%)
232b (R = *i*Bu, 78%)
232c (R = *n*Bu, 94%)
232d (R = *c*Hex, 90%)

Scheme 69

In another strategy to introduce fluorine, 2-benzoyloxy-1,4-oxazin-3-ones **225a-d** were smoothly bromofluorinated with 2.5 equiv of triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and 1.5 equiv of *N*-bromosuccinimide (NBS) in dichloromethane at room temperature for 24 hours, resulting in the regiospecific formation of a diastereomeric mixture of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **234a-d** and **235a-d** through *anti* addition across the C-C double bond (**234**/**235** = 67-80/20-33, Scheme 70, Table 16, the synthesis of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **234b,c** and **235b,c** was performed by a colleague[137]).



225a-d

234a-d (33-67%, *dr* >99/1)

235a-d

233a-d

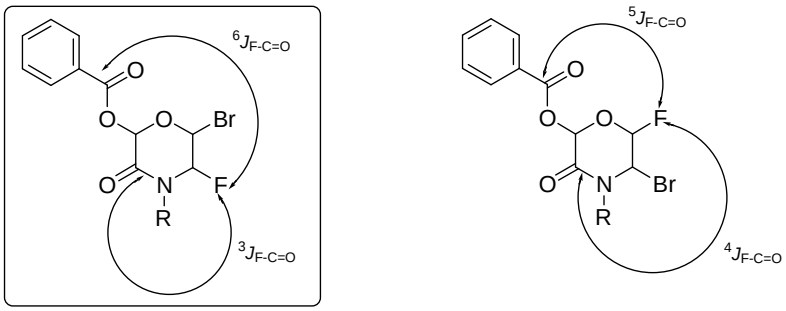
Scheme 70

Table 16. Synthesis of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones 234a-d and 235a-d

R	Ratio 234/235[a]	Compound 234 (yield)[b]
*i*Pr	75/25	**234a** (63%)
*i*Bu	80/20	**234b** (33%)
*n*Bu	80/20	**234c** (42%)
*c*Hex	67/33	**234d** (67%)

[a] Based on ^{1}H NMR and/or GC of the crude reaction mixture. [b] After purification by column chromatography (SiO_2) or recrystallization from EtOAc/hexane (30/1).

Detailed spectroscopic analysis of the obtained reaction mixtures revealed that the Br^+-initiated electrophilic addition across the double bond of 2-benzoyloxy-1,4-oxazin-3-ones **225** proceeded with complete regioselectivity, which was determined based on the experimental coupling pattern in the ^{13}C NMR spectra (Scheme 71), as one carbonyl carbon appeared as a singlet while the other clearly coupled with fluorine and appeared as a doublet with a coupling constant between 3.4 Hz and 3.5 Hz (^{13}C NMR, $CDCl_3$). Since these values are in good agreement with $^{3}J_{F\text{-}C=O}$-coupling constants of 0-3.4 Hz (^{13}C NMR, $CDCl_3$) reported in the literature for C(=O)NCHF-systems,[149] and no $^{4}J_{F\text{-}C=O}$-, $^{5}J_{F\text{-}C=O}$- and $^{6}J_{F\text{-}C=O}$-coupling pattern is described for compounds bearing analogous structural subunits,[149a-c,150] the regiospecificity was unambiguously assigned (Scheme 71), pointing to the *N*-acyliminium ion character of the intermediates **233** during the bromofluorination.



234/235 **236**

Scheme 71

With the intention to provide additional experimental evidence for the above-mentioned regiospecificity and to exclude the formation of regioisomers **236**, nucleophilic halide substitution *via* *N*-acyliminium intermediates through treatment of the diastereomeric reaction mixtures with external nucleophiles was envisaged. This reaction would involve the dislocation of the nitrogen lone pair, followed by halide dissociation leading to the formation of *N*-acyliminium ions, which are subsequently susceptible to intermolecular trapping by the additional nucleophile resulting in the

formation of new 2,5,6-trisubstituted 1,4-oxazin-3-one derivatives. As (cyclic) brominated amides are known to readily undergo substitution reactions via *N*-acyliminium intermediates[151] and fluoride is generally recognized as a poor leaving group, nucleophilic substitution *via* *N*-acyliminium ions is expected to occur only for 2-benzoyloxy-5-bromo-6-fluoromorpholin-3-ones **236**. Following this rationale, the diastereomeric reaction mixture obtained after bromofluorination of 2-benzoyloxy-1,4-oxazin-3-one **225a** was treated with potassium cyanide under different reaction conditions (Table 17, Entry 1-7). However, even in the presence of a silver salt, all attempts resulted in recovery of the starting material or formation of complex reaction mixtures in which no typical signals for the expected substitution products could be detected.

Alternatively, in order to accomplish the afore-mentioned goal, a bromine-lithium exchange reaction[152] was contemplated upon treatment with *n*BuLi and subsequent quenching with saturated aqueous NH_4Cl, again resulting in the formation of a complex reaction mixture (Table 17, Entry 8).

Finally, according to a literature procedure concerning the Zn-mediated radical dehalogenation of organic compounds,[153] the diastereomeric reaction mixture obtained after bromofluorination of 2-benzoyloxy-1,4-oxazin-3-one **225a** was treated with two equiv of Zn in acetic acid at room temperature for 22 hours, unfortunately resulting in both debromination and defluorination toward 2-benzoyloxy-1,4-oxazin-3-one **225a** in 80% yield (Table 17, Entry 9).

Table 17. Attempted conversion of the diastereomeric reaction mixture obtained after bromofluorination of 2-benzoyloxy-1,4-oxazin-3-one 225a

Entry	Substrate	Reaction conditions	Result[a]
1	**234a**/**235a** or **236a**	2 equiv KCN, CH_3CN, rt, 18 h	no reaction
2	**234a**/**235a** or **236a**	2 equiv KCN, CH_3CN, Δ, 6 h	no reaction
3	**234a**/**235a** or **236a**	2 equiv KCN, DMSO, 80 °C, 2 h	complex mixture
4	**234a**/**235a** or **236a**	1) 5 equiv Ag_2CO_3, DMSO, rt, 1 h 2) 2 equiv KCN, DMSO, rt, 18 h	no reaction
5	**234a**/**235a** or **236a**	1) 5 equiv Ag_2CO_3, DMSO, 60 °C, 1 h 2) 2 equiv KCN, DMSO, 60 °C, 3 h	complex mixture
6	**234a**/**235a** or **236a**	1 equiv $AgBF_4$, 3 equiv KCN, DMSO, rt, 18 h	no reaction
7	**234a**/**235a** or **236a**	1 equiv $AgBF_4$, 3 equiv KCN, DMSO, 60 °C, 2 h	complex mixture
8	**234a**/**235a** or **236a**	1) 1 equiv *n*BuLi, Et_2O, -78 °C, 1 h 2) sat. aq. NH_4Cl, Et_2O, rt, 20 h	complex mixture
9	**234a**/**235a** or **236a**	2 equiv Zn, HOAc, rt, 22 h	1,4-oxazin-3-one **225a**

[a] Based on ^1H NMR analysis of the crude reaction mixture.

Intensive efforts were thus devoted to experimentally confirm the assigned regiospecificity, but no conclusive support could be achieved without further investigation. Furthermore, no irrefutable proof could be obtained concerning the diastereoselectivity of the bromofluorination reaction based on spectral analysis of the obtained reaction products (Scheme 70). Finally, the full configuration of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **234** was established by single crystal X-ray analysis of 2-benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one **234a** (Figure 21), providing irrefutable proof for the formation of *cis*-2-benzoyloxy-6-bromomorpholin-3-ones **234** as the major diastereoisomers.

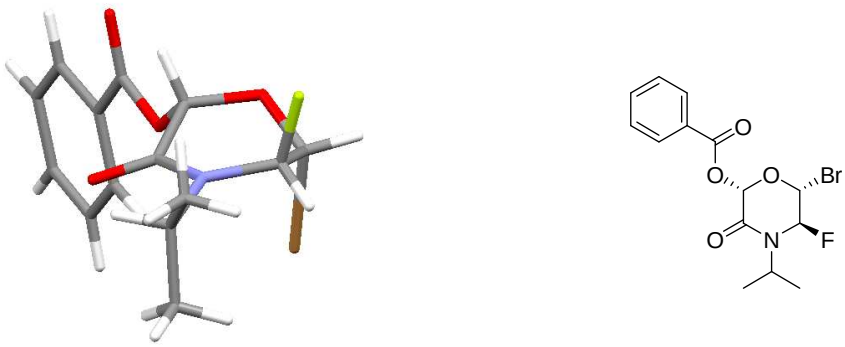
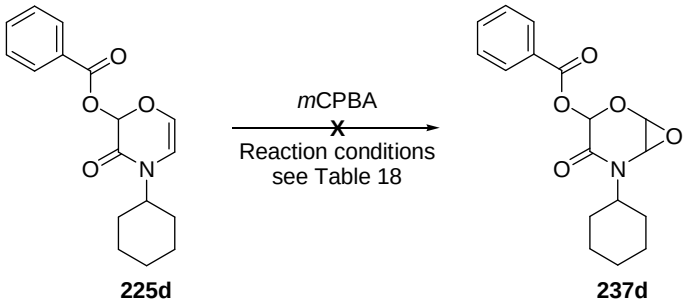


Figure 21. X-Ray crystallographic analysis of compound 234a

On the other hand, a direct epoxidation of the double bond in 2-benzoyloxy-1,4-oxazin-3-one **225d** with 3-chloroperbenzoic acid (*m*CPBA) was examined as a possible entry into morpholinone-fused bicyclic systems. For this purpose, upon treatment with 1.05 equiv of *m*CPBA in CH_2Cl_2 at room temperature or under reflux, either the starting 1,4-oxazin-3-one **225d** or complex reaction mixtures were obtained (Scheme 72, Table 18), probably because multiple side reactions, such as incomplete epoxidation and oxidation of the acetal moiety[154] can occur.



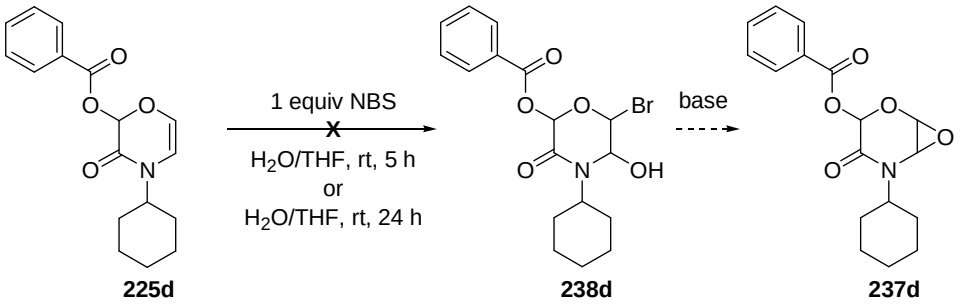
Scheme 72

Table 18. Reaction of 2-benzoyloxy-4-cyclohexyl-1,4-oxazin-3-one 225d with *m*CPBA

Reaction conditions	Result[a]
1.05 equiv *m*CPBA, CH_2Cl_2, rt, 18 h	no reaction
1.05 equiv *m*CPBA, CH_2Cl_2, rt, 48 h	no reaction
1.05 equiv *m*CPBA, CH_2Cl_2, Δ, 2 h	no reaction
1.05 equiv *m*CPBA, CH_2Cl_2, Δ, 7 h	complex mixture

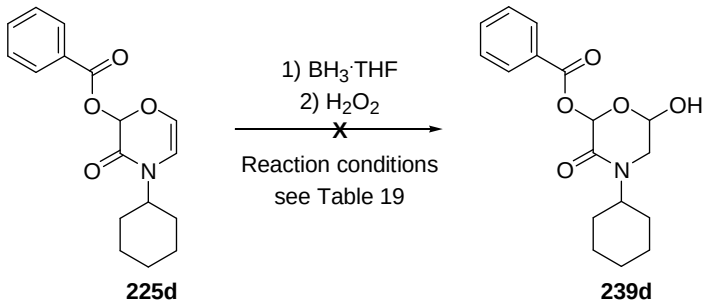
[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

After this unsuccessfull attempt, an indirect expoxidation of the double bond by preparation of the corresponding halohydrins as valuable precursors was contemplated. However, all attempts to selectively prepare bromohydrin **238d** by treatment of 1,4-oxazin-3-one **225d** with 1 equiv of *N*-bromosuccinimide (NBS) in water/THF (1/1) gave complex reaction mixtures (Scheme 73).



Scheme 73

A final objective of the present study comprised the transformation of 2-benzoyloxy-1,4-oxazin-3-ones **225** toward the corresponding 6-hydroxymorpholin-3-ones by a BH_3·THF-mediated hydroboration-oxidation protocol. Unfortunately, all attempts to perform a net addition of water at the double bond of 2-benzoyloxy-4-cyclohexyl-1,4-oxazin-3-one **225d** applying this methodology resulted in complete recovery of the starting oxazin-3-one **225d** or the formation of rather complex reaction mixtures (Scheme 74, Table 19), which can probably be attributed to the propensity of borane in THF to induce the reductive cleavage of acetals.[155]



225d **239d**

Scheme 74

Table 19. Hydroboration of 2-benzoyloxy-4-cyclohexyl-1,4-oxazin-3-one 225d

Reaction conditions	Result[a]
1) 1.1 equiv BH_3·THF (1M), THF, rt, 18 h 2) 1 equiv NaOH (3M), 3 equiv H_2O_2 (30%), THF, rt, 4 h	no reaction
1) 1.1 equiv BH_3·THF (1M), THF, rt, 1 h to Δ, 5 h 2) 2 equiv NaOH (3M), 3 equiv H_2O_2 (30%), THF, rt, 1 h to Δ, 3 h	complex mixture

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

3.4.4 Conclusions

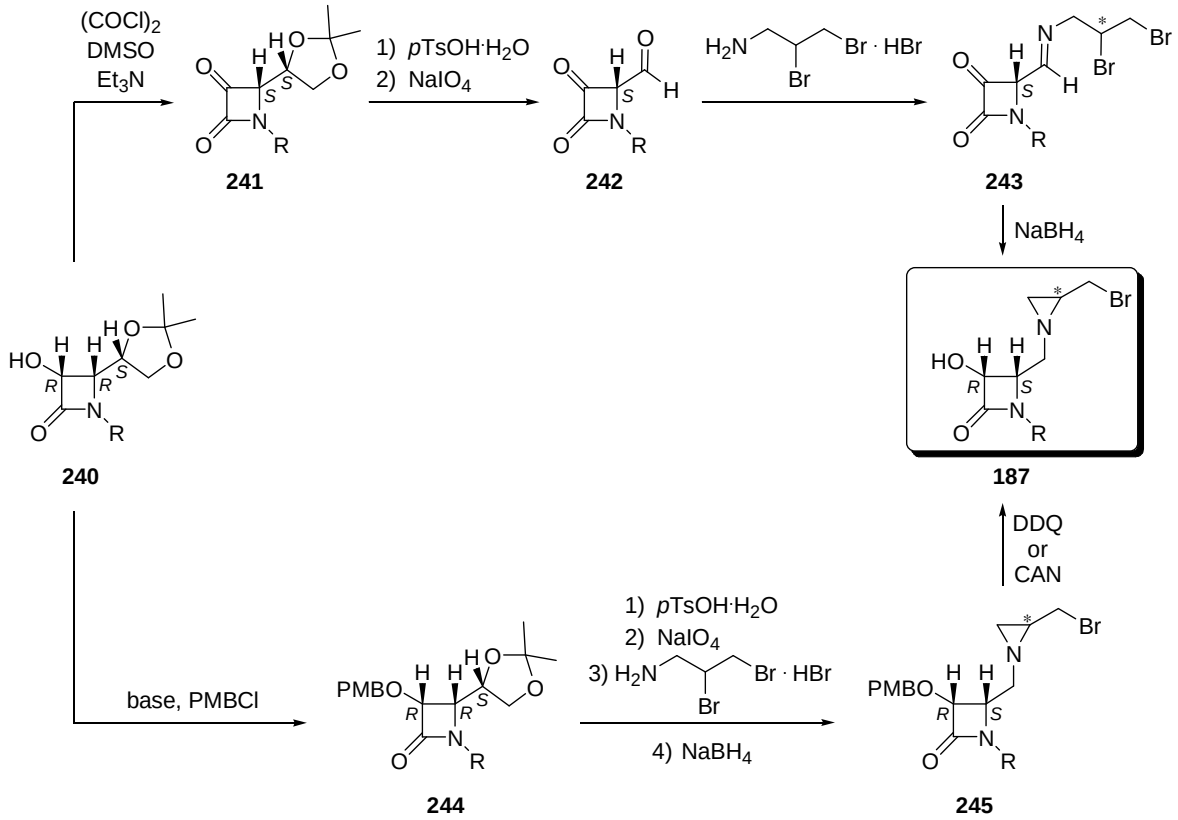
In conclusion, 2-hydroxy-1,4-oxazin-3-ones were prepared through ring transformation of the corresponding 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams involving an unexpected C3-C4 bond cleavage of the β-lactam nucleus in the intermediate 4-formyl-3-hydroxy-β-lactams, followed by a ring expansion. This peculiar transformation stands in sharp contrast with the known $NaIO_4$-mediated oxidation of 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams, which exclusively leads to the corresponding 4-formyl-β-lactams without a subsequent ring enlargement. Furthermore, the synthetic applicability of these novel oxazin-3-one derivatives was demonstrated by means of their transformation into the classes of substituted oxazin-3-ones, morpholin-3-ones, and pyrazinones. This comprises the first full and selective conversion of β-lactam scaffolds into 1,4-oxazin-3-ones in high yields and purity.

3.4.5 Perspectives

From the above-described unexpected ring-expanion reaction, it is clear that, in order to achieve the selective synthesis of 4-[2-(bromomethyl)aziridin-1-ylmethyl]-3-hydroxy-β-lactams **187** (Scheme 57), the elaboration of alternative hydroxyl protecting groups is highly recommended.

In the literature, the synthesis of azetidin-2,3-diones by Swern oxidation of the corresponding 3-hydroxy-β-lactams is known.[156] In this way, 3-hydroxy-4-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones **240**, obtained by hydrogenation of 3-benzyloxy-β-lactams **192**, could be transformed into the corresponding azetidin-2,3-diones **241**,[156] which might be eligible substrates for further elaboration toward 4-iminoazetidin-2,3-diones **243** upon consecutive treatment with *p*-toluenesulfonic acid, sodium periodate and 2,3-dibromopropylamine hydrobromide (Scheme 75). The latter β-lactams **243** can be further functionalized *via* $NaBH_4$-induced reduction, allowing the synthesis of a wide variety of the premised 4-[2-(bromomethyl)aziridin-1-ylmethyl]-3-hydroxy-β-lactams **187**, as $NaBH_4$ is reported to selectively reduce the carbonyl group at C-3 in azetidin-2,3-diones (R = alkyl, Scheme 75).[157]

Alternatively, the coupling of 3-hydroxy-β-lactams **240** with *p*-methoxybenzylchloride (PMBCl) can be investigated as a possible entry into the corresponding 4-[2-(bromomethyl)aziridin-1-ylmethyl]-3-(4-methoxybenzyloxy)-β-lactams **245**. Finally, deprotection with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ceric ammonium nitrate (CAN) can lead to the formation of the synthetically interesting β-lactam hybrids **187** (Scheme 75).

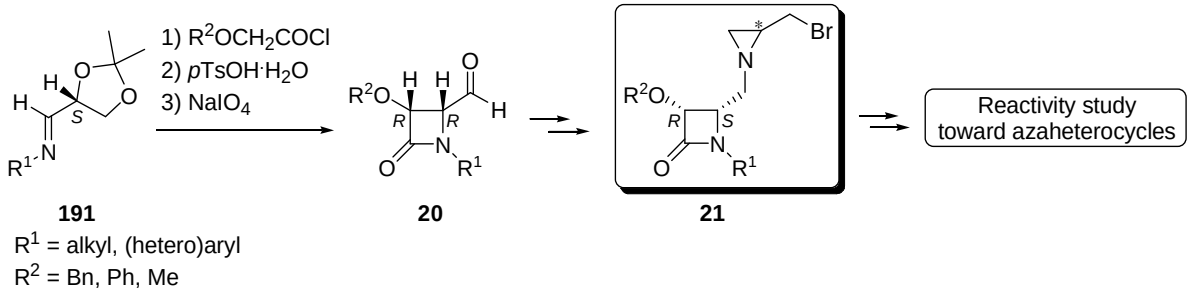


Scheme 75

4 Perspectives

As mentioned before, the selective synthesis of β-lactam-tethered 2-(bromomethyl)aziridines comprises a challenging topic as these synthons are expected to possess a broad synthetic potential, which can be attributed to the presence of two small-ring azaheterocycles and a brominated carbon atom. In that regard, a reactivity study toward functionalized azaheterocycles could provide a valuable and fruitfull research area.

Imination and $NaBH_4$-mediated reductive cyclization of 4-formyl-β-lactams **20** can lead to the formation of 4-[2-(bromomethyl)aziridin-1-ylmethyl]-β-lactams **21**, which might be eligible substrates for further elaboration toward nitrogen-containing heterocycles (Scheme 76).

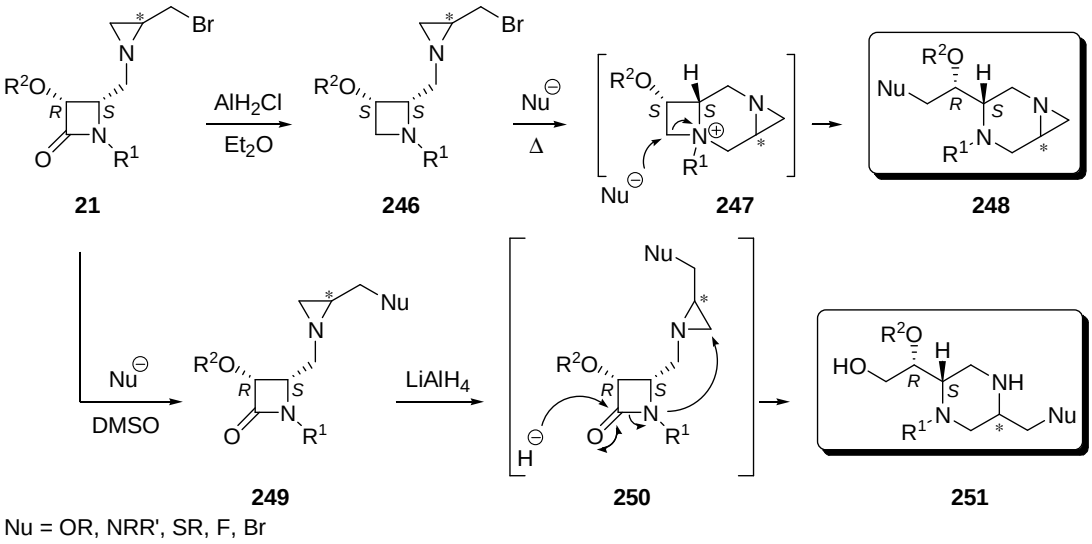


191 **20** **21**

R^1 = alkyl, (hetero)aryl
R^2 = Bn, Ph, Me

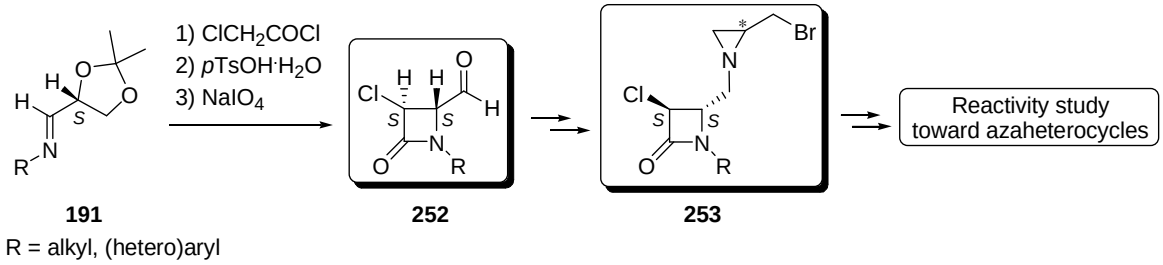
Scheme 76

In this PhD thesis, the synthetic usefulness of 2-(2-bromo-1,1-dimethylethyl)azetidines and 2-(2-mesyloxyethyl)azetidines was demonstrated by the preparation of a wide variety of functionalized piperidines *via* intermediate bicyclic azetidinium salts. Based on the same methodology, the construction of piperazines **248** from azetidines **246** can be envisaged, involving an intramolecular nucleophilic substitution reaction toward tricyclic azetidinium intermediates **247**, which are subsequently prone to undergo regioselective ring opening by the liberated leaving group or the additional nucleophile (Scheme 77). Furthermore, direct access to analogous monocyclic piperazines **251** *via* $LiAlH_4$-induced rearrangement of β-lactam-tethered aziridines **249**, which might be obtained by nucleophilic substitution of the starting compounds **21**, can be investigated (Scheme 77). During this transformation, $LiAlH_4$ is responsible for both β-lactam amide bond cleavage and the *in situ* activation of the aziridine moiety. It should be mentioned that a vast array of molecules containing the piperazine skeleton has been reported as antipsychotics,[158] antidepressants,[159] antihistamines,[160] and antianginals,[161] and others are known for the treatment of *inter alia* HIV,[162] and neuropathic pain.[163]



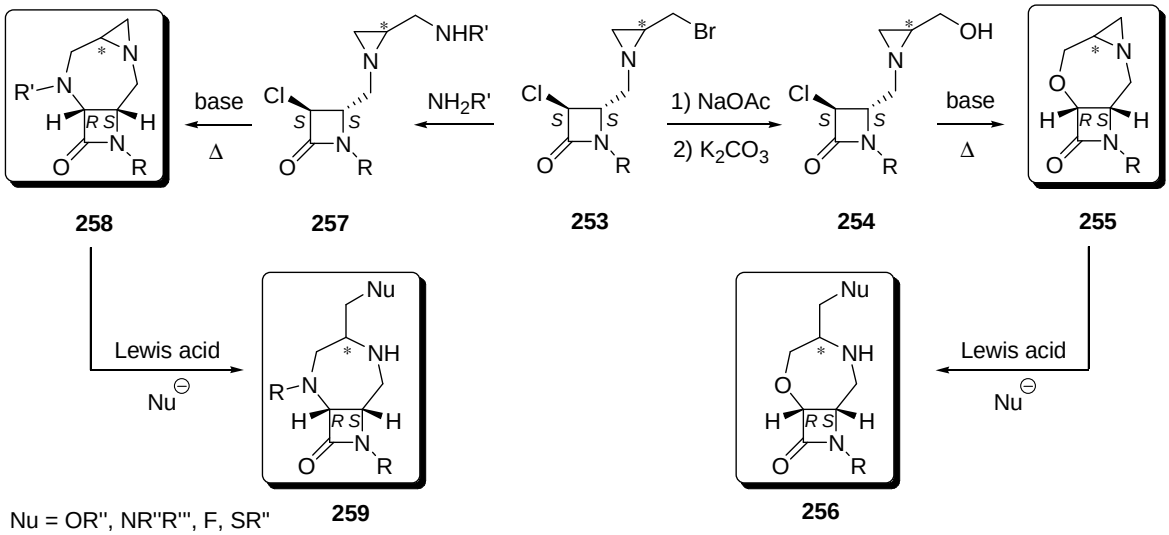
Scheme 77

Alternatively, this reactivity study can be extended to the chiral synthesis of the unexplored class of 3-chloro-4-formyl-β-lactams **252** as potential synthons for 4-[2-(bromomethyl)aziridin-1-ylmethyl]-3-chloro-β-lactams **253** (Scheme 78).



Scheme 78

In light of the continuous quest for new β-lactam antibiotics and β-lactamase inhibitors, efforts can be directed toward the deployment of β-lactam hybrids **253** in the synthesis of bi- and tricyclic systems containing medium-sized rings fused to the β-lactam nucleus. In that respect, introduction of a hydroxymethyl or aminomethyl moiety in β-lactams **254** or **257** can be studied as a suitable method for the formation of new oxazepane- or diazepane-fused tricyclic β-lactams **255** or **258** upon intramolecular cyclization. The latter can be further functionalized *via* nucleophile-induced aziridine ring opening, allowing the synthesis of a wide range of new *C*-fused bicyclic β-lactams **256** and **259** (Scheme 79). Oxazepanes and diazepanes are key structural features in many biologically active compounds, as illustrated by their use in the treatment of neurological and psychiatric diseases,[164] including epilepsy, Parkinson disease, and depression,[165] and by their reported anticancer,[166] anti-HIV,[167] inotropic,[168] and antihypertensive[169] activity.


base
Δ
NHR'
NH2R'
Br
1) NaOAc
2) K2CO3
OH
base
Δ
Lewis acid
Nu⊖
Lewis acid
Nu⊖
Nu = OR'', NR''R''', F, SR''
258
257
253
254
255
259
256

Scheme 79

5 Experimental Part

5.1 General methods

Diethyl ether, tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl or sodium, while dichloromethane was distilled from calcium hydride prior to use. Commercially available solvents and reagents were purchased from Sigma-Aldrich or Acros and used as such without further purification unless stated otherwise.

The purification of reaction mixtures was performed by column chromatography using a glass column filled with silica gel (Acros, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis on glass plates, coated with silica gel (Merck, Kieselgel $60F_{254}$, precoated 0.25 mm) using UV light or coloring with a potassium permanganate solution as detection methods.

High resolution ^{1}H NMR (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Jeol Eclipse FT 300 NMR spectrometer at room temperature. Peak assignments were obtained with the aid of DEPT, HSQC and/or 2D-COSY experiments. The compounds were diluted in a deuterated solvent, while tetramethylsilane (TMS) was used as an internal standard.

IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer. All compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory.

Low resolution mass spectra were recorded via direct injection on an Agilent 1100 Series LC/MSD type SL mass spectrometer with Electron Spray Ionisation Geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole).

Gas chromatography analysis was performed on an Agilent 6890 Series. The column was of the type Alltech EC-5 with a film thickness of 0.25 µm (length 30.0 m, i.d. 250 µm) with He as carrier gas. The GC was connected to a FID detector (H_2 gas).

Melting points of crystalline compounds were measured using a Büchi B-540 apparatus.

Elemental analyses were obtained by means of a Perkin-Elmer 2400 Series II apparatus.

High resolution electro spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight.

Optical rotations were taken with an JASCO P-2000 series polarimeter.

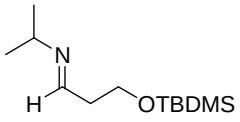
5.2 Synthesis of (*E*)-*N*-(alkylidene)amines

All imines were obtained in high purity (> 95% based on ^{1}H NMR) and were used as such in the next reaction step due to their hydrolytic instability (no HRMS data could be obtained).

5.2.1 Synthesis of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]amines

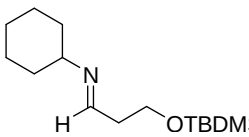
As a representative example, the synthesis of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isopropylamine **148a** is described. To a solution of 3-(*tert*-butyldimethylsilyloxy)propanal **147** (1.88 g, 10 mmol, 1 equiv) in anhydrous CH_2Cl_2 (40 mL) were added $MgSO_4$ (2.40 g, 20 mmol, 2 equiv) and isopropylamine (0.59 g, 10 mmol, 1 equiv). After stirring for 2 hours at room temperature, $MgSO_4$ was removed by filtration. After evaporation of the solvent *in vacuo*, (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isopropylamine **148a** was obtained in 70% yield.

(*E*)-*N*-[3-(*tert*-Butyldimethylsilyloxy)propylidene]isopropylamine 148a



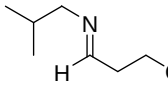
Yellow oil. Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.05 (6H, s, $Si(CH_3)_2$); 0.79 (9H, s, $SiC(CH_3)_3$); 1.05 (6H, d, *J* = 6.3 Hz, $(C\underline{H}_3)_2CHN$); 2.34 (2H, q, *J* = 5.8 Hz, $CH_2C{=}N$); 3.19 (1H, septet, *J* = 6.3 Hz, $(CH_3)_2C\underline{H}N$); 3.73 (2H, t, *J* = 5.8 Hz, CH_2O); 7.63 (1H, t, *J* = 5.8 Hz, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4 ($Si(CH_3)_2$); 18.2 (SiC_{quat}); 24.1 ($(\underline{C}H_3)_2CHN$); 25.9 ($SiC(\underline{C}H_3)_3$); 38.9 ($\underline{C}H_2C{=}N$); 60.5 (CH_2O); 61.5 ($(CH_3)_2\underline{C}HN$); 160.1 (C=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1666; ν_{max} = 2956, 2856, 1253, 1097, 834, 774, 733. MS (70 eV): m/z (%) 229 (M^+, 1), 214 (10), 172 (100), 142 (14), 130 (35), 100 (32), 73 (18), 59 (9), 43(10).

(*E*)-*N*-[3-(*tert*-Butyldimethylsilyloxy)propylidene]cyclohexylamine 148b



Yellow oil. Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (6H, s, $Si(CH_3)_2$); 0.89 (9H, s, $SiC(CH_3)_3$); 1.09-1.37, 1.40-1.53, 1.61-1.66 and 1.71-1.82 (10H, 4 × m, $(C\underline{H}_2)_5CHN$); 2.44 (2H, q, *J* = 5.7 Hz, $CH_2C{=}N$); 2.88-2.98 (1H, m, CHN); 3.83 (2H, t, *J* = 5.7 Hz, CH_2O); 7.74 (1H, t, *J* = 5.7 Hz, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3 ($Si(CH_3)_2$); 18.3 (SiC_{quat}); 24.9, 25.2 and 25.7 (3 × CH_2); 25.9 ($SiC(\underline{C}H_3)_3$); 34.4 and 36.3 (2 × CH_2); 39.2 ($\underline{C}H_2C{=}N$); 60.7 (CH_2O); 69.9 (CHN); 160.5 (C=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1667; ν_{max} = 2927, 2854, 1450, 1253, 1097, 834, 774. MS (70 eV): m/z (%) 270 (M^++1, 100).

(*E*)-*N*-[3-(*tert*-Butyldimethylsilyloxy)propylidene]isobutylamine 148c

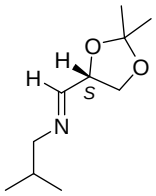


Yellow oil. Yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (6H, s, $Si(CH_3)_2$); 0.88 (9H, s, $SiC(CH_3)_3$); 0.89 and 0.90 (2 × 3H, 2 × d, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 1.90 (1H, nonet, *J* = 6.8 Hz, $(CH_3)_2C\underline{H}$); 2.47 (2H, q, *J* = 5.7 Hz, $CH_2C{=}N$); 3.19 (2H, d, *J* = 6.8 Hz, CH_2N); 3.85 (2H, t, *J* = 5.7 Hz, CH_2O); 7.61 (1H, t, *J* = 5.7 Hz, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4 ($Si(CH_3)_2$); 18.3 (SiC_{quat}); 20.6 ($(\underline{C}H_3)_2CH$); 25.9 ($SiC(\underline{C}H_3)_3$); 29.0 ($(CH_3)_2\underline{C}H$); 38.9 ($\underline{C}H_2C{=}N$); 60.6 (CH_2O); 69.6 (CH_2N); 163.6 (C=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1671; ν_{max} = 2954, 1471, 1254, 1097, 834, 774. MS (70 eV): m/z (%) 244 (M^++1, 100).

5.2.2 Synthesis of (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amines

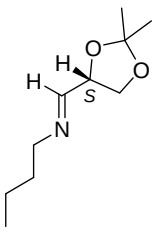
The synthesis of (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amines **191** was analogous to the synthesis of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]amines **148** (Section 5.2.1), using (*R*)-glyceraldehyde acetonide **190** as the starting material.

(*E*)-*N*-Isobutyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine 191b



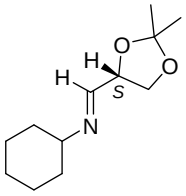
Yellow oil. Yield 94%. $[\alpha]_D$ = +60.9° (*c* = 1.51, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 and 0.91 (2 × 3H, 2 × d, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 1.41 and 1.46 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.91 (1H, nonet, *J* = 6.8 Hz, $(CH_3)_2C\underline{H}$); 3.19-3.30 (2H, m, CH_2N); 3.92 and 4.21 (2 × 1H, 2 × (d × d), *J* = 8.4, 6.3, 6.1 Hz, (HCH)O); 4.58 (1H, d × d × d, *J* = 6.3, 6.1, 5.4 Hz, CHO); 7.61 (1H, d, *J* = 5.4 Hz, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.3 ($(\underline{C}H_3)_2CH$); 25.3 and 26.4 ($(\underline{C}H_3)_2C$); 29.0 ($(CH_3)_2\underline{C}H$); 67.2 (CH_2O); 68.9 (CH_2N); 76.8 (CHO); 109.8 ($(CH_3)_2\underline{C}$); 162.9 (HC=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1674; ν_{max} = 2956, 1468, 1370, 1213, 1062, 846. MS (70 eV): m/z (%) 186 (M^++1, 100).

(*E*)-*N*-Butyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine 191c



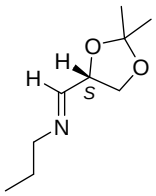
Yellow oil. Yield 95%. $[\alpha]_D$ = +61.3° (*c* = 2.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); 1.32 (2H, sextet, *J* = 7.2 Hz, $C\underline{H}_2CH_3$); 1.40 and 1.46 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.59 (2H, pentet, *J* = 7.2 Hz, $C\underline{H}_2CH_2N$); 3.42 (2H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_2N$); 3.91 and 4.20 (2 × 1H, 2 × (d × d), *J* = 8.5, 6.5, 6.2 Hz, (HCH)O); 4.57 (1H, d × d × d, *J* = 6.5, 6.2, 5.5 Hz, CHO); 7.63 (1H, d × t, *J* = 5.5, 1.4 Hz, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.6 ($CH_2\underline{C}H_3$); 20.1 ($\underline{C}H_2CH_3$); 25.2 and 26.3 ($(\underline{C}H_3)_2C$); 32.4 ($\underline{C}H_2CH_2N$); 60.5 (CH_2N); 67.1 (CH_2O); 76.8 (CHO); 109.7 ($(CH_3)_2\underline{C}$); 162.5 (HC=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1673; ν_{max} = 2932, 1457, 1213, 1061, 844. MS (70 eV): m/z (%) 186 (M^++1, 100).

(*E*)-*N*-Cyclohexyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine 191d



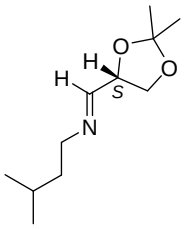
Colourless oil. Yield 90%. $[\alpha]_D$ = +55.4° (*c* = 1.60, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13-1.51 (5H, m, (C<u>H</u>$_2$)$_5$CHN); 1.40 and 1.46 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.59-1.80 (5H, m, (C<u>H</u>$_2$)$_5$CHN); 2.97-3.07 (1H, m, $(CH_2)_5$C<u>H</u>N); 3.88 and 4.20 (2 × 1H, 2 × (d × d), *J* = 8.3, 6.3, 6.3 Hz, (HCH)O); 4.55 (1H, d × d × d, *J* = 6.3, 6.3, 5.7 Hz, CHO); 7.65 (1H, d, *J* = 5.7 Hz, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 24.3 ((<u>C</u>H$_3$)$_2$C); 25.2, 25.3, 26.2, 33.7 and 33.9 ((<u>C</u>H$_2$)$_5$CHN); 67.1 (CH_2O); 68.8 ((CH_2)$_5$<u>C</u>HN); 76.8 (CHO); 109.6 ((CH$_3$)$_2$<u>C</u>); 160.4 (HC=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1672; ν_{max} = 2928, 1450, 1371, 1212, 1060, 843. MS (70 eV): m/z (%) 212 (M^++1, 100).

(*E*)-*N*-[((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methylidene]propylamine 191e



Colourless oil. Yield 92%. $[\alpha]_D$ = +70.7° (*c* = 1.62, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7.2 Hz, CH_2C<u>H</u>$_3$); 1.41 and 1.46 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.63 (2H, sextet, *J* = 7.2 Hz, C<u>H</u>$_2$CH$_3$); 3.39 (2H, t, *J* = 7.2 Hz, CH_2N); 3.92 and 4.20 (2 × 1H, 2 × (d × d), *J* = 8.2, 6.5, 6.4 Hz, (HCH)O); 4.57 (1H, d × d × d, *J* = 6.5, 6.4, 5.5 Hz, CHO); 7.63 (1H, d × t, *J* = 5.5, 1.3 Hz, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 11.5 (CH_2<u>C</u>H$_3$); 23.4 (<u>C</u>H$_2$CH$_3$); 25.3 and 26.3 ((<u>C</u>H$_3$)$_2$C); 62.6 (CH_2N); 67.2 (CH_2O); 76.8 (CHO); 109.8 ((CH$_3$)$_2$<u>C</u>); 162.7 (HC=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1673; ν_{max} = 2934, 1456, 1371, 1213, 1061, 844. MS (70 eV): m/z (%) 172 (M^++1, 100).

(*E*)-*N*-Isopentyl-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amine 191f



Colourless oil. Yield 85%. $[\alpha]_D$ = +69.7° (*c* = 1.61, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (6H, d, *J* = 7.7 Hz, (C<u>H</u>$_3$)$_2$CH); 1.40 and 1.46 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.48 (2H, q, *J* = 7.7 Hz, C<u>H</u>$_2$CH$_2$N); 1.61 (1H, nonet, *J* = 7.7 Hz, $(CH_3)_2$C<u>H</u>); 3.43 (2H, t, *J* = 7.7 Hz, CH_2N); 3.91 and 4.20 (2 × 1H, 2 × (d × d), *J* = 8.0, 6.9, 6.4 Hz, (HCH)O); 4.56 (1H, d × d × d, *J* = 6.9, 6.4, 5.2 Hz, CHO); 7.64 (1H, d, *J* = 5.2 Hz, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.3 ((<u>C</u>H$_3$)$_2$CH); 25.3 (<u>C</u>H$_3$CCH$_3$); 25.6 ((CH$_3$)$_2$<u>C</u>H); 26.3 (CH$_3$<u>C</u>CH$_3$); 39.4 (<u>C</u>H$_2$CH$_2$N); 59.0 (CH_2N); 67.2 (CH_2O); 76.8 (CHO); 109.8 (CH$_3$<u>C</u>CH$_3$); 162.5 (HC=N). IR (ATR, cm^{-1}): $\nu_{C=N}$ = 1673; ν_{max} = 2955, 1468, 1370, 1213, 1062, 848. MS (70 eV): m/z (%) 200 (M^++1, 100).

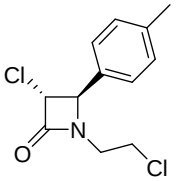
5.3 Synthesis of azetidin-2-ones

5.3.1 Synthesis of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones

As a representative example, the synthesis of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **2a** is described. To a solution of *N*-(4-methylphenylmethylidene)-(2-chloroethyl)amine **124a** (1.82 g, 10 mmol, 1 equiv) in dry benzene (50 mL) was added 2,6-lutidine (3.21 g, 30 mmol, 3 equiv), and the resulting mixture was heated under reflux. Immediately thereafter, chloroacetyl chloride (1.69 g, 15 mmol, 1.5 equiv) was added dropwise to the boiling

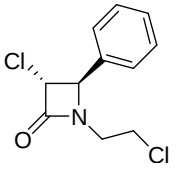
mixture, followed by a reflux period of 15 hours. Afterwards, the resulting suspension was filtered in order to remove 2,6-lutidine hydrochloride, after which the filtrate was washed with an aqueous solution of 1 M HCl (2 × 15 mL). The organic phase was dried over $MgSO_4$, followed by removal of the drying agent and evaporation of the solvent *in vacuo*. Purification by means of column chromatography on silica gel (hexane/EtOAc 6/1) afforded pure *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **2a** in 75% yield.

***Trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one 2a**



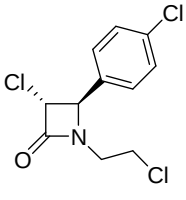
Yellow oil. R_f = 0.10 (hexane/EtOAc 6/1). Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (3H, s, CH_3); 3.20 (1H, d × d × d, *J* = 14.6, 7.4, 5.2 Hz, (HCH)N); 3.51-3.68 (2H, m, CH_2Cl); 3.84 (1H, d × d × d, *J* = 14.6, 6.1, 5.2 Hz, (HCH)N); 4.54 and 4.70 (2 × 1H, 2 × d, *J* = 1.6 Hz, CHCl and CHN); 7.20–7.28 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (CH_3); 41.3 (CH_2Cl); 42.7 (CH_2N); 63.3 and 66.9 (CHCl and CHN); 126.7 and 130.0 (4 x HC_{arom}); 131.6 and 139.8 (2 x $C_{arom,quat}$); 164.1 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767; ν_{max} = 1675, 1395, 821, 756. MS (70 eV): m/z (%) 258/60/2 (M^++1, 100). Anal. Calcd. for $C_{12}H_{13}Cl_2NO$: C 55.83, H 5.08, N 5.43. Found: C 55.70, H 5.46, N 5.47.

***Trans*-3-chloro-1-(2-chloroethyl)-4-phenylazetidin-2-one 2b**



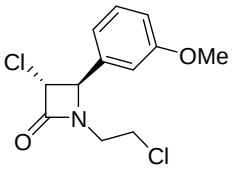
Yellow crystals. Mp 50.8 °C. R_f = 0.15 (hexane/EtOAc 6/1). Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (1H, d × d × d, *J* = 14.7, 7.6, 5.1 Hz, (HCH)N); 3.52–3.69 (2H, m, CH_2Cl); 3.86 (1H, d × d × d, *J* = 14.7, 6.1, 5.2 Hz, (HCH)N); 4.56 and 4.74 (2 × 1H, 2 × d, *J* = 1.7 Hz, CHCl and CHN); 7.32–7.35 and 7.41–7.48 (2H and 3H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.5 (CH_2Cl); 42.9 (CH_2N); 63.3 and 66.9 (CHCl and CHN); 126.9, 129.5 and 129.8 (5 x HC_{arom}); 134.7 ($C_{arom,quat}$); 164.1 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1765; ν_{max} = 1676, 1395, 738, 698. MS (70 eV): m/z (%) 244/6/8 (M^++1, 100). Anal. Calcd. for $C_{11}H_{11}Cl_2NO$: C 54.12, H 4.54, N 5.74. Found: C 53.91, H 4.64, N 5.48.

***Trans*-3-chloro-1-(2-chloroethyl)-4-(4-chlorophenyl)azetidin-2-one 2c**



Yellow crystals. Mp 55.3 °C. R_f = 0.12 (hexane/EtOAc 6/1). Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.19 (1H, d × d × d, *J* = 14.7, 7.7, 4.7 Hz, (HCH)N); 3.54–3.70 (2H, m, CH_2Cl); 3.87 (1H, d × d × d, *J* = 14.7, 5.8, 4.7 Hz, (HCH)N); 4.53 and 4.74 (2 × 1H, 2 × d, *J* = 2.0 Hz, CHCl and CHN); 7.28–7.36 and 7.41–7.46 (2 × 2H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.4 (CH_2Cl); 42.8 (CH_2N); 63.3 and 66.5 (CHCl and CHN); 128.1 and 129.6 (4 x HC_{arom}); 133.2 and 135.7 (2 x $C_{arom,quat}$); 163.8 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1768; ν_{max} = 1676, 1394, 1090, 828, 770. MS (70 eV): m/z (%) no M^+; 172 (M^+-3×Cl, 100), 137, 102, 101, 75. Anal. Calcd. for $C_{11}H_{10}Cl_3NO$: C 47.43, H 3.62, N 5.03. Found: C 47.21, H 3.77, N 5.13.

***Trans*-3-chloro-1-(2-chloroethyl)-4-(3-methoxyphenyl)azetidin-2-one 2d**

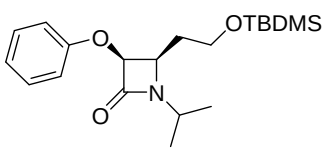


Yellow oil. R_f = 0.15 (hexane/EtOAc 6/1). Yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (1H, d × d × d, *J* = 14.4, 7.6, 5.4 Hz, (HCH)N); 3.54–3.69 (2H, m, CH_2Cl); 3.81–3.90 (1H, m, (HCH)N); 3.83 (3H, s, CH_3O); 4.56 and 4.70 (2 × 1H, 2 × d, *J* = 1.1 Hz, CHCl and CHN); 6.85–6.96 and 7.33–7.38 (3H and 1H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.5 (CH_2Cl); 43.0 (CH_2N); 55.5 (CH_3O); 63.3 and 66.7 (CHCl and CHN); 112.3, 115.1, 118.9, 130.5 (4 x HC_{arom}); 136.4 ($CHNC_{quat}$); 160.4 ($OC_{arom,quat}$); 163.9 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1768; ν_{max} = 1676, 1394, 1261, 1039, 779, 735, 695. MS (70 eV): m/z (%) 274/6/8 (M^++1, 100). Anal. Calcd. for $C_{12}H_{13}Cl_2NO_2$: C 52.57, H 4.78, N 5.11. Found: C 52.36, H 4.97, N 5.03.

5.3.2 Synthesis of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones and *N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]acetamides

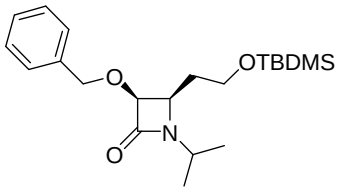
As a representative example, the synthesis of *cis*-3-benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isobutylazetidin-2-one **12d** and 2-benzyloxy-*N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]-*N*-isobutylacetamide **149d** is described. To an ice-cooled solution of (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]isobutylamine **148c** (2.43 g, 10 mmol, 1 equiv) and triethylamine (3.04 g, 30 mmol, 3 equiv) in anhydrous CH_2Cl_2 (25 mL) was added dropwise a solution of benzyloxyacetyl chloride (2.40 g, 13 mmol, 1.3 equiv) in CH_2Cl_2 (10 mL). After stirring for 15 hours at room temperature, the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded *cis*-3-benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isobutylazetidin-2-one **12d** and 2-benzyloxy-*N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]-*N*-isobutylacetamide **149d**, which were further purified in 5% and 66% yield, respectively, by column chromatography on silica gel (hexane/EtOAc 12/1).

***Cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one 12a**



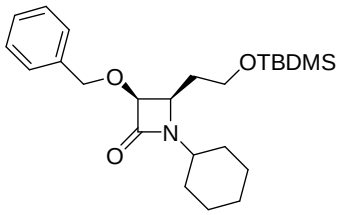
Yellow crystals. Mp 57.2 °C. R_f = 0.14 (hexane/EtOAc 6/1). Yield 47%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 and 0.04 (2 × 3H, 2 × s, $Si(CH_3)_2$); 0.89 (9H, s, $SiC(CH_3)_3$); 1.29 and 1.34 (2 × 3H, 2 × d, *J* = 6.8 Hz, $(CH_3)_2CHN$); 1.95-2.12 (2H, m, CH_2CHN); 3.60-3.68 and 3.71-3.78 (2 × 1H, 2 × m, (HCH)O); 3.85 (1H, septet, *J* = 6.8 Hz, $(CH_3)_2CHN$); 4.13 (1H, d × d × d, *J* = 8.8, 4.1, 4.1 Hz, CH_2CHN); 5.16 (1H, d, *J* = 4.1 Hz, CHO); 6.96-7.11 and 7.26-7.32 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.42 and -5.37 (2 × $SiCH_3$); 18.2 (SiC_{quat}); 20.1 and 21.8 ($(CH_3)_2CHN$); 25.9 ($SiC(CH_3)_3$); 32.7 (CH_2CHN); 44.6 ($(CH_3)_2CHN$); 54.3 (CH_2CHN); 59.7 (CH_2O); 79.7 (CHO); 115.6, 122.0 and 129.5 (5 x HC_{arom}); 157.8 ($OC_{arom,quat}$); 165.5 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1754; ν_{max} = 2954, 2929, 2857, 1238, 1085, 836, 774, 752. MS (70 eV): m/z (%) 364 (M^++1, 100). Anal. Calcd. for $C_{20}H_{33}NO_3Si$: C 66.07, H 9.15, N 3.85. Found: C 65.87, H 9.37, N 4.18.

***Cis*-3-benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropylazetidin-2-one 12b**



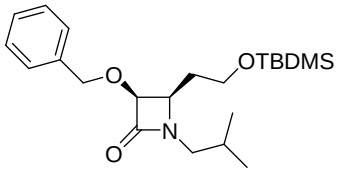
Yellow oil. R_f = 0.10 (hexane/EtOAc 6/1). Yield 35%. ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.07 and -0.06 (2 × 3H, 2 × s, $Si(CH_3)_2$); 0.87 (9H, s, $SiC(CH_3)_3$); 1.20 and 1.24 (2 × 3H, 2 × d, *J* = 6.6 Hz, $(CH_3)_2CHN$); 1.91-1.97 (2H, m, CH_2CHN); 3.58-3.81 (3H, m, CH_2CH_2O and $(CH_3)_2CHN$); 3.88 (1H, d × d × d, *J* = 8.8, 4.7, 4.4 Hz, CH_2CHN); 4.52 (1H, d, *J* = 4.7 Hz, CHO); 4.65 and 4.87 (2 × 1H, 2 × d, *J* = 11.9 Hz, O(HCH)Ph); 7.23-7.35 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4 and -5.3 (2 × $SiCH_3$); 18.3 (SiC_{quat}); 20.1 and 21.8 ($(CH_3)_2CHN$); 25.9 ($SiC(CH_3)_3$); 32.6 (CH_2CHN); 44.2 ($(CH_3)_2CHN$); 53.9 (CH_2CHN); 59.9 (CH_2CH_2O); 72.6 (OCH_2Ph); 80.6 (CHO); 127.8, 128.1 and 128.4 (5 x HC_{arom}); 137.5 ($C_{arom,quat}$); 167.3 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1747; ν_{max} = 2929, 1651, 1252, 1096, 833, 775, 734, 697. MS (70 eV): m/z (%) 378 (M^++1, 100). HRMS (ESI) Calcd. for $C_{21}H_{36}NO_3Si$ 378.2464 $[M + H]^+$, found 378.2463.

***Cis*-3-benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-cyclohexylazetidin-2-one 12c**



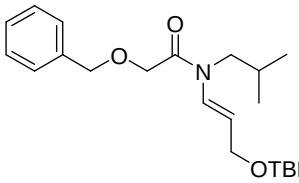
Colourless oil. R_f = 0.11 (hexane/EtOAc 9/1). Yield 55%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 and 0.01 (2 × 3H, 2 × s, $Si(CH_3)_2$); 0.86 (9H, s, $SiC(CH_3)_3$); 1.04-1.30, 1.34-1.47, 1.52-1.60 and 1.69-2.02 (12H, 4 × m, $(CH_2)_5CHN$ and CH_2CH_2O); 3.32-3.42 (1H, m, $(CH_2)_5CHN$); 3.58-3.83 (2H, m, CH_2CH_2O); 3.87 (1H, d × d × d, *J* = 8.7, 4.5, 4.0 Hz, OCH_2CH_2CHN); 4.52 (1H, d, *J* = 4.5 Hz, CHO); 4.65 and 4.87 (2 × 1H, 2 × d, *J* = 11.9 Hz, O(HCH)Ph); 7.26-7.32 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4 and -5.3 (2 × $SiCH_3$); 18.3 (SiC_{quat}); 25.2, 25.25 and 25.33 (3 × CH_2); 25.9 ($SiC(CH_3)_3$); 30.5 and 31.9 (2 × CH_2); 32.6 (CH_2CH_2O); 52.1 ($(CH_2)_5CHN$); 54.1 (OCH_2CH_2CHN); 59.8 (CH_2CH_2O); 72.6 (OCH_2Ph); 80.6 (CHO); 127.8, 128.37 and 128.39 (5 x HC_{arom}); 137.5 ($C_{arom,quat}$); 167.3 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1746; ν_{max} = 2929, 1254, 1095, 1056, 832, 812, 775, 734, 697. MS (70 eV): m/z (%) 418 (M^++1, 100). HRMS (ESI) Calcd. for $C_{24}H_{40}NO_3Si$ 418.2777 $[M + H]^+$, found 418.2788.

***Cis*-3-benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isobutylazetidin-2-one 12d**



Colourless oil. R_f = 0.05 (hexane/EtOAc 12/1). Yield 5%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (6H, s, $Si(CH_3)_2$); 0.88 (3H, d, *J* = 6.1 Hz, CH_3CHCH_3); 0.89 (9H, s, $SiC(CH_3)_3$); 0.92 (3H, d, *J* = 6.1 Hz, CH_3CHCH_3); 1.82-2.00 (3H, m, CH_2CHN and $(CH_3)_2CH$); 2.83 and 3.19 (2 × 1H, 2 × (d × d), *J* = 14.1, 8.3, 6.0 Hz, (HCH)N); 3.64-3.78 (2H, m, CH_2CH_2O); 3.88 (1H, d × d × d, *J* = 7.0, 5.4, 5.2 Hz, CHN); 4.66 (1H, d, *J* = 5.2 Hz, CHO); 4.69 and 4.90 (2 × 1H, 2 × d, *J* = 11.6 Hz, O(HCH)Ph); 7.29-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ -5.3 ($Si(CH_3)_2$); 18.4 (SiC_{quat}); 20.3 and 20.5 (CH_3CHCH_3); 26.0 ($SiC(CH_3)_3$); 27.3 ($(CH_3)_2CH$); 31.5 (CH_2CHN); 48.0 (CH_2N); 55.5 (CHN); 60.0 (CH_2CH_2O); 72.8 (OCH_2Ph); 81.3(CHO); 127.9 and 128.5 (5 x HC_{arom}); 137.5 ($C_{arom,quat}$); 168.3 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1750; ν_{max} = 2955, 1254, 1098, 1054, 833, 776, 732. MS (70 eV): m/z (%) 392 (M^++1, 100). HRMS (ESI) Calcd. for $C_{22}H_{38}NO_3Si$ 392.2621 $[M + H]^+$, found 392.2632.

2-Benzyloxy-*N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]-*N*-isobutylacetamide 149d

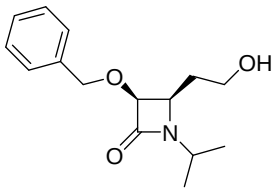


Yellow oil. R_f = 0.07 (hexane/EtOAc 12/1). Yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (6H, s, $Si(CH_3)_2$); 0.90 (6H, d, *J* = 6.1 Hz, $(C\underline{H}_3)_2CH$); 0.90 (9H, s, $SiC(CH_3)_3$); 2.01-2.10 (1H, m, $(CH_3)_2C\underline{H}$); 3.51 (2H, d, *J* = 7.7 Hz, CH_2N); 4.19 (2H, d, *J* = 5.3 Hz, $CHC\underline{H}_2O$); 4.29 and 4.62 (2 × 2H, 2 × s, $PhC\underline{H}_2O$ and CH_2CO); 5.15 (1H, d × d × d, *J* = 13.8, 5.3, 5.3 Hz, $HC{=}C\underline{H}CH_2$); 6.70 (1H, d, *J* = 13.8 Hz, $\underline{H}C{=}CHCH_2$); 7.28-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ -5.2 ($Si(CH_3)_2$); 18.3 (SiC_{quat}); 20.2 ($(\underline{C}H_3)_2CH$); 25.9 ($SiC(\underline{C}H_3)_3$); 26.0 ($(CH_3)_2\underline{C}H$); 49.6 (CH_2N); 62.1 ($CH\underline{C}H_2O$); 69.0 and 73.0 ($Ph\underline{C}H_2O$ and $\underline{C}H_2CO$); 110.9 ($HC{=}\underline{C}HCH_2$); 127.6 ($H\underline{C}{=}CHCH_2$); 127.8, 128.0 and 128.3 (5 x HC_{arom}); 137.3 ($C_{arom,quat}$); 168.0 (C=O). IR (ATR, cm^{-1}): $\nu_{C=C,C=O}$ = 1686, 1649; ν_{max} = 2929, 1251, 1108, 1061, 834, 775, 697. MS (70 eV): m/z (%) 392 (M^++1, 100). HRMS (ESI) Calcd. for $C_{22}H_{38}NO_3Si$ 392.2621 $[M + H]^+$, found 392.2634.

5.3.3 Synthesis of 4-(2-hydroxyethyl)azetidin-2-ones

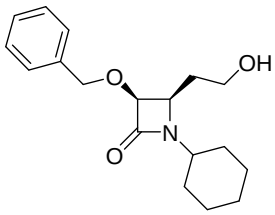
As a representative example, the synthesis of *cis*-3-benzyloxy-4-(2-hydroxyethyl)-1-isopropylazetidin-2-one **184a** is described. To an ice-cooled solution of *cis*-3-benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropylazetidin-2-one **12b** (0.76 g, 2 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added tetra-*n*-butylammonium fluoride (0.08 g, 2.2 mmol, 1.1 equiv), and the resulting solution was stirred at room temperature for 5 hours. Subsequently, the reaction mixture was poured into brine (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL), after which the organic fraction was dried ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent *in vacuo*. Purification by means of column chromatography on silica gel (hexane/EtOAc 1/1) gave pure *cis*-3-benzyloxy-4-(2-hydroxyethyl)-1-isopropylazetidin-2-one **184a** in 49% yield.

***Cis*-3-benzyloxy-4-(2-hydroxyethyl)-1-isopropylazetidin-2-one 184a**



Yellow oil. R_f = 0.49 (hexane/EtOAc 1/1). Yield 49%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 and 1.28 (2 × 3H, 2 × d, *J* = 6.9 Hz, $(C\underline{H}_3)_2CHN$); 1.96-2.18 (2H, m, $C\underline{H}_2CHN$); 2.26 (1H, t, *J* = 5.0 Hz, OH); 3.64-3.85 (3H, m, $C\underline{H}_2OH$ and $(CH_3)_2C\underline{H}N$); 3.91 (1H, d × d × d, *J* = 9.2, 4.7, 4.5 Hz, $CH_2C\underline{H}N$); 4.62 (1H, d, *J* = 4.7 Hz, CHO); 4.73 and 4.99 (2 × 1H, 2 × d, *J* = 11.3 Hz, $O(\underline{H}C\underline{H})Ph$); 7.28-7.40 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.2 and 21.8 ($(\underline{C}H_3)_2CHN$); 32.3 ($\underline{C}H_2CHN$); 44.3 ($(CH_3)_2\underline{C}HN$); 55.3 ($CH_2\underline{C}HN$); 59.4 (CH_2OH); 72.9 ($O\underline{C}H_2Ph$); 80.5 (CHO); 128.05, 128.12 and 128.6 (5 x HC_{arom}); 137.0 ($C_{arom,quat}$); 167.2 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1726; ν_{OH} = 3418; ν_{max} = 2930, 1340, 1024, 732, 698. MS (70 eV): m/z (%) 264 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{22}NO_3$ 264.1600 $[M + H]^+$, found 264.1598.

***Cis*-3-benzyloxy-1-cyclohexyl-4-(2-hydroxyethyl)azetidin-2-one 184b**



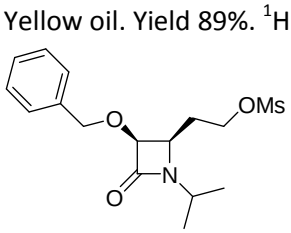
White crystals. Mp 70.0 °C. R_f = 0.18 (hexane/EtOAc 1/1). Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06-1.48, 1.52-1.65 and 1.73-1.95 (4H, 2H and 4H, 3 × m, ($C\underline{H}_2)_5$CHN); 1.97-2.15 (2H, m, $C\underline{H}_2CH_2O$); 2.37 (1H, d, *J* = 2.8 Hz, OH); 3.36-3.46 (1H, m, $(CH_2)_5C\underline{H}N$); 3.63-3.77 (2H, m, $C\underline{H}_2OH$); 3.91 (1H, d × d × d, *J* = 9.1, 4.7, 4.4 Hz, CHOC<u>H</u>N); 4.61 (1H, d, *J* = 4.7 Hz, CHO); 4.72 and 4.98 (2 × 1H, 2 × d, *J* = 11.6 Hz, O(<u>H</u>C<u>H</u>)Ph); 7.29-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.25, 25.28, 25.4, 30.6 and 32.0 (($\underline{C}H_2)_5$CHN); 32.3 ($\underline{C}H_2CH_2O$); 52.2 ($(CH_2)_5\underline{C}$HN); 55.4 (CHO<u>C</u>HN); 59.4 (CH_2OH); 72.8 (O<u>C</u>H_2Ph); 80.5 (CHO); 128.06, 128.12 and 128.6 (5 x HC_{arom}); 137.0 ($C_{arom,quat}$); 167.1 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1735; ν_{OH} = 3238; ν_{max} = 2932, 1454, 1252, 1065, 890, 833, 770, 735, 698. MS (70 eV): m/z (%) 304 (M^++1, 100). Anal. Calcd. for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62. Found: C 71.13, H 8.50, N 4.63.

5.3.4 Synthesis of 4-(2-mesyloxyethyl)azetidin-2-ones

As a representative example, the synthesis of *cis*-3-benzyloxy-1-isopropyl-4-(2-mesyloxyethyl)azetidin-2-one **17a** is described. To an ice-cooled solution of *cis*-3-benzyloxy-4-(2-hydroxyethyl)-1-isopropylazetidin-2-one **184a** (1.52 g, 5 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added 4-(dimethylamino)pyridine (0.06 g, 0.5 mmol, 0.1 equiv), Et_3N (0.56 g, 5.5 mmol, 1.1 equiv) and mesyl chloride (0.60 g, 5.25 mmol, 1.05 equiv), after which the mixture was stirred for 3 hours at 0 °C. Afterwards, the reaction mixture was washed with brine (2 × 30 mL) and a saturated $NaHCO_3$ solution (2 × 30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), after which the organic fraction was dried ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent *in vacuo*.

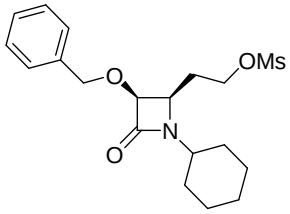
Azetidin-2-ones **17** were obtained in high purity (>95% based on ^{1}H NMR) and were used as such in the next reaction step.

***Cis*-3-benzyloxy-1-isopropyl-4-(2-mesyloxyethyl)azetidin-2-one 17a**



Yellow oil. Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 and 1.27 (2 × 3H, 2 × d, *J* = 6.3 Hz, ($C\underline{H}_3)_2$CHN); 2.14-2.23 (2H, m, $C\underline{H}_2$CHN); 2.93 (3H, s, CH_3SO_3); 3.80 (1H, septet, *J* = 6.3 Hz, $(CH_3)_2C\underline{H}$N); 3.91 (1H, d × d × d, *J* = 8.5, 4.6, 4.1 Hz, $CH_2C\underline{H}$N); 4.24-4.37 (2H, m, CH_2OSO_2); 4.62 (1H, d, *J* = 4.6 Hz, CHO); 4.68 and 4.93 (2 × 1H, 2 × d, *J* = 11.8 Hz, O(<u>H</u>C<u>H</u>)Ph); 7.28-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.2 and 21.8 (($\underline{C}H_3)_2$CHN); 29.6 ($\underline{C}H_2$CHN); 37.2 (CH_3SO_3); 44.4 ($(CH_3)_2\underline{C}$HN); 53.1 ($CH_2\underline{C}$HN); 66.9 (CH_2OSO_2); 73.0 (O<u>C</u>H_2Ph); 80.6 (CHO); 128.1, 128.2 and 128.6 (5 x HC_{arom}); 137.2 ($C_{arom,quat}$); 167.0 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1741; ν_{max} = 2974, 1351, 1172, 959, 732, 699. MS (70 eV): m/z (%) 342 (M^++1, 100). HRMS (ESI) Calcd. for $C_{16}H_{24}NO_5S$ 342.1375 $[M + H]^+$, found 342.1381.

***Cis*-3-benzyloxy-1-cyclohexyl-4-(2-mesyloxyethyl)azetidin-2-one 17b**

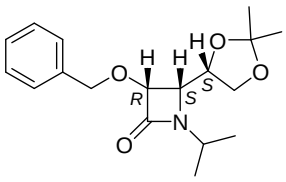


Yellow oil. Yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08-1.46, 1.51-1.66 and 1.75-1.93 (4H, 2H and 4H, 3 × m, ($C\underline{H}_2)_5CHN$); 2.11-2.29 (2H, m, $C\underline{H}_2CH_2O$); 2.94 (3H, s, CH_3SO_3); 3.37-3.47 (1H, m, $(CH_2)_5C\underline{H}N$); 3.92 (1H, d × d × d, *J* = 8.8, 4.7, 4.4 Hz, $CHOC\underline{H}N$); 4.26-4.38 (2H, m, CH_2OSO_2); 4.62 (1H, d, *J* = 4.7 Hz, CHO); 4.68 and 4.95 (2 × 1H, 2 × d, *J* = 11.5 Hz, $O(\underline{H}C\underline{H})Ph$); 7.28-7.38 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.2, 25.3, 29.6, 30.6 and 32.0 (($\underline{C}H_2)_5CHN$ and $\underline{C}H_2CH_2O$); 37.2 (CH_3SO_3); 52.2 (($CH_2)_5\underline{C}HN$); 53.3 ($CHO\underline{C}HN$); 67.0 (CH_2OSO_2); 72.9 ($O\underline{C}H_2Ph$); 80.7 (CHO); 128.0, 128.1 and 128.6 (5 x HC_{arom}); 137.2 ($C_{arom,quat}$); 166.9 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1740; ν_{max} = 2932, 1352, 1172, 960, 733, 699. MS (70 eV): m/z (%) 382 (M^++1, 100). HRMS (ESI) Calcd. for $C_{19}H_{28}NO_5$ 382.1688 $[M + H]^+$, found 382.1695.

5.3.5 Synthesis of (3*R*,4*S*)-3-benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones

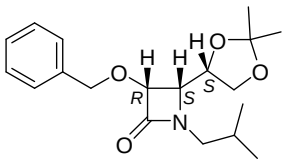
The synthesis of (3*R*,4*S*)-3-benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones **192** was analogous to the synthesis of *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **12** and *N*-[3-(*tert*-butyldimethylsilyloxy)prop-1-en-1-yl]acetamides **149** (Section 5.3.2), using (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]amines **191** as the starting material.

(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 192a



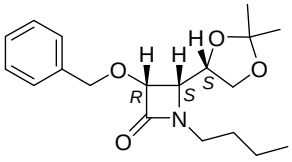
Colourless oil. R_f = 0.12 (hexane/EtOAc 6/1). Yield 81%. $[\alpha]_D$ = +102.8° (*c* = 0.97, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (6H, d, *J* = 6.7 Hz, $(C\underline{H}_3)_2CH$); 1.34 and 1.44 (2 × 3H, 2 × s, $(CH_3)_2C$); 3.62 (1H, d × d, *J* = 8.2, 6.1 Hz, $CHO(\underline{H}CH)O$); 3.69 (1H, d × d, *J* = 8.8, 5.0 Hz, $CHOC\underline{H}N$); 3.92 (1H, septet, *J* = 6.7 Hz, $(CH_3)_2C\underline{H}$); 4.16-4.30 (2H, m, $CHO(HC\underline{H})O$ and $C\underline{H}OCH_2O$); 4.54 (1H, d, *J* = 5.0 Hz, COCHO); 4.64 and 4.92 (2 × 1H, 2 × d, *J* = 11.9 Hz, $O(\underline{H}C\underline{H})Ph$); 7.28-7.38 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.5 and 21.3 (($\underline{C}H_3)_2CH$); 25.2 and 26.8 (($\underline{C}H_3)_2C$); 44.4 (($CH_3)_2\underline{C}H$); 59.8 ($CHO\underline{C}HN$); 66.9 ($CHO\underline{C}H_2O$); 72.8 ($O\underline{C}H_2Ph$); 77.2 ($\underline{C}HOCH_2O$); 79.6 ($CO\underline{C}HO$); 109.3 (($CH_3)_2\underline{C}$); 127.8, 128.0 and 128.5 (5 x HC_{arom}); 137.1 ($C_{arom,quat}$); 166.8 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1747; ν_{max} = 2981, 1370, 1209, 1064, 1024, 852, 698. MS (70 eV): m/z (%) 320 (M^++1, 100). HRMS (ESI) Calcd. for $C_{18}H_{26}NO_4$ 320.1862 $[M + H]^+$, found 320.1867.

(3*R*,4*S*)-3-Benzyloxy-1-isobutyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 192b



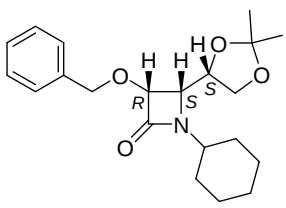
White crystals. Mp 103.5 °C. R_f = 0.22 (hexane/EtOAc 6/1). Yield 50%. $[\alpha]_D$ = +96.9° (*c* = 0.40, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 and 0.93 (2 × 3H, 2 × d, *J* = 7.2 Hz, $(C\underline{H}_3)_2CH$); 1.33 and 1.42 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.92-2.09 (1H, m, $(CH_3)_2C\underline{H}$); 3.07 and 3.23 (2 × 1H, 2 × (d × d), *J* = 13.6, 8.3, 6.3 Hz, (HCH)N); 3.63 (1H, d × d, *J* = 8.8, 6.3 Hz, CHO(H<u>C</u>H)O); 3.66 (1H, d × d, *J* = 8.8, 5.0 Hz, CHN); 4.15 (1H, d × d, *J* = 8.8, 6.3 Hz, CHO(HC<u>H</u>)O); 4.32 (1H, d × t, *J* = 8.8, 6.3 Hz, C<u>H</u>OCH_2O); 4.62 (1H, d, *J* = 5.0 Hz, COCHO); 4.64 and 4.92 (2 × 1H, 2 × d, *J* = 11.8 Hz, O(H<u>C</u>H)Ph); 7.28-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2 and 20.4 ($(\underline{C}H_3)_2CH$); 25.1 ($\underline{C}H_3CCH_3$); 26.8 and 27.0 ($CH_3\underline{C}CH_3$ and $(CH_3)_2\underline{C}H$); 48.7 (CH_2N); 60.8 (CHN); 66.7 (CHO<u>C</u>H_2O); 72.6 (O<u>C</u>H_2Ph); 77.2 (<u>C</u>HOCH_2O); 80.3 (CO<u>C</u>HO); 109.3 ($(CH_3)_2\underline{C}$); 127.7, 127.9 and 128.4 (5 x HC_{arom}); 137.2 ($C_{arom,quat}$); 167.6 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1737; ν_{max} = 2959, 1370, 1209, 1156, 1060, 858, 698. MS (70 eV): m/z (%) 334 (M^++1, 100). Anal. Calcd. for $C_{19}H_{27}NO_4$: C 68.44, H 8.16, N 4.20. Found: C 68.70, H 8.10, N 4.32.

(3*R*,4*S*)-3-Benzyloxy-1-butyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 192c



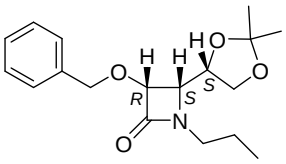
Light-brown crystals. Mp 98.8 °C. Recrystallization from absolute EtOH. Yield 43%. $[\alpha]_D$ = +96.7° (*c* = 0.51, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.3 Hz, $CH_2C\underline{H}_3$); 1.32 (2H, sextet, *J* = 7.3 Hz, $C\underline{H}_2CH_3$); 1.33 and 1.43 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.47-1.66 (2H, m, $C\underline{H}_2CH_2N$); 3.21 (1H, d × t, *J* = 13.8, 7.0 Hz, (<u>H</u>CH)N); 3.44 (1H, d × t, *J* = 13.8, 7.0 Hz, (HC<u>H</u>)N); 3.63 (1H, d × d, *J* = 8.2, 6.5 Hz, CHO(H<u>C</u>H)O); 3.64 (1H, d × d, *J* = 8.8, 4.9 Hz, CHN); 4.15 (1H, d × d, *J* = 8.2, 6.5 Hz, CHO(HC<u>H</u>)O); 4.31 (1H, d × t, *J* = 8.8, 6.5 Hz, C<u>H</u>OCH_2O); 4.59 (1H, d, *J* = 4.9 Hz, COCHO); 4.63 and 4.91 (2 × 1H, 2 × d, *J* = 11.6 Hz, O(H<u>C</u>H)Ph); 7.29-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.7 ($CH_2\underline{C}H_3$); 20.2 ($\underline{C}H_2CH_3$); 25.2 and 26.9 ($(\underline{C}H_3)_2C$); 29.5 ($\underline{C}H_2CH_2N$); 41.0 (CH_2N); 60.4 (CHN); 66.9 (CHO<u>C</u>H_2O); 72.9 (O<u>C</u>H_2Ph); 77.2 (<u>C</u>HOCH_2O); 80.3 (CO<u>C</u>HO); 109.6 ($(CH_3)_2\underline{C}$); 127.9, 128.1 and 128.6 (5 x HC_{arom}); 137.1 ($C_{arom,quat}$); 167.7 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1729; ν_{max} = 2955, 1372, 1210, 1153, 1072, 1044, 854, 734, 698. MS (70 eV): m/z (%) 334 (M^++1, 100). Anal. Calcd. for $C_{19}H_{27}NO_4$: C 68.44, H 8.16, N 4.20. Found: C 68.60, H 7.94, N 4.25.

(3*R*,4*S*)-3-Benzyloxy-1-cyclohexyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 192d



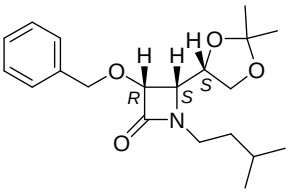
White crystals. Mp 99.8 °C. Recrystallization from absolute EtOH. Yield 65%. $[\alpha]_D$ = +109.9° (*c* = 0.95, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08-1.51 (3H, m, $(C\underline{H}_2)_5CHN$); 1.34 and 1.44 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.60-1.88 (7H, m, $(C\underline{H}_2)_5CHN$); 3.44-3.56 (1H, m, $(CH_2)_5C\underline{H}N$); 3.62 (1H, d × d, *J* = 8.4, 6.0 Hz, CHO(<u>H</u>CH)O); 3.69 (1H, d × d, *J* = 8.5, 4.8 Hz, CHOC<u>H</u>N); 4.18 (1H, d × d, *J* = 8.4, 6.3 Hz, CHO(HC<u>H</u>)O); 4.20-4.29 (1H, m, C<u>H</u>OCH_2O); 4.53 (1H, d, *J* = 4.8 Hz, COCHO); 4.63 and 4.92 (2 × 1H, 2 × d, *J* = 11.9 Hz, O(H<u>C</u>H)Ph); 7.28-7.38 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.16 ($\underline{C}H_3CCH_3$); 25.21 and 25.4 ($(\underline{C}H_2)_5CHN$); 26.8 ($CH_3C\underline{C}H_3$); 29.8 and 31.1 ($(\underline{C}H_2)_5CHN$); 52.4 ($(CH_2)_5\underline{C}HN$); 60.0 (CHO<u>C</u>HN); 67.0 (CHO<u>C</u>H_2O); 72.8 (O<u>C</u>H_2Ph); 77.2 (<u>C</u>HOCH_2O); 79.6 (CO<u>C</u>HO); 109.4 ($(CH_3)_2\underline{C}$); 127.8, 128.0 and 128.5 (5 x HC_{arom}); 137.1 ($C_{arom,quat}$); 167.0 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1724; ν_{max} = 2938, 1214, 1154, 1059, 860, 696. MS (70 eV): m/z (%) 360 (M^++1, 100). Anal. Calcd. for $C_{21}H_{29}NO_4$: C 70.17, H 8.13, N 3.90. Found: C 70.07, H 7.85, N 3.86.

(3*R*,4*S*)-3-Benzyloxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-propylazetidin-2-one 192e



Yellow oil. R_f = 0.12 (hexane/EtOAc 6/1). Yield 70%. $[\alpha]_D$ = +95.1° (*c* = 0.95, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$); 1.34 and 1.43 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.50-1.75 (2H, m, $C\underline{H}_2CH_3$); 3.15-3.24 and 3.34-3.43 (2 × 1H, 2 × m, (HCH)N); 3.63 (1H, d × d, *J* = 8.8, 6.1 Hz, CHO(HCH)O); 3.65 (1H, d × d, *J* = 8.8, 5.0 Hz, CHN); 4.15 (1H, d × d, *J* = 8.8, 6.1 Hz, CHO(HC$\underline{H}$)O); 4.31 (1H, d × t, *J* = 8.8, 6.1 Hz, C$\underline{H}$OCH$_2$O); 4.60 (1H, d, *J* = 5.0 Hz, COCHO); 4.64 and 4.92 (2 × 1H, 2 × d, *J* = 12.1 Hz, O(HC$\underline{H}$)Ph); 7.27-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5 ($CH_2\underline{C}H_3$); 20.8 ($\underline{C}H_2CH_3$); 25.1 and 26.8 ($(\underline{C}H_3)_2C$); 42.8 (CH_2N); 60.4 (CHN); 66.8 (CHO$\underline{C}H_2$O); 72.7 (O$\underline{C}H_2$Ph); 77.2 ($\underline{C}$HOCH$_2$O); 80.4 (CO$\underline{C}$HO); 109.3 ($(CH_3)_2\underline{C}$); 127.7, 127.9 and 128.5 (5 x HC_{arom}); 137.2 ($C_{arom,quat}$); 167.4 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1751; ν_{max} = 2934, 1371, 1210, 1153, 1064, 850, 698. MS (70 eV): m/z (%) 320 (M^++1, 100). HRMS (ESI) Calcd. for $C_{18}H_{26}NO_4$ 320.1862 $[M + H]^+$, found 320.1869.

(3*R*,4*S*)-3-Benzyloxy-1-isopentyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 192f



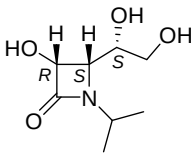
White crystals. Mp 93.9 °C. Recrystallization from absolute EtOH. Yield 50%. $[\alpha]_D$ = +106.6° (*c* = 0.92, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (6H, d, *J* = 6.1 Hz, $(C\underline{H}_3)_2$CH); 1.34 and 1.43 (2 × 3H, 2 × s, $(CH_3)_2C$); 1.39-1.58 (3H, m, $C\underline{H}_2CH_2N$ and $(CH_3)_2C\underline{H}$); 3.21 (1H, d × d × d, *J* = 14.3, 6.7, 6.7 Hz, (HCH)N); 3.48 (1H, d × d × d, *J* = 14.3, 7.0, 7.0 Hz, (HC$\underline{H}$)N); 3.62-3.66 (2H, m, CHN and CHO(HCH)O); 4.15 (1H, d × d, *J* = 7.7, 7.7 Hz, CHO(HC$\underline{H}$)O); 4.31 (1H, d × d × d, *J* = 7.7, 7.6, 7.6 Hz, C$\underline{H}$OCH$_2$O); 4.58 (1H, d, *J* = 5.0 Hz, COCHO); 4.63 and 4.91 (2 × 1H, 2 × d, *J* = 11.6 Hz, O(HC$\underline{H}$)Ph); 7.30-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.3 and 22.5 ($(\underline{C}H_3)_2$CH); 25.2 ($\underline{C}H_3CCH_3$); 25.9 ($(CH_3)_2\underline{C}$H); 26.9 ($CH_3C\underline{C}H_3$); 36.1 ($\underline{C}H_2CH_2N$); 39.6 (CH_2N); 60.2 (CHN); 66.9 (CHO$\underline{C}H_2$O); 72.9 (O$\underline{C}H_2$Ph); 77.2 ($\underline{C}$HOCH$_2$O); 80.2 (CO$\underline{C}$HO); 109.6 ($CH_3\underline{C}CH_3$); 127.9, 128.1 and 128.6 (5 x HC_{arom}); 137.1 ($C_{arom,quat}$); 167.6 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1727; ν_{max} = 2958, 1370, 1235, 1210, 1152, 1074, 853, 733, 698. MS (70 eV): m/z (%) 348 (M^++1, 100). Anal. Calcd. for $C_{20}H_{29}NO_4$: C 69.14, H 8.41, N 4.03. Found: C 69.16, H 8.44, N 4.01.

5.3.6 Synthesis of (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-ones

As a representative example, the synthesis of (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one **193a** is described. To a solution of (3*R*,4*S*)-3-benzyloxy-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one **192a** (3.19 g, 10 mmol, 1 equiv) in THF/H_2O (1/1, 100 mL) was added *p*TsOH·H_2O (1.72 g, 10 mmol, 1 equiv) in a single portion. After a reflux period of 4 hours, the resulting reaction mixture was allowed to cool to room temperature and was then neutralized with solid $NaHCO_3$. The mixture was extracted with EtOAc (3 × 40 mL), the combined organic layers was dried ($MgSO_4$), and the solvent was removed under reduced pressure. In the next step, palladium on activated carbon (20% w/w) was added to a solution of the latter diol (2.79 g, 10 mmol, 1 equiv) in methanol (60 mL) and the resulting mixture was placed in a Parr apparatus. The

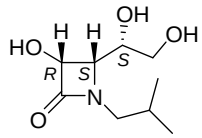
inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 18 hours at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite® and evaporation of the solvent *in vacuo* afforded crude (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one **193a**, which was purified by means of recrystallization from EtOAc/hexane (30/1).

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one 193a



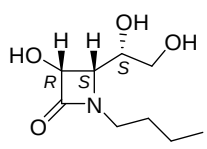
White crystals. Mp 85.0 °C. Recrystallization from EtOAc/hexane (30/1). Yield 83%. $[\alpha]_D$ = +171.5° (*c* = 0.78, MeOH). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 1.16 and 1.23 (2 × 3H, 2 × d, *J* = 6.7 Hz, $(C\underline{H}_3)_2CH$); 3.29-3.36 (1H, m, (<u>H</u>CH)OH); 3.46-3.60 (3H, m, (HC<u>H</u>)OH, CHOC<u>H</u>N, $CH_2C\underline{H}O$); 3.66 (1H, septet, *J* = 6.7 Hz, $(CH_3)_2C\underline{H}$); 4.53 (1H, d × d, *J* = 7.7, 4.4 Hz, COCHO); 4.57 (1H, t, *J* = 5.5 Hz, $CH_2O\underline{H}$); 4.77 (1H, d, *J* = 5.5 Hz, $CH_2CHO\underline{H}$); 5.91 (1H, d, *J* = 7.7 Hz, COCHO<u>H</u>). ^{13}C NMR (75 MHz, ref = $(CD_3)_2SO$): δ 20.5 and 21.8 ($(\underline{C}H_3)_2CH$); 45.2 ($(CH_3)_2\underline{C}H$); 59.6 (CHO<u>C</u>HN); 63.7 (CH_2OH); 72.5 ($CH_2\underline{C}HO$); 74.5 (CO<u>C</u>HO) 169.0 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3237; $\nu_{C=O}$ = 1706; ν_{max} = 1401, 1226, 1087, 814, 708. MS (70 eV): m/z (%) 190 (M^++1, 100). Anal. Calcd. for $C_8H_{15}NO_4$: C 50.78, H 7.99, N 7.40. Found: C 51.00, H 7.91, N 7.53.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isobutylazetidin-2-one 193b



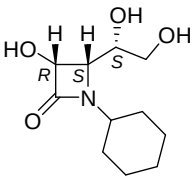
White crystals. Mp 98.3 °C. Recrystallization from EtOAc/hexane (30/1). Yield 74%. $[\alpha]_D$ = +152.8° (*c* = 0.93, MeOH). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 0.76 and 0.82 (2 × 3H, 2 × d, *J* = 7.1 Hz, $(C\underline{H}_3)_2CH$); 1.94 (1H, nonet, *J* = 7.1 Hz, $(CH_3)_2C\underline{H}$); 2.98 and 3.01 (2 × 1H, 2 × (d × d), *J* = 13.6, 7.1 Hz, (HCH)N); 3.28-3.36 (1H, m, (<u>H</u>CH)OH); 3.46 (1H, d × d × d, *J* = 11.0, 5.7, 3.9 Hz, (HC<u>H</u>)OH); 3.51 (1H, d × d, *J* = 8.3, 5.0 Hz, CHN); 3.60-3.68 (1H, m, $CH_2C\underline{H}O$); 4.56 (1H, t, *J* = 5.7 Hz, $CH_2O\underline{H}$); 4.65 (1H, d × d, *J* = 7.7, 5.0 Hz, COCHO); 4.75 (1H, d, *J* = 5.5 Hz, $CH_2CHO\underline{H}$); 5.92 (1H, d, *J* = 7.7 Hz, COCHO<u>H</u>). ^{13}C NMR (75 MHz, ref = $(CD_3)_2SO$): δ 20.5 and 20.9 ($(\underline{C}H_3)_2CH$); 26.8 ($(CH_3)_2\underline{C}H$); 49.0 (CH_2N); 59.8 (CHN); 63.7 (CH_2OH); 72.7 ($CH_2\underline{C}HO$); 75.0 (CO<u>C</u>HO), 169.8 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3284; $\nu_{C=O}$ = 1712; ν_{max} = 2951, 1425, 1166, 1082, 996, 831. MS (70 eV): m/z (%) 204 (M^++1, 100). Anal. Calcd. for $C_9H_{17}NO_4$: C 53.19, H 8.43, N 6.89. Found: C 53.37, H 8.13, N 6.49.

(3*R*,4*S*)-1-Butyl-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one 193c



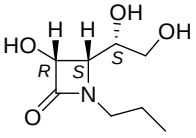
Yellow oil. R_f = 0.06 (EtOAc). Yield 63%. $[\alpha]_D$ = +185.6° (*c* = 0.72, MeOH). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 0.84 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$); 1.12-1.29 (2H, m, $C\underline{H}_2CH_3$); 1.47 (2H, pentet, *J* = 7.3 Hz, $C\underline{H}_2CH_2N$); 3.05-3.16 (1H, m, (<u>H</u>CH)N); 3.22-3.37 (2H, m, (HC<u>H</u>)N and (<u>H</u>CH)OH); 3.46 (1H, d × d × d, *J* = 11.1, 5.5, 3.4 Hz, (HC<u>H</u>)OH); 3.50 (1H, d × d, *J* = 8.6, 4.7 Hz, CHN); 3.59-3.67 (1H, m, $CH_2C\underline{H}O$); 4.60 (1H, t, *J* = 5.5 Hz, $CH_2O\underline{H}$); 4.61 (1H, d × d, *J* = 7.6, 4.7 Hz, COCHO); 4.80 (1H, d, *J* = 5.5 Hz, $CH_2CHO\underline{H}$); 5.93 (1H, d, *J* = 7.6 Hz, COCHO<u>H</u>). ^{13}C NMR (75 MHz, ref = $(CD_3)_2SO$): δ 14.1 ($CH_2\underline{C}H_3$); 20.1 ($\underline{C}H_2CH_3$); 29.5 ($\underline{C}H_2CH_2N$); 40.9 (CH_2N); 59.4 (CHN); 63.7 (CH_2OH); 72.7 ($CH_2\underline{C}HO$); 75.0 (CO<u>C</u>HO), 169.6 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3330; $\nu_{C=O}$ = 1719; ν_{max} = 2955, 1372, 1210, 1153, 1044, 854, 734, 698. MS (70 eV): m/z (%) 204 (M^++1, 100). HRMS (ESI) Calcd. for $C_9H_{18}NO_4$ 204.1236 $[M + H]^+$, found 204.1232.

(3*R*,4*S*)-1-Cyclohexyl-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one 193d



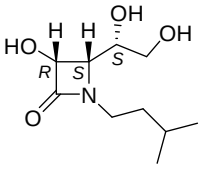
White crystals. Mp 101.3 °C. Recrystallization from EtOAc/hexane (30/1). Yield 88%. $[\alpha]_D$ = +218.3° (*c* = 0.62, MeOH). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 0.97-1.22 and 1.49-1.85 (3H and 7H, 2 × m, $(C\underline{H}_2)_5CHN$); 3.19-3.28 (1H, m, $(CH_2)_5C\underline{H}N$); 3.32 (1H, d × d, *J* = 11.3, 5.8 Hz, (HCH)OH); 3.44-3.61 (3H, m, (HC<u>H</u>)OH, CHOC<u>H</u>N and $CH_2C\underline{H}O$); 4.52 (1H, d × d, *J* = 7.7, 5.0 Hz, COCHO); 4.58 (1H, t, *J* = 5.8 Hz, $CH_2O\underline{H}$); 4.76 (1H, d, *J* = 4.9 Hz, $CH_2CHO\underline{H}$); 5.91 (1H, d, *J* = 7.7 Hz, COCHO<u>H</u>). ^{13}C NMR (75 MHz, ref = $(CD_3)_2SO$): δ 25.3, 25.6, 25.7, 30.5 and 31.2 ($(\underline{C}H_2)_5CHN$); 53.3 ($(CH_2)_5\underline{C}HN$); 59.4 (CHO<u>C</u>HN); 63.7 (CH_2OH); 72.6 ($CH_2\underline{C}HO$); 74.4 (CO<u>C</u>HO); 169.0 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3197; $\nu_{C=O}$ = 1704; ν_{max} = 2933, 1450, 1150, 1055, 699, 674. MS (70 eV): m/z (%) 230 (M^++1, 100). Anal. Calcd. for $C_{11}H_{19}NO_4$: C 57.62, H 8.35, N 6.11. Found: C 57.34, H 8.15, N 5.98.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-propylazetidin-2-one 193e



Yellow oil. R_f = 0.08 (EtOAc). Yield 68%. $[\alpha]_D$ = +229.6° (*c* = 0.55, MeOH). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 0.79 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$); 1.40-1.60 (2H, m, $C\underline{H}_2CH_3$); 3.04-3.12 and 3.15-3.26 (2 × 1H, 2 × m, (HCH)N); 3.27-3.36 (1H, m, (<u>H</u>CH)OH); 3.47 (1H, d × d × d, *J* = 11.0, 5.5, 3.3 Hz, (HC<u>H</u>)OH); 3.50 (1H, d × d, *J* = 8.3, 4.7 Hz, CHN); 3.59-3.67 (1H, m, $CH_2C\underline{H}O$); 4.57 (1H, t, *J* = 5.5 Hz, $CH_2O\underline{H}$); 4.62 (1H, d × d, *J* = 7.7, 4.7 Hz, COCHO); 4.77 (1H, d, *J* = 5.5 Hz, $CH_2CHO\underline{H}$); 5.92 (1H, d, *J* = 7.7 Hz, COCHO<u>H</u>). ^{13}C NMR (75 MHz, ref = $(CD_3)_2SO$): δ 11.9 ($CH_2\underline{C}H_3$); 20.8 ($\underline{C}H_2CH_3$); 43.1 (CH_2N); 59.4 (CHN); 63.7 (CH_2OH); 72.6 ($CH_2\underline{C}HO$); 75.0 (CO<u>C</u>HO); 169.7 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3319; $\nu_{C=O}$ = 1719; ν_{max} = 2935, 1419, 1070, 1026. MS (70 eV): m/z (%) 190 (M^++1, 100). HRMS (ESI) Calcd. for $C_8H_{16}NO_4$ 190.1079 $[M + H]^+$, found 190.1077.

(3*R*,4*S*)-3-Hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopentylazetidin-2-one 193f



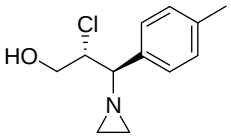
Colourless oil. R_f = 0.07 (EtOAc). Yield 93%. $[\alpha]_D$ = +163.9° (*c* = 0.52, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (6H, d, *J* = 6.1 Hz, $(C\underline{H}_3)_2CH$); 1.43-1.59 (3H, m, $C\underline{H}_2CH_2N$ and $(CH_3)_2C\underline{H}$); 3.10 (1H, d × d × d, *J* = 14.2, 6.9, 6.9 Hz, (<u>H</u>CH)N); 3.57 (1H, d × d × d, *J* = 14.2, 7.5, 7.4 Hz, (HC<u>H</u>)N); 3.65-3.82 (3H, m, CHN and $C\underline{H}_2OH$); 4.02-4.06 (1H, m, $CH_2C\underline{H}O$); 4.85 (1H, d, *J* = 4.4 Hz, COCHO). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.1 and 22.5 ($(\underline{C}H_3)_2CH$); 25.8 ($(CH_3)_2\underline{C}H$); 35.7 ($\underline{C}H_2CH_2N$); 40.2 (CH_2N); 59.4 (CHN); 64.1 (CH_2OH); 71.7 ($CH_2\underline{C}HO$); 74.6 (CO<u>C</u>HO); 170.6 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3326; $\nu_{C=O}$ = 1720; ν_{max} = 2955, 1420, 1072, 1034. MS (70 eV): m/z (%) 218 (M^++1, 100). HRMS (ESI) Calcd. for $C_{10}H_{20}NO_4$ 218.1392 $[M + H]^+$, found 218.1390.

5.4 Synthesis of 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines

As a representative example, the synthesis of *anti*-1-[2-chloro-3-hydroxy-1-(4-methylphenyl)propyl]aziridine **5a** is described. To an ice-cooled solution of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **2a** (2.07 g, 8 mmol, 1 equiv) in THF (50 mL) was added $LiAlH_4$ (0.30 g, 8 mmol, 1 molar equiv) in small portions. Subsequently, the resulting suspension was stirred at room temperature for 91 hours, after which water (10 mL) was added cautiously at 0 °C in

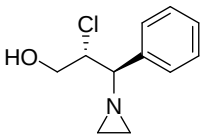
order to neutralize the excess of $LiAlH_4$. Afterwards, the mixture was filtered through Celite®, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent *in vacuo* afforded *anti*-1-[2-chloro-3-hydroxy-1-(4-methylphenyl)propyl]-aziridine **5a**, which was purified in 40% yield by column chromatography on silica gel (hexane/EtOAc 3/2).

***Anti*-1-[2-chloro-3-hydroxy-1-(4-methylphenyl)propyl]aziridine 5a**



White crystals. Mp 68.7 °C. R_f = 0.06 (hexane/EtOAc 3/2). Yield 40%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (1H, d × d, *J* = 6.5, 4.4 Hz, (HCH)N); 1.76 (1H, d × d, *J* = 5.7, 4.1 Hz, (HCH)N); 1.80 (1H, d × d, *J* = 6.5, 4.1 Hz, (HCH)N); 2.18 (1H, d × d, *J* = 5.7, 4.4 Hz, (HCH)N); 2.36 (3H, s, CH_3); 3.00 (1H, d, *J* = 4.4 Hz, CHN); 3.77–3.84 (1H, m, (HCH)OH); 4.08 (1H, d, *J* = 12.7 Hz, (HCH)OH); 4.16–4.22 (2H, m, CHCl and OH); 7.18 and 7.28 (2 × 2H, 2 × d, *J* = 8.2 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (CH_3); 25.2 and 31.6 (2 × CH_2N); 63.8 (CH_2OH); 66.1 (CHCl); 76.9 (CHN); 127.7 and 129.2 (4 x HC_{arom}); 136.5 and 137.8 (2 x $C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3188; ν_{max} = 2898, 1312, 1258, 1048, 1008, 856, 811, 690. MS (70 eV): m/z (%) 226/8 (M^++1, 100). Anal. Calcd. for $C_{12}H_{16}ClNO$: C 63.85, H 7.14, N 6.21. Found: C 63.62, H 7.54, N 6.41.

***Anti*-1-(2-chloro-3-hydroxy-1-phenylpropyl)aziridine 5b**



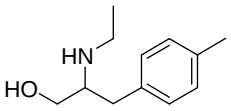
White crystals. Mp 73.5 °C. R_f = 0.10 (hexane/EtOAc 3/2). Yield 55%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (1H, d × d, *J* = 6.9, 4.6 Hz, (HCH)N); 1.77 (1H, d × d, *J* = 5.7, 4.4 Hz, (HCH)N); 1.81 (1H, d × d, *J* = 6.9, 4.4 Hz, (HCH)N); 2.20 (1H, d × d, *J* = 5.7, 4.6 Hz, (HCH)N); 3.03 (1H, d, *J* = 6.4 Hz, CHN); 3.80–3.84 (1H, m, (HCH)OH); 4.05-4.14 (2H, m, (HCH)OH and OH); 4.22 (1H, d × d, *J* = 6.4, 3.5 Hz, CHCl); 7.29–7.42 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3 and 31.6 (2 × CH_2N); 63.7 (CH_2OH); 66.0 (CHCl); 77.1 (CHN); 127.8, 128.0, 128.5 (5 x HC_{arom}); 139.5 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3322; ν_{max} = 2869, 1453, 1257, 1047, 1029, 756, 700. MS (70 eV): m/z (%) 212/4 (M^++1, 100). Anal. Calcd. for $C_{11}H_{14}ClNO$: C 62.41, H 6.67, N 6.62. Found: C 62.31, H 6.96, N 6.38.

5.5 Synthesis of 3-aryl-2-(ethylamino)propan-1-ols

As a representative example, the synthesis of 2-(*N*-ethylamino)-3-(4-methylphenyl)propan-1-ol **127a** is described. To an ice-cooled solution of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **2a** (0.52 g, 2 mmol, 1 equiv) in THF (30 mL) was added $LiAlH_4$ (0.23 g, 6 mmol, 3 molar equiv) in small portions. Subsequently, the resulting suspension was heated under reflux for 48 hours, after which water (5 mL) was added cautiously at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterwards, the mixture was filtered through Celite®, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent *in vacuo*

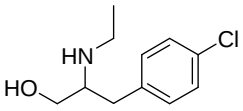
afforded 2-(*N*-ethylamino)-3-(4-methylphenyl)propan-1-ol **127a**, which was purified in 61% yield by recrystallization from EtOAc/hexane (30/1).

2-(*N*-Ethylamino)-3-(4-methylphenyl)propan-1-ol 127a



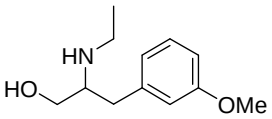
White crystals. Mp 102.3 °C. Recrystallization from EtOAc/hexane (30/1). Yield 61%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); 1.80 (2H, s(broad), OH and NH); 2.33 (3H, s, $C_{quat}CH_3$); 2.59–2.78 (4H, m, $C\underline{H}_2CH_3$ and $C\underline{H}_2C_{quat}$); 2.84–2.92 (1H, m, CHN); 3.29 and 3.60 (2 × 1H, 2 × (d × d), *J* = 10.5, 5.5, 3.9 Hz, (<u>H</u>C<u>H</u>)OH); 7.06 and 7.11 (2 × 2H, 2 × d, *J* = 8.0 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6 ($CH_2\underline{C}H_3$); 21.0 ($C_{quat}\underline{C}H_3$); 37.7 ($\underline{C}H_2C_{quat}$); 41.2 ($\underline{C}H_2CH_3$); 60.0 (CHN); 62.4 (CH_2OH); 129.0 and 129.3 (4 x HC_{arom}); 135.5 and 135.9 (2 x $C_{arom,quat}$). IR (ATR, cm^{-1}): $\nu_{OH,NH}$ = 3254; ν_{max} = 2821, 1445, 1121, 1074, 1038, 947, 931, 802. MS (70 eV): m/z (%) 194 (M^++1, 100). Anal. Calcd. for $C_{12}H_{19}NO$: C 74.57, H 9.91, N 7.25. Found: C 74.24, H 10.26, N 7.09.

3-(4-Chlorophenyl)-2-(*N*-ethylamino)propan-1-ol 127c



White crystals. Mp 101.3 °C. Recrystallization from EtOAc/hexane (30/1). Yield 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); 1.87 (2H, s(broad), OH and NH); 2.59–2.79 (4H, m, $C\underline{H}_2CH_3$ and $C\underline{H}_2C_{quat}$); 2.83–2.91 (1H, m, CHN); 3.28 and 3.59 (2 × 1H, 2 × (d × d), *J* = 10.6, 5.2, 3.9 Hz, (<u>H</u>C<u>H</u>)OH); 7.12 and 7.27 (2 × 2H, 2 × d, *J* = 8.0 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.5 ($CH_2\underline{C}H_3$); 37.4 ($\underline{C}H_2C_{quat}$); 41.3 ($\underline{C}H_2CH_3$); 60.0 (CHN); 62.2 (CH_2OH); 128.7 and 130.5 (4 x HC_{arom}); 132.2 and 137.1 (2 x $C_{arom,quat}$). IR (ATR, cm^{-1}): $\nu_{OH,NH}$ = 3268; ν_{max} = 2888, 1482, 1114, 1099, 838, 802. MS (70 eV): m/z (%) 214/6 (M^++1, 100). Anal. Calcd. for $C_{11}H_{16}ClNO$: C 61.82, H 7.55, N 6.55. Found: C 61.72, H 7.43, N 6.50.

2-(*N*-Ethylamino)-3-(3-methoxyphenyl)propan-1-ol 127d



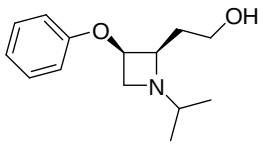
White crystals. Mp 101.6 °C. Recrystallization from EtOAc/hexane (30/1). Yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, t, *J* = 6.9 Hz, $CH_2C\underline{H}_3$); 2.01 (2H s(broad), OH and NH); 2.57–2.81 (4H, m, $C\underline{H}_2CH_3$ and $C\underline{H}_2C_{quat}$); 2.88–2.95 (1H, m, CHN); 3.32 and 3.61 (2 × 1H, 2 × (d × d), *J* = 10.5, 5.5, 3.8 Hz, (<u>H</u>C<u>H</u>)OH); 3.80 (3H, s, CH_3O); 6.73–6.79 and 7.19–7.25 (3H and 1H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.5 ($CH_2\underline{C}H_3$); 38.1 ($\underline{C}H_2C_{quat}$); 41.4 ($\underline{C}H_2CH_3$); 55.1 (CH_3O); 60.1 (CHN); 62.5 (CH_2OH); 111.7, 115.0, 121.6, 129.6 (4 x HC_{arom}); 140.3 ($CH_2\underline{C}_{quat}$); 159.8 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): $\nu_{OH,NH}$ = 3272; ν_{max} = 2805, 1586, 1488, 1252, 1152, 1030, 797, 779, 697. MS (70 eV): m/z (%) 210 (M^++1, 100). Anal. Calcd. for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69. Found: C 69.01, H 9.23, N 6.50.

5.6 Synthesis of azetidines

5.6.1 Synthesis of 2-(2-hydroxyethyl)azetidines

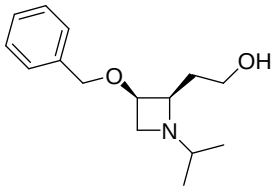
As a representative example, the synthesis of *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **151a** is described. To a solution of aluminium(III) chloride (1.07 g, 8 mmol, 1 equiv) in dry Et_2O (30 mL) was added carefully lithium aluminium hydride (0.91 g, 24 mmol, 3 molar equiv) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. Subsequently, a solution of *cis*-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidin-2-one **12a** (2.91 g, 8 mmol, 1 equiv) in dry Et_2O (15 mL) was added slowly, and after the addition was complete, the reaction mixture was stirred for 2 hours at 0 °C, after which water (10 mL) was added cautiously at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterwards, the reaction mixture was filtered and extracted with Et_2O (3 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded a mixture of *cis*-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-isopropyl-3-phenoxyazetidine and *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **151a**. In the next step, TBAF (2.30 g, 8.8 mmol, 1.1 equiv) was added to an ice-cooled solution of the latter reaction mixture in THF (30 mL), and the resulting solution was stirred at room temperature for 5 hours. Subsequently, the reaction mixture was poured into brine and extracted with CH_2Cl_2 (3 × 25 mL), after which the organic fraction was dried ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent *in vacuo*. Purification by means of column chromatography on silica gel (CH_2Cl_2/MeOH 95/5) afforded pure *cis*-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine **151a** in 48% yield.

Cis-2-(2-hydroxyethyl)-1-isopropyl-3-phenoxyazetidine 151a



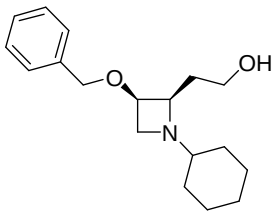
White crystals. Mp 70.2 °C. R_f = 0.10 (CH_2Cl_2/MeOH 95/5). Yield 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 and 1.07 (2 × 3H, 2 × d, *J* = 6.2 Hz, ($C\underline{H}_3$)$_2$CHN); 1.83-1.92 and 2.18-2.35 (2 × 1H, 2 × m, ($\underline{H}C\underline{H}$)CHN); 2.56 (1H, septet, *J* = 6.2 Hz, (CH_3)$_2$C$\underline{H}$N); 3.28 (1H, d × d, *J* = 9.9, 7.7 Hz, ($\underline{H}$CH)N); 3.62 (1H, d × d × d, *J* = 9.9, 2.9, 1.1 Hz, (HC$\underline{H}$)N); 3.70-3.79 (2H, m, ($\underline{H}$CH)OH and $CH_2C\underline{H}$N); 4.07 (1H, d × d × d, *J* = 11.7, 8.1, 2.9 Hz, ($\underline{H}$CH)OH); 4.91 (1H, d × d × d, *J* = 7.7, 7.7, 2.9 Hz, C$\underline{H}$OPh); 6.76-6.79, 6.93-6.98 and 7.23-7.29 (5H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 and 21.0 (($\underline{C}H_3$)$_2$CHN); 32.2 ($\underline{C}H_2$CHN); 56.7 (CH_2N); 57.7 ((CH_3)$_2\underline{C}$HN); 60.8 (CH_2OH); 66.0 ($CH_2\underline{C}$HN); 68.8 (CHO); 114.9, 121.1 and 129.5 (5 x HC_{arom}); 157.2 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3360; ν_{max} = 2966, 2932, 1587, 1495, 1239, 1116, 690. MS (70 eV): m/z (%) 236 (M^++1, 100). Anal. Calcd. for $C_{14}H_{21}NO_2$: C 71.46, H 8.99, N 5.95. Found: C 71.72, H 9.31, N 5.88.

***Cis*-3-benzyloxy-2-(2-hydroxyethyl)-1-isopropylazetidine 151b**



White crystals. Mp 76.3 °C. R_f = 0.10 (CH_2Cl_2/MeOH 95/5). Yield 49%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 and 1.01 (2 × 3H, 2 × d, *J* = 6.2 Hz, (C<u>H</u>$_3$)$_2$CHN); 1.76-1.85 and 2.15-2.27 (2 × 1H, 2 × m, (<u>H</u>C<u>H</u>)CHN); 2.47 (1H, septet, *J* = 6.2 Hz, (CH$_3$)$_2$C<u>H</u>N); 3.04 (1H, d × d, *J* = 9.4, 6.6 Hz, (<u>H</u>CH)N); 3.49-3.63 (2H, m, (HC<u>H</u>)N and CH$_2$C<u>H</u>N); 3.72 (1H, d × d × d, *J* = 10.4, 5.1, 4.3 Hz, (<u>H</u>CH)OH); 3.91 (1H, d × d × d, *J* = 10.4, 10.2, 3.0 Hz, (HC<u>H</u>)OH); 4.25 (1H, d × d × d, *J* = 6.6, 6.6, 2.8 Hz, CHO); 4.39 and 4.58 (2 × 1H, 2 × d, *J* = 11.8 Hz, O(<u>H</u>C<u>H</u>)Ph); 7.28-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.2 and 21.1 ((<u>C</u>H$_3$)$_2$CHN); 32.5 (<u>C</u>H$_2$CHN); 56.3 (CH$_2$N); 57.6 ((CH$_3$)$_2$<u>C</u>HN); 60.8 (CH$_2$OH); 67.0 (CH$_2$<u>C</u>HN); 70.5 (CHO); 70.9 (O<u>C</u>H$_2$Ph); 127.8, 128.4 and 128.4 (5 x HC_{arom}); 137.7 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3380; ν_{max} = 2963, 1454, 1351, 1198, 1119, 1056, 1028, 733. MS (70 eV): m/z (%) 250 (M^++1, 100). Anal. Calcd. for $C_{15}H_{23}NO_2$: C 72.25, H 9.30, N 5.62. Found: C 72.17, H 9.44, N 5.61.

***Cis*-3-benzyloxy-1-cyclohexyl-2-(2-hydroxyethyl)azetidine 151c**



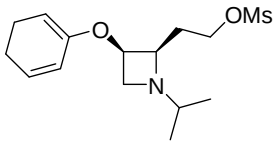
White crystals. Mp 93.3 °C. Recrystallization from EtOAc/hexane (25/1). Yield 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88-1.28 and 1.61-1.80 (5H and 6H, 2 × m, (C<u>H</u>$_2$)$_5$CHN and (<u>H</u>CH)CH$_2$O); 2.05-2.15 (1H, m, (CH$_2$)$_5$C<u>H</u>N); 2.17-2.26 (1H, m, (HC<u>H</u>)CH$_2$O); 3.02 and 3.55 (2 × 1H, 2 × (d × d), *J* = 9.5, 6.5, 2.8 Hz, (<u>H</u>C<u>H</u>)N); 3.57-3.59 (1H, m, OCH$_2$CH$_2$C<u>H</u>N); 3.71 and 3.92 (2 × 1H, 2 × (d × d × d), *J* = 10.3, 10.2, 5.1, 5.1, 3.1 Hz, (<u>H</u>C<u>H</u>)OH); 4.26 (1H, d × d × d, *J* = 6.6, 6.5, 2.8 Hz, CHO); 4.38 and 4.58 (2 × 1H, 2 × d, *J* = 11.9 Hz, O(<u>H</u>C<u>H</u>)Ph); 7.28-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 24.7, 24.8, 25.9, 30.4 and 31.5 ((<u>C</u>H$_2$)$_5$CHN); 32.7 (<u>C</u>H$_2$CH$_2$O); 56.1 (CH$_2$N); 61.0 (CH$_2$OH); 66.3 ((CH$_2$)$_5$<u>C</u>HN); 66.9 (OCH$_2$CH$_2$<u>C</u>HN); 71.0 (O<u>C</u>H$_2$Ph); 71.1 (CHO); 127.8, 128.48 and 128.49 (5 x HC_{arom}); 137.8 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3147; ν_{max} = 2929, 2854, 1355, 1182, 1116, 1046, 1017, 736, 698. MS (70 eV): m/z (%) 290 (M^++1, 100). Anal. Calcd. for $C_{18}H_{27}NO_2$: C 74.70, H 9.40, N 4.84. Found: C 74.52, H 9.54, N 4.84.

5.6.2 Synthesis of 2-(2-mesyloxyethyl)azetidines

The synthesis of 2-(2-mesyloxyethyl)azetidines **13** was analogous to the synthesis of 4-(2-mesyloxyethyl)azetidin-2-ones **17** (Section 5.3.4), using 2-(2-hydroxyethyl)azetidines **151** as the starting material.

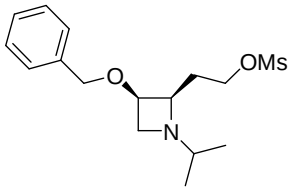
Due to the high intrinsic reactivity of azetidines **13**, no accurate HRMS data could be obtained.

***Cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine 13a**



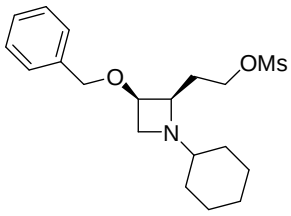
Colourless oil. Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 and 1.03 (2 × 3H, 2 × d, *J* = 6.1 Hz, ($C\underline{H}_3$)$_2$CHN); 2.01-2.12 (1H, m, ($\underline{H}$CH)CHN); 2.44-2.65 (2H, m, (CH_3)$_2$C$\underline{H}$N and (HC$\underline{H}$)CHN); 2.96 (3H, s, CH_3SO_3); 3.19 (1H, d × d, *J* = 9.4, 6.1 Hz, ($\underline{H}$CH)N); 3.50 (1H, d × d × d, *J* = 9.4, 1.9, 1.1 Hz, (HC$\underline{H}$)N); 3.63 (1H, d × d × d, *J* = 10.1, 6.3, 3.4 Hz, $CH_2C\underline{H}$N); 4.25-4.40 (2H, m, CH_2O); 4.83 (1H, d × d × d, *J* = 6.3, 6.1, 1.9 Hz, C$\underline{H}$OPh); 6.76-6.79, 6.88-7.03 and 7.23-7.34 (5H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.0 and 21.1 (($\underline{C}H_3$)$_2$CHN); 30.2 ($\underline{C}H_2$CHN); 37.3 (CH_3SO_3); 56.8 (CH_2N); 57.9 ((CH_3)$_2\underline{C}$HN); 64.0 ($CH_2\underline{C}$HN); 67.8 (CH_2O); 68.0 (CHO); 115.1, 121.3 and 129.7 (5 x HC_{arom}); 157.1 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): ν_{max} = 2966, 2939, 2872, 1492, 1352, 1234, 1171, 967, 930, 754, 692. MS (70 eV): m/z (%) 314 (M^++1, 100).

***Cis*-3-benzyloxy-1-isopropyl-2-(2-mesyloxyethyl)azetidine 13b**



Colourless oil. Yield 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 and 0.98 (2 × 3H, 2 × d, *J* = 6.3 Hz, ($C\underline{H}_3$)$_2$CHN); 1.90-2.01 (1H, m, ($\underline{H}$CH)CHN); 2.38-2.53 (2H, m, (CH_3)$_2$C$\underline{H}$N and (HC$\underline{H}$)CHN); 2.91 (3H, s, CH_3SO_3); 2.93-3.01 (1H, m, ($\underline{H}$CH)N); 3.35-3.55 (2H, m, (HC$\underline{H}$)N and $CH_2C\underline{H}$N); 4.15 (1H, d × d × d, *J* = 6.0, 6.0, 1.7 Hz, CHO); 4.21-4.35 (2H, m, $CH_2C\underline{H}_2O$); 4.36 and 4.61 (2 × 1H, 2 × d, *J* = 12.1 Hz, O($\underline{H}C\underline{H}$)Ph); 7.28-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.1 and 21.2 (($\underline{C}H_3$)$_2$CHN); 30.1 ($\underline{C}H_2$CHN); 37.1 (CH_3SO_3); 56.5 (CH_2N); 57.9 ((CH_3)$_2\underline{C}$HN); 64.4 ($CH_2\underline{C}$HN); 68.3 ($CH_2\underline{C}H_2O$); 69.6 (CHO); 70.8 (O$\underline{C}H_2$Ph); 127.76, 127.83 and 128.4 (5 x HC_{arom}); 138.0 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{max} = 2964, 2931, 2855, 1352, 1172, 960, 925, 813, 735, 698. MS (70 eV): m/z (%) 328 (M^++1, 100).

***Cis*-3-benzyloxy-1-cyclohexyl-2-(2-mesyloxyethyl)azetidine 13c**



Yellow oil. Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99-1.25 and 1.59-1.74 (6H and 4H, 2 × m, ($C\underline{H}_2$)$_5$CHN); 1.90-2.01 and 2.03-2.13 (2 × 1H, 2 × m, ($\underline{H}C\underline{H}$)$CH_2O$); 2.41-2.53 (1H, m, ($CH_2$)$_5C\underline{H}$N); 2.90 (3H, s, CH_3SO_3); 2.94-2.98 (1H, m, ($\underline{H}$CH)N); 3.44-3.51 (2H, m, (HC$\underline{H}$)N and $OCH_2CH_2C\underline{H}$N); 4.16 (1H, d × d × d, *J* = 6.1, 6.1, 1.1 Hz, CHO); 4.21-4.35 (2H, m, $CH_2C\underline{H}_2O$); 4.36 and 4.61 (2 × 1H, 2 × d, *J* = 11.9 Hz, O($\underline{H}C\underline{H}$)Ph); 7.28-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 24.6, 24.7, 25.8, 30.1 and 30.2 (($\underline{C}H_2$)$_5$CHN); 31.4 ($\underline{C}H_2CH_2O$); 37.1 (CH_3SO_3); 56.2 (CH_2N); 64.3 ($CH_2\underline{C}H_2O$); 66.4 ((CH_2)$_5\underline{C}$HN); 68.4 ($OCH_2CH_2\underline{C}$HN); 70.0 (O$\underline{C}H_2$Ph); 70.9 (CHO); 127.8, 127.9 and 128.4 (5 x HC_{arom}); 138.0 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{max} = 3029, 2927, 2853, 1350, 1172, 969, 921, 812, 734, 699. MS (70 eV): m/z (%) 368 (M^++1, 100).

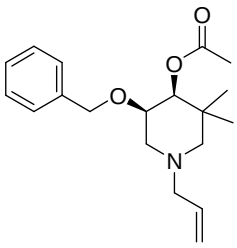
5.7 Synthesis of piperidines

5.7.1 Synthesis of 4-acetoxy-5,5-dimethylpiperidines

As a representative example, the synthesis of *cis*-4-acetoxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine **139c** is described. To a solution of *cis*-2-(2-bromo-1,1-dimethylethyl)-1-isopropyl-

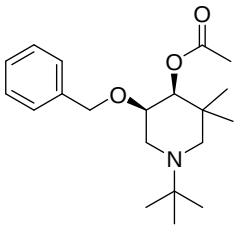
3-phenoxyazetidine **8c** (3.26 g, 10 mmol, 1 equiv) in DMSO (50 mL) was added NaOAc (8.20 g, 100 mmol, 10 equiv) at room temperature. After stirring at 100 °C for 18 hours, the reaction mixture was poured into water (40 mL) and extracted with Et_2O (3 × 25 mL). Afterwards, the organic phase was washed intensively with brine (4 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded *cis*-4-acetoxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine **139c**, which was further purified in 62% yield by column chromatography on silica gel (hexane/EtOAc 14/1).

Cis-4-acetoxy-1-allyl-3-benzyloxy-5,5-dimethylpiperidine 139a



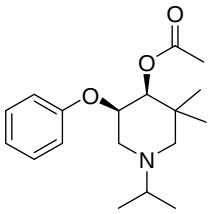
Colourless oil. R_f = 0.08 (hexane/EtOAc 10/1). Yield 64%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 and 1.07 (2 × 3H, 2 × s, C(C<u>H</u>$_3$)(C<u>H</u>$_3$)); 2.06 (1H, d, *J* = 11.0 Hz, N(<u>H</u>CH)C$_{quat}$); 2.11 (3H, s, CH_3C=O); 2.22-2.26 (2H, m, N(HC<u>H</u>)C$_{quat}$ and N(<u>H</u>CH)CHO); 2.76-2.78 (1H, m, N(HC<u>H</u>)CHO); 2.95 and 3.04 (2 × 1H, 2 × (d × d), *J* = 13.8, 6.3, 6.1 Hz, N(<u>H</u>C<u>H</u>)CH=CH$_2$); 3.80 (1H, d × d × d, *J* = 10.5, 4.7, 3.0 Hz, C<u>H</u>OBn); 4.43 and 4.65 (2 × 1H, 2 × d, *J* = 11.9 Hz, (HCH)O); 5.10-5.20 (3H, m, CHOC=O and C<u>H</u>$_2$=CH), 5.81 (1H, m, CH$_2$=C<u>H</u>); 7.23-7.36 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.0 (<u>C</u>H$_3$C=O); 24.4 and 24.9 (C(<u>C</u>H$_3$)(<u>C</u>H$_3$)); 35.2 (<u>C</u>(CH$_3$)$_2$); 53.3 (N<u>C</u>H$_2$CHO); 59.9 (N<u>C</u>H$_2$C$_{quat}$); 61.4 (N<u>C</u>H$_2$CH=CH$_2$); 70.8 (CH$_2$O); 73.0 (<u>C</u>HOBn); 73.6 (<u>C</u>HOC=O); 117.5 (<u>C</u>H$_2$=CH); 127.6, 127.8 and 128.4 (5 x HC$_{arom}$); 135.6 (CH$_2$=<u>C</u>H); 138.5 (C$_{arom,quat}$); 170.5 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1739; ν_{max} = 2955, 1371, 1236, 1117, 1091, 1018, 735, 698. MS (70eV): m/z (%) 318 (M^++1, 100). Anal. Calcd. for $C_{19}H_{27}NO_3$: C 71.89, H 8.57, N 4.41. Found: C 72.08, H 8.43, N 4.29.

Cis-4-acetoxy-3-benzyloxy-1-_tert_-butyl-5,5-dimethylpiperidine 139b



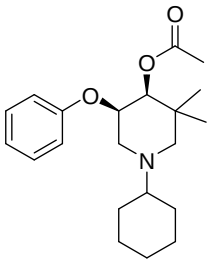
Colourless oil. R_f = 0.11 (hexane/EtOAc 6/1). Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, s, C(C<u>H</u>$_3$)(CH$_3$)); 1.03 (9H, s, C(CH$_3$)$_3$); 1.05 (3H, s, C(CH$_3$)(C<u>H</u>$_3$)); 2.11 (3H, s, CH_3C=O); 2.18 (1H, d, *J* = 11.0 Hz, N(<u>H</u>CH)C$_{quat}$); 2.28-2.32 (2H, m, N(HC<u>H</u>)C$_{quat}$ and N(<u>H</u>CH)CHO); 2.87-2.95 (1H, m, N(HC<u>H</u>)CHO); 3.72 (1H, d × d × d, *J* = 10.4, 4.7, 3.0 Hz, C<u>H</u>OBn); 4.40 and 4.66 (2 × 1H, 2 × d, *J* = 11.6 Hz, (HCH)O); 5.09 (1H, s(broad), CHOC=O); 7.28-7.36 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.1 (<u>C</u>H$_3$C=O); 24.4 and 24.8 (C(<u>C</u>H$_3$)(<u>C</u>H$_3$)); 26.6 (C(<u>C</u>H$_3$)$_3$); 35.1 (<u>C</u>(CH$_3$)$_2$); 46.4 (N<u>C</u>H$_2$CHO); 53.0 (N<u>C</u>H$_2$C$_{quat}$); 53.3 (<u>C</u>(CH$_3$)$_3$); 70.9 (CH$_2$O); 73.9 (<u>C</u>HOC=O); 74.4 (<u>C</u>HOBn); 127.6, 127.9 and 128.4 (5 x HC$_{arom}$); 138.6 (C$_{arom,quat}$); 170.7 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1737; ν_{max} = 2968, 1370, 1239, 1223, 1208, 1100, 980, 735, 697. MS (70eV): m/z (%) 334 (M^++1, 100). Anal. Calcd. for $C_{20}H_{31}NO_3$: C 72.04, H 9.37, N 4.20. Found: C 71.83, H 9.65, N 4.12.

***Cis*-4-acetoxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine 139c**



Colourless oil. R_f = 0.09 (hexane/EtOAc 14/1). Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, s, C(C<u>H</u>$_3$)(CH$_3$)); 1.01 (6H, d, *J* = 6.6 Hz, NCH(C<u>H</u>$_3$)$_2$); 1.13 (3H, s, C(CH$_3$)(C<u>H</u>$_3$)); 2.09 (3H, s, CH$_3$C=O); 2.14 and 2.34 (2 × 1H, 2 × d, *J* = 11.3 Hz, N(<u>H</u>C<u>H</u>)C$_{quat}$); 2.61 (1H, d × d, *J* = 10.2, 10.0 Hz, N(<u>H</u>CH)CHO); 2.72-2.85 (2H, m, N(HC<u>H</u>)CHO and NC<u>H</u>(CH$_3$)$_2$); 4.60 (1H, d × d × d, *J* = 10.0, 4.5, 3.2 Hz, C<u>H</u>OPh); 5.05 (1H, s(broad), CHOC=O); 6.81-6.95 and 7.21-7.28 (5H, 2 × m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8 and 18.4 (NCH(<u>C</u>H$_3$)(<u>C</u>H$_3$)); 20.9 (<u>C</u>H$_3$C=O); 23.8 and 24.8 (C(<u>C</u>H$_3$)(<u>C</u>H$_3$)); 35.3 (<u>C</u>(CH$_3$)$_2$); 48.7 (N<u>C</u>H$_2$CHO); 54.2 (N<u>C</u>H(CH$_3$)$_2$); 55.1 (N<u>C</u>H$_2$C$_{quat}$); 72.8 (<u>C</u>HOPh); 75.1 (<u>C</u>HOC=O); 116.1, 121.2 and 129.5 (5 x HC$_{arom}$); 157.8 (OC$_{arom,quat}$); 170.5 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1742; ν_{max} = 2963, 1598, 1493, 1372, 1226, 1166, 1050, 1036, 752. MS (70 eV): m/z (%) 306 (M$^+$+1, 100). Anal. Calcd. for $C_{18}H_{27}NO_3$: C 70.79, H 8.91, N 4.59. Found: C 70.62, H 9.14, N 4.77.

***Cis*-4-acetoxy-1-cyclohexyl-5,5-dimethyl-3-phenoxypiperidine 139d**

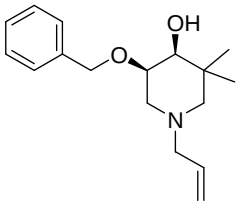


Colourless oil. R_f = 0.20 (hexane/EtOAc 19/1). Yield 72%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 and 1.13 (2 × 3H, 2 × s, C(C<u>H</u>$_3$)(C<u>H</u>$_3$)); 1.16-1.31, 1.55-1.65 and 1.68-1.87 (10H, 3 × m, (C<u>H</u>$_2$)$_5$CHN); 2.09 (3H, s, CH$_3$C=O); 2.19 (1H, d, *J* = 11.3 Hz, N(<u>H</u>CH)C$_{quat}$); 2.27-2.38 (1H, m, (CH$_2$)$_5$C<u>H</u>N); 2.42 (1H, d, *J* = 11.3 Hz, N(HC<u>H</u>)C$_{quat}$); 2.68 and 2.87 (2 × 1H, 2 × (d × d), *J* = 10.2, 9.7, 4.1 Hz, N(<u>H</u>C<u>H</u>)CHO); 4.59 (1H, d × d × d, *J* = 9.7, 4.1, 3.3 Hz, C<u>H</u>OPh); 5.04 (1H, s(broad), CHOC=O); 6.79-6.97 and 7.15-7.29 (5H, 2 × m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9 (<u>C</u>H$_3$C=O); 23.8 and 24.8 (C(<u>C</u>H$_3$)(<u>C</u>H$_3$)); 25.9, 26.0, 26.4, 28.6 and 29.1 ((<u>C</u>H$_2$)$_5$CHN); 35.4 (<u>C</u>(CH$_3$)$_2$); 49.1 (N<u>C</u>H$_2$CHO); 56.0 (N<u>C</u>H$_2$C$_{quat}$); 63.4 ((CH$_2$)$_5$<u>C</u>HN); 72.9 (<u>C</u>HOPh); 75.2 (<u>C</u>HOC=O); 116.1, 121.2 and 129.5 (5 x HC$_{arom}$); 157.8 (OC$_{arom,quat}$); 170.5 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1744; ν_{max} = 2929, 2853, 1599, 1493, 1373, 1243, 1051. MS (70 eV): m/z (%) 346 (M$^+$+1, 100). Anal. Calcd. for $C_{21}H_{31}NO_3$: C 73.01, H 9.04, N 4.05. Found: C 72.83, H 9.39, N 4.26.

5.7.2 Synthesis of 4-hydroxy-5,5-dimethylpiperidines

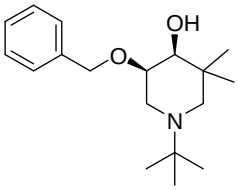
As a representative example, the synthesis of *cis*-4-hydroxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine **140c** is described. To a solution of *cis*-4-acetoxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine **139c** (3.05 g, 10 mmol, 1 equiv) in methanol (50 mL) was added LiOH·H$_2$O (1.26 g, 30 mmol, 3 equiv). After a reflux period of 15 hours, the solvent was removed *in vacuo* and the residue was washed with Et$_2$O (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was extracted with Et$_2$O (2 × 25 mL). Drying (MgSO$_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-4-hydroxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine **140c**, which was further purified in 86% yield by column chromatography on silica gel (hexane/EtOAc 9/1).

***Cis*-1-allyl-3-benzyloxy-4-hydroxy-5,5-dimethylpiperidine 140a**



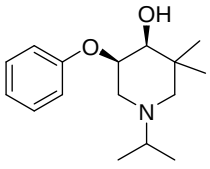
Colourless oil. R_f = 0.05 (hexane/EtOAc 6/1). Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (6H, s, $C(CH_3)_2$); 2.14 (2H, s, NCH_2C_{quat}); 2.23-2.35 (1H, m, N(HCH)CHO); 2.72 (1H, d × d, *J* = 9.4, 4.5 Hz, N(HCH)CHO); 2.93 and 3.02 (2 × 1H, 2 × (d × d), *J* = 13.8, 5.9, 5.7 Hz, N(HCH)CH=CH_2); 3.53 (1H, s(broad), CHOH); 3.80 (1H, d × d × d, *J* = 10.1, 4.5, 3.2 Hz, CHOBn); 4.58 (2H, s, CH_2O); 5.10-5.20 (2H, m, CH_2=CH); 5.81 (1H, m, CH_2=CH); 7.27-7.38 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2 and 24.8 ($C(CH_3)(CH_3)$); 35.3 ($C(CH_3)_2$); 51.8 (NCH_2CHO); 59.1 (NCH_2C_{quat}); 61.3 ($NCH_2CH=CH_2$); 70.5 (CH_2O); 72.8 (CHOH); 74.8 (CHOBn); 117.2 (CH_2=CH); 127.5, 127.7 and 128.3 (5 x HC_{arom}); 135.5 (CH_2=CH); 138.1 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3558; ν_{max} = 2949, 2809, 1112, 1072, 988, 917, 735, 697. MS (70 eV): m/z (%) 276 (M^++1, 100). Anal. Calcd. for $C_{17}H_{25}NO_2$: C 74.14, H 9.15, N 5.09. Found: C 74.01, H 9.32, N 4.93.

***Cis*-3-benzyloxy-1-*tert*-butyl-4-hydroxy-5,5-dimethylpiperidine 140b**



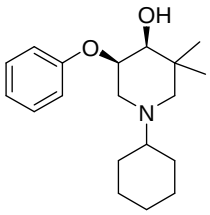
Yellow oil. R_f = 0.10 (hexane/EtOAc 4/1). Yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 and 0.99 (2 × 3H, 2 × s, $C(CH_3)(CH_3)$); 1.02 (9H, s, $C(CH_3)_3$); 2.19 and 2.27 (2 × 1H, 2 × d, *J* = 11.0 Hz, N(HCH)C_{quat}); 2.26-2.42 and 2.77-2.88 (2 × 1H, 2 × m, N(HCH)CHO); 3.51 (1H, d, *J* = 2.2 Hz, CHOH); 3.69-3.75 (1H, m, CHOBn); 4.56 and 4.58 (2 × 1H, 2 × d, *J* = 11.6 Hz, (HCH)O); 7.25-7.38 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 24.3 and 24.9 ($C(CH_3)(CH_3)$); 26.5 ($C(CH_3)_3$); 35.4 ($C(CH_3)_2$); 45.0 (NCH_2CHO); 52.4 (NCH_2C_{quat}); 53.5 ($C(CH_3)_3$); 70.8 (CH_2O); 73.2 (CHOH); 76.2 (CHOBn); 127.8, 127.9 and 128.6 (5 x HC_{arom}); 138.3 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3404; ν_{max} = 2966, 2928, 2867, 1363, 1098, 1070, 1027, 734, 697. MS (70 eV): m/z (%) 292 (M^++1, 100). Anal. Calcd. for $C_{18}H_{29}NO_2$: C 74.18, H 10.03, N 4.81. Found: C 74.44, H 10.29, N 4.62.

***Cis*-4-hydroxy-1-isopropyl-5,5-dimethyl-3-phenoxypiperidine 140c**



White crystals. Mp 82.5 °C. R_f = 0.11 (hexane/EtOAc 9/1). Yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 and 1.00 (2 × 3H, 2 × d, *J* = 6.3 Hz, NCH(CH_3)(CH_3)); 1.02 and 1.08 (2 × 3H, 2 × s, C(CH_3)(CH_3)); 2.07 and 2.41 (2 × 1H, 2 × d, *J* = 11.1 Hz, N(HCH)C_{quat}); 2.24 (1H, s(broad), OH); 2.61 (1H, d × d, *J* = 10.2, 9.8 Hz, N(HCH)CHO); 2.67-2.83 (2H, m, NCH(CH_3)$_2$ and N(HCH)CHO); 3.62 (1H, d, *J* = 3.0 Hz, CHOH); 4.58 (1H, d × d × d, *J* = 9.8, 4.6, 3.0 Hz, CHOPh); 6.87-7.00 and 7.27-7.32 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5 and 18.6 (NCH(CH_3)(CH_3)); 24.1 and 24.8 ($C(CH_3)(CH_3)$); 35.5 ($C(CH_3)_2$); 47.3 (NCH_2CHO); 53.9 (NCH_2C_{quat}); 54.2 ($NCH(CH_3)_2$); 74.0 (CHOH); 74.6 (CHOPh); 116.2, 121.5 and 129.6 (5 x HC_{arom}); 157.2 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3197; ν_{max} = 2958 1596, 1496, 1237, 1174, 981, 749. MS (70 eV): m/z (%) 264 (M^++1, 100). Anal. Calcd. for $C_{16}H_{25}NO_2$: C 72.96, H 9.57, N 5.32. Found: C 72.94, H 9.77, N 5.27.

***Cis*-1-cyclohexyl-4-hydroxy-5,5-dimethyl-3-phenoxypiperidine 140d**

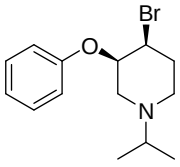


Colourless oil. R_f = 0.19 (hexane/EtOAc 14/1). Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 and 1.08 (2 × 3H, 2 × s, 2 × CH_3); 1.12-1.29, 1.56-1.63 and 1.68-1.81 (10H, 3 × m, ($C\underline{H}_2$)$_5$CHN); 2.11 (1H, d, *J* = 11.0 Hz, N($\underline{H}$CH)C_{quat}); 2.20-2.34 (1H, m, (CH_2)$_5$C$\underline{H}$N); 2.49 (1H, d, *J* = 11.0 Hz, N(HC$\underline{H}$)C_{quat}); 2.68 and 2.80 (2 × 1H, 2 × (d × d), *J* = 10.2, 9.9, 4.4 Hz, N($\underline{H}$C$\underline{H}$)CHO); 3.61 (1H, d, *J* = 2.6 Hz, C$\underline{H}$OH); 4.56 (1H, d × d × d, *J* = 9.9, 4.4, 2.6 Hz, C$\underline{H}$OPh); 6.92-6.98, 7.24-7.30 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1 and 24.8 (C($\underline{C}H_3$)($\underline{C}H_3$)); 26.0, 26.1, 26.4, 29.3 and 29.7 (($\underline{C}H_2$)$_5$CHN); 35.6 ($\underline{C}$(CH_3)$_2$); 47.7 (N$\underline{C}H_2$CHO); 54.8 (N$\underline{C}H_2C_{quat}$); 63.5 ((CH_2)$_5$$\underline{C}$HN); 74.1 (CHOH); 74.7 ($\underline{C}$HOPh); 116.2, 121.5 and 129.6 (5 x HC_{arom}); 157.2 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3589; ν_{max} = 2926, 2853, 1599, 1493, 1235, 1040, 982, 751. MS (70 eV): m/z (%) 304 (M^++1, 100). Anal. Calcd. for $C_{19}H_{29}NO_2$: C 75.21, H 9.63, N 4.62. Found: C 75.36, H 9.82, N 4.77.

5.7.3 Synthesis of 4-bromopiperidines

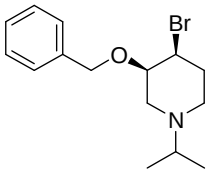
As a representative example, the synthesis of *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **154a** is described. To a solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **13a** (1.72 g, 5.5 mmol, 1 equiv) in acetonitrile (30 mL) was added LiBr (0.96 g, 11 mmol, 2 equiv) at room temperature. After a reflux period of 15 hours, the solvent was removed *in vacuo*, and the residue was washed with CH_2Cl_2 (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **154a**, which was further purified in 47% yield by column chromatography on silica gel (hexane/ EtOAc 9/1).

***Cis*-4-bromo-1-isopropyl-3-phenoxypiperidine 154a**



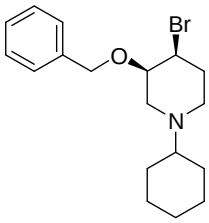
Light-yellow oil. R_f = 0.10 (hexane/EtOAc 9/1). Yield 47%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (6H, d, *J* = 6.6 Hz, ($C\underline{H}_3$)$_2$CHN); 2.17-2.23 (2H, m, NCH$_2$C$\underline{H}_2$); 2.60 (1H, d × t, *J* = 11.4, 4.0 Hz, N($\underline{H}$CH)CH_2); 2.70-2.89 (4H, m, N(HC$\underline{H}$)CH_2, NC$\underline{H}_2$CHO and (CH_3)$_2$C$\underline{H}$N); 4.31 (1H, d × d × d, *J* = 8.5, 4.0, 3.7 Hz, CHO); 4.64 (1H, d(broad), *J* = 3.7 Hz, CHBr); 6.96-7.01 and 7.28-7.33 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 and 18.3 (($\underline{C}H_3$)$_2$CHN); 32.8 (NCH$_2$$\underline{C}H_2$); 43.9 (N$\underline{C}H_2CH_2$); 48.1 (N$\underline{C}H_2$CHO); 53.5 (CHBr); 54.5 ((CH_3)$_2$$\underline{C}$HN); 74.8 (CHO); 117.0, 121.9 and 129.6 (5 x HC_{arom}); 156.9 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): ν_{max} = 2964, 2828, 2360, 1587, 1492, 1237, 1168, 1059, 752, 690. MS (70 eV): m/z (%) 298/300 (M^++1, 100). HRMS (ESI) Calcd. for $C_{14}H_{21}BrNO$ 298.0807 $[M + H]^+$, found 298.0797.

***Cis*-3-benzyloxy-4-bromo-1-isopropylpiperidine 154b**



White crystals. Mp 79.9 °C. Recrystallization from absolute EtOH. Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 and 1.04 (2 × 3H, 2 × d, *J* = 6.6 Hz, $(C\underline{H}_3)_2CHN$); 2.02-2.21 (2H, m, $NCH_2C\underline{H}_2$); 2.52-2.69 (4H, m, 2 × NCH_2); 2.76 (1H, septet, *J* = 6.6 Hz, $(CH_3)_2C\underline{H}N$); 3.47 (1H, d × d × d, *J* = 8.3, 3.9, 3.9 Hz, CHO); 4.52 (1H, d, *J* = 11.9 Hz, O(H$\underline{C}$H)Ph); 4.62 (1H, s(broad), CHBr); 4.69 (1H, d, *J* = 11.9 Hz, O(HC$\underline{H}$)Ph); 7.28-7.40 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.2 and 18.4 ($(\underline{C}H_3)_2CHN$); 32.7 ($NCH_2\underline{C}H_2$); 44.0 and 48.6 (2 × NCH_2); 54.5 and 54.7 (CHBr and $(CH_3)_2\underline{C}HN$); 70.4 (OCH_2); 75.2 (CHO); 127.9, 128.0 and 128.5 (5 x HC_{arom}); 138.0 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{max} = 3400, 3028, 2962, 2824, 1165, 1134, 1116, 1094, 1023, 1004, 750, 697. MS (70 eV): m/z (%) 312/314 (M^++1, 100). Anal. Calcd. for $C_{15}H_{22}BrNO$: C 57.70, H 7.10, N 4.49. Found: C 58.10, H 7.34, N 4.48.

***Cis*-3-benzyloxy-4-bromo-1-cyclohexylpiperidine 154c**

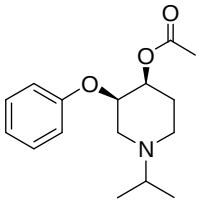


White crystals. Mp 76.6 °C. R_f = 0.06 (hexane/EtOAc 4/1). Yield 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.25, 1.60-1.65 and 1.78-1.80 (10H, 3 × m, $(C\underline{H}_2)_5CHN$); 2.01-2.20 (2H, m, $NCH_2C\underline{H}_2$); 2.27-2.37 (1H, m, CHN); 2.54-2.62 (1H, m, N(H$\underline{C}$H)CH_2); 2.66-2.78 (3H, m, N(HC$\underline{H}$)CH_2 and $NC\underline{H}_2CHO$); 3.46 (1H, d × d × d, *J* = 8.3, 3.9, 3.6 Hz, CHO); 4.53 (1H, d, *J* = 12.1 Hz, O(H$\underline{C}$H)Ph); 4.62 (1H, d(broad), *J* = 3.6 Hz, CHBr); 4.68 (1H, d, *J* = 12.1 Hz, O(HC$\underline{H}$)Ph); 7.28-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.1, 26.4, 28.7 and 29.0 ($(\underline{C}H_2)_5CHN$); 32.9 ($NCH_2\underline{C}H_2$); 44.4 ($N\underline{C}H_2CH_2$); 49.1 ($N\underline{C}H_2CHO$); 54.8 (CHBr); 63.8 (CHN); 70.3 (OCH_2); 75.3 (CHO); 127.8, 128.0 and 128.5 (5 x HC_{arom}); 138.1 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{max} = 3062, 3030, 2926, 2852, 1451, 1202, 1116, 1099, 1026, 948, 734, 696. MS (70 eV): m/z (%) 352/354 (M^++1, 100). Anal. Calcd. for $C_{18}H_{26}BrNO$: C 61.36, H 7.44, N 3.98. Found: C 61.57, H 7.77, N 4.10.

5.7.4 Synthesis of 4-acetoxypiperidines

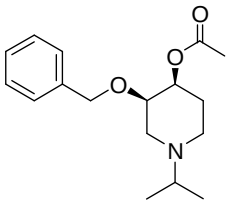
As a representative example, the synthesis of *cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine **157a** is described. To a solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **13a** (3.13 g, 10 mmol, 1 equiv) in acetonitrile (50 mL) was added NaOAc (1.64 g, 20 mmol, 2 equiv) at room temperature. After a reflux period of 15 hours, the solvent was removed *in vacuo* and the residue was washed with CH_2Cl_2 (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine **157a**, which was further purified in 63% yield by column chromatography on silica gel (hexane/EtOAc 2/1).

***Cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine 157a**



Colourless oil. R_f = 0.09 (hexane/EtOAc 2/1). Yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (6H, d, *J* = 6.1 Hz, ($C\underline{H}_3$)$_2$CHN); 1.76-1.86 (1H, m, NCH_2($H\underline{C}$H)); 2.06 (3H, s, CH_3CO); 1.98-2.14 (1H, m, NCH_2($H\underline{C}$H)); 2.51-2.64 (2H, m, $NC\underline{H}_2CH_2$); 2.77-2.89 (3H, m, (CH_3)$_2$C$\underline{H}$N and $NC\underline{H}_2CHO$); 4.49 (1H, d × d × d, *J* = 5.9, 5.9, 2.9 Hz, C$\underline{H}$OPh); 5.18-5.20 (1H, m, CHOCO); 6.91-6.98 and 7.23-7.29 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8 and 18.6 (($\underline{C}H_3$)$_2$CHN); 21.2 ($\underline{C}H_3CO$); 28.4 ($NCH_2\underline{C}H_2$); 44.5 ($N\underline{C}H_2CH_2$); 48.1 ($N\underline{C}H_2CHO$); 54.3 ((CH_3)$_2\underline{C}$HN); 69.5 (C$\underline{H}$OCO); 74.2 (C$\underline{H}$OPh); 116.6, 121.4 and 129.5 (5 x HC_{arom}); 157.8 ($OC_{arom,quat}$); 170.5 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1736; ν_{max} = 2964, 1492, 1234, 1176, 1047, 752, 692. MS (70 eV): m/z (%) 278 (M^++1, 100). HRMS (ESI) Calcd. for $C_{16}H_{24}NO_3$ 278.1756 [M + H]$^+$, found 278.1755.

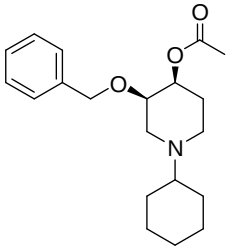
***Cis*-4-acetoxy-3-benzyloxy-1-isopropylpiperidine 157b**



Light-yellow oil. R_f = 0.05 (hexane/EtOAc 2/1). Yield 55%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 and 1.04 (2 × 3H, 2 × d, *J* = 6.3 Hz, ($C\underline{H}_3$)$_2$CHN); 1.66-1.77 and 1.91-2.00 (2 × 1H, 2 × m, NCH_2($H\underline{C}$H)); 2.10 (3H, s, CH_3CO); 2.44-2.53 (2H, m, $NC\underline{H}_2CH_2$); 2.57-2.66 (2H, m, $NC\underline{H}_2CHO$); 2.77 (1H, septet, *J* = 6.3 Hz, (CH_3)$_2$C$\underline{H}$N); 3.61 (1H, d × d × d, *J* = 8.1, 3.9, 3.9 Hz, $NCH_2C\underline{H}O$); 4.52 and 4.65 (2 × 1H, 2 × d, *J* = 12.1 Hz, O($H\underline{C}$H)Ph); 5.26 (1H, s(broad), CHOCO); 7.28-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.0 and 18.6 (($\underline{C}H_3$)$_2$CHN); 21.4 ($\underline{C}H_3CO$); 28.6 ($NCH_2\underline{C}H_2$); 44.1 ($N\underline{C}H_2CH_2$); 48.7 ($N\underline{C}H_2CHO$); 54.5 ((CH_3)$_2\underline{C}$HN); 68.5 (C$\underline{H}$OCO); 71.0 (OCH_2); 74.9 ($NCH_2\underline{C}HO$); 127.7, 127.9 and 128.5 (5 x HC_{arom}); 138.4 ($C_{arom,quat}$); 170.7 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1735; ν_{max} = 2963, 1369, 1241, 1092, 967, 736, 698. MS (70 eV): m/z (%) 292 (M^++1, 100). HRMS (ESI) Calcd. for $C_{17}H_{26}NO_3$ 292.1913 [M + H]$^+$, found 292.1916.

***Cis*-4-acetoxy-3-benzyloxy-1-cyclohexylpiperidine 157c**

Attempts to purify this compound failed. Spectral data are based on ^{1}H NMR and ^{13}C NMR of the crude reaction mixture (purity of **157c**: ~85%), and no HRMS analysis was performed.



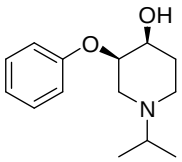
Colourless oil. Yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.33, 1.57-1.65 and 1.70-1.84 (4H, 1H and 6H, 3 × m, ($C\underline{H}_2$)$_5$CHN and NCH_2($H\underline{C}$H)); 1.88-1.99 (1H, m, NCH_2($H\underline{C}$H)); 2.10 (3H, s, CH_3CO); 2.29-2.38 (1H, m, CHN); 2.53-2.57 (2H, m, $NC\underline{H}_2CH_2$); 2.64-2.73 (2H, m, $NC\underline{H}_2CHO$); 3.60 (1H, d × d × d, *J* = 8.4, 4.0, 4.0 Hz, $NCH_2C\underline{H}O$); 4.52 and 4.64 (2 × 1H, 2 × d, *J* = 12.1 Hz, O($H\underline{C}$H)Ph); 5.25 (1H, s(broad), CHOCO); 7.23-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.4 ($\underline{C}H_3CO$); 22.7, 26.1, 26.4 and 28.6 (4 × CH_2); 29.0 ($NCH_2\underline{C}H_2$); 31.7 (CH_2); 44.4 ($N\underline{C}H_2CH_2$); 49.1 ($N\underline{C}H_2CHO$); 63.7 (CHN); 68.5 (C$\underline{H}$OCO); 70.9 (OCH_2); 74.9 ($NCH_2\underline{C}HO$); 127.7, 127.9 and 128.4 (5 x HC_{arom}); 138.4 ($C_{arom,quat}$); 170.7 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1737; ν_{max} = 2926, 1371, 1240, 1093, 1021, 735, 698. MS (70 eV): m/z (%) 332 (M^++1, 100).

5.7.5 Synthesis of 4-hydroxypiperidines

5.7.5.1 Synthesis of 4-hydroxypiperidines *via* 4-acetoxypiperidines

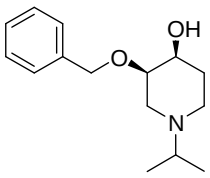
As a representative example, the synthesis of *cis*-4-hydroxy-1-isopropyl-3-phenoxypiperidine **158a** is described. To a solution of *cis*-4-acetoxy-1-isopropyl-3-phenoxypiperidine **157a** (1.66 g, 6 mmol, 1 equiv) in methanol (40 mL) was added K_2CO_3 (1.66 g, 12 mmol, 2 equiv). After a reflux period of 1 hour, the solvent was removed *in vacuo*, and the residue was washed with Et_2O (1 × 30 mL) and water (2 × 30 mL). The aqueous phase was extracted with Et_2O (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-4-hydroxy-1-isopropyl-3-phenoxypiperidine **158a**, which was further purified in 56% yield by column chromatography on silica gel (hexane/EtOAc 1/2).

Cis-4-hydroxy-1-isopropyl-3-phenoxypiperidine 158a



Colourless oil. R_f = 0.05 (hexane/EtOAc 1/2). Yield 56%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (6H, d, *J* = 6.6 Hz, $(C\underline{H}_3)_2CHN$); 1.77-1.88 and 1.94-2.03 (2 × 1H, 2 × m, $NCH_2(\underline{H}C\underline{H})$); 2.48-2.70 (4H, m, $NC\underline{H}_2CH_2$, $N(\underline{H}CH)CHO$ and OH); 2.75-2.85 (2H, m, $N(HC\underline{H})CHO$ and $(CH_3)_2C\underline{H}N$); 4.11-4.15 (1H, m, $C\underline{H}OH$); 4.43 (1H, d × d × d, *J* = 9.0, 4.4, 3.1 Hz, $NCH_2C\underline{H}O$); 6.95-7.00 and 7.26-7.33 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.0 and 18.5 ($(\underline{C}H_3)_2CHN$); 30.6 ($NCH_2\underline{C}H_2$); 43.2 ($N\underline{C}H_2CH_2$); 46.6 ($N\underline{C}H_2CHO$); 54.5 ($(CH_3)_2\underline{C}HN$); 66.4 (CHOH); 76.1 ($\underline{C}HOPh$); 116.3, 121.6 and 129.7 (5 x HC_{arom}); 157.2 ($OC_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3406; ν_{max} = 2964, 1596, 1493, 1239, 1173, 965, 752, 730, 691. MS (70 eV): m/z (%) 236 (M^++1, 100). HRMS (ESI) Calcd. for $C_{14}H_{22}NO_2$ 236.1651 $[M + H]^+$, found 236.1653.

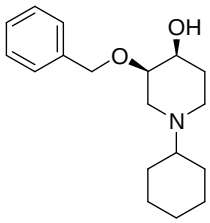
Cis-3-benzyloxy-4-hydroxy-1-isopropylpiperidine 158b



Colourless oil. R_f = 0.03 (hexane/EtOAc 1/3). Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 and 1.04 (2 × 3H, 2 × d, *J* = 6.7 Hz, $(C\underline{H}_3)_2CHN$); 1.63-1.74 and 1.86-1.95 (2 × 1H, 2 × m, $NCH_2(\underline{H}C\underline{H})$); 2.34 (1H, s(broad), OH); 2.39-2.45 (1H, m, $N(\underline{H}CH)CH_2$); 2.49-2.64 (3H, m, $N(HC\underline{H})CH_2$ and $NC\underline{H}_2CHO$); 2.76 (1H, septet, *J* = 6.7 Hz, $(CH_3)_2C\underline{H}N$); 3.58 (1H, d × d × d, *J* = 8.5, 4.1, 4.1 Hz, $NCH_2C\underline{H}O$); 3.98 (1H, s(broad), $C\underline{H}OH$); 4.58 and 4.63 (2 × 1H, 2 × d, *J* = 12.1 Hz, $O(\underline{H}C\underline{H})Ph$); 7.28-7.38 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.0 and 18.6 ($(\underline{C}H_3)_2CHN$); 30.5 ($NCH_2\underline{C}H_2$); 43.3 ($N\underline{C}H_2CH_2$); 47.4 ($N\underline{C}H_2CHO$); 54.5 ($(CH_3)_2\underline{C}HN$); 66.1 (CHOH); 70.8 (OCH_2); 76.9 ($NCH_2\underline{C}HO$); 127.86, 127.91 and 128.6 (5 x HC_{arom}); 138.3 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3445; ν_{max} = 2963, 1384, 1175, 1091, 963, 735, 697. MS (70 eV): m/z (%) 250 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{24}NO_2$ 250.1807 $[M + H]^+$, found 250.1812.

***Cis*-3-benzyloxy-1-cyclohexyl-4-hydroxypiperidine 158c**

Attempts to purify this compound failed. Spectral data are based on ^{1}H NMR and ^{13}C NMR of the crude reaction mixture (purity of **158c**: ~80%), and no HRMS analysis was performed.



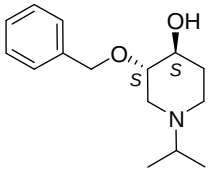
Colourless oil. Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.29, 1.53-1.73 and 1.74-1.92 (5H, 1H and 6H, 3 × m, $(C\underline{H}_2)_5CHN$ and $NCH_2C\underline{H}_2$); 2.28-2.38 (1H, m, CHN); 2.44-2.51 (1H, m, $N(\underline{H}CH)CH_2$); 2.56-2.71 (3H, m, $N(HC\underline{H})CH_2$ and $NC\underline{H}_2CHO$); 3.58 (1H, d × d × d, *J* = 8.5, 4.1, 4.1 Hz, $NCH_2C\underline{H}O$); 3.97 (1H, s(broad), $C\underline{H}OH$); 4.57 and 4.62 (2 × 1H, 2 × d, *J* = 11.8 Hz, $O(\underline{H}C\underline{H})Ph$); 7.25-7.35 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.1, 26.2, 26.4, 28.5 and 29.1 ($(\underline{C}H_2)_5CHN$); 30.6 ($NCH_2\underline{C}H_2$); 43.7 ($N\underline{C}H_2CH_2$); 47.7 ($N\underline{C}H_2CHO$); 63.9 (CHN); 66.1 (CHOH); 70.8 (OCH_2); 76.8 ($NCH_2\underline{C}HO$); 127.8, 127.9 and 128.6 (5 x HC_{arom}); 138.3 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3428; ν_{max} = 2925, 2852, 1451, 1091, 1074, 966, 734, 697. MS (70 eV): m/z (%) 290 (M^{+}+1, 100).

5.7.5.2 Synthesis of 4-hydroxypiperidines *via* enzymatic reduction of piperidin-4-ones

5.7.5.2.1 Synthesis of (4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines

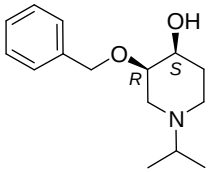
3-Benzyloxy-1-isopropylpiperidin-4-one **15b** (250 mg, 50 mM), NADH (71 mg, 5 mM), isopropylalcohol (1 mL) and an *S*-specific alcohol dehydrogenase[111] (100 mg) were dissolved in MES-buffer (19 mL, 50 mM, pH 6.5). The mixture was incubated overnight in a thermoshaker (Eppendorf) at 300 rpm and 30 °C, yielding (3*S*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **176** and (3*R*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **177** in quantitative yield (ratio 1/1, based on ^{1}H NMR).

(3*S*,4*S*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 176



Colourless oil. R_f = 0.04 (hexane/EtOAc 1/3). Yield 45%. $[\alpha]_D$ = +27.7° (*c* = 1.01, CH_2Cl_2). *ee* = 98.8%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (6H, d, *J* = 6.1 Hz, $(C\underline{H}_3)_2CHN$); 1.59 (1H, d × d × d × d, *J* = 17.2, 11.2, 5.9, 3.6 Hz, $NCH_2(\underline{H}CH)$); 1.94-2.05 (2H, m, $NCH_2(HC\underline{H})$ and $N(\underline{H}CH)CHO$); 2.20 (1H, d × d, *J* = 11.2, 10.7 Hz, $N(\underline{H}CH)CH_2$); 2.74-2.85 (2H, m, $(CH_3)_2C\underline{H}N$ and $N(HC\underline{H})CH_2$); 3.11 (1H, d(broad), *J* = 11.0 Hz, $N(HC\underline{H})CHO$); 3.35-3.49 (2H, m, $NCH_2C\underline{H}O$ and $C\underline{H}OH$); 4.56 and 4.70 (2 × 1H, 2 × d, *J* = 11.6 Hz, (HCH)O); 7.30-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.2 and 18.4 ($(\underline{C}H_3)_2CHN$); 31.5 ($NCH_2\underline{C}H_2$); 46.6 ($N\underline{C}H_2CH_2$); 50.8 ($N\underline{C}H_2CHO$); 54.4 ($(CH_3)_2\underline{C}HN$); 72.0 ($O\underline{C}H_2Ph$); 73.2 and 81.5 (CHOH and $\underline{C}HOPh$); 127.9 and 128.6 (5 x HC_{arom}); 138.5 ($C_{arom,quat}$). IR (ATR, cm^{-1}): ν_{OH} = 3445; ν_{max} = 2963, 1384, 1175, 1091, 963, 735, 697. MS (70 eV): m/z (%) 250 (M^{+}+1, 100). HRMS (ESI) Calcd. for $C_{15}H_{24}NO_2$ 250.1807 $[M + H]^{+}$, found 250.1812.

(3*R*,4*S*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 177

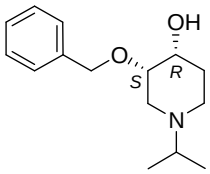


Colourless oil. R_f = 0.03 (hexane/EtOAc 1/3). Yield 43%. $[\alpha]_D$ = +7.6° (*c* = 0.95, $CHCl_3$). *ee* = 98.8%. The spectral data of (3*R*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **177** were judged to be identical to those for *cis*-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **158b** (Section 5.7.5.1).

5.7.5.2.2 Synthesis of (4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines

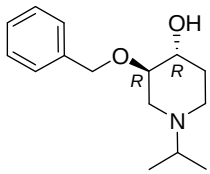
The synthesis of (4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines **178** and **179** was analogous to the synthesis of (4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidines **176** and **177** using an *R*-specific alcohol dehydrogenase,[112] yielding (3*S*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **178** and (3*R*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **179** in quantitative yield (ratio 1/1, based on ^{1}H NMR).

(3*S*,4*R*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 178



Colourless oil. R_f = 0.03 (hexane/EtOAc 1/3). Yield 49%. $[\alpha]_D$ = -7.6° (*c* = 0.98, $CHCl_3$). *ee* = 96.2%. The spectral data of (3*S*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **178** were judged to be identical to those for *cis*-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **158b** (Section 5.7.5.1).

(3*R*,4*R*)-3-Benzyloxy-4-hydroxy-1-isopropylpiperidine 179



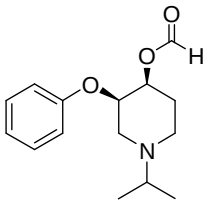
Colourless oil. R_f = 0.04 (hexane/EtOAc 1/3). Yield 44%. $[\alpha]_D$ = -27.7° (*c* = 0.97, CH_2Cl_2). *ee* = 95.8%. The spectral data of (3*R*,4*R*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **179** were judged to be identical to those for (3*S*,4*S*)-3-benzyloxy-4-hydroxy-1-isopropylpiperidine **176** (Section 5.7.5.2.1).

5.7.6 Synthesis of 4-(formyloxy)piperidines

As a representative example, the synthesis of *cis*-4-formyloxy-1-isopropyl-3-phenoxypiperidine **173a** is described. A solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **13a** (0.31 g, 1 mmol, 1 equiv) in DMF (15 mL) was heated at 80 °C for 3 hours. Subsequently, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 15 mL). Afterwards, the organic phase

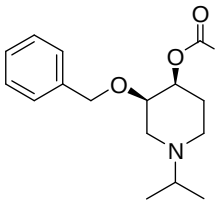
was washed intensively with brine (4 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-4-formyloxy-1-isopropyl-3-phenoxypiperidine **173a**, which was further purified in 53% yield by column chromatography on silica gel (hexane/EtOAc 2/1).

Cis-4-formyloxy-1-isopropyl-3-phenoxypiperidine 173a



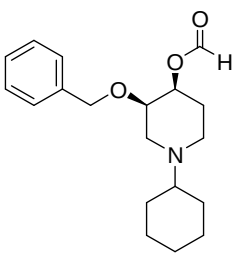
Colourless oil. R_f = 0.07 (hexane/EtOAc 2/1). Yield 53%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (6H, d, *J* = 6.1 Hz, $(C\underline{H}_3)_2CHN$); 1.82-1.93 and 2.04-2.13 (2 × 1H, 2 × m, $NCH_2(\underline{H}C\underline{H})$); 2.57-2.60 (2H, m, $NC\underline{H}_2CH_2$); 2.70-2.87 (3H, m, $(CH_3)_2C\underline{H}N$ and $NC\underline{H}_2CHO$); 4.49 (1H, d × d × d, *J* = 8.4, 4.0, 4.0 Hz, $C\underline{H}OPh$); 5.34-5.36 (1H, m, CHOC=O); 6.90-6.99 and 7.24-7.31 (5H, 2 × m, CH_{arom}); 8.14 (1H, s, HC=O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9 and 18.4 ($(\underline{C}H_3)_2CHN$); 28.7 ($NCH_2\underline{C}H_2$); 43.8 ($N\underline{C}H_2CH_2$); 47.7 ($N\underline{C}H_2CHO$); 54.4 ($(CH_3)_2\underline{C}HN$); 69.2 ($\underline{C}HOC=O$); 74.0 ($\underline{C}HOPh$); 116.3, 121.6 and 129.6 (5 x HC_{arom}); 157.3 and 160.5 ($OC_{arom,quat}$ and C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1721; ν_{max} = 2964, 1492, 1238, 1166, 752, 692. MS (70 eV): m/z (%) 264 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{22}NO_3$ 264.1600 $[M + H]^+$, found 264.1602.

Cis-3-benzyloxy-4-formyloxy-1-isopropylpiperidine 173b



Colourless oil. R_f = 0.06 (hexane/EtOAc 1/2). Yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 and 1.04 (2 × 3H, 2 × d, *J* = 6.3 Hz, $(C\underline{H}_3)_2CHN$); 1.71-1.82 and 1.94-2.02 (2 × 1H, 2 × m, $NCH_2(\underline{H}C\underline{H})$); 2.45-2.63 (3H, m, $NC\underline{H}_2CH_2$ and $N(\underline{H}CH)CHO$); 2.68-2.72 (1H, m, $N(HC\underline{H})CHO$); 2.79 (1H, septet, *J* = 6.3 Hz, $(CH_3)_2C\underline{H}N$); 3.64 (1H, d × d × d, *J* = 9.1, 4.1, 4.1 Hz, $NCH_2\underline{C}HO$); 4.54 and 4.66 (2 × 1H, 2 × d, *J* = 11.9 Hz, $O(\underline{H}C\underline{H})Ph$); 5.38 (1H, s(broad), CHOC=O); 7.24-7.39 (5H, m, CH_{arom}); 8.15 (1H, s, HC=O). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.0 and 18.5 ($(\underline{C}H_3)_2CHN$); 28.8 ($NCH_2\underline{C}H_2$); 43.6 ($N\underline{C}H_2CH_2$); 48.4 ($N\underline{C}H_2CHO$); 54.5 ($(CH_3)_2\underline{C}HN$); 68.4 ($\underline{C}HOC=O$); 71.1 (OCH_2); 74.8 ($NCH_2\underline{C}HO$); 127.9, 128.0 and 128.5 (5 x HC_{arom}); 138.1 ($C_{arom,quat}$); 160.7 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1720; ν_{max} = 2963, 1170, 1090, 736, 698. MS (70 eV): m/z (%) 278 (M^++1, 100). HRMS (ESI) Calcd. for $C_{16}H_{24}NO_3$ 278.1756 $[M + H]^+$, found 278.1770.

Cis-3-benzyloxy-1-cyclohexyl-4-(formyloxy)piperidine 173c

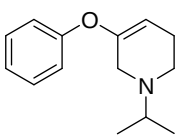


Colourless oil. R_f = 0.06 (hexane/EtOAc 4/1). Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.28, 1.59-1.66 and 1.73-1.83 (6H, 1H and 4H, 3 × m, $(C\underline{H}_2)_5CHN$ and $NCH_2(\underline{H}CH)$); 1.92-2.01 (1H, m, $NCH_2(HC\underline{H})$); 2.29-2.38 (1H, m, CHN); 2.54-2.60 (2H, m, $NC\underline{H}_2CH_2$); 2.63-2.78 (2H, m, $NC\underline{H}_2CHO$); 3.62 (1H, d × d × d, *J* = 9.0, 3.9, 3.9 Hz, $NCH_2C\underline{H}O$); 4.54 and 4.64 (2 × 1H, 2 × d, *J* = 11.6 Hz, $O(\underline{H}C\underline{H})Ph$); 5.36 (1H, s(broad), CHOC=O); 7.28-7.36 (5H, m, CH_{arom}); 8.14 (1H, s, HC=O). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.09, 26.13, 26.4, 28.6 and 28.9 ($(\underline{C}H_2)_5CHN$); 29.1 ($NCH_2\underline{C}H_2$); 44.0 ($N\underline{C}H_2CH_2$); 48.9 ($N\underline{C}H_2CHO$); 63.8 (CHN); 68.6 ($\underline{C}HOC=O$); 71.0 (OCH_2); 74.9 ($NCH_2\underline{C}HO$); 127.8, 127.9 and 128.5 (5 x HC_{arom}); 138.2 ($C_{arom,quat}$); 160.8 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1724; ν_{max} = 2926, 1452, 1177, 1099, 734, 696. MS (70 eV): m/z (%) 318 (M^++1, 100). HRMS (ESI) Calcd. for $C_{19}H_{28}NO_3$ 318.2069 $[M + H]^+$, found 318.2077.

5.8 Synthesis of 1,2,5,6-tetrahydropyridines

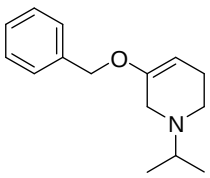
As a representative example, the synthesis of 1-isopropyl-3-phenoxy-1,2,5,6-tetrahydropyridine **155a** is described. To a solution of *cis*-4-bromo-1-isopropyl-3-phenoxypiperidine **154a** (2.98 g, 10 mmol, 1 equiv) in DMSO (50 mL) was added NaH (1.6 g, 40 mmol, 4 equiv, 60% dispersion in mineral oil), after which the resulting suspension was stirred for 15 hours at 150 °C. Subsequently, the reaction mixture was poured into water (40 mL) and extracted with Et_2O (3 × 25 mL). Afterwards, the organic phase was washed intensively with brine (4 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded 1-isopropyl-3-phenoxy-1,2,5,6-tetrahydropyridine **155a**, which was further purified in 56% yield by column chromatography on silica gel (hexane/EtOAc 2/1).

1-Isopropyl-3-phenoxy-1,2,5,6-tetrahydropyridine 155a



Yellow oil. R_f = 0.08 (hexane/EtOAc 2/1). Yield 56%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (6H, d, *J* = 6.4 Hz, $(C\underline{H}_3)_2CHN$); 2.16-2.21 (2H, m, $NCH_2C\underline{H}_2$); 2.60 (2H, ~t, *J* = 5.8 Hz, $NC\underline{H}_2CH_2$); 2.82 (1H, septet, *J* = 6.4 Hz, $(CH_3)_2C\underline{H}N$); 3.17 (2H, s(broad), NCH_2C_{quat}); 4.91-4.94 (1H, m, C=CH); 7.03-7.10 and 7.29-7.34 (5H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.6 ($(\underline{C}H_3)_2CHN$); 24.4 ($NCH_2\underline{C}H_2$); 45.9 ($N\underline{C}H_2CH_2$); 48.9 ($N\underline{C}H_2C_{quat}$); 54.0 ($(CH_3)_2\underline{C}HN$); 102.7 (C=$\underline{C}$H); 119.5, 123.3 and 129.6 (5 x HC_{arom}); 152.1 and 155.9 (2 × OC_{quat}). IR (ATR, cm^{-1}): $\nu_{C=C}$ = 1685; ν_{max} = 2964, 1590, 1489, 1220, 1176, 753, 693. MS (70 eV): m/z (%) 218 (M^++1, 100). HRMS (ESI) Calcd. for $C_{14}H_{20}NO$ 218.1545 $[M + H]^+$, found 218.1548.

3-Benzyloxy-1-isopropyl-1,2,5,6-tetrahydropyridine 155b



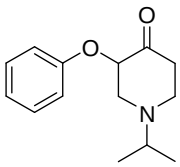
Light-brown oil. R_f = 0.04 (hexane/EtOAc 2/1). Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 and 1.09 (2 × 3H, 2 × d, *J* = 6.5 Hz, $(C\underline{H}_3)_2CHN$); 2.16-2.23 (2H, m, $NCH_2C\underline{H}_2$); 2.56 (2H, ~t, *J* = 5.5 Hz, $NC\underline{H}_2CH_2$); 2.77 (1H, septet, *J* = 6.5 Hz, $(CH_3)_2C\underline{H}N$); 3.08 (2H, s(broad), NCH_2C_{quat}); 4.74 (2H, s, OCH_2); 4.77 (1H, t, *J* = 3.3 Hz, C=CH); 7.27-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.7 ($(\underline{C}H_3)_2CHN$); 24.5 ($NCH_2\underline{C}H_2$); 46.4 ($N\underline{C}H_2CH_2$); 49.9 ($N\underline{C}H_2C_{quat}$); 54.0 ($(CH_3)_2\underline{C}HN$); 69.0 ($OCH_2$); 92.6 (C=$\underline{C}$H); 127.7, 127.9 and 128.5 (5 x HC_{arom}); 137.4 ($C_{arom,quat}$); 153.2 (OC_{quat}). IR (ATR, cm^{-1}): $\nu_{C=C}$ = 1677; ν_{max} = 2963, 1217, 1183, 1016, 797, 734, 697. MS (70 eV): m/z (%) 232 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{22}NO$ 232.1701 $[M + H]^+$, found 232.1700.

5.9 Synthesis of piperidin-4-ones

As a representative example, the synthesis of 1-isopropyl-3-phenoxypiperidin-4-one **15a** is described. To a solution of *cis*-1-isopropyl-2-(2-mesyloxyethyl)-3-phenoxyazetidine **13a** (3.15 g, 10 mmol, 1 equiv) in DMSO (40 mL) was added K_2CO_3 (6.90 g, 50 mmol, 5 equiv). After stirring at 100 °C for 18 hours, the reaction mixture was poured into water (40 mL) and extracted with diethyl ether (3 × 50

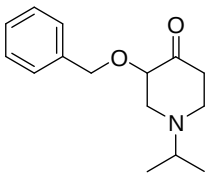
mL). Afterwards, the organic phase was washed intensively with brine (4 × 40 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded 1-isopropyl-3-phenoxypiperidin-4-one **15a**, which was further purified in 43% yield by column chromatography on silica gel (hexane/EtOAc 1/1).

1-Isopropyl-3-phenoxypiperidin-4-one 15a



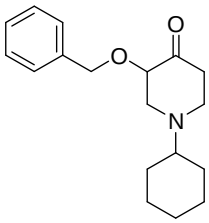
Colourless oil. R_f = 0.10 (hexane/EtOAc 1/1). Yield 43%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (6H, d, *J* = 6.5 Hz, $(C\underline{H}_3)_2CHN$); 2.52-2.70 and 3.06-3.13 (4H and 1H, 2 × m, NCH_2CH_2 and $N(\underline{H}CH)CHO$); 3.00 (1H, septet, *J* = 6.5 Hz, $(CH_3)_2C\underline{H}N$); 3.42 (1H, d × d × d, *J* = 10.8, 6.3, 2.9 Hz, $N(HC\underline{H})CHO$); 4.83 (1H, d × d, *J* = 10.3, 6.3 Hz, CHO); 6.85-6.91, 6.94-7.00 and 7.23-7.31 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.4 and 18.5 ($(\underline{C}H_3)_2CHN$); 41.0 and 49.0 (NCH_2CH_2); 53.9 ($N\underline{C}H_2CHO$); 54.0 ($(CH_3)_2\underline{C}HN$); 79.2 (CHO); 115.5, 121.6 and 129.6 (5 x HC_{arom}); 157.7 ($C_{arom,quat}$); 205.6 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1733; ν_{max} = 2966, 1588, 1493, 1241, 1174, 907, 751. MS (70 eV): m/z (%) 234 (M^++1, 100). HRMS (ESI) Calcd. for $C_{14}H_{20}NO_2$ 234.1494 $[M + H]^+$, found 234.1496.

3-Benzyloxy-1-isopropylpiperidin-4-one 15b



Colourless oil. R_f = 0.06 (hexane/EtOAc 1/1). Yield 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (6H, d, *J* = 6.6 Hz, $(C\underline{H}_3)_2CHN$); 2.36-2.51 and 2.82-2.98 (4H and 2H, 2 × m, NCH_2CH_2, $N(\underline{H}CH)CHO$ and $(CH_3)_2C\underline{H}N$); 3.19 (1H, d × d × d, *J* = 10.7, 6.3, 2.8 Hz, $N(HC\underline{H})CHO$); 4.00 (1H, d × d, *J* = 10.2, 6.3 Hz, CHO); 4.49 and 4.84 (2 × 1H, 2 × d, *J* = 12.1 Hz, (HCH)O); 7.21-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.38 and 18.42 ($(\underline{C}H_3)_2CHN$); 40.9 and 48.8 (NCH_2CH_2); 54.0 ($(CH_3)_2\underline{C}HN$); 54.4 ($N\underline{C}H_2CHO$); 72.4 (OCH_2); 80.1 (CHO); 127.9, 128.0 and 128.5 (5 x HC_{arom}); 137.9 ($C_{arom,quat}$); 208.0 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1727; ν_{max} = 2965, 1455, 1121, 1104, 1018, 736, 697. MS (70 eV): m/z (%) 248 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{22}NO_2$ 248.1651 $[M + H]^+$, found 248.1653.

3-Benzyloxy-1-cyclohexylpiperidin-4-one 15c

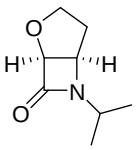


Colourless oil. R_f = 0.04 (hexane/EtOAc 4/1). Yield 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19-1.31, 1.62-1.66 and 1.78-1.81 (5H, 1H and 4H, 3 × m, $(C\underline{H}_2)_5CHN$); 2.40-2.64 (5H, m, $N(\underline{H}CH)CHO$, $N(\underline{H}CH)C\underline{H}_2$ and $(CH_2)_5C\underline{H}N$); 3.03-3.09 (1H, m, $N(HC\underline{H})CH_2$); 3.29 (1H, d × d × d, *J* = 11.0, 6.5, 2.8 Hz, $N(HC\underline{H})CHO$); 4.03 (1H, d × d, *J* = 10.2, 6.5 Hz, CHO); 4.53 and 4.87 (2 × 1H, 2 × d, *J* = 12.1 Hz, (HCH)O); 7.27-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.0, 26.2, 29.0 and 29.1 ($(\underline{C}H_2)_5CHN$); 41.0 ($NCH_2\underline{C}H_2$); 49.2 ($N\underline{C}H_2CH_2$); 54.9 ($N\underline{C}H_2CHO$); 62.9 ($(CH_2)_5\underline{C}HN$); 72.2 (OCH_2); 80.2 (CHO); 127.7, 127.8 and 128.4 (5 x HC_{arom}); 138.0 ($C_{arom,quat}$); 207.6 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1727; ν_{max} = 2926, 1451, 1149, 1100, 734, 697. MS (70 eV): m/z (%) 288 (M^++1, 100). HRMS (ESI) Calcd. for $C_{18}H_{26}NO_2$ 288.1964 $[M + H]^+$, found 288.1965.

5.10 Synthesis of *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones

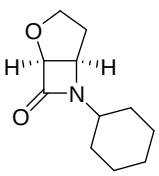
As a representative example, the synthesis of *cis*-6-isopropyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **18a** is described. Palladium on activated carbon (20% w/w) was added to a solution of *cis*-3-benzyloxy-1-isopropyl-4-(2-mesyloxyethyl)azetidin-2-one **17a** (1.54 g, 4.5 mmol, 1 equiv) in methanol (30 mL), and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 60 hours at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite® and evaporation of the solvent *in vacuo* afforded *cis*-3-hydroxy-1-isopropyl-4-(2-mesyloxyethyl)azetidin-2-one in high purity (> 90%, ^{1}H NMR), which was used as such in the next reaction step. To an ice-cold solution of the latter β-lactam (1.18 g, 4.5 mmol, 1 equiv) in tetrahydrofuran (30 mL) was added sodium hydride (0.18 g, 4.5 mmol, 1 equiv, 60% dispersion in mineral oil), after which the mixture was heated under reflux for 15 hours. The reaction mixture was poured into brine (1 × 30 mL) and extracted with ethyl acetate (3 × 30 mL), after which the organic fraction was dried ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent *in vacuo*. Purification by means of column chromatography on silica gel (hexane/EtOAc 1/1) afforded pure *cis*-6-isopropyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **18a** in 52% yield.

Cis-6-isopropyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 18a



Colourless oil. R_f = 0.10 (hexane/EtOAc 1/1). Yield 52%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 and 1.28 (2 × 3H, 2 × d, *J* = 6.6 Hz, ($C\underline{H}_3$)$_2$CHN); 1.60-1.73 (1H, m, ($\underline{H}$CH)CHN); 2.07 (1H, ~(d × d), *J* = 13.8, 5.0 Hz, (HC$\underline{H}$)CHN); 3.86-3.98 (2H, m, (CH_3)$_2$C$\underline{H}$N and ($\underline{H}$CH)O); 4.20-4.29 (2H, m, (HC$\underline{H}$)O and $CH_2C\underline{H}$N); 5.03 (1H, d, *J* = 3.3 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 and 21.9 (($\underline{C}H_3$)$_2$CHN); 29.7 ($\underline{C}H_2$CHN); 43.9 ((CH_3)$_2\underline{C}$HN); 56.9 ($CH_2\underline{C}$HN); 67.2 (CH_2O); 85.7 (CHO); 165.6 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1732; ν_{max} = 2974, 1390, 1230, 1099, 922, 772. MS (70 eV): m/z (%) 156 (M^++1, 100). HRMS (ESI) Calcd. for $C_8H_{14}NO_2$ 156.1025 $[M + H]^+$, found 156.1020.

Cis-6-cyclohexyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one 18b

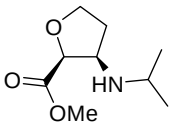


Colourless oil. R_f = 0.05 (hexane/EtOAc 3/1). Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09-1.98 (11H, m, ($C\underline{H}_2$)$_5$CHN and OCH_2($\underline{H}$CH)); 2.06 (1H, ~(d × d), *J* = 13.5, 4.7 Hz, OCH_2(HC$\underline{H}$)); 3.48-3.58 (1H, m, (CH_2)$_5$C$\underline{H}$N); 3.89 (1H, d × d × d, *J* = 11.6, 9.3, 5.0 Hz, ($\underline{H}$CH)O); 4.20-4.28 (2H, m, (HC$\underline{H}$)O and CHOC$\underline{H}$N); 5.02 (1H, d, *J* = 3.3 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 25.1, 25.3, 29.8, 30.8 and 32.2 (($\underline{C}H_2$)$_5$CHN and $OCH_2\underline{C}H_2$); 51.7 ((CH_2)$_5\underline{C}$HN); 57.2 (CHO$\underline{C}$HN); 67.1 (CH_2O); 85.8 (CHO); 165.6 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1736; ν_{max} = 2930, 1391, 1085, 924. MS (70 eV): m/z (%) 196 (M^++1, 100). HRMS (ESI) Calcd. for $C_{11}H_{18}NO_2$ 196.1338 $[M + H]^+$, found 196.1335.

5.11 Synthesis of methyl *cis*-3-aminotetrahydrofuran-2-carboxylates

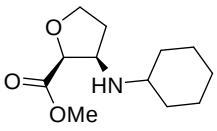
As a representative example, the synthesis of methyl *cis*-3-(isopropylamino)tetrahydrofuran-2-carboxylate **19a** is described. To a solution of *cis*-6-isopropyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-one **18a** (0.38 g, 2.44 mmol, 1 equiv) in methanol (20 mL) was added a solution of HCl in MeOH (3 M, 4.1 mL), followed by a reflux period of 24 hours. Afterwards, methanol was removed *in vacuo*, followed by the addition of anhydrous CH_2Cl_2 (20 mL) and triethylamine (0.49 g, 4.88 mmol, 2 equiv). Subsequently, the resulting mixture was heated under reflux for 4 hours, after which the solvent was removed under reduced pressure. Addition of dry diethyl ether, filtration of the precipitated triethylamine hydrochloride, drying of the filtrate ($MgSO_4$), filtration of the drying agent and removal of the solvent *in vacuo* yielded methyl *cis*-3-(isopropylamino)tetrahydrofuran-2-carboxylate **19a**, which was further purified in 66% yield by means of column chromatography on silica gel (hexane/EtOAc 4/1).

Methyl *cis*-3-(isopropylamino)tetrahydrofuran-2-carboxylate 19a



Light-yellow oil. R_f = 0.08 (hexane/EtOAc 4/1). Yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 and 1.04 (2 × 3H, 2 × d, *J* = 6.3 Hz, $(C\underline{H}_3)_2CHN$); 1.83-1.95 and 2.10-2.21 (2 × 1H, 2 × m, $(\underline{H}C\underline{H})CHN$); 2.83 (1H, septet, *J* = 6.3 Hz, $(CH_3)_2C\underline{H}N$); 3.67 (1H, ~q, *J* = 6.6 Hz, $CH_2C\underline{H}N$); 3.75 (3H, s, CH_3O); 3.92 (1H, d × d × d, *J* = 8.3, 8.3, 7.5 Hz, $(\underline{H}CH)O$); 4.18 (1H, d × d × d, *J* = 8.3, 8.3, 5.5 Hz, $(HC\underline{H})O$); 4.47 (1H, d, *J* = 6.6 Hz, CHO). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 23.1 and 23.4 ($(\underline{C}H_3)_2CHN$); 32.6 ($\underline{C}H_2CHN$); 47.3 ($(CH_3)_2\underline{C}HN$); 51.7 (CH_3O); 58.4 ($CH_2\underline{C}HN$); 67.7 (CH_2O); 80.4 (CHO); 171.9 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1742; ν_{max} = 2959, 1437, 1204, 1174, 1094, 752. MS (70 eV): m/z (%) 188 (M^++1, 100). HRMS (ESI) Calcd. for $C_9H_{18}NO_3$ 188.1287 $[M + H]^+$, found 188.1289.

Methyl *cis*-3-(cyclohexylamino)tetrahydrofuran-2-carboxylate 19b

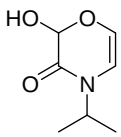


Colourless oil. R_f = 0.07 (hexane/EtOAc 6/1). Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96-1.30, 1.57-1.61 and 1.68-1.94 (5H, 1H and 5H, 3 × m, $(C\underline{H}_2)_5CHN$ and $OCH_2(\underline{H}CH)$); 2.09-2.19 (1H, m, $OCH_2(HC\underline{H})$); 2.40-2.49 (1H, m, $(CH_2)_5C\underline{H}N$); 3.73 (1H, d × d × d, *J* = 10.3, 5.5, 5.4 Hz, $CHOC\underline{H}N$); 3.75 (3H, s, CH_3O); 3.91 and 4.18 (2 × 1H, 2 × ~q, *J* = 7.5 Hz, $(\underline{H}C\underline{H})O$); 4.46 (1H, d, *J* = 5.5 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 25.0, 26.2, 32.7, 33.6 and 34.2 ($(\underline{C}H_2)_5CHN$ and $OCH_2\underline{C}H_2$); 51.5 ($(CH_2)_5\underline{C}HN$); 55.1 (CH_3O); 58.0 ($CHO\underline{C}HN$); 67.6 (CH_2O); 80.6 (CHO); 171.8 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1742; ν_{max} = 2925, 1448, 1202, 1179, 1096, 730. MS (70 eV): m/z (%) 228 (M^++1, 100). HRMS (ESI) Calcd. for $C_{12}H_{22}NO_3$ 228.1600 $[M + H]^+$, found 228.1603.

5.12 Synthesis of 2-hydroxy-1,4-oxazin-3-ones

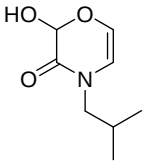
As a representative example, the synthesis of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a** is described. Saturated aqueous sodium hydrogen carbonate (2 mL) was added to a solution of (3*R*,4*S*)-3-hydroxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one **193a** (1.89 g, 10 mmol, 1 equiv) in CH_2Cl_2 (30 mL). Solid sodium periodate (4.28 g, 20 mmol, 2 equiv) was added over a 10 min. period with vigorous stirring, and the reaction was allowed to proceed for 2 hours at room temperature. The solid was removed by filtration and the filtrate was washed with water (25 mL), after which the organic fraction was dried over $MgSO_4$, followed by removal of the drying agent by filtration. Removal of the solvent *in vacuo* yielded 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a**, which was further purified in 69% yield by means of column chromatography on silica gel (hexane/EtOAc 1/1).

2-Hydroxy-4-isopropyl-1,4-oxazin-3-one 194a



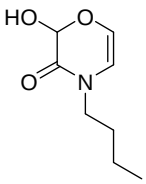
Yellow oil. R_f = 0.32 (hexane/EtOAc 1/1). Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 and 1.24 (2 × 3H, 2 × d, *J* = 6.6 Hz, $(C\underline{H}_3)_2CH$); 4.39 (1H, d, *J* = 4.7 Hz, OH); 4.74 (1H, septet, *J* = 6.6 Hz, $(CH_3)_2C\underline{H}$); 5.41 (1H, d, *J* = 4.7 Hz, OCHO); 5.78 and 6.24 (2 × 1H, 2 × d, *J* = 4.1 Hz, HC=CH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.9 and 20.5 ($(\underline{C}H_3)_2CH$); 44.5 ($(CH_3)_2\underline{C}H$); 90.6 (OCHO); 104.8 and 128.3 (HC=CH); 160.6 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3288; $\nu_{C=O,C=C}$ = 1671, 1642; ν_{max} = 1406, 1213, 1069, 1027, 955, 699. MS (70 eV): m/z (%) 158 (M^++1, 100). HRMS (ESI) Calcd. for $C_7H_{12}NO_3$ 158.0817 $[M + H]^+$, found 158.0819.

2-Hydroxy-4-isobutyl-1,4-oxazin-3-one 194b



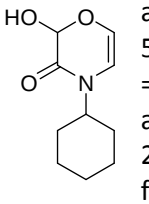
Yellow oil. R_f = 0.41 (hexane/EtOAc 1/1). Yield 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 and 0.93 (2 × 3H, 2 × d, *J* = 7.2 Hz, $(C\underline{H}_3)_2CH$); 2.00 (1H, nonet, *J* = 7.2 Hz, $(CH_3)_2C\underline{H}$); 3.31 and 3.37 (2 × 1H, 2 × (d × d), *J* = 13.5, 7.2, 7.2 Hz, (HCH)N); 4.72 (1H, d, *J* = 4.7 Hz, OH); 5.47 (1H, d, *J* = 4.7 Hz, OCHO); 5.69 and 6.18 (2 × 1H, 2 × d, *J* = 4.1 Hz, HC=CH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.8 ($(\underline{C}H_3)_2CH$); 27.6 ($(CH_3)_2\underline{C}H$); 53.1 (CH_2N); 90.6 (OCHO); 110.6 and 127.3 (HC=CH); 161.5 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3288; $\nu_{C=O,C=C}$ = 1672, 1649; ν_{max} = 2961, 1389, 1283, 1028, 959, 729. MS (70 eV): m/z (%) 172 (M^++1, 100). HRMS (ESI) Calcd. for $C_8H_{14}NO_3$ 172.0974 $[M + H]^+$, found 172.0971.

4-Butyl-2-hydroxy-1,4-oxazin-3-one 194c



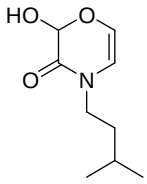
Yellow crystals. Mp 85.5 °C. R_f = 0.24 (hexane/EtOAc 1/1). Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); 1.34 (2H, sextet, *J* = 7.2 Hz, $C\underline{H}_2CH_3$); 1.59 (2H, pentet, *J* = 7.2 Hz, $C\underline{H}_2CH_2N$); 3.44 and 3.60 (2 × 1H, 2 × (d × t), *J* = 13.7, 7.2 Hz, (HCH)N); 5.55 (1H, s, OCHO); 5.70 and 6.19 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.8 ($CH_2\underline{C}H_3$); 19.8 ($\underline{C}H_2CH_3$); 30.2 ($\underline{C}H_2CH_2N$); 45.9 (CH_2N); 90.6 (OCHO); 110.2 and 127.7 (HC=CH); 161.2 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3301; $\nu_{C=O,C=C}$ = 1672, 1650; ν_{max} = 2959, 1432, 1030, 959, 728. MS (70 eV): m/z (%) 172 (M^++1, 100). HRMS (ESI) Calcd. for $C_8H_{14}NO_3$ 172.0974 $[M + H]^+$, found 172.0965.

4-Cyclohexyl-2-hydroxy-1,4-oxazin-3-one 194d



Yellow oil. R_f = 0.43 (hexane/EtOAc 1/1). Yield 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.22, 1.33-1.48 and 1.68-1.88 (1H, 4H and 5H, 3 × m, $(C\underline{H}_2)_5CHN$); 4.25-4.41 (2H, m, $(CH_2)_5C\underline{H}N$ and OH); 5.40 (1H, s, OCHO); 5.81 and 6.21 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.3, 25.5, 30.2 and 30.9 ($(\underline{C}H_2)_5CHN$); 52.2 ($(CH_2)_5\underline{C}HN$); 90.6 (OCHO); 105.7 and 127.9 (HC=CH); 160.7 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3297; $\nu_{C=O,C=C}$ = 1671, 1646; ν_{max} = 2931, 1409, 1196, 1026, 957, 728. MS (70 eV): m/z (%) 198 (M^++1, 100). HRMS (ESI) Calcd. for $C_{10}H_{16}NO_3$ 198.1130 $[M + H]^+$, found 198.1132.

2-Hydroxy-4-isopentyl-1,4-oxazin-3-one 194e

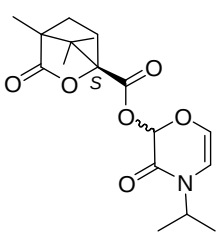


Colourless oil. R_f = 0.35 (hexane/EtOAc 1/1). Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (6H, d, *J* = 6.6 Hz, $(C\underline{H}_3)_2CH$); 1.43-1.53 (2H, m, $C\underline{H}_2CH_2N$); 1.55-1.68 (1H, m, $(CH_3)_2C\underline{H}$); 3.45-3.62 (2H, m, CH_2N); 4.30 (1H, d, *J* = 6.1 Hz, OH); 5.43 (1H, d, *J* = 6.1 Hz, OCHO); 5.71 and 6.19 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.5 ($(\underline{C}H_3)_2CH$); 25.7 ($(CH_3)_2\underline{C}H$); 36.8 ($\underline{C}H_2CH_2N$); 44.4 (CH_2N); 90.6 (OCHO); 109.9 and 127.7 (HC=CH); 161.1 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3300; $\nu_{C=O,C=C}$ = 1671, 1649; ν_{max} = 2956, 1429, 1263, 1035, 953, 726. MS (70 eV): m/z (%) 186 (M^++1, 100). HRMS (ESI) Calcd. for $C_9H_{16}NO_3$ 186.1130 $[M + H]^+$, found 186.1132.

5.13 Synthesis of 2-camphanoyloxy-4-isopropyl-1,4-oxazin-3-one

To a solution of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a** (1.57 g, 10 mmol, 1 equiv) and (1*S*)-(-)-camphanic chloride (2.17 g, 10 mmol, 1 equiv) in dry dichloromethane (50 mL) was added triethylamine (3.04 g, 30 mmol, 3 equiv) dropwise at 0 °C. The mixture was stirred at the same temperature for 2 hours, after which the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (30 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with a 10% aq. HCl solution (2 × 20 mL) and water (20 mL). Drying ($MgSO_4$), removal of the drying agent by filtration and evaporation of the solvent *in vacuo* afforded crude 2-camphanoyloxy-4-

isopropyl-1,4-oxazin-3-one **198**, which was further purified as a diastereoisomeric mixture by means of recrystallization.

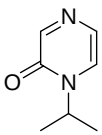


White crystals. Mp 141.0 °C. Recrystallization from EtOAc/hexane (30/1). Yield 33%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95, 0.97, 1.03, 1.04 and 1.11 (4 × 3H and 6H, 5 × s, 6 × $C_{quat}CH_3$); 1.23, 1.25 and 1.27 (6H, 3H and 3H, 3 × d, *J* = 6.6 Hz, 2 × ($C\underline{H}_3$)$_2$CH); 1.64-1.75, 1.88-1.98, 2.01-2.10 and 2.37-2.47 (4 × 2H, 4 × m, 4 × CH_2); 4,80 (2H, septet, *J* = 6.6 Hz, 2 × (CH_3)$_2$C$\underline{H}$); 5.87, 5.89, 6.20 and 6.22 (4 × 1H, 4 × d, *J* = 4.4 Hz, 2 × HC=CH); 6.59 and 6.61 (2 × 1H, 2 × s, 2 × OCHO). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 9.7, 16.59, 16.62 and 16.7 (6 × $C_{quat}\underline{C}H_3$); 20.0, 20.51 and 20.54 (2 × ($\underline{C}H_3$)$_2$CH); 29.0, 30.5 and 30.7 (4 × CH_2); 44.7 and 44.8 (2 × (CH_3)$_2\underline{C}$H); 54.7, 54.8, 54.9 (4 × $\underline{C}_{quat}CH_3$); 88.9 and 89.0 (2 × OCHO); 90.66 and 90.75 (2 × C_{quat}O); 105.8, 126.9 and 127.0 (2 × HC=CH); 156.3, 166.0, 166.1 and 178.0 (6 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1785, 1764, 1747; $\nu_{NC=O,C=C}$ = 1682, 1666; ν_{max} = 2956, 2043, 1432, 1267, 1223, 1174, 1099, 1078, 1052, 986, 960, 926, 740. MS (70eV): m/z (%) 337 (M$^+$, 64), 308 (43), 140 (48), 128 (57), 125 (100), 98 (40), 97 (56), 83 (96).

5.14 Synthesis of 1*H*-pyrazin-2-ones

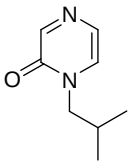
As a representative example, the synthesis of 1-isopropyl-1*H*-pyrazin-2-one **211a** is described. To a solution of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a** (15.7 mg, 0.1 mmol, 1 equiv) in EtOAc (1.0 mL) was added NH_4OAc (92.4 mg, 1.2 mmol, 12 equiv) and HOAc (1.0 mL). After a reflux period of 24 hours, the resulting reaction mixture was neutralized with solid $NaHCO_3$, after which EtOAc (10 mL) was added. Subsequently, the reaction mixture was washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (5 mL). Drying ($MgSO_4$), removal of the drying agent by filtration and evaporation of the solvent *in vacuo* afforded crude 1-isopropyl-1*H*-pyrazin-2-one **211a**, which was further purified in 45% yield by means of recrystallization from EtOAc/hexane (30/1).

1-Isopropyl-1*H*-pyrazin-2-one 211a



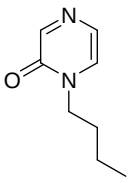
White crystals. Mp 85.2 °C. Recrystallization from EtOAc/hexane (30/1). Yield 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (6H, d, *J* = 6.8 Hz, ($C\underline{H}_3$)$_2$CH); 5.13 (1H, septet, *J* = 6.8 Hz, (CH_3)$_2$C$\underline{H}$); 7.15 (1H, d × d, *J* = 4.4, 1.1 Hz, HC=NC$\underline{H}$); 7.37 (1H, d, *J* = 4.4 Hz, HC=NCHC$\underline{H}$); 8.14 (1H, d, *J* = 1.1 Hz, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.4 (($\underline{C}H_3$)$_2$CH); 46.9 ((CH_3)$_2\underline{C}$H); 124.0 (HC=N$\underline{C}$H); 124.4 (HC=NCH$\underline{C}$H); 149.4 (HC=N); 155.9 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=N,C=C}$ = 1660, 1651, 1590; ν_{max} = 2978, 1490, 1450, 1251, 1225, 1188, 1105, 799. MS (70eV): m/z (%) 139 (M$^+$+1, 100). HRMS (ESI) Calcd. for $C_7H_{11}N_2O$ 139.0871 [M + H]$^+$, found 139.0870.

1-Isobutyl-1*H*-pyrazin-2-one 211b



Orange oil. R_f = 0.20 (hexane/EtOAc 1/1). Yield 51%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (6H, d, *J* = 7.2 Hz, $(C\underline{H}_3)_2CH$); 2.10 (1H, nonet, *J* = 7.2 Hz, $(CH_3)_2C\underline{H}$); 3.64 (2H, d, *J* = 7.2 Hz, CH_2N); 7.00 (1H, d × d, *J* = 4.4, 1.1 Hz, HC=NC<u>H</u>); 7.23 (1H, d, *J* = 4.4 Hz, $CH_2NC\underline{H}$); 8.07 (1H, s, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.8 ($(\underline{C}H_3)_2CH$); 27.7 ($(CH_3)_2\underline{C}H$); 56.7 (CH_2N); 123.5 ($CH_2N\underline{C}H$); 129.2 (HC=N<u>C</u>H); 149.8 (HC=N); 156.4 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=N,C=C}$ = 1649, 1590; ν_{max} = 2961, 1496, 1454, 1142, 1102, 800. MS (70eV): m/z (%) 153 (M^++1, 100). HRMS (ESI) Calcd. for $C_8H_{13}N_2O$ 153.1028 $[M + H]^+$, found 153.1027.

1-Butyl-1*H*-pyrazin-2-one 211c

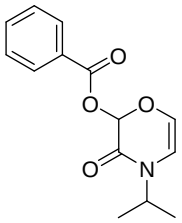


Orange oil. R_f = 0.15 (hexane/EtOAc 1/1). Yield 30%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.4 Hz, CH_3); 1.33-1.45 (2H, m, $C\underline{H}_2CH_3$); 1.69-1.79 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.90 (2H, t, *J* = 7.4 Hz, $C\underline{H}_2(CH_2)_2CH_3$); 7.12 (1H, d × d, *J* = 4.4, 1.1 Hz, HC=NC<u>H</u>); 7.32 (1H, d, *J* = 4.4 Hz, $CH_2NC\underline{H}$); 8.14 (1H, s, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.7 (CH_3); 19.8 ($\underline{C}H_2CH_3$); 30.7 ($\underline{C}H_2CH_2CH_3$); 49.3 ($\underline{C}H_2(CH_2)_2CH_3$); 123.8 ($CH_2N\underline{C}H$); 128.7 (HC=N<u>C</u>H); 149.7 (HC=N); 156.3 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=N,C=C}$ = 1649, 1590; ν_{max} = 2958, 1496, 1457, 1190, 1140, 1102, 799, 623. MS (70eV): m/z (%) 153 (M^++1, 100). HRMS (ESI) Calcd. for $C_8H_{13}N_2O$ 153.1028 $[M + H]^+$, found 153.1027.

5.15 Synthesis of 2-benzoyloxy-1,4-oxazin-3-ones

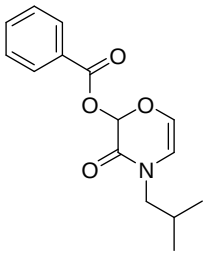
As a representative example, the synthesis of 2-benzoyloxy-4-isopropyl-1,4-oxazin-3-one **225a** is described. To a solution of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a** (1.57 g, 10 mmol, 1 equiv) and benzoyl chloride (4.22 g, 30 mmol, 3 equiv) in dry dichloromethane (50 mL) was added triethylamine (3.04 g, 30 mmol, 3 equiv) dropwise at 0 °C. The mixture was stirred at the same temperature for 2 hours, after which the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (30 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with a 10% aq. HCl solution (2 × 20 mL) and water (20 mL). Drying ($MgSO_4$), removal of the drying agent by filtration and evaporation of the solvent *in vacuo* afforded crude 2-benzoyloxy-4-isopropyl-1,4-oxazin-3-one **225a**, which was further purified in 45% yield by means of recrystallization from EtOAc/hexane (30/1).

2-Benzoyloxy-4-isopropyl-1,4-oxazin-3-one 225a



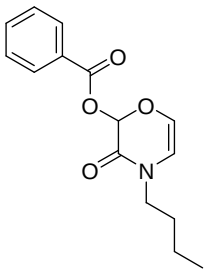
White crystals. Mp 99.3 °C. Recrystallization from EtOAc/hexane (30/1). Yield 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 and 1.32 (2 × 3H, 2 × d, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 4.89 (1H, septet, *J* = 6.8 Hz, $(CH_3)_2C\underline{H}$); 5.90 and 6.23 (2 × 1H, 2 × d, *J* = 4.7 Hz, HC=CH); 6.72 (1H, s, OCHO); 7.42-7.47, 7.56-7.62 and 8.00-8.03 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.2 and 20.6 ($(\underline{C}H_3)_2CH$); 44.6 ($(CH_3)_2\underline{C}H$); 88.9 (OCHO); 105.5 and 127.4 (HC=CH); 128.6 (2 × HC_{arom}); 129.0 ($C_{arom,quat}$); 130.2 and 133.8 (3 × HC_{arom}); 157.0 and 164.8 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1731; $\nu_{NC=O,C=C}$ = 1679, 1664; ν_{max} = 1429, 1261, 1215, 1052, 987, 945, 702. MS (70 eV): m/z (%) 261 (M^+, 3), 156 (10), 140 (3), 105 (100), 98 (3), 77 (17). Anal. Calcd. for $C_{14}H_{15}NO_4$: C 64.36, H 5.79, N 5.36. Found: C 64.40, H 5.58, N 5.48.

2-Benzoyloxy-4-isobutyl-1,4-oxazin-3-one 225b



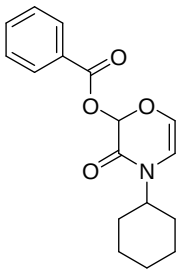
Colourless oil. R_f = 0.11 (hexane/EtOAc 19/1). Yield 64%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (6H, d, *J* = 6.6 Hz, $(C\underline{H}_3)_2CH$); 1.98-2.12 (1H, m, $(CH_3)_2C\underline{H}$); 3.37 and 3.48 (2 × 1H, 2 × (d × d), *J* = 13.4, 7.7, 7.4 Hz, (HCH)N); 5.86 and 6.18 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH); 6.79 (1H, s, OCHO); 7.37-7.42, 7.52-7.57 and 7.98-8.08 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.7 and 19.8 ($(\underline{C}H_3)_2CH$); 27.6 ($(CH_3)_2\underline{C}H$); 53.1 (CH_2N); 88.7 (OCHO); 111.2 and 126.4 (HC=CH); 128.6 and 130.0 (4 × HC_{arom}); 133.5 ($C_{arom,quat}$); 133.8 (HC_{arom}); 157.8 and 164.6 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1734; $\nu_{NC=O,C=C}$ = 1687; ν_{max} = 2960, 1451, 1427, 1256, 1246, 1207, 1079, 1052, 1024, 987, 947, 733, 707, 686. MS (70eV): m/z (%) 275 (M^+, 8), 246 (4), 170 (12), 154 (4), 122 (4), 106 (7), 105 (100), 77 (15).

2-Benzoyloxy-4-butyl-1,4-oxazin-3-one 225c



Colourless oil. R_f = 0.09 (hexane/EtOAc 19/1). Yield 93%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.3 Hz, CH_3); 1.39 (2H, sextet, *J* = 7.3 Hz, $C\underline{H}_2CH_3$); 1.65 (2H, pentet, *J* = 7.3 Hz, $C\underline{H}_2CH_2CH_3$); 3.53-3.71 (2H, m, $C\underline{H}_2(CH_2)_2CH_3$); 5.84 and 6.19 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH); 6.74 (1H, s, OCHO); 7.40-7.45, 7.55-7.60 and 8.00-8.03 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.8 (CH_3); 19.8 ($\underline{C}H_2CH_3$); 30.2 ($\underline{C}H_2CH_2CH_3$); 45.9 ($\underline{C}H_2(CH_2)_2CH_3$); 88.7 (OCHO); 110.7 and 126.8 (HC=CH); 128.6 (2 × HC_{arom}); 128.9 ($C_{arom,quat}$); 130.1 (2 × HC_{arom}); 133.9 (HC_{arom}); 157.6 and 164.8 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1734; $\nu_{NC=O,C=C}$ = 1686; ν_{max} = 2959, 1451, 1427, 1246, 1079, 1051, 1023, 986, 945, 707, 686. MS (70eV): m/z (%) 275 (M^+, 6), 246 (2), 170 (10), 154 (3), 122 (3), 106 (7), 105 (100), 77 (13).

2-Benzoyloxy-4-cyclohexyl-1,4-oxazin-3-one 225d

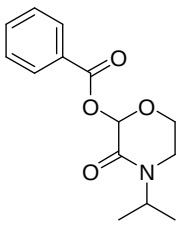


White crystals. Mp 94.6 °C. Recrystallization from EtOAc/hexane (30/1). Yield 34%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08-1.25, 1.35-1.58 and 1.70-1.93 (1H, 4H and 5H, 3 × m, $(C\underline{H}_2)_5CHN$); 4.42-4.53 (1H, m, $(CH_2)_5C\underline{H}N$); 5.92 and 6.20 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH); 6.72 (1H, s, OCHO); 7.42-7.47, 7.56-7.62 and 8.00-8.03 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.3, 25.5, 30.4 and 31.0 ($(\underline{C}H_2)_5CHN$); 52.3 ($(CH_2)_5\underline{C}HN$); 88.9 (OCHO); 106.4 and 127.0 (HC=CH); 128.6 (2 × HC_{arom}); 128.9 ($C_{arom,quat}$); 130.1 and 133.8 (3 × HC_{arom}); 157.1 and 164.8 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1783; $\nu_{NC=O,C=C}$ = 1727, 1687; ν_{max} = 1450, 1209, 1173, 1014, 986, 871, 702, 670. MS (70 eV): m/z (%) 301 (M^+, 10), 272 (5), 196 (15), 105 (100), 77 (15), 55 (5). Anal. Calcd. for $C_{17}H_{19}NO_4$: C 67.76, H 6.36, N 4.65. Found: C 67.82, H 6.15, N 4.38.

5.16 Synthesis of 2-benzoyloxymorpholin-3-ones

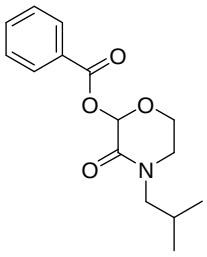
As a representative example, the synthesis of 2-benzoyloxy-4-isopropylmorpholin-3-one **226a** is described. Palladium on activated carbon (20% w/w) was added to a solution of 2-benzoyloxy-4-isopropyl-1,4-oxazin-3-one **225a** (2.61 g, 10 mmol, 1 equiv) in methanol (60 mL) and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 18 hours at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite® and evaporation of the solvent *in vacuo* afforded crude 2-benzoyloxy-4-isopropylmorpholin-3-one **226a**, which was purified in 69% yield by means of recrystallization from EtOAc/hexane (30/1).

2-Benzoyloxy-4-isopropylmorpholin-3-one 226a



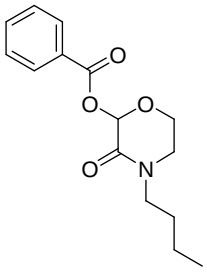
White crystals. Mp 124.2 °C. Recrystallization from EtOAc/hexane (30/1). Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 and 1.22 (2 × 3H, 2 × d, *J* = 6.7 Hz, $(C\underline{H}_3)_2CH$); 3.23 (1H, d × d × d, *J* = 12.3, 3.2, 1.4 Hz, (<u>H</u>CH)N); 3.53 (1H, d × d × d, *J* = 12.3, 11.9, 4.8 Hz, (HC<u>H</u>)N); 3.98 (1H, d × d × d, *J* = 11.8, 4.8, 1.4 Hz, (<u>H</u>CH)O); 4.20 (1H, d × d × d, *J* = 11.8, 11.9, 3.2 Hz, (HC<u>H</u>)O); 4.90 (1H, septet, *J* = 6.7 Hz, $(CH_3)_2C\underline{H}$); 6.40 (1H, s, CHO); 7.42-7.47, 7.56-7.61 and 8.07-8.10 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.0 and 19.4 ($(\underline{C}H_3)_2CH$); 39.2 (CH_2N); 44.4 ($(CH_3)_2\underline{C}H$); 59.7 (CH_2O); 89.2 (CHO); 128.5 (2 × HC_{arom}); 129.5 ($C_{arom,quat}$); 130.2 (2 × HC_{arom}) and 133.6 (HC_{arom}); 162.1 and 165.4 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1719; $\nu_{NC=O}$ = 1654; ν_{max} = 2927, 1475, 1263, 1210, 1178, 1138, 1081, 1062, 1024, 995, 961, 908, 712, 684. MS (70eV): m/z (%) 264 (M^++1, 100). HRMS (ESI) Calcd. for $C_{14}H_{18}NO_4$ 264.1236 $[M + H]^+$, found 264.1233.

2-Benzoyloxy-4-isobutylmorpholin-3-one 226b



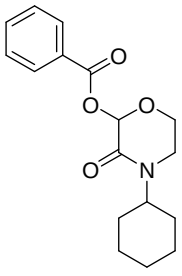
Yellow oil. R_f = 0.18 (hexane/EtOAc 3/1). Yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 and 0.84 (2 × 3H, 2 × d, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 1.92 (1H, nonet, *J* = 6.8 Hz, $(CH_3)_2C\underline{H}$); 3.12 (1H, d × d, *J* = 12.4, 2.5 Hz, $(CH_2(\underline{H}CH)N)$; 3.18 (2H, d, *J* = 6.8 Hz, $CHC\underline{H}_2N$); 3.55 (1H, d × d × d, *J* = 12.4, 12.0, 3.9 Hz, $(CH_2(HC\underline{H})N)$; 3.80 (1H, d × d, *J* = 12.0, 3.9 Hz, $(\underline{H}CH)O)$; 4.14 (1H, d × d × d, *J* = 12.0, 12.0, 2.5 Hz, $(HC\underline{H})O)$; 6.33 (1H, s, CHO); 7.22-7.33, 7.37-7.47 and 7.86-7.96 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.9 and 20.1 $((\underline{C}H_3)_2CH)$; 26.3 $((CH_3)_2\underline{C}H)$; 46.4 $(CH_2\underline{C}H_2N)$; 54.0 $(CH\underline{C}H_2N)$; 59.3 (CH_2O); 89.0 (CHO); 128.5 (2 × HC_{arom}); 129.3 ($C_{arom,quat}$); 130.0 (2 × HC_{arom}); 133.6 (HC_{arom}); 163.1 and 165.2 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1727; $\nu_{NC=O}$ = 1669; ν_{max} = 2960, 1451, 1259, 1152, 1082, 1063, 1024, 1012, 955, 907, 709, 687. MS (70eV): m/z (%) 278 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{20}NO_4$ 278.1392 $[M + H]^+$, found 278.1391.

2-Benzoyloxy-4-butylmorpholin-3-one 226c



Yellow oil. R_f = 0.30 (hexane/EtOAc 3/1). Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.3 Hz, CH_3); 1.36 (2H, sextet, *J* = 7.3 Hz, $C\underline{H}_2CH_3$); 1.50-1.67 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.23 (1H, d × d, *J* = 12.4, 2.6 Hz, $OCH_2(\underline{H}CH)N$); 3.36-3.56 (2H, m, $C\underline{H}_2(CH_2)_2CH_3$); 3.68 (1H, d × d × d, *J* = 12.4, 12.0, 4.0 Hz, $(OCH_2(HC\underline{H})N)$; 3.91 (1H, d × d, *J* = 11.8, 4.0 Hz, $(\underline{H}CH)O)$; 4.24 (1H, d × d × d, *J* = 12.0, 11.8, 2.6 Hz, $(HC\underline{H})O)$; 6.40 (1H, s, CHO); 7.39-7.44, 7.53-7.58 and 8.05-8.08 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.8 (CH_3); 20.0 ($\underline{C}H_2CH_3$); 28.9 ($\underline{C}H_2CH_2CH_3$); 45.8 ($OCH_2\underline{C}H_2N$); 46.7 ($\underline{C}H_2(CH_2)_2CH_3$); 59.3 ($CH_2O$); 89.0 (CHO); 128.5 (2 × HC_{arom}); 129.4 ($C_{arom,quat}$); 130.1 (2 × HC_{arom}); 133.6 (HC_{arom}); 162.6 and 165.2 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1728; $\nu_{NC=O}$ = 1667; ν_{max} = 2931, 1451, 1258, 1151, 1082, 1063, 1024, 947, 881, 710, 687. MS (70eV): m/z (%) 278 (M^++1, 100). HRMS (ESI) Calcd. for $C_{15}H_{20}NO_4$ 278.1392 $[M + H]^+$, found 278.1392.

2-Benzoyloxy-4-cyclohexylmorpholin-3-one 226d

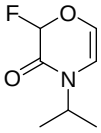


Light-yellow crystals. Mp 96.1 °C. R_f = 0.63 (EtOAc). Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.19, 1.34-1.54 and 1.69-1.90 (1H, 4H and 5H, 3 × m, $(C\underline{H}_2)_5CHN$); 3.26 (1H, d × d × d, *J* = 12.4, 3.3, 1.6 Hz, $(\underline{H}CH)N)$; 3.54 (1H, d × d × d, *J* = 12.4, 11.9, 4.4 Hz, $(HC\underline{H})N)$; 3.96 (1H, d × d × d, *J* = 11.9, 4.4, 1.6 Hz, $(\underline{H}CH)O)$; 4.20 (1H, d × d × d, *J* = 11.9, 11.9, 3.3 Hz, $(HC\underline{H})O)$; 4.41-4.52 (1H, m, $(CH_2)_5C\underline{H}N)$; 6.39 (1H, s, OCHO); 7.42-7.47, 7.55-7.61 and 8.07-8.11 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.5, 25.6, 29.5 and 29.6 $((\underline{C}H_2)_5CHN)$; 40.4 ($CH_2N$); 52.6 $((CH_2)_5\underline{C}HN)$; 59.8 ($CH_2O$); 89.3 (OCHO); 128.5 (2 × HC_{arom}); 129.5 ($C_{arom,quat}$); 130.1 and 133.6 (3 × HC_{arom}); 162.2 and 165.4 (2 × C=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1724; $\nu_{NC=O}$ = 1649; ν_{max} = 2924, 1398, 1251, 1079, 888, 688. MS (70 eV): m/z (%) 304 (M^++1, 100). Anal. Calcd. for $C_{17}H_{21}NO_4$: C 67.31, H 6.98, N 4.62. Found: C 67.56, H 6.89, N 4.78.

5.17 Synthesis of 2-fluoro-1,4-oxazin-3-ones

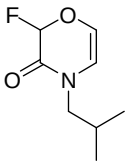
As a representative example, the synthesis of 2-fluoro-4-isopropyl-1,4-oxazin-3-one **232a** is described. To a solution of 2-hydroxy-4-isopropyl-1,4-oxazin-3-one **194a** (1.57 g, 10 mmol, 1 equiv) in dry dichloromethane (50 mL) at -78 °C under nitrogen atmosphere was added Morph-DAST (3.50 g, 20 mmol, 2 equiv) dropwise. The resulting mixture was allowed to warm to room temperature and was further stirred for 5 hours. A saturated solution of $NaHCO_3$ (50 mL) was carefully dropped to the mixture and the mixture was stirred for 15 min. The organic layer was separated and washed with water (25 mL) and brine (25 mL), after which the organic fraction was dried over $MgSO_4$, followed by removal of the drying agent by filtration. After evaporation of the solvent *in vacuo*, the crude reaction mixture was purified by means of column chromatography on silica gel (hexane/EtOAc 9/1), affording pure 2-fluoro-4-isopropyl-1,4-oxazin-3-one **228a** in 87% yield.

2-Fluoro-4-isopropyl-1,4-oxazin-3-one 232a



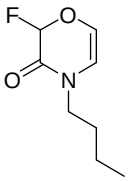
Colourless oil. R_f = 0.10 (hexane/EtOAc 9/1). Yield 87%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 and 1.27 (2 × 3H, 2 × d, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 4.80 (1H, septet, *J* = 6.8 Hz, $(CH_3)_2C\underline{H}$); 5.90 (1H, d, *J* = 52.7 Hz, CHF); 5.92 and 6.27 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH). ^{19}F NMR (282 MHz, $CDCl_3$): δ -127.92 (d, *J* = 52.7 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.9 and 20.6 ($(\underline{C}H_3)_2CH$); 44.7 ($(CH_3)_2\underline{C}H$); 102.0 (d, *J* = 234.2 Hz, CHF); 105.8 and 126.5 (HC=CH); 156.0 (d, *J* = 32.3 Hz, C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=C}$ = 1685, 1664; ν_{max} = 2980, 1424, 1223, 1073, 985, 951, 769, 699. MS (70eV): m/z (%) 159 (M^+, 83), 117 (100), 88 (37), 69 (43), 43 (17), 41 (25), 40 (11).

2-Fluoro-4-isobutyl-1,4-oxazin-3-one 232b



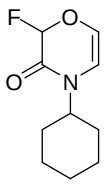
Colourless oil. R_f = 0.24 (hexane/EtOAc 9/1). Yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (6H, d, *J* = 7.0 Hz, $(C\underline{H}_3)_2CH$); 2.02 (1H, nonet, *J* = 7.0 Hz, $(CH_3)_2C\underline{H}$); 3.38 (2H, d × d, *J* = 7.0, 1.1 Hz, CH_2N); 5.83 (1H, d, *J* = 4.4 Hz, $\underline{H}C$=CH); 5.91 (1H, d, *J* = 52.7 Hz, CHF); 6.22 (1H, d, *J* = 4.4 Hz, HC=C$\underline{H}$). ^{19}F NMR (282 MHz, $CDCl_3$): δ -127.69 (d, *J* = 52.7 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.80 and 19,84 ($(\underline{C}H_3)_2CH$); 27.7 ($(CH_3)_2\underline{C}H$); 53.3 (CH_2N); 102.0 (d, *J* = 234.2 Hz, CHF); 111.4 and 125.6 (HC=CH); 156.8 (d, *J* = 32.3 Hz, C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=C}$ = 1686; ν_{max} = 2963, 1426, 1285, 1211, 1072, 989, 954, 727. MS (70eV): m/z (%) 173 (M^+, 61), 130 (13), 117 (100), 102 (52), 69 (16), 57 (13), 41 (20).

4-Butyl-2-fluoro-1,4-oxazin-3-one 232c



Light-yellow oil. R_f = 0.20 (hexane/EtOAc 9/1). Yield 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.5 Hz, CH_3); 1.35 (2H, sextet, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 1.56-1.66 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.48-3.66 (2H, m, $C\underline{H}_2(CH_2)_2CH_3$); 5.85 (1H, d, *J* = 4.4 Hz, $\underline{H}C$=CH); 5.90 (1H, d, *J* = 52.8 Hz, CHF); 6.23 (1H, d, *J* = 4.4 Hz, HC=C$\underline{H}$). ^{19}F NMR (282 MHz, $CDCl_3$): δ -127.57 (d, *J* = 52.8 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.7 (CH_3); 19.7 ($\underline{C}H_2CH_3$); 30.1 ($\underline{C}H_2CH_2CH_3$); 45.9 ($\underline{C}H_2(CH_2)_2CH_3$); 102.0 (d, *J* = 234.2 Hz, CHF); 110.9 and 125.8 (HC=CH); 156.5 (d, *J* = 32.3 Hz, C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=C}$ = 1686; ν_{max} = 2960, 1427, 1071, 987, 955, 728. MS (70eV): m/z (%) 173 (M^+, 99), 144 (52), 131 (17), 130 (27), 124 (24), 117 (100), 102 (57), 88 (17), 69 (33), 57 (19), 41 (35).

4-Cyclohexyl-2-fluoro-1,4-oxazin-3-one 232d

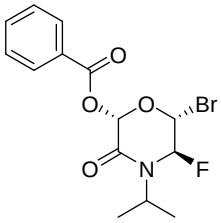


Yellow crystals. Mp 91.2 °C. R_f = 0.51 (hexane/EtOAc 1/1). Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.20, 1.34-1.51 and 1.68-1.89 (1H, 4H and 5H, 3 × m, $(C\underline{H}_2)_5CHN$); 4.34-4.45 (1H, m, $(CH_2)_5C\underline{H}N$); 5.90 (1H, d, *J* = 53.7 Hz, CHF); 5.93 and 6.24 (2 × 1H, 2 × d, *J* = 4.4 Hz, HC=CH). ^{19}F NMR (282 MHz, $CDCl_3$): δ -127.83 (d, *J* = 53.7 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.2, 25.4, 25.5, 30.2 and 30.9 ($(\underline{C}H_2)_5CHN$); 52.3 ($(CH_2)_5\underline{C}HN$); 102.0 (d, *J* = 233.1 Hz, CHF); 106.6 and 126.1 (HC=CH); 156.0 (d, *J* = 32.3 Hz, C=O). IR (ATR, cm^{-1}): $\nu_{C=O,C=C}$ = 1684, 1662; ν_{max} = 2932, 1421, 1205, 1075, 987, 956, 728. MS (70 eV): m/z (%) 200 (M^++1, 100). Anal. Calcd. for $C_{10}H_{14}FNO_2$: C 60.29, H 7.08, N 7.03. Found: C 60.50, H 6.99, N 7.08.

5.18 Synthesis of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones

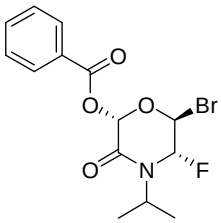
As a representative example, the synthesis of 2-benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one **234a** and **235a** is described. To a solution of 2-benzoyloxy-4-isopropyl-1,4-oxazin-3-one **225a** (2.61 g, 10 mmol, 1 equiv) in dry dichloromethane (50 mL) was added $Et_3N{\cdot}3HF$ (4.03 g, 25 mmol, 2.5 equiv) at 0 °C. Subsequently, *N*-bromosuccinimide (3.67 g, 15 mmol, 1.5 equiv) was added at 0 °C and the resulting mixture was stirred at room temperature for 24 hours. Afterwards, the mixture was poured in aq. 0.5 M NaOH (50 mL) and extraction was performed with dichloromethane (3 × 50 mL). The combined organic layers were washed with aq. 1 M NaOH (2 × 50 mL) and brine (50 mL). After drying with $MgSO_4$ and filtration of the drying agent, the solvent was evaporated *in vacuo*, affording a diastereoisomeric mixture of 2-benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one **234a** and **235a**, which were separated by means of recrystallization from EtOAc/hexane (30/1).

2-Benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one 234a *(major diastereoisomer)*



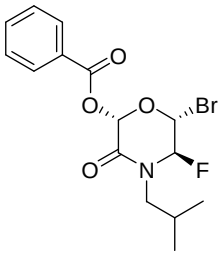
White crystals. Mp 122.8 °C. Recrystallization from EtOAc/hexane (30/1). Yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (3H, d × d, *J* = 6.7, 1.4 Hz, $C\underline{H}_3CHCH_3$); 1.33 (3H, d, *J* = 6.7 Hz, $CH_3CHC\underline{H}_3$); 4.84 (1H, septet × d, *J* = 6.7, 1.2 Hz, $CH_3C\underline{H}CH_3$); 5.72 (1H, d × d, *J* = 56.8, 1.5 Hz, CHF); 6.38 (1H, d × d, *J* = 5.1, 1.5 Hz, CHBr); 6.69 (1H, s, OCHO); 7.43-7.48, 7.57-7.63 and 8.10-8.13 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -118.95 (d × d, *J* = 56.8, 5.1 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.5 and 20.6 ($(\underline{C}H_3)_2CH$); 45.9 (d, *J* = 2.3 Hz, $(CH_3)_2\underline{C}H$); 75.0 (d, *J* = 33.4 Hz, CHBr); 85.8 (OCHO); 91.5 (d, *J* = 210.0 Hz, CHF); 128.6, 130.4 and 134.0 (HC_{arom}, $C_{arom,quat}$); 161.2 (d, *J* = 3.5 Hz, NC=O); 164.7 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1735; $\nu_{NC=O}$ = 1690; ν_{max} = 2978, 2600, 2494, 1474, 1450, 1396, 1384, 1266, 1226, 1172, 1143, 1105, 1079, 1062, 1036, 973, 945, 807, 708. MS (70eV): m/z (%) 360/2 (M^++1, 100). Anal. Calcd. for $C_{14}H_{15}BrFNO_4$: C 46.69, H 4.20, N 3.89. Found: C 46.89, H 4.66, N 4.45.

2-Benzoyloxy-6-bromo-5-fluoro-4-isopropylmorpholin-3-one 235a *(minor diastereoisomer)*



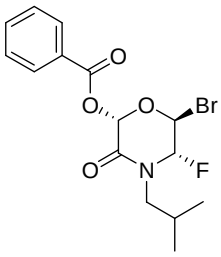
Colourless oil. Filtrate after recrystallization from EtOAc/hexane (30/1). Yield 16%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28-1.35 (6H, m, $(C\underline{H}_3)_2CH$); 4.82 (1H, septet × d, *J* = 6.6, 1.5 Hz, $(CH_3)_2C\underline{H}$); 5.68 (1H, d × d, *J* = 57.4, 1.3 Hz, CHF); 6.44 (1H, d, *J* = 1.1 Hz, OCHO); 6.46 (1H, d × d, *J* = 4.5, 1.3 Hz, CHBr); 7.38-7.48, 7.57-7.63 and 8.08-8.13 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -116.94 (d × d, *J* = 57.4, 4.5 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.3 and 20.5 ($(\underline{C}H_3)_2CH$); 46.0 (d, *J* = 2.3 Hz, $(CH_3)_2\underline{C}H$); 78.0 (d, *J* = 35.7 Hz, CHBr); 87.4 (OCHO); 91.2 (d, *J* = 211.1 Hz, CHF); 128.2 ($C_{arom,quat}$); 128.6, 130.4 and 134.2 (HC_{arom}); 161.8 (d, *J* = 3.5 Hz, NC=O); 164.3 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1736; $\nu_{NC=O}$ = 1691; ν_{max} = 2980, 1451, 1263, 1225, 1144, 1105, 1078, 1058, 1024, 970, 944, 706. MS (70eV): m/z (%) 360/2 (M^++1, 100).

2-Benzoyloxy-6-bromo-5-fluoro-4-isobutylmorpholin-3-one 234b *(major diastereoisomer)*



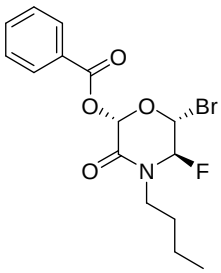
Colourless oil. R_f = 0.14 (hexane/EtOAc 19/1). Yield 33%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (6H, d, *J* = 7.2 Hz, $(C\underline{H}_3)_2CH$); 2.03-2.17 (1H, m, $(CH_3)_2C\underline{H}$); 3.29 and 3.64 (2 × 1H, 2 × (d × d × d), *J* = 13.9, 7.2, 1.2 Hz, (HCH)N); 5.68 (1H, d × d, *J* = 57.7, 1.4 Hz, CHF); 6.34 (1H, d × d, *J* = 5.3, 1.4 Hz, CHBr); 6.70 (1H, s, OCHO); 7.44-7.49, 7.58-7.64 and 8.10-8.13 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -122.75 (d × d, *J* = 57.7, 5.3 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.1 and 20.2 ($(\underline{C}H_3)_2CH$); 27.5 ($(CH_3)_2\underline{C}H$); 53.3 (CH_2N); 74.2 (d, *J* = 33.5 Hz, CHBr); 85.9 (OCHO); 95.7 (d, *J* = 212.3 Hz, CHF); 128.6, 130.5 and 134.0 (HC_{arom}, $C_{arom,quat}$); 161.9 (d, *J* = 3.5 Hz, NC=O); 164.6 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1736; $\nu_{NC=O}$ = 1704; ν_{max} = 2964, 1467, 1374, 1257, 1222, 1152, 1091, 1060, 1017, 965, 908, 728, 708. MS (70eV): m/z (%) 374/6 (M^++1, 100).

2-Benzoyloxy-6-bromo-5-fluoro-4-isobutylmorpholin-3-one 235b *(minor diastereoisomer)*



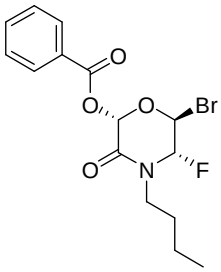
Colourless oil. R_f = 0.14 (hexane/EtOAc 19/1). Yield 12%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 and 1.04 (2 × 3H, 2 × d, *J* = 7.2 Hz, ($C\underline{H}_3$)$_2$CH); 2.08 (1H, nonet, *J* = 7.2 Hz, (CH_3)$_2$C$\underline{H}$); 3.29 and 3.65 (2 × 1H, 2 × (d × d × d), *J* = 13.9, 7.2, 1.5 Hz, (HCH)N); 5.62 (1H, d × d, *J* = 58.0, 1.2 Hz, CHF); 6.43 (1H, d × d, *J* = 5.4, 1.2 Hz, CHBr); 6.47 (1H, d, *J* = 1.2 Hz, OCHO); 7.44-7.49, 7.59-7.64 and 8.08-8.13 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -121.17 (d × d, *J* = 58.0, 5.4 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.07 and 20.13 (($\underline{C}H_3$)$_2$CH); 27.3 ((CH_3)$_2$$\underline{C}$H); 53.1 ($CH_2$N); 77.3 (d, *J* = 32.3 Hz, CHBr); 87.4 (OCHO); 95.5 (d, *J* = 212.3 Hz, CHF); 128.2 ($C_{arom,quat}$); 128.7, 130.5 and 134.2 (HC_{arom}); 162.8 (d, *J* = 3.5 Hz, NC=O); 164.3 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1744; $\nu_{NC=O}$ = 1705; ν_{max} = 2963, 1468, 1377, 1257, 1225, 1155, 1110, 1078, 1060, 1024, 972, 707. MS (70eV): m/z (%) 374/6 (M^++1, 100).

2-Benzoyloxy-6-bromo-4-butyl-5-fluoromorpholin-3-one 234c *(major diastereoisomer)*



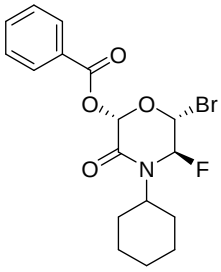
Colourless oil. R_f = 0.12 (hexane/EtOAc 19/1). Yield 42%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.5 Hz, CH_3); 1.44 (2H, sextet, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 1.61-1.81 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.44-3.54 and 3.71-3.81 (2 × 1H, 2 × m, ($C\underline{H}_2$(CH_2)$_2$$CH_3$); 5.67 (1H, d × d, *J* = 57.9, 1.1 Hz, CHF); 6.33 (1H, d × d, *J* = 5.4, 1.1 Hz, CHBr); 6.68 (1H, s, OCHO); 7.44-7.49, 7.58-7.64 and 8.10-8.14 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -122.55 (d × d, *J* = 57.9, 5.4 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.8 (CH_3); 20.0 ($\underline{C}H_2CH_3$); 29.6 ($\underline{C}H_2CH_2CH_3$); 46.3 ($\underline{C}H_2$(CH_2)$_2$$CH_3$); 74.3 (d, *J* = 32.3 Hz, CHBr); 85.8 (OCHO); 95.5 (d, *J* = 212.3 Hz, CHF); 128.6, 130.5 and 134.0 (HC_{arom}, $C_{arom,quat}$); 161.5 (d, *J* = 3.4 Hz, NC=O); 164.6 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1736; $\nu_{NC=O}$ = 1702; ν_{max} = 2959, 1452, 1380, 1247, 1148, 1093, 1059, 1017, 964, 706, 686. MS (70eV): m/z (%) 374/6 (M^++1, 100).

2-Benzoyloxy-6-bromo-4-butyl-5-fluoromorpholin-3-one 235c *(minor diastereoisomer)*



Colourless oil. R_f = 0.12 (hexane/EtOAc 19/1). Yield 13%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.4 Hz, CH_3); 1.42 (2H, sextet, *J* = 7.4 Hz, $C\underline{H}_2CH_3$); 1.64-1.76 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.39-3.53 and 3.72-3.82 (2 × 1H, 2 × m, ($C\underline{H}_2$(CH_2)$_2$$CH_3$); 5.61 (1H, d × d, *J* = 58.2, 1.1 Hz, CHF); 6.42 (1H, d × d, *J* = 5.7, 1.1 Hz, CHBr); 6.44 (1H, d, *J* = 1.1 Hz, OCHO); 7.43-7.48, 7.58-7.64 and 8.08-8.13 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -120.66 (d × d, *J* = 58.2, 5.7 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.8 (CH_3); 19.9 ($\underline{C}H_2CH_3$); 29.5 ($\underline{C}H_2CH_2CH_3$); 46.1 ($\underline{C}H_2$(CH_2)$_2$$CH_3$); 77.4 (d, *J* = 34.6 Hz, CHBr); 87.3 (OCHO); 95.4 (d, *J* = 213.5 Hz, CHF); 128.2 ($C_{arom,quat}$); 128.7, 130.5 and 134.2 (HC_{arom}); 162.4 (d, *J* = 3.4 Hz, NC=O); 164.3 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1743; $\nu_{NC=O}$ = 1702; ν_{max} = 2960, 1453, 1378, 1248, 1225, 1110, 1059, 1024, 953, 908, 730, 705. MS (70eV): m/z (%) 374/6 (M^++1, 100).

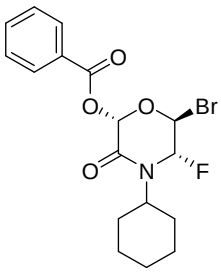
2-Benzoyloxy-6-bromo-4-cyclohexyl-5-fluoromorpholin-3-one 234d *(major diastereoisomer)*



White crystals. Mp 101.5 °C. Recrystallization from EtOAc/hexane (30/1). Yield 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08-1.25, 1.34-1.54, 1.69-1.75 and 1.86-1.99 (1H, 4H, 1H and 4H, 4 × m, $(C\underline{H}_2)_5CHN$); 4.41-4.50 (1H, m, $(CH_2)_5C\underline{H}N$); 5.73 (1H, d × d, *J* = 57.3, 1.3 Hz, CHF); 6.36 (1H, d × d, *J* = 4.7, 1.3 Hz, CHBr); 6.69 (1H, s, OCHO); 7.43-7.48, 7.58-7.63 and 8.10-8.13 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -117.86 (d × d, *J* = 57.3, 4.7 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.4, 25.5, 25.8, 30.0 and 31.0 ($(\underline{C}H_2)_5CHN$); 53.4 ($(CH_2)_5\underline{C}HN$); 75.0 (d, *J* = 33.4 Hz, CHBr); 85.9 (OCHO); 91.8 (d, *J* = 211.2 Hz, CHF); 128.6, 130.4, 134.0 (HC_{arom}, $C_{arom,quat}$); 161.2 (d, *J* = 3.4 Hz, NC=O); 164.7 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1736; $\nu_{NC=O}$ = 1681; ν_{max} = 2936, 1452, 1247, 1090, 987, 708. MS (70 eV): m/z (%) 400/2 (M^++1, 100). Anal. Calcd. for $C_{17}H_{19}BrFNO_4$: C 51.01, H 4.78, N 3.50. Found: C 51.13, H 4.78, N 3.45.

2-Benzoyloxy-6-bromo-4-cyclohexyl-5-fluoromorpholin-3-one 235d *(minor diastereoisomer)*

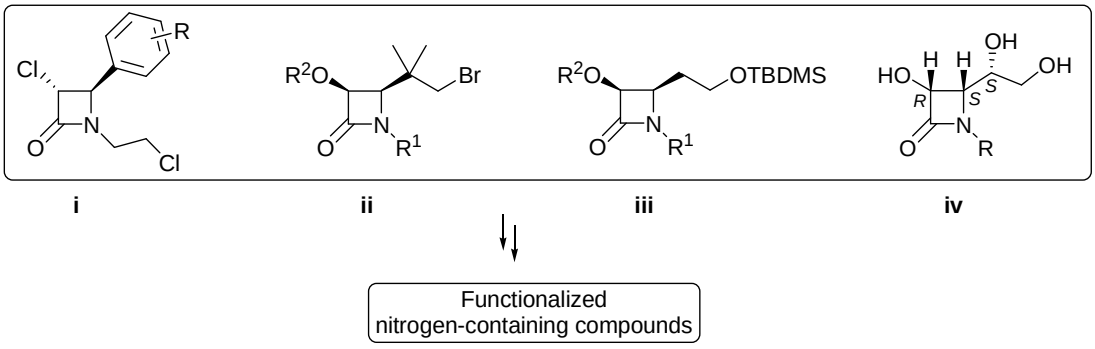
Spectral data based on ^{1}H NMR and ^{13}C NMR of the crude reaction mixture.



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08-1.23, 1.34-1.54, 1.70-1.74 and 1.86-1.99 (1H, 4H, 1H and 4H, 4 × m, $(C\underline{H}_2)_5CHN$); 4.37-4.51 (1H, m, $(CH_2)_5C\underline{H}N$); 5.69 (1H, d × d, *J* = 56.7, 1.1 Hz, CHF); 6.43 (1H, d, *J* = 1.1 Hz, OCHO); 6.45 (1H, d × d, *J* = 4.9, 1.1 Hz, CHBr); 7.43-7.49, 7.58-7.64 and 8.08-8.14 (2H, 1H and 2H, 3 × m, CH_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -115.96 (d × d, *J* = 56.7, 4.9 Hz, CHF). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.4, 25.5, 25.8, 29.8 and 31.1 ($(\underline{C}H_2)_5CHN$); 53.5 ($(CH_2)_5\underline{C}HN$); 77.9 (d, *J* = 35.8 Hz, CHBr); 87.4 (OCHO); 91.5 (d, *J* = 212.3 Hz, CHF); 128.3 ($C_{arom,quat}$); 128.6, 130.4, 134.2 (HC_{arom}); 161.8 (d, *J* = 3.5 Hz, NC=O); 164.4 (OC=O). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1736; $\nu_{NC=O}$ = 1681; ν_{max} = 2936, 1452, 1247, 1090, 987, 708. MS (70 eV): m/z (%) 400/2 (M^++1, 100).

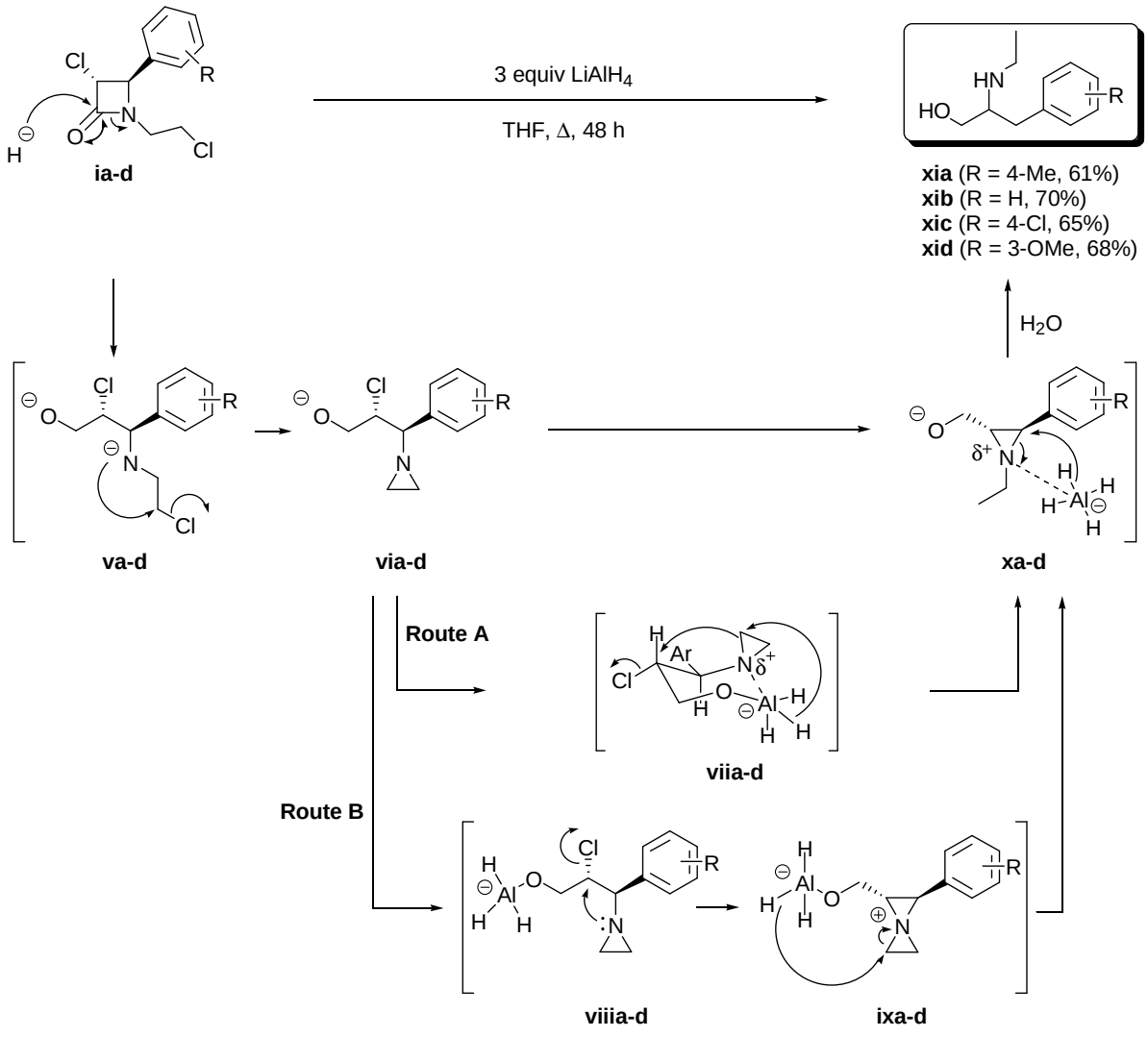
6 Summary

β-Lactams comprise a very interesting class of compounds both from a biological and a chemical point of view. Besides their well-known significance as antibacterial agents in the treatment of bacterial infections and microbial diseases, a renewed interest has been focused on the synthesis and selective functionalization of β-lactams possessing diverse pharmacological properties such as cholesterol absorption inhibitory activity, antidiabetic, anti-HIV, antiviral, antiparkinsonian, and anti-inflammatory activity. In addition to their indisputable importance as bioactive agents, β-lactams have also been widely recognized as excellent and versatile building blocks in organic chemistry for further elaboration toward a variety of nitrogen-containing acyclic and heterocyclic target compounds by exploiting the strain energy associated with the four-membered ring system. Indeed, selective bond cleavage of the β-lactam nucleus followed by further intruiging synthetic transformations renders these compounds powerful synthetic building blocks (this had led to the introduction of the term "β-lactam synthon method"). In that respect, the synthesis and synthetic applicability of four classes of β-lactams, i.e., 3-chloro-1-(2-chloroethyl)azetidin-2-ones **i**, 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **ii**, 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **iii** and 3-hydroxy-4-(1,2-dihydroxyethyl)azetidin-2-ones **iv**, were accomplished in this PhD thesis, resulting in the selective synthesis of a variety of valuable new structures with diverse potential applications.

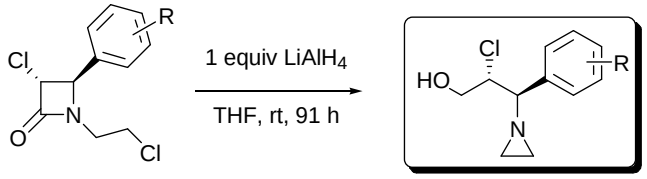


In a first approach, *trans*-4-aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones **i**, prepared *via* Staudinger reaction between *N*-(arylmethylidene)-(2-chloroethyl)amines and chloroacetyl chloride, were selectively transformed into novel 3-aryl-2-(ethylamino)propan-1-ols **xi** in 61-70% yield upon treatment with three molar equiv of $LiAlH_4$ in THF under reflux for 48 hours. β-Aminoalcohols are applied extensively in organic chemistry as building blocks in designing natural and biologically active substances, and their chiral versions are also used in asymmetric synthesis. In order to elucidate the mechanistic background of this intriguing transformation, different experiments were conducted involving variation of the reaction time, reaction temperature, solvent and number of molar equiv of $LiAlH_4$, thus revealing the intermediacy of γ-aminoalcohols **v**, 1-(1-aryl-2-chloro-3-

hydroxypropyl)aziridines **vi** and *trans*-2-aryl-1-ethyl-3-(hydroxymethyl)aziridines **x**. From a mechanistic point of view, these results were rationalized considering an initial hydride-induced 1,2-fission of the amide bond in the starting β-lactams **i**, followed by intramolecular displacement of the chloride at the primary carbon atom by the nucleophilic nitrogen, furnishing 1-(2-chloro-3-hydroxypropyl)aziridines **vi**, which subsequently underwent a hydride-mediated rearrangement toward 1-ethyl-3-(hydroxymethyl)aziridines **x**. The latter peculiar transformation was explained considering the intramolacular activation of the aziridine moiety in chair-like intermediates **vii** by the Lewis acid character of aluminium, resulting in aziridine ring opening and consecutive nucleophilic attack at the chlorinated carbon atom. Alternatively, initial intramolecular displacement of chloride by the nucleophilic nitrogen lone pair in aziridines **viii** toward reactive *N*-spiro bis-aziridinium intermediates **ix**, followed by hydride-induced ring opening could not be excluded. Finally, regioselective transfer of hydride to the C-2 carbon atom of aziridines **x** resulted in the formation of 3-aryl-2-(ethylamino)propan-1-ols **xi**.



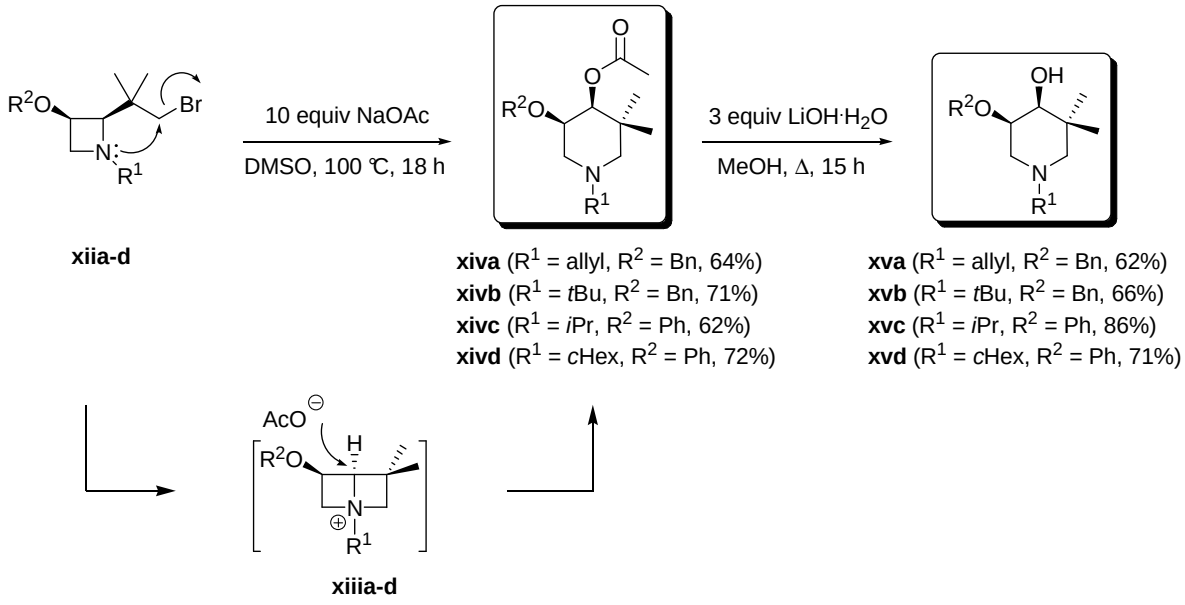
In addition, reductive ring contraction of 3-chloro-1-(2-chloroethyl)azetidin-2-ones **ia,b** toward 1-(2-chloro-3-hydroxypropyl)aziridines **via,b** was achieved utilizing one molar equiv of $LiAlH_4$ at room temperature.



ia,b

via (R = 4-Me, 40%)
vib (R = H, 50%)

The piperidine ring comprises an important structural unit in natural products and biologically active agents, and a broad variety of drugs accommodating this skeleton in their structure are on the market. Furthermore, azetidines are frequently deployed as versatile synthetic intermediates for the preparation of a variety of (a)cyclic amines *via* regio- and stereoselective transformations. In that respect, as an extension of the previously reported ring expansion toward 4-bromo-, 4-cyano-, 4-azido-, and 4-fluoro-5,5-dimethylpiperidines, 2-(2-bromo-1,1-dimethylethyl)azetidines **xii**, prepared *via* monochloroalane reduction of the corresponding β-lactams, were used as building blocks for the stereoselective synthesis of novel 4-acetoxy-5,5-dimethylpiperidines **xiv** *via* transient 1-azoniabicyclo[2.2.0]hexanes **xiii**. Eventually, 4-acetoxypiperidines **xiv** were hydrolyzed toward the corresponding 4-hydroxypiperidines **xv**, which are valuable target compounds as a vast array of molecules containing the 4-hydroxypiperidine skeleton has been used in the treatment of *inter alia* arrhythmia, hypotension, tuberculosis, diarrhea, rheumatoid arthritis, multiple sclerosis and Crohn's disease.



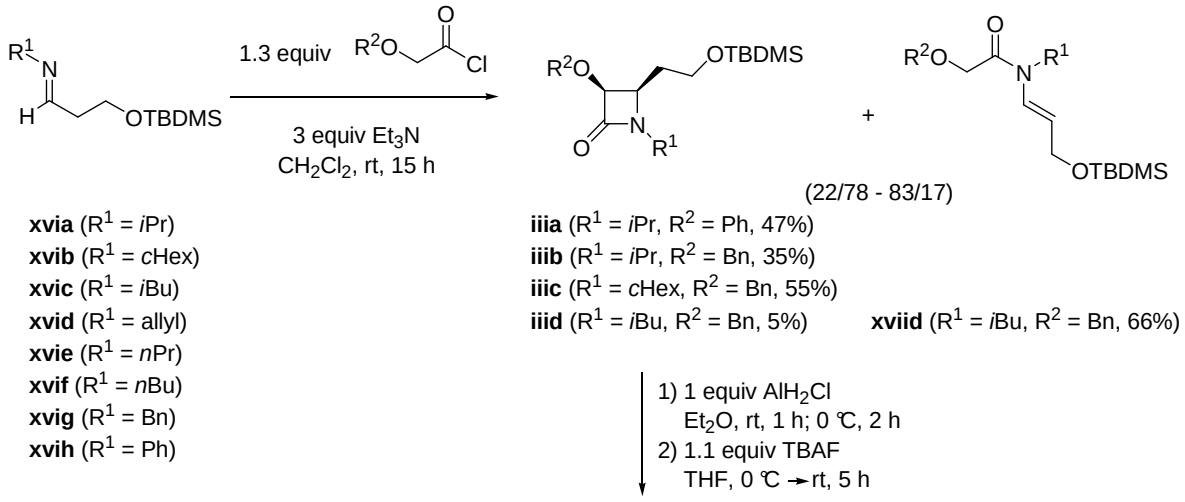
xiia-d

xiva (R^1 = allyl, R^2 = Bn, 64%)
xivb (R^1 = *t*Bu, R^2 = Bn, 71%)
xivc (R^1 = *i*Pr, R^2 = Ph, 62%)
xivd (R^1 = *c*Hex, R^2 = Ph, 72%)

xva (R^1 = allyl, R^2 = Bn, 62%)
xvb (R^1 = *t*Bu, R^2 = Bn, 66%)
xvc (R^1 = *i*Pr, R^2 = Ph, 86%)
xvd (R^1 = *c*Hex, R^2 = Ph, 71%)

xiiia-d

In a third part of this work, the synthesis of the dinor-dimethyl analogues of the aforementioned 5,5-dimethylpiperidines was investigated, as, given the broad medicinal relevance of piperidines in general, the absence of a 5,5-*gem*-dimethyl group might modify the related bioactivity due to changes in conformational and stereochemical properties. In order to achieve this goal, special attention was devoted to the diastereoselective Staudinger synthesis of 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-ones **iii** from (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]amines **xvi**, inevitable leading to the formation of mixtures of β-lactams **iii** and *N*-acyl enamines **xvii** (22/78 – 83/17). Because of the combination of a strained four-membered ring system, a nucleophilic nitrogen lone pair (after elaboration) and an electrophilic center in the side chain, β-lactams **iii**, which were isolated in pure form by column chromatography on silica gel, proved to be eligible substrates for further elaboration toward a variety of azaheterocyclic compounds as they were converted in 2-(2-mesyloxyethyl)azetidines **xix** upon consecutive monochloroalane reduction, TBAF-mediated deprotection, and mesylation. In this way, mesylated azetidines **xix** were prepared in high yields and purity as the dinor-dimethyl variants of brominated azetidines **xii**.



xvia (R^1 = *i*Pr)
xvib (R^1 = *c*Hex)
xvic (R^1 = *i*Bu)
xvid (R^1 = allyl)
xvie (R^1 = *n*Pr)
xvif (R^1 = *n*Bu)
xvig (R^1 = Bn)
xvih (R^1 = Ph)

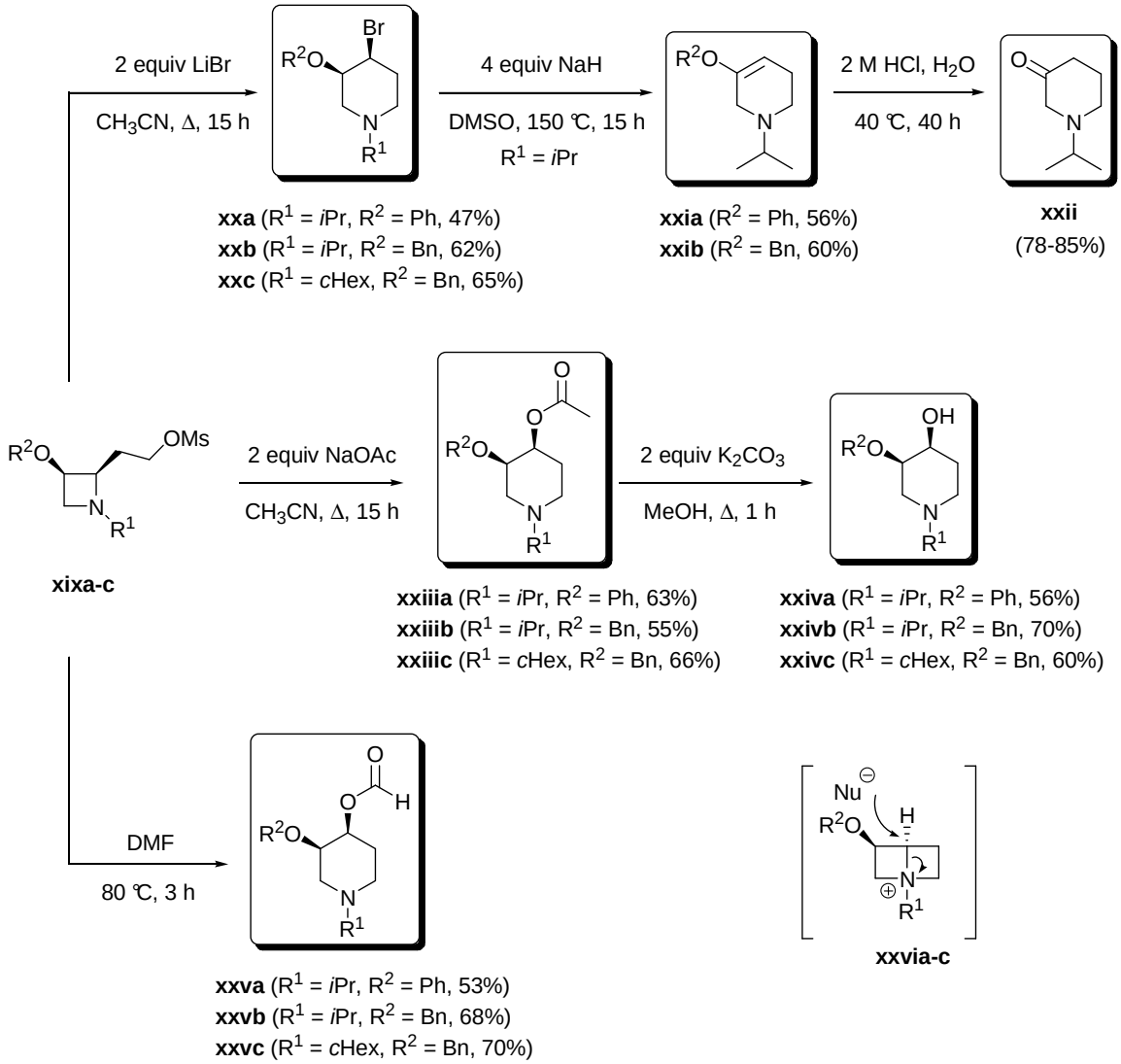
iiia (R^1 = *i*Pr, R^2 = Ph, 47%)
iiib (R^1 = *i*Pr, R^2 = Bn, 35%)
iiic (R^1 = *c*Hex, R^2 = Bn, 55%)
iiid (R^1 = *i*Bu, R^2 = Bn, 5%)
xviid (R^1 = *i*Bu, R^2 = Bn, 66%)

xixa (R^1 = *i*Pr, R^2 = Ph, 90%)
xixb (R^1 = *i*Pr, R^2 = Bn, 88%)
xixc (R^1 = *c*Hex, R^2 = Bn, 85%)

xviiia (R^1 = *i*Pr, R^2 = Ph, 48%)
xviiib (R^1 = *i*Pr, R^2 = Bn, 49%)
xviiic (R^1 = *c*Hex, R^2 = Bn, 50%)

In the next phase, the reactivity of 2-(2-mesyloxyethyl)azetidines **xix** toward different nucleophiles was evaluated for the first time, resulting in the stereoselective ring enlargement toward a variety of 4-acetoxy- **xxiii**, 4-hydroxy- **xxiv**, 4-bromo- **xx** and 4-(formyloxy)piperidines **xxv** through regioselective S_N2 ring opening of intermediate 1-azoniabicyclo[2.2.0]hexanes **xxvi**. It has to be

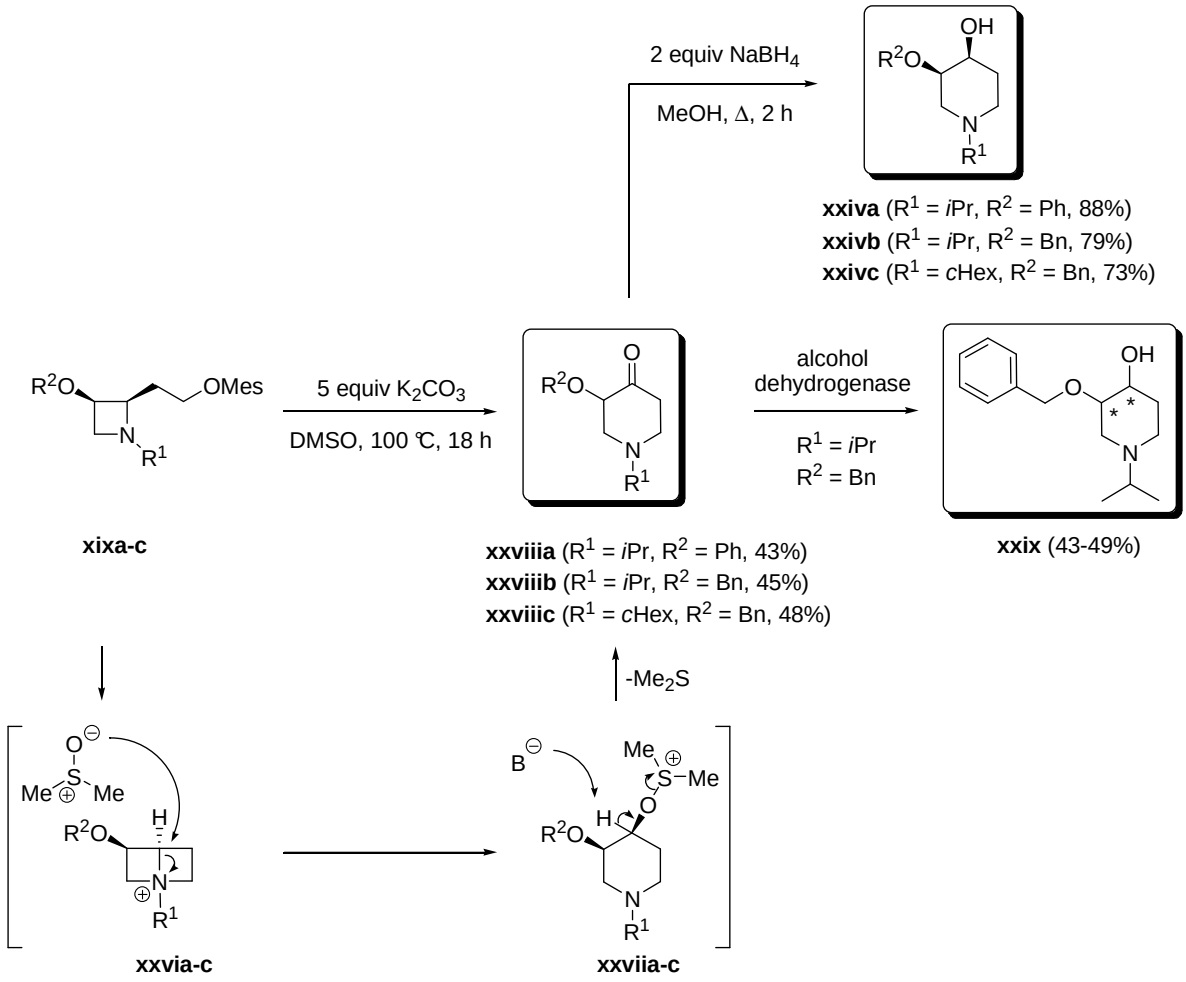
mentioned that in all cases small amounts of 2-vinylazetidines (2-9%) were observed in the crude reaction mixtures as well. This approach constitutes a convenient alternative for the above-mentioned preparation of 3,4-disubstituted 5,5-dimethylpiperidines, providing an easy access to the 5,5-dinor-dimethyl analogues as valuable templates in medicinal chemistry. Furthermore, a new entry into the piperidin-3-one scaffold is provided through dehydrobromination of 4-bromo-3-(phenoxy- or benzyloxy)piperidines **xx** followed by acid hydrolysis. In addition to the experimental results, the intermediacy of transient 1-azoniabicyclo[2.2.0]hexanes **xxvi** in these four- to six-membered ring expansion reactions was further verified by means of high-level computational analysis (performed at the Centre for Molecular Modeling, UGent).



Attempts toward the selective synthesis of 4-fluoro-5,5-dinor-dimethylpiperidines failed under the applied reaction conditions and clearly needs further elaboration.

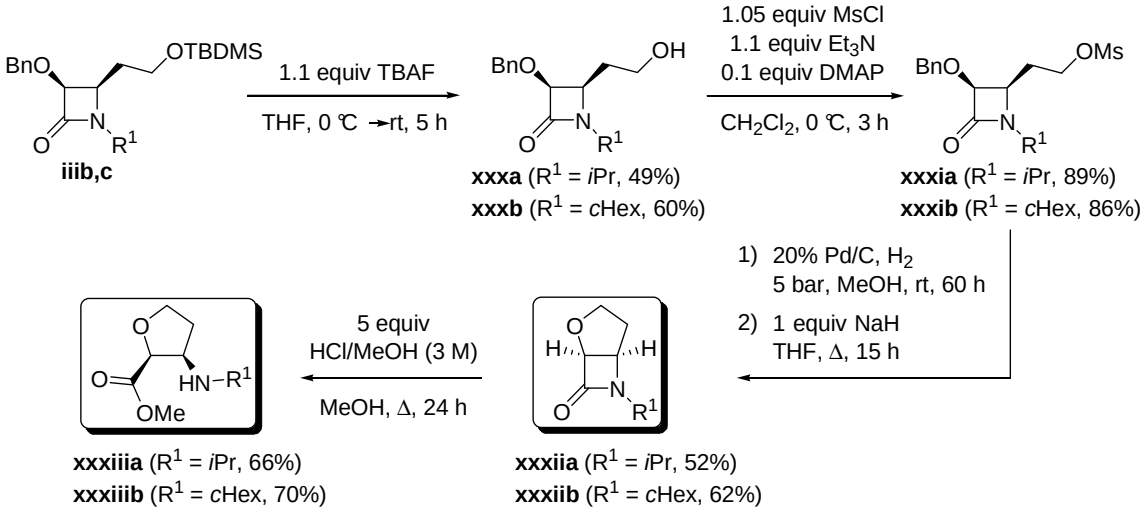
In a fourth part of this work, the intrinsic reactivity of 2-(2-mesyloxyethyl)azetidines **xix** upon heating in DMSO in the presence of K_2CO_3 was envisaged, resulting in the selective formation of piperidin-4-

ones **xxviii** *via* DMSO-mediated regioselective ring opening of bicyclic azetidinium intermediates **xxvi**. From a biological point of view, piperidin-4-ones represent an important class of azaheterocycles exhibiting antiviral, antitumor, analgesic, local anaesthetic, antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, CNS stimulant and depressant activities. In addition, the synthetic applicability of the latter 5,5-dinor-dimethylpiperidin-4-ones **xxviii** was demonstrated by means of both a chemical and an enzymatic reduction. Whereas the $NaBH_4$-induced reduction is characterized by a *cis*-diastereoselectivity, the alcohol dehydrogenase-mediated reductions proceeded with *S*- or *R*-enantioselectivity at the carbonyl functionality.

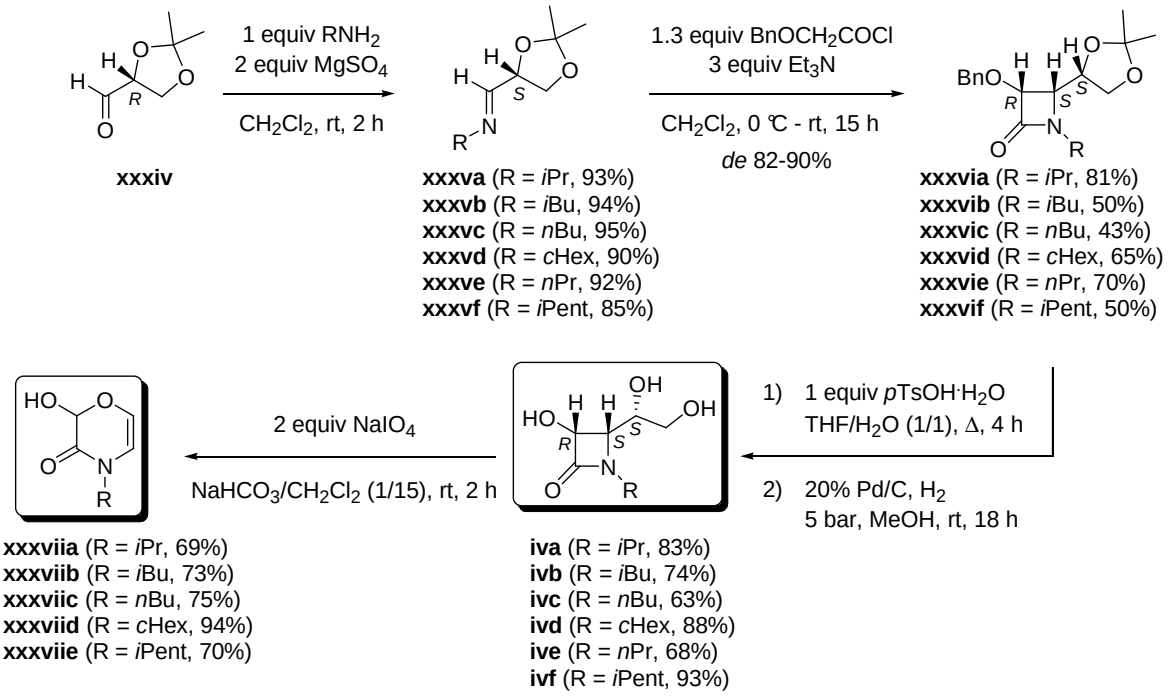


Next, the synthesis of novel unconventional 3,4-fused (*C*-fused) bicyclic β-lactams as potential antimicrobial agents and/or β-lactamase inhibitors was studied. 3-Benzyloxy-4-(2-mesyloxyethyl)-β-lactams **iii** were transformed into novel *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones **xxxii** in 52-62% overall yield through hydrogenolysis and subsequent intramolecular nucleophilic substitution by means of sodium hydride addition. Conversion of the latter bicyclic β-lactams **xxxii** into *cis*-3-aminotetrahydrofuran-2-carboxylates **xxxiii** was accomplished in 66-70% yield by means of acidic methanolysis. β-Amino acids comprise a valuable class of compounds because of their broad

biological and synthetic applicability. In particular, cyclic β-amino acids are present in a variety of natural products, and β-peptides form much more stable secondary structures than their α-peptidic natural counterparts. This approach comprises a valuable alternative for the known preparation of 4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-ones and 3-amino-4,4-dimethyletrahydrofuran-2-carboxylates, thus furnishing their dinor-dimethyl analogues.



In a final part of this PhD thesis, the reactivity of 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactams **iv**, prepared through consecutive acidic hydrolysis of the acetal functionality and hydrogenolysis of the benzylether substituent in β-lactams **xxxvi**, with regard to the oxidant sodium periodate was evaluated for the first time, unexpectedly resulting in the exclusive formation of novel 2-hydroxy-1,4-oxazin-3-ones **xxxvii**, most probably *via* a C3-C4 bond cleavage of the intermediate 4-formyl-3-hydroxy-β-lactams followed by ring enlargement. This transformation is indeed peculiar, as 3-alkoxy- and 3-phenoxy-4-(1,2-dihydroxyethyl)-β-lactams are known to be oxidized to the corresponding 4-formyl-β-lactam derivatives under the same reaction conditions without subsequent rearrangement into six-membered heterocycles. In addition to the experimental results, the rationale of this novel ring-expansion reaction was further validated by means of theoretical calculations performed at the Centre for Molecular Modeling (UGent).



xxxiv

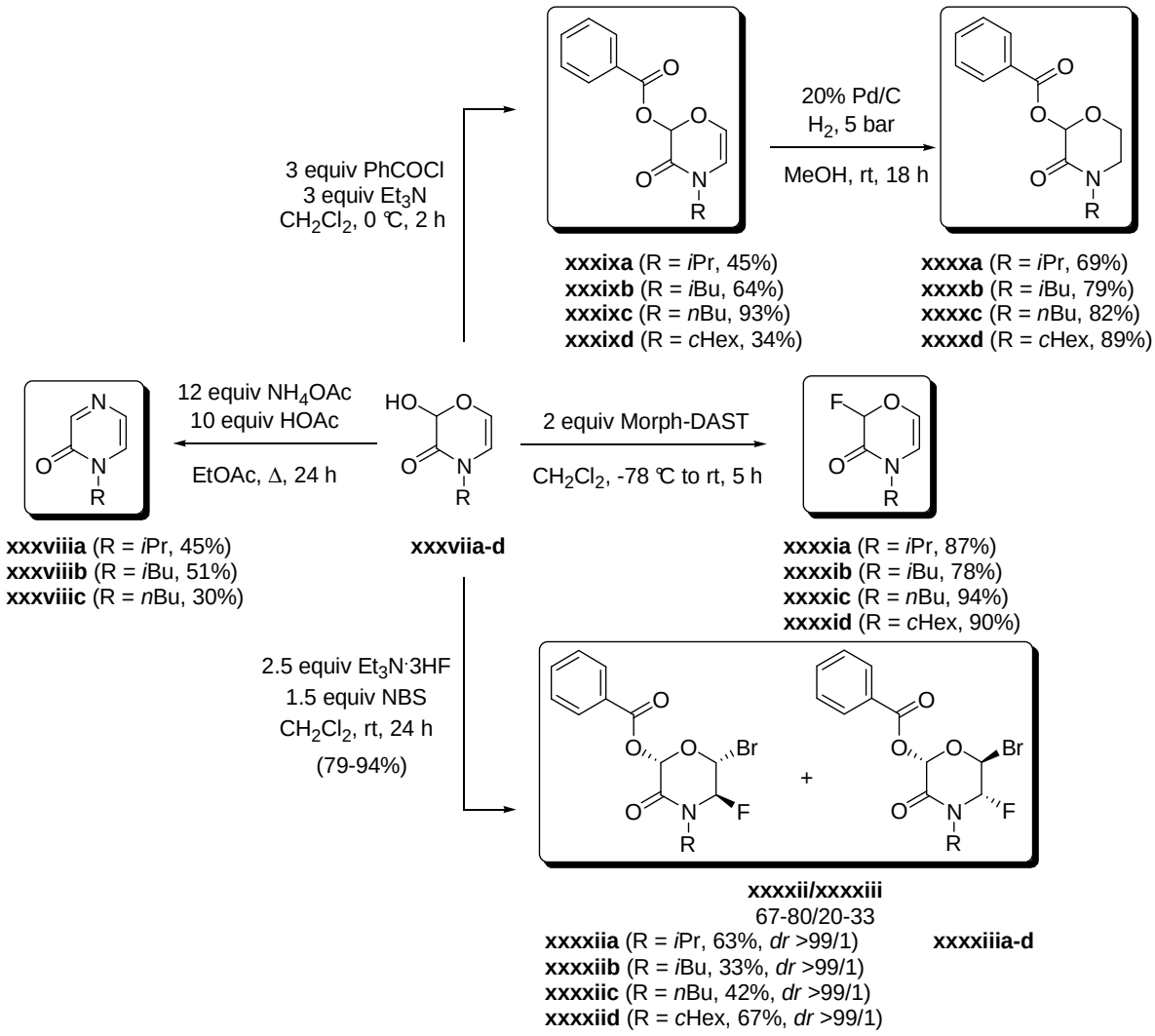
xxxva (R = *i*Pr, 93%)
xxxvb (R = *i*Bu, 94%)
xxxvc (R = *n*Bu, 95%)
xxxvd (R = *c*Hex, 90%)
xxxve (R = *n*Pr, 92%)
xxxvf (R = *i*Pent, 85%)

xxxvia (R = *i*Pr, 81%)
xxxvib (R = *i*Bu, 50%)
xxxvic (R = *n*Bu, 43%)
xxxvid (R = *c*Hex, 65%)
xxxvie (R = *n*Pr, 70%)
xxxvif (R = *i*Pent, 50%)

xxxviia (R = *i*Pr, 69%)
xxxviib (R = *i*Bu, 73%)
xxxviic (R = *n*Bu, 75%)
xxxviid (R = *c*Hex, 94%)
xxxviie (R = *i*Pent, 70%)

iva (R = *i*Pr, 83%)
ivb (R = *i*Bu, 74%)
ivc (R = *n*Bu, 63%)
ivd (R = *c*Hex, 88%)
ive (R = *n*Pr, 68%)
ivf (R = *i*Pent, 93%)

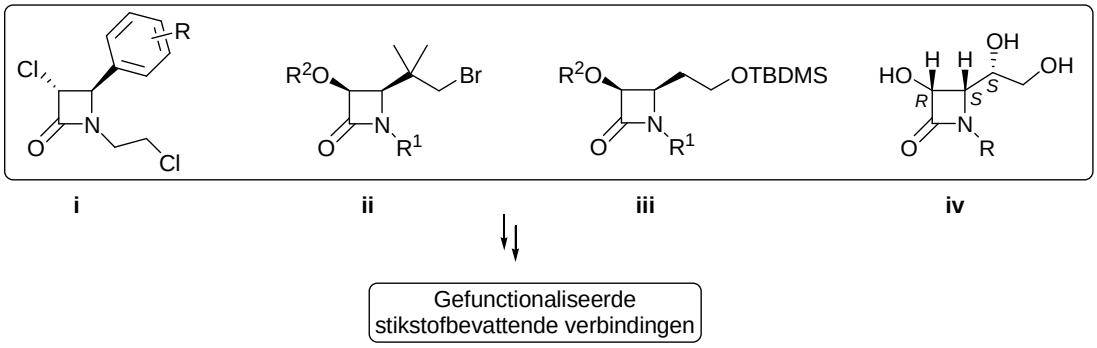
In order to show the capacity of this new ring-expanion reaction to prepare a broad array of six-membered heterocycles bearing chemical diversity, 2-hydroxy-1,4-oxazin-3-ones **xxxvii** were used as building blocks for the selective synthesis of novel heterocyclic compounds. 2-Hydroxy-1,4-oxazin-3-ones **xxxvii** were converted into novel 2-benzoyloxy-1,4-oxazin-3-ones **xxxix** *via* protection of the hydroxyl moiety upon treatment with benzoylchloride. The latter heterocycles **xxxix** were then used as eligible substrates for the synthesis of 2-benzoyloxymorpholin-3-ones **xxxx** in 69-89% yield. Morpholin-3-ones comprise a very interesting class of compounds as they are for example used as cornea permeable calpain inhibitors exhibiting anticataract properties, potassium channel openers useful in the treatment of urinary incontinence, and non-peptide ligands with high affinity and selectivity for tachykinin receptors. Furthermore, with the intention to incorporate fluorine in a site-selective manner, 2-hydroxy-1,4-oxazin-3-ones **xxxvii** were employed as substrates for the construction of 2-fluoro-1,4-oxazin-3-ones **xxxxi** and 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **xxxxii** and **xxxxiii** upon treatment with Morph-DAST and triethylamine trihydrofluoride, respectively. Finally, 2-hydroxy-1,4-oxazin-3-ones **xxxvii** smoothly rearranged into 1*H*-pyrazin-2-ones **xxxviii** in 30-51% yield using NH_4OAc and HOAc in ethyl acetate.



In this PhD thesis, the high synthetic potential of diversely functionalized azetidin-2-ones as synthons in organic chemistry has been illustrated by means of their elaboration toward a vast number of novel acyclic and cyclic nitrogen-containing compounds, including β-aminoalcohols, aziridines, azetidines, piperidines, piperidin-4-ones, oxazin-3-ones, morpholin-3-ones, pyrazinones, cyclic β-amino acids and bicyclic β-lactams. It is clear that, although the β-lactam nucleus has been extensively studied in the past, the impressive variety of transformations which can be derived from this system renders β-lactam chemistry a very intriguing and promising area of research for the synthesis of different types of novel (azaheterocyclic) compounds.

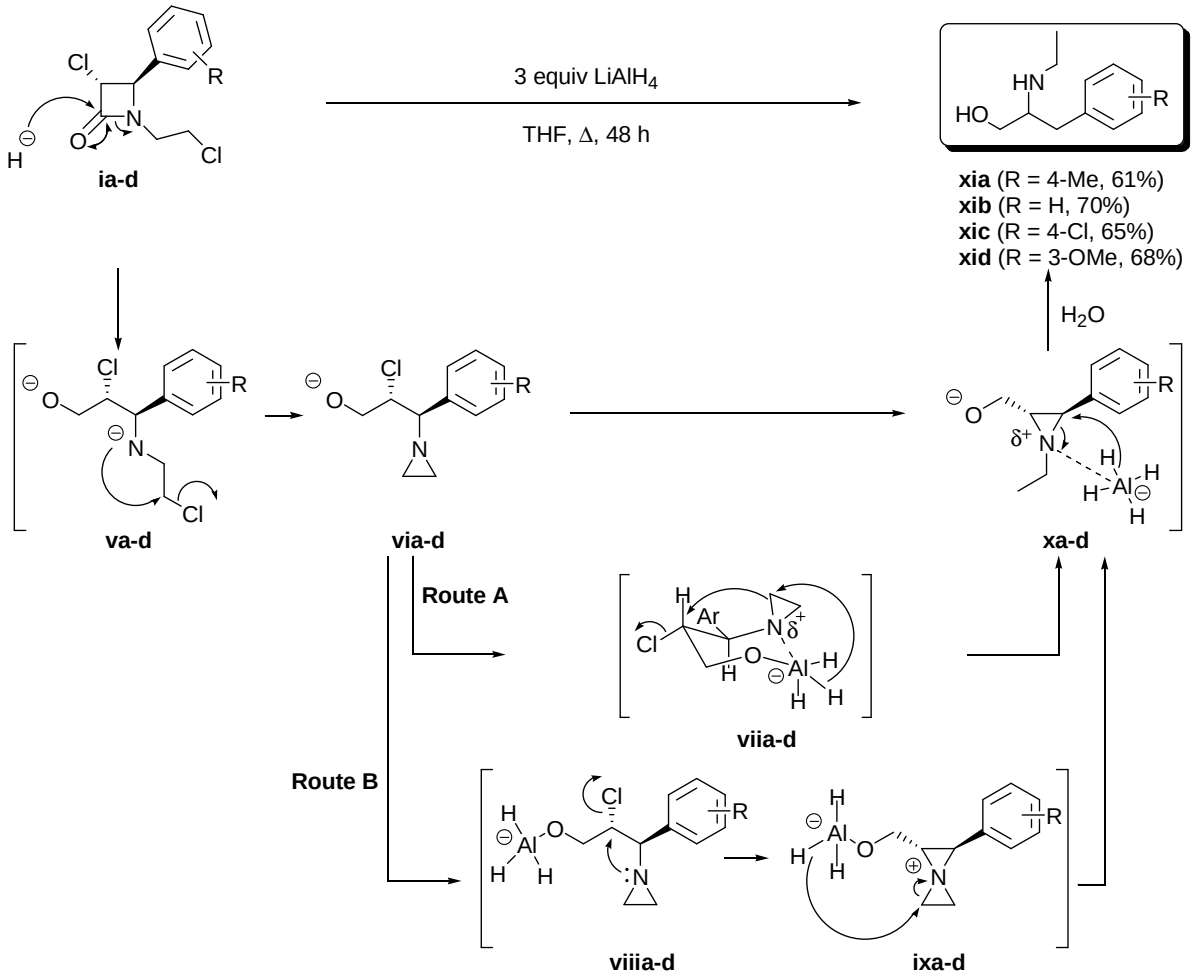
7 Samenvatting

β-Lactamen vormen een zeer interessante klasse van verbindingen, zowel vanuit een biologisch als vanuit een chemisch standpunt. Zo vormen β-lactamen gegeerde targets in de geneeskunde wegens hun uitgesproken antibiotische eigenschappen en het klassieke probleem van resistentievorming. Bovendien vertonen verschillende β-lactamen andere belangrijke biologische eigenschappen; ze worden bijvoorbeeld gebruikt als cholesterolabsorptie-inhibitoren en ontstekingsremmers en bij de behandeling van onder meer diabetes, HIV, en parkinson. Naast hun waarde als biologisch actieve verbindingen worden β-lactamen algemeen beschouwd als uitstekende bouwstenen in de organische chemie voor verdere omzetting tot een brede waaier aan stikstofhoudende acyclische en heterocyclische verbindingen door gebruik te maken van de spanningsenergie geassocieerd met de vierringstructuur. Selectieve splitsing van één der bindingen van de β-lactamkern gevolgd door verdere interessante synthetische omzettingen maakt deze verbindingen krachtige synthetische bouwstenen (dit heeft geleid tot de introductie van de term "β-lactam synthon method"). Vanuit dit standpunt werden in dit doctoraatsonderzoek de synthese en transformatie van vier klassen van β-lactamen, namelijk 3-chloor-1-(2-chloorethyl)azetidin-2-onen **i**, 4-(2-broom-1,1-dimethylethyl)azetidin-2-onen **ii**, 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-onen **iii** en 3-hydroxy-4-(1,2-dihydroxyethyl)azetidin-2-onen **iv**, voltooid, resulterend in de selectieve synthese van verscheidene waardevolle nieuwe verbindingen met diverse potentiële toepassingen.

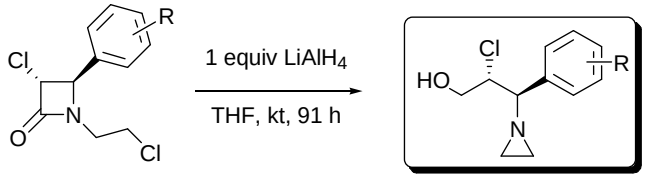


In een eerste luik werden *trans*-4-aryl-3-chloor-1-(2-chloorethyl)-β-lactamen **i**, bereid *via* Staudingerreactie tussen *N*-(arylmethylideen)-(2-chloorethyl)aminen en chlooracetylchloride, selectief omgezet tot nieuwe 3-aryl-2-(ethylamino)propan-1-olen **xi** in 61-70% rendement door behandeling met drie molaire equiv $LiAlH_4$ in THF onder reflux voor 48 uur. β-Aminoalcoholen worden veelvuldig ingezet in de organische chemie als synthons in de bereiding van natuurproducten en biologisch actieve stoffen, en chirale β-aminoalcoholen worden ook gebruikt in katalytische asymmetrische synthese. Om de mechanistische achtergrond van deze intrigerende transformatie op te helderen werden verschillende experimenten uitgevoerd door variatie van de reactietijd,

reactietemperatuur, solvent en aantal molaire equiv $LiAlH_4$, aldus wijzend op de tussenkomst van intermediaire γ-aminoalcoholen **v**, 1-(1-aryl-2-chloor-3-hydroxypropyl)aziridinen **vi** en *trans*-2-aryl-1-ethyl-3-(hydroxymethyl)aziridinen **x** in het reactiemechanisme. Vanuit mechanistisch oogpunt werd een initiële hydride-geïnduceerde splitsing van de amidebinding in β-lactamen **i** gevolgd door intramoleculaire substitutie van chloride door aanval van het nucleofiele stikstofatoom op het primair gechloreerd koolstofatoom, hetgeen aanleiding gaf tot de selectieve vorming van 1-(2-chloor-3-hydroxypropyl)aziridinen **vi**, dewelke vervolgens via een hydride-geïnduceerde omlegging werden omgezet in 1-ethyl-3-(hydroxymethyl)aziridinen **x**. Deze opmerkelijke transformatie werd verklaard aan de hand van intramoleculaire activatie van de aziridinering door het Lewiszuur karakter van aluminium ter vorming van stoelvormintermediairen **vii**, uiteindelijk resulterend in aziridine ringopening en daaropvolgende nucleofiele aanval op het secundair gechloreerd koolstofatoom. Als alternatieve route kan een initiële intramoleculaire substitutie van chloride door het vrij elektronenpaar van stikstof in aziridinen **viii** aanleiding geven tot de vorming van reactieve *N*-spiro-bis-aziridiniumintermediaten **ix**, dewelke vervolgens een hydride-geïnduceerde ringopening ondergaan. Uiteindelijk werden 3-aryl-2-(ethylamino)propan-1-olen **xi** bekomen via regioselectieve hydride-transfer.



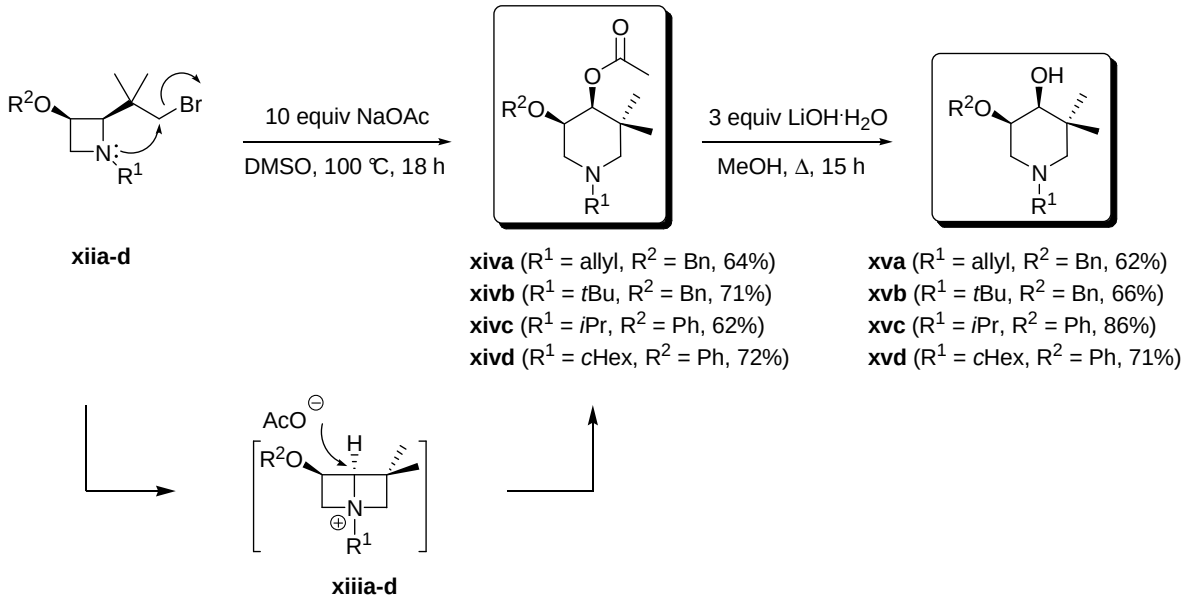
Daarnaast werden 1-(2-chloor-3-hydroxypropyl)aziridines **via,b** selectief gevormd in 40-50% rendement na behandeling van 3-chloor-1-(2-chloorethyl)azetidin-2-ones **ia,b** met één equiv $LiAlH_4$ bij kamertemperatuur.



ia,b

via (R = 4-Me, 40%)
vib (R = H, 50%)

De piperidinering vormt een belangrijke structurele eenheid in natuurproducten en biologisch actieve agentia, en een grote variëteit aan geneesmiddelen bevatten deze bouwsteen in hun structuur. Daarnaast worden azetidinen vaak aangewend als veelvuldige precursoren in de synthese van (a)cyclische aminen, via regio- en stereoselectieve transformaties. In dat opzicht werden, als uitbreiding op de eerder bestudeerde ringexpansie tot 4-broom-, 4-cyaan-, 4-azide- en 4-fluor-5,5-dimethylpiperidinen, 2-(2-broom-1,1-dimethylethyl)azetidinen **xii**, bereid uit de overeenkomstige β-lactamen via monochlooralaanreductie, ingezet als synthetische bouwstenen voor de stereoselectieve synthese van nieuwe biologisch relevante 4-acetoxy-5,5-dimethylpiperidinen **xiv** via transiente 1-azoniabicyclo[2.2.0]hexanen **xiii**. Uiteindelijk werden 4-acetoxypiperidinen **xiv** gehydrolyseerd tot de overeenkomstige 4-hydroxypiperidinen **xv**, dewelke als waardevolle structurele eenheden worden gebruikt in de behandeling van onder meer hartritmestoornissen, hypotensie, tuberculose, diarree, reumatoïde artritis, multiple sclerose, en de ziekte van Crohn.



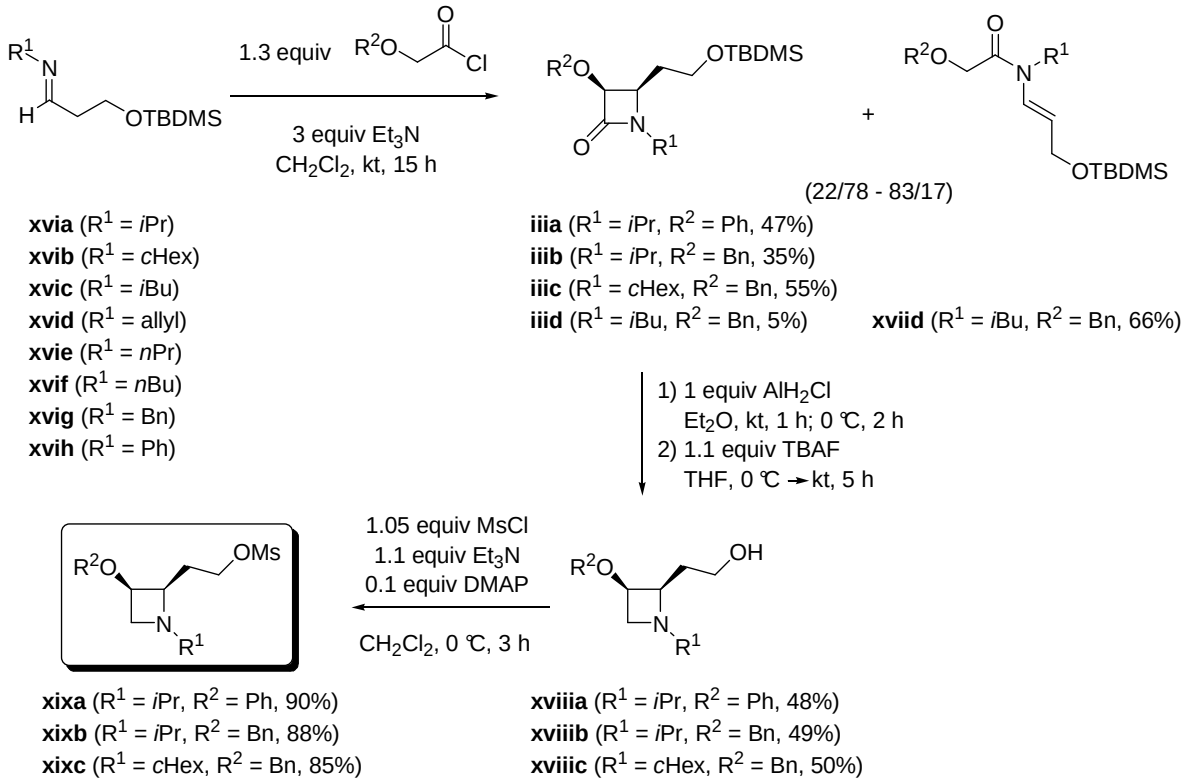
xiia-d

xiva (R^1 = allyl, R^2 = Bn, 64%)
xivb (R^1 = *t*Bu, R^2 = Bn, 71%)
xivc (R^1 = *i*Pr, R^2 = Ph, 62%)
xivd (R^1 = *c*Hex, R^2 = Ph, 72%)

xva (R^1 = allyl, R^2 = Bn, 62%)
xvb (R^1 = *t*Bu, R^2 = Bn, 66%)
xvc (R^1 = *i*Pr, R^2 = Ph, 86%)
xvd (R^1 = *c*Hex, R^2 = Ph, 71%)

xiiia-d

In een derde luik van dit werk werd bijzondere aandacht besteed aan de stereoselectieve bereiding van de overeenkomstige dinor-dimethylanaloga van bovenvermelde 5,5-dimethylpiperidinen, daar, gezien de belangrijke biologische eigenschappen van de piperidinering, de afwezigheid van een 5,5-dimethylgroep een grote invloed kan uitoefenen op de bioactiviteit ten gevolge van wijzigingen in conformationele en stereochemische eigenschappen. Teneinde deze doelstelling te realiseren werden nieuwe methodologieën ontwikkeld voor de diastereoselectieve Staudingersynthese van 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-onen **iii** uitgaande van (*E*)-*N*-[3-(*tert*-butyldimethylsilyloxy)propylidene]aminen **xvi**, hetgeen onvermijdelijk resulteerde in de vorming van mengsels van β-lactamen **iii** en *N*-acylenaminen **xvii** (22/78 – 83/17). Omwille van de aanwezigheid van een gespannen vierringstructuur, een nucleofiel stikstofatoom (na omzetting) en een elektrofiel centrum in de zijketen, bleken β-lactamen **iii**, dewelke werden geïsoleerd via kolomchromatografie op silicagel, uitstekende substraten te zijn voor verdere omzetting tot andere azaheterocyclische verbindingen waaronder 2-(2-mesyloxyethyl)azetidinen **xix** via opeenvolgende reductie met monochlooralaan, ontscherming met TBAF en mesylering. Op deze manier werden gemesyleerde azetidinen **xix** aangemaakt in hoge rendementen en zuiverheid als de dinor-dimethylvarianten van gebromineerde azetidinen **xii**.



xvia (R^1 = *i*Pr)
xvib (R^1 = *c*Hex)
xvic (R^1 = *i*Bu)
xvid (R^1 = allyl)
xvie (R^1 = *n*Pr)
xvif (R^1 = *n*Bu)
xvig (R^1 = Bn)
xvih (R^1 = Ph)

iiia (R^1 = *i*Pr, R^2 = Ph, 47%)
iiib (R^1 = *i*Pr, R^2 = Bn, 35%)
iiic (R^1 = *c*Hex, R^2 = Bn, 55%)
iiid (R^1 = *i*Bu, R^2 = Bn, 5%)

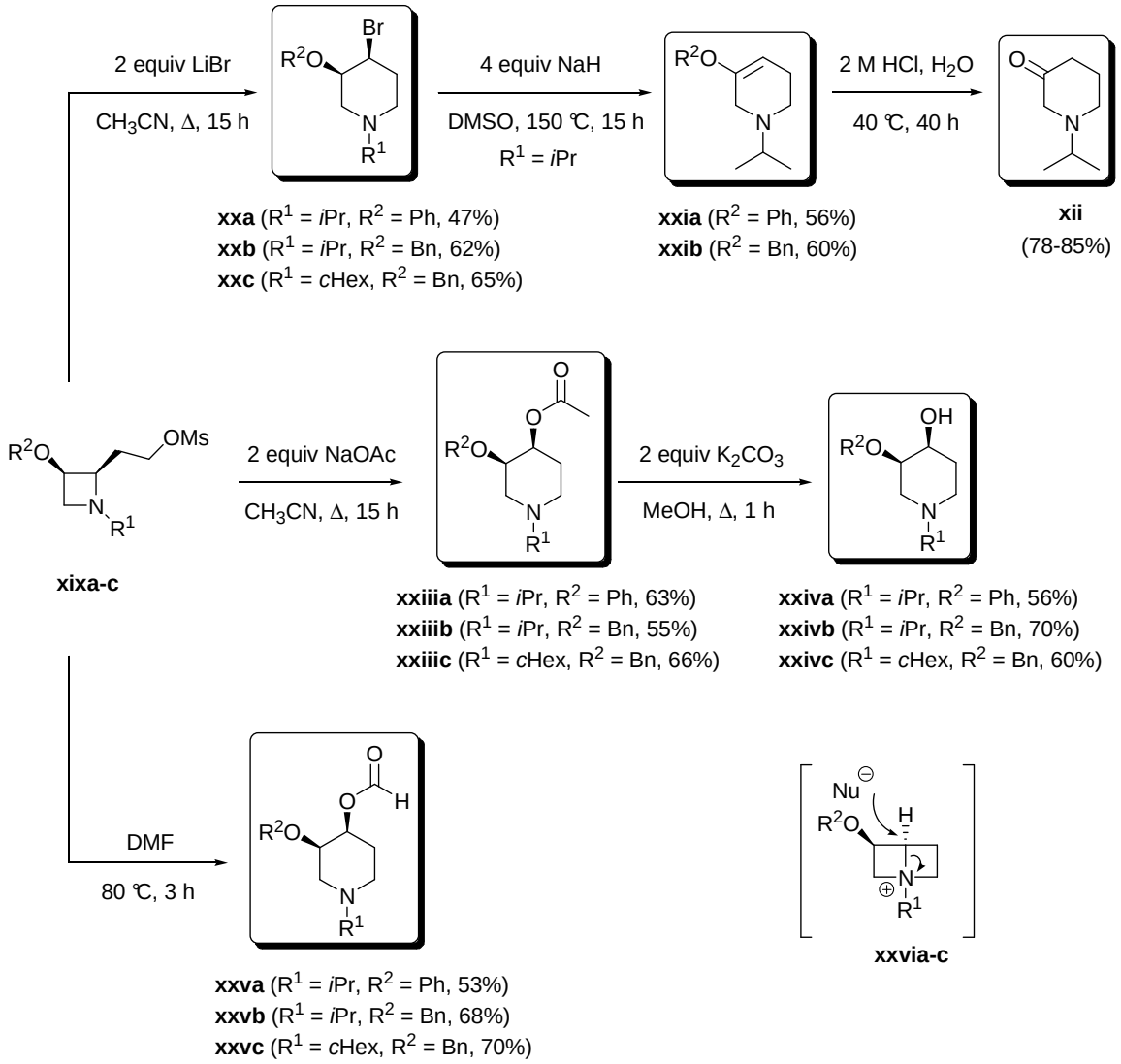
xviid (R^1 = *i*Bu, R^2 = Bn, 66%)

xixa (R^1 = *i*Pr, R^2 = Ph, 90%)
xixb (R^1 = *i*Pr, R^2 = Bn, 88%)
xixc (R^1 = *c*Hex, R^2 = Bn, 85%)

xviiia (R^1 = *i*Pr, R^2 = Ph, 48%)
xviiib (R^1 = *i*Pr, R^2 = Bn, 49%)
xviiic (R^1 = *c*Hex, R^2 = Bn, 50%)

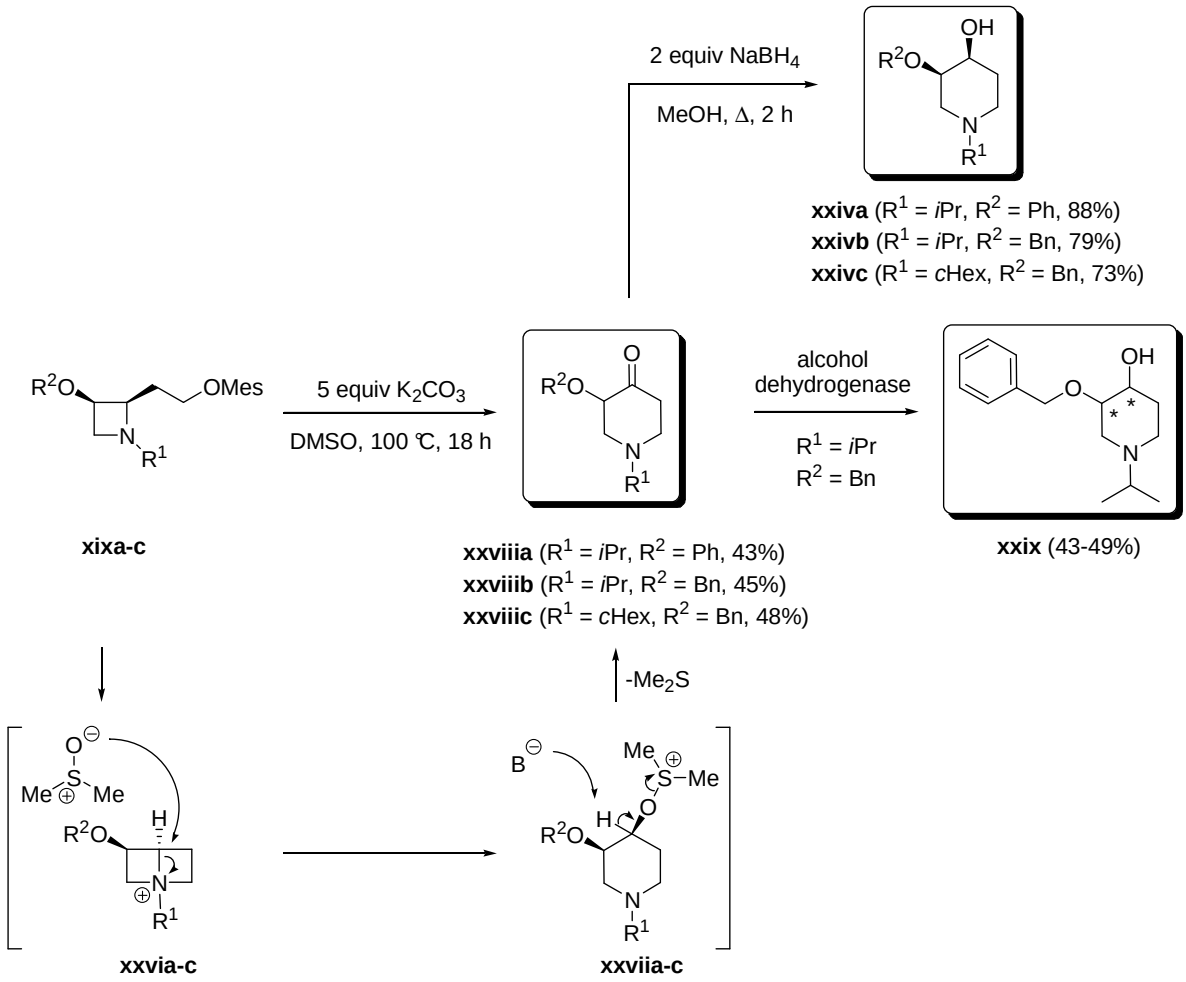
Vervolgens werd het reactiviteitsprofiel van 2-(2-mesyloxyethyl)azetidinen **xix** ten opzichte van verschillende nucleofielen in detail bestudeerd teneinde inzicht te verwerven in hun synthetisch potentieel, hetgeen resulteerde in de stereoselectieve ringexpansie tot biologisch interessante 4-

acetoxy- **xxiii**, 4-hydroxy- **xxiv**, 4-broom- **xx** en 4-(formyloxy)piperidinen **xxv** via regioselectieve S_N2 ringopening van intermediaire bicyclische azetidiniumionen **xxvi**. Hierbij dient opgemerkt te worden dat in alle gevallen kleine hoeveelheden van de overeenkomstige 2-vinylazetidinen (2-9%) aanwezig waren in de reactiemengsels. Deze benadering vormt een waardig alternatief voor de aanwezigheid van de *gem*-dimethylgroep in de hierboven onderzochte 3,4-digesubstitueerde 5,5-dimethylpiperidinen, en vormt aldus een efficiënte toegang tot de 5,5-dinor-dimethylanaloga als waardevolle templates in de medicinale chemie. Bovendien werd een nieuwe toetreding tot de interessante klasse der piperidin-3-onen uitgewerkt via dehydrobrominering van 4-bromo-3-(phenoxy- or benzyloxy)piperidinen **xx** gevolgd door zure hydrolyse. Deze experimentele resultaten werden onderbouwd met theoretische berekeningen (uitgevoerd aan het centrum voor Moleculaire Modellering, UGent), hetgeen de aanwezigheid van bicyclische azetidiniumionen **xxvi** in de ringexpansie van azetidinen **xix** tot piperidinen **xx**, **xxiii** en **xxv** ondersteunde.

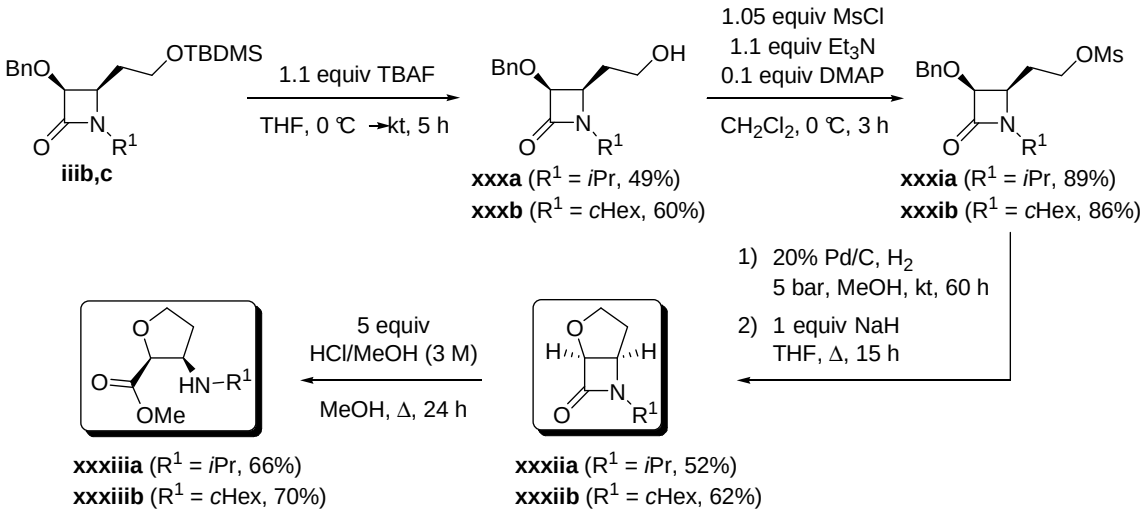


Pogingen tot de selectieve synthese van 4-fluor-5,5-dinor-dimethylpiperidinen faalden echter onder de gebruikte reactieomstandigheden en vergen duidelijk verder onderzoek.

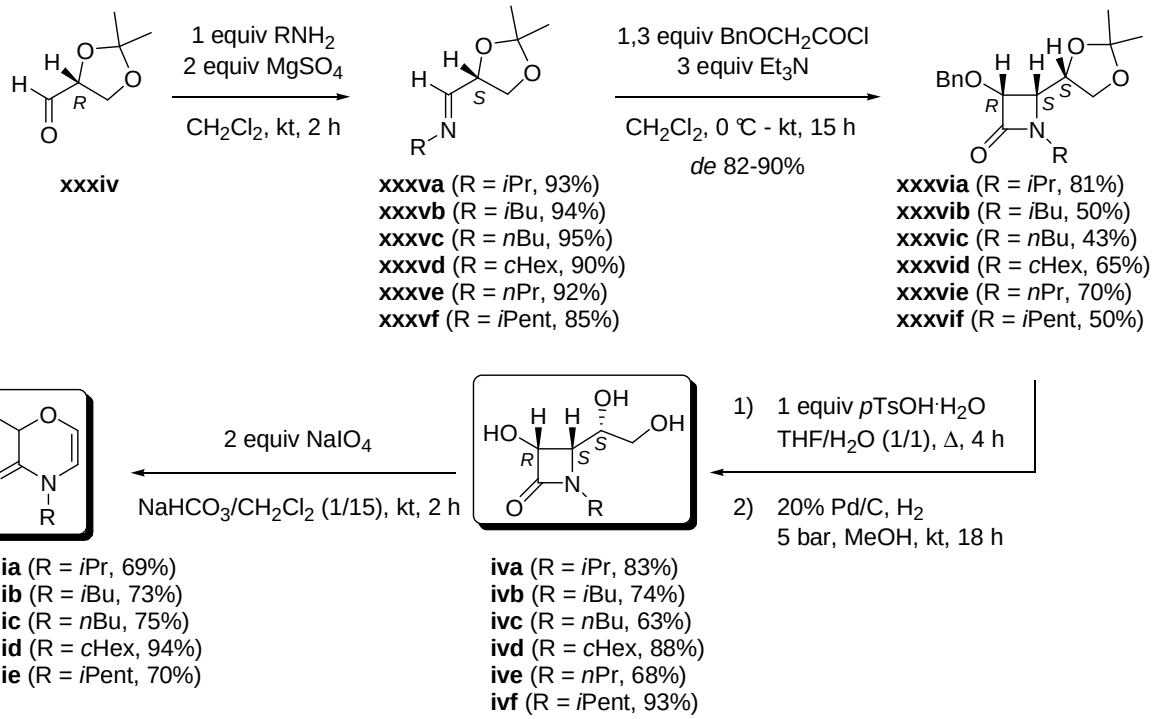
In een vierde deel van dit werk werd, als uitbreiding op de eerder bestudeerde ringexpansie-oxidatie van 2-(broomethyl)azetidinen **xii**, de intrinsieke reactiviteit van 2-(2-mesyloxyethyl)azetidinen **xix** ten aanzien van verwarmen in DMSO in aanwezigheid van K_2CO_3 onderzocht, hetgeen aanleiding gaf tot de selectieve vorming van piperidin-4-onen **xxviii** via DMSO-geïnduceerde regioselectieve ringopening van bicyclische azetidiniumintermediairen **xxvi**. Vanuit biologisch oogpunt vormen piperidin-4-onen een belangrijke klasse van azaheterocyclische verbindingen met onder meer antivirale, antitumor, pijnstillende, antimicrobiële, fungicidale, herbicidale, en ontstekingsremmende activiteiten. Bovendien werd het synthetisch nut van deze 5,5-dinor-dimethylpiperidin-4-onen **xxviii** aangetoond door middel van zowel een chemische als een enzymatische reductie van 3-benzyloxy-1-isopropylpiperidin-4-on **xxviiib**. Daar waar de $NaBH_4$-geïnduceerde reductie werd gekenmerkt door een *cis*-diastereoselectiviteit, verliep de alcohol dehydrogenase-geïnduceerde reductie met een *S*- of *R*-enantioselectiviteit ter hoogte van de carbonylfunctionaliteit.



In een volgende fase werd de aanmaak van nieuwe niet-conventionele bicyclische β-lactamen als potentieel antimicrobiële verbindingen en/of β-lactamase-inhibitoren beoogd. 3-Benzyloxy-4-(2-mesyloxyethyl)-β-lactamen **iii** werden omgezet tot nieuwe *cis*-2-oxa-6-azabicyclo[3.2.0]heptan-7-onen **xxxii** in 52-62% totaalrendement via hydrogenolyse gevolgd door intramoleculaire nucleofiele substitutie door additie van NaH. Via zure methanolyse werden de gesynthetiseerde bicyclische verbindingen **xxxii** vervolgens omgezet tot de overeenkomstige *cis*-3-aminotetrahydrofuran-2-carboxylaten **xxxiii** in 66-70% rendement. β-Aminozuren vormen een zeer waardevolle klasse van verbindingen, die zowel van synthetisch als biologisch nut zijn. Meer specifiek zijn cyclische β-aminozuren als basisskelet aanwezig in een brede waaier aan natuurproducten, en β-peptiden vormen stabielere secundaire structuren in vergelijking met hun α-peptide natuurlijke tegenhangers. Deze benadering vormt een waardig alternatief voor de gekende synthese van 4,4-dimethyl-2-oxa-6-azabicyclo[3.2.0]heptan-7-onen en 3-amino-4,4-dimethyletrahydrofuran-2-carboxylaten, resulterend in de efficiënte bereiding van de overeenkomstige dinor-dimethylanaloga.



In een laatste deel van deze thesis werd de reactiviteit van 3-hydroxy-4-(1,2-dihydroxyethyl)-β-lactamen **iv**, bereid via zure hydrolyse van de acetaaleenheid gevolgd door hydrogenolyse van de benzylethersubstituent in β-lactamen **xxxvi**, ten opzichte van het oxidant natriumperiodaat voor het eerst uitgebreid geëvalueerd, hetgeen onverwacht aanleiding gaf tot de exclusieve vorming van nieuwe 2-hydroxy-1,4-oxazin-3-onen **xxxvii**, meest waarschijnlijk via splitsing van de C3-C4-binding in intermediaire 4-formyl-3-hydroxy-β-lactamen gevolgd door ringexpansie. Deze transformatie is inderdaad merkwaardig gezien 3-alkoxy- en 3-fenoxy-4-(1,2-dihydroxyethyl)-β-lactamen onder identieke omstandigheden worden omgezet tot de overeenkomstige 4-formyl-β-lactamderivaten zonder verdere omleggingen. Deze resultaten werden onderbouwd met theoretische berekeningen (uitgevoerd aan het centrum voor Moleculaire Modellering, UGent).



xxxiv

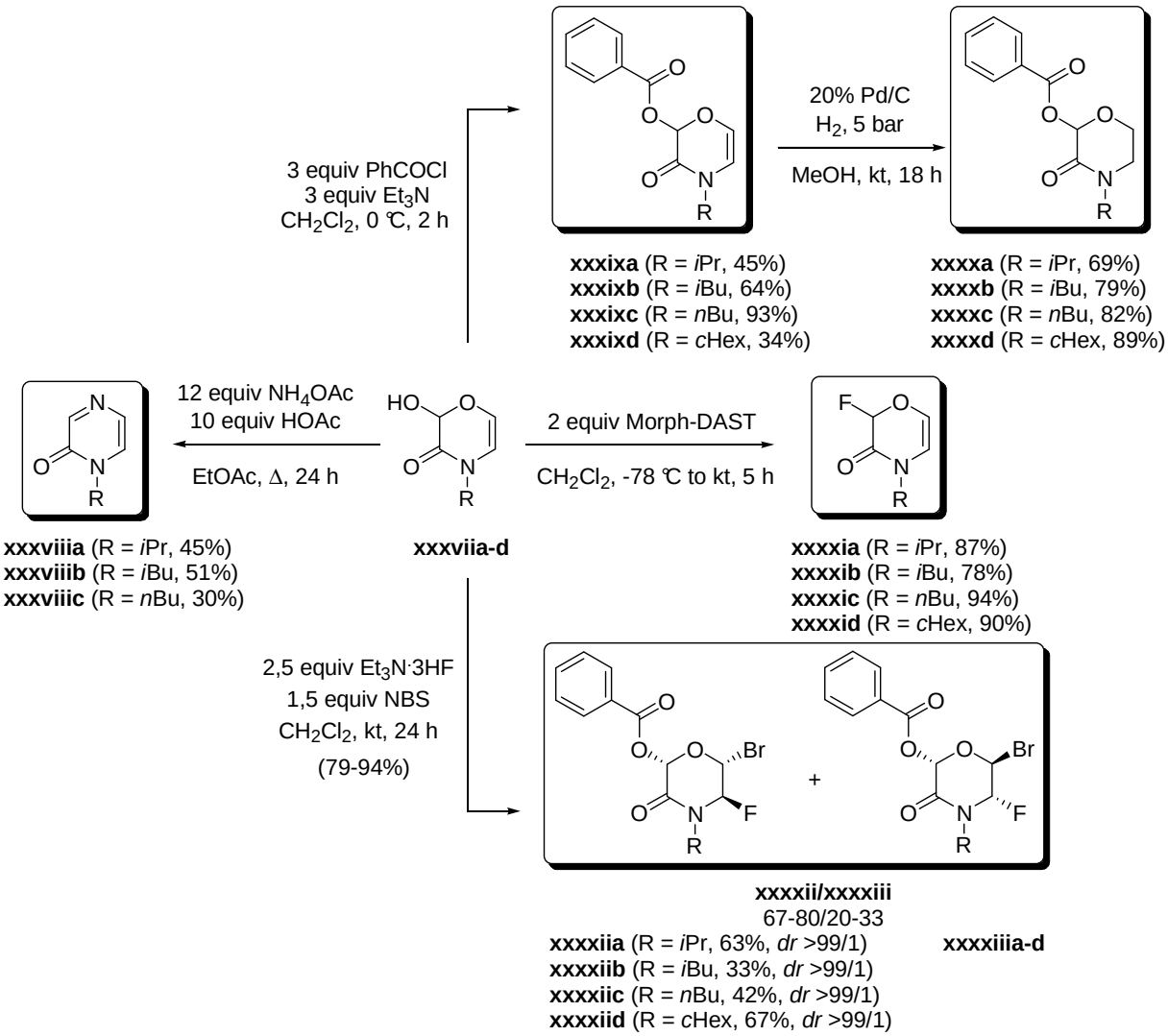
xxxva (R = *i*Pr, 93%)
xxxvb (R = *i*Bu, 94%)
xxxvc (R = *n*Bu, 95%)
xxxvd (R = *c*Hex, 90%)
xxxve (R = *n*Pr, 92%)
xxxvf (R = *i*Pent, 85%)

xxxvia (R = *i*Pr, 81%)
xxxvib (R = *i*Bu, 50%)
xxxvic (R = *n*Bu, 43%)
xxxvid (R = *c*Hex, 65%)
xxxvie (R = *n*Pr, 70%)
xxxvif (R = *i*Pent, 50%)

xxxviia (R = *i*Pr, 69%)
xxxviib (R = *i*Bu, 73%)
xxxviic (R = *n*Bu, 75%)
xxxviid (R = *c*Hex, 94%)
xxxviie (R = *i*Pent, 70%)

iva (R = *i*Pr, 83%)
ivb (R = *i*Bu, 74%)
ivc (R = *n*Bu, 63%)
ivd (R = *c*Hex, 88%)
ive (R = *n*Pr, 68%)
ivf (R = *i*Pent, 93%)

Vervolgens werden de gesynthetiseerde 2-hydroxy-1,4-oxazin-3-onen **xxxvii** aan een uitgebreide reactiviteitsstudie onderworpen met het oog op de selectieve aanmaak van heterocyclische targets, waarbij verschillende strategieën op hun haalbaarheid werden getest. Vooreerst werden 2-hydroxy-1,4-oxazin-3-onen **xxxvii** gebruikt als geschikte substraten voor de bereiding van nieuwe 2-benzoyloxy-1,4-oxazin-3-onen **xxxix** via bescherming van de hydroxylgroep door behandeling met benzoylchloride. Deze gesynthetiseerde heterocyclische verbindingen **xxxix** werden dan ingezet in de synthese van 2-benzoyloxymorfolin-3-onen **xxxx** in 69-89% rendement. Morfolin-3-onen vertonen interessante biologische eigenschappen; zo staan ze onder meer in de belangstelling als hoornvlies doorlatende calpaïne-remmers met anticatarct eigenschappen, kaliumkanaal openers bruikbaar in de behandeling van urine-incontinentie, en niet-peptide liganden met hoge affiniteit en selectiviteit voor tachykinine receptoren. Met het oog op het inbouwen van fluor op een plaatsspecifieke wijze werden 2-hydroxy-1,4-oxazin-3-onen **xxxvii** behandeld met Morf-DAST en triethylamine trihydrofluoride voor de selectieve constructie van respectievelijk 2-fluor-1,4-oxazin-3-onen **xxxxi** en 2-benzoyloxy-6-broom-5-fluormorpholin-3-onen **xxxxii** en **xxxxiii**. Ten slotte werden 2-hydroxy-1,4-oxazin-3-onen **xxxvii** ingezet in de eenstapssynthese van 1*H*-pyrazin-2-onen **xxxviii** in 30-51% rendement via behandeling met NH_4OAc en HOAc in ethylacetaat.



In deze doctoraatsthesis werd het synthetisch potentieel van divers gefunctionaliseerde azetidinonen als nieuwe synthons in de organische chemie geïllustreerd aan de hand van hun omzettingen tot een groot aantal nieuwe acyclische en cyclische stikstofbevattende verbindingen, inclusief β-aminoalcoholen, aziridinen, azetidinen, piperidinen, piperidin-4-onen, oxazin-3-onen, morfolin-3-onen, pyrazinonen, cyclische β-aminozuren en bicyclische β-lactamen. Het is duidelijk dat, ondanks het feit dat de β-lactamkern reeds uitgebreid werd bestudeerd in het verleden, de β-lactamchemie nog steeds een zeer intrigerend en veelbelovend onderzoeksdomein vormt voor de aanmaak van nieuwe (a)cyclische targets omwille van de indrukwekkende verscheidenheid aan mogelijke transformaties.

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Publications in International Journals with Peer-Review (denominated "a1" in Belgium)

- D'hooghe, M.; Dekeukeleire, S.; **Mollet, K.**; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. Synthesis of novel 2-alkoxy-3-amino-3-arylpropan-1-ols and 5-alkoxy-4-aryl-1,3-oxazinanes with antimalarial activity. *J. Med. Chem.* **2009**, *52*, 4058.
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Active Participation at Conferences

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- **Mollet, K.**; D'hooghe, M.; De Kimpe, N. Stereoselective synthesis of 2-aryl-3-(hydroxymethyl)aziridines from 4-aryl-3-chloro-β-lactams and study of their ring opening (*poster*). BOSS XII 12th Belgian Organic Synthesis Symposium P122. (July 11-16, **2010**, Namur)
- **Mollet, K.**; D'hooghe, M.; De Kimpe, N. Transformation of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones into 3-aryl-2-(ethylamino)propan-1-ols *via* 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines and *trans*-2-aryl-3-(hydroxymethyl)aziridines (*poster*). The 14th Sigma-Aldrich Organic Synthesis Meeting P41. (December 2-3, **2010**, Spa)
- **Mollet, K.**; Catak, S.; Waroquier, M.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. Stereoselective synthesis of *cis*-3,4-disubstituted piperidines through ring transformation of 2-(2-mesyloxyethyl)azetidines (*poster*). The 15th Sigma-Aldrich Organic Synthesis Meeting P37. (December 1-2, **2011**, Spa)
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- **Mollet, K.**; D'hooghe, M.; De Kimpe, N. Stereoselective synthesis of *cis*-3,4-disubstituted piperidines through ring transformation of 2-(2-bromo-1,1-dimethylethyl)azetidines and 2-(2-mesyloxyethyl)azetidines (*oral communication*). 12th Eurasia Conference on Chemical Sciences P52. (April 16-21, **2012**, Dassai Bay, Corfu, Greece)